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EDITORIAL

COVID-19 and ethnicity: Spotlight on the global rheumatology issues in developing and developed countries

A key issue in the response to the coronavirus disease 2019 (COVID-19) pandemic is the internationally recognized observation that COVID-19 disproportionally affects the Black and minority ethnic population (BAME).[1] We focus predominantly on UK, USA, and India COVID-19 rheumatology challenges and examples. This unprecedented public health crisis started in China in December 2019, following an infection caused by a novel coronavirus strain, named as SARS-CoV2.[2] The World Health Organization in March 2020 declared this public health emergency as a pandemic.[2] COVID-19 pandemic has moved from country to country, peaking at different times despite implementation of strict preventive measures, including complete lockdown periods with varied success. Case mortality rates have been highly variable across nations as well as different ethnic groups.[3]

A number of observational studies from UK and USA indicated that the death rate of COVID-19 is disproportionately higher in BAME.[4,5] The plausible reasons for increased mortality could be poor socio-economic status, poor housing, pre-existing comorbidity, obesity, and vitamin D deficiency.[6,7] The ongoing observations even implicate genetic variation in BAME groups for increased mortality.[5] Some genetic differences may in fact be relevant such as variations in angiotensin-converting enzyme receptor levels in BAME patients[8] and undiagnosed metabolic syndrome in South Asian communities may also be contributory, given that diabetes is such a key predisposition in the UK.[9] Even among healthcare workers (HCW), where most of these factors may not be operative, the mortality has been higher in HCW from BAME backgrounds.[8] Although data from the Office of National Statistics in the UK linked the increase deaths of BAME to age, gender, co-morbidities and occupation,[9] the data remain inadequate.[6] The variation in COVID-19 testing among BAME, HCW and front-line workers maybe a possible reason for increased reported deaths, as patients not admitted to hospital were not included initially in mortality figures.[6] These observations need further investigation and the UK Government has initiated inquiry by Public Health England.[6,7]

The increased migration from India, Pakistan, Bangladesh and other South Asian countries to developed countries such as UK and USA, with the USA particularly benefiting from the influx of Hispanic individuals, have played an important role in economic growth of these countries. However, the gaps in health inequalities among minorities were always there.[4] In the USA, analyses of COVID-19 deaths from different states that house various ethnic populations revealed more deaths in Asians, Hispanics and African-Americans than in White Americans.[4,6] Many people from ethnic minorities hold critical skilled or unskilled jobs in health and social care, retail, public transport, and other sectors, putting them on the front line and at risk of exposure to COVID-19.[6] Data from Australia, though, showed low mortality in general, but had higher representation in migrant populations.[3]

Surprisingly the death rate due to COVID-19 in India and other Asian countries is low relative to Western countries.[10] Furthermore, the majority of patients are asymptomatic or have milder symptoms and need for intensive care support is lower compared to developed countries.[10] The population of India (1 387 297 452) is 4 times that of the USA (331 002 651); however, the number of cases as well as deaths due to COVID-19 has been very low in India. On May 18, the WHO reported 3029 deaths in India among 96 169 total cases, which contrasts with USA, where 87 180 deaths have been reported among 1 432 265 cases.[2] While under-reporting of cases due to non-reporting, low testing figures, higher false negative rates due to improper training of healthcare staff, as well as collection and handling of samples, are likely to have contributed, large numbers of deaths could not have gone unnoticed. Moreover, case fatality rates vary between different states (0.0%-9.1%), and it is impossible to factor in the differences that might result in the variation.[6] For example, states reporting less than 0.5% to gross domestic product (GDP; equivalent to some of the African nations' total GDP) have no mortality.[11] This means socio-economic factors may not fully explain the differences. There is perceptible stigma among the patients as well as healthcare workers as they don't come forward for testing; how this will affect the incidence and case fatality rates is difficult to compound.[12] This is something similar to minority ethnic populations across the world.[13] For sure the discrepancy between higher deaths in BAME in developed countries compared to countries of origin remain complex.[3] Socio-economic deprivation gaps are heightened during these challenging times.[10,14] The increased deaths are also linked with pre-existing respiratory diseases in developed countries; however, respiratory diseases are more common in

India.[10] Clearly, there is disparity in COVID-19 deaths among ethnic minorities between developing and developed countries. Other than these medical reasons, bureaucratic issues and political pressures go unaccounted for in most reports.[4]

These global patterns present challenges for rheumatology communities serving populations from BAME backgrounds.[13] Certain rheumatic diseases are more common among BAME groups, such as systemic lupus erythematosus (SLE).[15,16] Previous studies from the UK identified health inequalities in managing chronic diseases, such rheumatoid arthritis and SLE.[17,18] Studies demonstrated patient-related factors may play a key role in adherence to treatments among BAME rheumatology patients.[19,20] The patient-related factors noted in studies are similar to those from developing and developed countries.[21,22] A significant analytical challenge is that these patients are on various immunosuppressive treatments, which also increase the risk of infections.[23] However, data suggest the medications used in rheumatology, such as tocilizumab and anakinra, may have some beneficial effect in COVID-19 patients.[24,25] Although trials and registries have been set up, BAME patients are usually under-represented. The Global COVID-19 Rheumatology registry is trying to overcome this.[26] Being a global alliance, this might help us comprehend the complex interactions between COVID-19, rheumatological diseases and ethnic diversity.[27]

In the UK, rheumatology colleagues, together with patient rheumatology charities, acted independently of governmental efforts to reach out to BAME communities where English language proved to be a problem in understanding the guidelines around COVID-19.[13] Working closely with policy makers, such as the British Society for Rheumatology, to collect departmental data on patient shielding was also an initiative taken by some of the authors. The UK Government developed a screening formula to identify those "at risk" for taking immunosuppressive treatment to be directed to shield for 12 weeks. As the lockdowns across countries release, the challenges for each country will vary. For example, in the USA, Black or African American minorities and Hispanic groups are less likely to have health insurance, with consequent reduced healthcare access.[4] Moreover, in some cases the insurance policy benefits may be lost due to unemployment. Of course, there are many factors influencing baseline health status and subsequent access to health care. The casualization of the workforce, particularly younger persons, and particular trades, for example hospitality, has meant that in any downturn they become unemployed, yet may not be eligible for the same support. Furthermore, in places like Australia if a business was closed because of a lockdown or insufficient work, even though people may not be unemployed and will return to the business when it resumes, people are unable to access their sick leave. In other countries, public health insurance is enmeshed with employment, and may not be part of casual employment.

Similarly, in India, the challenges to accessing health care due to loss of wages and lack of health insurance as well as disability allowances, and long-distance travel to reach a hospital, are overwhelming. In addition, there is limited availability of hydroxychloroquine and immunosuppressive drugs at local medical shops and hospitalization is difficult for serious patients as most hospitals are working at lower capacity and some are wary of admitting patients due to fear of COVID-19 infections. This has been further complicated by the lockdown and inability to access health facilities at tertiary care centers due to lack of public transport. It is arduous to get permission from administration to travel under prevailing circumstances. However, the silver lining is that many of our rheumatic disease patients are relatively young, therefore at working age. It is difficult to contemplate how these services will resume once lockdowns are relaxed; rheumatologists working as private practitioners will be unsure how to start their services and administrations in government hospitals are busy reorganizing scarce resources around tackling COVID-19 and non-COVID-19 emergencies.

From the spotlight on the data and discussion above, we consider there are at least 3 areas that merit global prioritization. First, there is an urgent need to understand more deeply the reasons behind and implications of a disproportionately high clinical impact of COVID-19 on certain ethnic groups; second, there is public policy and how this should be framed within individual countries to adapt to needs of diverse population groups; third, there is the issue about communication of intelligence about COVID-19 to ethnic groups. Understanding the reasons for the initial evidence of excess mortality in BAME and minority groups is essential for the successful implementation of mitigation strategies, particularly if substantial disease emerges in the future. Epidemiologic and scientific studies may lead to more targeted health interventions.[14] A range of different studies is needed to investigate this from the scientific and treatment perspective and from a global public health viewpoint. In the USA the National Institute of Minority Health and Disparities (NIMHD) is soliciting such studies.[26] In the UK the National Institute of Health Research (NIHR) and the UK Research and Innovation (UKRI) are jointly calling for research proposals to investigate the evidence and impact of COVID-19 on ethnicity.[6] Concerns are being voiced about the particularly high risk of healthcare and other key workers who belong to BAME groups, as well as more generally, the evidence of a poorer outcome from COVID-19 infection in people from BAME backgrounds. These studies should provide us the results for effective control and treatment. In order to achieve health equity in vulnerable groups it is essential that trials should include diverse participants who may be at high risk, and take cognizance of the factors that may impose added vulnerability for risk stratification. This is particularly important for patients with rheumatic diseases, wherein many conditions are linked to the immune system, and patients may be on multiple medications that include immunomodulatory as well as immunosuppressive therapy.[24,28] Additionally, these patients may have disease-induced frailty, all of which taken together are relevant for risk stratification, that may be heightened by ethnicity.

Public policy can enhance health but should also incorporate ethnic-specific adjustments if it is not to exacerbate differences in health care.[6,29] Culturally adapted mental health services have been shown to be more effective compared to standard services, when

applied to persons of color.[28] Optimal promotion of health equity in minority groups can be achieved only by policies that express a level of cultural competence for the target community.[7] This requires reasonable adjustments to accommodate individual, family and community ethnic-specific differences in order to promote health equity, especially at a time of this COVID-19 pandemic.[13] Implementation and messaging of such policies should chime with the values of all sectors of the population. The COVID-19 pandemic requires an understanding of its effects and how it is spread, as well as the acceptance of such intelligence by minority ethnic people in order for the population in this group to comfortably adopt positive measures for personal safety as well as to limit the spread of infection. Adequate knowledge of COVID-19 that is delivered in an understandable and acceptable format to the recipient is a determinant for such behavior.[12] It is through the communication of such knowledge in a way that is culturally competent, that is vital to its acceptance, with the assurance that minority populations may adapt to such positive behaviors as are required in this time of global crisis. Some of the authors have already developed partnerships of joined-up thinking between the National Rheumatoid Arthritis Society and Ambassadors for Ethnicity Health, in the UK, to communicate, disseminate and raise awareness of COVID-19 among the BAME populations.[13] Similar interventions in other nations may prove to be of value.

Looking into the future with COVID-19, 2021 and beyond, interdisciplinary and international collaborative research projects to investigate the impacts are required as it is difficult to extrapolate the findings to different societies. Furthermore, there is much to be learned from comparing and contrasting between different countries that will better inform the approach individual countries may take as well as our global response. Collaborative datasets, as well as exploiting existing data, are also necessary to better bridge the health inequalities in rheumatology and beyond.

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ORIGINAL ARTICLE

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Association of FcγRIIA-R/H131 polymorphism and systemic lupus erythematosus lupus nephritis risk: A meta-analysis

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Abstract

Aim: Previous studies have discussed association of FcγRIIA-R/H131 polymorphism and systemic lupus erythematosus (SLE), lupus nephritis (LN) risk. However, conclusions were inconsistent.

Methods: A meta-analysis was performed in this study with allelic contrast (allele R vs H), additive model (genotype RR vs HH), recessive model (genotype RR vs RH + HH), and dominant model (genotype RR + RH vs HH).

Results: A total of 33 studies discussed the correlation between FcγRIIA-R/H131 polymorphism and SLE, involving 5652 SLE patients and 6322 controls. Allele R was significantly related to SLE in the overall population (odds ratio [OR] = 1.238, $P < .001$), Asian (OR = 1.237, $P < .001$) and European population (OR = 1.212, $P = .012$). Additive, recessive and dominant models were correlating with SLE in the overall population (OR = 1.448, $P < .001$; OR = 1.303, $P < .001$; OR = 1.310, $P < .001$), Asian population (OR = 1.640, $P = .001$; OR = 1.437, $P < .001$; OR = 1.344, $P = .005$), respectively. In addition, 22 studies evaluated relation of FcγRIIA-R/H131 polymorphism with LN, involving 2065 patients with LN, and 2023 patients without LN. Results showed that allele R and the other 3 models related to LN susceptibility in the overall population when discussing differences of polymorphism between patients with/without LN. We further compared differences of polymorphism between patients with LN and controls, showing that additive and recessive models related to LN risk in the overall population, Asian, European and North American populations.

Conclusion: In summary, FcγRIIA-R/H131 polymorphism is associated with SLE and LN.

KEYWORDS

FcγRIIA, lupus, nephritis, polymorphism

1 | INTRODUCTION

Systemic lupus erythematosus (SLE) is an inflammatory autoimmune disorder characterized by varieties of manifestations such as organs/systems damage, for example, involving kidney, joint, skin.[1] This complicated disease mainly affects women in childbearing age. Lupus nephritis (LN) is the most serious complication of SLE, contributing to the bulk of morbidity and mortality in SLE patients. Although the etiology of SLE/LN has not been clarified, genetic, epigenetic, environmental factors have been discovered to correlate with pathogenesis and development of SLE/LN.[2] All these abnormalities may lead to dysfunction of immunity.

Antibodies in immune cells can form immune complexes after encountering the corresponding cognate antigen. Immunoglobulin G (IgG)-immune complex is an activator for the immune system by interacting with the receptor for the Fc part of IgG.[3] Fc gamma receptors (FcγRs) are a family of glycoproteins that are expressed on the membrane of different immune cells. This complex family binds to IgG, triggering a variety of cellular functions, mediating the innate and adaptive immune response.[4] There are 6 members in humans, including a high-affinity receptor (FcγRI), 5 low-to-medium-affinity FcγRs (FcγRIIA, FcγRIIB, FcγRIIC, FcγRIIIA, FcγRIIIB). All of them contain a ligand-binding α subunit with 2 or 3 extracellular Ig-like domains, a transmembrane domain, a cytoplasmic domain and the genes encoding FcγRs are located at the distal end of chromosome 1.[5] FcγRIIA is a ~40 kD weight protein molecule. FcγRIIA has a single polypeptide chain, by which an immunoreceptor tyrosine-based activating motif (ITAM) exists in the intracellular domain.[6] FcγRIIA has been demonstrated to be the most widely expressed subfamily of the FcγRII. It is expressed on distinct immune cells, such as monocytes, macrophages, dendritic cells, T cells. It is able to activate the ITAM-dependent signaling pathway, for instance, phosphorylating spleen tyrosine kinase, phosphatidylinositide 3-kinase, and then regulate immune responses, inflammatory cytokines/chemokines production.[7] There are 2 common allelic isoforms for FcγRIIA, where polymorphisms in the gene encoding FcγRIIA are decided by a G to A substitute, leading to replacement of arginine with histidine at position 131 of this protein.[8] This polymorphism (FcγRIIA-R/H131, rs1801274) decreases affinity of FcγRIIA for IgG2. Recent studies have discussed association of this polymorphism and human diseases, especially autoimmune disorders. In a study about FcγRIIA-R/H131 polymorphism and ulcerative colitis (UC) risk in a Chinese Han population, frequency of the minor homozygote of FcγRIIA-R/H131 was lower in UC patients than that in healthy controls.[9] In contrast, Beppler et al evaluated whether the FcγRIIA-R/H131 polymorphism is a marker of genetic susceptibility for sepsis by a case-control study conducted in Brazil. The authors found that comparison of frequencies of genotypes or alleles of FcγRIIA-R/H131 had no differences between patients and controls.[10] To date, many studies have tested the association of FcγRIIA-R/H131 polymorphism and SLE/LN risk as well. However, the conclusion is inconsistent, which may relate to small sample size, racial/ethnic differences, study quality, and so on. Therefore, a meta-analysis was designed in this study, where we assessed FcγRIIA-R/H131 polymorphism and SLE/LN genetic susceptibility by a comprehensive analysis.

2 | METHODS

2.1 | Studies selection

A comprehensive screen for research about relationship between FcγRIIA-R/H131 polymorphism and SLE/LN risk was performed up to 1 September, 2019. Databases including PubMed, Medline, Scopus, EMBASE, Web of Science, and Cochrane were used to find possible articles where FcγRIIA-R/H131 polymorphism was discussed in SLE/LN patients and controls. A different panel of keywords was designed, including "systemic lupus erythematosus" or "SLE" or "lupus nephritis" or "LN", "Fc gamma receptor" or "FcγR" or "Fc gamma receptor IIA" or "FcγRIIA" or "FCGR2A", "polymorphism" or "variant". In addition, references listed in the original article were checked for other possible studies that had not been identified. We did not limit language when screening for the studies in this meta-analysis. Investigations were recruited according to the following criteria: (a) the study was about human subjects; (b) the study was a case-control study or cohort study; (c) it contained original data (independence among studies); (d) there were enough data for calculating odds ratios (OR) with 95% confidence intervals (CI) either directly extracted from the paper or after contacting the authors; (e) the study assessed association between FcγRIIA-R/H131 polymorphism and SLE/LN risk; (f) there were at least 2 comparison groups (SLE vs control groups; SLE with LN vs SLE without LN groups). Investigations were excluded according to the criteria: (a) there were overlapping data; (b) information about genotypes or alleles could not be obtained; (c) family studies in which analysis was based on linkage considerations. The process for searching for possible studies is summarized in Figure 1.

2.2 | Data collection

Data were extracted by 2 independent reviewers (YX, HW). If there was discrepancy when extracting the data, another reviewer (JZ) needed to resolve the problem in addition to the 2 reviewers. In the present meta-analysis, the following data were extracted and recorded: name of the first author, time of publication (year), ethnicity, number of cases/controls, frequencies of genotypes/alleles for FcγRIIA-R/H131 polymorphism.

2.3 | Quality assessment

The methodological quality of recruited studies was evaluated according to the Newcastle-Ottawa scale (NOS) score.[11] The NOS criteria measure quality of a study by 3 aspects, including study selection, comparability of the groups, exposure. The score ranges from 0 to 9, by which total score 8 or 9 means high quality, 6 or 7 is moderate quality, less than 5 is low quality.

2.4 | Statistics

All the data were analyzed by STATA 11.0 (StataCorp). Evaluation of genotype frequencies in controls discussed whether the selection of controls from the original study accorded with Hardy-Weinberg expectation (HWE). Four models were conducted in this meta-analysis: allelic contrast (allele R vs H), additive model (genotype RR vs HH), recessive model (genotype RR vs RH + HH), and dominant model

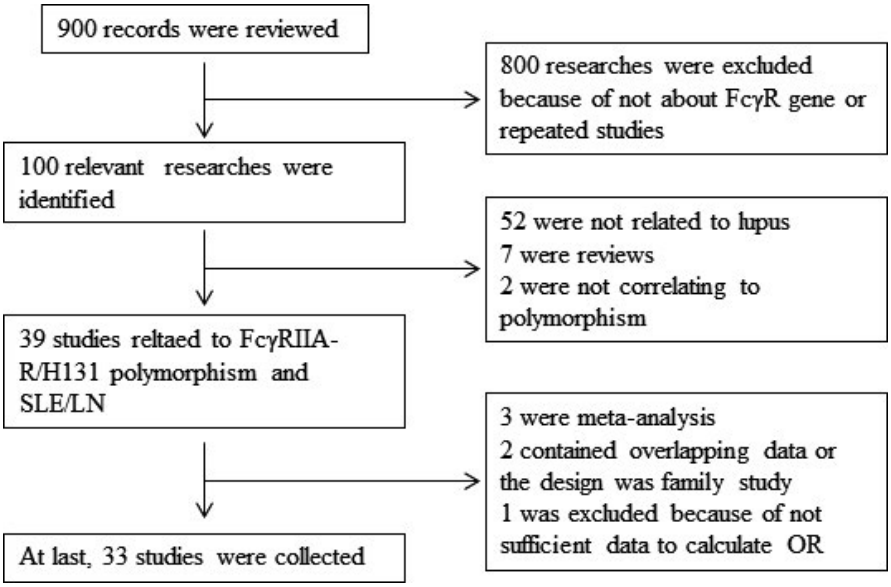

FIGURE 1 Progress of selecting studies

(genotype RR + RH vs HH). Point estimate of risk, OR, 95% CI were assessed for individual studies. Cochran's Q-statistic tested studies' variation/heterogeneity. If a *P* value of the examination of heterogeneity was less than .10, it suggested there was significant heterogeneity. Consequently, a random effects model was adopted. As is known, many of the published papers considered ethnicity, quality score as potential source of heterogeneity.[12-14] In this meta-analysis, these factors were considered, and stratification of groups explored the effect of heterogeneity. If a *P* value of the examination of heterogeneity was higher than .10, this indicated no significant heterogeneity, and the fixed effect model was used.[15] Sensitivity analysis was conducted to evaluate the influence of individual studies on the summary effect.

2.5 | Publication bias assessment

Funnel plots were selected to examine publication bias for each model when discussing association of FcγRIIA-R/H131 polymorphism and SLE/LN genetic susceptibility. Egger's test was additionally selected for evaluating potential publication bias.[16]

3 | RESULTS

3.1 | Characteristics of studies collected in the meta-analysis

When searching for potential publications about FcγRIIA-R/H131 polymorphism and SLE/LN, 900 records were first reviewed. After screening the studies according to inclusion criteria, a total of 33 studies discussed association of FcγRIIA-R/H131 polymorphism and SLE risk.[17-49] In detail, 5652 SLE patients and 6322 controls were recruited. There were 17 studies about participants in Asia,[18,20,23,25,30,32,34-40,42,43,45,47] 12 studies from Europe,[19,21,22,24,27-29,31,33,41,44,48] 3 studies on African-Americans[17,26,49] and 1 study from South America.[46] Interestingly, 3 studies had more than 1 comparison.[18,19,25] Therefore, a summary of 37 comparisons were obtained in the study, including 18 comparisons for Asia, 14 comparisons for Europe, 4 comparisons for North America, and 1 comparison for South America (Table 1). For LN analysis, 22 different studies discussed association of FcγRIIA-R/H131 polymorphism and LN risk.[17-27,30,32,37-40,45-47,49,50] Among the studies, 11 were about Asians,[20,23,25,30,32,37-40,45,47] 7 were about Europeans,[18,19,21,22,24,27,50] 3 were about North Americans[17,26,49] and 1 was South American.[46] Interestingly, 4 studies had more than 1 comparison.[18,19,25,50] Therefore, a total of 27 comparisons (2065 patients with LN, and 2023 patients without LN) were recruited for discussing the relationship of FcγRIIA-R/H131 polymorphism and LN (Table S1). Distribution of genotypes of FcγRIIA-R/H131 polymorphism in the control groups was consistent with HWE (Table 1). Quality assessment of the recruited studies is listed in Table 1. Results displayed that according to the NOS, all the studies had high quality or moderate quality.

3.2 | Association of FcγRIIA-R/H131 polymorphism and SLE

With respect to relationship between FcγRIIA-R/H131 polymorphism and SLE, results of the meta-analysis found that allele R was significantly correlating with SLE in the overall population (OR = 1.238, 95% CI: 1.138-1.346, $P < .001$, Table 2, Figure 2). Stratification by ethnicity showed there was significant association of allele R and SLE in Asian populations (OR = 1.237, 95% CI: 1.114-1.374, $P < .001$), European populations (OR = 1.212, 95% CI: 1.043-1.408, $P = .012$), respectively. Regarding association of RR genotype of FcγRIIA-R/H131 polymorphism and SLE, results showed that genotype RR was strongly related to SLE in the overall population (additive model) (OR = 1.448, 95% CI: 1.287-1.629, $P < .001$). Subgroup analysis found

TABLE 1 Characteristics of included studies for systemic lupus erythematosus patients controls

		Numbers		Case					Control						
Author	Ethnicity	Case	Control	RR	RH	HH	R	H	RR	RH	HH	R	H	HWE (*P* value)	NOS score
Salmon 1996	North American	257	139	96	120	41	312	202	33	65	41	131	147	.863	7
Botto-1 1996	European	215	259	72	97	46	241	189	82	120	57	284	234	.777	6
Botto-2 1996	North American	70	77	25	37	8	87	53	25	35	17	85	69	.850	6
Botto-3 1996	Asian	46	49	5	23	18	33	59	5	20	24	30	68	.993	6
Smyth-1 1997	European	81	66	22	49	10	93	69	16	38	12	70	62	.627	8
Smyth-2 1997	European	42	52	12	16	14	40	44	8	24	20	40	64	.995	8
Song 1998	Asian	73	64	9	56	8	74	72	5	37	22	47	81	.333	7
Manger 1998	European	108	187	31	37	40	99	117	50	84	53	184	190	.617	7
Koene 1998	European	70	87	21	33	16	75	65	19	44	24	82	92	.997	7
Hatta 1999	Asian	81	217	2	30	49	34	128	7	71	139	85	349	.936	6
Norsworthy 1999	European	195	283	67	96	32	230	160	90	131	62	311	255	.723	9
Yap-1 1999	Asian	175	108	25	91	59	141	209	17	63	28	97	119	.414	8
Yap-2 1999	Asian	50	50	4	26	20	34	66	8	21	21	37	63	.913	8
Oh 1999	North American	63	69	17	35	11	69	57	25	29	15	79	59	.735	6
Dijsteblocm 2000	European	230	154	68	108	54	244	216	32	80	42	144	164	.923	7
Michel 2000	European	80	183	28	34	18	90	70	33	94	56	160	206	.914	7
D'Alfonson 2000	European	172	87	—	—	—	—	—	—	—	—	77	97	—	6
Sato 2001	Asian	90	96	17	66	7	100	80	13	47	36	73	119	.954	8
Zuniga 2001	European	67	53	23	39	5	85	49	14	28	11	56	50	.927	8
Yun 2001	Asian	300	197	54	114	132	222	378	16	99	82	131	263	.380	6
Hilde 2002	European	180	163	55	90	35	200	160	36	82	45	154	172	.998	7
Kyogoku 2002	Asian	193	303	8	72	113	88	298	11	95	197	117	489	.998	8
Siriboonrit 2003	Asian	87	187	10	40	37	60	114	18	76	93	112	262	.970	8
Kobayashi 2003	Asian	60	84	8	24	28	40	80	2	33	49	37	131	.617	7
Lee 2003	Asian	299	144	54	114	131	222	376	11	66	67	88	200	.823	6
Khoa 2003	Asian	48	43	8	36	4	52	44	4	23	16	31	55	.699	9
Chu 2004	Asian	163	129	21	70	72	112	214	18	58	53	94	164	.965	9
Chen 2004	Asian	302	311	49	122	131	220	384	37	144	130	218	404	.985	8
Jönsen 2004	European	143	200	46	72	25	164	122	51	102	47	204	196	.980	7

(Continues)

TABLE 1 (Continued)

Author	Ethnicity	Numbers		Case				Control				HWE (*P* value)	NOS score
		Case	Control	RR	RH	HH	R	H	RR	RH	HH	R	H		
Hirankarn 2006	Asian	195	159	16	101	78	133	257	18	50	91	86	232	.235	7
Tetsuo 2007	Asian	71	102	6	31	34	43	99	2	42	58	46	158	.402	6
Hellquist 2009	European	265	344	50	188	27	288	242	50	245	49	345	343	.100	9
Zhou 2011	Asian	589	477	82	269	238	433	745	48	220	209	316	638	.825	8
Isabel 2014	South American	157	160	59	75	23	193	121	43	82	35	168	152	.975	8
Haidy 2014	Asian	90	90	25	45	20	95	85	18	50	22	86	94	.712	7
Michel 2016	European	265	919	56	133	76	245	285	269	463	187	1001	837	.940	9
Clancy 2019	North American	80	30	20	24	36	64	96	4	16	10	24	36	.864	6

Abbreviations: HWE, Hardy-Weinberg expectation; NOS, Newcastle-Ottawa scale

that genotype RR was strongly related to SLE in Asian populations (RR vs HH, OR = 1.640, 95% CI: 1.224-2.197, *P* = .001), European populations (RR vs HH, OR = 1.453, 95% CI: 1.058-1.996, *P* = .021) and North Americans (RR vs HH, OR = 2.037, 95% CI: 1.334-3.111, *P* = .001, Table 2). When frequencies of genotype RR were compared with RH + HH (recessive model), there was significant relation to SLE in the overall population (OR = 1.303, 95% CI: 1.182-1.437, *P* < .001). Stratification by ethnicity showed that the recessive model was strongly related to SLE in Asian populations (OR = 1.437, 95% CI: 1.213-1.703, *P* < .001), European populations (OR = 1.283, 95% CI: 1.044-1.577, *P* = .018). Interestingly, frequencies of genotype RR + RH compared with HH (dominant model) indicated a significant relation to SLE in the overall population (OR = 1.310, 95% CI: 1.134-1.512, *P* < .001, Table 2, Figure 3). With respect to association of the dominant model and Asian populations, European populations and North American risk, the Asian population showed significant relation to SLE genetic susceptibility (OR = 1.344, 95% CI: 1.095-1.648, *P* = .005, Table 2), whereas the European population and North Americans did not correlate with SLE risk under the dominant model (*P* > .05, Table 2). When considering study quality as one of the potential sources of heterogeneity, subgroup analysis was conducted. Results showed that allele R, the additive model and dominant model correlated with SLE risk both in high quality and moderate quality studies (all *P* < .05). The recessive model was related to SLE susceptibility in moderate quality studies (*P* < .001, Table 2).

To discuss the association of FcγRIIA-R/H131 polymorphism and SLE regarding age, meta-analysis was performed. Overall information about populations regarding age is summarized in Table S2. Results showed that all the genetic models did not significantly relate to SLE risk in the overall population regarding age at diagnosis (all *P* > .05). In contrast, all the genetic models were significantly related to SLE risk in the overall population, and Asians regarding age at enrollment (Table S3). Because of insufficient data, we did not conduct a meta-analysis to discuss association of FcγRIIA-R/H131 polymorphism and SLE regarding age at onset.

3.3 | Association of FcγRIIA-R/H131 polymorphism between SLE patients with LN and patients without LN

Since several studies discussed association of FcγRIIA-R/H131 polymorphism between SLE patients with LN and patients without LN, there were inconsistent results. Therefore, a meta-analysis was utilized to evaluate the relationship. With respect to allele R in comparison with allele H, there was significant relation with LN in the overall population (OR = 1.153, 95% CI: 1.051-1.266, *P* = .003, Table 3, Figure 4). Stratification by ethnicity showed there was significant association of allele R and LN in Asian populations (OR = 1.162, 95% CI: 1.028-1.313, *P* = .016), whereas allele R did not relate to LN in European and North American populations (*P* > .05, Table 3). Frequencies of genotype RR compared with HH displayed that the additive model was correlating with LN in the

TABLE 2 Meta-analysis of the FcγRIIa R/H131 polymorphism and SLE

			Test of association				Test of heterogeneity			Publication bias
Comparison	Population	No. of Comparison	Model	OR (95% CI)	Z	*P*	χ^2	*P*	I^2 (%)	*P*
R vs H	Overall	37	R	1.238 (1.138-1.346)	7.98	<.001	76.57	<.001	53.0	.377
	Asian	18	R	1.237 (1.114-1.374)	3.97	<.001	25.77	.079	34.0	.133
	European	14	R	1.212 (1.043-1.408)	2.51	.012	39.71	<.001	67.3	.077
	North American	4	R	1.267 (0.917-1.751)	1.43	.152	6.30	.098	52.4	.105
	High quality	16	R	1.164 (1.014-1.336)	2.16	.031	43.52	<.001	65.5	.221
	Moderate quality	21	F	1.307 (1.197-1.427)	5.98	<.001	23.91	.246	16.3	.252
RR vs HH	Overall	36	R	1.448 (1.287-1.629)	6.15	<.001	80.59	<.001	56.6	.357
	Asian	18	R	1.640 (1.224-2.197)	3.32	.001	33.53	.010	49.3	.181
	European	13	R	1.453 (1.058-1.996)	2.31	.021	35.91	<.001	66.6	.132
	North American	4	F	2.037 (1.334-3.111)	3.30	.001	4.18	.242	28.3	.227
	High quality	16	R	1.447 (1.043-2.008)	2.21	.027	47.85	<.001	68.6	.147
	Moderate quality	20	F	1.718 (1.388-2.127)	4.98	<.001	26.43	.119	28.7	.261
RR vs RH + HH	Overall	36	R	1.303 (1.182-1.437)	5.32	<.001	58.85	.007	40.5	.151
	Asian	18	F	1.437 (1.213-1.703)	4.18	<.001	24.03	.119	29.3	.935
	European	13	R	1.283 (1.044-1.577)	2.37	.018	24.88	.015	51.8	.068
	North American	4	R	1.308 (0.768-2.227)	0.99	.322	6.69	.083	55.1	.694
	High quality	16	R	1.182 (0.982-1.423)	1.76	.078	22.49	.085	34.6	.069
	Moderate quality	20	R	1.502 (1.242-1.816)	4.20	<.001	29.60	.057	35.8	.087
RR + RH vs HH	Overall	36	R	1.310 (1.134-1.512)	3.68	<.001	88.59	<.001	60.5	.867
	Asian	18	R	1.344 (1.095-1.648)	2.83	.005	49.36	<.001	65.6	.132
	European	13	R	1.203 (0.957-1.512)	1.58	.113	26.82	.008	55.3	.893
	North American	4	R	1.474 (0.825-2.635)	1.31	.190	6.89	.076	56.4	.387
	High quality	16	R	1.309 (1.029-1.665)	2.19	.029	52.80	<.001	71.6	.321
	Moderate quality	20	R	1.326 (1.121-1.570)	3.29	.001	33.08	.024	42.6	.218

Abbreviations: F, fixed model; R, random model; SLE, systemic lupus erythematosus.

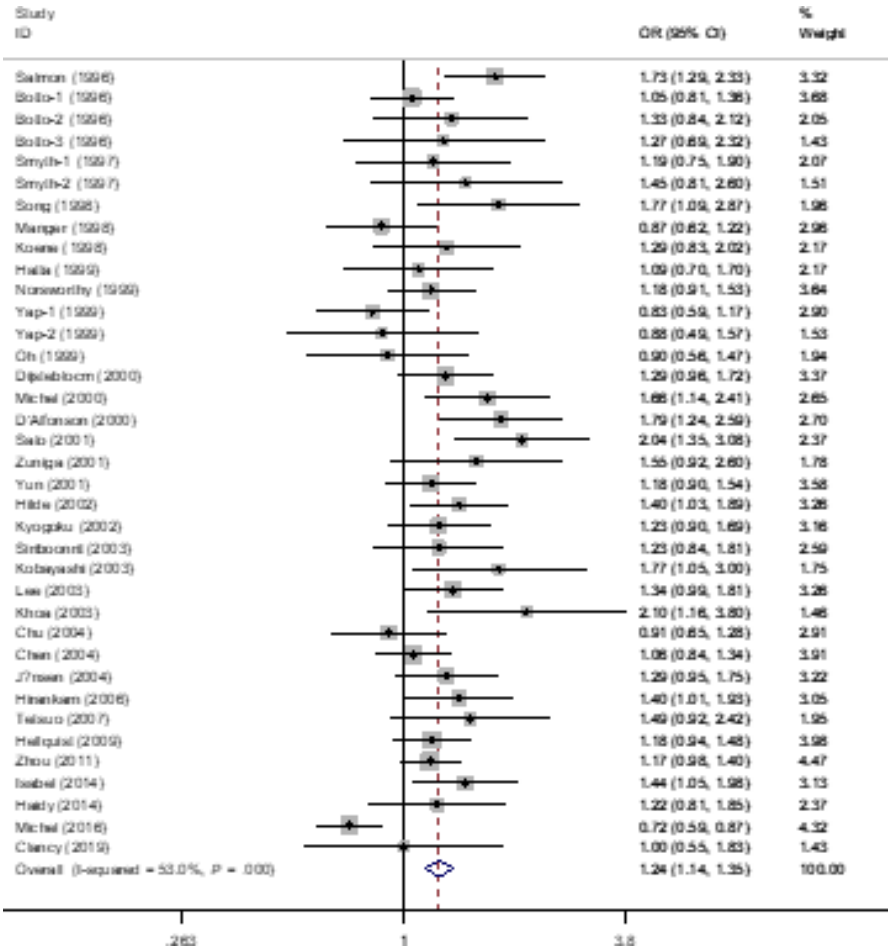

FIGURE 2 Association of FcγRIIA-R/H131 polymorphism and systemic lupus erythematosus (SLE) by allelic contrast. Association of FcγRIIA-R/H131 polymorphism and SLE risk was conducted by comparing the polymorphism between SLE patients and controls in all participants. Odds ratios and 95% CIs for each investigation and pooled data for association between allele R vs H of FcγRIIA-R/H131 polymorphism

overall population (OR = 1.328, 95% CI: 1.093-1.613, P = .004) and Asian populations (OR = 1.364, 95% CI: 1.052-1.768, P = .019). However, the additive model was not related to LN in European populations (OR = 1.064, 95% CI: 0.588-1.924, P = .839) and North Americans (OR = 1.479, 95% CI: 0.866-2.528, P = .152). In addition, the recessive model (RR vs RH + HH) was related to LN in the overall population (OR = 1.203, 95% CI: 1.025-1.411, P = .024), whereas the relation of the recessive model to LN was not significant regarding Asian populations (OR = 1.212, 95% CI: 0.959-1.533, P = .107), European populations (OR = 1.049, 95% CI: 0.667-1.650, P = .835) and North Americans (OR = 1.255, 95% CI: 0.852-1.848, P = .250) by subgroup analysis (Table 3). Furthermore, the dominant model showed significant correlation with LN in the overall population (OR = 1.209, 95% CI: 1.046-1.397, P = .010, Table 3, Figure 5), Asian populations (OR = 1.219, 95% CI: 1.023-1.452, P = .027), but not European populations (OR = 1.077, 95% CI: 0.662-1.751, P = .764) and North Americans (OR = 1.256, 95% CI: 0.798-1.978, P = .0325). Moreover, on the basis of quality score, the stratified meta-analysis found that allele R (OR = 1.190, 95% CI: 1.039-1.363, P = .012), additive model (OR = 1.390, 95% CI: 1.055-1.830, P = .019) and dominant model (OR = 1.307, 95% CI: 1.055-1.620, P = .014) correlated with LN in moderate quality studies, respectively (Table 3). All the genetic models did not significantly relate to LN risk in high-quality studies (all P > .05, Table 3).

To reveal the association of FcγRIIA-R/H131 polymorphism between SLE patients with LN and patients without LN regarding age at enrollment, meta-analysis was performed. Results showed that allelic contrast, the additive model and dominant model were related to LN risk in the overall population, Asians regarding age at enrollment (all P < .04, Table S4). The recessive model was significantly correlated with LN risk in Asians regarding age at enrollment (OR = 1.354, 95% CI: 1.030-1.780, P = .030). Owing to insufficient data, meta-analysis to discuss association of FcγRIIA-R/H131 polymorphism between SLE patients with LN and patients without LN regarding age at onset, age at diagnosis, was not performed.

3.4 | Comparison of FcγRIIA-R/H131 polymorphism between SLE patients with LN and controls

As discussed above, the FcγRIIA-R/H131 polymorphism was partly related to SLE/LN when comparing the polymorphism between SLE patients and controls, or comparing the polymorphism between patients with LN and patients without LN. However, what is the relationship of the polymorphism between SLE patients with LN and controls? The meta-analysis was further conducted and showed that allele R was significantly associated with LN risk in the overall population (OR = 1.278, 95% CI: 1.128-1.448, P < .001, Table 4).

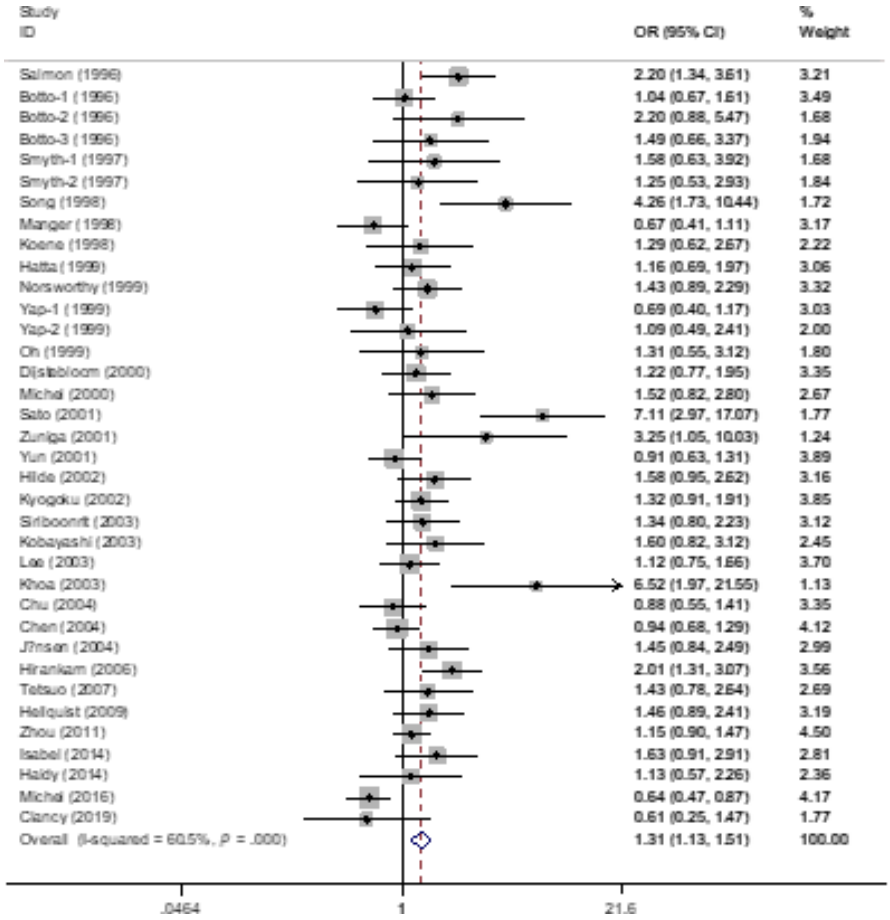

FIGURE 3 Association of FcγRIIA-R/H131 polymorphism and systemic lupus erythematosus (SLE) by dominant model. Odds ratios and 95% CI for each investigation and pooled data for association between genotype RR + RH vs HH of FcγRIIA-R/H131 polymorphism and SLE

Stratification by ethnicity showed there was significant association of allele R and LN in Asian populations (OR = 1.229, 95% CI: 1.095-1.542, *P* = .003) and European populations (OR = 1.249, 95% CI: 1.032-1.512, *P* = .023). With respect to the additive model, there were significant differences between LN patients and controls either for the overall population (OR = 1.788, 95% CI: 1.338-2.389, *P* < .001) or Asian populations (OR = 2.013, 95% CI: 1.285-3.154, *P* = .002) or European populations (OR = 1.487, 95% CI: 1.025-2.158, *P* = .037) or North Americans (OR = 2.528, 95% CI: 1.456-4.387, *P* = .001, Table 4). The recessive model was also significantly related to LN risk regarding the overall population (OR = 1.550, 95% CI: 1.333-1.802, *P* < .001), Asian populations (OR = 1.673, 95% CI: 1.244-2.248, *P* = .001), European populations (OR = 1.478, 95% CI: 1.104-1.977, *P* = .009) and North Americans (OR = 1.496, 95% CI: 1.009-2.219, *P* = .045). Moreover, there was strong relationship among the dominant model and LN risk in the overall population (OR = 1.347, 95% CI: 1.078-1.682, *P* = .009), Asian populations (OR = 1.391, 95% CI: 1.016-1.906, *P* = .040) and North Americans (OR = 1.976, 95% CI: 1.247-3.131, *P* = .004, Table 4). Stratification by quality score showed that allele R (OR = 1.315, 95% CI: 1.126-1.536, *P* = .001), additive model (OR = 1.929, 95% CI: 1.334-2.789, *P* < .001), recessive model (OR = 1.611, 95% CI: 1.204-2.155, *P* = .001), dominant model (OR = 1.331, 95% CI: 1.022-1.733, *P* = .034) was significantly related to LN risk in moderate quality studies (Table 4). The recessive model was correlated with LN in high-quality studies (OR = 1.335, 95% CI: 1.074-1.660, *P* = .009, Table 4).

Since several studies had different populations regarding age, we evaluated association of FcγRIIA-R/H131 polymorphism between SLE patients with LN and controls regarding age at enrollment. Meta-analysis showed that allelic contrast, the additive model and recessive model were significantly related to LN risk in the overall population, Asians regarding age at enrollment (all *P* < .05, Table S5). However, the dominant model was not correlated with LN susceptibility regarding age at enrollment. Because of insufficient data, meta-analysis to evaluate association of FcγRIIA-R/H131 polymorphism between SLE patients with LN and controls regarding age at onset, age at diagnosis was not performed.

3.5 | Association of FcγRIIA-R/H131 polymorphism with mixing populations (SLE + LN)

To evaluate the association of FcγRIIA-R/H131 polymorphism with mixing populations (SLE + LN), we combined populations in 1 group to discuss the relationship. Results showed that all the genetic models were significantly related to mixing populations (SLE + LN) in the overall population, Asians and North Americans (all *P* < .05, Table S6). In addition, allelic contrast, the additive model and recessive model was correlated with mixing populations (SLE + LN) in Europeans (all *P* < .05, Table S6).

TABLE 3 Meta-analysis of the FcγRIIa R/H131 polymorphism and SLE with/without lupus nephritis

			Test of association				Test of heterogeneity			Publication bias
Comparison	Population	No. of comparison	Model	OR (95% CI)	Z	*P*	χ^2	*P*	I^2 (%)	*P*
R vs H	Overall	27	F	1.153 (1.051-1.266)	3.00	.003	30.67	.241	15.2	.056
	Asian	13	F	1.162 (1.028-1.313)	2.40	.016	10.95	.533	0.0	.522
	European	8	R	1.059 (0.794-1.412)	0.39	.696	14.91	.037	53.0	.558
	North American	5	F	1.189 (0.920-1.538)	1.32	.186	3.76	.440	0.0	.449
	High quality	14	F	1.121 (0.986-1.274)	1.75	.080	16.75	.211	22.4	.163
	Moderate quality	13	F	1.190 (1.039-1.363)	2.51	.012	13.52	.333	11.2	.219
RR vs HH	Overall	26	F	1.328 (1.093-1.613)	2.86	.004	27.55	.329	9.3	.058
	Asian	13	F	1.364 (1.052-1.768)	2.34	.019	9.34	.674	0.0	.055
	European	7	R	1.064 (0.588-1.924)	0.20	.839	12.68	.048	52.7	.512
	North American	5	F	1.479 (0.866-2.528)	1.43	.152	3.97	.410	0.0	.579
	High quality	14	F	1.270 (0.965-1.671)	1.70	.089	15.09	.302	13.9	.086
	Moderate quality	12	F	1.390 (1.055-1.830)	2.34	.019	12.20	.349	9.8	.096
RR vs RH + HH	Overall	26	F	1.203 (1.025-1.411)	2.26	.024	24.88	.469	0.0	.061
	Asian	13	F	1.212 (0.959-1.533)	1.61	.107	10.32	.588	0.0	.141
	European	7	R	1.049 (0.667-1.650)	0.21	.835	12.39	.054	51.6	.294
	North American	5	F	1.255 (0.852-1.848)	1.15	.250	1.57	.813	0.0	.684
	High quality	14	F	1.210 (0.965-1.517)	1.65	.099	17.15	.192	24.2	.214
	Moderate quality	12	F	1.195 (0.952-1.499)	1.54	.124	7.72	.738	0.0	.192
RR + RH vs HH	Overall	26	F	1.209 (1.046-1.397)	2.57	.010	29.44	.246	15.1	.159
	Asian	13	F	1.219 (1.023-1.452)	2.21	.027	12.51	.406	4.1	.129
	European	7	R	1.077 (0.662-1.751)	0.30	.764	11.54	.073	48.0	.781
	North American	5	R	1.256 (0.798-1.978)	0.98	.325	4.55	.337	12.1	.661
	High quality	14	F	1.133 (0.931-1.378)	1.25	.213	17.13	.194	24.1	.321
	Moderate quality	12	F	1.307 (1.055-1.620)	2.44	.014	11.43	.408	3.7	.293

Abbreviations: F, fixed model; R, random model; SLE, systemic lupus erythematosus

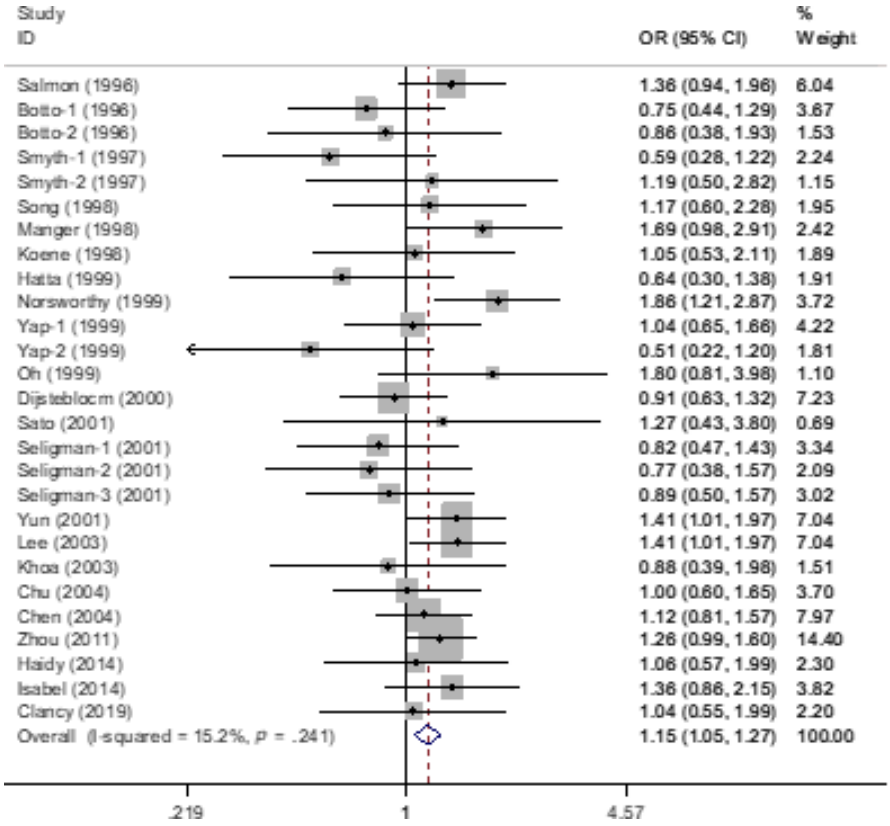

FIGURE 4 Relation of FcγRIIA-R/H131 polymorphism and lupus nephritis risk by allelic contrast. Association of FcγRIIA-R/H131 polymorphism and lupus nephritis risk was conducted by comparing the polymorphism between systemic lupus erythematosus (SLE) patients with nephritis and patients without nephritis. Odds ratios and 95% CI for each investigation and pooled data for association between allele R vs H of FcγRIIA-R/H131 polymorphism

3.6 | Sensitivity analysis

Sensitivity analysis was designed to identify the potential influence of individual study on the pooled ORs, by which a single study was deleted each time in the meta-analysis. Results found that sequential omission of every study in each genetic model of the meta-analysis did not significantly influence the pooled ORs, suggesting that the results were stable (data not shown).

3.7 | Publication bias

Results showed there was no evidence of publication bias for FcγRIIA-R/H131 polymorphism and SLE/LN in all comparisons (Tables 2-4, Tables S3-S6).

4 | DISCUSSION

In recent years, association of the FcγRIIA-R/H131 polymorphism and SLE/LN risk has been widely discussed. Nevertheless, different investigations with distinct sample sizes, ethnicities, quality scores showed inconsistent results. For example, a study discussed FcγRIIA-R/H131 polymorphism and SLE/LN genetic susceptibility in Brazil, and observed association of allele R with SLE (OR = 1.44, P = .020), genotype RR with SLE (RR vs HH, OR = 2.09, P = .030). The association was higher with allele R and genotype RR when LN was considered, by which OR was 1.67 (P < .010) when allele R was compared with allele H between SLE patients with LN and patients without LN (OR = 2.85, P = .010) when genotype RR was compared with genotype HH between SLE patients with LN and patients without LN.[46] In contrast, Haidy et al performed a case-control study about FcγRIIA-R/H131 polymorphism and SLE/LN risk in Egypt, and found that neither the genotype RR nor allele R was related to SLE. Similarly, neither the genotype RR nor allele R was correlated with LN risk in Egypt.[47] Therefore, to deduce a more precise assessment on the genetic risk of FcγRIIA-R/H131 variant for SLE/LN, a comprehensive meta-analysis of available data was executed. Our findings revealed that allele R was significantly correlated with SLE risk when SLE patients were compared with controls in the overall population, Asian and European populations. Different genotypes of FcγRIIA-R/H131 variant correlated with SLE in the overall population, Asian, European population and North Americans for the additive model, recessive model and dominant model, except for the recessive/dominant mode with SLE in North Americans (P = .322, P = .190), the dominant model in European populations (P = .113). In addition, when discussing the relation of FcγRIIA-R/H131 variant and LN risk, we first compared the polymorphism between SLE patients with LN and patients without LN. We found that allele R was related to LN risk in the overall population, Asian populations, the additive model/dominant model was related to LN in the overall population, Asians, and the recessive model correlated with LN risk in the overall population. Second, we compared the polymorphism between SLE patients with LN and controls. Findings revealed that all the models (allelic contrast, additive/recessive/dominant model) were related to LN risk except for allelic contrast in North Americans and dominant

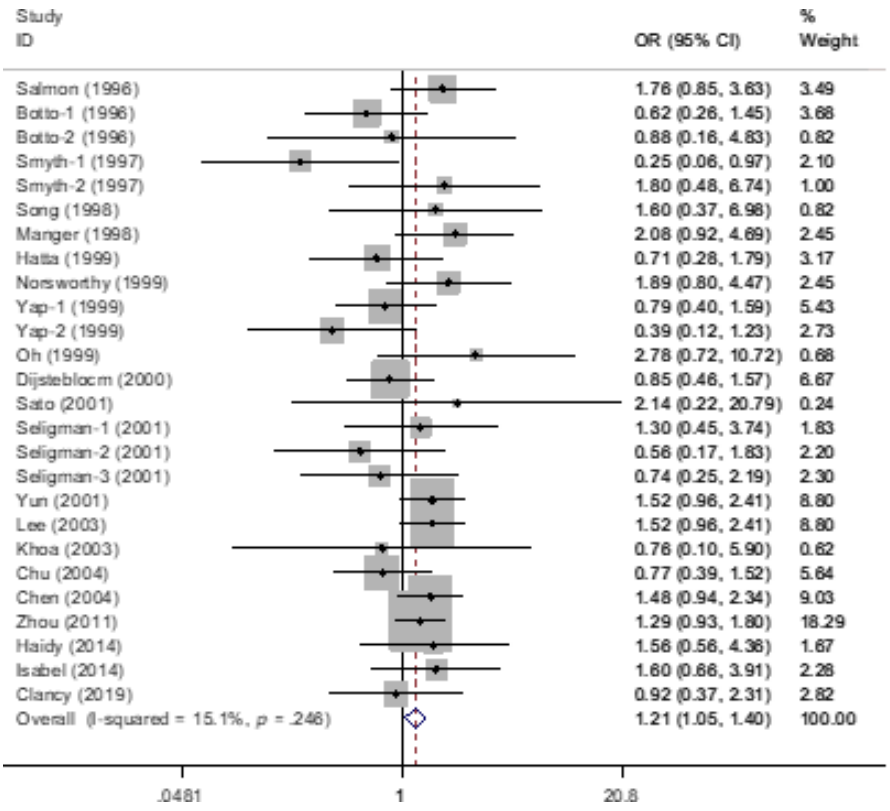

FIGURE 5 Relation of FcγRIIA-R/H131 polymorphism and lupus nephritis risk by dominant model. Odds ratios and 95% CI for each investigation and pooled data for association between genotype RR + RH vs HH of FcγRIIA-R/H131 polymorphism and lupus nephritis

model in European populations. Our results also showed that quality score may be the factor of heterogeneity across all studies. In the quality score-based stratification analysis, the meta-analysis revealed diverse association between FcγRIIA-R/H131 polymorphism and SLE, LN risk. Collectively, our meta-analysis suggested that the FcγRIIA-R/H131 polymorphism not only correlated with SLE risk, but also related to LN genetic susceptibility.

Comparing our findings with previous meta-analysis, there are several improvements. Zhang et al included only 2 studies to discuss association of FcγRIIA-R/H131 polymorphism and SLE risk.[51] Li et al conducted a meta-analysis to evaluate association of FcγRIIA-R/H131 polymorphism with susceptibility to SLE/LN in an Asian population.[52] Zhu et al also discussed relationship between FcγRIIA-R/H131 polymorphism and SLE risk, where the meta-analysis recruited 28 studies, involving 5082 SLE patients and 4951 controls.[53] Regarding our study, we recruited 33 studies, involving 5652 SLE patients and 6322 controls. The sample size is larger than the previous studies. In addition, when discussing the difference of polymorphism between SLE patients and controls, we added the additive model to further reveal the association of polymorphism and SLE risk. However, the study conducted by Zhu et al did not discuss the correlation. Moreover, the present study discussed relationship between FcγRIIA-R/H131 polymorphism and LN risk when comparing the polymorphism between SLE patients with LN and patients without LN, where Li et al only discussed the association in an Asian population, and the other studies did not evaluate the relation. Furthermore, to deeply reveal the association of FcγRIIA-R/H131 polymorphism and LN risk, we compared the polymorphism between SLE patients with LN and controls that the previous meta-analysis did not design. All these advances in the present meta-analysis may enhance the statistical power and draw a more reliable conclusion.

FcγRs play critical roles in immune response. Bone marrow-derived macrophages from *FcγRIIB* gene deficient (−/−) lupus mice treated with lipopolysaccharides (LPS) revealed fewer phosphoproteins, such as protein kinase C-β type II.[49] Addition of phorbol 12-myristate 13-acetate (PMA) weakened the severity of mice with cecal ligation and puncture on LPS tolerance preconditioning in FcγRIIB−/− cells.[54] Monocytes isolated from healthy donors treated with serum from SLE patients showed elevated expression of interferon-stimulated genes (ISGs).[55] By contrast, knock-down of FcγRIIA in monocytes by short interfering RNA down-regulated expression ISGs such as *IFIT1* after incubating with SLE serum. It is notable that monocytes treated with anti-FcγRIIA antibody showed a significant reduction of *IFIT1* in the presence of SLE serum, suggesting that activation of FcγRIIA by SLE serum mediates inflammatory phenotype in monocytes.[55] SLE is characterized by multiple autoantibodies production, such as antibodies against nucleic acids. Neutrophils isolated from lupus patients stimulated with SLE patient's serum having anti-Sm/RNP antibody can release reactive oxygen species (ROS), and promote interleukin (IL)-8 production.[56] Blocking FcγRIIA to neutrophils down-regulated binding, phagocytosis of RNA-containing immune complex, and neutrophils stimulated with nucleic acid-containing immune complex under anti-FcγRIIA antibody showed reduced ROS, IL-8 generation, indicating that neutrophil activation in SLE is a FcγRIIA dependent pathway.[56] In our meta-analysis, allele R or genotype RR was found to be related to

TABLE 4 Meta-analysis of the FcγRIIa R/H131 polymorphism and SLE with nephritis, healthy controls

			Test of association				Test of heterogeneity			Publication bias
Comparison	Population	No. of comparison	Model	OR (95% CI)	Z	*P*	χ^2	*P*	I^2 (%)	*P*
R vs H	Overall	24	R	1.278 (1.128-1.448)	3.84	<.001	44.61	.004	48.4	.571
	Asian	13	R	1.229 (1.095-1.542)	2.99	.003	28.43	.005	57.8	.915
	European	6	F	1.249 (1.032-1.512)	2.28	.023	7.42	.191	32.6	.468
	North American	4	R	1.356 (0.902-2.038)	1.46	.143	6.34	.096	52.7	.157
	High quality	13	R	1.173 (0.976-1.409)	1.71	.088	30.33	.004	57.1	.423
	Moderate quality	11	F	1.315 (1.126-1.536)	3.46	.001	15.28	.170	28.0	.369
RR vs HH	Overall	23	R	1.788 (1.338-2.389)	3.93	<.001	45.13	.003	51.2	.786
	Asian	12	R	2.013 (1.285-3.154)	3.05	.002	30.21	.001	63.6	.832
	European	6	F	1.487 (1.025-2.158)	2.09	.037	6.77	.238	26.2	.620
	North American	4	F	2.528 (1.456-4.387)	3.30	.001	4.16	.245	27.8	.175
	High quality	13	R	1.457 (0.987-2.152)	1.89	.058	27.76	.010	53.2	.392
	Moderate quality	10	R	1.929 (1.334-2.789)	3.49	<.001	17.55	.093	37.3	.297
RR vs RH + HH	Overall	23	F	1.550 (1.333-1.802)	5.70	<.001	29.87	.122	26.3	.068
	Asian	12	R	1.673 (1.244-2.248)	3.41	.001	17.86	.085	38.4	.289
	European	6	F	1.478 (1.104-1.977)	2.63	.009	3.71	.592	0.0	.296
	North American	4	F	1.496 (1.009-2.219)	2.00	.045	5.60	.133	46.4	.419
	High quality	13	F	1.335 (1.074-1.660)	2.61	.009	14.87	.315	12.6	.414
	Moderate quality	10	F	1.611 (1.204-2.155)	3.21	.001	16.59	.121	33.7	.352
RR + RH vs HH	Overall	23	R	1.347 (1.078-1.682)	2.62	.009	51.90	<.001	57.6	.160
	Asian	12	R	1.391 (1.016-1.906)	2.06	.040	37.34	<.001	70.5	.141
	European	6	F	1.176 (0.855-1.617)	1.00	.318	5.73	.333	12.8	.880
	North American	4	F	1.976 (1.247-3.131)	2.90	.004	5.11	.164	41.3	.587
	High quality	13	R	1.268 (0.915-1.759)	1.43	.154	36.04	.001	63.9	.621
	Moderate quality	10	R	1.331 (1.022-1.733)	2.12	.034	17.46	.095	37.0	.295

Abbreviations: F, fixed model; R, random model; SLE, systemic lupus erythematosus.

SLE, LN risk. This may relate to the mechanism that allele R offered the risk of a participant-developed SLE owing to impairment of binding IgG2-containing immune complex.[46] This deficiency can result in defective clearance of deposition of the immune complex in organs/systems. Kidney is one of the most vulnerable organs in SLE, and patients with LN showed severe damage because of immune complex deposition. In our study, patients with LN were strongly related to FcγRIIA-R/H131 polymorphism compared with non-LN patients or controls, supporting an important role of FcγRIIA in lupus immune complex-mediated nephritis. However, what is the clear mechanism of FcγRIIA-R/H131 polymorphism in mediating immune complex production, deposition in LN? If FcγRIIA-R/H131 polymorphism regulates the inflammatory phenotype of monocytes, do neutrophils then promote the generation of immune complex? All these need to elucidated. FcγRII expression on neutrophils of SLE patients was reduced compared with that in controls.[57] Neutrophil subsets were dysregulated in lupus patients, and the cells heightened capacity to synthesize neutrophil extracellular traps (NETs) that displayed elevated externalization of bactericidal, immunostimulatory proteins, autoantigens, such as the peptide LL-37, IL-17, and double-stranded DNA.[58] Neutrophils augmented capacity to kill endothelial cells and stimulated interferon (IFN)-α synthesis through NETosis, indicating the role of neutrophils in endothelial damage in lupus.[58] DNA-containing immune complexes (ICs) from SLE patients' sera stimulated with plasmacytoid DCs (pDCs) can promote production of IL-8 and IFN-α.[59] pDCs stimulated with anti-FcγRII blocked SLE ICs and induced IFN-α production. Measurement of internalized fluorescence-conjugated SLE ICs found that antibodies for FcγRII blocked pDCs uptake of fluorescence-conjugated SLE ICs, suggesting that lupus autoantibody-DNA complexes activated DCs through cooperation of FcγRII.[59] It is known that G to A substitute in *FcγRIIA* gene leads to replacement of arginine with histidine at position 131. Since FcγRII expression was abnormal in lupus and FcγRII plays functional roles in immune cells related to SLE pathogenesis, it is possible that FcγRIIA-R/H131 polymorphism affects FcγRII expression/function, contributing to SLE/LN development. However, the clear mechanism needs clarification in the future.

Some limitations should be paid attention to in the present study. First, potential gene-environment interaction and gene susceptibility haplotypes were not discussed because of insufficient data. Second, although the overall sample sizes were huge in the present study, some of the original studies had small sample sizes. Therefore, a large sample size of a well-designed case-control study is needed in the future to demonstrate the relation of FcγRIIA-R/H131 polymorphism and SLE/LN. Third, meta-analysis is a method of retrospective study, which is subject to the methodological deficiency of the collected investigations. Fourth, when we compared different genetic models to evaluate association of FcγRIIA-R/H131 polymorphism and SLE, LN risk, significant heterogeneity existed. The heterogeneity may result from several factors, such as subjects with different genders, age at onset, age at diagnosis. However, subgroup studies were not fully conducted because of insufficient data on these factors.

In summary, FcγRIIA-R/H131 polymorphism was related to SLE, LN susceptibility.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Yuan Xu, Hui-Ting Wei, Jun-Ju Zou and Yue-Rong MA designed the study, analyzed data. Yuan Xu and Yue-Rong MA wrote the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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ORIGINAL ARTICLE

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Comparison of the efficacy and safety of tofacitinib and peficitinib in patients with active rheumatoid arthritis: A Bayesian network meta-analysis of randomized controlled trials

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Abstract

Objectives: The relative efficacy and safety of tofacitinib and peficitinib were assessed in patients with rheumatoid arthritis (RA) with an inadequate response to disease-modifying antirheumatic drugs (DMARDs).

Method: We performed a Bayesian network meta-analysis to combine direct and indirect evidence from randomized controlled trials (RCTs) to examine the efficacy and safety of tofacitinib and peficitinib in combination with DMARDs in patients with an inadequate response to DMARDs.

Results: Nine RCTs, including 3836 patients, met the inclusion criteria. Fifteen pairwise comparisons were performed, including six direct comparisons of seven interventions. Tofacitinib 10 mg+methotrexate (MTX) and peficitinib 150 mg+MTX were among the most effective treatments for patients with active RA with an inadequate DMARD response. The efficacy of tofacitinib 10 mg+MTX, peficitinib 150 mg+MTX or tofacitinib 5 mg+MTX tended to be higher than that of adalimumab+MTX. The ranking probability based on the surface under the cumulative ranking curve indicated that tofacitinib 10 mg+MTX had the greatest probability of being the best treatment to achieve the American College of Rheumatology 20 response rate, followed by peficitinib 150 mg+MTX, tofacitinib 5 mg+MTX, adalimumab+MTX, peficitinib 100 mg+MTX, and placebo+MTX. No significant differences were observed in the incidence of serious adverse events after treatment with tofacitinib+MTX, peficitinib+MTX, adalimumab+MTX, or placebo+MTX.

Conclusions: In patients with RA with an inadequate response to DMARDs, tofacitinib 10 mg+MTX and peficitinib 150 mg+MTX were the most efficacious interventions and were not associated with a significant risk of serious adverse events.

KEYWORDS

network meta-analysis, peficitinib, rheumatoid arthritis, tofacitinib

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disorder characterized by chronic inflammation of the synovial joints, which results in disability and reduced quality of life.[1] Disease-modifying antirheumatic drugs (DMARDs) have been used in patients with RA to decrease inflammation, delay bone loss, and increase functional ability. Methotrexate (MTX), an efficient antirheumatic DMARD[2] is one of

the most commonly used DMARDs for RA.[3] However, not all patients respond to this drug; 30% of the patients stop treatment within 1 year, typically owing to lack of effectiveness or the occurrence of adverse effects.[4] Patients with an inadequate response to MTX are often treated with biological DMARDs (bDMARDs). Introduction of bDMARDs definitely made possible remission from the disease and inhibition of joint damages.[5] Since a substantial proportion of patients do not respond adequately to these therapies or experience unacceptable side effects[6] and those with inadequate responses to bDMARDs have shown poorer responses with subsequent bDMARD treatment, new therapies are needed.[7] Intracellular pathways, including those mediated by Janus-activated kinases (JAKs: JAK1, JAK2, JAK3, and tyrosine kinase 2 [Tyk2]), are essential to immune cell activation, cytokine production, and cytokine signaling.[8] Small-molecule JAK inhibitors for the treatment of RA are therefore under development for clinical use.[9] Tofacitinib selectively inhibits JAK-1, JAK-2, and JAK-3 with specificity for JAK-1 and JAK-3 over JAK-2, and effectively modulates adaptive and innate immunity.[10,11] Tofacitinib is an approved JAK inhibitor that can be used for RA treatment. Peficitinib (ASP015K) is an effective selective JAK3 inhibitor that blocks signal transduction and consequently prevents immune reactions. For patients with moderate to severe active RA who did not respond adequately or who could not tolerate conventional synthetic DMARDs (csDMARDs), peficitinib has been investigated.[12-14]

For patients with active RA who have incomplete DMARD response, multiple clinical trials have been conducted to determine the efficacy and safety of tofacitinib and peficitinib.[12,13,15-21] All these drugs were very effective in placebo-controlled trials; however, owing to a lack of head-to-head tests, the relative efficacy and safety of tofacitinib and peficitinib are uncertain. In the absence of head-to-head trials with relevant comparators, it is important for the assessment of the effect of one procedure against another to incorporate evidence from randomized controlled trials (RCTs). Network meta-analysis is a possible method to assess the comparative efficiencies of several treatments by integrating evidence across a network of RCTs, even when head-to-head comparisons have not been performed,[22,23] as opposed to traditional meta-analysis.[24-28] The purpose of this study was to use a network meta-analysis to examine the relative effectiveness and safety of tofacitinib and peficitinib in patients with active RA.

2 | MATERIALS AND METHODS

2.1 | Identification of eligible studies and data extraction

We conducted an exhaustive search for studies that examined the efficacy and safety of tofacitinib and peficitinib in patients with active RA who showed an inadequate response to DMARDs including MTX. A literature search of the MEDLINE and EMBASE database, the Cochrane Controlled Trials Register, and conference proceedings from the American College of Rheumatology (ACR) and European League against Rheumatism (EULAR) was used to identify available articles published up to November 2019. The following key words and subject terms were used in the search: "tofacitinib", "peficitinib", and "rheumatoid arthritis". All references in the studies were reviewed to identify additional works not included in the electronic databases. RCTs were included if they met the following criteria: (a) the study compared tofacitinib or peficitinib with DMARDs to placebo+DMARDs for the treatment of active RA which responded inadequately to DMARDs; (b) the study provided endpoints for the clinical efficacy and safety of tofacitinib or peficitinib at 3 or 6 months; and (c) the study included patients diagnosed with RA based on the American College of Rheumatology (ACR) criteria for RA[29] or the 2010 ACR/EULAR classification criteria.[30] The exclusion criteria were: (a) the study included duplicate data; and (b) the study did not contain adequate data for inclusion. The efficacy outcome was the number of patients who fulfilled the ACR 20% improvement criteria (achieved an ACR20 response), and the safety outcome was the number of patients who experienced serious adverse events (SAEs). The following information was extracted from each study: first author, year of publication, country in which the study was conducted, dosages of tofacitinib and peficitinib, follow-up period for the outcome evaluation, and efficacy and safety outcomes. The data were extracted from original studies by two independent reviewers. Any discrepancy between the reviewers was resolved by consensus. We quantified the methodological quality of studies using a Jadad score[31] ranging from 0 to 5. Quality was classified as high (a score of 3-5) or low (a score of 0-2). We conducted this network meta-analysis in accordance with the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[32]

2.2 | Evaluation of statistical associations for network meta-analysis

In RCTs that compared multiple doses of tofacitinib and peficitinib in different arms, the results from the different arms were simultaneously analyzed. The efficacy and safety of tofacitinib and peficitinib in different arms were ordered according to the probability of being ranked as the best performing regimen. We performed a Bayesian random-effects network meta-analysis using NetMetaXL[33] and WinBUGS statistical analysis program version 1.4.3 (MRC Biostatistics Unit, Institute of Public Health, Cambridge, UK). The Bayesian approach offers greater flexibility in the use of more complex models and different outcome types, enabling the simultaneous comparison of all treatment options. Bayesian method combines a prior probability distribution, which reflects a prior belief of the possible values of the pooled effect, with a likelihood distribution of the pooled effect based on the observed data to obtain a posterior probability distribution.[34] In order not to influence the observed results by the prior distribution, a non-informative or vague prior distribution often is used for the pooled effect.[35] In this case, posterior results are not influenced by the prior distribution but are affected by the observed data as in a frequentist meta-analysis.[35,36] Although frequentists use the sampling distribution as the basis of statistical inference, the posterior distribution obtained with the Bayesian

approach permits calculating the probability that each treatment can produce better outcomes than those produced by competing interventions.[34,37] We chose a random-effects model for the network meta-analysis, as it incorporates between-study variations and utilizes a conservative method. The random network model was selected prior to the statistical analysis. We used the Markov chain Monte Carlo method to obtain pooled effect sizes.[38] All chains were run with 10 000 burn-in iterations followed by 10 000 monitoring iterations. The information on relative effects was converted to a probability that a treatment was the best, second best, and so on, or to the ranking of each treatment, which was called the surface under the cumulative ranking curve (SUCRA)[39] and was expressed as a percentage. The SUCRA value was 1 when a treatment was certain to be the best and 0 when a treatment was certain to be the worst. SUCRA values enabled the overall ranking of treatments for a particular outcome, simplifying the information on the effect of each treatment into a single number and consequently facilitating decision-making. A league table can arrange the presentation of summary estimates by ranking the treatments in the order of the most pronounced impact on the outcome under consideration, based on the SUCRA value.[39] We reported the pairwise odds ratio (OR) and 95% credible interval (CrI) (or Bayesian confidence interval) and adjusted for multiple-arm trials. Pooled results were considered statistically significant if the 95% CrI did not contain the value 1.

2.3 | Inconsistency assessment

Inconsistency refers to the extent of disagreement between direct and indirect evidence.[40] Assessments of inconsistency are

TABLE 1 Characteristics of individual studies included in the meta-analysis and systematic review

Study	No. of patients	Subjects	JAK inhibitor	Doses, twice daily (no.)	Follow-up time point for evaluation
(A)					
Kremer, 2013[15]	795	DMARD-IR	Tofacitinib	Placebo+MTX (159), tofacitinib 5 mg+MTX (318), tofacitinib 10 mg+MTX (318)	6 mo
Van der Heijde, 2013[16]	797	MTX-IR	Tofacitinib	Placebo+MTX (160), tofacitinib 5 mg+MTX (321), tofacitinib 10 mg+MTX (316)	6 mo
Van Vollenhoven, 2012[17]	717	MTX-IR	Tofacitinib	Placebo+MTX (108), tofacitinib 5 mg+MTX (204), tofacitinib 10 mg+MTX (201), adalimumab 40 mg+MTX (204)	3 mo
Kremer, 2012[18]	214	MTX-IR	Tofacitinib	Placebo+MTX (69), tofacitinib 5 mg+MTX (71), tofacitinib 10 mg+MTX (74)	3 mo
Tanaka, 2011[19]	84	MTX-IR	Tofacitinib	Placebo+MTX (28), tofacitinib 5 mg+MTX (28), tofacitinib 10 mg+MTX (28)	3 mo
(B)					
Tanaka, 2019[20]	307	DMARD-IR	Peficitinib	Placebo+MTX (102), peficitinib 100 mg+MTX (101), peficitinib 150 mg+MTX (104)	3 mo
Takeuchi, 2019[21]	518	MTX-IR	Peficitinib	Placebo+MTX (174), peficitinib 100 mg+MTX (170), peficitinib 150 mg+MTX (174)	3 mo
Genovese 2017[12]	173	DMARD-IR	Peficitinib	Placebo+MTX (51), peficitinib 100 mg+MTX (58), peficitinib 150 mg+MTX (64)	3 mo
Kivitz 2016[13]	234	MTX-IR	Peficitinib	Placebo+MTX (72), peficitinib 100 mg+MTX (84), peficitinib 150 mg+MTX (78)	3 mo

(C) Comparison	Study no.	Patient no.
Placebo+MTX vs. tofacitinib 5 mg+MTX	5	1466
Placebo+MTX vs. tofacitinib 10 mg+MTX	5	1461
Tofacitinib 5 mg+MTX vs. tofacitinib 10 mg+MTX	5	1879
Placebo+MTX vs. adalimumab+MTX	1	312
Tofacitinib 5 mg+MTX vs. adalimumab+MTX	1	408
Tofacitinib 10 mg+MTX vs. adalimumab+MTX	1	405
Placebo+MTX vs. peficitinib 100 mg+MTX	4	811
Placebo+MTX vs. peficitinib 150 mg+MTX	4	812
Peficitinib 100 mg+MTX vs. peficitinib 150 mg+MTX	4	835

Abbreviations: adalimumab 40 mg, once every alternate week; DMARDs, disease-modifying antirheumatic drugs; Doses: peficitinib, once daily; Doses: tofacitinib, twice daily; IR, incomplete response; MTX, methotrexate or conventional synthetic DMARDs, including MTX; MTX, once a week.

important when conducting a network meta-analysis, because an inconsistency plot yields information that can help identify the loops in which the inconsistency is present.[41] We plotted the posterior mean deviance of the individual data points in the inconsistency model against the posterior mean deviance in the consistency model to assess the network inconsistency between the direct and indirect estimates in each loop.[42] A sensitivity test was performed by comparing the random and fixed-effects models.

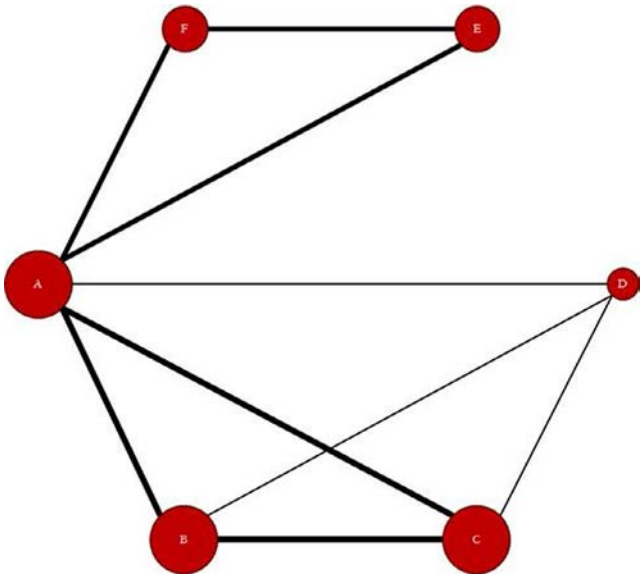

FIGURE 1 Evidence network diagram of network meta-analysis comparisons. The width of each edge is proportional to the number of randomized controlled trials comparing each pair of treatments, and the size of each treatment node is proportional to the number of randomized participants (sample size). (A) Placebo+MTX, (B) tofacitinib 5 mg+MTX, (C) tofacitinib 10 mg+MTX, (D) adalimumab+MTX, (E) peficitinib 100 mg+MTX, (F) peficitinib 150 mg+MTX. MTX, methotrexate

3 | RESULTS

3.1 | Studies included in the meta-analysis

In total, 682 studies were identified through the electronic or manual searches; of these, 12 were selected for a full-text review based on the title and abstract details. Three studies were excluded because they were duplicate or irrelevant. Thus, 9 RCTs, which included 3836 patients (1887 efficacy-related events and 1428 safety-related events) met the inclusion criteria.[12,13,15-21] The search results contained 15 pairwise comparisons, including 6 direct comparisons and 7 interventions (Table 1, Figure 1). The Jadad scores of the studies were between 3 and 5, which were indicative of high-quality studies. The relevant features of the studies included in the meta-analysis are provided in Table 1.

3.2 | Network meta-analysis of the efficacy of tofacitinib and peficitinib in RCTs

Tofacitinib 10 mg+MTX is listed in the top-left of the diagonal of the league table (OR, 4.20; 95% CrI, 2.23-8.80), because it was associated

TABLE 2 League tables showing the results of the network meta-analysis comparing the effects of all drugs including odds ratios and 95% credible intervals. (A) Efficacy: odds ratio > 1 indicates that the top-left treatment is better. (B) Tolerability: odds ratio < 1 indicates that the top-left treatment is better

(A) Tofacitinib 10 mg+MTX					
1.03 (0.40-3.07)	Peficitinib 150 mg+MTX				
1.14 (0.56-2.14)	1.10 (0.36-2.76)	Tofacitinib 5 mg+MTX			
1.43 (0.43-4.96)	1.39 (0.31-5.74)	1.25 (0.39-4.55)	Adalimumab+MTX		
1.59 (0.63-4.83)	1.55 (0.74-3.28)	1.40 (0.57-4.40)	1.12 (0.27-4.96)	Peficitinib 100 mg+MTX	
4.20 (2.23-8.80)	4.07 (1.89-8.62)	3.68 (2.00-8.22)	2.93 (0.88-10.47)	2.63 (1.22-5.44)	Placebo+MTX
(B) Peficitinib 150 mg+MTX					
0.87 (0.17-4.02)	Adalimumab+MTX				
0.72 (0.27-2.01)	0.85 (0.24-2.81)	Placebo+MTX			
0.52 (0.20-1.52)	0.61 (0.13-2.67)	0.72 (0.26-1.83)	Peficitinib 100 mg+MTX		
0.38 (0.11-1.25)	0.46 (0.13-1.33)	0.53 (0.25-1.03)	0.72 (0.23-3.06)	Tofacitinib 10 mg+MTX	
0.36 (0.11-1.21)	0.43 (0.13-1.27)	0.51 (0.24-1.00)	0.68 (0.22-2.52)	0.95 (0.56-1.67)	Tofacitinib 5 mg+MTX

Abbreviation: MTX, methotrexate.

TABLE 3 Rank probability of the efficacy of tofacitinib and peficitinib based on the number of patients who achieved an American College of Rheumatology 20% response (A) and the safety based on the number of serious adverse events (B)

Treatment	SUCRA
(A) Efficacy	
Tofacitinib 10 mg+MTX	0.760
Peficitinib 150 mg+MTX	0.730
Tofacitinib 5 mg+MTX	0.640
Adalimumab+MTX	0.484
Peficitinib 100 mg+MTX	0.378
Placebo+MTX	0.010
(B) Safety	
Peficitinib 150 mg+MTX	0.816
Adalimumab+MTX	0.729
Placebo+MTX	0.675
Peficitinib 100 mg+MTX	0.411
Tofacitinib 10 mg+MTX	0.207
Tofacitinib 5 mg+MTX	0.163

Abbreviations: MTX, methotrexate; SUCRA, surface under the cumulative ranking curve.

with the most favorable SUCRA for the ACR20 response rate, whereas placebo+MTX is listed in the bottom right of the diagonal of the league table because it was associated with the least favorable results (Table 2). All doses of JAK inhibitors achieved a significant ACR20 response compared with placebo+MTX (Table 2). The efficacy of tofacitinib 10 mg+MTX, peficitinib 150 mg+MTX, and tofacitinib 5 mg+MTX tended to be greater than that of adalimumab+MTX (Table 2, Figure 2). The ranking probability based on SUCRA indicated that tofacitinib 10 mg+MTX had the highest probability of being the best treatment in terms of the ACR20 response rate, followed by peficitinib 150 mg+MTX, tofacitinib 5 mg+MTX, adalimumab+MTX, peficitinib 100 mg+MTX, and placebo+MTX (Table 3).

3.3 | Network meta-analysis of the safety of tofacitinib and peficitinib in RCTs

The number of SAEs in the peficitinib 150 mg+MTX, adalimumab+MTX, placebo+MTX, and peficitinib 100 mg+MTX groups tended to be lower than that in the tofacitinib 10 mg+MTX and tofacitinib 5 mg+MTX groups (Table 2, Figure 2). However, the number of SAEs did not differ significantly between the tofacitinib and peficitinib groups (Table 2, Figure 2). The ranking probability

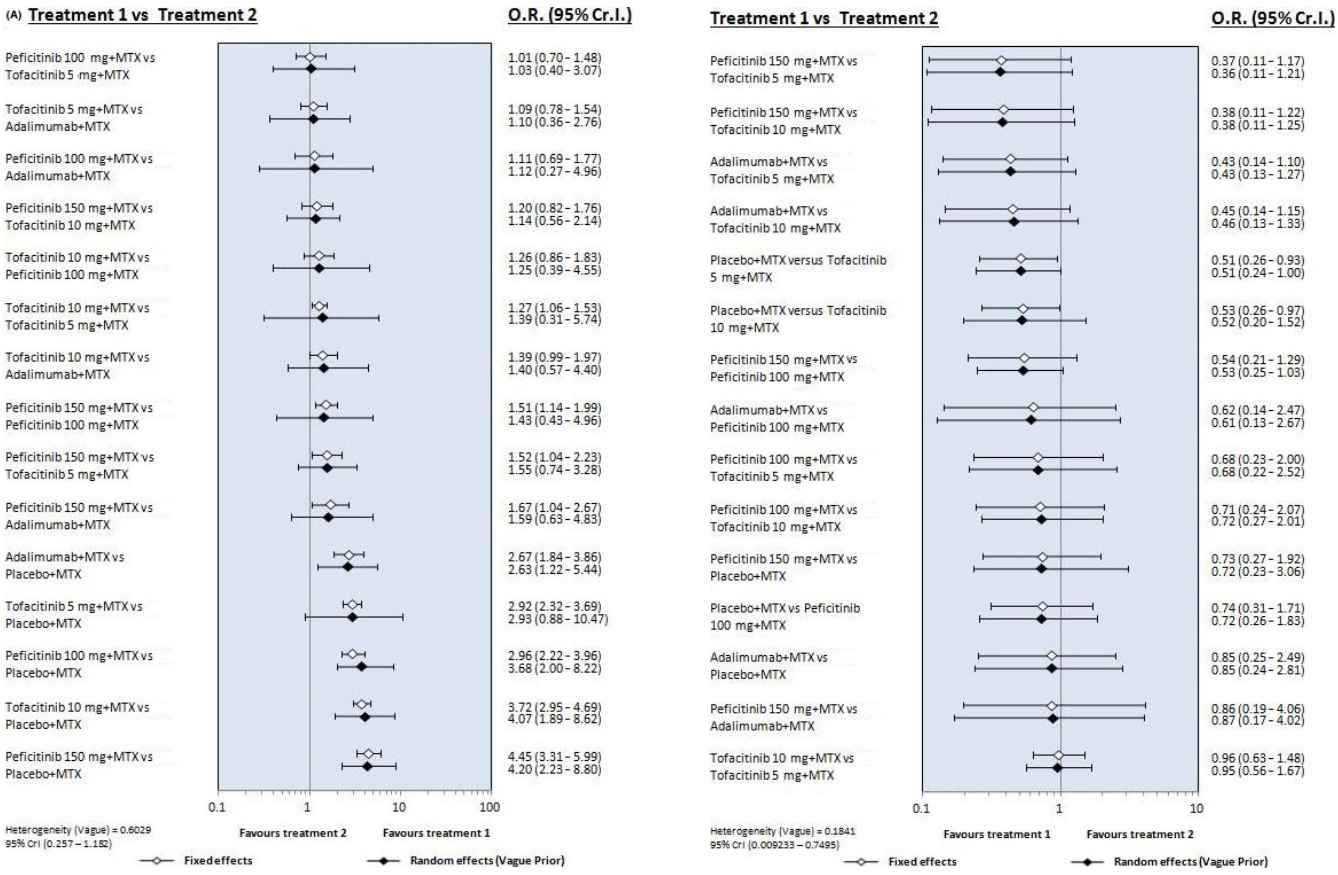

FIGURE 2 Bayesian network meta-analysis results of randomized controlled studies on the relative efficacy (A) and safety (B) of tofacitinib and peficitinib. MTX, methotrexate; OR, odds ratio; CrI., credible interval

based on SUCRA values indicated that peficitinib 150 mg+MTX, adalimumab+MTX, and placebo+MTX had higher probabilities of being the safest treatment, followed by peficitinib 100 mg+MTX, tofacitinib 10 mg+MTX, and tofacitinib 5 mg+MTX (Table 3).

3.4 | Inconsistency and sensitivity analyses

Inconsistency plots were used to assess the network inconsistencies between the direct and indirect estimates. Some inconsistencies between direct and indirect estimates were found in the network meta-analysis of efficacy. Two points in the plot of the efficacy (placebo from the Kivitz et al study and tofacitinib 10 mg from the Tanaka et al study) appeared to have a higher than expected posterior mean deviance. However, a sensitivity analysis that removed the outlier studies did not meaningfully change the network meta-analysis results, indicating a low possibility of inconsistencies that might significantly affect the network meta-analysis results. In addition, the results of the random- and fixed-effects models yielded the same interpretation, indicating that the results of this network meta-analysis were robust (Figure 2).

4 | DISCUSSION

Recent studies of RA treatment have focused on small molecules that can inhibit intracellular kinases (such as those in the JAK pathways). Trends in the treatment of the new small molecules have begun to include specific targeting of the JAK pathways. As patients with RA may receive tofacitinib or peficitinib if they are refractory or intolerant to or contraindicated by DMARDs, it is important to determine the optimal treatment methods. In addition to efficacy, the safety of tofacitinib and peficitinib is a key factor in the selection of therapeutic treatment in patients with RA.

We performed a network meta-analysis to compare the efficacy and safety of tofacitinib and peficitinib in patients with active RA and an inadequate response to DMARDs. With regard to effectiveness, our network meta-analysis showed that tofacitinib 10 mg+MTX and peficitinib 150 mg+MTX were the most effective treatments for active RA, followed by tofacitinib 5 mg+MTX, adalimumab+MTX, peficitinib 100 mg+MTX, and placebo+MTX. Although no explanation was determined for these findings, discrepancies in the efficacy between JAK inhibitors and adalimumab were suggested. The safety of peficitinib 150 mg+MTX, adalimumab+MTX, placebo+MTX, and peficitinib 100 mg+MTX treatments was higher than that for tofacitinib 10 mg+MTX and tofacitinib 5 mg+MTX. Nonetheless, the number of SAEs was not significantly different among the six treatments, suggesting comparable safety among the different tofacitinib and peficitinib regimens. Tofacitinib has been approved for use by the Food and Drug Administration (FDA), USA, as a JAK inhibitor; peficitinib is used in Japan and is undergoing evaluation for FDA approval. Treatment with tofacitinib and peficitinib shows a statistically significant improvement in the ACR20 response criteria compared with placebo, with no statistically significant variations in the incidence of SAEs between the JAK inhibitors and placebo. However, rank probability of the safety based on the number of SAEs showed a better SUCRA in perficitinib 150 mg+MTX than other treatments. Nevertheless, our network meta-analysis offers different information from previous reviews, as it has produced a standardized order for the relative efficacy and safety of JAK inhibitors in patients with active RA.

The results of the network meta-analysis that combined evidence from both direct and indirect comparisons to evaluate relative efficacy and safety of peficitinib were consistent with previous meta-analyses, and indicated that treatment with tofacitinib and peficitinib resulted in a statistically substantial improvement on the basis of the ACR20 response criteria.[43,44] However, our network meta-analysis is different from previous meta-analyses, as we were able to generate a ranking order of the relative effectiveness and safety of tofacitinib and peficitinib treatments in patients with active RA.

Our findings should be viewed with caution because of the limitations to this analysis. First, only 3 or 6 months were used for follow-up. Therefore, for assessing the long-term effects, the follow-up period was too short and longer comparative studies are required. Second, the nature and patient characteristics of the trials included were heterogeneous; hence, disparities among the studies could have influenced the analytical results. Second, the efficacy and safety effects of tofacitinib and peficitinib in patients with RA were not discussed in depth in this study. Instead, the study was focused on the effectiveness based only on the number of patients achieving ACR20 and on the safety based on the number of SAEs, without evaluation of all other outcomes.[45] Nevertheless, this meta-analysis has several strengths. First, the RCTs included in this network meta-analysis were all of high quality and considerably consistent. Second, the number of patients in each study ranged from 84 to 797, and this analysis included a total of 3836 patients. Network meta-analysis integrates all available data to allow for the simultaneous comparisons of different treatment options that lack direct head-to-head comparisons. In contrast with the individual studies, more accurate data were obtained by increasing the statistical power and resolution through a pooling of the independent analyses and ranking of the efficacy and safety of JAK inhibitors at the doses tested in patients with active RA. This was the first network meta-analysis of the relative efficacy and safety of tofacitinib and peficitinib in individuals with RA.

In summary, we performed a meta-examination of a Bayesian network of 9 RCTs and found that the most successful treatments for patients with RA with inadequate response to DMARD therapy were tofacitinib 10 mg+MTX and peficitinib 150 mg+MTX and that neither of these treatments were associated with a considerable risk of an SAE. The relative efficacy and safety of tofacitinib and peficitinib in many patients with active RA who have an inadequate response to DMARDs should be assessed in long-term studies.

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CONFLICT OF INTEREST

The researchers have no conflicts of interest in financial or non-financial terms.

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ORIGINAL ARTICLE

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A comparative study of PF-06438179/GP1111 (an infliximab biosimilar) and reference infliximab in patients with moderate to severe active rheumatoid arthritis: A subgroup analysis

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Abstract

Aim: PF-06438179/GP1111 (PF-SZ-IFX) is a biosimilar of reference infliximab (Remicade®). This analysis compared the efficacy of PF-SZ-IFX and reference infliximab sourced from the European Union (IFX-EU) in patient subgroups from a randomized, comparative study of PF-SZ-IFX versus IFX-EU.

Methods: Patients with rheumatoid arthritis were randomized 1:1 to PF-SZ-IFX (n = 324) or IFX-EU (n = 326); study drug (3 mg/kg) was administered intravenously at weeks 0, 2, and 6, then every 8 weeks thereafter. Subgroup analyses of efficacy endpoints such as American College of Rheumatology criteria for ≥20% clinical improvement (ACR20), change in high-sensitivity C-reactive protein (hs-CRP), and change in Disease Activity Score in 28 joints, four components based on hs-CRP (DAS28-CRP) at weeks 14 and 30 were performed by age, gender, race, region, immunogenicity status, and treatment history.

Results: Overall, ACR20 response rates as well as changes in DAS28-CRP and hs-CRP at week 14 were similar between PF-SZ-IFX and IFX-EU within the subgroups of age, gender, race, region, treatment history, and immunogenicity status. Results to week 30 support overall similarity in efficacy between the two treatment arms in all subgroups.

Conclusion: Overall, PF-SZ-IFX and IFX-EU were similar in efficacy within the analyzed subgroups of age, gender, race, region, treatment history, and immunogenicity status. The efficacy results from these subgroup analyses were aligned with the previously described results for the overall population up to week 30.

KEYWORDS

arthritis – rheumatoid, biosimilar pharmaceuticals, infliximab, Japan, Latin America

Clinical Trial registration: ClinicalTrials.gov (NCT02222493) and EU Clinical Trials Register (EudraCT number: 2013-004148-49).

1 | INTRODUCTION

Biosimilars are biologic drugs that are highly similar to licensed (ie reference or originator) biologic products, without any clinically meaningful differences in efficacy, safety, and purity.[1,2] The introduction of biosimilars has been associated with cost savings and improved patient access to biologic therapies.[3] The infliximab biosimilar PF-06438179/GP1111 (PF-SZ-IFX) has been approved by several regulatory agencies, such as the US Food and Drug Administration (IXIFI™ [infliximab-qbtx]: Pfizer Inc, New York, NY, USA), the European Medicines Agency (Zessly®: Sandoz GmbH, Kundl, Austria), the Pharmaceuticals and Medical Devices Agency (Infliximab BS for IV Infusion 100 mg [Pfizer]; Pfizer Japan Inc, Tokyo, Japan), and the Brazilian Health Surveillance Agency (Agência Nacional de Vigilância Sanitária, ANVISA; Xilfya®: Wyeth Industria Farmaceutica LTDA, São Paulo, Brazil) for all eligible indications of the reference product (Remicade®; Janssen Biotech, Horsham, PA, USA, and Janssen Biologics BV, Leiden, The Netherlands) in each region.[4-7]

PF-SZ-IFX has the same primary amino acid sequence as the reference infliximab product sourced from the European Union (IFX-EU).[8] A phase I pharmacokinetic (PK) similarity trial conducted in healthy subjects demonstrated PK similarity of PF-SZ-IFX to IFX-EU. Both products displayed comparable safety and immunogenicity profiles.[9] A phase III randomized, double-blind study in patients with moderate to severe active rheumatoid arthritis (RA) confirmed the similarity of PF-SZ-IFX to IFX-EU.[10] The primary efficacy endpoint of American College of Rheumatology (ACR) criteria for ≥20% clinical improvement (ACR20) at week 14 was met, with the 95% and 90% confidence intervals (CIs) for the treatment difference between groups entirely contained within the prespecified equivalence margins, respectively.[10] In addition, PF-SZ-IFX and IFX-EU demonstrated similar safety and immunogenicity profiles up to week 30.[10] Here we report results of the efficacy of PF-SZ-IFX compared with IFX-EU in various subgroups at weeks 14 and 30.

2 | METHODS

The study methodology has been described in detail in previous publications[10,11] and is briefly summarized here.

2.1 | Study population

Adults (aged ≥ 18 years) with a diagnosis of RA ≥4 months, based on the 2010 ACR/European League Against Rheumatism criteria and ACR classes I–III functional status, based on the 1991 revised criteria, were eligible.[12,13] Moderate to severe active RA was defined as ≥6 swollen joints and ≥6 tender joints, at screening and baseline, and high-sensitivity C-reactive protein (hs-CRP) ≥10 mg/L at screening. Patients received oral or parenteral methotrexate (MTX; 10-25 mg/week) for 12 or more weeks and oral folic/folinic acid (≥5 mg/week) for 21 days or longer before the first dose of the study drug. Patients intolerant to 10-25 mg/week MTX received a dose as low as 7.5 mg/week. A lower MTX dose of 6.0 mg/week was allowed in geographic regions where specified by local guidance or standard of care.

Patients were excluded from the study if they were treated with infliximab or lymphocyte-depleting therapies; however, patients were allowed ≤2 doses of a non-depleting, non-infliximab biologic if discontinued ≥12 weeks or 5 half-lives before receiving the first dose of the study drug. Other main exclusion criteria were: clinically significant laboratory abnormalities at screening including inadequate bone marrow, liver, renal, and immune system function; current infection or infection requiring hospitalization or parenteral antimicrobial therapy, judged clinically significant by the investigator within 6 months prior to the first dose of the study drug; evidence or history of heart failure or malignancy within the previous 5 years; positivity for human immunodeficiency virus, or hepatitis B or C virus; and evidence of untreated or inadequately treated latent or active tuberculosis.

2.2 | Study design and treatments

This was a randomized, double-blind, multinational study in patients with moderate to severe active RA in 174 centers in 28 countries. The initial treatment period was 30 weeks (treatment period 1). At the start of treatment period 1, patients were randomized 1:1 to PF-SZ-IFX or IFX-EU. Randomization was stratified by geographic region: North America and Western Europe, Japan, Republic of Korea, Latin America, and Rest of the World. Intravenous infusions of 3 mg/kg PF-SZ-IFX or IFX-EU were administered at weeks 0, 2, and 6, and then every 8 weeks thereafter.

All patients continued on stable background dosages of oral or parenteral MTX (10-25 mg/week) and folic/folinic acid supplementation throughout the study. One-time dose escalation to 5 mg/kg (with PF-SZ-IFX or IFX-EU) was permitted starting at or after week 14 in patients who failed to achieve ≥20% improvement from baseline in both tender (68) and swollen (66) joint counts. Treatment period 1 was followed by two 24-week treatment periods, in which patients who were initially treated with IFX-EU switched to PF-SZ-IFX at week 30 (treatment period 2) or week 54 (treatment period 3), and patients who were initially treated with PF-SZ-IFX continued PF-SZ-IFX treatment (Figure 1).

This study was conducted in compliance with the provisions of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines, and it was reviewed and approved by an institutional review board or independent ethics committee(s) at each of the participating

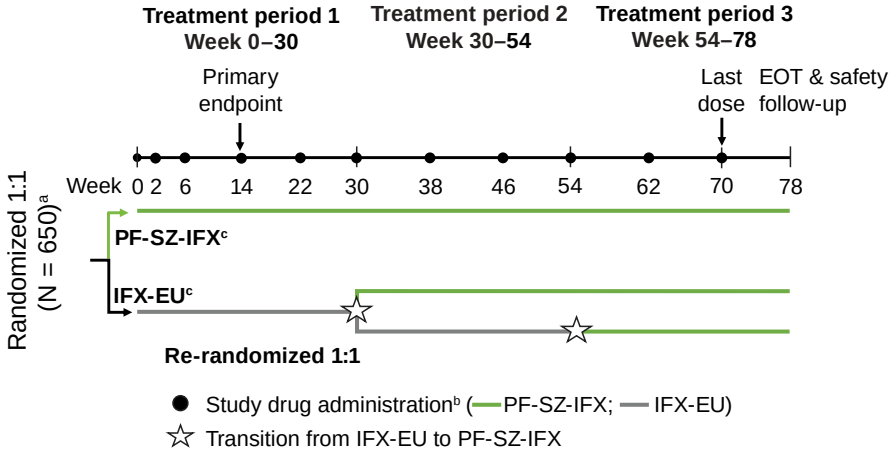

FIGURE 1 Study design.[10] [a]A sample size of approximately 614 patients was planned for enrollment. One patient in the PF-SZ-IFX treatment arm was randomized twice; data were not collected for this patient's second randomization. [b]Intravenous PF-SZ-IFX or IFX-EU (3 mg/kg) in combination with MTX were administered at weeks 0, 2, and 6, and then every 8 weeks thereafter. Dose escalation to 5 mg/kg (with PF-SZ-IFX or IFX-EU) was permitted starting at or after week 14 in patients with an inadequate clinical response. [c]Treatment group evaluation. EOT, end of treatment; IFX-EU, reference infliximab sourced from the European Union; MTX, methotrexate; PF-SZ-IFX, PF-06438179/GP1111. Adapted from Cohen et al. *Arthritis Res Ther* 2018;20:155. ©The Author(s). Reprinted with permission (https://creativecommons.org/licenses/by/4.0)

investigational sites. All patients provided informed consent before undergoing any screening procedures. The study was supported by Pfizer Inc and is registered at ClinicalTrials.gov (NCT02222493) and EU Clinical Trials Register (EudraCT number: 2013-004148-49).

2.3 | Efficacy analyses for subgroups

The primary efficacy endpoint was ACR20 at week 14. Among other secondary efficacy endpoints were ACR20 at week 30, and changes in Disease Activity Score in 28 joints, 4 components based on hs-CRP (DAS28-CRP) and hs-CRP at weeks 14 and 30. Subgroup analyses of ACR20, hs-CRP, and DAS28-CRP were performed by age, gender, race, region, immunogenicity status (anti-drug antibody [ADA]-positive or ADA-negative, and neutralizing antibody [NAb]-positive or NAb-negative), and treatment history (MTX dose and duration and corticosteroid use). For ACR20 response rate, CIs of the treatment differences were calculated using the Wald method (ie normal approximation). Analysis of covariance was used for treatment comparisons of DAS28-CRP and hs-CRP, adjusting for baseline values.

The intent-to-treat population, defined as all patients who were randomized to receive study treatment, was used as the primary analysis population and for the subgroup analysis. For the subgroup analysis, statistical analysis was conducted using observed data without imputation to missing data. Point estimates and two-sided 95% CIs of the differences between the two treatment arms were presented for each parameter. No inference on equivalence was made for any of the subgroups.

3 | RESULTS

3.1 | Patient demographics

There were no notable differences in patient demographics or disease characteristics between the treatment arms at baseline (Table 1).[10]

3.2 | Efficacy

Week 14 ACR20 response rates were similar between PF-SZ-IFX and IFX-EU within each of the subgroups analyzed, including age, gender, race, region, treatment history, and immunogenicity status (Figure 2). ACR20 response rates at week 14 trended higher for ADA-negative and NAb-negative patients than for ADA-positive and NAb-positive patients (Figure 2). However, ACR20 response rates were similar between the two treatment arms in ADA-positive, ADA-negative, NAb-positive, and NAb-negative subgroups. In the PF-SZ-IFX and IFX-EU treatment arms, respectively, week 14 ACR20 response rates were 51.0% and 49.5% for the ADA-positive patients, 69.1% and 71.2% for ADA-negative patients, 50.0% and 45.7% for the NAb-positive patients, and 67.5% and 70.5% for NAb-negative patients (which included all ADA-negative samples not tested for NAb).

Week 30 ACR20 response rates were similar between PF-SZ-IFX and IFX-EU within the subgroups of age, gender, race, region, treatment history, and immunogenicity status (Figure S1); changes from baseline in DAS28-CRP and hs-CRP at week 14 or at week 30 were also similar between treatments within subgroups (Figures S2 and S3).

TABLE 1 Patient demographics and baseline disease characteristics[10]

	PF-SZ-IFX (n = 324)	IFX-EU (n = 326)
Age, mean (SD), y	52.8 (13.3)	52.8 (12.9)
Gender		
Female	258 (79.4)	264 (81.0)
Male	66 (20.4)	62 (19.0)
Race, n (%)		
White	257 (79.3)	247 (75.8)
Black	5 (1.5)	9 (2.8)
Asian	46 (14.2)	45 (13.8)
Other	15 (4.6)	25 (7.7)
Unspecified	1 (0.3)	0
Region, n (%)		
North America and Western Europe	50 (15.4)	51 (15.6)
Japan	24 (7.4)	23 (7.1)
South Korea	4 (1.2)	5 (1.5)
Latin America	22 (6.8)	22 (6.7)
Rest of the World	224 (69.1)	225 (69.0)
MTX dose, mean (SD), mg/wk	14.2 (4.5)[a]	14.4 (4.5)
Corticosteroid use, n (%)	178 (54.9)	192 (58.9)
Duration of MTX use, n (%)		
<6 mo	52 (16.0)	58 (17.8)
≥6 mo to <1 y	78 (24.1)	83 (25.5)
≥1 y to <3 y	86 (26.5)	93 (28.5)
≥3 y	107 (33.0)	92 (28.2)
Sulfasalazine drug use,[b] n (%)	2 (0.6)	2 (0.6)
Anti-malarial drug use,[b] n (%)	2 (0.6)	5 (1.5)
hs-CRP, mean (SD), mg/L	25.8 (24.3)	25.3 (28.4)
DAS28-CRP, mean (SD)	6.0 (1.0)	6.0 (0.9)

Note: Adapted from Cohen et al. *Arthritis Res Ther* 2018;20:155. ©The Author(s). Reprinted with permission (https://creativecommons.org/licenses/by/4.0/).

Abbreviations: DAS28-CRP, Disease Activity Score in 28 joints, 4 components based on high-sensitivity C-reactive protein; hs-CRP, high-sensitivity C-reactive protein; IFX-EU, reference infliximab sourced from the European Union; MTX, methotrexate; PF-SZ-IFX, PF-06438179/GP1111; RF, rheumatoid factor; SD, standard deviation.

[a]Total weekly dose of MTX was 16 mg/wk for one patient (PF-06438179/GP1111) but incorrectly recorded as 32 mg/wk; incorrect dose was the maximum value of the MTX dose range and was used for calculation of mean dose.

[b]Use of sulfasalazine and anti-malarial drugs was allowed only in the original protocol, but not in subsequent protocol amendments.

4 | DISCUSSION

Overall, subgroup analyses suggested that age, gender, race, region, treatment history, and immunogenicity status did not influence similarity of efficacy between the two treatment arms as measured by ACR20 response at week 14. Results to week 30 continued to show that efficacy, as measured by ACR20 response and change from baseline in DAS28-CRP and hs-CRP, was similar overall between PF-SZ-IFX and IFX-EU in all subgroups beyond week 14.

Biologic therapies, including biosimilars, may elicit an immunogenic response, which could potentially impact the pharmacokinetics, efficacy, and safety of the medication.[14] In the previous analysis of the overall population, the safety profiles (including immunogenicity) of PF-SZ-IFX and IFX-EU were shown to be similar, with no clinically meaningful differences observed between arms during treatment periods 1 or 2.[10,11] Moreover, a population PK analysis of data from the same study established that the PK parameters for PF-SZ-IFX and IFX-EU were similar and were significantly influenced by the same covariates (baseline body weight, gender, and ADA titer), but were unaffected by ethnicity, based on consideration of Japanese versus non-Japanese patients.[15] In the current analysis of patient subgroups, ACR20 response rates trended higher and changes from baseline in DAS28-CRP and hs-CRP were greater for ADA-negative and NAb-negative patients than for ADA-positive and NAb-positive patients. However, these measures of efficacy were similar between the two treatment arms in each immunogenicity subgroup over the 30-week treatment period.

One limitation of the current study is that DAS28-CRP and hs-CRP subgroup analyses were created post hoc. Nevertheless, results demonstrate that efficacy, as measured by ACR20 response and change from baseline in DAS28-CRP and hs-CRP, was similar overall between PF-SZ-IFX and IFX-EU in all subgroups examined up to week 30. The efficacy results based on these subgroup analyses were aligned with the previously reported results for the overall population.[10]

DATA-SHARING

Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the USA and/or EU, or (2) in programs that have been terminated (ie development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

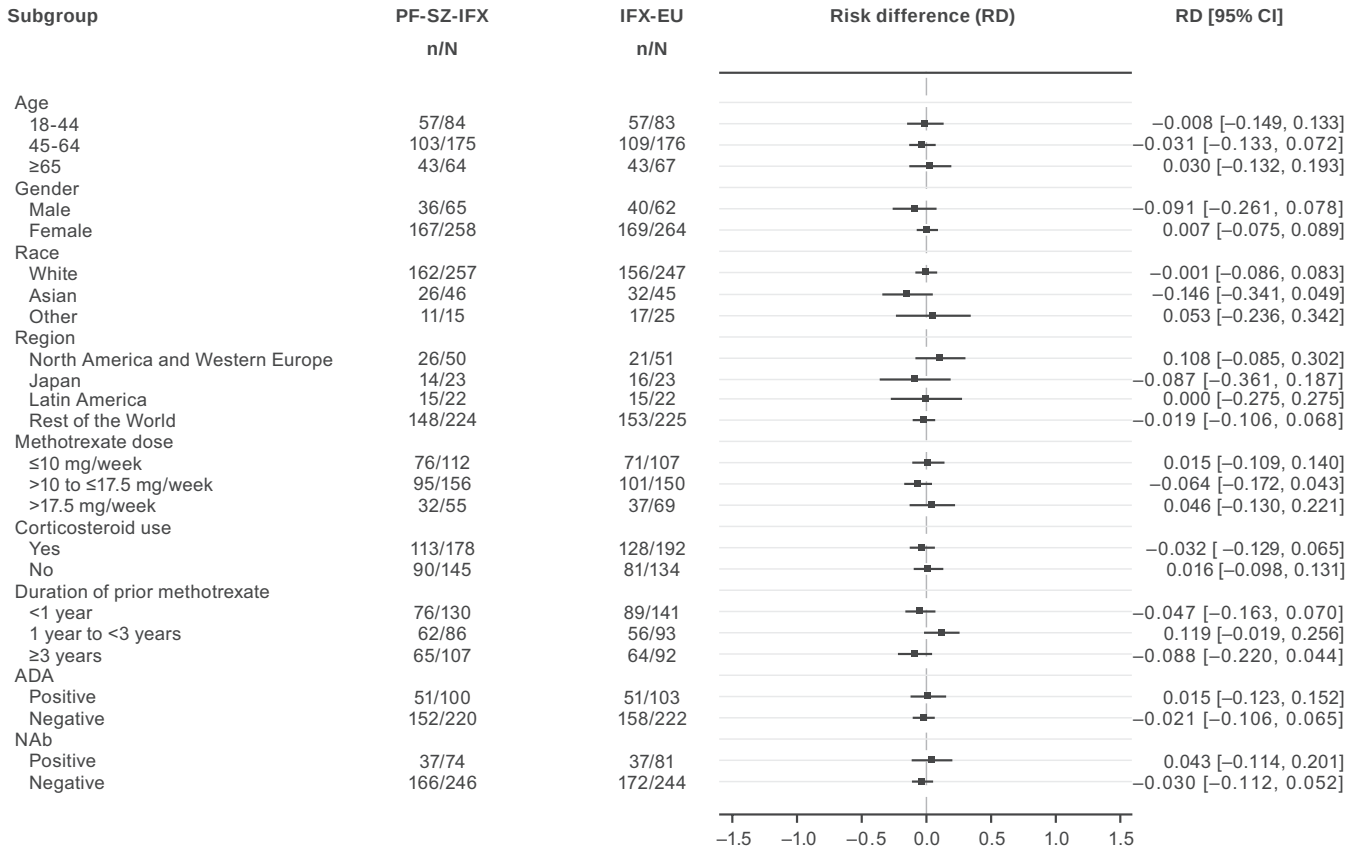

FIGURE 2 Subgroup analysis of ACR20 response at week 14. ACR20, American College of Rheumatology criteria for ≥20% clinical improvement; ADA, anti-drug antibody; CI, confidence interval; IFX-EU, reference infliximab sourced from the European Union; NAb, neutralizing antibody; PF-SZ-IFX, PF-06438179/GP1111

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CONFLICTS OF INTEREST

HK reports grants from Pfizer; grants and personal fees from AbbVie GK, Asahi Kasei Pharma, Astellas Pharma Inc, Chugai Pharmaceutical Co. Ltd., Eisai Co. Ltd., Mitsubishi Tanabe Pharma, and Novartis; and personal fees from Bristol-Myers Squibb, Eli Lilly Japan KK, and Janssen Pharmaceutical KK. EU has no competing interests to disclose. TA reports personal fees for consulting from Chugai Pharmaceutical Co. Ltd., Eli Lilly Japan KK, GlaxoSmithKline KK, Pfizer, and UCB Japan Co. Ltd; grants and personal fees for speakers' bureaus from AbbVie Inc, Astellas Pharma Inc, Bristol-Myers Squibb, Chugai Pharmaceutical Co. Ltd., Daiichi Sankyo Co. Ltd., Eisai Co. Ltd., Eli Lilly Japan KK, Mitsubishi Tanabe Pharma Co., Otsuka Pharmaceutical Co. Ltd., Pfizer, Takeda Pharmaceutical Co. Ltd, and UCB Japan Co. Ltd; and grants from Alexion Pharmaceuticals, Inc. CA-M reports personal fees for speakers' bureaus from Pfizer, Lilly, Abbvie, and Roche. KK is an employee of Pfizer. TM, DPL, MIR, and MZ are employees of and own stock or options in Pfizer. SCR has received research grants from Pfizer.

AUTHOR CONTRIBUTIONS

HK, EU, TA, CA-M, and SCR contributed to the acquisition of data; MIR contributed to conception or design of the study; KK, TM, and DPL contributed to design of the post hoc analysis, and MZ contributed to data analysis. All authors participated in the interpretation of the data, contributed to the drafting or revision of the manuscript, read and gave final approval of the submitted manuscript, were involved in the decision to submit the manuscript for publication, and accept accountability for all aspects of the work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Tofacitinib in the treatment of Indian patients with rheumatoid arthritis: A post hoc analysis of efficacy and safety in Phase 3 and long-term extension studies over 7 years

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Funding information
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Abstract

Objectives: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). We characterized tofacitinib efficacy/safety in Indian vs rest of the world (ROW; excluding India) RA patients.

Methods: Efficacy data were pooled for disease-modified antirheumatic drug (DMARD) inadequate responders from Phase (P)3 studies. For Indian patients, ORAL Solo and ORAL Scan; ROW (excluding India), these studies plus ORAL Step, ORAL Sync, and ORAL Standard. Safety data also included ORAL Start (P3; methotrexate-naïve) and ORAL Sequel (long-term extension [LTE] study; data cut-off March 2017) for Indian patients, and these studies plus A3921041 (LTE study; Japanese study) for ROW. Efficacy outcomes at months 3/6: American College of Rheumatology (ACR)20/50/70; Disease Activity Score in 28 joints, erythrocyte sedimentation rate remission/low disease activity; change from baseline in Health Assessment Questionnaire-Disability Index. Incidence rates (IRs; patients with events/100 patient-years) for adverse events of special interest (AESIs) were assessed throughout. Descriptive data underwent no formal comparison.

Results: One-hundred-and-ninety-seven Indian and 3879 ROW patients were included. Compared with ROW patients, Indian patients were younger, had lower body mass index, shorter RA duration, and higher baseline disease activity; most Indian patients were non-smokers and all were biologic DMARD (bDMARD)-naïve. Month 3 ACR20 rates with tofacitinib 5 mg twice daily/10 mg twice daily/placebo were 67.4%/82.1%/40.9% (India) and 59.0%/66.1%/28.2% (ROW), and month 6 rates were 76.2%/92.1%/88.9% (India) and 69.0%/74.2%/66.5% (ROW). Month 3/6 improvements in other outcomes were generally numerically greater with tofacitinib vs placebo, and similar in both populations. Compared with ROW, Indian patients had numerically fewer AEs/serious AEs, and similar IRs for discontinuations due to AEs

and AESIs, except that tuberculosis (TB) IR was higher in Indian (IR = 1.21; 95% CI 0.49, 2.49) vs ROW patients (IR = 0.17; 95% CI 0.11, 0.25).

Conclusions: Tofacitinib efficacy/safety were similar in both populations, except TB IR, which was higher in Indian patients but in line with those in bDMARD-treated RA patients from high-risk countries (IR = 0.00-2.56; TB IR >0.05 [World Health Organization]). Limitations included the small Indian population and baseline differences between populations.

KEYWORDS

clinical aspects, drug treatment, India, rheumatoid arthritis, tofacitinib

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, debilitating autoimmune disease characterized by inflammation of the articular synovium, joint damage, deformity, and progressive disability, and carries a significant burden of morbidity and economic impact.[1,2] RA has an estimated global prevalence of 0.24%.[3] However, RA receives a low level of economic support in low-to-middle income countries, such as India where age-/gender-adjusted RA prevalence is reported to be 0.34% (95% confidence interval [CI] 0.08-0.79).[4,5]

The Asia-Pacific League of Associations for Rheumatology acknowledges that treatment of RA in Asia-Pacific regions should be considered independently from the rest of the world (ROW), due to potential differences in disease prevalence/manifestation, treatment response, increased prevalence of certain infections (eg, tuberculosis [TB], hepatitis B/C) and country-specific challenges with respect to healthcare resources.[6] Filling existing gaps in our understanding of treatment responses in these countries may help to inform clinical practice.

India is among 30 countries considered to have a high TB burden, and has some of the highest global rates of TB (incidence rate [IR] = 0.2 per 100 patient-years[7]) and latent TB infection.[8] India also accounts for 23% and 36% of the global and regional burden of pneumonia, respectively.[9]

Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of RA. The clinical development program for tofacitinib includes data from 7061 patients, representing 22 875 patient-years of exposure up to 9.5 years.[10] While tofacitinib long-term extension (LTE) studies have included Asia-Pacific patients,[11-14] understanding of tofacitinib efficacy/safety in India is restricted to a post hoc analysis conducted in 8 Asia-Pacific countries (China, India, Japan, Korea, Malaysia, the Philippines, Taiwan, and Thailand; total N = 1464).[15] Efficacy outcomes for tofacitinib in this post hoc analysis of data pooled from Phase 2/3 studies were comparable with, or slightly higher than, those in global studies. Greater improvements with tofacitinib vs placebo were observed in disease activity and health status (measured by Health Assessment Questionnaire-Disability Index [HAQ-DI]) after 3 months, which persisted to 24 months. Safety outcomes (based on pooled data from Phase 2/3/LTE studies) were generally comparable with those seen in global patients; however, the infection incidence (including TB) was higher in Asia-Pacific patients.[15]

In this post hoc analysis, we characterized tofacitinib efficacy and safety in Indian patients with RA, vs patients from ROW (all patients excluding Indian patients).

2 | METHODS

2.1 | Study design and patients

This post hoc analysis pooled data from 6 double-blind, randomized controlled Phase 3 studies[16-21] and two open-label LTE studies[11,12,22] of tofacitinib in patients with RA (Table S1).

Full study details have been reported previously (summarized in Table S1). Briefly, patients were ≥18 years of age, with a diagnosis of active RA based on the American College of Rheumatology (ACR) 1987 revised criteria,[23] and had active disease at screening and baseline. Key exclusion criteria included any infection requiring antimicrobial therapy within 2 weeks prior to the first dose or history of infection requiring hospitalization or parenteral antimicrobial therapy within 6 months of randomization, history of recurrent or disseminated herpes zoster (HZ), or other opportunistic infection, evidence of active, latent, or inadequately treated *Mycobacterium tuberculosis* infection, and history of malignancy.

In Phase 3 studies, patients were randomized to receive tofacitinib 5 or 10 mg twice daily or placebo, either alone or with background conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). Patients receiving placebo advanced to tofacitinib 5 or 10 mg twice daily at month 3 or month 6. Patients in LTE studies initiated treatment with tofacitinib 5 or 10 mg twice daily, with dose adjustments permitted at the discretion of the investigator.

All studies were conducted in compliance with the Declaration of Helsinki and the Good Clinical Practice Guidelines established by the International Conference for Harmonization. Study protocols were approved by the Institutional Review Board or Independent Ethics Committee at each center. All patients provided written informed consent.

TABLE 1 Patient demographics and baseline disease characteristics

	Phase 3 studies[a] (efficacy analysis set)					
	India			Rest of the world		
	Tofacitinib 5 mg b.i.d. (N = 51)	Tofacitinib 10 mg b.i.d. (N = 43)	Placebo (N = 26)	Tofacitinib 5 mg b.i.d. (N = 1165)	Tofacitinib 10 mg b.i.d. (N = 1171)	Placebo (N = 655)
Female, n (%)	48 (94.1)	38 (88.4)	23 (88.5)	979 (84.0)	992 (84.7)	530 (80.9)
Age, y, mean (SD)	45.4 (11.9)	47.8 (11.2)	44.2 (9.6)	53.5 (11.5)	52.7 (11.6)	52.8 (12.0)
Body weight, kg, mean (SD)	60.8 (10.9)	54.9 (10.8)	58.2 (11.6)	71.6 (20.0)	71.8 (19.1)	72.9 (21.3)
BMI, kg/m^2, mean (SD)	25.3 (5.0)	23.2 (4.2)	24.1 (4.9)	27.1 (6.8)	27.3 (6.5)	27.4 (6.9)
Race, n (%)						
White	0	0	0	737 (63.3)	741 (63.3)	439 (67.0)
Black	0	0	0	45 (3.9)	35 (3.0)	24 (3.7)
Asian	51 (100.0)	43 (100.0)	26 (100.0)	276 (23.7)	271 (23.1)	140 (21.4)
Other	0	0	0	107 (9.2)	124 (10.6)	52 (7.9)
Smoking status, n (%)						
Current smoker	0	0	0	166 (14.3)	212 (18.1)	130 (19.9)
Ex-smoker	0	0	0	242 (20.8)	194 (16.6)	124 (18.9)
Never smoked	51 (100.0)	43 (100.0)	26 (100.0)	757 (65.0)	765 (65.3)	399 (60.9)
Duration of RA, y, mean (SD)	4.1 (4.7)	6.4 (6.5)	4.4 (3.7)	8.9 (8.1)	9.2 (8.3)	9.5 (8.6)
DAS28-4(ESR), mean (SD)	7.0 (0.9)	7.1 (0.9)	7.0 (1.0)	6.4 (1.0)	6.4 (1.0)	6.4 (1.0)
CDAI, mean (SD)	43.6 (11.7)	44.3 (13.2)	41.8 (12.2)	37.2 (12.3)	36.9 (12.5)	37.1 (12.9)
HAQ-DI, mean (SD)	1.5 (0.7)	1.6 (0.6)	1.5 (0.6)	1.5 (0.7)	1.5 (0.7)	1.4 (0.7)
ESR, mm/h, mean (SD)	59.4 (29.2)	63.2 (27.8)	60.4 (30.3)	49.9 (26.1)	50.1 (26.7)	48.9 (25.2)
CRP, mg/L, mean (SD)	15.8 (28.3)	16.6 (20.2)	14.6 (15.5)	17.9 (22.2)	17.5 (22.6)	16.1 (19.2)
RF+, n (%)	31 (60.8)	35 (81.4)	21 (80.8)	821 (71.3)	814 (70.0)	437 (67.0)
Anti-CCP+, n (%)	35 (68.6)	35 (81.4)	24 (92.3)	882 (75.7)	857 (73.2)	476 (72.7)
Treatment history, n (%)						
MTX	44 (86.3)	39 (90.7)	23 (88.5)	1118 (96.0)	1115 (95.2)	626 (95.6)
csDMARDs (excluding MTX)	38 (74.5)	29 (67.4)	23 (88.5)	707 (60.7)	716 (61.1)	375 (57.3)
TNFi	0	0	0	294 (25.2)	286 (24.4)	201 (30.7)
Non-TNFi bDMARDs	0	0	0	75 (6.4)	72 (6.2)	46 (7.0)
Concomitant treatments						
MTX dose, mg/wk, mean (SD)	9.1 (9.0)	9.1 (8.5)	10.5 (8.8)	10.9 (7.5)	11.2 (7.8)	11.5 (7.7)
Glucocorticoid dose mg/d, mean (SD)	2.7 (3.0)	2.7 (3.1)	3.9 (4.1)	3.6 (3.9)	3.4 (3.8)	3.6 (4.0)

Note: N and N1 are patient numbers for both populations assessed for efficacy (Phase 3) and safety (Phase 3/LTE), respectively; the numbers of patients assessed for each endpoint may be lower than N/N1.

Abbreviations: bDMARD, biologic disease-modifying antirheumatic drug; b.i.d., twice daily; BMI, body mass index; CCP, cyclic citrullinated peptide; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28-4(ESR), Disease Activity Score in 28 joints, erythrocyte sedimentation rate; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; LTE, long-term extension; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation; TDD, total daily dose; TNFi, tumor necrosis factor inhibitor; y, years.

[a]ORAL Step (NCT00960440),[16] ORAL Scan (NCT00847613),[17] ORAL Sync (NCT00856544),[19] ORAL Solo (NCT00814307),[20] and ORAL Standard (NCT00853385).[21]

[b]ORAL Step (NCT00960440),[16] ORAL Scan (NCT00847613),[17] ORAL Start (NCT01039688),[18] ORAL Sync (NCT00856544),[19] ORAL Solo (NCT00814307),[20] ORAL Standard (NCT00853385),[21] and ORAL Sequel (NCT00413699); main study database locked at time of analysis: March 2, 2017),[12,22] and Study A3921041 (NCT00661661); Japanese study.[11]

[c]Includes all patients receiving tofacitinib in Phase 3 and LTE studies.

[d]The average TDD of tofacitinib for each patient was calculated as the sum of all doses received divided by the number of days of treatment over the entire study duration for each patient; average tofacitinib doses of 5 mg b.i.d. and 10 mg b.i.d. were defined as TDD <15 mg b.i.d. and TDD ≥15 mg b.i.d., respectively.

Phase 3/LTE[b] (safety analysis set)[c]					
India			Rest of the world		
Average tofacitinib 5 mg b.i.d. (N1 = 58) [d]	Average tofacitinib 10 mg b.i.d. (N1 = 139) [d]	All tofacitinib (N1 = 197)	Average tofacitinib 5 mg b.i.d. (N1 = 1005)	Average tofacitinib 10 mg b.i.d. (N1 = 2874) [d]	All tofacitinib (N1 = 3879)
48 (82.8)	125 (89.9)	173 (87.8)	838 (83.4)	2366 (82.3)	3204 (82.6)
43.3 (13.1)	44.9 (10.6)	44.4 (11.4)	53.3 (12.2)	52.1 (11.7)	52.4 (11.8)
59.6 (12.5)	57.1 (11.4)	57.8 (11.8)	69.3 (18.5)	73.0 (19.5)	72.0 (19.3)
24.5 (5.6)	23.8 (4.5)	24.0 (4.9)	26.5 (6.3)	27.4 (6.5)	27.1 (6.4)
0	0	0	529 (52.6)	2055 (71.5)	2584 (66.6)
0	1 (<1.0)	1 (<1.0)	31 (3.1)	98 (3.4)	129 (3.3)
58 (100)	138 (99.3)	196 (99.5)	354 (35.2)	401 (14.0)	755 (19.5)
0	0	0	91 (9.1)	320 (11.1)	411 (10.6)
0	1 (<1.0)	1 (<1.0)	143 (14.2)	545 (19.0)	688 (17.7)
0	0	0 (0.0)	195 (19.4)	495 (17.2)	690 (17.8)
58 (100)	138 (99.3)	196 (99.5)	667 (66.4)	1831 (63.7)	2498 (64.4)
2.6 (3.1)	4.0 (5.0)	3.6 (4.6)	7.9 (8.0)	7.8 (8.1)	7.8 (8.1)
7.1 (0.9)	7.1 (0.9)	7.1 (0.9)	6.4 (1.0)	6.4 (1.0)	6.4 (1.0)
43.4 (12.2)	42.9 (13.5)	43.1 (13.1)	36.5 (12.7)	37.6 (12.3)	37.3 (12.5)
1.6 (0.6)	1.6 (0.6)	1.6 (0.6)	1.5 (0.7)	1.5 (0.7)	1.5 (0.7)
64.2 (30.9)	66.6 (29.3)	65.9 (29.8)	51.0 (25.3)	50.0 (26.5)	50.3 (26.2)
20.4 (29.9)	19.0 (22.2)	19.4 (24.6)	18.1 (22.3)	18.3 (23.1)	18.2 (22.9)
42 (73.7)	113 (81.9)	155 (79.5)	741 (74.5)	2043 (71.6)	2784 (72.3)
46 (79.3)	117 (84.8)	163 (83.2)	793 (79.4)	2152 (75.6)	2945 (76.6)
30 (51.7)	73 (52.5)	103 (52.3)	798 (79.4)	2203 (76.7)	3001 (77.4)
40 (69.0)	96 (69.1)	136 (69.0)	603 (60.0)	1562 (54.3)	2165 (55.8)
0	0	0	80 (8.0)	140 (4.9)	220 (5.7)
0	0	0	49 (4.9)	142 (4.9)	191 (4.9)
5.9 (8.4)	5.3 (8.1)	5.5 (8.2)	9.2 (7.6)	8.9 (8.4)	9.0 (8.2)
3.9 (3.1)	5.0 (17.4)	4.6 (14.7)	3.5 (4.0)	3.3 (4.2)	3.4 (4.1)

2.2 | Post hoc analysis of efficacy and safety in Indian vs ROW populations

Efficacy analyses were based on pooled data from csDMARD and biologic (b)DMARD inadequate responders (csDMARD-IR and bDMARD-IR, respectively) enrolled in Phase 3 studies. The Indian population comprised patients in ORAL Scan and ORAL Solo. The ROW efficacy population included patients in ORAL Step, ORAL Scan, ORAL Solo, ORAL Sync, and ORAL Standard.

Efficacy outcomes were evaluated at months 3 and 6, and included the proportion of patients achieving 20%, 50%, or 70% improvement in ACR criteria (ACR20/50/70 response rates, respectively); the proportion of patients achieving Disease Activity Score in 28 joints, erythrocyte sedimentation rate (DAS28-4[ESR])-defined remission (<2.6) or low disease activity (≤3.2); and change from baseline in HAQ-DI.

Safety analyses were based on data from patients who received ≥1 dose of tofacitinib in Phase 3/LTE studies. Indian patients were enrolled in ORAL Scan, ORAL Solo, ORAL Start, and ORAL Sequel. ROW data were pooled from ORAL Step, ORAL Scan, ORAL Solo, ORAL Sync, ORAL Start, ORAL Standard, ORAL Sequel, and A3921041.

Safety analyses included adverse events (AEs), serious AEs (SAEs), discontinuations due to AEs, confirmed laboratory abnormalities (based on two sequential measurements), mortality rates and IRs (patients with events per 100 patient-years) for AEs of special interest (AESIs; TB, interstitial lung disease [ILD], opportunistic infections, HZ, serious infection events [SIEs], major adverse cardiovascular events [MACE], malignancies excluding non-melanoma skin cancer [NMSC], lymphoma and lymphoproliferative disorders, and gastrointestinal [GI] perforations). In addition, the Data Safety Monitoring Board for tofacitinib rheumatology studies recently determined that the frequency of pulmonary embolism (PE) in the tofacitinib 10 mg twice daily arm was higher than the frequency of PE in the tumor necrosis factor inhibitor (TNFi) comparator arm in a US Food and Drug Administration post-marketing requirement safety study (A3921133; NCT02092467),[24] designed to evaluate the long-term risk of MACE and malignancy. Study A3921133 is an ongoing, open-label, endpoint-driven study, evaluating the safety of tofacitinib 5 and 10 mg twice daily, compared with TNFi in patients with RA. Patients had to be ≥50 years of age, have ≥1 cardiovascular risk factor, and be on a stable dose of methotrexate (MTX) to be eligible for enrollment. Subsequently, based on information from Study A3921133 and consideration of information pertaining to PE for other JAK inhibitors, Pfizer has determined that PE is an important potential risk for treatment with tofacitinib. Therefore, incidence of venous thromboembolic events (VTE, including PE or deep vein thrombosis) was also assessed in the present analysis.

SAEs were defined as any AEs that were life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability, incapacity or congenital birth defects, or death.

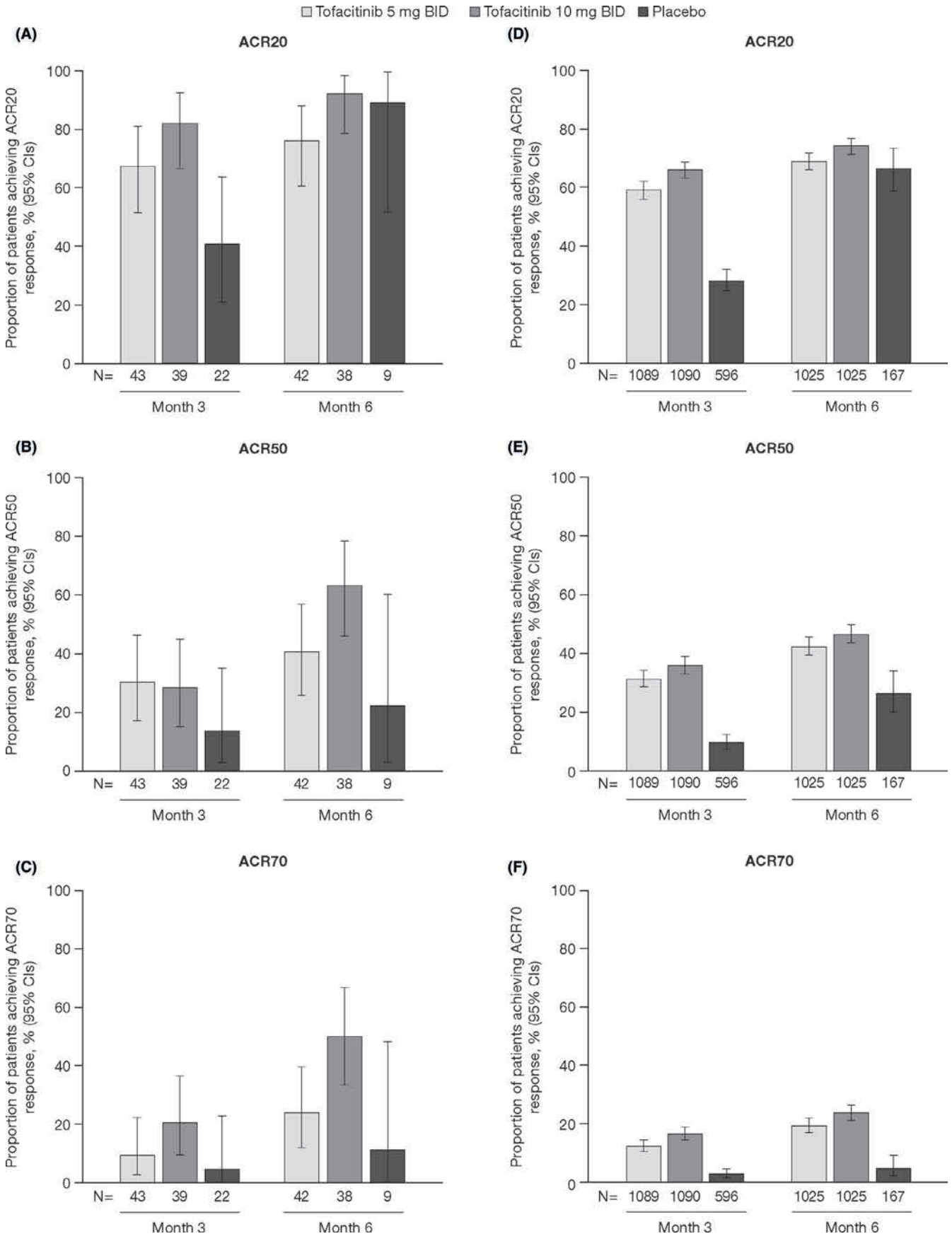
Screening for latent TB infection was carried out using QuantiFERON-GOLD®™ or Mantoux purified protein derivative tuberculin skin tests at baseline of Phase 3 studies, unless tested and documented within 3 months of the screening visit. Patients with latent TB infections were permitted to enroll in the study; however, those with untreated/inadequately treated latent TB infections had to enroll after ≥1 month of isoniazid treatment. Per protocol, regular QuantiFERON-GOLD®™ testing was performed post-baseline in patients from countries with a TB prevalence of >50 cases per 100 000 persons (eg, India)[7] who were negative for latent TB infection at baseline. Follow-up chest radiographs were required for patients with positive latent TB infection results post-baseline; only those without active TB infection by chest radiograph were allowed to continue.

2.3 | Statistical analysis

Efficacy analyses were based on the full analysis set, which included all patients who received ≥1 dose of study drug for whom data were available from ≥1 post-baseline assessment. Treatment differences were assessed using 95% CI, calculated using the Clopper-Pearson (Exact) method and *t* statistics for binary and continuous endpoints, respectively. Treatments were considered different if 95% CI did not overlap, or numerically different if 95% CI marginally overlapped. Baseline was defined as the start of the qualifying index study for patients enrolled in Phase 3 studies; for patients in LTE studies, baseline was defined as the start of the qualifying index study for patients enrolling within ≤14 days of index study completion, or the start of the LTE for patients enrolling >14 days after index study completion.

Safety endpoints were reported throughout each study, and were based on all treated patients who received ≥1 dose of study drug. IRs and 95% CI, calculated via the Exact Poisson method adjusted for exposure time, were based on the number of unique patients with first events occurring between first and last dose plus 28 days, divided by the time accrued during the risk period (ie between first and last dose plus 28 days, or the time accrued to the first event, whichever occurred earlier).

FIGURE 1 The proportion of Indian patients achieving (A) ACR20, (B) ACR50, and (C) ACR70 responses at months 3 and 6; and the proportion of ROW patients achieving (D) ACR20, (E) ACR50, and (F) ACR70 responses at months 3 and 6. Patients receiving placebo in ORAL Solo and ORAL Step advanced in a blinded manner to tofacitinib 5 or 10 mg b.i.d. at month 3; placebo-treated non-responders (defined as patients not achieving ≥20% reduction from baseline in swollen and tender joint counts) in ORAL Scan, ORAL Sync, and ORAL Standard advanced in a blinded manner to tofacitinib 5 or 10 mg b.i.d. at month 3; remaining placebo-treated patients advanced at month 6; efficacy analyses were based on observed cases without imputation for missing data; all endpoints are reported by descriptive statistics with no formal hypothesis testing. ACR, American College of Rheumatology; b.i.d., twice daily; CI, confidence interval; ROW, rest of the world


Tofacitinib 5 mg BID
Tofacitinib 10 mg BID
Placebo
(A)
ACR20
Proportion of patients achieving ACR20 response, % (95% CIs)
100
80
60
40
20
0
N= 43 39 22 42 38 9
Month 3
Month 6
(D)
ACR20
Proportion of patients achieving ACR20 response, % (95% CIs)
N= 1089 1090 596 1025 1025 167
Month 3
Month 6
(B)
ACR50
Proportion of patients achieving ACR50 response, % (95% CIs)
N= 43 39 22 42 38 9
Month 3
Month 6
(E)
ACR50
Proportion of patients achieving ACR50 response, % (95% CIs)
N= 1089 1090 596 1025 1025 167
Month 3
Month 6
(C)
ACR70
Proportion of patients achieving ACR70 response, % (95% CIs)
N= 43 39 22 42 38 9
Month 3
Month 6
(F)
ACR70
Proportion of patients achieving ACR70 response, % (95% CIs)
N= 1089 1090 596 1025 1025 167
Month 3
Month 6

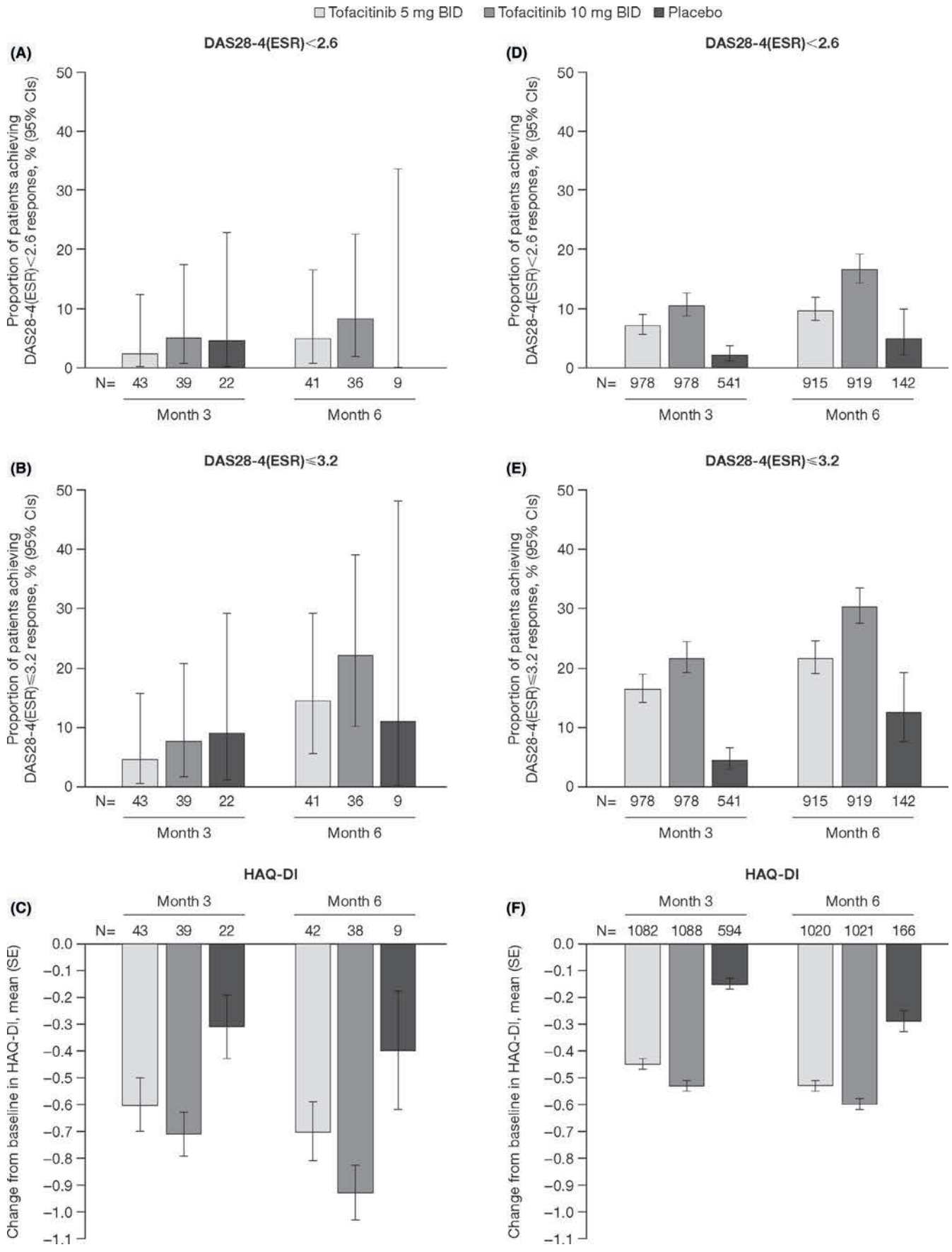

Tofacitinib 5 mg BID
Tofacitinib 10 mg BID
Placebo
(A)
DAS28-4(ESR)<2.6
Proportion of patients achieving DAS28-4(ESR)<2.6 response, % (95% CIs)
N= 43 39 22 41 36 9
Month 3
Month 6
(D)
DAS28-4(ESR)<2.6
Proportion of patients achieving DAS28-4(ESR)<2.6 response, % (95% CIs)
N= 978 978 541 915 919 142
Month 3
Month 6
(B)
DAS28-4(ESR)≤3.2
Proportion of patients achieving DAS28-4(ESR)≤3.2 response, % (95% CIs)
N= 43 39 22 41 36 9
Month 3
Month 6
(E)
DAS28-4(ESR)≤3.2
Proportion of patients achieving DAS28-4(ESR)≤3.2 response, % (95% CIs)
N= 978 978 541 915 919 142
Month 3
Month 6
HAQ-DI
(C)
Month 3
Month 6
N= 43 39 22 42 38 9
Change from baseline in HAQ-DI, mean (SE)
HAQ-DI
(F)
Month 3
Month 6
N= 1082 1088 594 1020 1021 166
Change from baseline in HAQ-DI, mean (SE)

FIGURE 2 The proportion of Indian patients achieving (A) DAS28-4(ESR) <2.6, (B) DAS28-4(ESR) ≤3.2, and (C) change from baseline in HAQ-DI, at months 3 and 6; and the proportion of ROW patients achieving (D) DAS28-4(ESR) <2.6, (E) DAS28-4(ESR) ≤3.2, and (F) change from baseline in HAQ-DI, at months 3 and 6. Patients receiving placebo in ORAL Solo and ORAL Step advanced in a blinded manner to tofacitinib 5 or 10 mg b.i.d. at month 3; placebo-treated non-responders (defined as patients not achieving ≥20% reduction from baseline in swollen and tender joint counts) in ORAL Scan, ORAL Sync, and ORAL Standard advanced in a blinded manner to tofacitinib 5 or 10 mg b.i.d. at month 3; remaining placebo-treated patients advanced at month 6; efficacy analyses were based on observed cases without imputation for missing data. b.i.d., twice daily; CI confidence interval; DAS28-4(ESR), Disease Activity Score in 28 joints, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; ROW, rest of the world; SE, standard error

All analyses were based on observed cases without imputation for missing data. No multiplicity adjustment was made for any comparisons.

3 | RESULTS

3.1 | Patients

The safety analysis set included 197 patients from India and 3879 ROW patients (total exposure [all tofacitinib doses], 564.2 patient-years and 14 279.9 patient-years in Indian and ROW patients, respectively). The efficacy analysis set included 51 Indian patients receiving tofacitinib 5 mg twice daily (total exposure, 51.7 patient-years), 43 Indian patients receiving tofacitinib 10 mg twice daily (total exposure, 49.2 patient-years), and 26 Indian patients receiving placebo (total exposure, 8.7 patient-years); and 1165 ROW patients receiving tofacitinib 5 mg twice daily (total exposure, 1081.2 patient-years), 1171 ROW patients receiving tofacitinib 10 mg twice daily (total exposure, 1099.1 patient-years), and 655 ROW patients receiving placebo (total exposure, 194.0 patient-years).

Patient demographics and baseline disease characteristics are shown in Table 1. Some numerical differences were observed between populations. Indian patients were younger, had lower body weight, lower body mass index (BMI), shorter disease duration, higher baseline disease activity, and were more likely to be non-smokers, compared with patients from ROW. Prior treatment for Indian patients predominantly comprised non-MTX csDMARDs, and no Indian patients previously received bDMARDs. ROW patients had mostly received MTX and some ROW patients had previously received bDMARDs.

3.2 | Efficacy at months 3 and 6

ACR20, ACR50, and ACR70 response rates for the Indian population are shown in Figure 1A-C respectively; ACR20, AC50, and ACR70 response rates for the ROW population are shown in Figure 1D-F respectively. At month 6, ACR20 response rates were 76.2%, 92.1%, and 88.9% in Indian patients, and 69.0%, 74.2%, and 66.5% in ROW patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and placebo, respectively (Figure 1A,D).

In Indian patients receiving tofacitinib 5 mg twice daily/tofacitinib 10 mg twice daily/placebo, ACR50 response rates at months 3 and 6 were 30.2%/28.2%/13.6% and 40.5%/63.2%/22.2%, respectively; and ACR70 response rates were 9.3%/20.5%/4.6% and 23.8%/50.0%/11.1% at months 3 and 6, respectively. In ROW patients receiving tofacitinib 5 mg twice daily/tofacitinib 10 mg twice daily/placebo, ACR50 response rates at months 3 and 6 were 31.1%/35.7%/9.7% and 42.2%/46.4%/26.4%, respectively; and ACR70 response rates were 12.4%/16.5%/2.9% and 19.3%/23.8%/4.8% at months 3 and 6, respectively (Figure 1B,C,E,F).

The proportions of Indian patients achieving DAS28-4(ESR) remission or low disease activity are shown in Figure 2A,B, respectively; change from baseline in HAQ-DI in Indian patients is shown in Figure 2C. The proportions of ROW patients achieving DAS28-4(ESR) remission or low disease activity, and change from baseline in HAQ-DI in ROW patients, is shown in Figure 2D-F respectively.

In Indian patients receiving tofacitinib 5 mg twice daily/tofacitinib 10 mg twice daily/placebo, the proportions achieving DAS28-4(ESR) remission at months 3 and 6 were 2.3%/5.1%/4.6% and 4.9%/8.3%/0.0%, respectively; and DAS28-4(ESR) low disease activity was achieved by 4.7%/7.7%/9.1% and 14.6%/22.2%/11.1% at months 3 and 6, respectively. In ROW patients receiving tofacitinib 5 mg twice daily/tofacitinib 10 mg twice daily/placebo, rates of DAS28-4(ESR) remission at months 3 and 6 were 7.2%/10.4%/2.0% and 9.7%/16.7%/4.9%, respectively; and DAS28-4(ESR) low disease activity rates were 16.6%/21.8%/4.4% and 21.8%/30.5%/12.7% at months 3 and 6, respectively (Figure 2D,E).

In Indian patients receiving tofacitinib 5 mg twice daily/tofacitinib 10 mg twice daily/placebo, change from baseline in HAQ-DI at months 3 and 6 was -0.60/-0.71/-0.31 and -0.70/-0.93/-0.40, respectively (Figure 2C). In ROW patients receiving tofacitinib 5 mg twice daily/tofacitinib 10 mg twice daily/placebo, change from baseline in HAQ-DI at months 3 and 6 was -0.45/-0.53/-0.15 and -0.53/-0.60/-0.29 respectively (Figure 2F).

3.3 | Safety

Safety data from pooled Phase 3/LTE studies are summarized in Table 2. A lower proportion of Indian patients experienced AEs, compared with ROW patients (36.0% vs 50.3% respectively, up to month 3; 23.4% vs 38.4%, respectively, from months 3-6; 60.9% vs 79.5%, respectively, post-month 6). Likewise, Indian patients were less likely to experience SAEs, compared with ROW patients (15.7% vs 29.3%, respectively). Rates of discontinuations due to AEs were similar in both populations. Incidence of mortality was also similar between Indian and ROW patients (IR = 0.17 per 100 patient-years; 95% CI 0.00-0.96 vs IR = 0.23 per 100 patient-years; 95% CI 0.16-0.32, respectively).

Considering AESIs, the incidence of ILD, opportunistic infections excluding TB, HZ, SIEs, MACE, malignancies excluding NMSC, lymphoma, and GI perforations were similar between Indian and ROW patients. Of these, HZ (IR = 2.93, 95% CI 1.67-4.76 and IR = 3.62, 95% CI 3.31-3.96 per 100 patient-years, for Indian and ROW patients, respectively) and SIEs (IR = 2.59, 95% CI 1.45-4.28 and IR = 2.47, 95% CI 2.22-2.74 per 100 patient-years, for Indian and ROW patients, respectively) were of the highest incidence; others had an IR of <0.8 per 100 patient-years. There were no cases of VTE in Indian patients in the safety analysis set.

TB rates were higher in Indian vs ROW patients. TB incidence in the Indian population was 1.21 per 100 patient-years (based on seven events overall; three events in Phase 3 studies, and four events in LTE studies; all patients were receiving 10 mg twice daily at onset). In contrast, TB IR in ROW patients was 0.17 per 100 patient-years (based on 25 events overall; six events in Phase 3 studies [all patients were receiving 10 mg twice daily at onset], and 19 events in LTE studies [three patients were receiving 5 mg twice daily and 16 patients were receiving 10 mg twice daily at onset]). Mean time to onset of TB was shorter in Indian vs ROW patients (635.1 days vs 725.8 days, respectively).

In total, 23 Indian patients had latent TB infections at baseline of Phase 3 studies, which was adequately treated in 14 patients, and untreated/inadequately treated in nine patients. In the ROW population, 216 patients had latent TB infections at Phase 3 baseline, which was adequately treated in 200 patients and untreated/inadequately treated in 16 patients. No Indian patients with latent TB infections developed TB during Phase 3/LTE studies. However, in the subgroup of ROW patients with latent TB infections, four patients developed TB; one case occurred during Phase 3 studies and three cases occurred during LTE studies. All of these patients were receiving tofacitinib 10 mg twice daily at the time of the event, and all were previously adequately treated for latent TB infections. In addition, there were 31 patients from high-risk TB countries (including five Indian patients) with no evidence of latent TB at baseline, but who subsequently tested positive for latent TB infection post-baseline (of these, 26 patients were negative for latent TB infection at baseline, three patients had an indeterminate infection status, and two patients were not tested). However, none of these patients had active TB, as assessed by follow-up chest radiogram.

A summary of confirmed laboratory abnormalities is shown in Table 3. IRs for laboratory abnormalities were generally similar in Indian and ROW patients, except for lymphocyte counts ≥1.5-<2 × 1000/mm^3, which were higher in Indian vs ROW patients, and lymphocyte counts ≥0.5-<1.5 × 1000/mm^3 and increases in alanine aminotransferase (ALT) >1 × upper limit of normal (ULN), which were lower in Indian vs ROW patients.

4 | DISCUSSION

In this post hoc analysis, we present a comprehensive characterization of the efficacy and safety of tofacitinib in Indian and ROW patients with RA enrolled in Phase 3 and LTE studies. This fills an important gap in knowledge regarding tofacitinib treatment in this country of high RA burden.

In this post hoc analysis of data from Phase 3 and LTE studies of tofacitinib, numerical differences were observed between the Indian and ROW populations; however, patient numbers were low, 95% CIs were large in the Indian population, and endpoints were reported descriptively, which should be taken into consideration when interpreting the results. Compared with ROW patients, Indian patients were younger, had lower body weight, lower BMI, shorter disease duration, and higher baseline disease activity. In addition, unlike ROW patients, most Indian patients were non-smokers and all were bDMARD-naïve. We observed that improvements in efficacy outcomes at months 3 and 6 were generally numerically similar in Indian vs ROW patients, and, in general, tofacitinib was superior to placebo. Efficacy was generally numerically greater with tofacitinib 10 mg twice daily vs 5 mg twice daily in ROW patients, but comparable with both tofacitinib doses in Indian patients.

Overall, AE and SAE rates were lower in Indian vs ROW patients, but discontinuations due to AEs were similar between populations. One possible explanation for this observation is that Indian patients may discontinue medications sooner than ROW patients, as it would be expected that the likelihood of developing a treatment-emergent AE would increase with longer treatment exposure, whereas, conversely, patients who discontinue sooner would be expected to be at a lower risk of treatment-emergent complications. To date, no analyses of discontinuation rates have been carried out in Indian patients with RA; however, it has previously been reported that patients of South Asian origin have lower self-reported drug adherence rates, and may discontinue RA medications early, compared with British/North European patients with RA,[25,26] which may be due to negative beliefs about medicines, problems with effective communication, and cultural differences in attitudes to chronic illness in patients of South Asian origin.[26,27]

The incidence of AESIs was generally low (IR <0.8 per 100 patient-years) in both populations, aside from HZ (India: IR = 2.93 per 100 patient-years; ROW: IR = 3.62 per 100 patient-years), SIEs (India: IR = 2.59 per 100 patient-years; ROW: IR = 2.47 per 100 patient-years), and TB (India: IR = 1.21 per 100 patient-years; ROW: IR = 0.17 per 100 patient-years). Of these, the incidence of TB was greater in Indian vs ROW patients, which may reflect the higher background incidence of TB in India.[7] In addition, higher BMI has been shown to be associated with a reduced TB risk,[28,29] and Indian patients in this analysis had lower body weight and BMI compared with the ROW population, which may have also influenced the increased TB IR in the Indian cohort.

There were no cases of VTE in the Indian population. In this analysis, Indian patients were younger and had lower BMI, compared with ROW patients. Older age and obesity are known risk factors for VTE,[30] and, in addition, obesity has been shown to be a time-dependent risk factor for VTEs in patients with RA.[31] Furthermore, unlike ROW patients, no Indian patients in this analysis had prior bDMARD experience. It has previously been reported that

TABLE 2 Summary of safety

	India			Rest of the world		
	Average tofacitinib 5 mg b.i.d. (N = 58) [a]	Average tofacitinib 10 mg b.i.d. (N = 139) [a]	All tofacitinib (N = 197)	Average tofacitinib 5 mg b.i.d. (N = 1005) [a]	Average tofacitinib 10 mg b.i.d. (N = 2874) [a]	All tofacitinib (N = 3879)
Total tofacitinib exposure, patient-y	90.9	473.3	564.2	2521.0	11 758.9	14 279.9
Tofacitinib treatment duration, y, mean (SD)	1.6 (1.4)	3.4 (2.2)	2.9 (2.2)	2.5 (2.0)	4.1 (2.2)	3.7 (2.3)
Patients with treatment-emergent AEs, n (%)						
Up to month 3	25 (43.1)	46 (33.1)	71 (36.0)	503 (50.0)	1450 (50.5)	1953 (50.3)
Months 3-6	17 (29.3)	29 (20.9)	46 (23.4)	375 (37.3)	1115 (38.8)	1490 (38.4)
Post-month 6	31 (53.4)	89 (64.0)	120 (60.9)	668 (66.5)	2416 (84.1)	3084 (79.5)
Patients with discontinuations due to AEs, n (%)	19 (32.8)	29 (20.9)	48 (24.4)	294 (29.3)	699 (24.3)	993 (25.6)
Patients with SAEs, n (%)	11 (19.0)	20 (14.4)	31 (15.7)	256 (25.5)	881 (30.7)	1137 (29.3)
Patients with mortality within 30 d, all-cause, n (%); IR (95% CI)	1 (1.7) 1.05 (0.03-5.84)	0 (0.0) 0.00 (0.00-0.76)	1 (0.5) 0.17 (0.00-0.96)	12 (1.2) 0.46 (0.24-0.81)	21 (0.7) 0.18 (0.11-0.27)	33 (0.9) 0.23 (0.16-0.32)
Patients with AESIs, n (%); IR (95% CI)						
TB[b]	1 (1.7) 1.05 (0.03-5.85)	6 (4.3) 1.24 (0.45-2.69)	7 (3.6)[c] 1.21 (0.49-2.49)	4 (0.4) 0.15 (0.04-0.39)	21 (0.7) 0.18 (0.11-0.27)	25 (0.6)[d] 0.17 (0.11-0.25)
ILD	0 (0.0) 0.00 (0.00-3.87)	1 (0.7) 0.21 (0.01-1.16)	1 (0.5) 0.17 (0.00-0.97)	5 (0.5) 0.19 (0.06-0.45)	21 (0.7) 0.18 (0.11-0.27)	26 (0.7) 0.18 (0.12-0.26)
Opportunistic infections, excluding TB[b]	0 (0.0) 0.00 (0.00-3.87)	1 (0.7) 0.21 (0.01-1.16)	1 (0.5) 0.17 (0.00-0.96)	12 (1.2) 0.46 (0.24-0.81)	43 (1.5) 0.36 (0.26-0.48)	55 (1.4) 0.38 (0.28-0.49)
HZ	3 (5.2) 3.20 (0.66-9.35)	13 (9.4) 2.87 (1.53-4.91)	16 (8.1) 2.93 (1.67-4.76)	92 (9.2) 3.82 (3.08-4.69)	394 (13.7) 3.58 (3.24-3.95)	486 (12.5) 3.62 (3.31-3.96)
Serious infections	7 (12.1) 7.47 (3.00-15.39)	8 (5.8) 1.65 (0.71-3.25)	15 (7.6) 2.59 (1.45-4.28)	91 (9.1) 3.52 (2.84-4.33)	266 (9.3) 2.24 (1.98-2.53)	357 (9.2) 2.47 (2.22-2.74)
MACE[b]	0 (0.0) 0.00 (0.00-3.87)	0 (0.0) 0.00 (0.00-0.76)	0 (0.0) 0.00 (0.00-0.64)	7 (0.7) 0.27 (0.11-0.56)	10 (0.3) 0.08 (0.04-0.15)	17 (0.4) 0.12 (0.07-0.19)

(Continues)

TABLE 2 (Continued)

	India			Rest of the world		
	Average tofacitinib 5 mg b.i.d. (N = 58) [a]	Average tofacitinib 10 mg b.i.d. (N = 139) [a]	All tofacitinib (N = 197)	Average tofacitinib 5 mg b.i.d. (N = 1005) [a]	Average tofacitinib 10 mg b.i.d. (N = 2874) [a]	All tofacitinib (N = 3879)
Malignancies (excl. NMSC)[b]	1 (1.7) 1.05 (0.03-5.84)	0 (0.0) 0.00 (0.00-0.76)	1 (0.5) 0.17 (0.00-0.96)	23 (2.3) 0.88 (0.56-1.33)	88 (3.1) 0.73 (0.59-0.91)	111 (2.9) 0.76 (0.63-0.92)
Lymphoma and lymphoproliferative disorders[b]	0 (0.0) 0.00 (0.00-3.87)	0 (0.0) 0.00 (0.00-0.76)	0 (0.0) 0.00 (0.00-0.64)	0 (0.0) 0.00 (0.00-0.14)	9 (0.3) 0.08 (0.03-0.14)	9 (0.2) 0.06 (0.03-0.12)
GI perforations[b]	0 (0.0) 0.00 (0.00-3.87)	0 (0.0) 0.00 (0.00-0.76)	0 (0.0) 0.00 (0.00-0.64)	1 (0.1) 0.04 (0.00-0.21)	13 (0.05) 0.11 (0.06-0.19)	14 (0.4) 0.10 (0.05-0.16)
Mean (SD) time to onset of TB, d	974.0 (0.0)	578.7 (532.0)	635.1 (508.1)	638.2 (255.7)	747.8 (486.1)	725.8 (447.2)

Note: N are patient numbers for both populations in the safety analysis set; n are number of patients with an event; IRs are patients with events per 100 patient-years; for the Indian population, safety data were pooled from ORAL Scan, ORAL Solo, ORAL Start, and LTE study ORAL Sequel; ROW safety data were pooled from ORAL Step, ORAL Scan, ORAL Solo, ORAL Sync, ORAL Start, ORAL Standard, ORAL Sequel, and A3921041.

Abbreviations: AE, adverse event; AESI, adverse event of special interest; b.i.d., twice daily; CI, confidence interval; GI, gastrointestinal; HZ, herpes zoster; ILD, interstitial lung disease; IR, incidence rate; LTE, long-term extension; MACE, major adverse cardiovascular events; NMSC, non-melanoma skin cancer; ROW, rest of the world; SAE, serious adverse event; SD, standard deviation; TB, tuberculosis; TDD, total daily dose.

[a]The average TDD of tofacitinib for each patient was calculated as the sum of all doses received divided by number of days of treatment over the entire study duration for each patient; average tofacitinib doses of 5 mg b.i.d. and 10 mg b.i.d. were defined as TDD <15 mg b.i.d. and TDD ≥15 mg b.i.d., respectively.

[b]Adjudicated event.

[c]For 7 TB cases in the Indian population, Phase 3: n = 3, LTE: n = 4 (all patients were receiving tofacitinib 10 mg b.i.d. at onset).

[d]For 25 TB cases in the ROW population, Phase 3: n = 6 (all patients were receiving tofacitinib 10 mg b.i.d. at onset), LTE: n = 19 (3 patients were receiving tofacitinib 5 mg b.i.d. and 16 patients were receiving tofacitinib 10 mg b.i.d. at onset).

TABLE 3 Confirmed laboratory abnormalities

n (%); IR (95% CI)	India			Rest of the world		
	Average tofacitinib 5 mg b.i.d. (N = 58) [a]	Average tofacitinib 10 mg b.i.d. (N = 139) [a]	All tofacitinib (N = 197)	Average tofacitinib 5 mg b.i.d. (N = 1005) [a]	Average tofacitinib 10 mg b.i.d. (N = 2874) [a]	All tofacitinib (N = 3879)
ALT, IU/L						
>1 × ULN	8 (13.8) 10.33 (4.46-20.35)	14 (10.1) 3.14 (1.72-5.27)	22 (11.2) 4.21 (2.64-6.37)	204 (20.3) 10.06 (8.73-11.54)	654 (22.8) 6.83 (6.32-7.38)	858 (22.1) 7.40 (6.91-7.91)
>2 × ULN	2 (3.4) 2.22 (0.27-8.01)	7 (5.0) 1.53 (0.62-3.15)	9 (4.6) 1.64 (0.75-3.12)	40 (4.0) 1.65 (1.18-2.24)	106 (3.7) 0.93 (0.76-1.12)	146 (3.8) 1.05 (0.89-1.24)
>3 × ULN	1 (1.7) 1.10 (0.03-6.13)	2 (1.4) 0.42 (0.05-1.53)	3 (1.5) 0.53 (0.11-1.55)	27 (2.7) 1.08 (0.71-1.58)	69 (2.4) 0.59 (0.46-0.75)	96 (2.5) 0.68 (0.55-0.83)
AST, IU/L						
>1 × ULN	8 (13.8) 10.05 (4.34-19.79)	16 (11.5) 3.75 (2.14-6.09)	24 (12.2) 4.74 (3.04-7.05)	198 (19.7) 9.59 (8.30-11.02)	655 (22.8) 6.73 (6.22-7.26)	853 (22.0) 7.23 (6.75-7.73)
>2 × ULN	1 (1.7) 1.10 (0.03-6.13)	4 (2.9) 0.86 (0.23-2.20)	5 (2.5) 0.90 (0.29-2.10)	25 (2.5) 1.00 (0.65-1.48)	58 (2.0) 0.50 (0.38-0.64)	83 (2.1) 0.59 (0.47-0.73)
>3 × ULN	0 (0.0) 0.00 (0.00-4.06)	2 (1.4) 0.42 (0.05-1.53)	2 (1.0) 0.35 (0.04-1.28)	13 (1.3) 0.52 (0.28-0.88)	28 (1.0) 0.24 (0.16-0.35)	41 (1.1) 0.29 (0.21-0.39)
Hb, g/dL						
≥1-≤2 decrease	7 (12.1) 8.15 (3.28-16.79)	24 (17.3) 5.73 (3.67-8.52)	31 (15.7) 6.14 (4.17-8.71)	138 (13.7) 6.15 (5.17-7.27)	583 (20.3) 5.83 (5.37-6.33)	721 (18.6) 5.89 (5.47-6.34)
>2-<3 decrease; or Hb >7-<8	2 (3.4) 2.21 (0.27-7.98)	11 (7.9) 2.44 (1.22-4.36)	13 (6.6) 2.40 (1.28-4.10)	26 (2.6) 1.05 (0.69-1.54)	139 (4.8) 1.20 (1.01-1.42)	165 (4.3) 1.18 (1.01-1.37)
≥3 decrease; or Hb ≤7	0 (0.0) 0.00 (0.00-4.06)	0 (0.0) 0.00 (0.00-0.78)	0 (0.0) 0.00 (0.00-0.65)	6 (0.6) 0.24 (0.09-0.52)	54 (1.9) 0.46 (0.35-0.60)	60 (1.5) 0.42 (0.32-0.54)
Serum creatinine, ≥50% increase from baseline, mg/dL	6 (10.3) 17.18 (2.63-15.63)	0 (0.0) NA	6 (3.0) 1.08 (0.40-2.34)	53 (5.3) 2.20 (1.65-2.87)	166 (5.8) 1.46 (1.25-1.70)	219 (5.6) 1.59 (1.38-1.81)
Lymphocyte count, (×1000/mm^3) [b]						
≥1.5-<2	10 (17.2) 13.63 (6.54-25.07)	39 (28.1) 9.78 (6.95-13.37)	49 (24.9) 10.38 (7.68-13.72)	197 (19.6) 8.65 (7.48-9.94)	525 (18.3) 4.91 (4.50-5.35)	722 (18.6) 5.57 (5.17-5.99)
≥0.5-<1.5	20 (34.5) 31.23 (19.07-48.23)	81 (58.3) 32.64 (25.92-40.57)	101 (51.3) 32.35 (26.35-39.31)	595 (59.2) 57.97 (53.40-62.82)	1993 (69.3) 39.32 (37.61-41.08)	2588 (66.7) 42.46 (40.84-44.13)
<0.5	0 (0.0) 0.00 (0.00-4.06)	0 (0.0) 0.00 (0.00-0.78)	0 (0.0) 0.00 (0.00-0.65)	9 (0.9) 0.36 (0.16-0.68)	45 (1.6) 0.38 (0.28-0.51)	54 (1.4) 0.38 (0.29-0.50)

(Continues)

TABLE 3 (Continued)

n (%); IR (95% CI)	India			Rest of the world		
	Average tofacitinib 5 mg b.i.d. (N = 58) [a]	Average tofacitinib 10 mg b.i.d. (N = 139) [a]	All tofacitinib (N = 197)	Average tofacitinib 5 mg b.i.d. (N = 1005) [a]	Average tofacitinib 10 mg b.i.d. (N = 2874) [a]	All tofacitinib (N = 3879)
Neutrophil count, ×1000/mm^3 [b]						
≥1.5-<2	2 (3.4) 2.25 (0.27-8.12)	4 (2.9) 0.88 (0.24-2.25)	6 (3.0) 1.10 (0.40-2.40)	71 (7.1) 3.03 (2.37-3.83)	178 (6.2) 1.58 (1.36-1.83)	249 (6.4) 1.83 (1.61-2.07)
≥0.5-<1.5	0 (0.0) 0.00 (0.00-4.06)	1 (0.7) 0.21 (0.01-1.19)	1 (0.5) 0.18 (0.00-1.00)	25 (2.5) 1.02 (0.66-1.50)	61 (2.1) 0.53 (0.40-0.68)	86 (2.2) 0.61 (0.49-0.76)
<0.5	0 (0.0) 0.00 (0.00-4.06)	0 (0.0) 0.00 (0.00-0.78)	0 (0.0) 0.00 (0.00-0.65)	0 (0.0) 0.00 (0.00-0.15)	0 (0.0) 0.00 (0.00-0.03)	0 (0.0) 0.0 (0.00-0.03)

Note: Confirmed values are based on two sequential measurements; N are patient numbers for both populations in the safety analysis set; the numbers of patients assessed for each endpoint may be lower than N; IRs are patients with events per 100 patient-years; for the Indian population, safety data were pooled from ORAL Scan, ORAL Solo, ORAL Start, and LTE study ORAL Sequel; ROW safety data were pooled from ORAL Step, ORAL Scan, ORAL Solo, ORAL Sync, ORAL Start, ORAL Standard, ORAL Sequel, and A3921041.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; b.i.d., twice daily; CI, confidence interval; Hb, hemoglobin; IR, incidence rate; IU/L, international units per liter; LTE, long-term extension; NA, not available; ROW, rest of the world; TDD, total daily dose; ULN, upper limit of normal.

[a]The average TDD of tofacitinib for each patient was calculated as the sum of all doses received divided by the number of days of treatment over the entire study duration for each patient; average tofacitinib doses of 5 mg b.i.d. and 10 mg b.i.d. were defined as TDD <15 mg BID and TDD ≥15 mg b.i.d., respectively.

[b]Abnormality is defined as a count of <2×1000/mm^3.

there is an increased short-term risk of hospitalization for VTEs in patients initiating bDMARDs, compared with MTX,[32] although other studies have found no association between bDMARD use and risk of VTE[33]; therefore, the evidence for bDMARD use as a risk factor for VTE has not been confirmed.

Previously identified risk factors for ILD in patients with RA include older age, male gender, smoking status, disease activity, and high levels of serum rheumatoid factor (RF+) and antibodies against cyclic citrullinated peptide (anti-CCP+).[34,35] Also, in a recent post hoc analysis of data from the global tofacitinib clinical development program, ILD events were found to be associated with Asian ethnicity, smoking/history of smoking, and prior treatment with MTX, non-MTX csDMARDs, or TNFi.[36] In this analysis, rates of ILD were similar in Indian and ROW patients, despite higher rates of Asian ethnicity, overall RF+, and anti-CCP+ and prior non-MTX csDMARD use in the Indian population. This may be attributed to the fact that Indian patients were younger, and less likely to have smoked or have received prior treatment with MTX or TNFi, vs the ROW population.

IRs for laboratory abnormalities were generally similar in Indian and ROW patients, except for increased ALT >1 × ULN and lymphocyte counts ≥1.5-<2 × 1000/mm^3 and ≥0.5-<1.5 × 1000/mm^3, which did not translate into a difference in infection risk. Of note, no Indian patients receiving tofacitinib exhibited a lymphocyte count <0.5 × 1000/mm^3, which has previously been associated with increased risk of SIEs and an indication that the drug should be discontinued.[37]

These results are consistent with a prior post hoc analysis of tofacitinib efficacy and safety in 8 Asia-Pacific countries, which also found improvements in ACR20 response rates and change from baseline in HAQ-DI with tofacitinib, vs placebo, in Asia-Pacific and ROW populations at month 3.[15] The safety of tofacitinib was generally similar in both populations, but consistent with our findings, Asia-Pacific patients had higher rates of TB (IR = 0.6, 95% CI 0.4-0.9), compared with the global population (IR = 0.2, 95% CI 0.1-0.2). However, unlike the present analysis, this previous analysis found that, compared with the global population, Asia-Pacific patients had lower mortality rates (IR = 0.1, 95% CI 0.1-0.3 vs IR = 0.5, 95% CI 0.4-0.6 for the global population), and higher rates of discontinuations due to AEs (IR = 9.1, 95% CI 8.3-10.1 vs IR = 7.2, 95% CI 6.9-7.6 for the global population), SIEs (IR = 3.7, 95% CI 3.2-4.3 vs IR = 2.6, 95% CI 2.4-2.9 for the global population), and HZ (serious and non-serious; IR = 5.9, 95% CI 5.2-6.7 vs IR = 3.8 95% CI 3.5-4.1 for the global population), primarily driven by Japanese and Korean patients.

Previously, TB incidence following treatment with tofacitinib was evaluated in patients from countries at low, medium, and high risk of TB (IR = 0.02, 95% CI 0.003-0.15; IR = 0.08, 95% CI 0.03-0.21; and IR = 0.75, 95% CI 0.49-1.15, respectively).[38] The high-risk group included 1326 patients from 12 countries, including 194 patients from India. It was suggested that patients with latent TB infections could be treated with isoniazid during tofacitinib therapy. In the current analysis, Indian patients with untreated/inadequately treated latent TB infections received isoniazid for ≥1 month prior to enrollment, and no Indian patients developed TB during the analysis. Some patients from countries with a high risk of TB, but without latent TB at baseline, were subsequently positive in QuantiFERON-GOLD®™ testing post-baseline. However, none had active TB in follow-up chest radiograms. This highlights the importance of continuous monitoring of TB status during tofacitinib treatment, which is in line with annual testing for latent TB infection, as recommended in various guidelines for patients with a high risk of TB, especially those without latent TB prior to bDMARD treatment.[39-42]

Tuberculosis incidence with tofacitinib in Indian patients in this analysis was in line with that previously observed in country-specific data for patients with RA from countries with high TB incidence (Taiwan, Korea) receiving bDMARDs (IR = 0.00-2.56 per 100 patient-years).[43-46] TB incidence with tofacitinib in ROW patients was also consistent with that in global clinical trials of tofacitinib over 9.5 years (IR = 0.2, 95% CI 0.1-0.2).[10]

In India, advanced treatments for RA have not been used routinely, as drug costs are generally borne by the patient, which can be a challenge for those with a relatively low income.[47,48] Consequently, assessment of advanced therapies in Indian patients has been limited. One study evaluated the effects of etanercept or infliximab in patients with an inadequate response to csDMARDs, and the effects of rituximab, abatacept, or tocilizumab in Indian patients who had previously failed TNFi. Significant reductions from baseline in disease activity (as measured by DAS28-4[ESR] scores) were observed with bDMARDs in both cohorts; however, rates of DAS28-4(ESR)-defined remission and low disease activity could not be determined, due to the small study population.[47]

This analysis had a number of limitations and data should therefore be interpreted with caution. This was a post hoc analysis, which used data pooled from studies with different study designs and methodologies, and different study populations. There were differences in the studies included for the Indian and ROW populations, as not all Phase 3/LTE studies included patients from India. In the safety analysis, more Indian patients were from the ORAL Start study and were MTX-naïve, compared with ROW patients, and all Indian patients were bDMARD-naïve, whereas the ROW population included TNFi-inadequate responders from ORAL Step. These differences may partially explain the comparatively lower proportion of Indian patients with AEs and SAEs, compared with the ROW population, as there is evidence that the risk of some AEs is increased by the use of RA treatments,[49-52] and the risk of some AEs has also been shown to differ in csDMARD-IR vs bDMARD-IR patients receiving tofacitinib.[53] However, conversely, rates of AESI were similar in both populations, despite Indian patients being younger, having no prior bDMARD experience, shorter disease duration, and higher baseline disease activity, compared with the ROW population. It is also possible that there were differences in undertreatment or delayed treatment between the two populations, which may confound interpretation of these results. It is also important to note that the sample size and patient exposure in the Indian population were smaller than in the ROW population, and 95% CIs were wide, limiting our ability to discern differences (numerical or otherwise) between populations. Also, all analyses were descriptive in nature, only general trends are described, and no formal statistical analyses were carried out.

In conclusion, the efficacy of tofacitinib in Indian patients with RA was similar to that in ROW patients. These results help provide insight into the benefit: risk profile of tofacitinib in Indian patients with RA.

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CONFLICT OF INTEREST

A. Chopra, V. Shobha, S. Chandrashekara, R. Sharma, U.R. Rao, S. Wagh, and J.K. Kadel were paid investigators for Pfizer Inc; A.V. Thorat, C. Adhav, P. Santos Estrella, W. Yu, K. Kwok, and A. Wouters are employees and stockholders of Pfizer Inc; S.C.M. Veeravalli and S. Pandya have declared no conflicts.

AUTHOR CONTRIBUTIONS

A. Chopra, A.V. Thorat, P. Santos Estrella, K. Kwok, and A. Wouters were involved in conception and design of the analysis; K. Kwok, A. Wouters, and A.V. Thorat were involved in data analysis; all authors were involved in data interpretation, and in development and revision of the manuscript and approved the final version.

DATA AVAILABILITY STATEMENT

Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices: (1) for indications that have been approved in the USA and/or EU; or (2) in programs that have been terminated (ie development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data-access agreement with Pfizer.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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ORIGINAL ARTICLE

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Elevating the role of carers in rheumatoid arthritis management in the Asia-Pacific region

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Abstract

Aim: Carers may offer valuable insight into the true health status of patients with rheumatoid arthritis (RA). This multinational, multi-stakeholder, exploratory study in Australia, China and Japan aimed to enrich our understanding of the role and potential impact of carers on RA management.

Method: This study used a 2-phase sequential mixed methods approach involving 3 key stakeholder groups: rheumatologists, RA patients and carers. The first phase involved an in-depth qualitative exploratory survey (n = 30), which informed the development of the subsequent quantitative validation survey (n = 908). In both phases, patients and carers provided self-assessments of disease and support parameters.

Results: In the qualitative phase, patients usually understated the amount of physical support required, compared to carers. Rheumatologists underestimated the amount of physical and emotional care required, compared to carers and patients; however, in the quantitative phase, rheumatologists overestimated the level of support

provided by carers. Levels of support provided by carers increased as disease severity increased. Active participation of carers in clinical consultations and treatment decision-making was deemed important by 55% of all patients and 82% of all carers. All stakeholders believed carers' insights into the physical and emotional conditions of patients were useful and should be considered in clinical decision-making. Over 95% of rheumatologists reported soliciting input from the carer.

Conclusion: Carers provide valuable input that can give clinicians greater insight into the patients' physical and emotional states, and treatment adherence. Development of standardized carer-reported outcomes that correlate with patient-reported outcomes and clinical parameters will ensure clinical meaningfulness and external validity.

KEYWORDS

carer reported, holistic, patient centred, qualitative

1 | INTRODUCTION

Effective management of rheumatoid arthritis (RA) requires the coordinated efforts of a multidisciplinary team with the patient as its central focus.[1] Patient-reported outcomes (PROs) are at the core of assessing RA treatment response.[2] However, PROs have several limitations. To obtain accurate data, patients must be willing to provide information, and this may be influenced by factors such as the length of the questionnaire, patients' perception of usefulness, and anxiety about use of the information provided to limit services.[3-5] Additionally, clinicians' perceptions of the usefulness of PROs may also impact implementation in clinical practice.[3,5]

For patients with RA, carers may be key to addressing some of these limitations. Given their time investment, carers may offer important insight into the patient's true health status. As first-hand observers, carers may provide rheumatologists with a more complete picture of the patient's physical and emotional status. They may also help patients understand and adhere to their treatments, keep track of their appointments, follow nutritional guidelines and manage other aspects of life.[6,7]

The role of carers is complex, and involves providing physical, emotional and financial support.[6,7] However, studies evaluating their role in RA are scarce.[8,9] One study in patients with RA found that patients were inclined to significantly underscore their level of pain, compared with their carers.[8] This could affect the rheumatologist's decision to adjust the management strategy and undermine efforts to achieve optimal results, unless further information is obtained from the carer.[8] Another study highlighted carers may help to illuminate factors that patients may not consider themselves.[9] For instance, patients were more likely to consider intensive management acceptable if their previous treatments had failed. However, carers took into consideration the patient's past experiences of side effects, treatment duration, and response to current treatment (both emotionally and physically).[9] This implies carers may provide rheumatologists with a more holistic view of the patient's situation.

Current management paradigms for RA tend to neglect the views of carers. This regional, multinational, multi-stakeholder, exploratory study was conducted to enrich our understanding of the roles and potential impact of carers on RA management in the Asia-Pacific region.

2 | METHODS

2.1 | Study design

We used a sequential mixed methods approach to understand the roles of carers and the potential impact of carer involvement. The initial qualitative phase used semi-structured interviews to understand the role of carers in RA management. The key themes highlighted in this phase informed the development of the quantitative validation survey.[10] This was a multinational, uni-region study conducted in Australia, China and Japan.

2.2 | Qualitative methods

The phase I survey was conducted between 14 May 2018 and 15 June 2018. It adopted a qualitative, exploratory approach using semi-structured in-depth face-to-face interviews with carers, patients and rheumatologists. Recruitment across China, Japan and Australia consisted of triads of treating rheumatologists, patients living with RA, and their carers. Rheumatologist eligibility criteria included: aged 30-65 years; currently registered and practicing; registered for ≥2 years; and currently treating RA patients of mild, moderate and severe conditions. Patients were eligible to participate if they were: aged >18 years; and self-assessed as mild, moderate or severe RA during recruitment. RA severity for research recruitment categorization was based on the patients' self-reported definition. Carer eligibility criteria included: aged >18 years; and had been a carer for ≥6 months (to include influencing treatment and care decision-making or providing direct assistance for ≥4 hours per day). Interview topics included: (a) RA patient journey and experiences, highs and lows; (b) role and importance of carers; (c) met and unmet needs; (d) treatment decisions; (e) adherence; (f) improving patient

outcomes; (g) supporting carers; and (h) improving care of the patient. Thematic analysis was used to extract recurring themes.

2.3 | Stakeholder insight

On 19 July 2018, a panel of experts, the "CollAboRatE Coalition", met to provide feedback on the qualitative exploratory study findings, provide input on the quantitative validation study and advise on the approach to share the research findings and address the insights generated. CollAboRatE is a regional initiative led by a multi-stakeholder coalition of rheumatologists, patient and carer organizations across Asia-Pacific which aims to understand and elevate the role of carers in the clinical management of RA, empower carers to become involved in and contribute to treatment decisions, and build the capacity and influence of rheumatology carer and patient organizations.

2.4 | Quantitative methods

The phase II survey was conducted between 7 August 2018 and 21 August 2018. This online validation survey consisted of 3 separate questionnaires designed specifically for carers, patients and rheumatologists. Questionnaires were reverse-translated from English to Japanese and simplified Chinese (and responses to English) by professional NAATI (National Accreditation Authority for Translators and Interpreters) translators. Questionnaires were deployed via an online scripted survey approach. Respondents were pre-screened via an online screener or telephone screening. Rheumatologist eligibility criteria included self-identified as currently registered for ≥2 years and treating patients with RA. Patient eligibility criteria included >18 years of age and self-identified as being diagnosed with RA. Patients were further classified based on self-descriptions of severity and disease activity. Definitions of severity: mild defined as "I live an active and independent life most of the time"; moderate defined as "I sometimes require physical support"; and severe defined as "I require physical support most of the time". Definitions of disease activity: stable defined as "My symptoms have been well managed for the last 3 months"; and progressive defined as "My symptoms have been getting worse over the last 3 months". Carer eligibility criteria included ≥18 years of age and self-identified as being a carer of a person with RA. The main carer was defined as the person who provides the most physical support to someone, in managing their RA condition. Recruitment was not conducted in triads or pairs. Carers were asked to describe the current RA condition of the person they are caring for (mild, moderate or severe). The final data set was tabulated and descriptively analyzed. Responses to the same questions from patients, carers and rheumatologists were compared and contrasted. A further descriptive analysis was conducted to better understand the role of a carer in the moderate-to-severe patient subgroup.

2.5 | Ethics approval and consent to participate

No ethics approval was required as this was a quality assurance activity, which is in line with the standards and guidelines for ethics review in all 3 countries[11-13] as well as with the practice of similar studies published recently in the area of carers in rheumatology.[14-17] Written informed consent was obtained from all participants in both the qualitative and quantitative studies.

3 | RESULTS

3.1 | Qualitative

In total, 30 stakeholders from Australia (n = 12), China (n = 12), and Japan (n = 6), participated in the qualitative exploratory survey, comprising 10 rheumatologists, 10 patients with RA and 10 carers. Each interview was conducted by a different interviewer (30 interviewers). Recruitment consisted of 3 triads (9 participants) composed of treating rheumatologist, patient and carer, and 5 pairs (10 participants) composed of patient and carer. All other participants (7 rheumatologists, 2 patients and 2 carers) were not part of a triad or pair.

3.1.1 | Role of the carer

Carers of patients with RA provided physical care, helped with medication and emotional support. Patients with severe RA required physical care "daily" while some patients with moderate RA required physical care "very often" or "most of the time". Carers reported spending ≥10 hours per week with severe patients and ≥3 hours per week with moderate patients, providing physical care, help with medication and emotional support.

Patients tended to understate the amount of physical support required, compared to carer reports. In contrast, while rheumatologists acknowledged RA patients needed some level of emotional and physical care, they underestimated how much physical and emotional care was required, compared to carers and patients. The role of carers is described further in Table S1, with patient, carer and rheumatologist perspectives on the role of the carer expanded in Table S2.

> "She is fiercely independent and if I say, "I will help you", "no, no, it is fine, I can do it", even though sometimes she is struggling."
>
> (Carer of sever patient, Australia)

> "The carer is more for emotional support for mild and moderate patients… [O]nly the very severe type patients will require daily carer assistance…"
>
> (Rheumatologist, China)

3.1.2 | Carer involvement in consultations

During initial and ongoing management consultations, rheumatologists considered carers were more likely to be present for severe patients followed by moderate and then mild patients. The behavior and attitude of rheumatologists toward carers was highly variable. Many carers stated strongly that their input, if/when taken into account by the rheumatologist during consultations, significantly improves treatment decision-making and patient outcomes. However, some carers were frustrated as their role in caring for the patient and possible contributions in treatment decision-making were not adequately recognized by rheumatologists.

> "They [carers] enhance communication with doctors, help to supervise the patient and implement my medical advice."
>
> (Rheumatologist, China)

> "I basically talk only to the patient unless they have mostly no judgment ability, which is rare in cases of RA."
>
> (Rheumatologist, Japan)

> "Usually resented. They [doctors] like to tell you what the answer is but they don't have to live with it…we have to put with whatever their solution they choose, we have to cope with that."
>
> (Carer of severe patient, Australia)

3.1.3 | Carer support

Typically, one main primary carer provided most of the care for each RA patient. All carers of severe patients and some carers of moderate patients admitted to experiencing repeated bouts of depression and physical exhaustion themselves.

> "I'm very stressed. Taking care of a patient."
>
> (Carer of moderate patient, China)

> "I get very tired. I have just gone through a period of a few weeks where I didn't want to get out of bed in the morning."
>
> (Carer of severe patient, Australia)

TABLE 1 Quantitative study demographics

	Australia	China	Japan
Rheumatologists (n)	49	42	40
Gender (% female)	35%	45%	10%
Mean y in practice (SD)	11.3 (5.1)	12.5 (3.3)	17.3 (6.6)
Patients (n)	112	110	160
Gender (% female)	63%	56%	55%
Mean age in y (SD)	54.6 (15.3)	43.6 (11.5)	55.9 (12.6)
Severity			
Mild	44%	45%	83%
Moderate	41%	52%	15%
Severe	15%	3%	2%
Disease activity			
Stable	76%	84%	96%
Progressive	24%	16%	4%
Mean duration since RA diagnosis in y (SD)	8.5 (6.4)	3.9 (3.5)	11.3 (5.9)
Status of carer[a]			
Paid[b]	21%	71%	8%
Unpaid	64%	19%	88%
Mix of paid and unpaid	14%	10%	4%
Carers (n)	122	122	151
Gender (% female)	48%	65%	29%
Mean age in y	45.5 (14.2)	35.8 (9.6)	54.7 (13.4)
Severity (of RA patient cared for)			
Mild	23%	25%	56%
Moderate	57%	59%	33%
Severe	20%	16%	11%
Mean duration caring for patient with RA in y (SD)	6.4 (5.5)	5.2 (3.5)	7.5 (5.6)
Status of carer[a]			
Paid[b]	32%	56%	11%
Unpaid	58%	40%	85%
Mix of paid and unpaid	10%	4%	5%

Abbreviation: RA, rheumatoid arthritis

[a]Patients and carers were not recruited in dyads.

[b]Based on response to the question of whether the carer was paid to provide care for the patient with RA.

3.2 | Quantitative

3.2.1 | Stakeholder demographics

A total of 131 rheumatologists, 382 patients and 395 carers participated in the study. Table 1 displays the baseline characteristics of respondents from each country. Rheumatologists in the Japanese sample were on average more experienced than those in the Chinese and Australian sample (17.3 mean years in practice vs 12.5 and 11.3 years, respectively). The proportion of female rheumatologists was below 50% in all 3 countries, and the lowest in Japan (45%, 35% and 10% female in China, Australia and Japan, respectively).

The duration since RA diagnosis was longest in Japan and shortest in China (11.3 years vs 3.9 years, respectively). A majority of

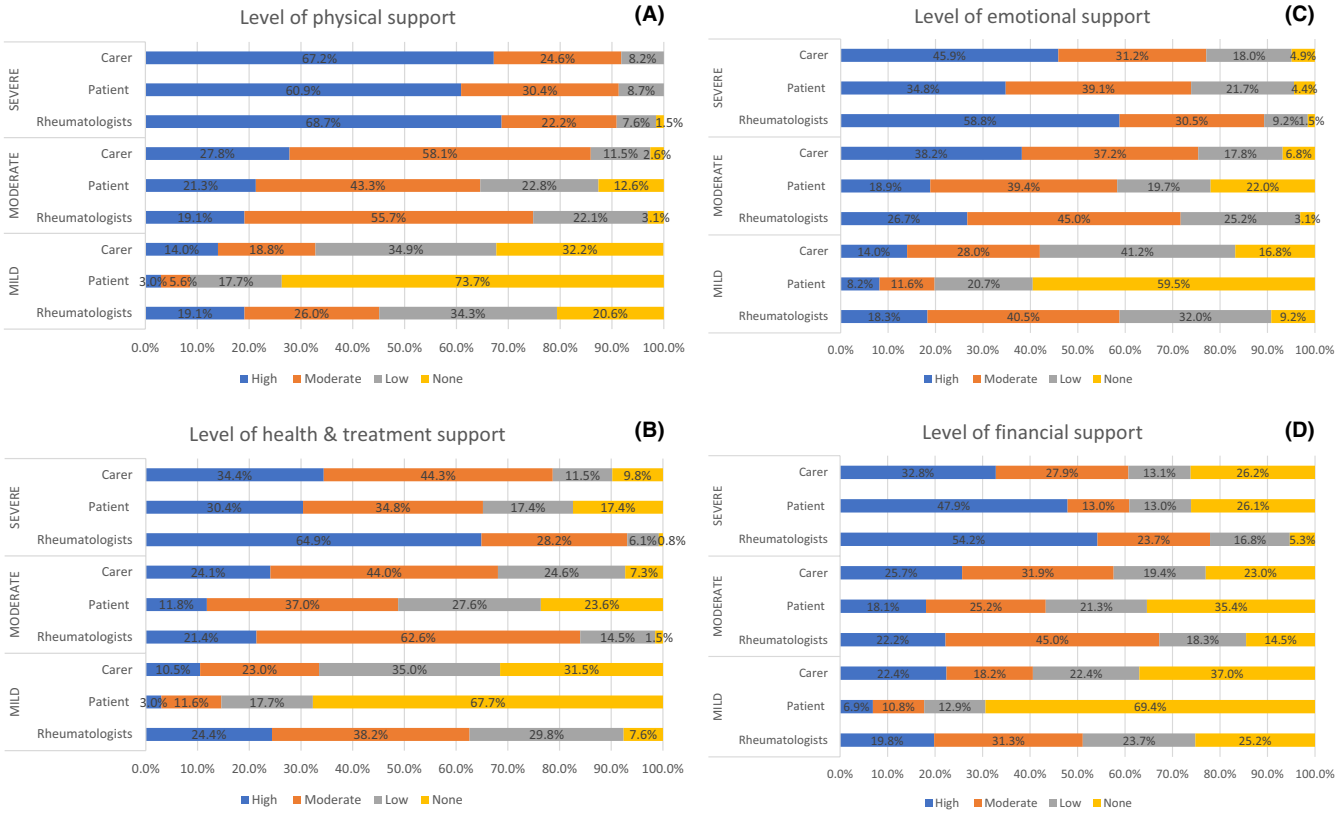


FIGURE 1 Estimates of level of support provided by the carer, received by patient and estimated by rheumatologist across all assessed domains. Patients were classified as mild, moderate or severe based on self-assessments. A, Level of physical support (such as help with personal care like washing hair, mobility such as assistance with moving around the house, meal preparation, transportation, household cleaning and cooking, shopping and buying groceries, etc). B, Level of health and treatment support (such as researching or discussing treatment options, arranging or giving medications, planning for medical appointments, reminding, encouraging and supporting the rheumatoid arthritis (RA) patient to take a medication or follow a prescribed treatment). C, Level of emotional support (such as reassuring and calming the RA patient if they feel distressed, providing support through events the RA patient is worried about, motivating and assisting the RA patient to reframe thoughts in a positive manner, etc). D, Level of financial support (such as providing household income, paying for living expenses, paying for medical expenses, etc)

the patients self-reported their RA severity as mild or moderate in Australia and China. However, in Japan, 83% self-reported their RA severity as mild and only 15% as moderate. Australia had the largest proportion of patients self-reporting severe disease (15% vs 3% in China and 2% in Japan). The majority of the patients in Japan had stable disease, followed by China and Australia (96%, 84% and 76%, respectively).

Carers in China were predominantly female whereas those in Japan were predominantly male (65% vs 29% female, respectively). Additionally, carers in China were on average younger than carers in Japan and Australia (35.8 years vs 54.7 and 45.5 years, respectively). A greater proportion of carers in China were paid, compared to carers in Japan and Australia (56% vs 11% and 32%, respectively).

A separate descriptive analysis of moderate-to-severe patients and their carers was conducted to better understand the role of the carer in this subgroup. Within this group (150 patients and 252 carers), 71% of patients self-reported their disease as stable and 29% as progressive. Among severe patients, 48% described their disease as progressive. In a country-specific analysis of moderate-to-severe patients, 93% of patients in Japan self-reported their disease as stable, compared with 72% and 60% in China and Australia, respectively.

3.2.2 | Role of the carer

Carers reported providing the following health and treatment support to the patients they cared for: reminders to take medication; monitoring medication intake; recognizing patient's physical and emotional state; recognizing when the patient is not being truthful when describing their condition to the doctor; recognizing when a change in medication or treatment is needed; understanding treatment options; interpreting advice from the rheumatologist; and suggesting alternative treatments based on own research that have not been provided by rheumatologist. The majority of carers (76%) provided reminders to take medication; this was highest in China (96%), followed by Australia (75%), and lowest in Japan (62%). Reminders to take medication were slightly higher in the moderate-to-severe

TABLE 2 Carer's influence on treatment decision-making

	Country			Rheumatoid arthritis severity		
	Australia	China	Japan	Mild	Moderate	Severe
Patient	N = 112	N = 110	N = 160	N = 232	N = 127	N = 23
Experienced anxiety at initial diagnosis	69%	88%	84%	78%	85%	83%
Believed education on all treatments at diagnosis would help to reduce anxiety	51%	87%	39%	47%	73%	57%
Educated on all treatment options:						
At initial diagnosis	55%	28%	31%	56%	54%	39%
For ongoing management	37%	17%	16%	69%	73%	78%
Agree carer participation in clinical consultations and treatment decision-making is important	58%	93%	27%	41%	78%	65%
Rheumatologist	n = 49	n = 42	n = 40	-	-	-
Agree education on all available treatments at diagnosis would help to lower anxiety	96%	95%	70%	-	-	-
Discuss all available treatment options:						
At initial diagnosis	96%	69%	85%	-	-	-
For ongoing management	92%	84%	80%	-	-	-
Agree carers play a role in treatment decision-making:						
For mild patients	88%	83%	72%	-	-	-
For moderate patients	100%	93%	75%	-	-	-
For severe patients	100%	95%	77%	-	-	-
Frequently solicited input from carer when they were present	98%	100%	95%	-	-	-
Carer	n = 122	n = 122	n = 151	n = 143	n = 191	n = 61
Agree carer participation in clinical consultations and treatment decision-making is important	81%	95%	52%	69%	89%	95%
Reported influencing treatment decisions for the patient they care for	61%	89%	58%	59%	72%	80%
Perceived carer input in treatment decisions to be important	81%	95%	52%	61%	83%	78%
Believed rheumatologists valued their input	80%	94%	79%	80%	85%	92%

subgroup (83%); highest in China (97%), followed by Australia (76%) and Japan (73%).

Overall, stakeholder estimates of level of physical, health and treatment, emotional and financial support provided by the carer tended to increase as disease severity increased. Carers consistently estimated the level and importance of the support they provide to be higher across physical, health and treatment, and emotional domains, compared to the level of support patients said they received (Figure 1). Estimates of time spent providing support was higher for carers compared with patients for every domain measured.

Rheumatologists consistently overestimated the level of support provided by the carer, compared with the estimates from carers and patients. However, estimates of level of physical support provided were high across all stakeholders. The support provided by carers was deemed "quite important" or "very important" by at least 1 in 2 rheumatologists. Rheumatologists considered health and treatment support to be the most important type of support provided by carers of moderate-to-severe patients. On the other hand, patients with moderate-to-severe disease and their carers considered physical support to be the most important. In terms of financial support for patients with severe RA, rheumatologists in Japan and China estimated higher required levels of financial support than those in Australia (60% in both China and Japan vs 45% in Australia). While patients with severe RA in Australia and Japan reflected the views of rheumatologists in those countries (35% and 67%, respectively), patients in China were even more reliant on their carers for financial support (100%) than estimated by rheumatologists in China.

3.2.3 | Carer influence on treatment decision-making

Active participation of carers in clinical consultations and treatment decision-making was considered important by most of the patients and carers (Table 2). Patients and carers in Australia and China

placed greater importance on active carer participation than those from Japan. Patients reported carers could potentially help them to discuss treatment options with their rheumatologist, understand the importance of taking medications as recommended, provide reassurance regarding the treatment, understand how to take their medications correctly and help the rheumatologist to better understand their condition.

The vast majority of patients reported experiencing anxiety at the time of their diagnosis. More than half of all patients believed education on all available treatments would have helped to reduce the anxiety of being diagnosed with RA; however, this belief was more common in China than in Australia and Japan.

The majority of the rheumatologists agreed education on all available treatment options at the point of diagnosis may help lower anxiety of being diagnosed with a chronic condition. However, 28% of rheumatologists from Japan were not sure if this would be helpful (compared to 2% in both China and Australia). In current practice, more than 80% of rheumatologists reported discussing all available treatments at initial RA diagnosis as well as for ongoing RA management. However, 37% of all patients said they were not educated on treatment options available at initial diagnosis, and 23% for ongoing RA management. In the moderate-to-severe subgroup, over half of the patients reported not being educated on all treatment options at initial diagnosis and a quarter for ongoing RA management.

More than half of all carers said they had influenced treatment decisions for the patient they care for (Table 3). On the other hand, almost half of the carers in Japan (48%) believed their input in treatment decision-making was not very important, compared with 19% in Australia and 5% in China. The majority of the carers believed the rheumatologists valued their input as a carer. In the moderate-to-severe subgroup, 76% of patients considered the carer's input in treatment decision-making to be important: 93% in China, 81% in Australia and 48% in Japan. The majority of carers of moderate-to-severe patients considered their input in treatment decision-making to be important: 98% in China, 84% in Australia and 57% in Japan. In addition, the majority of carers reported influencing treatment decisions for the moderate-to-severe patients they cared for: 91% in China, 69% in Japan and 62% in Australia. The highest levels of influence were reported by carers of patients with severe disease (80%). The majority of carers for this subgroup (87%) believed the rheumatologist valued their input as a carer.

From the rheumatologists' perspective, 98% reported soliciting input from the carer when they were present. According to rheumatologists in China, carer attendance increased as the disease severity increased. However, in Japan and Australia, higher attendance was reported for moderate than severe patients. The majority of the rheumatologists in Australia and China believed carers played a role in treatment decision-making for moderate and severe patients. However, almost a quarter of the rheumatologists in Japan considered carers had no influence in treatment decision-making for moderate and severe patients.

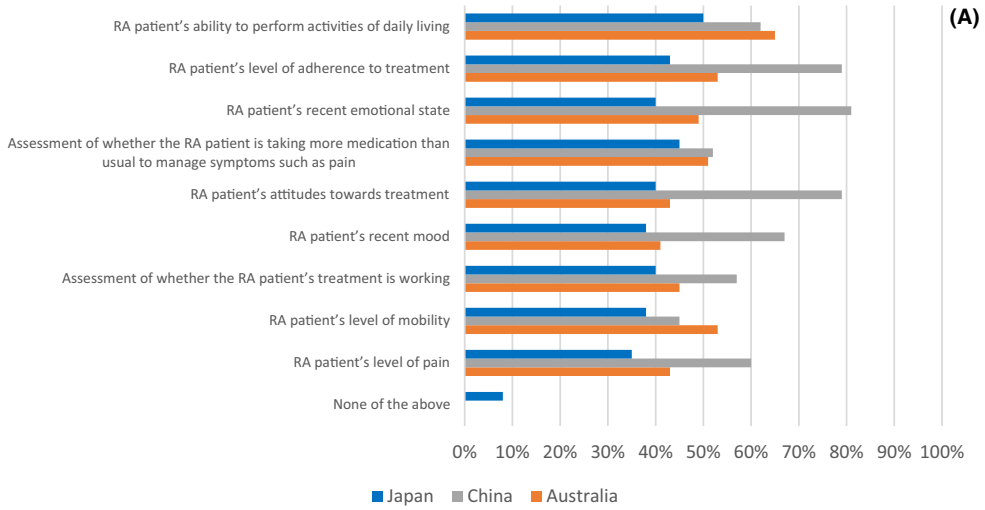
3.2.4 | Impact of carer observations

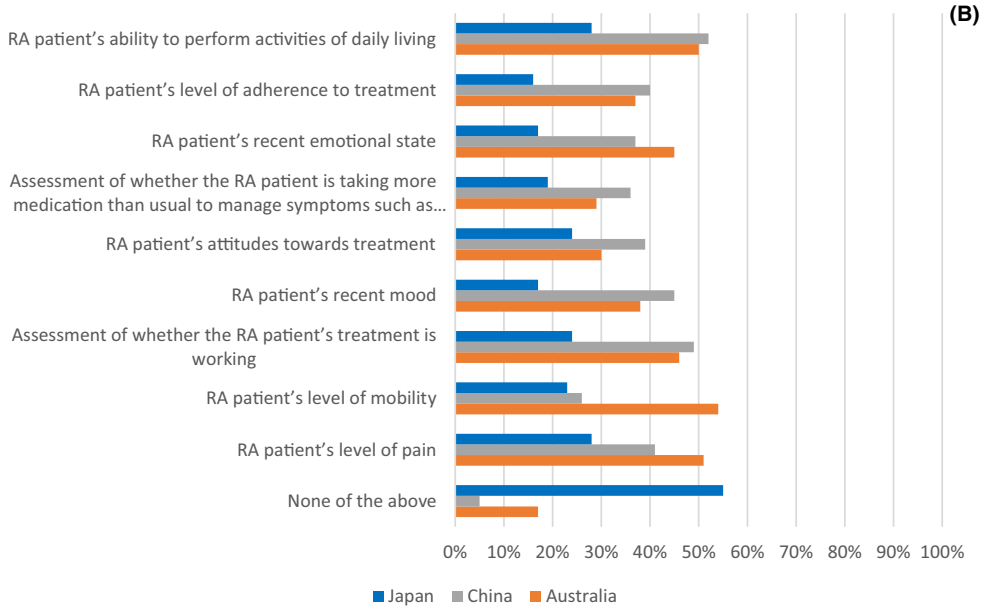
All stakeholders believed carer observations on the physical and emotional wellbeing of the patient could be valuable. Among the patients, 95% in China, 65% in Australia and 38% in Japan suggested these observations would be useful to their rheumatologists in managing their RA. Within the carer cohort, 99% of carers in China, 91% in Australia and 72% in Japan suggested these observations would be useful to the rheumatologist. Within the rheumatologist cohort, 100% of rheumatologists in Australia, 98% in China and 83% in Japan said these observations would be useful to them for managing the patient. In the moderate-to-severe subgroup, 94% of rheumatologists, 92% of carers and 78% of patients agreed carer observations of the patient's physical and emotional condition would be useful to the rheumatologist. However,

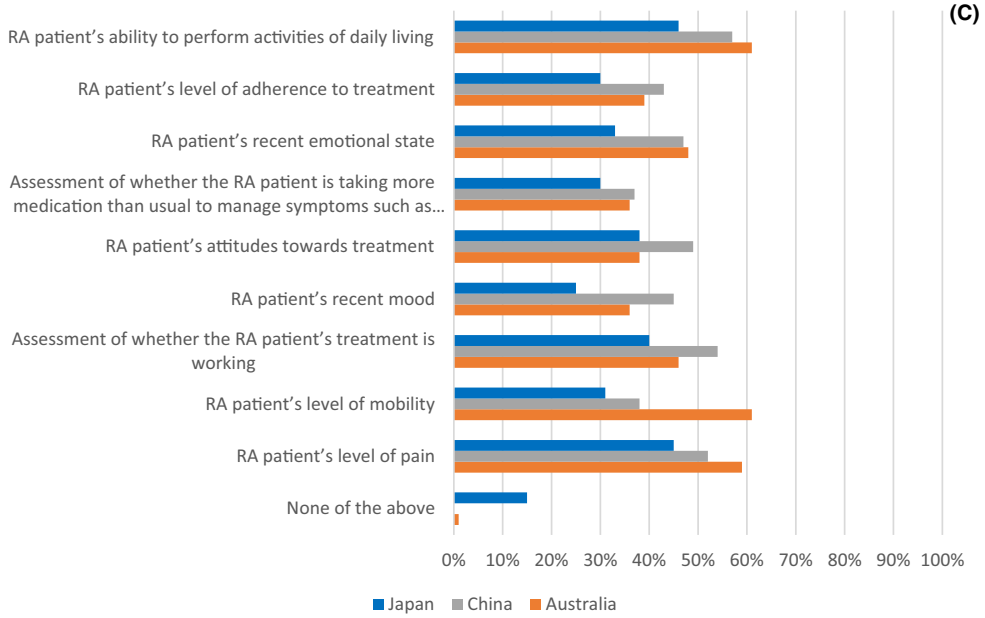
TABLE 3 Decisions influenced by carers

	Patient-reported influence			Carer-reported influence		
Treatment decision-making	Mild N = 232	Moderate N = 127	Severe N = 23	Mild N = 143	Moderate N = 191	Severe N = 61
Start a treatment regimen	26%	32%	35%	35%	31%	43%
Choose 1 treatment over another	29%	35%	26%	32%	38%	37%
Consider alternative treatment options	18%	30%	26%	29%	31%	39%
Follow the doctor's recommended treatment regimen	42%	56%	61%	38%	45%	55%
Stop following the doctor's recommended treatment regimen	10%	17%	26%	26%	28%	35%

FIGURE 2 Potentially useful carer observations for clinical management. A, Carer observations that rheumatologists believed would be most useful in the assessment and management of rheumatoid arthritis patients. B, Carer observations patients were comfortable for their carer to share with their rheumatologist while in the consultation room with them. C, Observations the carers were comfortable sharing with the rheumatologist about the patient they care for


(A)
RA patient's ability to perform activities of daily living
RA patient's level of adherence to treatment
RA patient's recent emotional state
Assessment of whether the RA patient is taking more medication than usual to manage symptoms such as pain
RA patient's attitudes towards treatment
RA patient's recent mood
Assessment of whether the RA patient's treatment is working
RA patient's level of mobility
RA patient's level of pain
None of the above
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Japan China Australia


(B)
RA patient's ability to perform activities of daily living
RA patient's level of adherence to treatment
RA patient's recent emotional state
Assessment of whether the RA patient is taking more medication than usual to manage symptoms such as...
RA patient's attitudes towards treatment
RA patient's recent mood
Assessment of whether the RA patient's treatment is working
RA patient's level of mobility
RA patient's level of pain
None of the above
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Japan China Australia


(C)
RA patient's ability to perform activities of daily living
RA patient's level of adherence to treatment
RA patient's recent emotional state
Assessment of whether the RA patient is taking more medication than usual to manage symptoms such as...
RA patient's attitudes towards treatment
RA patient's recent mood
Assessment of whether the RA patient's treatment is working
RA patient's level of mobility
RA patient's level of pain
None of the above
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Japan China Australia

41% of patients in Japan, 17% in Australia and 2% in China were unsure. From the rheumatologists' perspective, the top 3 most useful carer observations were the patient's ability to perform activities of daily living, patient's level of adherence to treatment and the patient's recent emotional state. Both patients' and carers' comfort levels for these carer observations to be shared with the rheumatologist were moderately high (Figure 2). However, 55% of patients in Japan were not comfortable with carers sharing any observations outlined in the study questionnaire. Overall, 44% of all patients who were uncomfortable with carers sharing any observations had mild disease, 6% had moderate and 17% had severe disease.

Carer observations may also bring a new perspective to the consultation room. The perception of disease severity differed between carers and patients. More carers described the patient they were caring for as moderate or severe, compared to patients' self-descriptions in each country.

3.2.5 | Support for carers

A quarter of all carers stated they did not receive enough support in their capacity as a carer while 18% of patients (34% unsure) and 16% of rheumatologists (21% unsure) believed carers did not receive enough support. The type of support carers considered they needed varied between countries (Figure 3). The majority of the carers preferred to receive support and information from the rheumatologist. The top places where carers sought information were the internet and the rheumatologist's practice.

4 | DISCUSSION

This sequential mixed methods study aimed to understand the potential impact of carer involvement on patients with RA and the role of carers in clinical management of RA.

Carers in the study reported providing a range of health and treatment support to the patients they cared for. However, carers consistently estimated the level and importance of their support to be higher, compared with the support patients reported receiving. This suggests patients may be underestimating the level of care they require or are receiving. It is possible that patient appreciation of carer support increases as disease severity progresses. This was reflected in the study findings as all stakeholder estimates of level of physical, health and treatment, emotional and financial support provided by the carer tended to increase as disease severity increased. It should be noted patients, carers and rheumatologists were not recruited in triads due to privacy issues. It is possible our sample included a greater proportion of carers of severe patients.

At least 1 in 2 rheumatologists estimated RA patients required moderate to high levels of support from their carer, regardless of level of disease severity (with the exception of physical support provided by carers of mild patients). For moderate-to-severe patients, stakeholders placed different levels of importance on the types of support provided by the carer. Rheumatologists considered health and treatment support to be the most important, whereas patients and carers deemed physical support as the most important.

Rheumatologists in Japan and China estimated higher required levels of financial support for patients with severe RA than those in Australia. Interestingly, patients with severe RA in Australia and Japan reflected the views of rheumatologists, while patients in China were even more reliant on their carers for financial support than estimated by rheumatologists. This may be a reflection of the expected financial burden in these countries. In Australia, the Pharmaceutical Benefits Scheme provides universal coverage of subsidized medicines for Australian residents with a fixed patient co-payment.[18] Japan also has coverage for all Japanese citizens via the National Health Insurance Scheme with patient co-payment ranging from 0% to 30% depending on the age and employment status of the patient. In contrast, China's Basic Health Insurance Scheme (BHIS) only provides basic drug coverage within a cost-containment setting.[18,19] However, reforms are currently being undertaken to reimburse more costly medicines with the aim of reducing out-of-pocket costs for patients in China.[20]

The majority of rheumatologists believed carers played an important role in RA management and reported soliciting information from the carer if they were present. The highest perceived values for carer input across all 3 stakeholder groups were seen in China, followed by Australia and then Japan. Patients reported carers could potentially help them to discuss treatment options with their rheumatologist, understand the importance of taking medications as recommended, provide reassurance regarding the treatment, understand how to take their medications correctly and help the rheumatologist to better understand their condition. These findings were reflected in the moderate-to-severe subgroup. The high value of carer input in China may be due to Chinese culture recognizing the high involvement of carers (ie accepting caregiving as part of life), which may then flow on into clinical practice.[21,22] In Australia, a majority of rheumatologists and carers agreed carer observations contributed to RA management; however, only 63% of patients held this view. This may be due to Australian culture and clinical practice placing emphasis on independence and ownership of the disease.[23,24] In contrast, almost a quarter of rheumatologists in Japan believed carers did not influence treatment decision-making for moderate and severe patients. Patients in Japan were also less likely to believe carer observations could contribute to their RA management than in China and Australia. A majority of the patients in the Japanese sample were between the ages of 18 and 50, which may have contributed to this. Younger patients are more likely than older patients to express their views and take an active part in treatment decision-making.[25] Furthermore, a larger proportion of the patients in the Japanese sample had mild and stable disease, compared to Australia and China, suggesting they may have required less carer input. Japanese culture also emphasizes traditional clinician-centered practice where patients rely on the clinician to make decisions about their treatment.[26]

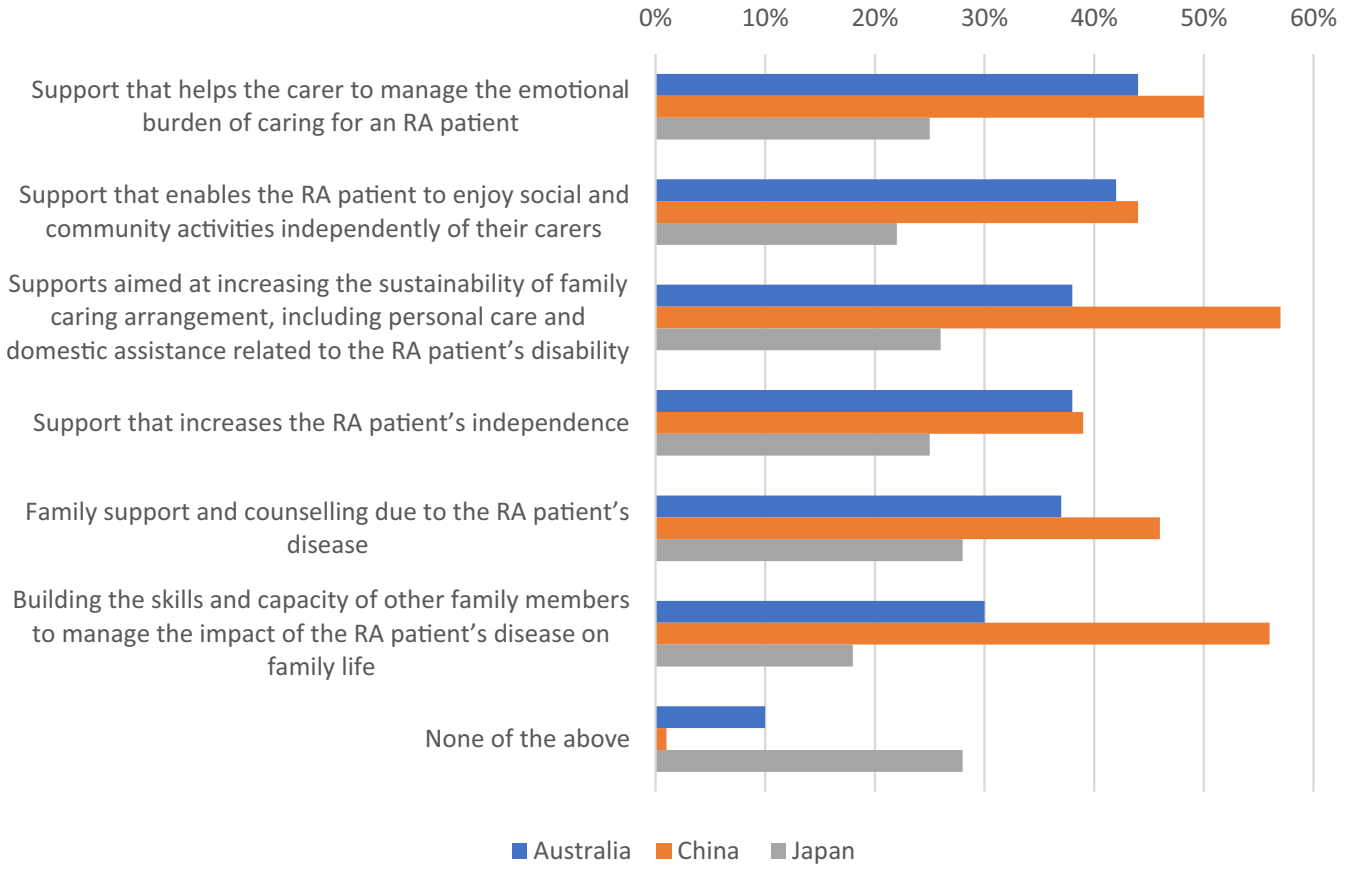


FIGURE 3 Types of support carers would like to receive in each country

Rheumatologists identified the following carer observations as useful: patient's ability to perform activities of daily living, patient's level of adherence to treatment and patient's recent emotional state. Both patients' and carers' comfort levels for these carer observations to be shared with the rheumatologist were moderately high. Patients from Australia were most comfortable with carers sharing observations relating to level of mobility, pain, and ability to perform activities of daily living, and least comfortable with observations of medication frequency and attitudes toward treatment. In China, patients were most comfortable with carers sharing observations of ability to perform activities of daily living, assessment of whether the treatment is working and recent mood, and least comfortable with observations of level of mobility. Patients from Japan were generally less comfortable with carers sharing observations than Australia and China, with 55% of patients not comfortable with any observations being shared. However, overall analysis showed 44% of all patients who were uncomfortable with carers sharing any observations had mild disease. Since 83% of the patients in the Japanese sample had mild disease, it may have influenced the finding. The large variation in patient and carer comfort levels for sharing observations seen in this study suggests a need to consider cultural sensitivities and values when gathering carer-reported outcomes.

Carers may also bring a new perspective to the consultation. In all 3 countries, more carers described the patient they were caring for as moderate or severe, compared to patient's self-description. However, patients and carers were not recruited in dyads. Despite this limitation, the data may suggest patients could be understating the severity of their symptoms. This is in line with a previous study, which found health status ratings given by carers were higher than those recorded by the patients themselves.[8] However, 47.5% of carers in the study reported mild-to-moderate burden of caregiving, suggesting carer perception of health status of the patient may be proportional to the level of caregiving burden.[8]

Involving a carer during consultations may also help to alleviate some of the anxiety experienced by patients. On average, 80% of patients experienced anxiety at the time of their diagnosis. The proportion of patients experiencing anxiety was higher in China compared with Australia and Japan. The increased anxiety expressed by patients in China may be a reflection of the expected financial burden. In addition, the Chinese sample had a lower mean age and shorter duration of disease than the Australian and Japanese samples, suggesting they were more likely to be employed or require employment, potentially contributing to their anxiety.

In addition, more patients in China believed anxiety would have been improved if they were educated on all available treatments

at the time of diagnosis, compared with Australia and Japan. This knowledge could provide patients and their carers with some reassurance on what to expect and how to plan for the future. A majority of rheumatologists agreed providing this knowledge at the point of diagnosis could help lower anxiety of being diagnosed. However, 28% of rheumatologists from Japan were not sure if this was the case (compared to 2% in both China and Australia). This may be a direct reflection of patient expectations as only 39% of patients in Japan believed knowledge of all treatments would help to lower anxiety at the time of diagnosis.

Interestingly, despite a majority of the rheumatologists reporting provision of this information, 37% of all patients said they were not educated on all the treatment options at initial diagnosis and 23% for ongoing RA management. In the moderate-to-severe patient group, the gap was even more pronounced with over half the patients reporting not being educated on all treatment options at initial diagnosis. This disconnect between patient-reported and rheumatologist-reported provision of education may reflect the patients' unmet expectation of education and/or their failure to understand the information provided. A number of factors could affect a patient's ability to absorb the information provided, including anxiety associated with being diagnosed, how the information is delivered, use of difficult medical terminology, and so on.[27]

Carers' influence on treatment was not limited to continuing treatments as prescribed. Patients and their carers reported carers could influence patients to stop prescribed treatments or consider other treatment options as well. As such it is important to involve carers in the treatment decision-making process and provide education so as to harness their influence to ensure the best outcomes.

All stakeholders agreed carers required some level of support. The impact of caring for an RA patient on both the mental and physical health of the carer has been previously documented.[28-31] The type of support carers sought varied greatly from country to country and may be a reflection of the different cultures and value systems, or different carer demographics.

This study has several limitations. Since this was an exploratory study with a small sample size, only a descriptive analysis of the data was conducted to better understand patterns in carer involvement in each country. Due to privacy issues, it was also not possible to recruit triads of patients, carers and rheumatologists. Therefore, it was not possible to draw conclusions when comparing different perspectives. The majority of the carers in the study described the patient they were caring for as moderate or severe, limiting the applicability of the results to mild patients. In addition, the lack of validated carer-reported outcomes in rheumatology or for the care of RA patients specifically was a limitation. Consequently, there was a degree of overlap in definitions of potential carer-reported outcomes evaluated in the survey (ie, "recent mood" vs "emotional state"), which may have confounded the results on the most useful carer-reported outcomes. In addition, "treatment" may have meant something different to patients and carers, compared to rheumatologists. For patients, treatment may have encompassed holistic management.

5 | CONCLUSION

This study investigated the roles and potential impact of carers in RA management in the Asia-Pacific region. Carers play an important role in RA management by providing physical, emotional and financial support to patients, especially for patients with moderate-to-severe disease. They may also help to optimize treatment outcomes by reinforcing important information about the disease and treatment, and providing observations that may help rheumatologists in treatment decision-making.

While stakeholders considered carer observations to be valuable, they were obtained on an ad hoc basis. Development of validated carer-reported outcomes and a framework for their routine collection would facilitate their inclusion in routine consultations. Validation would require correlation with PROs and other clinical measures, and assessment of their utility. Any impact on clinician decision-making by carer-reported measures will also require investigation and careful assessment of acceptability to all stakeholders in different settings. Finally, integration of carer-reported outcomes into clinical discussions should not interfere with workflow or add to the workload of rheumatologists.

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CONFLICT OF INTEREST

K. Pile has received grants and personal fees from Janssen Pharmaceuticals. KA Gibson has received grants from Novartis and personal fees from Janssen and UCB. W. Favorito has received honoraria from Johnson and Johnson Services. R. Mu has received consulting fees from Xian Janssen and Johnson & Johnson Pte Ltd. outside the submitted work. H. Nahakara has received consulting fees from Janssen Pharmaceutical; speaker fees from Chugai Pharmaceutical, Bristol-Myers Squibb, Mitsubishi Tanabe Pharma Corporation, Eisai Co. Ltd, UCB, and Abbvie; and has received patent royalties from Chugai Pharmaceutical. M. Kishimoto has received honoraria from Janssen. S. Hirata has received grants from AbbVie,

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AUTHOR CONTRIBUTIONS

All authors contributed equally to the conception and design of the study, analysis and interpretation of the data, and final approval of the version of the article to be published.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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ORIGINAL ARTICLE

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Cross-cultural adaptation and validation of the Gait, Arms, Legs, Spine locomotor screening test for detecting musculoskeletal disorders in Mexican adults

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Abstract

Aim: Developed in the United Kingdom, the Gait, Arms, Legs and Spine (GALS) sensitive screening test enables doctors to examine joints and positions at rest and during motion. Therefore, patients with an early diagnosis for musculoskeletal (MSK) disorders, can enjoy a better quality of life than those diagnosed at a later stage. The objective was to adapt and validate a Mexican-Spanish version of the GALS measurement instrument for MSK disorders in Mexican adults.

Materials and methods: We conducted a cross-sectional diagnostic test study among 18- 60-year-old adults in a hospital in the city of Guadalajara, Mexico. Based on international guidelines, we divided our work into 2 phases: first, we developed and adapted a cross-cultural, Mexican-Spanish version of the GALS; second, we validated the instrument as a diagnostic test among Mexican patients.

Results: The adapted version yielded the following scores as a measurement instrument: 0.92 under Cronbach's alpha, 0.695 (95% CI, 0.592-0.797) in the kappa index, 98.2% (95% CI, 90.3%-100%) in sensitivity, 80.6% (95% CI, 72.9%-86.9%) in specificity, and 5.06 for positive likelihood ratio. It also covered an area of 0.89 (95% CI, 0.85-0.93) under the receiver operating characteristic curve.

Conclusions: The GALS diagnostic test proved valid for detecting MSK disorders among Mexican adults. It can be used by specialized physicians, family doctors, general practitioners and even physicians in training.

KEYWORDS

adult, cross-sectional study, diagnostic test, musculoskeletal disorders, screening, validation studies

1 | INTRODUCTION

Musculoskeletal (MSK) disorders are the leading contributor to disability worldwide, and are not just conditions of older age. They are prevalent across the life-course, and constitute a lifelong condition affecting mostly adolescents and older adults.[1] The most common MSK disorders include osteoarthritis, back and neck pain, fractures associated with osteoporosis, injuries and systemic inflammatory conditions such as rheumatoid arthritis and/or systemic lupus erythematosus.[1,2]

Between 2000 and 2016, mortality from MSK disorders grew at a rate of 57.2% globally but remained stable at 2.1 per 100 000 individuals by age and gender; patients above 60 years represented over 75% and women 67.3% of total deaths.[3] Of the nearly 103 million disability-adjusted life years (DALYs) attributed to MSK disorders in 2016 (33.8% more than in 2000), lower-middle and upper-middle income countries contributed the majority of cases (71.9%).[3]

In 2016, out of the total of DALYs, 98.6 million (95.9%) were years lost due to disability (YLDs) attributed to MSK disorders (33.6% more than in 2000), and women represent a higher number of YLDs at 57.3 million (58.1% of the total YLDs), and 30-59-year-olds are the ages that contribute most to YLDs, both for men and women.[3] Lower-middle and upper-middle income countries contributed as well with 70.1 million of YLDs (72%).[3] According to the Global Burden of Disease Study 2017, MSK disorders was the first cause of YLDs with an average percentage increase of 38.4% between 1990 and 2017.[4]

From 20% to 33% of those living with a MSK disorder experience pain and disability. They are subject to significant mobility and dexterity limitations which compromise their working capacity, require them to seek early retirement and reduce their economic and mental wellbeing.[1]

Recognizing patients with MSK abnormalities early on offers them an opportunity to enjoy a better quality of life than those whose cases are detected at a later stage. In 1992, Doherty et al[5] developed the Gait, Arms, Legs and Spine (GALS), sensitive screening method for examining joints as well as positions at rest and during motion. This test serves as an introduction to, not a substitute for, detailed examination of the locomotor system; it specifically enables primary-care physicians to identify whether a MSK disorder exists and, if so, to continue the diagnosis in order to establish which disease is involved.[5]

The GALS is a 2-phase measurement instrument. First, the doctors ask patients a series of questions about symptoms and activities that reveal their ability to undertake activities of daily living. Second, the doctors perform an observational and physical examination of patients in order to detect any significant MSK abnormalities.[5] As its name indicates, the GALS test is comprised of 4 sections: posture (Gait), upper extremity (Arms), lower extremity (Legs) and back (Spine). Constituting a concise system that even medical students can easily administer, the GALS has been incorporated into medical school programs and is applied as a part of routine clinical assessments in the UK.[6]

The objective of this study was to adapt and validate a Mexican-Spanish version of the GALS measurement instrument for MSK disorders in Mexican adults.

2 | MATERIALS AND METHODS

We conducted a cross-sectional diagnostic test study in order to establish the cross-cultural adaptation and validation of the GALS instrument in a Mexican-Spanish version.

2.1 | Participants

Participants were adults between the ages of 18 and 60 years undergoing treatment at Regional General Hospital Number 46 (*HGR46*) from November 2017 to May 2018. *HGR46* operates under the Mexican Social Security Institute (*IMSS* by its Spanish initials) in the city of Guadalajara, Mexico.

2.2 | Inclusion criteria

We formed 2 comparison groups: (a) patients without a MSK disorder who sought consultation at *HGR46* for a non-MSK health problem and (b) patients with a rheumatologist-diagnosed MSK disorder.

2.3 | Exclusion criteria

Patients who sought services at *HGR46* for an acute or traumatic accidental injury corroborated by emergency or traumatology clinical staff, or patients with a mental condition impeding the comprehension or execution of instructions were excluded.

2.4 | Validation phases

In accordance with international guidelines, GALS validation was conducted in 2 phases. First, we adapted a cross-cultural, Mexican-Spanish version of the instrument, and second, we validated the Mexican-Spanish version as a diagnostic test.

2.4.1 | Phase 1. Cross-cultural adaptation of the GALS instrument

In accordance with the international guidelines proposed by Guillemin et al[7] and Beaton et al[8] for the cross-cultural adaptation of instruments, the first phase of our study included 5 steps. First, we viewed the GALS demo video and obtained authorization for our project from the author of the GALS, Dr Michael Doherty, University of Nottingham, Notts Division of Academic Rheumatology.[5] Then, we tasked 2 independent and blinded professional translators whose native language was Spanish to carry out 2 initial translations from the language in which the instrument was originally elaborated (British English) into our target language: Mexican Spanish. Both translators delivered written reports of their work, identifying those words, phrases and concepts that raised difficulties in translation and specifying the grounds on which they made their final word choices. Second, an expert panel composed of a rheumatologist, a general practitioner and an epidemiologist examined both Spanish translations and submitted a written report. Based on the recommendations of the experts, we synthesized and integrated the 2 translations into 1 final version of the instrument in Spanish. Third,

we tasked 2 independent and blinded professional translators whose native language was British English to perform a back-translation from the Spanish version obtained in the previous step. Both translators delivered written reports of their work, indicating the difficulties encountered and the reasons for their final word choices. Fourth, we requested that the above-mentioned expert panel review the back-translation. And finally, we verified the construct and semantic validity of the Mexican-Spanish version in relation to the original version through a pilot test of the instrument administered to 30 patients by general practitioners and medical residents receiving training in the area of rehabilitation. The final version proved comprehensible and the validity of the GALS instrument in Mexican Spanish was established.

2.4.2 | Phase 2. Validation of the GALS instrument as a diagnostic test

The GALS screening test was implemented by medical residents receiving training in the area of rehabilitation. After receiving an explanation of the instrument, they independently evaluated the patients without knowing whether they were ill.

To establish the validity of the construct, we relied on the assessment of the instrument by a rheumatologist as the gold standard and estimated a tetrachoric correlation matrix among the sections of the test.

Reproducibility was achieved by means of inter-observer validity based on Cohen's Kappa statistic. Internal consistency was evaluated through Cronbach's alpha test. And again, we used the assessment of a rheumatologist as the gold standard to corroborate the properties of the instrument as a diagnostic test. This allowed us to calculate the sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio, and receiver operating characteristic (ROC) curve of the instrument. Statistical analysis was performed using the R Project for Statistical Computing version 3.5.2 statistical program.[9]

2.5 | Ethical issues

Our study was authorized by the Ethics and Research Committee of the Mexican Social Security Institute (*IMSS* by its initials in Spanish) in Jalisco Delegation (Registration Number R-2019-1305-032). Informed consent forms were signed by all study participants.

3 | RESULTS

A total of 189 adult patients participated in our study: 55 with and 134 without MSK disorders. Of these, 144 patients (76.2%) were women and 45 (23.8%) men. The average age was 40.2 years, with a standard deviation (SD) of 14.3 years. Participants exhibited an average height of 1.63 m (SD: 0.086) and an average weight of 72 kg (SD: 13), with a body mass index (BMI) of 27.3 (SD: 4.4). BMI figures were distributed as follows: 3 patients (1.6%) were underweight, 59 (31.2%) were of normal weight, and 81 (42.9%) were overweight, while 46 (24.3%) were obese. The average time for administering the GALS was 4:15 minutes with a SD of 53 seconds (range: 2:37-6:40).

The patients suffering from MSK disorders are described below: 24 (43.7%) were diagnosed with rheumatoid arthritis, the predominant rheumatic illness reported, followed by 19 (34.6%) with primary osteoarthritis, 8 (14.6%) with ankylosing spondylitis, and the remaining 4 (7.1%) with various rheumatic illnesses. Fifty-two of the patients (94.5%) were women and 3 (5.5%) were men, with an average age of 59 years (SD: 10.4) and a BMI of 29.3 (SD: 4.8). In comparing the variables of those with and without MSK disorders we found significant differences by gender, age and BMI (Table 1).

TABLE 1 Demographic characteristics of patients the completing cross-sectional diagnostic test

	Patients with MSK disorders (n = 55)		Patients without MSK disorders (n = 134)		
Variable	**Mean**	**SD**	**Mean**	**SD**	***P* value**
Age, y	55.9	10.4	33.8	10.00	.000
Weight, kg	73.4	13.9	72.6	12.6	.700
Height, m	1.58	0.07	1.65	0.08	.005
Gender	**n**	**%**	**n**	**%**	
Male	52	94.5	92	68.7	.000
Female	3	5.5	42	31.3	
Body mass index	**n**	**%**	**n**	**%**	
Underweight	0	0.0	3	2.2	.006
Normal weight	11	20.0	48	35.8	
Overweight	22	40.0	59	44.0	
Obese	22	40.0	24	17.9	

Abbreviation: MSK, musculoskeletal.

TABLE 2 Gait, Arms, Legs and Spine (GALS) tetrachoric correlation matrix

	Pain	Dressing	Up-/down-stairs	Standing	Walking	Hands out	Hands over	Index/thumb	Fingers/thumb	Squeeze join
Pain	1.0000									
Dressing	**0.8850**	1.0000								
Up-/down-stairs	**0.9504**	**0.6189**	1.0000							
Standing	**0.7681**	0.4570	0.5130	1.0000						
Walking	**0.9291**	0.5313	0.5888	**0.7822**	1.0000					
Hands out	**0.8205**	**0.6672**	0.2237	0.6518	**0.7931**	1.0000				
Hands over	**0.8743**	**0.6744**	0.4862	0.6023	0.6662	**0.8745**	1.0000			
Index thumb	0.6982	0.6852	0.2884	0.4548	0.5864	**0.9623**	**0.8758**	1.0000		
Fingers/thumb	**0.8205**	**0.7350**	0.4090	0.5767	**0.7351**	**0.9635**	**0.8745**	**0.9623**	1.0000	
Squeeze join	**0.9178**	**0.6224**	**0.7963**	0.4934	**0.6581**	0.4640	0.5719	0.6104	0.6256	1.0000
Hands together	**0.8382**	0.6185	0.4997	**0.6260**	**0.7749**	**0.8024**	**0.8423**	**0.7998**	**0.7449**	0.5947
Reach up	**0.8331**	0.6276	0.5336	0.6254	**0.7641**	**0.8824**	**0.8055**	**0.9187**	**0.9220**	0.5980
Hands/neck	0.6629	0.6672	0.4090	0.4925	0.6712	**0.8975**	**0.7725**	**0.9302**	**0.9348**	0.5491
Shoulder/ear	**0.8652**	**0.7586**	0.5129	0.5550	**0.7421**	**0.8859**	**0.8837**	**0.9286**	**0.9788**	**0.7139**
Open mouth	0.5415	0.4083	0.3771	0.6254	0.5720	0.7089	0.6858	0.5876	**0.7765**	0.5980
Fell knee	0.6164	0.2455	0.5207	0.6601	0.7082	0.0638	0.2076	-1.0000	-1.0000	0.5365
Active movement knee	**0.9411**	**0.7218**	**0.8622**	**0.7356**	**0.7423**	**0.7228**	**0.6848**	0.6633	**0.7842**	**0.8478**
Passive movement hip	**0.8764**	0.5738	**0.7177**	**0.7207**	**0.8274**	**0.8121**	**0.6927**	**0.8189**	**0.9061**	**0.7780**
Tighten foot	**0.8908**	0.5638	0.6145	**0.8246**	**0.7292**	0.4288	0.3169	0.2473	0.4288	**0.7992**
Spine	**0.7096**	0.4687	0.5785	**0.7207**	**0.6581**	0.6945	0.5719	0.6104	0.6945	0.6376

Note: Bold values indicate $P \leq .001$.

3.1 | Construct validity

We used the tetrachoric correlation coefficient to assess this characteristic, inasmuch as the variables of interest were dichotomous for each subgroup (Table 2).

3.2 | Internal consistency

Under Cronbach's alpha test, this characteristic obtained a score of 0.92.

3.3 | Reproducibility

This characteristic obtained a kappa of 0.695 with a 95% confidence interval (95% CI, 0.592-0.797).

3.4 | Properties as a diagnostic test (screening)

We found a 29% prevalence of MSK disorders in our sample. As a measuring tool, the GALS instrument demonstrated a sensitivity of 98.2% (95% CI, 90.3%-100%), with a specificity of 80.6% (CI 72.9%-86.9%), a likelihood ratio for a positive result (LR+) of 5.06, and an area of 0.89 under the ROC curve (95% CI, 0.85%-0.93%) (Figure 1). This showed a positive predictive value of 67.5% (95% CI, 56.1%-77.6%) and a negative predictive value of 99.1% (95% CI, 95%-100%).

We performed a univariate logistic regression analysis using age, gender, weight, height and BMI as independent variables and comparing them with the GALS dependent variable. Only age yielded a significant *P* value, indicating that, for each additional year, it becomes more likely that the GALS screening test will diagnose a MSK disorder. The multivariate logistic regression test revealed basically the same behavior (Table 3).

4 | DISCUSSION

The Mexican-Spanish version of the GALS locomotor screening test adapted and validated during our study is suitable for use in detecting musculoskeletal (MSK) disorders among Mexican adults. It provides a diagnostic screening test that is easy to apply and understand by health staff, helping to obtain rheumatological assessment in primary-care centers. As indicated in several studies,[10-12] the GALS can be effectively administered by a diversity of healthcare

Hands together	Reach up	Hands/ neck	Shoulder/ ear	Open mouth	Fell knee	Active movement knee	Passive movement hip	Tighten foot	Spine
1.0000									
0.7203	1.0000								
0.7449	**0.9766**	1.0000							
0.8166	**0.9064**	**0.8859**	1.0000						
0.4976	0.6878	0.6301	0.7023	1.0000					
0.4744	0.0461	0.0638	0.2233	0.2750	1.0000				
0.7347	**0.8577**	**0.7842**	**0.7626**	0.6231	0.7327	1.0000			
0.7551	**0.9191**	**0.8618**	**0.9228**	0.6669	0.5365	**0.8784**	1.0000		
0.6595	0.4976	0.5229	0.5129	0.4976	0.7684	**0.8926**	**0.7992**	1.0000	
0.6531	**0.7291**	0.6945	**0.7657**	0.5980	0.4214	**0.6959**	**0.8169**	**0.7065**	1.0000

providers ranging from personnel in family medicine units to medical practitioners and nursing staff.

As a diagnostic test, the Mexican-Spanish version of the GALS screening test has a sensitivity behavior of 98% and specificity of 80%, characteristics similar to those of the original GALS version, which registers sensitivity and specificity scores of 100% and 95%, respectively. The Mexican-Spanish version also provides an adequate and optimal ROC curve for use as a diagnostic test by health staff.[13]

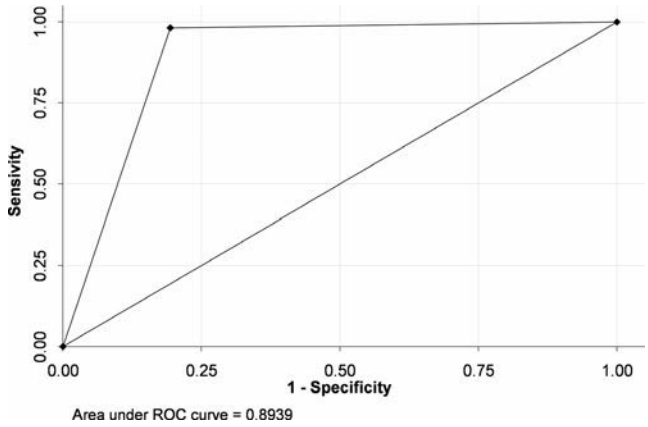

FIGURE 1 ROC curve graph

We were able to calculate the reproducibility of the GALS screening test with a high degree of agreement (70%) among observers, a result similar to that reported by Beattie et al[10-12] Another point in favor of the Mexican-Spanish version of GALS is that we followed the published and accepted cross-cultural adaptation and validation standards in order to ensure adequate comprehension and application by health staff.[7,8] Its construct validity and internal consistency levels denote the characteristics proposed by published guides, thus confirming an adequate cross-cultural adaptation and validation

TABLE 3 Logistic regression for the Gait, Arms, Legs and Spine (GALS) and variables of interest

Variable	Odds ratio	95% CI
Male	1.14	0.31-4.11
Age	**1.15**	**1.10-1.20**
Weight	0.98	0.90-1.07
Height	1.03	0.92-1.13
Body mass index		
Underweight	6.41	0.38-107.32
Overweight	1.62	0.41-6.37
Obesity	3.51	0.28-44.03

Bold values indicate statistically significant effects

based on its equivalence with the source version as regards criteria, items, semantics and measurement.[7,8,14,15]

Instrument application time makes it attractive for use in outpatient consulting in family medicine units. In countries like Mexico, where medical consultations have a pre-established limit, the GALS screening test facilitates rapid evaluation for appropriate referrals to specialized treatment, for instance, by a rheumatologist.

The GALS test has been accepted as part of routine structured MSK examination, in university medical education and in postgraduate clinical practice. As with the pediatric GALS (pGALS) and the Regional Examination of the Musculoskeletal System (REMS), a number of versions translated into other languages have been developed given the importance and impact of clinical evaluation of patients to provide early diagnosis. Therefore, validation of instruments of this kind in other languages such as Mexican Spanish is appropriate for assisting routine medical evaluations by personnel, particularly at the first level of health care.[6]

In spite of being published in 1992, the GALS[5] has been increasingly used in recent years, not only because of the surge in the number of MSK diseases, but also for being available and allowing for rapid implementation, as well as for offering sensitivity and specificity levels appropriate for screening purposes in routine clinical practice. The GALS test has been validated by different kinds of health staff and adapted for pediatric use by Foster et al[13] with one of the authors of this manuscript having participated in the cross-cultural adaptation and validation of the pGALS in Mexican Spanish with positive results.[16]

Unlike the pGALS, which has been translated into various languages including Mexican Spanish,[16] Peruvian Spanish[17] and Turkish,[18] the GALS had not been cross-culturally adapted or validated until now, with our Mexican-Spanish version thus representing a pioneering effort. Developed in accordance with standardized international guidelines, the present adaptation benefits other Spanish-speaking populations with social and cultural characteristics similar to those of Mexico.

4.1 | Conclusions

The GALS is a brief screening examination to detect significant abnormalities of the MSK system, which takes 3-4 minutes, and it has been adapted and validated to Mexican Spanish according to international guidelines; it can be used as a diagnostic test proved valid for detecting MSK disorders among Mexican adults. The GALS can be performed by specialized physicians, family doctors, general practitioners and even physicians in training, therefore, it will be necessary to conduct a study to assess the sensitivity and specificity in these Mexican health workers.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest. The authors declare that tables and figures used are original.

AUTHOR CONTRIBUTIONS

LAMT: designed, analyzed data and co-wrote the manuscript. CEVA: analyzed data and co-wrote the manuscript. AAFJ: supervised the research and co-wrote the manuscript.

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ORIGINAL ARTICLE

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Cross-culture adaptation and validation of English version of Rheumatoid Arthritis Knowledge Assessment Scale (RAKAS) in patients with rheumatoid arthritis

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Abstract

Aim: To carry out cross-culture adaptation and validation of the English version of Rheumatoid Arthritis Knowledge Assessment Scale (RAKAS) in patients with rheumatoid arthritis (RA).

Methods: A cross-sectional study was conducted for 2 months in 2 tertiary care hospitals in Karachi, Pakistan. Sample size was calculated based on item-subject ratio. The translation was carried out using standard procedures for translation and cross-culture adaptation. The validation process included estimation of discrimination power, item difficulty index, factorial, convergent, construct and known group validities and reliability. Reliability of the scale was estimated using Kuder-Richardson Formula 20 and a value of $\sigma^2 \geq 0.6$ was acceptable. SPSS v23, Remark Classic OMR v6 software and MedCalc Statistical Software v16.4.3, were used to analyze the data. The study was approved by the relevant ethics committee (IRB#NOV:15).

Results: The mean score was 7.68 ± 2.52 (95% CI: 7.31-8.05) for 177 patients. The $\sigma^2 = 0.601$, that is, >0.6, test-retest reliability $\rho = .753$, $P < .05$. The average discrimination power = 47.27, average Item Difficulty Index = 0.557. The fit indices were acceptable in a range that established its factorial validity and average factor loading was ≥0.7 which established convergent validity. A significant association ($\chi^2 = 33.074$, $P < .01$) between score interpretation and previous counseling by pharmacists established its construct validity. A significant association ($\chi^2 = 19.113$, $P < .05$) between score interpretation and patient occupation established known group validity.

Conclusion: The English version of RAKAS was deemed a reliable and validated tool to measure knowledge about disease in Pakistani patients with RA.

KEYWORDS

arthritis, disease knowledge, patient knowledge, rheumatoid, validation

1 | INTRODUCTION

One of the most common musculoskeletal conditions that result in disability is rheumatoid arthritis (RA). It is an autoimmune disease characterized by swelling in joints, stiffness and pain.[1,2] In most cases, synovial joints are affected, and patients may suffer from acute flares and pain.[3,4] The disease is chronic and progressive, causes joint deformity and significantly hampers mobility of patients.[5] Gradually, it reduces a patient's ability to perform daily routine tasks and productivity that drastically impacts health-related quality of life.[6] Epidemiological data highlights that the disease mostly affects individuals in middle ages.[5] The importance of patient knowledge is intensified if the patients are working since the disease could result in presenteeism and reduced work ability and consequently, absenteeism or productivity loss, if not managed.[3,7] Moreover, the socioeconomic impact of the disease may be even more if the individual is associated with household activities.[7]

Studies mention that apart from the medication therapy, other treatment interventions such as behavioral counseling and disease education help patients to accommodate the disease in daily life.[7-9] Disease education aimed at empowering patients' knowledge, symptom attribution and self-management of their condition has shown better outcomes.[3] Evidence indicates that patient knowledge regarding RA may indicate their ability to cope up with the disease-related complications and self-manage their condition at home or at work.[3,4,10] It enables the patients to actively partake in clinical decision-making regarding management of their disease. Hence, patient knowledge may be a determinant of self-care.[3,4,7,11]

Several scales have been developed to document patient knowledge of RA. These include Patient Knowledge Questionnaire (PKQ), Arthritis Community Research and Evaluation Unit (ACREU), the scale developed by Hennel and colleagues and a scale formulated by Khalil et al[12-17] Naqvi et al mentioned that the PKQ has a difficult structure and presents challenges for patients to fill while the ACREU is not suitable to document general patient knowledge.[7,13,14] The scale formulated by Hennel et al is suitable to document knowledge from patients with early RA diagnosis only while the Khalil et al scale lacked psychometric evaluation.[7,14,15] After observing the shortcomings of all previous scales, Naqvi and colleagues developed a novel scale known as the Rheumatoid Arthritis Knowledge Assessment Scale (RAKAS) in Urdu language and validated it in Pakistani patients with RA. The scale had good psychometric properties; however, it was lacking in terms of non-availability in the English language.[7] With an increasing demand for the scale from other parts of the world, a need to translate and validate an English version of RAKAS was felt. This study aimed to validate the English version of RAKAS in patients with RA.

2 | METHODS

A cross-sectional study with repeated measures was conducted for 2 months (Sept-Oct 2019) in out-patient rheumatology clinics of 2 tertiary care hospitals in Karachi, Pakistan.

2.1 | Venues and duration of study

The study venues were out-patient rheumatology clinics of 2 tertiary care hospitals. One health facility was state-funded while the other was private. Since patients in Pakistan use both private and state-funded healthcare facilities, it was important to include both sectors to have a representative sample.[18]

2.2 | Participants and eligibility criteria

Patients with RA were identified as target segments and all male and female patients above 18 years who were diagnosed with RA according to American College of Rheumatology/European League Against Rheumatism criteria at least 3 months before the study were invited to participate.[5,19] Patients who agreed to participate were briefed about the study and were asked to provide written informed consent.

2.3 | Sample size calculation

The sample size was calculated based on item-subject ratio. A ratio of 1:10 was selected and based on this ratio the required sample was 130 patients. A 3% drop-out rate was added, and final sample size was 169 patients.[20]

2.4 | Sampling strategy

Convenience sampling procedure was used since English was not the local language and there were few patients who opted to use the English version of the scale. The sampling strategy helped researchers gather enough responses to satisfy sample size criterion according to item-subject ratio.[21]

2.5 | Translation of the research instrument

The translation of the instrument was carried out using standard guidelines for cross-culture adaptation.[3,22] Forward translation of the original Urdu version of the scale was carried out by 2 researchers whose first language was Urdu and spoke English as a second language with near native competence. Both versions were compared, and any disagreement in language, concepts and technical equivalence were sorted out. After this step, the final English version of RAKAS was approved. This version was back-translated into Urdu by another researcher and any disagreements were sorted out at this moment. The final English version of the scale was peer-reviewed by an English linguist and was later declared fit for use.

2.6 | RAKAS scoring

The RAKAS scale categorized patients into 4 categories based on their score. Patients with a score ≥11 have excellent knowledge

while patients with a score ≥8 and ≤10 have adequate knowledge. Those with a score ≥5 and ≤7 have low knowledge whereas patients with a score ≤4 have poor knowledge. The scoring is described in detail by Naqvi et al in a separate article.[7]

2.7 | Data collection

The data were collected every day from 9:00 AM to 4:00 PM Patients who visited the clinics and met the eligibility criteria were invited to participate in the study. Those who indicated their willingness to participate were asked to provide a written informed consent. Patients were provided with a demographic information form and RAKAS questionnaire to fill in their response. At the second appointment, the patients filled a second copy of RAKAS questionnaire for test-retest purpose. All documents, that is, demographic form and 1st and 2nd copies of RAKAS were collected in a separate patient file indicated by a medical record number.

2.8 | Validation procedure

The validation of RAKAS-E (English) included estimation of its discrimination power, item difficulty, validities including factorial, convergent, known group and construct, as well as reliability.

2.9 | Discrimination and Item Difficulty Indices

The validation process of the research instrument included a myriad of techniques to demonstrate the effectiveness of the tool in documenting knowledge from patients. It included calculation of discrimination and Item Difficulty Indices. Discrimination index of a knowledge tool highlights the ability of the tool to discriminate between patients based on their knowledge. The acceptable range for discrimination index was between 10-80.[23,24]

Item Difficulty Index was a measure of proportion of patients correctly answering the questions. A question that was answered incorrectly by many patients would be considered as a difficult item. The threshold for having a satisfactory Item Difficulty Index was less than 0.95.[23,24]

2.10 | Factorial validity

Factorial validity of the tool was assessed by exploratory factor analysis (EFA) using principle components analysis (PCA) with Varimax rotation at first to get an idea of the factor structure. Items with a loading >0.5 and non-salient loadings <0.5 were considered as a single factor. The Kaiser-Mayer-Olkin measure of sampling adequacy, significance of Bartlett's test of sphericity, degrees of freedom (*df*) values and null model χ^2 values were noted.

The factor structure obtained in EFA was later confirmed in another sample of patients using partial confirmatory factor analysis (PCFA) using maximum likelihood analysis (MLA) with same rotation. The values for implied model χ^2 and *df* were noted. Based on the values obtained in EFA and PCFA, fit indices, namely normed fit index (NFI), Tucker Lewis index (TLI), comparative fit index (CFI), incremental fit index (IFI) and root mean square error of approximation (RMSEA) were calculated. The model indicated good fit if the values of all indices except RMSEA were >0.9, and <0.3 for RMSEA.[20,25].

2.11 | Convergent validity

The convergent validity of an instrument is its ability to measure the required outcome.[26] The tool measured disease knowledge of RA patients and therefore, the scale must have high factor loadings. An average factor loading >0.7 was considered acceptable for establishing convergent validity.

2.12 | Construct validity

The construct validity of the scale was estimated through cross-tabulation of knowledge score categories with the variable of previous pharmacist counseling regarding RA. It was hypothesized that since the scale measured knowledge about the disease, patients who had pharmacist counseling regarding disease would be knowledgeable and would be discriminated by the scale. The construct validity was established if *P* values were less than .05.[27,28]

2.13 | Known group validity

Known group validity indicated the ability of the scale to measure the knowledge in groups known to indicate a certain level of knowledge.[29,30] It was hypothesized that the patients who were employed would have better knowledge about the disease since they would have to manage the symptoms and take care of their condition to avoid absenteeism. This was done by cross-tabulating knowledge score categories with the demographic variable of occupation. The known group validity was established if *P* values were less than .05.[31]

2.14 | Reliability analyses

The reliability of the tool was estimated using Kuder-Richardson Formula 20 (KR20).[32,33] A value of $\sigma^2 \geq 0.6$ was acceptable. Test-retest reliability was estimated by documenting responses from participants after 3 weeks. A value of test-retest correlation coefficient $\rho > .7$ with significant *P* value <.05 was considered satisfactory.[34]

2.15 | Sensitivity analysis

The sensitivity, specificity and accuracy of RAKAS was calculated using MedCalc Statistical Software version 16.4.3 (MedCalc Software bv, Ostend, Belgium; 2016). Sensitivity is the ability of the scale to correctly identify knowledgeable patients and specificity is the ability of the scale to correctly exclude patients with low knowledge.[35]

2.16 | Data analyses and presentation

IBM SPSS version 23, Remark Classic OMR version 6 and MedCalc Statistical Software version 16.4.3 were used to analyze the data. The factor analyses, convergent, construct and known group validities were analyzed using IBM SPSS v23, while test normality, discrimination and difficulty indices and, reliability were analyzed through Remark Classic OMR v6 software. Sensitivity analyses were conducted through MedCalc. The data were expressed as sample counts (n), frequencies (%) and, where applicable, in 95% confidence intervals (CIs). A *P* value less than .05 for an association was considered acceptable.

2.17 | Ethics approval and patient consent

The study was approved by the Institutional Review Board (IRB) of Allied Med Ethics (Ref# NOV: 15) and was granted permission by the respective committees of each tertiary care hospital that served as study venues.

3 | RESULTS

Most patients were adults (n = 133, 75.1%), female (n = 119, 67.2%) and were married (n = 141, 79.7%). The majority of patients were graduates (n = 106, 59.9%). Most were either employed (n = 69, 39%) or associated with household activities (n = 69, 39%). Most patients (n = 74, 41.8%) had a monthly family income between PKR 25 000-50 000, no medical insurance (n = 90, 50.8%) and lived in urban localities (n = 144, 81.4%). Most patients (n = 105, 59.3%) had a normal body mass index and no comorbidities (n = 130, 73.4%) while more than a third (n = 64, 36.2%) had an illness duration >3 years (Table 1).

The summary of responses from the knowledge scale is tabulated in Table 2.

There was a normal distribution of scores among the participants (Figure 1). The mean percentage score was 59.06%. The mean score was 7.68 ± 2.52 (95% CI: 7.31-8.05), range was 12 and variance was 6.35. The 25th percentile score was 6 while the score at 75th percentile was 9.5. Based on scoring criterion, most patients (n = 62, 35%) had adequate knowledge while less than a third (n = 48, 27.1%) had low knowledge. Some patients (n = 47, 26.6%) had excellent knowledge while few (n = 20, 11.3%) had poor knowledge.

3.1 | Discrimination and Item Difficulty Indices

The average discrimination power of RAKAS was 47.27. The highest discrimination was reported to be 70.84 while lowest was 12.5. The average Item Difficulty Index was 0.557 and was reported between 0.42-0.76. It was less than 0.95 and was in an acceptable range (Table 3).

3.2 | Factorial validity

Exploratory factor analysis was carried out using PCA with Varimax rotation. The EFA revealed a 5-factor solution and the KMO value was 0.7 with significant Bartlett's test ($P < .001$). The null model χ^2 was 349.725 ($df = 78$). Average factor loading in factor 1 = 0.72, factor 2 = 0.826, factor 3 = 0.7, factor 4 = 0.655 and factor 5 = 0.638. Factor 1 measured knowledge related to spread of disease, genetic predisposition and disease resultant deformity. Factor 2 measured knowledge related to treatment while factor 3 measured knowledge related to RA disease and its risk factors. Factor 4 measured knowledge related to symptoms, gender-wise disease burden and effect of disease on bones. Factor 5 measured knowlegde of disease resultant disability, laboratory diagnosis and nature of illness.

Partial confirmatory factor analysis with MLA and same rotation was carried out and the number of factors was fixed at 5. The implied model χ^2 was 26.256 and $df = 23$. The values for NFI = 0.924, TLI = 0.959, CFI = 0.988 and IFI = 0.990, that is, >0.9; while RMSEA = 0.028, that is, <0.03. The values indicated a good model fit (Table 4).

3.3 | Convergent validity

The average factor loading was 0.7, that is, ≥0.7 and hence convergent validity was established.

3.4 | Construct validity

Cross-tabulation between score interpretation and previous counseling by a pharmacist on RA, showed a significant association with χ^2 value of 33.074 and *P* value <.01. Hence, construct validity was established (Table 5).

3.5 | Known group validity

There was a significant association between score interpretation and occupation of patients, with χ^2 value of 16.607 and *P* value <.02. Hence, the hypothesis was validated and known group validity was established (Table 6).

TABLE 1 Patients information (N = 177)

Patients information	n	%
Age groups		
Geriatric (>65 years)	44	24.9
Adult	133	75.1
Gender		
Male	58	32.8
Female	119	67.2
Marital status		
Single	36	20.3
Married	141	79.7
Education		
Primary (up to 6 y of education)	11	6.2
Secondary (up to 10 y of education)	31	17.5
Higher secondary (12 y of education)	10	5.6
Graduate (up to 16 y of education)	106	59.9
Postgraduate (more than 16 y of education)	19	10.7
Occupation		
Employed	69	39
Unemployed	23	13
Retired	16	9
Household	69	39
Income		
Less than PKR 10 000, ie, USD < 60.05	10	5.6
More than PKR 10 000 but less than PKR 25 000, ie, USD 60.0-150.12	20	11.3
More than PKR 25 000 but less than PKR 50 000, ie, USD 150.12-300.25	74	41.8
More than PKR 50 000, ie, USD > 300.25	73	41.2
Residence		
Urban	144	81.4
Rural	33	18.6
Health insurance		
Yes, full medical insurance	21	11.9
Yes, partial medical insurance	66	37.3
No medical insurance	90	50.8
Body mass index		
Malnutrition	25	14.1
Normal	105	59.3
Obesity	47	26.6
Duration of illness		
Less than 1 y	12	6.8
More than 1 y but less than 3 y	33	18.6
More than 3 y but less than 5 y	64	36.2
More than 5 y but less than 10 y	50	28.2
More than 10 y	18	10.2
Comorbidity		
Yes	47	26.6
No	130	73.4

Note: 1 USD equals 166.5 PKR at the time of this writing.

TABLE 2 Patients' knowledge of rheumatoid arthritis

Patients' knowledge	Sample (n)	Percentage (%)
Do you know what rheumatoid arthritis is?		
Yes, completely aware	78	44.1
Yes, to some extent	88	49.7
No	11	6.2
Which of the following is a symptom of rheumatoid arthritis?		
Low blood sugar	2	1.1
Joint pain	149	84.2
High blood pressure	15	8.5
Feeling sleepy	11	6.2
Which of the following is a risk factor of rheumatoid arthritis?		
High blood pressure	20	11.3
High blood sugar	21	11.9
Presence of diabetes in parents	23	13
Presence of rheumatoid arthritis in parents	93	52.5
I don't know	20	11.3
In your opinion, does rheumatoid arthritis only affects bones/joints?		
Yes	77	43.5
No	74	41.8
I don't know	26	14.7
In your opinion, can rheumatoid arthritis result in disability?		
Yes	107	60.5
No	42	23.7
I don't know	28	15.8
In your opinion, can rheumatoid arthritis result in deformity?		
Yes	117	66.1
No	36	20.3
I don't know	24	13.6
In your opinion, can rheumatoid arthritis spread from person to person?		
Yes	49	27.7
No	94	53.1
I don't know	34	19.2
Does the disease run in the family?		
Yes	90	50.8
No	46	26
I don't know	41	23.2
In terms of gender, who is more prone to suffer from this disease?		
Male	23	13
Female	108	61
Both have equal chance of suffering	46	26
Which of the following laboratory tests is commonly used to assess this disease?		
Erythrocyte sedimentation rate	103	58.2
Random blood sugar	15	8.5
Blood pressure	31	17.5
Serum cholesterol	18	10.2
I don't know	10	5.6
In your opinion, is rheumatoid arthritis completely curable?		
Yes	49	27.7
No	101	57.1
I don't know	27	15.3
In your opinion, does it require lifelong treatment?		
Yes	87	49.2
No	62	35
I don't know	28	15.8
Is physical therapy helpful in this disease?		
Yes	114	64.4
No	31	17.5
I don't know	32	18.1

3.6 | Reliability analyses

The split-half reliability of RAKAS using KR20 was in an acceptable range. It was .601, that is, >.5, while the test-retest reliability (ρ) was .753, $P < .05$ (Figure 2).

3.7 | Sensitivity analysis

The sensitivity of the scale was 87.71% (95% CI: 69.74%-95.19%) while its specificity was 93.67% (95% CI: 85.84%-97.91%). The accuracy of the scale was 91.23% (95% CI: 84.46%-95.71%).

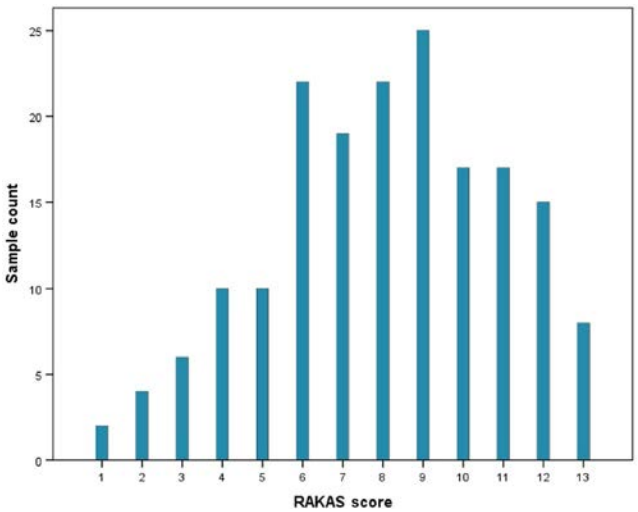

FIGURE 1 Score distribution

TABLE 3 Condensed test results

Questions	Correct answer/s	Response frequencies					Correct group responses			Discrimination index	Item Difficulty Index	Point biserial
		A	B	C	D	E	Non-distractor	Total %	Upper 27%	Lower 27%			
1.	A/B	44.07	49.15	6.21	–	–	DE	93.22	100	83.33	16.67	0.44-0.49	–
2.	B	1.13	76.27	7.34	6.21	–	E	76.27	91.67	60.42	31.25	0.76	0.28
3.	D	11.30	10.73	11.3	52.54	10.73	–	52.54	85.42	14.58	70.84	0.52	0.57
4.	B	42.94	42.37	13.56	0.56	–	E	42.37	45.83	33.33	12.5	0.42	0.12
5.	A	59.89	23.16	15.25	–	–	DE	59.89	89.58	25	64.58	0.59	0.5
6.	A	63.84	19.77	12.43	–	–	DE	63.84	83.33	31.25	52.08	0.63	0.47
7.	B	24.29	51.41	17.51	–	–	DE	51.41	81.25	27.08	54.17	0.51	0.46
8.	A	49.15	25.42	20.34	–	–	DE	49.15	77.08	18.75	58.33	0.49	0.47
9.	B	11.86	60.45	24.29	0.56	–	E	60.45	89.58	37.5	52.08	0.60	0.41
10.	A	58.19	9.04	16.95	10.17	5.65	–	58.19	91.67	29.17	62.5	0.58	0.5
11.	B	27.68	56.5	15.25	–	–	DE	56.5	72.92	39.58	33.34	0.56	0.31
12.	A	48.02	33.9	14.69	–	–	DE	48.02	75	18.75	56.25	0.48	0.47
13.	A	55.93	16.38	17.51	0.56	–	E	55.93	81.25	31.25	50	0.55	0.41

TABLE 4 Factor solution

S. no.	Items	Components				
		1	2	3	4	5
1.	6	0.642				
2.	7	0.780				
3.	8	0.738				
4.	12		0.832			
5.	13		0.830			
6.	1			0.642		
7.	3			0.758		
8.	2				0.620	
9.	4				0.709	
10.	9				0.636	
11.	5					0.575
12.	10					0.630
13.	11					0.709

4 | DISCUSSION

This study evaluated the psychometric properties of the English version of RAKAS through several validation techniques. It included estimation of a myriad of validities, observation of item discrimination and difficulty indices, evaluation of reliability and sensitivity of the scale. The sample size was calculated based on item-subject ratio of 1:10 plus a 3% drop-out rate. It is worthwhile mentioning that previous studies except for original RAKAS validation, have not used the item response theory for sample

TABLE 5 Cross-tabulation of score interpretation and occupation

RAKAS score interpretation	Sample count	Previous counseling by pharmacist on disease	
		Yes	No
Excellent knowledge	Count	32	8
	Expected count	16.5	23.5
	% Within counseling	43.8%	7.7%
Adequate knowledge	Count	22	42
	Expected count	26.4	37.6
	% Within counseling	30.1%	40.4%
Low knowledge	Count	14	38
	Expected count	21.4	30.6
	% Within counseling	19.2%	36.5%
Poor knowledge	Count	5	16
	Expected count	8.7	12.3
	% Within counseling	6.8%	15.4%

Abbreviation: RAKAS, Rheumatoid Arthritis Knowledge Assessment Scale.

TABLE 6 Cross-tabulation of score interpretation and occupation

RAKAS score interpretation	Count	Occupation		
		Employed	Unemployed	Household
Excellent knowledge	Count	27	5	15
	Expected count	18.3	10.4	18.3
	% Within score	57.4%	10.6%	31.9%
	% Within occupation	39.1%	12.8%	21.7%
Adequate knowledge	Count	26	12	24
	Expected count	24.2	13.7	24.2
	% Within score	41.9%	19.4%	38.7%
	% Within occupation	37.7%	30.8%	34.8%
Low knowledge	Count	13	15	20
	Expected count	18.7	10.6	18.7
	% Within score	27.1%	31.3%	41.7%
	% Within occupation	18.8%	38.5%	29%
Poor knowledge	Count	3	7	10
	Expected count	7.8	4.4	7.8
	% Within score	15.0%	35%	50%
	% Within occupation	4.3%	17.9%	14.5%

Abbreviation: RAKAS, Rheumatoid Arthritis Knowledge Assessment Scale.

size calculation for a validation study in this patient population.[7] Randomization was not possible since the scale was in English language and was sampled in a non-native English-speaking patient population. Therefore, convenience sampling strategy was opted to gather as many patients as possible to satisfy the sample size requirements. Nonetheless, the study gathered more responses than required which shows that it had no issues in patient acceptability and a 100% response rate was achieved. This aspect highlights the ease of understanding of language.

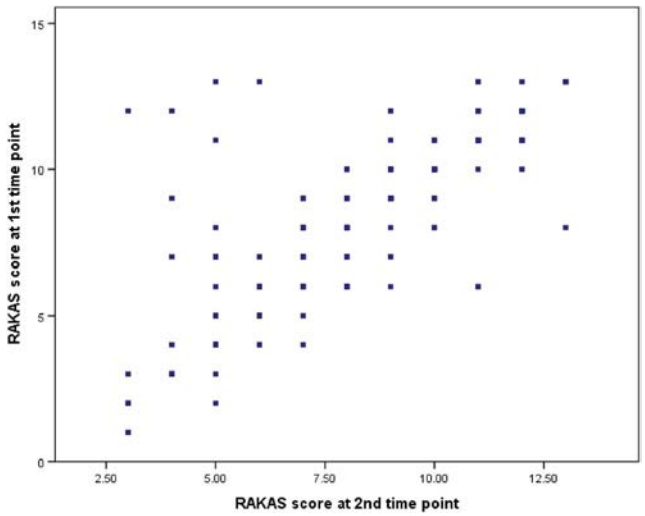

FIGURE 2 Test-retest correlation of Rheumatoid Arthritis Knowledge Assessment Scale (RAKAS) scores at time points 1 and 2

The reliability of the scale was.601 which was acceptable. It was similar to the findings of Naqvi and colleagues for the original Urdu version of RAKAS and was consistent with PKQ and Arthritis Knowledge Questionnaire.[7,14,16] The test-retest reliability coefficient correlation was significant and >.7 which established its test-retest reliability. Although the test-retest reliability values were less than those obtained for the original Urdu version of RAKAS and PKQ (ie, >.9), nevertheless, the values obtained from this study were in the recommended acceptable range.[7,14]

Two important aspects of any assessment that assess knowledge are the level of difficulty and discrimination power of the items in the test. These were evaluated in the Urdu version of RAKAS and therefore the English version was also subjected to the same.[7] The English version had an excellent discrimination power around 47.2% and average difficulty at 55.7%. A possible reason for a slightly lower than 50% discrimination could be the education level of patients as most of them (59.9%) were graduates. Graduates have more opportunities to learn and could benefit more from consultations as compared to patients with lower levels of education. In addition, the sensitivity analyses highlighted that the scale had an excellent sensitivity >85% and specificity >90%. These values together with a high accuracy >90% highlights the ability of the scale to have few false (+) or (−) results, that demonstrate scientific robustness of the scale.[35]

Factorial validity was established by calculating fit indices and observing if they were in an acceptable range. All fit indices were in acceptable ranges. The convergent validity of the English version of RAKAS was estimated for the first time as it was not estimated in the Urdu version.[7] The average factor loading was >0.7 which established its convergent validity. A high factor loading close to −1 or +1 indicates that the factor has a high influence on variables.[10] Having a high average factor loading indicates the relevance of the scale items to knowledge. The construct validity was checked through cross-tabulation of knowledge score interpretation with previous disease counseling by a pharmacist. Since it was a knowledge assessment, having an educational session with a healthcare professional would significantly affect a patient's knowledge about the disease. A significant association between the variables indicated that patients who had educational counseling had better knowledge. This established construct validity of the scale.

The known group validity was checked through cross-tabulation of knowledge score interpretation with the demographic variable of occupation. This was done assuming that patients who were associated with any external or household work would have better knowledge of disease since they require self-care of disease-related complications more actively as compared to unemployed patients. The cross-tabulation highlighted that patients associated with employment or household activities had better knowledge and the association was significant. This established the known group validity of the scale.

The availability of a validated English version of the scale would allow healthcare professionals to evaluate knowledge among RA patients in other parts of the world. The English version would also provide the opportunity to carry out translation in other languages which would increase its application. Since knowledge is a significant determinant of self-care and management of disease, clinicians could use this scale during regular history taking and assess a patient's level of understanding of disease. This could give an idea about the patient's ability to take care of the disease and manage the symptoms. Based on the knowledge score, patients could be provided educational counseling in areas where they are lacking. For instance, 1 item of the scale evaluates patient's understanding about role of physical therapy (PT) in RA. Evidence highlights that patients who require PT often have a low adherence.[36] This could be indicated by the scale. In this way the scale could contribute to achievement of positive treatment outcomes in patients with RA.

5 | CONCLUSION

The English version of RAKAS was successfully validated in the study. This version could be used to document knowledge about the disease in English-speaking patients. Further, the validation provides the benefits of this scale to a larger international community and offers the opportunity to translate the scale into other languages for clinical use.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

AAN conceived the idea with MAH and designed the study with WI, SS, MZ, MF and MSI. The methodology was written by AAN, WI, SS, MZ, MF, MSI, MZI, MTI, MAK, MA and AH. The data were collected by SS, MZ, MF and WI. The data were entered by SS, MZ, MF, WI, MZI and MSI. All authors contributed to data analysis and manuscript writing. The study was supervised by MAH. All authors read and approved final manuscript.

DATA AVAILABILITY STATEMENT

The dataset generated are the property of the organization and are not publicly available. However, they are available from the corresponding author on reasonable request.

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ORIGINAL ARTICLE

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Reliability and validity of culturally adapted Turkish Short Musculoskeletal Function Assessment questionnaire (SMFA-TR)

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Abstract

Aim: This study aimed to culturally adapt and validate the Turkish version of the Short Musculoskeletal Function Assessment Questionnaire (SMFA-TR) which primarily assesses the functional status of patients.

Methods: The translation and cross-cultural adaptation of SMFA to Turkish was made by the standardized procedure and tested for clinimetric quality. The following analyses were made to evaluate clinimetric quality of the SMFA-TR: reliability with factor analysis and Chronbach's α (construct validity), correlations between SMFA-TR and Short Form (SF)-36 (concurrent validity), test-retest reliability (intraclass correlation analyses), floor and ceiling effects. The questionnaire was applied to 166 patients with musculoskeletal problems. All patients filled in the SMFA-TR and the validated Turkish SF-36 questionnaire. Forty-two patients returned to complete the same questionnaires at 10 days.

Results: Factor analysis revealed a 4-factor structure of the SMFA-TR. Cronbach's α values were over 0.88 for both original subscales (dysfunction and bother) of the SMFA. Internal consistency (0.88-0.94) and test-retest reliability coefficients (0.90-0.98) were high for both subscales. Turkish SF-36 questionnaire conventional subscales showed significant correlations with SMFA-TR subscales. No floor or ceiling effects were found.

Conclusion: The Turkish version of the SMFA was found to be reliable and valid for Turkish-speaking patients with musculoskeletal injuries or disorders.

KEYWORDS

cross-cultural adaptation, reliability, short musculoskeletal function assessment, Turkish, validity

1 | INTRODUCTION

Musculoskeletal diseases are a major health problem causing significant loss of labor and an important increase in health expenses. Studies in this field are increasing day by day. Patient-reported outcome measures are effective tools summarizing the patients' functional status. However, the fact that most of these measurements are developed in English makes it difficult to apply these measurements to patients with different native languages. In this sense, widely preferred questionnaires are being translated into different

languages and culturally adapted to provide a tool for determining the results of the patient groups in different regions and comparing them with other populations. There are numerous questionnaires available in the literature to assess the function of a specific region (Disabilities of the Arm, Shoulder and Hand; Oxford Knee Score, etc) or evaluating the patient's general functional status (short Form [SF]-36, Short Musculoskeletal Functional Assessment [SMFA] etc).[1-4] SMFA is a widely preferred tool for the functional assessment of patients since it can be applied to different patient groups and patients with multiple injuries.[4,5]

The main advantage of SMFA over the other patient-reported health outcome scales is the ability to assess whole body parts rather than a specific region. Most of the functional assessment scales are prepared as region-specific and when multiple injuries exist, they might not be helpful. Additionally, it is not possible to report the complete health status of the patients by just their physical status. SMFA provides information about how the functional status of the patients affects their emotional status by the questions included in the "bother index". This is also a distinctive feature of the questionnaire compared to other scales.

SMFA, which has been translated and culturally adapted to several languages,[6-11] does not have a version in the Turkish language, which has over 70 million native speakers. This prevents the use of SMFA in Turkish-speaking patients and assessing their functional and emotional status. Therefore, it is not also possible to compare the treatment outcomes of the Turkish population to other nationalities who were evaluated by SMFA. In this study, we aimed to translate, culturally adapt and validate a Turkish version of SMFA. Thus, it will be possible to evaluate the functional outcomes of Turkish-speaking patients for both patient follow up and clinical research.

2 | MATERIALS AND METHODS

2.1 | Translation and cross-cultural adaptation

The permission from Swiontkowski et al[4] who developed the original questionnaire, was obtained to culturally adapt the SMFA questionnaire to Turkish and test its validity and reliability. The guideline of the American Academy of Orthopedic Surgeons for the cross-cultural adaptation of health status measures[12] was utilized during the translation and cross-cultural adaptation of the SMFA questionnaire. The forward translation was made by two bilingual translators, whose native language is Turkish. One of the translators had a medical background and was aware of the study while the other translator did not have a medical background and was not aware of the study. After the forward translations were obtained, two translators discussed the differences and a synthesis from these translations was formed. Then, the backward translation of the questionnaire to English was made by 2 bilingual translators, whose native language is English. Again, one of the translators had a medical background and was aware of the study while the other was not.

The expert committee, which includes a methodologist, 3 health professionals, 2 language professionals and 4 translators (2 forward and 2 backward translators), discussed and produced the pre-final version of the questionnaire. The content validity of each survey item in SMFA-TR was assessed by the expert committee on a 4-point Likert scale where 1 meant not relevant, 2 somewhat relevant, 3 moderately relevant, and 4 very relevant. Ethics approval from the local ethics committee was obtained before the study to apply the questionnaire to the patients (ethical approval number: 605.02.23). A pilot study on 20 patients with musculoskeletal diseases was conducted to test the pre-final version of SMFA-TR. The patients were asked if they found any question difficult or confusing. All patients found the questions easily understandable. Some minor changes were made by the expert committee according to patient feedback. The final version was approved by the expert committee (Appendix A).

2.2 | Study design

The questionnaire was applied to 166 patients who were referred to the outpatient clinic with musculoskeletal injuries or disorders, between 18 and 65 years old and a native-speaker of Turkish language, between July and December 2017. Patients with neuromuscular disorders, neurological dysfunction, cancer, comorbidity restricting functional status, reading or writing disabilities, cognitive or psychiatric disorders, were excluded.

2.3 | Instruments

The participants were administrated 2 questionnaires: SMFA-TR and SF-36. The SMFA questionnaire which was developed by Swiontkowski et al is an important patient-reported outcome measure tool being used frequently in the evaluation of a broad range of musculoskeletal diseases.[4] It includes 2 subscales (dysfunction and bother) and 46 questions. "Dysfunction Index" consisting of 34 questions examines the difficulties experienced by patients during their activities under 4 subcategories (daily activities, emotional status, function of the arm and hand, mobility), while "bother index" consisting of 12 questions examines how much the patients are bothered by their functional problems. Therefore, SMFA also provides information about the emotional status of the patients in addition to physical function. This is an important feature of SMFA, distinguishing it from the other physical function outcome scales. While the score ranges from 0 to 100, higher scores indicate poorer function.

The SF-36 is a 36-item, patient-reported survey which gives an opinion about health-related quality of life. The SF-36 consists of 8 subcategories including general health, physical function, social function, mental health, physical role, emotional role, bodily pain, and vitality. The sum of the scores ranges between 0 and 100; lower scores indicate more disability. The SF-36 Turkish version has been tested for reliability, validity, and applicability.[13]

2.4 | Statistical analysis

The Statistical Package of Social Science (SPSS), version 22.0, was used to analyze the data. *P* values less than .05 were considered significant. Demographic analysis of the study group was made by descriptive analyses employing means and percentages with 95% confidence intervals (CIs). Frequency, means and standard deviations (SD) were calculated for the variables. The final Turkish version of the questionnaire was tested for clinimetric characteristics including factor analysis, internal consistency, concurrent validity, retest reliability, and floor and ceiling effects (content validity).

2.5 | Validity

Validity is defined as the ability of an instrument to measure what it is intended to measure. Concurrent validity was determined by comparing the scores of SMFA-TR to the Turkish version of SF-36. Between the indices of the SMFA-TR and the related subscales of the SF-36, Spearman's Rho correlation coefficients were calculated. Spearman's correlation coefficients were interpreted as follows: little = 0.00-0.25; weak = 0.26-0.49; moderate = 0.50-0.69; strong = 0.70-0.89; very strong = 0.90-1.00.[14]

The ceiling and floor effects of SMFA-TR were also analyzed by percentage frequency of the lowest or highest possible score obtained. The participants with the lowest or highest possible scores prevent the correct measurement of validity and reliability. The ceiling and floor effects of more than 15% were considered significant.[6]

2.6 | Reliability

Reliability is the ability of an instrument to create reproducible results. Exploratory factor analysis was performed on all SMFA-TR items by principal component analyses with varimax rotation. The factor loading values more than 0.4 were accepted as significant[15] Internal consistency was examined with factor analysis and Cronbach's α for each subscale. A Cronbach's α of at least 0.70 was considered acceptable and less than 0.70 was considered low.[16] Forty-eight patients who did not receive any intervention in 10 days after their first referral to the outpatient clinic, due to ongoing laboratory or radiological tests, were requested to participate in test-retest reliability 10 days after the first assessment. Forty-two of them returned the questionnaires. Intraclass correlation coefficients (ICC) with corresponding 95% CIs were calculated to examine retest reliability.

3 | RESULTS

3.1 | Demographic and clinical characteristics

A total of 166 patients (92 male, 74 female) with various musculoskeletal injuries and disorders participated in this study. The mean age of the patients was 42 ± 9.8 years (range 18-64). An important majority of the patients (80.7%) had at least a high school degree. Most of the patients were married (73.5%). The patients had various diagnoses including soft tissue contusion (26.5%), fracture (19.3%), osteoarthritis (21.1%), tendinitis (12.6%) and chronic conditions of the spine (13.8%). The demographic and clinical characteristics of the patients ae given in Table 1.

TABLE 1 Demographic and clinical characteristics of the participants

Characteristics	N = 166
Gender (%)	92 male (55.5%), 74 female (44.5%)
Age, mean (SD, range)	42 (±9.8, 18-64)
Body mass index, kg/m^2, mean (SD)	21.5 (±3.9)
Education level (%)	
Elementary school	32 (19.3%)
High school	63 (37.9%)
College or higher	71 (42.8%)
Marital status	
Single	44 (26.5%)
Married	67 (40.4%)
Married and have children	55 (33.1%)
Location (%)	
Upper extremity	46 (27.7%)
Lower extremity	55 (33.1%)
Pelvis	21 (12.6%)
Spine	36 (21.6%)
Multiple	8 (4.8%)
Diagnosis (%)	
Soft tissue contusion	44 (26.5%)
Fracture	32 (19.3%)
Osteoarthritis	35 (21.1%)
Tendinitis	21 (12.6%)
Chronic condition of the spine	23 (13.8%)
Other	11 (6.6%)

3.2 | Clinimetric characteristics

The Kaiser–Meyer–Olkin value was 0.94, indicating the factor analysis was appropriate and the variables were correlated. Factor analyses revealed that the 4-factor construct was the most appropriate with 70.8% of the variance when compared to 2, 3 or 5-factor solutions. All items of SMFA-TR loaded on 1 of the 4 factors ranging between 0.51 and 0.93 (Appendix B). The newly identified subscales included upper extremity dysfunction (7 items), mobility (10 items), daily activities (21 items), and mental and emotional problems (8 items; Table 2). Cronbach's α was 0.90 (95% CI 0.88-0.94) for the dysfunction index and 0.91 (95% CI 0.89-0.94) for the bother index.

TABLE 2 Spearman's rank correlation coefficients between the SMFA-TR indices and the Turkish SF-36 subscales

	Turkish SF-36							
SMFA-TR	General health	Physical function	Social function	Mental health	Physical role	Emotional role	Bodily pain	Vitality
Dysfunction	0.57	0.76	0.71	0.54	0.62	0.54	0.58	0.59
Bother	0.58	0.70	0.72	0.57	0.65	0.52	0.62	0.55
Total index	0.57	0.73	0.71	0.59	0.63	0.52	0.60	0.56
Upper extremity dysfunction[a]	0.42	0.46	0.56	0.43	0.55	0.35	0.47	0.51
Mobility[a]	0.64	0.68	0.62	0.36	0.59	0.46	0.56	0.42
Daily activities[a]	0.44	0.79	0.55	0.32	0.68	0.47	0.66	0.57
Mental and emotional problems[a]	0.54	0.46	0.59	0.65	0.55	0.62	0.49	0.53

Note: The values were interpreted as follows: little = 0.00-0.25; weak = 0.26-0.49; moderate = 0.50-0.69; strong = 0.70-0.89; very strong = 0.90-1.00.

Abbreviations: SF-36, Short Form 36SMFA-TR, Short Musculoskeletal Function Assessment-Turkish.

[a]Newly identified subscales after the factor analysis.

When newly identified subscales were evaluated, Cronbach's α values were 0.90 for upper extremity dysfunction, 0.91 for mobility, 0.94 for daily activities and 0.88 for mental and emotional problems. Both values were satisfactory for internal consistency reliability.

The SMFA-TR categories and the subscales of the SF-36 showed moderate to strong correlations in all comparisons. The strongest correlations were with physical function and social function in both dysfunction and bother indices of SMFA-TR, while the other subscales of SF-36 showed moderate correlations (Table 2). ICC for retest reliability of dysfunction (0.96) and Bother (0.93) indices between the 1st and 10th days were high (Table 3). There was no minimum "0" score of the SMFA-TR, which indicates the best functional status was recorded; and no maximum "100" score of the SMFA-TR, which indicates the worst functional status was recorded. Overall, no floor or ceiling effect was found for any of the subscales of the SMFA.

4 | DISCUSSION

This study aimed to culturally adapt and validate the Turkish version of SMFA to provide a useful instrument in evaluating the functional outcomes of Turkish-speaking patients. SMFA-TR showed sufficient reliability, validity and repeatability to be used as an instrument in assessing the functional status and life quality of Turkish patients with a wide variety of musculoskeletal injuries or disorders. All original and factor analysis-identified subscales of the SMFA-TR demonstrated adequate internal reliability and showed good correlation with respective subscales of the validated Turkish SF-36.[13]

Cronbach's α values for the SMFA-TR were excellent in both conventional subscales: 0.90 for the dysfunction and 0.91 for the bother index. These results indicate that SMFA-TR has good reliability, similar to the results of the initial validation of the original SMFA[4] as well as other studies validating some other language versions.[7,8,11,17] Wollmerstedt et al reported Cronbach's α values between 0.88-0.97 for both indices of the German version of SMFA (SMFA-D) in all their patient groups including osteoarthritis of the hip or knee, rheumatoid arthritis or rotator cuff tear undergoing surgical or medical inpatient treatment.[11] Ponzer et al found Cronbach's α values of 0.94 for the dysfunction index and 0.90 for the bother index in their study with the Swedish version of SMFA (SMFA-Swe).[7] Bohm et al reported Cronbach's α values of 0.93 and 0.88 for dysfunction and bother indices with the German version of SMFA in their study with patients undergoing rotator cuff repair.[17] Taylor et al reported similar Cronbach's α values for the Brazilian Portuguese version of SMFA (SMFA-BR) (0.95 for the dysfunction and 0.91 for the Bother indices) in their patient group with various musculoskeletal diseases which was similar to our patient group.[8] Our results showed that SMFA-TR is an internally consistent tool and has high reliability.

We compared both the conventional and newly identified subscales of the SMFA-TR with all subscales of Turkish SF-36, to investigate the concurrent validity. Both indices of the SMFA-TR showed a good correlation with the original subscales of Turkish SF-36. Physical function and social function subscales of SF-36 showed strong correlations in both dysfunction and bother indices of SMFA-TR, while the other subscales of SF-36 showed moderate correlations. When newly identified subscales were evaluated, some of the correlations were weak, especially in upper extremity problems and mobility scales. This might be due to the broad range of questions in SMFA-TR assessing the patient as a whole, preventing it to be used for the outcomes of specific parts of the body. These results were comparable to the original SMFA validation study by Swiontkowski et al[4] and several other translated versions of the SMFA.[6,8,17-19]

Swiontkowski et al found significant correlations between both indices of original SMFA and all subscales of SF-36.[4] In the study by Taylor et al, the strongest correlation was also with the physical function subscale of SF-36 for both indices of SMFA-BR.[8]

TABLE 3 Descriptive statistics and repeatability measures of the SMFA-TR (N = 42)

	Baseline mean (SD)	Retest mean (SD)	Mean difference (95% CI)	ICC (95% CI)	SEM
Dysfunction index	17.6 (13.4)	17.1 (14.5)	0.5 (−1.2-1.7)	0.96 (0.93-0.98)	4.23
Bother index	21.9 (16.5)	23.2 (19.2)	1.3 (−0.3-1.9)	0.93 (0.90-0.95)	6.02
Total index	39.5 (15.1)	40.3 (16.8)	0.8 (−0.6-1.8)	0.94 (0.91-0.96)	7.18

Abbreviations: CI, confidence interval; ICC, intraclass correlation coefficient; SD, standard deviation; SEM, standard error of measurement; SMFA-TR, Short Musculoskeletal Function Assessment-Turkish.

Reininga et al found strong relationship between both dysfunction and bother indices of SMFA-NL and physical function, physical role, and bodily pain subscales of the SF-36, while they found moderate correlations with the SF-36 subscales social function and vitality.[6] Reininga et al also found a 4-factor solution and they also showed weak correlations between upper and lower extremity problem subscales of SMFA-NL and subscales of SF-36. Brazilian Portuguese and Spanish versions of SMFA found 3-factor solutions, but several items of these versions did not load on 1 of the 3 factors.[8,10] However, all items of SMFA-TR loaded into the 4-factor solution. The Chinese version of SMFA identified 6 different subscales.[18]

Bohm et al reported significant correlations among the SMFA-D Bother and Function indices and all subscales of SF-36 except physical role.[17] The highest correlation was reported between the dysfunction index of SMFA-D and the physical function subscale of SF-36 (0.76) and between the bother index of SMFA-D and the physical function subscale of SF-36 (0.63). However, 1 year postoperatively, both indices of SMFA-D showed a significant correlation with all SF-36 subscales. Kirschner et al also found a significant relationship between both SMFA-D subscales and all SF-36 subscales in a prospective study of 63 patients with primary knee osteoarthritis.[19]

ICC of the dysfunction index was 0.96, while it was 0.93 for the bother index between the 1st and 10th days, indicating a good test-retest reliability. The original SMFA validation study demonstrated similar values (0.93 and 0.88 for the dysfunction and bother indices, respectively) at average 7.8 days in 150 patients with various musculoskeletal disorders.[4] The other several translated versions of the SMFA also showed comparable results.[6-8] Taylor et al reported high ICC values (0.97-0.99) for retest reliability at 1 and 7 days in SMFA-BR.[8] In their evaluation of 63 patients with a stable orthopedic condition, Ponzer et al found ICC values of 0.93 and 0.88 for the dysfunction index and bother index of the SMFA-Swe, respectively.[7] Reininga et al reported ICC values ranging between 0.91-0.96 with their cross-culturally adapted Dutch version of SMFA (SMFA-NL).[6]

Although there are some studies reporting ceiling effects,[4,6,17] we found no floor or ceiling effects for any of the SMFA-TR subscales, similar to the study by Lindahl et al[9] We think the most probable reason behind the ceiling effects in other studies was including healthy patients or patients with long follow-ups after their conservative treatment or surgery. For example; Reininga et al included patients with up to 2 years follow up after their surgical treatment.[6] In our patient group; all patients referred to the outpatient clinic had an acute or chronic complaint. This was the possible reason behind the "no ceiling effect" in our study.

To the best of our knowledge; this study is the first to culturally adapt the SMFA into a Turkish version and evaluate its validity and reliability. However, the lack of responsiveness evaluation is an important limitation to this study and it should be analyzed in future research. Item analysis and confirmatory factor analyses were also not evaluated. Concurrent validity was evaluated only with the SF-36 questionnaire, which can also be counted as one of the limitations of this study. However, since the SMFA is not a region-specific questionnaire, several studies also used the same methodology, including the validation study of the original SMFA questionnaire.[4,8,9]

5 | CONCLUSION

The reliability, validity and repeatability of SMFA-TR were found sufficient to assess the functional status of Turkish-speaking patients with musculoskeletal problems. This study will provide a valid questionnaire for Turkish-speaking patients and will aid further research on patients with musculoskeletal disabilities.

AUTHOR CONTRIBUTIONS

Bedri Karaismailoglu: design of the study, interpretation of the results and writing the manuscript. Salih Candost Yetismis: data collection. Gokhan Kaynak, Berna Karaismailoglu: interpretation of the results and reviewing the manuscript.

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APPENDIX A

Short Musculoskeletal Function Assessment – Turkish (SMFA-TR)

KISA KAS-İSKELET SİSTEMİ FONKSİYON DEĞERLENDİRME ANKETİ (SMFA-TR)

Açıklamalar

- Yaralanmanız (sakatlığınız) veya eklem rahatsızlığınızın bu hafta sizi nasıl etkilediğini ve günlük aktivitelerinizde yaralanmanız (sakatlığınız) veya eklem rahatsızlığınıza bağlı yaşadığınız problemleri bilmek istiyoruz.
- Lütfen tüm soruları, sizi en iyi tarif eden seçeneğin yanındaki kutucuğa işaret koyarak yanıtlayınız.
- Herhangi bir soruya yorum yapmak isterseniz, lütfen kenarlardaki boşlukları kullanınız.
- Bazı sorular yaralanmanız (sakatlığınız) veya eklem rahatsızlığınızla ilgili olmasa bile lütfen tüm sorulara cevap veriniz.

BU SORULAR, YARALANMANIZ (SAKATLIĞINIZ) VEYA EKLEM RAHATSIZLIĞINIZ SEBEBİYLE BU HAFTA GÜNLÜK AKTİVİTELERİNİZDE NE KADAR ZORLUK YAŞADIĞINIZ HAKKINDADIR

1. Alçak bir sandalyeye oturmak veya alçak bir sandalyeden kalkmak sizin için ne kadar zordur?

Hiç Zor Değil	Biraz Zor	Orta Derecede Zor	Çok Zor	Yapmak Olanaksız
☐	☐	☐	☐	☐

2. İlaç şişelerini veya kavanozları açmak sizin için ne kadar zordur?

Hiç Zor Değil	Biraz Zor	Orta Derecede Zor	Çok Zor	Yapmak Olanaksız
☐	☐	☐	☐	☐

3. Gıda veya diğer şeyler için alışveriş yapmak sizin için ne kadar zordur?

Hiç Zor Değil	Biraz Zor	Orta Derecede Zor	Çok Zor	Yapmak Olanaksız
☐	☐	☐	☐	☐

4. Merdiven çıkmak sizin için ne kadar zordur?

Hiç Zor Değil	Biraz Zor	Orta Derecede Zor	Çok Zor	Yapmak Olanaksız
☐	☐	☐	☐	☐

5. Sıkı bir yumruk yapmak sizin için ne kadar zordur?

Hiç Zor Değil	Biraz Zor	Orta Derecede Zor	Çok Zor	Yapmak Olanaksız
☐	☐	☐	☐	☐

6. Bir küvete veya duşa girmek ya da bir küvetten veya duştan çıkmak sizin için ne kadar zordur?

Hiç Zor Değil	Biraz Zor	Orta Derecede Zor	Çok Zor	Yapmak Olanaksız
☐	☐	☐	☐	☐

7. Rahat bir uyku almak sizin için ne kadar zordur?

Hiç Zor Değil	Biraz Zor	Orta Derecede Zor	Çok Zor	Yapmak Olanaksız
☐	☐	☐	☐	☐

8. Öne eğilmek veya diz çökmek sizin için ne kadar zordur?

Hiç Zor Değil	Biraz Zor	Orta Derecede Zor	Çok Zor	Yapmak Olanaksız
☐	☐	☐	☐	☐

9. Düğme, çıtçıt, çengel ya da fermuarları kullanmak sizin için ne kadar zor?

Hiç Zor Değil	Biraz Zor	Orta Derecede Zor	Çok Zor	Yapmak Olanaksız
☐	☐	☐	☐	☐

10. Kendi tırnaklarınızı kesmek sizin için ne kadar zordur?

Hiç Zor Değil	Biraz Zor	Orta Derecede Zor	Çok Zor	Yapmak Olanaksız
☐	☐	☐	☐	☐

11. Kendi kendinize giyinmek sizin için ne kadar zordur?

Hiç Zor Değil	Biraz Zor	Orta Derecede Zor	Çok Zor	Yapmak Olanaksız
☐	☐	☐	☐	☐

12. Yürümek sizin için ne kadar zordur?

Hiç Zor Değil	Biraz Zor	Orta Derecede Zor	Çok Zor	Yapmak Olanaksız
☐	☐	☐	☐	☐

13. Bir süre oturduktan veya uzandıktan sonra yürümek sizin için ne kadar zordur?

Hiç Zor Değil	Biraz Zor	Orta Derecede Zor	Çok Zor	Yapmak Olanaksız
☐	☐	☐	☐	☐

14. Kendi başınıza dışarı çıkmak sizin için ne kadar zordur?

Hiç Zor Değil	Biraz Zor	Orta Derecede Zor	Çok Zor	Yapmak Olanaksız
☐	☐	☐	☐	☐

15. Araba sürmek sizin için ne kadar zordur?

Hiç Zor Değil	Biraz Zor	Orta Derecede Zor	Çok Zor	Yapmak Olanaksız
☐	☐	☐	☐	☐

16. Banyo esnasında kendi temizliğinizi yapmak sizin için ne kadar zordur?

Hiç Zor Değil	Biraz Zor	Orta Derecede Zor	Çok Zor	Yapmak Olanaksız
☐	☐	☐	☐	☐

17. Tokmakları veya kolları çevirmek (örneğin; kapı tokmağını çevirerek kapıyı açmak veya cam açma kolunu çevirerek araba camını açmak) sizin için ne kadar zordur?

Hiç Zor Değil	Biraz Zor	Orta Derecede Zor	Çok Zor	Yapmak Olanaksız
☐	☐	☐	☐	☐

18. Kalemle veya tuşlara basarak yazı yazmak sizin için ne kadar zordur?

Hiç Zor Değil	Biraz Zor	Orta Derecede Zor	Çok Zor	Yapmak Olanaksız
☐	☐	☐	☐	☐

19. Tek ayak üzerinde dönme hareketi yapmak sizin için ne kadar zordur?

Hiç Zor Değil	Biraz Zor	Orta Derecede Zor	Çok Zor	Yapmak Olanaksız
☐	☐	☐	☐	☐

20. Bisiklet sürme, yürüyüş ya da koşu gibi her zamanki eğlence amaçlı fiziksel aktivitelerinizi yapmak sizin için ne kadar zordur?

Hiç Zor Değil	Biraz Zor	Orta Derecede Zor	Çok Zor	Yapmak Olanaksız
☐	☐	☐	☐	☐

21. Hobiler, el sanatları, bahçe işleri, kart oyunları ya da arkadaşlarınızla dışarı çıkma gibi her zamanki boş zaman aktivitelerinizi yapmak sizin için ne kadar zordur?

Hiç Zor Değil	Biraz Zor	Orta Derecede Zor	Çok Zor	Yapmak Olanaksız
☐	☐	☐	☐	☐

22. Cinsel aktivitelerinizde ne kadar zorluk yaşıyorsunuz?

Hiç Zor Değil	Biraz Zor	Orta Derecede Zor	Çok Zor	Yapmak Olanaksız
☐	☐	☐	☐	☐

23. Toz alma, bulaşık yıkama ya da çimleri sulama gibi hafif ev veya bahçe işlerini yapmak sizin için ne kadar zordur?

Hiç Zor Değil	Biraz Zor	Orta Derecede Zor	Çok Zor	Yapmak Olanaksız
☐	☐	☐	☐	☐

24. Yerleri yıkama, süpürme ya da çim biçme gibi ağır ev veya bahçe işi yapmak sizin için ne kadar zordur?

Hiç Zor Değil	Biraz Zor	Orta Derecede Zor	Çok Zor	Yapmak Olanaksız
☐	☐	☐	☐	☐

25. Ücret karşılığı çalıştığınız iş, ev işleri ya da gönüllü aktiviteler gibi her zamanki işlerinizi yapmak sizin için ne kadar zordur?

Hiç Zor Değil	Biraz Zor	Orta Derecede Zor	Çok Zor	Yapmak Olanaksız
☐	☐	☐	☐	☐

SIRADAKİ SORULAR YARALANMANIZ (SAKATLIĞINIZ) VEYA EKLEM RAHATLIĞINIZ SEBEBİYLE BU HAFTA NE SIKLIKTA PROBLEMLER YAŞADIĞINIZI SORGULAMAKTADIR

26. Ne sıklıkta topallayarak yürürsünüz?

Hiçbir Zaman	Çok Az Bir Zaman	Bazı Zamanlar	Çoğu Zaman	Her Zaman
☐	☐	☐	☐	☐

27. Ağrılı uzvunuzu (uzuvlarınızı) ya da sırtınızı kullanmaktan ne sıklıkta kaçınırsınız?

Hiçbir Zaman	Çok Az Bir Zaman	Bazı Zamanlar	Çoğu Zaman	Her Zaman
☐	☐	☐	☐	☐

28. Bacağınızda ne sıklıkta kilitlenme ya da boşalma hissedersiniz?

Hiçbir Zaman	Çok Az Bir Zaman	Bazı Zamanlar	Çoğu Zaman	Her Zaman
☐	☐	☐	☐	☐

29. Ne sıklıkta konsantrasyon problemi yaşıyorsunuz?

Hiçbir Zaman	Çok Az Bir Zaman	Bazı Zamanlar	Çoğu Zaman	Her Zaman
☐	☐	☐	☐	☐

30. Bir gün içinde çok fazla şey yapmak bir sonraki gün yapacaklarınızı ne sıklıkta etkiliyor?

Hiçbir Zaman	Çok Az Bir Zaman	Bazı Zamanlar	Çoğu Zaman	Her Zaman
☐	☐	☐	☐	☐

31. Ne sıklıkta çevrenizdekilere karşı asabi davranırsınız? (örneğin; insanları terslemek, iğneli cevaplar vermek veya kolayca eleştirmek gibi)

Hiçbir Zaman	Çok Az Bir Zaman	Bazı Zamanlar	Çoğu Zaman	Her Zaman
☐	☐	☐	☐	☐

32. Ne sıklıkta yorgun hissediyorsunuz?

Hiçbir Zaman	Çok Az Bir Zaman	Bazı Zamanlar	Çoğu Zaman	Her Zaman
☐	☐	☐	☐	☐

33. Ne sıklıkta kendinizi engelli (sakat) hissediyorsunuz?

Hiçbir Zaman	Çok Az Bir Zaman	Bazı Zamanlar	Çoğu Zaman	Her Zaman
☐	☐	☐	☐	☐

34. Bu yaralanmanız (sakatlığınız) veya eklem rahatsızlığı sebebiyle kendinizi ne sıklıkta kızgın veya hüsrana uğramış hissediyorsunuz?

Hiçbir Zaman	Çok Az Bir Zaman	Bazı Zamanlar	Çoğu Zaman	Her Zaman
☐	☐	☐	☐	☐

BU SORULAR, YARALANMANIZ (SAKATLIĞINIZ) YA DA EKLEM RAHATSIZLIĞINIZA BAĞLI OLUŞAN PROBLEMLER NEDENİYLE BU HAFTA NE KADAR RAHATSIZ HİSSETTİĞİNİZ HAKKINDADIR

SİZİ NE KADAR RAHATSIZ EDİYOR.

35. Ellerinizi, kollarınızı veya bacaklarınızı kullanırken yaşadığınız problemler sizi ne kadar rahatsız ediyor?

Hiç Rahatsız Edici Değil	Az Rahatsız Edici	Orta Derecede Rahatsız Edici	Çok Rahatsız Edici	Aşırı Derecede Rahatsız Edici
☐	☐	☐	☐	☐

36. Sırtınızı kullanırken yaşadığınız problemler sizi ne kadar rahatsız ediyor?

Hiç Rahatsız Edici Değil	Az Rahatsız Edici	Orta Derecede Rahatsız Edici	Çok Rahatsız Edici	Aşırı Derecede Rahatsız Edici
☐	☐	☐	☐	☐

37. Evinizin etrafındaki işlerinizi yaparken yaşadığınız problemler sizi ne kadar rahatsız ediyor?

Hiç Rahatsız Edici Değil	Az Rahatsız Edici	Orta Derecede Rahatsız Edici	Çok Rahatsız Edici	Aşırı Derecede Rahatsız Edici
☐	☐	☐	☐	☐

38. Banyo yapma, giyinme, süslenme ya da diğer kişisel bakımlarla ilgili problemler sizi ne kadar rahatsız ediyor?

Hiç Rahatsız Edici Değil	Az Rahatsız Edici	Orta Derecede Rahatsız Edici	Çok Rahatsız Edici	Aşırı Derecede Rahatsız Edici
☐	☐	☐	☐	☐

39. Uyku ve dinlenme ile ilgili problemler sizi ne kadar rahatsız ediyor?

Hiç Rahatsız Edici Değil	Az Rahatsız Edici	Orta Derecede Rahatsız Edici	Çok Rahatsız Edici	Aşırı Derecede Rahatsız Edici
☐	☐	☐	☐	☐

40. Boş zaman ya da eğlence aktiviteleri ile ilgili problemler sizi ne kadar rahatsız ediyor?

Hiç Rahatsız Edici Değil	Az Rahatsız Edici	Orta Derecede Rahatsız Edici	Çok Rahatsız Edici	Aşırı Derecede Rahatsız Edici
☐	☐	☐	☐	☐

41. Arkadaşlarınız, aileniz ya da hayatınızdaki diğer önemli insanlarla ilgili problemler sizi ne kadar rahatsız ediyor?

Hiç Rahatsız Edici Değil	Az Rahatsız Edici	Orta Derecede Rahatsız Edici	Çok Rahatsız Edici	Aşırı Derecede Rahatsız Edici
☐	☐	☐	☐	☐

42. Düşünme, konsantre olma ya da hatırlamayla ilgili problemler sizi ne kadar rahatsız ediyor?

Hiç Rahatsız Edici Değil	Az Rahatsız Edici	Orta Derecede Rahatsız Edici	Çok Rahatsız Edici	Aşırı Derecede Rahatsız Edici
☐	☐	☐	☐	☐

43. Yaralanmanız (sakatlığınız) ya da eklem rahatsızlığınıza alışma veya onunla başa çıkma ile ilgili problemler sizi ne kadar rahatsız ediyor?

Hiç Rahatsız Edici Değil	Az Rahatsız Edici	Orta Derecede Rahatsız Edici	Çok Rahatsız Edici	Aşırı Derecede Rahatsız Edici
☐	☐	☐	☐	☐

44. Her zamanki günlük işlerinizi yaparken yaşadığınız problemler sizi ne kadar rahatsız ediyor?

Hiç Rahatsız Edici Değil	Az Rahatsız Edici	Orta Derecede Rahatsız Edici	Çok Rahatsız Edici	Aşırı Derecede Rahatsız Edici
☐	☐	☐	☐	☐

45. Başkalarına bağımlı hissetme ile ilgili problemler sizi ne kadar rahatsız ediyor?

Hiç Rahatsız Edici Değil	Az Rahatsız Edici	Orta Derecede Rahatsız Edici	Çok Rahatsız Edici	Aşırı Derecede Rahatsız Edici
☐	☐	☐	☐	☐

46. Tutulma ve ağrı ile ilgili problemler sizi ne kadar rahatsız ediyor?

Hiç Rahatsız Edici Değil	Az Rahatsız Edici	Orta Derecede Rahatsız Edici	Çok Rahatsız Edici	Aşırı Derecede Rahatsız Edici
☐	☐	☐	☐	☐

KATILIMINIZ İÇİN TEŞEKKÜR EDERİZ...

APPENDIX B

Factor loading values for the four-factor construct of the SMFA-TR. The values more than 0.4 were accepted as significant.

Item	Factor 1 (Upper extremity dysfunction)	Factor 2 (Mobility)	Factor 3 (Daily activities)	Factor 4 (Mental and emotional problems)
Difficulty in…				
1. Getting in or out of a low chair	0.06	0.74	0.48	0.11
2. Opening medicine bottles or jars	0.81	0.12	0.30	0.18
3. Shopping for groceries or other things	0.42	0.54	0.61	0.16
4. Climbing stairs	0.08	0.85	0.35	0.10
5. Making a tight fist	0.85	0.03	0.23	0.11
6. Getting in or out of the bathtub or shower	0.34	0.76	0.41	0.14
7. Getting comfortable to sleep	0.09	0.11	0.27	0.51
8. Bending or kneeling down	0.07	0.91	0.33	0.11
9. Using buttons, snaps, hooks, or zippers	0.93	0.11	0.32	0.19
10. Cutting own fingernails	0.88	0.22	0.29	0.02
11. Dressing oneself	0.52	0.49	0.58	0.10
12. Walking	0.16	0.86	0.23	0.11
13. Getting moving sitting or lying down	0.02	0.75	0.29	0.38
14. Going out by oneself	0.25	0.82	0.22	0.15
15. Driving	0.44	0.52	0.63	0.15
16. Cleaning oneself after going to the bathroom	0.39	0.24	0.62	0.09
17. Turning knobs or levers	0.82	-0.03	0.36	0.09
18. Writing or typing	0.79	0.04	0.19	0.21
19. Pivoting	0.13	0.81	0.24	0.11
20. Doing usual physical recreational activities	0.18	0.58	0.69	0.21
21. Doing usual leisure activities	0.44	0.46	0.60	0.33
22. Sexual activity	0.19	0.24	0.56	0.33
23. Doing light housework or yard work	0.41	0.40	0.61	0.21
24. Doing heavy housework or yard work	0.41	0.49	0.62	0.34
25. Doing usual work	0.44	0.41	0.58	0.41
Frequency of…				
26. Walking with a limp	-0.08	0.76	0.42	0.39
27. Avoiding using painful limb(s) or back	0.23	0.61	0.69	0.34
28. Leg locks or gives way	-0.08	0.71	0.42	0.21
29. Problems with concentration	0.04	0.03	0.29	0.88
30. Doing too much in one day affects what you do the next day	0.31	0.41	0.64	0.47
31. Acting irritable towards those around you	-0.03	0.16	0.14	0.72
32. Being tired	0.21	0.31	0.69	0.55
33. Feeling disabled	0.34	0.53	0.74	0.66
34. Feeling angry or frustrated because of injury	-0.04	0.19	0.44	0.67
Bothered by problems with…				
35. Using hands, arms, or legs	0.79	0.11	0.33	0.29
36. Using your back	0.11	0.32	0.61	0.44
37. Doing work around home	0.33	0.49	0.66	0.35
38. Bathing, dressing, toileting	0.44	0.45	0.53	0.18
39. Sleep and rest	0.11	0.07	0.57	0.52

(Continues)

APPENDIX B (Continued)

Item	Factor 1 (Upper extremity dysfunction)	Factor 2 (Mobility)	Factor 3 (Daily activities)	Factor 4 (Mental and emotional problems)
40. Leisure or recreational activities	0.19	0.51	0.71	0.29
41. Friends, family	0.09	0.17	0.22	0.58
42. Thinking, concentrating	0.04	0.01	0.11	0.66
43. Adjusting or coping with injury	0.29	0.39	0.52	0.71
44. Doing usual work	0.34	0.41	0.72	0.43
45. Feeling dependent on others	0.38	0.52	0.49	0.68
46. Stiffness and pain	0.10	0.53	0.67	0.37

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ORIGINAL ARTICLE

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Translation, validation and cross-cultural adaptation of the Revised Fibromyalgia Impact Questionnaire (FIQR) in Nepali language

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Abstract

Objective: To translate, cross-culturally adapt and test the psychometric properties of the Revised Fibromyalgia Impact Questionnaire (FIQR) in Nepali language (Nepali FIQR).

Methods: The translation was performed following the methodological standards described by Beaton. Comprehensibility testing of the preliminary version was done in 40 fibromyalgia patients, and a pre-final version was prepared after making changes in the original version to maintain the equivalence with the target version. Psychometric testing was done in another group of 130 fibromyalgia patients to test for content validity and reliability. Construct validity was tested with visual analog score (VAS) for pain and Short Form (SF)-36.

Results: Nepali FIQR was comprehensible to 92.5% patients. The internal consistency was also acceptable with Cronbach's alpha of 0.900, 0.714 and 0.863 for function, overall and symptoms domain, respectively. Construct validity was also acceptable with a moderate correlation between Nepali FIQR and VAS and SF-36. Test-retest reliability of the total Nepali FIQR and of each item were acceptable with intraclass correlation coefficient (ICC) of >0.7 in all items except for question 1 of function domain (ICC: 0.65).

Conclusions: Nepali FIQR is a comprehensible, reliable and valid tool for evaluation of the functional status of Nepalese patients with fibromyalgia and should be implemented in routine clinical care and research settings.

KEYWORDS

fibromyalgia, FIQ, FIQR, Nepal, translation

1 | INTRODUCTION

Fibromyalgia or fibromyalgia syndrome (FMS) is a chronic condition characterized by chronic widespread pain, fatigue, poor sleep, cognitive dysfunction and somatic symptoms.[1-3] FMS has shown to have a significant impact on the quality of life of an affected individual. The prevalence of FMS ranges from 6% to 15% in various studies from the United States whereas a recent review has shown values of fibromyalgia prevalence in the general population between 0.2% and 6.6%, in women between 2.4% and 6.8%, in urban areas between

0.7% and 11.4%, in rural areas between 0.1% and 5.2%.[3-5] Although the prevalence is quite high in the general population, the data from Nepal remain sparse.

Fibromyalgia syndrome is not associated with any characteristic biochemical or serological abnormalities and there are no specific biomarkers to diagnose or monitor the disease.[6] The diagnosis is still based on either the American College of Rheumatology (ACR) 1990 classification criteria[7] or 2010 preliminary diagnostic criteria[8] and the assessment and monitoring of activity has relied on the use of the Revised Fibromyalgia Impact Questionnaire (FIQR).[9] The FIQR was revised from the original Fibromyalgia Impact Questionnaire (FIQ) version[10] to address a wider range of symptoms including also tenderness to touch, memory disturbances, postural balance, hyperalgesia or sensitivity to environmental factors.[9] Some questions in the FIQR were modified to suit both male and female patients of all socioeconomic levels. The FIQ has been translated into more than 14 languages and FIQR to more than 6 languages.

With increasing diagnosis of FMS in the Nepalese population, there has been an increasing need of this tool in the local Nepali language for clinical and research use. The aim of this study was to translate, cross-culturally adapt and validate the Nepali version of FIQR.

2 | METHODS

Fibromyalgia Impact Questionnaire is a self-reported patient outcome measure questionnaire consisting of 21 questions in three different domains (9 on function, 2 on impact and 10 on symptoms). Each item is rated on an 11-point (0-10) Likert scale indicating 0 for no difficulty/no problem to 10 for extremely difficult/ unable to perform/ extremely severe symptoms.

2.1 | Study population

Patients with FMS based on the ACR 1990 criteria[7] (which is more specific and still more widely used than the revised 2010 diagnostic criteria)[7,11] by two rheumatologists (BV and SN) were included in the study. All patients were >18 years of age, provided informed verbal consent and did not have any diagnosed mental illness.

2.2 | Translation

The translation was carried out following the guidelines by Beaton et al[12] for the cross-cultural adaptation of self-report questionnaires and completed the steps of translation, synthesis, back-translation and final draft preparation. Translation of English FIQR to Nepali versions (T1 and T2) was performed by two independent native Nepali speakers. The 1st was a rheumatologist (SN) who was aware of the concept of the items and the 2nd translator was a non-medical person unaware of the concept of the items examined. A synthesized version, T12, was prepared after joint meeting of the two translators to sort out any confusion.

Back-translation of the T12 version to English was then done by two independent translators: one with a Master's degree in journalism with English major (B1) and another post-graduate rheumatology registrar (MB; B2). A final steering committee was formed consisting of all the translators, rheumatologists, rheumatology registrar, methodologist, and a research officer. The committee reviewed all the translated and back-translated versions (T1, T2, T12, B1 and B2) and compared the similarities and differences in terms of conceptual equivalence with the original English FIQR. They finally developed the "preliminary" version in Nepali language.

2.3 | Comprehensibility and cross-cultural adaptation

Comprehensibility testing of the "preliminary draft" was done in a group of 40 patients with FMS, classified according to ACR 1990 criteria, by the research officer (RJ) and the rheumatology registrar (MB). The patients were individually interviewed by them and each item question was administered. Respondents were probed to ensure their understanding of the intended meaning of each source item. Further, they were asked to rate their level of understanding of Nepali FIQR on a 4-level rating scale (0-not comprehensible; 1-slightly comprehensible; 2-easily comprehensible; and 3-very easily comprehensible). For each item, a score of 2 or more was considered comprehensible. Words or items causing confusion to respondents were noted by the interviewers. After the comprehensibility study, the same committee again ensured semantic, idiomatic, experiential and conceptual equivalence among the source and target versions. The source items that were considered confusing were modified by the expert committee with items that included activities common with Nepali culture and a "pre-final draft" prepared for further psychometric testing.

2.4 | Psychometric evaluation

For psychometric evaluation, another 130 patients with FMS fulfilling the same criteria as for the comprehensibility testing were enrolled by consecutive sampling method. The sample size calculation considered the minimum acceptable correlation as 0.6 (a = 0.05, b = 0.1), and the maximum acceptable change for correlation as 0.04. The actual sample size taken considered the possibility of 10% dropout during the retest. The selected patients were called on a particular day for a patient education program. During the program, the patients were explained regarding the questionnaire items and the same interviewers and patient's relatives helped the illiterate patients to fill them. They were simultaneously given to fill the visual analog scale (VAS) for pain and Short Form-36 (SF-36) at the same visit. A follow-up visit was scheduled at 48 hours for physiotherapy training and an uninformed retest was taken.

TABLE 1 Cross-cultural adaptation in English Revised Fibromyalgia Impact Questionnaire

Domain	Item	English version	Nepali version	Remarks
Function	1	Brush or comb your hair (0-10)	No change	
	2	Walk continuously for 20 min (0-10)	No change	
	3	Prepare a homemade meal (0-10)	No change	
	4	Vacuum, scrub or sweep floor (0-10)	Addition of bending forward to touch floor	
	5	Lift and carry a bag full of groceries (0-10)	No change	
	6	Climb 1 flight of stairs (0-10)	Addition of walking uphill for 5 min	People living in rural areas may not have multi-story houses
	7	Change bed sheets (0-10)	No change	
	8	Sit in a chair for 45 min (0-10)	No change	
	9	Shop for groceries (0-10)	No change	
Overall	1	Fibromyalgia prevented me from accomplishing goals for the wk (0-10)	No change	
	2	I was completely overwhelmed by my fibromyalgia symptoms (0-10)	No change	
Symptoms	1	Please rate the level of pain (0-10)	No change	
	2	Please rate your level of energy (0-10)	No change	
	3	Please rate your level of stiffness (0-10)	No change	
	4	Please rate the quality of sleep (0-10)	No change	
	5	Please rate your level of depression (0-10)	The word "depression" was retained	Nepali population understands the word depression better than its Nepali term
	6	Please rate your level of memory problems (0-10)	No change	
	7	Please rate your level of anxiety (0-10)	No change	
	8	Please rate your level of tenderness to touch (0-10)	No change	
	9	Please rate your level of balance problems (0-10)	No change	
	10	Please rate your level of sensitivity to loud noises, bright lights, odors, and cold (0-10)	No change	

2.5 | Statistical analysis

2.5.1 | Comprehensibility

Simple descriptive analysis was used to express the percentage of patients with easy or very easy comprehensibility.

2.5.2 | Reliability

Internal consistency of each item was evaluated by Cronbach alpha for the all 21 items and three domains of Nepali FIQR. For individual domain, Cronbach's alpha was derived by deleting that domain from the questionnaire. Test-retest reliability of Nepali FIQR was analyzed

using intraclass correlation coefficient (ICCs). The ICCs and their confidence intervals were calculated using random-effects model and an ICC of 0.85 or higher was considered acceptable.[13]

2.5.3 | Validity

The construct validity of Nepali FIQR was measured by calculating the Spearman's correlation coefficient for Nepali FIQR with VAS for pain and SF-36. A correlation coefficient greater than 0.7 was considered as strong correlation.[14]

3 | RESULTS

3.1 | Translation

During translation, there was a level of disagreement between translators and back-translators on a few words like anxiety and depression. A telephonic opinion was taken from two psychiatry colleagues for the appropriate words used by them in daily practice. There was a final agreement in committee on the Nepali word for anxiety. However, it was decided that the word "depression" would be kept as it is in the Nepali form because the term was considered well understood and of frequent use by the native speakers (Table 1).

3.2 | Comprehensibility and cross-cultural adaptation

Overall there was good comprehension in the initial administration of the "preliminary" version. As most of the items addressed the activities common to both genders and all socioeconomic strata, the committee did not feel a need to modify any items to retain the semantic, idiomatic, experiential and conceptual equivalence with the original FIQR. A rating of more than 2 on comprehensibility rating were given by 92.5% (37/40) patients.

3.3 | Psychometric testing

Out of 130 participants, 90.7% were female. The mean age of the participants was 38.28 ± 10.63 years. Other baseline parameters are shown in Table 2. The internal consistency was also acceptable with Cronbach's alpha of 0.900, 0.714 and 0.863 for function, overall and symptoms domain of Nepali FIQR, respectively (Table 3). All alpha values if the item was deleted were above 0.8 (Table 4), indicating significant internal consistency irrespective of individual item/ question. Moderate correlation was observed when the question number 1 of symptom domain (pain) was compared with VAS for pain (rho: 0.530, Pearson: 0.546) and question number 21 of SF-36 (rho: 0.443, Pearson: 0.385). Weak correlation was observed between the 2nd question of symptom domain of FIQR (energy) and question number 27 of SF-36 (rho 0.247, Pearson 0.289) (Table 5). Test-retest reliability of each item were acceptable with ICC of >0.7 in all items except for question 1 of function domain (ICC: 0.65) (Table 3) and 0.89 for overall score (total FIQR).

TABLE 2 Sociodemographic and clinical profile of the participants (N = 130)

Characteristics	Mean ± SD or n (%)
Age	38.28 ± 10.63
Gender	
Male	12 (9.3)
Female	118 (90.7)
Education	
Illiterate	2 (1.5)
Can sign	16 (12.3)
Primary level	10 (7.7)
Secondary level	28 (21.6)
Higher secondary and more	74 (56.9)
Occupation	
Home-maker	63 (48.4)
Student	8 (6.2)
Office worker	34 (26.2)
Others	25 (19.2)
Disease duration in mo	Median 12.0
VAS pain	4.51 ± 1.91
Comorbidities	
Diabetes mellitus	2 (1.5)
Hypertension	10 (7.7)
Rheumatic diseases	13 (10.0)
Hypothyroidism	11 (8.4)
FIQR pretest	29.4 ± 18.8
FIQR post-test	28.5 ± 21.4

Abbreviations: FIQR, Revised Fibromyalgia Impact Questionnaire; VAS, visual analog scale.

4 | DISCUSSION

Fibromyalgia is a common health problem ranking next to low back pain and osteoarthritis as a cause of chronic musculoskeletal pain.[15,16] There are no biomarkers for the diagnosis of this complex syndrome, nor is there any monitoring test.[6] The problem is compounded by the involvement of the cognitive, mental and psychological axis in the majority of patients which needs to be addressed for measuring the impact of FMS.[8] Self-reported outcome measures are important tools to measure the health status of the society as well as to improve them. The FIQ was developed by the Oregon Health & Science University in 1991,[10] 1 year after the classification criteria for FMS was published by ACR.[7] Although it was widely accepted and translated into more than 14

TABLE 3 Test-retest reliability for Nepali version of Revised Fibromyalgia Impact Questionnaire

Domain	Item	ICC (95% CI)	Cronbach's alpha
Function	1	0.65 (0.40-0.80)	0.900
	2	0.94 (0.89- 0.96)	
	3	0.85 (0.73-0.91)	
	4	0.89 (0.82-0.94)	
	5	0.84 (0.72-0.91)	
	6	0.907 (0.84-0.95)	
	7	0.77 (0.60-0.87)	
	8	0.74 (0.54-0.85)	
	9	0.79 (0.63-0.88)	
Overall	1	0.87 (0.78-0.93)	0.714
	2	0.87 (0.77-0.92)	
Symptoms	1	0.86 (0.76-0.93)	0.863
	2	0.72 (0.60-0.87)	
	3	0.94 (0.89-0.96)	
	4	0.94 (0.90-0.97)	
	5	0.79 (0.64-0.88)	
	6	0.90 (0.83-0.94)	
	7	0.86 (0.76-0.92)	
	8	0.76 (0.61-0.87)	
	9	0.71 (0.50-0.84)	
	10	0.90 (0.83-0.94)	

TABLE 4 Item-total correlation and Cronbach's alpha if item deleted for Nepali version of the Revised Fibromyalgia Impact Questionnaire

Domain	Item	Correlation item: total correlation	α if item deleted
Function	1	0.448	0.902
	2	0.714	0.883
	3	0.757	0.880
	4	0.737	0.881
	5	0.608	0.892
	6	0.583	0.893
	7	0.757	0.881
	8	0.643	0.889
	9	0.749	0.880
Overall	1	0.554	-
	2	0.554	-
Symptoms	1	0.594	0.849
	2	0.583	0.848
	3	0.642	0.843
	4	0.571	0.850
	5	0.513	0.854
	6	0.661	0.842
	7	0.728	0.837
	8	0.490	0.856
	9	0.444	0.859
	10	0.562	0.851

TABLE 5 Correlation between domains of Nepali FIQR with domains of SF-36 and VAS pain

	Spearman's rho	Pearson correlation
FIQR 3-1 and VAS pain	.530	0.546
FIQR 3-1 and SF-36 Q. 21	.443	0.385
FIQR 3-2 and SF-36 Q. 27	.247	0.289

Abbreviations: FIQR, Revised Fibromyalgia Impact Questionnaire; SF-36, Short Form-36; VAS, visual analog scale.

different languages, over the period of time it was realized that the tool used many items pertaining to American women, particularly being treated in a single center. The scoring and interpretation were more complex. A revised questionnaire, FIQR was then formulated which had items more relatable to both genders and all socioeconomic strata.[9] Also, the original 7 symptom questions in the 3rd domain were expanded to include cognitive function, tenderness, balance, and overall sensitivity to environmental stimuli such as bright lights and loud noises. The authors showed there was a good correlation between the total scores for the FIQR and the FIQ (r = .88, P < .001). There was good internal consistency (Cronbach's alpha of 0.95) and construct validity of FIQR.[9,13] Moreover, the inclusion of the four new symptoms items, namely memory, balance, tenderness, and environmental sensitivity, provided good discriminant validity between the FMS group and the other cases of rheumatoid arthritis, lupus and so on.[9] With these added advantages and generalizability, we chose to translate FIQR into Nepali language for daily clinical and research works.

This study describes the rigorous methodological requirements followed for preparing this instrument. The internal consistency of the domains was acceptable with lowest value of Cronbach's alpha obtained for the domain of overall impact (0.71) and highest for the domain of function (0.90). It is lower than the original version (0.95)[9] and Portuguese version (0.94)[17] but in line with other study groups like Spanish (0.91),[18] Turkish (0.89),[19] Moroccan (0.91), [20] Jordanian Arabic (0.91),[21] Persian (0.87)[22] and Brazilian (0.96)[23] versions. The test-retest reliability of Nepali FIQR was acceptable ranging from 0.65 to 0.94 for individual items and 0.89 for overall score. It is comparable to the test-retest reliability of the Spanish (r = .82),[18] Turkish (r = .84),[19] Moroccan (r = .84),[20] and Jordanian Arabic (r = .93)[21] study groups. However, the content validity was not tested for the translated questionnaire.

It may be concluded that the Nepali version of FIQR has good comprehensibility, reliability, validity and has been adapted according to the local culture. It has shown moderate correlation with other similar instruments like SF-36 and VAS. Thus, Nepali FIQR may be used for assessment of disease activity in patients with fibromyalgia.

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CONFLICT OF INTEREST

None.

ETHICAL APPROVAL

Informed consent was obtained from each participant before interviews.

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Clinical characteristics and outcomes of 566 Thais with systemic sclerosis: A cohort study

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Abstract

Background: Most Thai patients with systemic sclerosis (SSc) have diffuse cutaneous SSc (dcSSc) unlike most Caucasians and some Asians. A longitudinal cohort study among Thai dcSSc is needed.

Objectives: We aimed to determine the overall clinical characteristics, define the clinical difference between limited cutaneous SSc (lcSSc) and dcSSc, and ascertain the mortality rate and the factors associated with mortality.

Method: We conducted a cohort study including 566 Thai adult SSc patients between January 2013 and June 2019. Clinical difference between lcSSc and dcSSc was investigated using generalized estimating equations (GEE).

Results: Females presented more than males (356 vs 210 cases). The majority of cases were dcSSc (411; 72.6%). The median duration of disease at the time of pulmonary fibrosis (PF) detection was 2.5 years, pulmonary arterial hypertension 8.1 years, and renal crisis 4.1 years. By GEE analysis, dcSSc was significantly associated with salt-and-pepper skin, hand deformity, and every 1-point increase in modified Rodnan skin score (mRSS). A greater mortality risk was associated with age at onset >60 years (hazards ratio [HR] 5.5), a World Health Organization functional class (FC) III (HR 5.1), FC IV (HR 34.8), edematous skin (HR 11.4), early onset of PF (HR 1.7), each 5-point increase in the mRSS (HR 4.5), and ≥2 internal organ involvements (HR 10.1).

Conclusion: dcSSc is a common SSc subset among Thais. PF was an early complication in SSc and earlier PF detection was associated with a poorer prognosis. Elderly onset, high FC, severe skin tightness, and multiple organ involvements were associated with a greater mortality risk.

KEYWORDS

clinical trial, cohort study, mortality, scleroderma, systemic sclerosis

1 | INTRODUCTION

Systemic sclerosis (SSc) or scleroderma is a rare connective tissue disease and skin tightness is a telltale sign. There are two major subsets: lcSSc or limited cutaneous SSc, and dcSSc or diffuse cutaneous SSc.[1] lcSSc includes skin tightness of the face, hands, feet, forearms and legs; while dcSSc includes skin tightness of the trunk and both extremities. DcSSc, associated with internal organ fibrosis and prognosis, is more severe than the limited type.

The prevalence of SSc varies between 31 and 658 per 1 000 000 people and the incidence is between 3.7 and 23 per 1 000 000 person-years depending on ethnicity.[2] In Thailand, the prevalence and incidence of SSc is not well-defined. Foocharoen et al reported the prevalence of hospitalization of SSc in Thailand was 136.1 per 100 000 admissions in 2015 and SSc was the second most common primary diagnosis in 2010 compared to other connective tissue diseases.[3] The disease is commonly detected in women with a female-to-male ratio between 1.5 and 17 to 1.0.[4-9] dcSSc is the most common SSc subset among Thais,[5] Chinese,[10] and New Zealanders[11] while lcSSc is more common among other Asian populations including Indians,[12] Japanese,[4,13] Iranians,[14] and most Caucasians (Australian, European, US, and Canadian).[15-20] The proportion of lcSSc and dcSSc is nearly equal among Koreans[21] and some other Caucasians (Greek).[22]

Fibrosis is a predominant pathological finding in scleroderma and it can present in the skin but also in internal organs (ie, kidneys, lungs, heart, and intestines).[23] Gastrointestinal involvement is a common internal organ involvement in SSc with a prevalence between 50% and 80%, particularly in the dcSSc subset.[7,24] The clinical findings include dysphagia, heartburn, early satiety, bloating, diarrhea, and constipation. Cardiopulmonary involvement is the leading cause of death in SSc, having overtaken renal crisis in the last decade.[25] These complications are commonly detected in dcSSc; however, cardiopulmonary involvements have been reported in lcSSc[26] for which fibrosis is not a major clinical feature. A renal crisis is a serious internal organ involvement in SSc and a major cause of death in the last decade. The prevalence of renal crisis is between 5% and 20% in the first 4 years after disease onset, particularly in dcSSc.[27] Renal outcome is good among patients who had renal recovery within 18 months of diagnosis or did not need dialysis. However, the prognosis is poor among those needing long-term renal replacement or peritoneal dialysis.[28]

Most Thai SSc patients (70%) have dcSSc in contradistinction to most Caucasians and some Asians (17%-37%).[8,17,20] The clinical features of Thai SSc might differ from other ethnic groups among whom lcSSc predominates; for example, internal organ fibrosis is earlier and more severe. The outcomes of dcSSc are worse than lcSSc. Our objectives were to: (a) determine the overall clinical characteristics among Thais with SSc; (b) define the clinical difference between lcSSc and dcSSc; and (c) determine the mortality rate and the factors associated with mortality among Thai SSc patients.

2 | METHODS

Between January 1, 2013 and June 30, 2019, we conducted a cohort study of SSc patients over 15 years of age, diagnosed with SSc, attending the Scleroderma Clinic at Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand. All the patients had a diagnosis of SSc based on the American College of Rheumatology (ACR) criteria and/or that they fulfilled the classification criteria for SSc by the ACR/EULAR (European League Against Rheumatism) 2013.[29] SSc was classified as the limited or diffuse type as per LeRoy et al.[30]

2.1 | Operational definitions

The onset of disease is considered the date of first symptoms. Digital ulcer is defined when there is painful denuded area with well-demarcated borders that locates on the volar aspect of the fingers.[31] Hand deformity is defined when the finger joints are flexion contractures resembling claw deformities.[32] Disability of hands is defined by difficulty with occupational activities and/or activities of daily living.[32] The definition of pulmonary fibrosis (PF) is fulfilled when interstitial fibrosis is detected by high-resolution computed tomography (HRCT). Pulmonary arterial hypertension (PAH) is diagnosed when the mean pulmonary arterial pressure (mPAP) is >20 mm Hg at rest with a pulmonary artery wedge pressure of ≤15 mm Hg with a pulmonary vascular resistance of ≥3 Wood units, as confirmed by right heart catheterization.[33] Pulmonary hypertension due to interstitial lung disease (PH-ILD) is defined by an mPAP between 20 and 34.9 mm Hg and a forced vital capacity (FVC) <70%, or forced expiratory volume in 1 second (FEV_1) <60% predicted or ≥20% involvement of PF evaluated by HRCT. Esophageal involvement is defined when any esophageal symptoms of SSc are present (ie, esophageal dysphagia, heartburn, or reflux symptoms). Stomach involvement is defined by the symptom of early satiety or vomiting.[34] Intestinal involvement is determined by symptoms of diarrhea, bloating, malabsorption, constipation, and/or ileus or pseudo-intestinal obstruction. Myocardial involvement is defined when the left ventricular ejection fraction ≤50%. Renal crisis is indicated when there is: (a) a rapid, progressive rise in serum creatinine; (b) the abrupt onset of hypertension; and/or (c) microangiopathic hemolytic anemia. Weight loss is defined as unintentional loss of >5% of usual body weight over 6-12 months.[35] The definition of anemia is fulfilled if hemoglobin is <12.0 g/dL in women and <13.0 g/dL in men.[36]

The start date was the date of the first symptom of SSc and the end date was the end date of the study (June 30, 2019). The patient was censored if lost to follow-up or was still alive at the end date. The status lost to follow-up was retrieved from the government office and the information was reviewed and the cause of death ascertained by a physician. Time-to-event (death) was the time calculated by subtracting the end date from the date of first symptom of SSc.

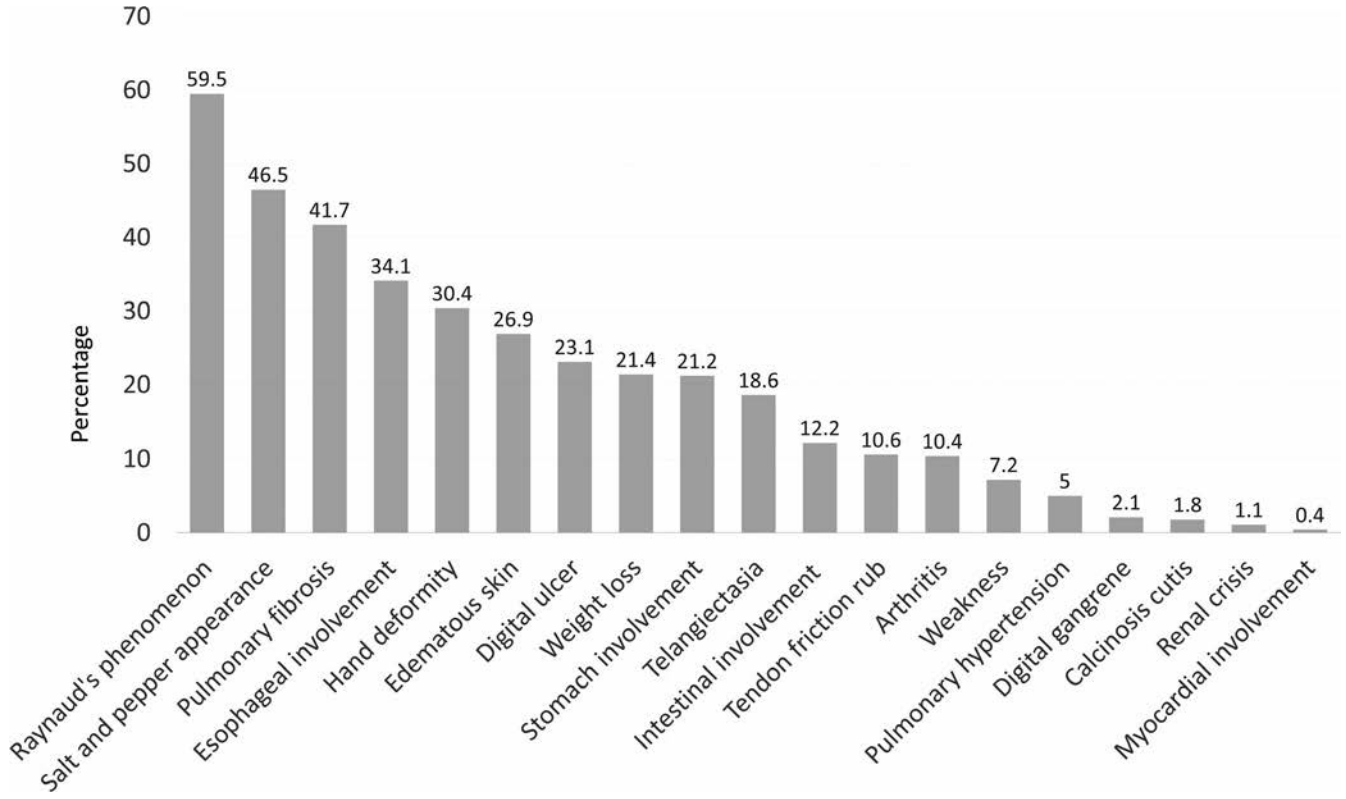

FIGURE 1 Clinical features at onset

2.2 | Statistical analysis

Clinical characteristics were categorized. The data were divided into dichotomous or polytomous or continuous variables. The codes were set for each categorical variable.

The clinical difference between lcSSc and dcSSc of the longitudinal data was investigated using generalized estimating equations (GEE). Variables with $P < .1$ were entered into a generalized linear mixed model and mixed-effects models.

The mortality rate was calculated with its 95% confidence interval (95% CI). The hazard ratio (HR) and its 95% CI between the prognostic factors and death were assessed. Univariate analysis was used to evaluate dichotomous categorical variables. As for polytomous categorical variables, the data were put into a dummy table and the median survival time, HR, confidence interval, and P value calculated. The Kaplan-Meier method was applied to estimate the probability of death and median survival time. The HRs that accounted for the effects of several variables (ie, variables with $P < .10$) were entered into a Cox regression model and the interaction effects evaluated. Variables were tested for significance using the Wald χ^2 statistic and all statistical tests were two-tailed. $P < .05$ was considered statistically significant. The data were analyzed using STATA version 11.2 (StataCorp., College Station, TX, USA).

The study was designed by the authors and approved by the Human Research Ethics Committee of Khon Kaen University as per the Helsinki Declaration and the Good Clinical Practice Guidelines (HE621404). All eligible patients signed informed consent before entry into the cohort study. The parents consented on behalf of their children who were under 18 years of age. The sponsor had no role in the study.

3 | RESULTS

There was a total of 631 SSc patients from the Scleroderma Clinic, of whom 65 were excluded due to being lost to follow-up after the first visit. Thus 566 cases were included into the study. Women presented more frequently than men (356 to 210 cases for a ratio of 1.7:1). The mean age at onset of first symptom and mean age on study date was 50.0 ± 11.8 years (range 14.0-84.1) and 54.6 ± 10.8 years (19.5-84.3), respectively. The majority of cases was dcSSc (411 cases; 72.6%). The mean duration of SSc was 8.3 ± 6.2 years (range 0.3-45.4).

At onset, Raynaud's phenomenon was the most common initial presentation among Thai SSc (59.5%) followed by salt-and-pepper skin appearance (46.5%). PF was the most common internal organ involvement at onset (41.7%) followed by esophageal involvement (34.1%). Constitutional symptoms, particularly weight loss, occurred in around 20% while renal crisis and myocardial involvement were rare at onset (Figure 1). The median modified Rodnan skin score (mRSS) at onset among all the patients was 6 (interquartile range [IQR] 0-14). Classification by number of internal organ involvement (esophagus, stomach, intestine, lungs, hearts, and renal) revealed that 182 cases (32.2%) had no internal organ involvement

at onset, 194 (34.3%) had 1, 119 (21.0%) had 2, 62 (11.0%) had 3, and 9 (1.6%) had 4 (Table 1). PF and esophageal involvement were the most common coexisting internal organ involvements at onset (87 cases; 15.4%), followed by esophagus and stomach involvements (68 cases; 12.0%), then PF and stomach involvements (60 cases; 10.6%).

At the study date, 204 cases (36.0%) had only 1 internal organ involvement, 191 (33.8%) had 2, 50 (8.8%) had more than 3 (one case had 4 and one had 5). Among those with more than 1 internal organ involvement, PF with gastrointestinal involvement was the most common (186 cases; 32.9%), followed by PF with pulmonary hypertension (PH) (79 cases; 14.0%) (32 were PF with PAH, 47 were PF with PH-ILD), then PAH with gastrointestinal involvement (55 cases; 9.7%). The median duration of disease at time of PF detection was 2.5 years (IQR 1.1-4.9), while PAH was 8.1 years (IQR 6.9-11.1), and renal crisis was 4.1 years (IQR 2.1-16.4).

According to the univariate analysis, female gender, positive for anti-topoisomerase I, less body mass index, FC ≥ II, the presence of digital ulcer, telangiectasia, salt-and-pepper skin appearance, tendon friction rub, hand deformity, arthritis, muscle weakness, stomach involvement, weight loss, renal crisis, and high mRSS, presented more frequently in dcSSc than in lcSSc. Internal involvement, particularly PF, PAH, renal crisis, impaired left ventricular function, and duration of disease at time of PF and PAH detection were not significantly different between the lcSSc and dcSSc groups. The overall clinical characteristics and clinical comparison between lcSSc and dcSSc are presented in Table 2.

According to the GEE analysis, salt-and-pepper skin appearance, hand deformity, and every 1 point increase in mRSS were significantly associated with dcSSc: the respective coefficients were 1.70 (95% CI 0.29-3.11), 2.16 (95% CI 0.34-3.98), and 0.28 (95% CI 0.03-0.26) (Table 3).

During the total 4692.03 person-years of the study, 164 SSc patients died, for an overall mortality rate in SSc of 3.5 per 100 person-years (95% CI 3.0-4.1). Of the 164, 138 had dcSSc and 26 lcSSc, and the respective mortality rate was 4.1 and 2.0 per 100 person-years (P = .004). The mean age at death was 59.0 ± 11.9 years. The respective survival rate of the mortality cases at 1, 3, 5 and 10 years was 97.1%, 92.0%, 84.0% and 69.9%. The survival rate of lcSSc at 1, 3, 5 and 10 years was significantly higher than dcSSc (98.7% vs 96.6% at 1 year, 95.1% vs 90.9% at 3 years, 88.7% vs 82.2% at 5 years, and 80.5% vs 66.2% at 10 years).

The major causes of death (104 cases; 63.4%) was related to SSc disease itself and the most common cause of death was due to SSc unspecified organ involvement (41 cases; 39.4%), followed by cardiac involvement (29 cases; 27.9%), and PF (18 cases; 17.3%). The most common non-SSc-related cause of death was pulmonary infection (21 cases; 35%), followed by septicemia (16 cases: 26.7%), natural death (5 cases; 8.3%), and cancer (5 cases; 8.3%). SSc-related deaths were revealed in both dcSSc (91; 65.9%) and lcSSc (13; 50%); however, there was no statistical significant (P = .13; Table 4).

The factors significantly associated with mortality risk in SSc by univariate analysis include: female gender, age at onset >60 years, dcSSc, positive for anti-topoisomerase I antibody, FC II, III, IV, presenting with Raynaud's phenomenon, digital ulcers, salt-and-pepper skin appearance, edematous skin, tendon friction rub, muscle weakness, esophageal involvement, intestinal involvement, weight loss, PF, early onset of PF, renal crisis, poor left ventricular ejection fraction, high mRSS, anemia, high numbers of internal organ involvement, PF with gastrointestinal involvement, and PF with renal crisis (Table 5). The factors associated with mortality risk in SSc according to the Cox regression analysis were: age at onset >60 years, FCs III, IV, edematous skin, early onset of PF, every 5-point increase in mRSS, and multiple internal organ involvement (Table 6).

Kaplan-Meier survival graphs of all the SSc patients, stratified by organ involvement are shown in Figures 2 and 3.

4 | DISCUSSION

We conducted a cohort study of Thai SSc patients and analyzed the clinical characteristics including clinical features at onset, clinical features during follow-up, clinical difference between dcSSc and lcSSc and mortality. We found that some of the demographic and clinical features of Thai SSc are different and some similar to those of Caucasian and some Asian SSc. The proportion of Thai male-to-female SSc is comparable in contrast to the higher ratio of women among Europeans, Australians, Americans, and other Asians (Koreans, Japanese, Indians, Iranians, and Chinese).[9,13,14,17,18,20,37,38]

TABLE 1 Internal organ involvement at onset

	Internal organ involvement						
Number of internal organ involvements at onset	Lungs n = 236	Esophagus n = 193	Stomach n = 120	Intestine n = 69	PAH n = 28	Myocardial involvement n = 2	Renal crisis n = 6
1 (n = 194)	99	56	21	12	4	0	2
2 (n = 119)	79	74	47	22	12	2	2
3 (n = 62)	50	54	44	29	9	0	0
4 (n = 9)	8	9	8	6	3	0	2

Abbreviation: PAH, pulmonary arterial hypertension.

TABLE 2 Overall clinical characteristics and comparison between lcSSc and dcSSc

Clinical characteristic	Overall N = 566 (%)	SSc subset		*P* value
		lcSSc N = 155 (%)	dcSSc N = 411 (%)	
Female	356 (62.9)	116 (74.8)	240 (58.4)	<.001*
Age at onset, y, mean ± SD (range)	50.0 ± 11.8 (14.0-84.1)	50.3 ± 12.4 (18.7-84.1)	49.9 ± 11.7 (13.9-80.2)	.71
Age on the study date, y, mean ± SD (range)	54.6 ± 10.8 (19.5-84.3)	54.3 ± 11.5 (19.5-84.3)	54.7 ± 10.6 (20-83.2)	.72
Duration of disease, y, mean ± SD (range)	8.3 ± 6.2 (0.3-45.4)	8.4 ± 5.9 (0.6-29.3)	8.2 ± 6.3 (0.3-45.4)	.77
Serological test				
Positive for anti-topoisomerase I antibody, n = 245	198 (80.8)	50 of 74 (67.6)	148 of 171 (86.6)	.001*
Positive for anti-centromere antibody, n = 158	25 (15.8)	13 of 49 (26.5)	12 of 109 (11.0)	.05
BMI, kg/m^2, mean ± SD (range)	16.5 (2.1)	15.9 (3.2)	16.6 (1.7)	.01*
Clinical characteristics				
Functional class				
I	194 (45.6)	67 (58.8)	127 (40.8)	.01*
II	179 (42.1)	38 (33.3)	141 (45.3)	
III	48 (11.3)	8 (7.0)	40 (12.9)	
IV	4 (0.9)	1 (0.9)	3 (1.0)	
Raynaud phenomenon	90 (15.9)	26 (16.8)	64 (15.6)	.72
Digital ulcer	108 (19.1)	11 (7.1)	97 (19.1)	<.001*
Digital gangrene	11 (1.9)	1 (0.7)	10 (2.4)	.30
Telangiectasia	187 (33.0)	29 (18.7)	158 (38.4)	<.001*
Calcinosis cutis	27 (4.8)	5 (3.2)	22 (5.4)	.29
Salt-and-pepper appearance	220 (38.9)	27 (17.4)	193 (47.0)	<.001*
Edematous skin	45 (7.9)	7 (4.5)	37 (9.0)	.80
Tendon friction rub	77 (13.6)	9 (5.8)	68 (16.6)	<.001*
Hand deformity	202 (35.7)	20 (12.9)	182 (44.3)	<.001*
Arthritis	27 (4.8)	2 (1.3)	25 (6.1)	.014*
Muscle weakness	30 (5.3)	2 (1.3)	28 (6.8)	<.001*
Esophageal involvement	229 (40.5)	55 (35.5)	174 (42.3)	.14
Stomach involvement	86 (15.2)	16 (10.3)	70 (17.0)	.042*
Intestinal involvement	99 (17.5)	20 (12.9)	79 (19.2)	.08
Weight loss	74 (13.1)	13 (8.4)	61 (14.8)	.04*
Pulmonary fibrosis	265 (46.8)	60 (38.7)	205 (49.9)	.21
Duration of disease at time of pulmonary fibrosis detection, y, median (IQR)	2.5 (1.1-4.9)	2.2 (1.3-2.7)	2.7 (1.1-5.4)	.45
Pulmonary arterial hypertension	102 (18.0)	22 (14.2)	80 (19.5)	.15
Duration of disease at time of pulmonary arterial hypertension detection, y, median (IQR)	8.1 (6.9-11.1)	6.0 (3.0-8.3)	9.4 (7.6-11.4)	.11
Renal crisis	11 (1.9)	0 (0)	11 (2.7)	.04*
Duration of disease at time of renal crisis detection, y, median (IQR)	4.1 (2.1-16.4)	-	4.1 (2.1-16.4)	NA
Myocardial involvement, n = 312	7 (2.2)	1 of 83 (1.2)	6 of 229 (2.6)	.68
mRSS, mean ± SD	7.68 ± 8.09	2.87 ± 3.94	9.50 ± 8.50	<.001*
mRSS > 20 points	61 (10.8)	2 (1.3)	59 (14.4)	<.001*
Anemia	296 (52.3)	73 (47.1)	223 (54.3)	.12

Abbreviations: BMI, body mass index; dcSSc, diffuse cutaneous systemic sclerosis; IQR, interquartile range; lcSSc, limited cutaneous systemic sclerosis; mRSS modified Rodnan skin score; NA, data not available due to statistical limitation (one cell was zero); SD, standard deviation; SSc, systemic sclerosis.

*Statistical significance.

TABLE 3 Generalized linear mixed model of clinicals associated with diffuse cutaneous systemic sclerosis

Clinical characteristic	Coefficient (95% CI)	*P* value
Female	0.92 (−0.47 to 2.31)	.20
Positive for anti-topoisomerase antibody	1.28 (−0.86 to 3.42)	.24
BMI, per 1 kg/m^2	-1.04 (−3.25 to 1.17)	.36
Functional class		
I	-	
II	0.45 (−1.09 to 1.99)	.57
III	17.52 (−4530.39 to 4565.45)	.99
IV	−13.79 (−4135.95 to 4108.36)	.99
Digital ulcer	0.45 (−1.51 to 2.41)	.65
Telangiectasia	−0.06 (−1.84 to 1.72)	.95
Salt-and-pepper appearance	1.70 (0.29-3.11)	.02*
Tendon friction rub	−0.15 (−1.82 to 1.53)	.86
Hand deformity	2.16 (0.34-3.98)	.02*
Arthritis	−1.05 (−3.33 to 1.23)	.37
Muscle weakness	−0.21 (−2.75 to 2.34)	.87
Stomach involvement	−0.89 (−2.78 to 0.99)	.36
Intestinal involvement	−1.54 (−3.49 to 0.41)	.12
Weight loss	−1.30 (−2.81 to 0.20)	.09
Renal crisis	15.36 (−3757.30 to 3788.01)	.99
mRSS, per 1 point	0.28 (0.03-0.26)	.02*

Abbreviations: mRSS modified Rodnan skin score; BMI, body mass index; CI, confidence interval.

*Statistical significance.

TABLE 4 Causes of death

Cause of death	Overall N = 164 (%)	lcSSc N = 26 (%)	dcSSc N = 138 (%)
SSc-related death	104 (63.4)	13 (50)	91 (65.9)
SSc unspecified organ involvement	41 (39.4)	5 (19.2)	36 (26.1)
Cardiac involvement	29 (27.9)	4 (15.3)	25 (18.1)
Pulmonary fibrosis	18 (17.3)	2 (7.7)	16 (11.6)
Renal crisis	9 (8.7)	0	9 (6.5)
Pulmonary arterial hypertension	5 (4.8)	1 (3.8)	4 (2.9)
Gastrointestinal involvement	2 (1.9)	1	1 (0.7)
Non-SSc-related death	60 (36.6)	13 (50)	47 (34.1)
Pulmonary infection	21 (35)	2 (7.7)	19 (13.8)
Septicemia	16 (26.7)	5 (19.2)	11 (8.0)
Natural death	5 (8.3)	2 (7.7)	3 (2.2)
Cancer	5 (8.3)	2 (7.7)	3 (2.2)
Coronary artery disease	4 (5.7)	1 (3.8)	3 (2.2)
Chronic kidney disease	1 (1.7)	0	1 (0.7)
Cirrhosis	1 (1.7)	0	1 (0.7)
Upper gastrointestinal bleeding	1 (1.7)	0	1 (0.7)
Others	6 (10.0)	1 (3.8)	5 (3.6)

Abbreviations: dcSSc, diffuse cutaneous systemic sclerosis; lcSSc, limited cutaneous systemic sclerosis; SSc, systemic sclerosis.

The majority of Thai SSc is dcSSc (73%), whereas most Caucasians and Asians have lcSSc.[4,13-15,17,18,20,37-39] The findings might be explained by differences in ethnicity (ie, genetics) among SSc patients, including differences in the human leukocyte antigen (HLA) gene (HLA-DRB1*1502, DRB5*0102 and DQB1*0501 among Thai, HLA-DRB1*0101 and DRB1*0501 among Japanese, and HLA-DRB1*1104, DQA1*0501 and DQB1*0301 among Caucasians).[40]

Several clinical features of SSc among Thais and their respective prevalence are comparable to other populations, including: (a) age at onset being mostly middle-aged[41]; (b) PF being an early complication within 5 years of onset with an overall prevalence of 47% among Thai and between 42% and 60% in other series[26,41]; and (c) PAH being a major vascular complication in SSc with a prevalence of 18% among Thais versus between 7% and 15% in other studies.[17,42] However, Thais with dcSSc seemed to have PAH more often than lcSSc, albeit the difference is not statistically significant.

Raynaud's phenomenon was the most common initial presentation in Thai SSc and nearly one-fourth of cases had digital ulcers (vascular complications) despite the warm climate in Thailand. Vasculopathy remains a major presentation even in patients living near the equator. Although vasculopathy is a major problem in Thai SSc at onset, the proportion of the patients with Raynaud's phenomenon was much less than in patients from Europe, North America, Latin America, and East Asia (60% vs 92%-97%).[41] The explanation might be the warmer climate in Thailand and/or the greater prevalence of the dcSSc subset for which Raynaud's phenomenon is not a major presentation. Further study of the comparison between warm and cool climate with the attack rate of Raynaud's phenomenon is needed.

We assessed the longitudinal data during follow-up using GEE analysis and found that calcinosis cutis, telangiectasia, esophageal involvement, Raynaud's phenomenon, and vascular complications (digital ulcers, digital gangrene) were less common in Thai SSc than other series.[41] All these clinical features are part of CREST syndrome (ie, calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) which is a common clinical feature of lcSSc in Caucasians and some Asians. Since dcSSc is the more common subset in Thai SSc, it is not surprising that those clinical features were less common.

The clinical presentation at onset of Thai SSc tends to be complicated by multiple organ involvements and disability at the initial

TABLE 5 Wilcoxon (Breslow) test for equality of survivor functions

Clinical characteristic	Survival N = 402	Death N = 164	Hazard ratio (95% CI)	*P* value
Female	269 (66.9)	87 (53.1)	0.48 (0.35-0.66)	<.001*
Age at onset > 60 y	65 (16.2)	47 (28.7)	3.55 (2.49-5.05)	<.001*
Diffuse cutaneous systemic sclerosis	273 (67.9)	138 (84.2)	2.03 (1.34-3.10)	.001*
Positive for anti-topoisomerase I antibody, n = 245	132 (76.74)	66 (90.41)	2.53 (1.16-5.15)	.02*
Positive for anti-centromere antibody, n = 158	17 (14.9)	8 (18.2)	0.83 (0.36-1.89)	.66
BMI, kg/m^2, mean ± SD	21.6 ± 3.9	20.8 ± 3.6	0.96 (0.88-1.06)	.47
Clinical characteristics				
Functional class				
I	263 (65.4)	73 (44.5)	1	-
II	124 (30.9)	54 (32.9)	1.56 (1.10-2.23)	<.01*
III	15 (3.7)	33 (20.1)	3.87 (2.55-5.87)	<.001*
IV	0	4 (2.4)	5.66 (2.06-15.54)	.001*
Raynaud phenomenon	174 (43.3)	98 (59.8)	2.13 (1.56-2.92)	<.001*
Digital ulcer	57 (14.2)	51 (31.1)	2.01 (1.44-2.81)	<.001*
Digital gangrene	8 (2.0)	3 (1.8)	0.91 (0.29-2.85)	.87
Telangiectasia	128 (31.8)	58 (35.4)	0.84 (0.61-1.16)	.29
Calcinosis cutis	19 (4.7)	8 (4.9)	0.85 (0.42-1.74)	.66
Salt-and-pepper appearance	131 (32.6)	90 (54.9)	2.70 (1.98-3.69)	<.001*
Edematous skin	22 (5.5)	23 (14.0)	5.17 (3.3-8.11)	<.001*
Tendon friction rub	46 (11.4)	31 (18.9)	1.66 (1.12-2.47)	.01*
Hand deformity	130 (32.3)	71 (43.3)	1.27 (0.93-1.74)	.13
Arthritis	17 (4.2)	10 (6.1)	1.36 (0.72-2.59)	.35
Muscle weakness	12 (3.0)	18 (11.0)	3.06 (1.85-5.06)	<.001*
Esophageal involvement	142 (35.3)	87 (53.1)	1.94 (1.42-2.63)	<.001*
Stomach involvement	56 (13.9)	30 (18.3)	1.35 (0.91-2.01)	.14
Intestinal involvement	58 (14.4)	41 (25.0)	1.51 (1.06-2.15)	.02*
Weight loss	40 (10.0)	33 (20.1)	1.82 (1.24-2.67)	.002*
Pulmonary fibrosis	224 (55.7)	115 (70.1)	1.77 (1.26-2.47)	.001*
Duration of disease at time of pulmonary fibrosis detection, y, median (IQR)	3.45 (1.05-7.7)	3.1 (1.2-7.4)	0.79 (0.75-0.83)	<.001*
Pulmonary arterial hypertension	64 (15.9)	38 (23.2)	1.21 (0.84-1.74)	.30
Duration of disease at time of pulmonary arterial hypertension detection, y, median (IQR)	5.7 (3.1-10.6)	5.7 (2.6-9.3)	0.67 (0.59-1.45)	.12
Renal crisis	1 (0.3)	10 (6.1)	3.17 (1.66-6.06)	<.001*
Duration of disease at time of renal crisis detection, y, median (IQR)	4.5	3.5 (1.8-16.4)	0.54 (0.28-1.03)	.06
Myocardial involvement, n = 312	4 of 234 (1.7)	3 of 78 (3.9)	4.03 (1.25-13.00)	.02*
mRSS, median (IQR)	2 (1-6)	8 (2-20)	1.09 (1.07-1.10)	<.001*
mRSS every 5 points increasing			1.53 (1.44-1.64)	<.001*
Anemia	189 (47.0)	98 (59.8)	1.43 (1.04-1.95)	.03*
Numbers of internal organ involvement				
None	103 (25.6)	18 (11.0)	1	
1 organ	146 (36.3)	58 (35.4)	2.32 (1.35-3.98)	.002*

(Continues)

TABLE 5 (Continued)

Clinical characteristic	Survival N = 402	Death N = 164	Hazard ratio (95% CI)	*P* value
2 organs	130 (32.3)	61 (37.2)	2.92 (1.70-5.00)	<.001*
≥3 organs	23 (5.7)	27 (16.5)	3.66 (1.99-6.71)	<.001*
Pulmonary fibrosis with pulmonary arterial hypertension	48 (11.9)	31 (18.9)	1.24 (0.84-1.84)	.28
Pulmonary fibrosis with gastrointestinal involvement	116 (28.9)	70 (42.7)	1.73 (1.26-2.36)	.001*
Pulmonary fibrosis with renal crisis	1 (0.3)	8 (4.9)	1.86 (1.38-2.51)	<.001*
Pulmonary fibrosis with cardiac involvement	2 (0.5)	2 (1.2)	4.02 (0.99-16.34)	.05

Abbreviations: BMI, body mass index; CI, confidence interval; IQR, interquartile range; mRSS, modified Rodnan skin score.
*Statistical significance.

presentation. Around 34% of Thai SSc patients have at least 2 internal organ involvements at onset. In addition, around one-third had signs of disability of hands (hand deformity) at presentation. The findings might be related to the high proportion of the dcSSc subset among Thai SSc, which is more severe and has a poorer outcome than the lcSSc subset. Multiple organ involvement was also related to poor survival outcomes among Thai SSc. Once a patient has 1 or 2 internal organ involvements at anytime, survival is 5 to 10 times worse than those who have no internal organ involvement. As with the high prevalence of early PF and multiple organ involvements, we conducted initial screening for PF and other internal organ involvements in all SSc patients at first visit and monitored the progression of disease in order to provide early management.

Coexisting PF and esophageal involvement was the most common coexisting internal organ involvement at onset in our patients. A previous study showed the association between esophageal reflux and PF in SSc, particularly in the patients who had more severe reflux.[43] The coexistance of PF and esophageal involvement in our SSc patients might be explained by microaspiration due to esophageal dysmotility and it leads to PF development. Hence, reflux-reducing treatments such as prokinetic agents and/or antacid might have a benefit for PF prevention; however, the data are currently limited and uncertain. Further study of early treatment of esophageal dysmotility to prevent PF development needs to be investigated.

Only skin signs, like hand deformity and salt-and-pepper appearance, are a clinical clue for discriminating between dcSSc and lcSSc. Other clinical and laboratory features include signs of vasculopathy (ie, Raynaud's phenomenon, digital ulcer, telangiectasia, PAH, renal crisis), fibrosis (ie, tendon friction rub, PF, intestinal involvement), and serology was not significantly different between dcSSc and lcSSc. The findings suggest that the attending physician should be aware, monitor the patient closely, and treat patients with either hand deformity or salt-and-pepper appearance as an empirical dcSSc subset even without evidence of extensive skin tightness at presentation.

PF was the most common internal organ involvement at onset and during follow-up in Thai SSc. Although PF is reportedly more frequently found in dcSSc than in lcSSc,[26] PF can be seen in both.[44] Our study confirmed that PF can be found in both subsets, including during long-term follow-up. In addition, we found that duration of disease at time of PF detection in dcSSc and lcSSc was not significantly different and the duration of disease at time of PF detection commonly occurred at 2.5 years after onset (2.2 years in lcSSc and 2.7 in dcSSc). The patients who had a shorter duration of PF after onset also had a poorer outcome based on the longitudinal data analysis. We conclude that early PF, particularly in the first 3 years after onset, relates to a poor prognosis in both dcSSc and lcSSc despite treatment (data not shown). Immunosuppressants, including cyclophosphamide both oral and intravenous infusion, mycophenolate mofetil, azathioprine, and other target therapies (ie, nintedanib, rituximab) have been reported to stabilize lung function[45-50]; however, no survival outcome assessment has been done after treatment of PF in SSc. The outcome in PF is uncertain if treatment is given very early during asymptomatic PF, mild PF, or before PF detection, so further study is needed.

The mortality rate of the Thai dcSSc subset is 2 times higher than the lcSSc subset. Our results are comparable to previous studies[51] and not unexpected due to the high rate of serious complications in dcSSc. The most common cause of SSc-related death is from cardiopulmonary involvement, while pulmonary infection is the common cause of non-SSc-related death.[25,51] The overall survival rate of our SSc patients (including both subsets) was less than that reported by Rubio-Rivas et al[51] who included 17 studies in a meta-analysis (mostly studies from Europe, the USA, North America, Australia, and few from Asia). The difference might be related to: (a) the more frequent occurrence of dcSSc in the Thai population which is more complicated and severe; (b) a limitation of treatment for refractory, progressive, or extensive SSc disease; and (c) budget limitations for prescribing some specific treatments such as treatment for PAH or stem cell transplantation.

Edematous skin or puffy skin is an early sign of SSc, thus is a sign of skin inflammation before turning into tightness.[52] The skin

TABLE 6 Cox regression analysis

Clinical characteristic	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)	*P* value
Female	0.48 (0.35-0.66)	0.79 (0.362-1.97)	.62
Age at onset > 60 y	3.55 (2.49-5.05)	5.51 (1.78-17.09)	.003*
Diffuse cutaneous systemic sclerosis	2.03 (1.34-3.10)	0.36 (0.10-1.22)	.10
Positive for anti-topoisomerase I antibody	2.53 (1.16-5.15)	NA	-
Functional class			
II	1.56 (1.10-2.23)	2.28 (0.70-7.43)	.17
III	3.87 (2.55-5.87)	5.11 (1.27-20.54)	.02*
IV	5.66 (2.06-15.54)	34.84 (3.88-313.22)	.002*
Raynaud phenomenon	2.13 (1.56-2.92)	0.66 (0.28-1.58)	.35
Digital ulcer	2.01 (1.44-2.81)	1.20 (0.40-3.64)	.75
Salt-and-pepper appearance	2.70 (1.98-3.69)	1.96 (0.69-5.62)	.21
Edematous skin	5.17 (3.3-8.11)	11.35 (3.05-42.19)	<.001*
Tendon friction rub	1.66 (1.12-2.47)	0.33 (0.10-1.03)	.06
Muscle weakness	3.06 (1.85-5.06)	1.16 (0.20-6.80)	.87
Esophageal involvement	1.94 (1.42-2.63)	1.99 (0.44-8.97)	.37
Intestinal involvement	1.51 (1.06-2.15)	0.76 (0.26-2.23)	.62
Weight loss	1.82 (1.24-2.67)	2.68 (0.93-7.72)	.07
Duration of disease at time of pulmonary fibrosis detection every 1 year increasing	0.79 (0.75-0.83)	0.59 (0.46-0.75)	<.001*
Renal crisis	3.17 (1.66-6.06)	3.24 (0.42-24.87)	.26
Left ventricular ejection fraction < 50%	1.43 (1.04-1.95)	5.13 (0.29-91.07)	.27
mRSS every 5 points increasing	1.53 (1.44-1.64)	4.51 (1.15-1.96)	.003*
Anemia	1.43 (1.04-1.95)	0.41 (0.16-1.07)	.07
Numbers of internal organ involvement			
1 organ	2.32 (1.35-3.98)	5.25 (3.56-77.31)	<.001*
2 organs	2.92 (1.70-5.00)	10.11 (2.81-36.61)	<.001*
≥3 organs	3.66 (1.99-6.71)	NA	NA
Pulmonary fibrosis with gastrointestinal involvement	1.73 (1.26-2.36)	10.06 (0.67-150.12)	.09
Pulmonary fibrosis with renal crisis	1.86 (1.38-2.51)	NA	-
Pulmonary fibrosis with cardiac involvement	4.02 (0.99-16.34)	NA	-

Abbreviations: CI, confidence interval; IQR, interquartile range; mRSS modified Rodnan skin score; NA, data not available due to limited number of the events.

*Statistical significance.

pathology in this phase reveals the infiltration of collagen types I and III in the reticular dermis, and inflammatory cells might be found between collagen bundles in the perivascular, subcutaneous tissue and/or sweat glands. Early treatment given in this phase is believed to help slow down skin tightness progression; however, no known treatment can stop disease progression. We found around 27% of patients had edematous skin at onset while 8% of patients still had edematous skin during longitudinal follow-up. Most commonly patients with dcSSc (rather than lcSSc) had edematous skin during follow-up. We also found that edematous skin was associated with high mortality in Thai SSc patients (odds ratio 11.4). The implication is that the inflammatory process of the skin is commonly revealed at onset and can be ongoing throughout the period of follow-up, especially in patients with dcSSc. The reason for the high mortality

of patients with edematous skin might be related to the ongoing of inflammatory process of both skin and internal organs but it is unknown whether the inflammation would be present in the internal organs or not. Further investigation of the association between edematous skin and mortality is needed.

The severity of fibrosis, particularly extensive skin tightness (high mRSS) and internal organ involvement (cardiopulmonary involvement), is associated with mortality risk in SSc regardless of the period of the study.[21,25,51] We also found the greater the number of internal organ involvements, the poorer the outcome. The respective risk of mortality of 1 and 2 internal organ involvements was 5 and 10 times greater than no internal organ involvement. The results might reflect the poor outcome of currently available treatments for stopping the fibrotic process or preventing the progression of fibrosis in patients with extensive disease. Since the exact pathogenesis of SSc remains unknown and the current treatment can only stabilize the fibrosis, the cause of death and the mortality risk continue to be related to SSc itself. The SSc patient at risk of poor outcomes should thus be concerned about disease progression, close monitoring, early treatment, and prevention of complications.

There is a small number of Thai SSc patients with renal crisis despite the high proportion of dcSSc among Thai SSc. The prevalence of renal crisis in the current study might have been underestimated. A proportion of our patients were lost to follow-up (126 cases; 22.3%) and the retrieved data from the government office revealed they had died due to SSc itself. We are unable to determine the organ(s) associated with death in those patients and cannot define whether they had renal crisis or not. We cannot, therefore, provide the exact number of patients with renal crisis or the mortality rate of renal crisis. Notwithstanding, renal crisis is frequently found in

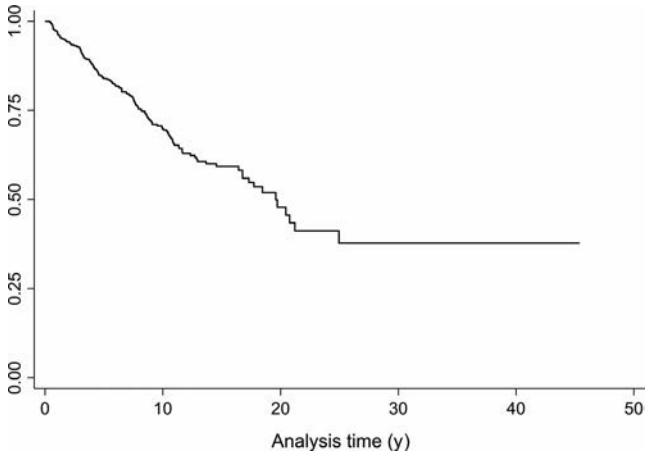

FIGURE 2 Kaplan-Meier survival graph

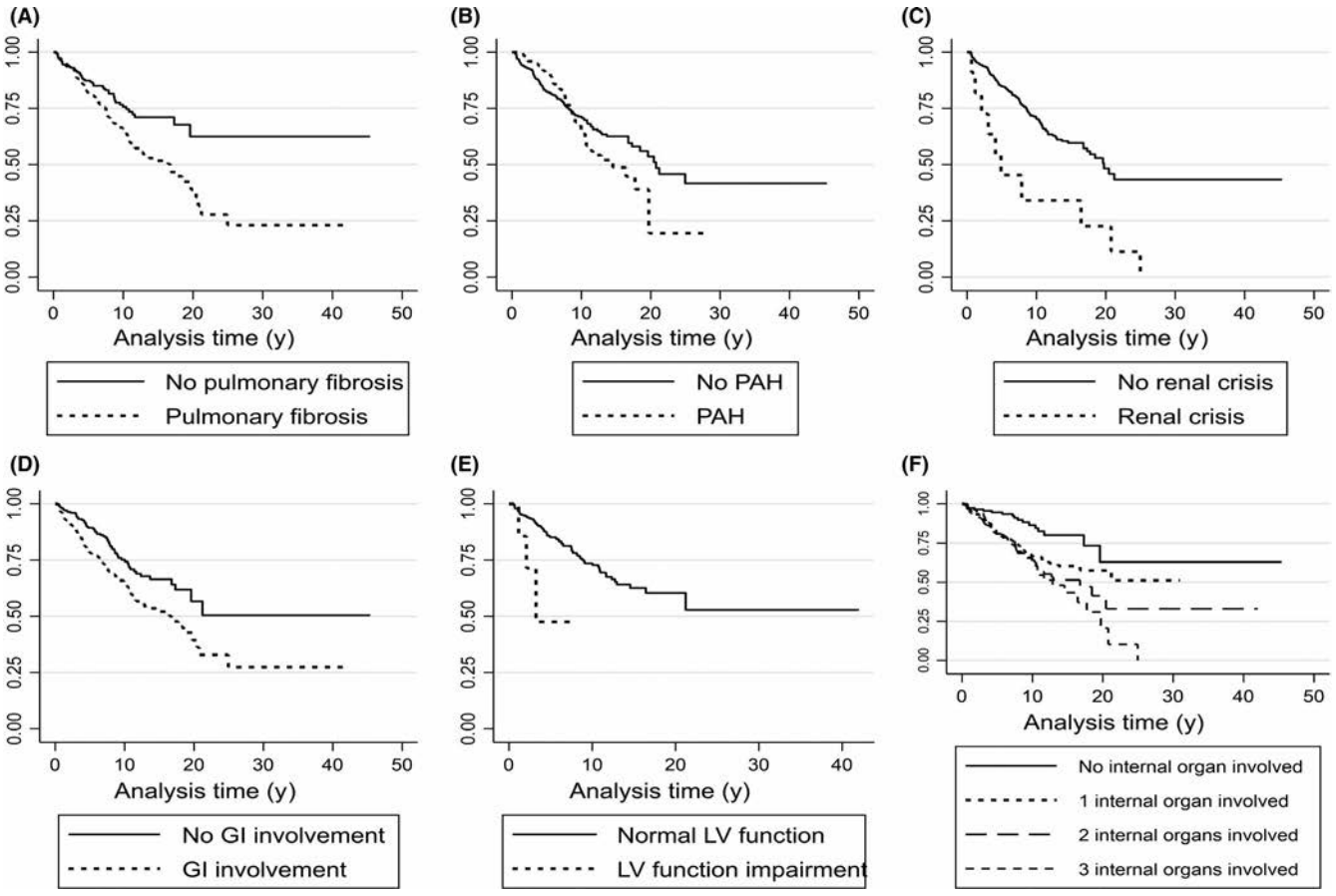

FIGURE 3 Kaplan-Meier survival graph of SSc patients for A, PF; B, PAH; C, renal crisis; D, GI; E, impaired LV function; and F, number of internal organ involvements. GI, gastrointestinal; LV, left ventricular, PF, pulmonary fibrosis; PAH, pulmonary arterial hypertension; SSC, systemic sclerosis

dcSSc and sufferers do have a high mortality in Thai SSc. Due to the small number of SSc with renal crisis, the analysis showed no statistically significant association between renal crisis and the SSc subset/mortality due to low statistical power.

Our study has some limitations, including: (a) the limitation of bronchoalveolar lavage and lung biopsy among SSc patients related to difficult mouth opening and moderate to high risk of intra-operative complications. None of our patients with PF, therefore, underwent any intervention to investigate the nature of PF or to evaluate whether they had alveolitis or not. The pulmonary function test (particularly FVC) and HRCT of chest were performed for all SSc patients with PF in order to closely monitor the progression of PF and to guide PF management. (b) We did not classify the severity of PF because we have limited ability to perform the severity stratification, so we cannot provide the details of the association between the severity of PF and mortality in our SSc patients. (c) Not all patients were tested for specific autoantibodies of SSc (anti-topoisomerase I antibody and anti-centromere antibody) because of budget limitations. (d) A minority of patients were tested for specific autoantibodies of SSc other than anti-topoisomerase I and anti-centromere antibody (anti-RNA polymerase III, anti-Th/To). Due to the low prevalence of other related autoantibodies among Thai SSc and no clinical relevance,[53] we did not analyze the clinical characteristics and outcomes with those antibodies. (e) We did not put the detail of our treatment in the study because the data would be overwhelmed according to the organ-based treatment and various treatment options or modalities. The outcome of treatments will thus be separately reported based on organ involvement.

The strengths of our study include: (a) the large number of SSc patients included, providing a high power of an analysis; (b) the parameters of interest included (ie, onset of internal organ involvement [PF, PAH, renal crisis] and number of internal organ involvements), so that the clinical outcomes of those with a different onset of internal organ involvement can be defined; and (c) the use of GEE for analyzing longitudinal data, yielding a more appropriate interpretation and reliable conclusion.

5 | CONCLUSION

DcSSc is a common SSc subset in the Thai population. At least 1 internal organ involvement was identified during follow-up in around 80% of cases. PF was an early complication in SSc and earlier PF detection was associated with a poorer prognosis. Elderly onset, high FC, edematous skin, severe skin tightness, and multiple organ involvement were associated with mortality risk in Thai SSc.

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CONFLICT OF INTERESTS

The authors have no competing interests.

AUTHOR CONTRIBUTIONS

CF did the study conception, study design, data collection, and drafted the manuscript. AM, SS, and PP did the data collection. UP did the statistical analyses. CF, AM, SS, PP, PK, and RN proofread the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Human Research Ethics Committee of Khon Kaen University approved the study as per the Helsinki Declaration and the Good Clinical Practice Guidelines (HE621404). All eligible patients signed informed consent before entry to the cohort study. The parents consented on behalf of their children who were under 18 years of age.

CONSENT FOR PUBLICATION

All the authors consent to publication and grant the publisher exclusive license of the full copyright.

DATA AVAILABILITY

Data and material available as per request.

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ORIGINAL ARTICLE

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Distinct HLA and non-HLA associations in different subtypes of ANCA-associated vasculitides in North India

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Abstract

Aim: Antineutrophil cytoplasmic antibody-associated vasculitis (AAV) is an autoimmune disease characterized by necrotizing small vessel vasculitis that can affect various organs and present multiple symptoms. Susceptibility to AAV is multifactorial and most likely caused by an amalgamation of genetic and environmental factors. The aim of the present study was to explore the distribution of human leukocyte antigen (HLA)-DRB1/DQB1, protein tyrosine phosphatase non-receptor type 22 (PTPN22) and cytotoxic T-Lymphocyte-associated protein 4 (CTLA-4) polymorphisms in North Indian AAV patients and their associations with clinical and pathological characteristics associated with the disease.

Methods: A total of 150 AAV patients and 150 healthy controls were recruited. The clinical classification showed 128 as granulomatosis with polyangiitis (GPA) and 21 as microscopic polyangiitis. Only 1 case of eosinophilic granulomatosis with polyangiitis was encountered, which was excluded from analysis. HLA-DRB1/DQB1 alleles were determined by polymerase chain reaction-sequence-specific primer (PCR-SSP) method and single nucleotide variant genotyping for CTLA-4 and PTPN22 was done by simple probe-based SNP arrays.

Results: A significant predispositional association of DRB1*03 and DQB1*02 alleles, were confirmed in proteinase 3 (PR3)-AAV patients, whereas DRB1*10, DRB1*14 and DQB1*05 were protective alleles in AAV, PR3-AAV and GPA patients. GG genotype of CTLA-4 + 49A/G was increased in patients as compared to controls and showed an association with AAV, PR3-AAV and GPA patients.

Conclusion: The study indicated strong genetic associations were linked with PR3 antineutrophil cytoplasmic antibody specificity and it appears that PR3-AAV and MPO-AAV have distinct genetic backgrounds.

KEYWORDS

ANCA-associated vasculitis, granulomatosis with polyangiitis, microscopic polyangiitis, myeloperoxidase, proteinase 3

1 | INTRODUCTION

Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitides (AAV) is a complex immunological disease, characterized by necrotizing small vessel vasculitis, which frequently affects the kidneys.[1] In 1994, the first Chapel Hill Consensus Conference (CHCC) proposed a nomenclature based on the size of the blood vessels involved[2]; this was later updated in 2012, wherein ANCA was included to define a vasculitic group called AAV. It comprises three entities: granulomatosis with polyangiitis (GPA, Wegener), eosinophilic granulomatosis with polyangiitis (EPGA, Churg-Strauss syndrome) and microscopic polyangiitis (MPA).[3] According to EC/BCR project for ANCA assay standardization (1998), MPA is characterized by the presence of myeloperoxidase (MPO)-ANCA in 58% of the subjects and proteinase 3 (PR3) in 26% of subjects, while in the case of GPA 66% of subjects are associated with PR3-ANCA, and 24% with MPO-ANCA.[4] EGPA is rare in our north Indian cohort.

Susceptibility to AAV is caused by interplay of genetic and environmental factors.[5] Genome-wide association studies (GWAS) have pinpointed risk loci including human leukocyte antigen (HLA)-DP, DQ (class II alleles), proteinase 3 and Serpin Family A Member 1, while candidate genes involved in pre-GWAS include protein tyrosine phosphatase, non-receptor type 22 (PTPN22), cytotoxic T-Lymphocyte-associated protein 4 (CTLA-4), interleukin (IL)10, HLA-DR and -DQ.[6] However, HLA and disease association is not completely understood. There are two major hypotheses, used to explain the same. The molecular mimicry hypothesis states that, certain HLA alleles (susceptibility) are more efficacious in presentation of pathogens peptides, which bear homology to self-peptides. This leads to breach of tolerance, and hence, autoimmune disease. The central selection failure hypothesis suggests that, some HLA alleles are less effectual in the presentation of self-peptides to mature T cells with failure of negative selection in thymus, and hence development of autoimmunity. In contrast, protective HLA alleles are those, which, instead of initiating an immune response, induce formation of regulatory cells, which protect against disease development.[7]

The fundamental role of T cells in AAV has been recognized.[8] PTPN22 and CTLA-4/CD152 are two regulatory proteins expressed on the T cell surface.[9,10] Known polymorphisms in the genes encoding these proteins, are part of the non-HLA genes contributing to susceptibility to AAV.[11] There are very few studies showing HLA and non-HLA disease association in Asian populations. We conducted a case-control association study examining HLA (DRB1/DQB1) alleles and 8 non-HLA candidate loci (3 single nucleotide variants [SNVs] for PTPN22 rs2476601, rs1217412, rs2488457 and 5 for CTLA-4 rs3087243, rs231775, rs5742909, rs4553808, rs733618) in a north Indian population.

2 | MATERIALS AND METHODS

2.1 | Study population

One hundred and fifty unrelated patients presenting with clinical signs and symptoms of AAV and fulfilling the guidelines of the

TABLE 1 Demographic and clinicopathological characteristics of the study population

Characteristics	AAV (n = 150)	GPA (n = 128)	MPA (n = 21)	EGPA (n = 1)	PR3 (n = 90)	MPO (n = 60)
Mean age	41.9 ± 17.3	41.6 ± 17.4	45.3 ± 17.5	50	41.1 ± 17.4	42.8 ± 17.4
Gender ratio (F/M)	1/1.3	1/1.3	1/0.9	1	1/1.1	1/1.5
ANCA specificity (PR3)	90 (60)	88 (68.8)	2 (9.5)	0	90	-
MPO	60 (40)	40 (31.2)	19 (90.5)	1 (100)	-	60
c-ANCA	85 (56.7)	82 (64)	3 (14.3)	0	76 (84.5)	9 (15)
p-ANCA	56 (37.3)	36 (28.1)	19 (90.5)	1 (100)	3 (3.4)	52 (86.7)
IIF negative	10 (6.7)	10 (7.8)	0	0	7 (7.8)	3 (5)
Organ involvement at diagnosis, n (%)						
Constitutional symptoms	102 (68)	90 (70.3)	12 (57.1)	0	62 (68.9)	40 (66.7)
Mucous membranes/eyes	50 (33.4)	48 (38.2)	1 (4.8)	1 (100)	37 (41.1)	13 (21.7)
Cutaneous	49 (32.7)	44 (34.4)	4 (19)	1 (100)	35 (38.9)	14 (23.3)
Ear/nose/throat	91 (60.6)	90 (70.3)	1 (4.8)	0	67 (74.4)	24 (40)
Lung	100 (66.7)	84 (65.6)	15 (71.4)	1 (100)	61 (67.80)	39 (65)
Cardiovascular	13 (8.7)	11 (8.6)	2 (9.5)	0	5 (5.6)	8 (13.3)
Gastrointestinal tract	15 (10.0)	14 (10.9)	1 (4.8)	0	8 (8.9)	7 (11.7)
Kidney	90 (60.0)	71 (55.5)	19 (90.5)	0	38 (42.2)	52 (86.7)
Nervous system	30 (20.0)	23 (17.9)	6 (28.6)	1 (100)	17 (18.9)	13 (21.7)

AAV, antineutrophil cytoplasmic antibody-associated vasculitis; ANCA, antineutrophil cytoplasmic antibodies; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; IIF, indirect immunofluorescence; MPA, microscopic polyangiitis; MPO-AAV, myeloperoxidase positive ANCA-associated vasculitis; PR3, proteinase 3.

American College of Rheumatology (ACR) and CHCC were enrolled in this study. Patients were recruited from the Department of Internal Medicine and Department of Nephrology, Post Graduate Institute of Medical Education and Research, Chandigarh, India. One hundred and fifty unrelated healthy controls were also included in the study. The controls were age, gender and ethnicity matched with the patients. The controls included friends or spouses who accompanied patients and volunteers from the hospital staff. First, patients were dichotomized into two groups, on the basis of positivity for antigen specificity for anti-PR3/MPO determined by enzyme-linked immunosorbent assay (ELISA). Further, patients were clinically categorized into GPA, MPA and EGPA. Primarily ACR and Lanham criteria were applied for EGPA and ACR for GPA, as they tended to be most specific. Then, surrogate markers for GPA were incorporated to differentiate GPA from MPA, and MPA was classified using the CHCC definition, and a surrogate marker for renal vasculitis. Written informed consent was obtained from all the participants after explaining the prospects of the study. The study was approved by our institutional ethics committee (INT/IEC/2016/2515).

2.2 | Sample collection

Five milliliters of peripheral venous blood sample was obtained from the patients and was divided into two portions: 3 mL in plain vials for serum separation and 2 mL in vials with ethylenediaminetetraacteic acid for DNA extraction.

2.3 | Detection of ANCA

Antineutrophil cytoplasmic autoantibody screening was performed by indirect immunofluorescence (IIF) followed by an obligatory ELISA to decipher the target antigen. Serum was separated from blood and patterns of ANCA (c-ANCA, p-ANCA and atypical ANCA) were obtained by IIF using a standardized in-house method on ethanol-fixed neutrophils from O^+ individual, and antigen specificity for anti-PR3 and anti-MPO were determined by ELISA (Varelisa; Phadia).

2.4 | DNA extraction and HLA typing

DNA extraction was done using spin column-based kits (QIAamp DNA, from Qiagen). Concentration and purity of DNA extracted were assessed by A_{260} and A_{260}/A_{280} measurements on a spectrophotometer. One hundred and fifty patients and 150 controls were typed for HLA class II loci DRB1 and DQB1 using low-resolution polymerase chain reaction-based sequence-specific primers (PCR-SSP) Morgan HLA SSP DRB/DQB typing kits. The PCR was performed according to the manufacturer's instructions (for detail see Appendix S1).

2.5 | SNV genotyping for CTLA-4 and PTPN22 genes

SNV genotyping for 8 SNVs, 5 in the CTLA-4 gene (+ 49 A/G [rs 231775], −318 C/T [rs 5742909], CT 60 [+6230G/A, rs3087243], −1722 C/T [rs 733618], −1661 A/G [rs 4553808]) and 3 in PTPN22 gene (+ 2740 A/G [rs 1217412], −1123 C/G/T [rs 2488457], +1858 C/T [rs 2476601]) was done in the patients and the controls by simple probe-based SNP arrays (Roche Diagnostics), (for detail see Appendix S1).

2.6 | Statistical analysis

Data are expressed as mean with standard deviation and median with interquartile range, as applicable. Allelic and genotypic frequencies were compared between patients and controls and between subgroups of patients, using χ^2 test with Yates' correction. Calculations of odds ratios (ORs) and 95% confidence intervals (CIs) for relative risks were performed, after application of Fisher's exact test, if appropriate. To compare the allele and genotype frequencies of subjects stratified by clinical and antigen specificity parameters, χ^2 test, Fisher's exact test, or nonparametric test was used, as appropriate. Bonferroni correction was applied to correct the results. Two-sided *P* values less than .05 were considered significant. The analysis was done by SPSS software (version 13.0; SPSS Inc).

3 | RESULTS

3.1 | Clinical characteristics of the study participants

Among the 150 patients diagnosed with AAV, 84 were female, and 66 were male with a mean age of 41 years. We stratified patients according to ANCA serotypes and clinical diagnosis. Out of these 150 patients, 90 (60%) were positive for anti-PR3 antibodies, and 60 (40%) were positive for anti-MPO antibodies. The clinical classification showed 128 as GPA, 21 as MPA and 1 as EGPA. Due to the low incidence of EGPA, statistical analysis was only focused on GPA and MPA; EGPA was excluded from further analysis. Among patients with GPA, 87/128 (68%) were PR3-ANCA positive and the other 31.2% were MPO-ANCA positive. Among patients with MPA, 19/21 (90.5%) were MPO-ANCA positive, and 9.5% were PR3-ANCA positive. On further categorization, 64/150 (42.7%) were organ limited, and 86/150 (57.3%) were systemic AAVs. Demographic and clinicopathological data of patients are shown in Table 1. The most common clinical presentation among all groups was constitutional symptoms (68%). It can be seen that out of MPA and GPA groups, the most frequently involved organ was renal (90.5%) in the MPA group as compared to the AAV (60%) and GPA (55.5%) groups. The involvement of ear/nose/throat, skin and eye ailments were more prevalent in GPA than MPA patients.

3.2 | HLA DRB1/DQB1 alleles and susceptibility

The frequencies of alleles DRB1*10 (*P* = .002, OR: 0.160, CI: 0.046-0.557, *P* value with Bonferroni correction [*Pc*] = 0.036), DRB1*14 (*P* = .000, OR: 0.235, CI: 0.108-0.513, *Pc* = 0.000), DQB1*05 (*P* = .000, OR: 0.326, CI: 0.202-0.525, *Pc* = 0.000) were significantly less prevalent in AAV patients as compared to healthy controls, suggesting a protective association (Table 2). The allele frequency of DRB1*03 (*P* = .004, OR: 2.014, CI = 1.219-3.326, *Pc* = 0.072), DQB1*02 (*P* = .013, OR: 1.740, CI: 1.093-2.768, *Pc* = 00.234) and DQB1*03 (*P* = .004, OR: 2.114, CI: 1.239-3.606, *Pc* = 0.072) was elevated in AAV patients as compared to healthy controls. However, the association failed to attain statistical significance following the Bonferroni correction.

Human leukocyte antigen association analysis was also done by using ANCA antigen specificity (PR3/MPO) (Table 3) as well as clinical disease classification (Table S1). Predispositional association of DRB1*03 (*P* = .001, OR: 2.629, CI: 1.498-4.612, *Pc* = 0.018) and DQB1*02 (*P* = .000, OR: 2.579, CI: 1.508-4.411, *Pc* = 0.000) alleles was also observed in PR3-AAV patients. PR3-AAV and AAV groups had similar protective associations with DRB1/DQB1, while in MPO-AAV, a protective association was detected with DQB1*06 (*P* = .002, OR: 0.385, CI: 0.202-0.735, *Pc* = 0.036).

Microscopic polyangiitis and renal-limited AAV did not have any association with DRB1/DQB1. In GPA, similar protective association with DRB1/DQB1 (DRB1*10 *P* = .002, OR: 0.140, CI: 0.032-0.618, *Pc* = 0.036; DRB1*14 *P* = .000, OR: 0.205, CI: 0.082-0.509, *Pc* = 0.000; DQB1*05 *P* = .000, OR: 0.307, CI: 0.182-0.516, *Pc* = 0.000) was detected (Table S1) as shown for AAV and the PR3-AAV subgroup.

3.3 | Non-HLA gene association

Hardy-Weinberg equilibrium was tested in all the SNVs using the online encyclopedia for genetic epidemiology studies (OEGE) tool. All the SNVs were in equilibrium, except PTPN22 −1858 C/T and PTPN22 - 2740 A/G ,as χ^2 values in all other SNVs were less than 3.8. The genotype and allele frequencies of CTLA-4 and PTPN22 were compared between the AAV patients and controls. In this association study, 7 out of the 8 SNVs (5 CTLA-4 and 3 PTPN22) tested did not show any association with AAV. The GG genotype of CTLA-4 + 49 A/G was over-represented in patients as compared with controls and showed an association of AAV with the + 49 A/G genotype (*P* = .048). We also tested by discriminating genotype in the different categories of AAV according to the ANCA antigen specificity (PR3/MPO) as well as by clinical classification, which showed the association of disease-associated allele skewed toward GPA and PR3-ANCA. GG genotype of CTLA-4 49A/G was significantly increased in patients with PR3-ANCA (17.8%; *P* = .039) and GPA (21.2%; *P* = .023) as compared to the controls, respectively.

TABLE 2 Distribution of HLA-DRB1/DQB1 frequency in patients and controls

	HLA allele	AAV (n = 150)	Control (n = 150)	AAV vs. control			
No.	DRB1/DQB1 typing	%	%	*P* value	*Pc*	OR	95% CI
1.	DRB1*01	2.0	9.3	.010	0.180	0.198	0.056-0.705
2.	DRB1*03	38.0	23.3	.004	0.072	2.014	1.219-3.326
3.	DRB1*04	11.3	14.0	.302	5.436	0.785	0.396-1.556
4.	DRB1*07	29.3	20.7	.055	0.990	1.593	0.939-2.704
5.	DRB1*08	5.3	2.7	.378	6.804	2.056	0.606-6.981
6.	DRB1*09	2.0	0	.247	4.446	2.020	1.801-2.266
7.	DRB1*10	2.0	11.3	.002	**0.036**	0.160	0.046-0.557
8.	DRB1*11	16.0	17.3	.439	7.902	0.908	0.495-1.668
9.	DRB1*12	0.7	0	1.000	18.000	2.007	1.791-2.248
10.	DRB1*13	12.7	17.3	.166	12.456	0.692	0.365-1.312
11.	DRB1*14	6.0	21.3	.000	**0.000**	0.235	0.108-0.513
12.	DRB1*15	43.3	40.0	0.320	5.760	1.147	0.725-1.816
13.	DRB1*16	2.7	2.7	1.000	18.000	1.000	0.245-4.075
17.	DQB1*02	48.0	34.7	.013	0.234	1.740	1.093-2.768
18.	DQB1*03	32.7	18.7	.004	0.072	2.114	1.239-3.606
19.	DQB1*04	4.0	4.0	.615	18.000	1.000	0.315-3.174
20.	DQB1*05	29.3	56.0	.000	**0.000**	0.326	0.202-0.525
21.	DQB1*06	36.7	50.7	.010	0.180	0.564	0.355-0.894

Abbreviations: 95% CI, 95% confidence Interval; AAV, antineutrophil cytoplasmic antibody-associated vasculitis; HLA, human leukocyte antigen; OR, odds ratio; Pc, *P* value corrected with Bonferroni correction.

TABLE 3 Distribution of HLA-DRB1/DQB1 frequency according to ANCA specificity (PR3-AAV and MPO-AAV) and healthy controls

HLA allele	MPO-AAV (n = 60)	PR3-AAV (n = 90)	HC (n = 150)	MPO vs HC		PR3 vs HC		MPO vs PR3	
DRB1/DQB1 typing	%	%	%	*P* value (*Pc*)	OR (95%CI)	*P* value (*Pc*)	OR (95%CI)	*P* value (*Pc*)	OR (95%CI)
DRB1*01	1.7	2.2	9.3	.072 (1.296)	0.165 (0.021-1.281)	.034 (0.612)	0.221 (0.049-0.995)	1.000 (18.00)	0.746 (0.066-8.412)
DRB1*03	28.3	44.4	23.3	.278 (5.004)	1.299 (0.660-2.557)	**.001 (0.018)**	**2.699 (1.498-4.612)**	.034 (0.612)	0.494 (0.246-0.994)
DRB1*04	16.7	7.8	14.0	.383 (6.894)	1.229 (0.541-2.792)	.105 (1.890)	0.518 (0.211-1.273)	.079 (1.422)	2.371 (0.849-6.627)
DRB1*07	28.3	30	20.7	.155 (2.790)	1.518 (0.764-3.016)	.070 (1.260)	1.645 (0.903-2.996)	.487 (8.766)	0.922 (0.449-1.895)
DRB1*08	3.3	6.7	2.7	1.000 (18.00)	1.259 (0.224-7.060)	.123 (2.214)	2.607 (0.715-9.503)	.477 (8.586)	0.483 (0.094-2.476)
DRB1*09	1.7	2.2	0	.286 (5.148)	3.542 (2.854-4.397)	.140 (2.520)	2.705 (2.291-3.192)	1.000 (18.00)	0.746 (0.066-8.412)
DRB1*10	3.3	1.1	11.3	.107 (1.926)	0.270 (0.060-1.206)	**.002 (0.036)**	**0.088 (0.011-0.672)**	.564 (10.152)	3.069 (0.272-34.622)
DRB1*11	20	13.3	17.3	.393 (7.074)	1.192 (0.557-2.552)	.264 (4.752)	0.734 (0.350-1.538)	.193 (3.474)	1.625 (0.676-3.907)
DRB1*12	0	1.1	0	.....	.....	.375 (6.750)	2.685 (2.278-3.166)	1.000 (18.00)	1.674 (1.467-1.910)
DRB1*13	8.3	15.6	17.3	.070 (1.260)	0.434 (0.158-1.188)	.433 (7.794)	0.879 (0.432-1.786)	.146 (2.628)	0.494 (0.168-1.451)
DRB1*14	8.3	4.4	21.3	.017 (0.306)	0.335 (0.124-0.907)	**.000 (0.000)**	**0.172 (0.058-0.503)**	.261 (4.698)	1.955 (0.503-7.597)
DRB1*15	53.3	36.7	40.0	.054 (0.972)	1.714 (0.938-3.134)	.354 (6.372)	0.868 (0.507-1.489)	.032 (0.576)	1.974 (1.016-3.835)
DRB1*16	0	4.4	2.7	.580 (10.44)	1.411 (1.293-1.540)	.478 (8.604)	1.698 (0.414-6.962)	.150 (2.700)	1.698 (1.483-1.944)
DQB1*02	33.3	57.8	34.7	.494 (8.892)	0.942 (0.500-1.775)	**.000 (0.000)**	**2.579 (1.508-4.411)**	.003 (0.054)	0.365 (0.185-0.722)
DQB1*03	31.7	33.3	18.7	.034 (0.612)	2.019 (1.021-3.992)	.008 (0.144)	2.179 (1.195-3.972)	.487 (8.766)	0.927 (0.461-1.864)
DQB1*04	3.3	4.4	4.0	1.000 (18.00)	0.828 (0.162-4.228)	1.000 (18.00)	1.116 (0.306-4.068)	1.000 (18.00)	0.741 (0.131-4.181)
DQB1*05	45	18.9	56.0	.099 (1.782)	0.643 (0.352-1.174)	**.000 (0.000)**	**0.183 (0.099-0.340)**	**.001 (0.018)**	**3.513 (1.688-7.312)**
DQB1*06	28.3	42.2	50.7	**.002 (0.036)**	**0.385 (0.202-0.735)**	.128 (2.304)	0.712 (0.420-1.205)	.059 (1.062)	0.541 (0.269-1.090)

Abbreviations: ANCA, antineutrophil cytoplasmic antibodies; HC, healthy controls; MPO-AAV, myeloperoxidase positive ANCA-associated vasculitis; Pc, *P* value with Bonferroni correctionPR3, proteinase 3.

4 | DISCUSSION

Our study highlights ethnic variations in genetics of AAV in a north Indian population. Among AAV, GPA is frequently observed in north India as seen in Western countries, particularly in northern Europe[12] and White Caucasian populations (USA, Australia and New Zealand), whereas in Japanese and African-American populations, MPA is frequently observed.[13,14]

The distribution of HLA-DRB1/DQB1 showed a positive association of DQB1*02 and DRB1*03 alleles with PR3-AAV patients from north India. DRB1*03 is frequently observed in northern European populations[15] as well as in India and is associated with various autoimmune diseases such as type 1 diabetes,[16] autoimmune thyroiditis,[17] autoimmune hepatitis,[18] systemic lupus erythematosus, multiple sclerosis and myasthenia gravis.[19] DRB1*10, DRB1*14 and DQB1*05 were identified as protective alleles for AAV, PR3-AAV and GPA. Protective effect of DRB1*14 has been previously reported from China,[20] whereas, DRB1*10 and DRB1*14 have been shown to have a protective association with multiple sclerosis in a Portuguese population.[21] MPO-AAV on the other hand showed distinct protective association with DQB1*06. No HLA class II association was seen with MPA and renal-limited AAV. An interesting observation was that 128 clinically classified GPA patients and the PR3-AAV group showed similar protective allele associations; this may be due to presence of high PR3 antigen specificity (68%) among the clinically classified GPA group.

Within the GPA subgroup, susceptibility and protective associations were seen skewed toward the patients with PR3-AAV (Table S2). This finding is consistent with the previous results from GWAS, demonstrating genetic association with ANCA specificity, rather than with clinically defined syndromes GPA and MPA.[22] These genetic associations with autoantibody specificity suggest that it might contribute to the clinical classification of GPA and MPA, and the difference between PR3 and MPO antibodies could have different immunopathogenic mechanisms of action. Lack of HLA class II association with MPA could be due to the small number of cases included in the study. Salient reports on HLA association with AAV in different ethnic groups are illustrated in Table S3.

PTPN22 and CTLA4 are now strongly established as susceptibility loci along with HLA genes in various autoimmune diseases. Our results confirm + 49 A/G association with AAV as previously reported in a larger population of European patients with small vessel vasculitis.[23] Rahmattula et al[24] also reported an increased risk of AAV with + 49 A/G. Analysis based on antigen specificity and clinical categorization indicates that the G allele of + 49 A/G is associated with PR3-ANCA and GPA patients; these results were similar to the results obtained in a HLA study, which showed associations with PR3-AAV and GPA. In GG genotype of + 49 SNV the alanine being replaced with threonine in the leader peptide, would impede CTLA-4 downregulation and lead to increased T cell activation.[25] Of the other 4 SNVs evaluated in the CTLA-4 gene, none were found to be associated with the disease group, although a study on Caucasians (UK) has described the association of CT 60 SNV with the disease[23] and the same was confirmed by Carr et al[11] in 2009.

Mutation in PTPN22 gene may increase susceptibility to various autoimmune diseases such as type 1 diabetes,[26] rheumatoid arthritis and other autoimmune diseases.[27] Jagiello et al[28] performed the first meta-analysis on −1858 C/T demonstrating a significant association in a German GPA cohort. Later, the result was confirmed in Italian AAV patients[29] and British GPA and MPA patients.[11] Similar to our study, earlier studies have demonstrated the absence of −1858 C/T association with autoimmune diseases in the Asian population.[30]

The small size of our study and low-resolution HLA typing are the major limitations of this study. The study cohort has been drawn from a tertiary referral center, from north India, taking care to recruit only north Indian patients; however multicentric recruitment from north India would yield more power to the study.

In conclusion, GPA is more prevalent than MPA in north India, and EGPA is rare. HLA DRB1*03 has strong association with PR3-AAV, while the CTLA4 + 49 A/G shows significant association with PR3-AAV as well as AAV and GPA. HLA and non-HLA genes were not associated with MPO-AAV, but may be due to their small number in our study. To prove isolated HLA DRB1*03 association with PR3-AAV and not in linkage with HLA-DP, will require a larger cohort.

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CONFLICT OF INTERESTS

None of the authors has any conflict of interest to disclose.

AUTHOR CONTRIBUTIONS

JS: executed the study, analyzed the data, and wrote the manuscript as part of his PhD thesis. AS: helped in recruitment of patients, treated the patients, and provided the clinical details of the patients. LR: wrote the project for government funding and recruited some patients. NK: contributed in execution of the study and analyzed the data. SA: contributed in execution of real-time PCR for single nucleotide variant. BS: helped in designing the study. SJ: helped in patient recruitment and assisted in clinical classification of patients. RN: reported and provided the details of kidney biopsy. RWM: designed the study, analyzed the data, edited and corrected the manuscript. All authors approved the final version of the article and concurred on its submission.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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ORIGINAL ARTICLE

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High levels of cathepsin S and cystatin C in patients with fibromyalgia syndrome

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Abstract

Objectives: Although the etiopathogenesis of fibromyalgia syndrome (FM) is not yet clear, central sensitization is thought to be responsible for the pathogenesis of FM. The aim of this study was to compare the serum cathepsin S (CatS) and cystatin C (CysC) levels between patients with FM and healthy control subjects.

Methods: This study was conducted in the Physical Medicine and Rehabilitation Clinic between January 2019 and October 2019. The study included 145 FM patients newly diagnosed with primary FM according to the 2010 American College of Rheumatology criteria and 129 healthy volunteers. The age, gender, and body mass index (BMI) of the participants were recorded. Venous blood samples were collected from both groups for the measurement of the levels of serum CatS and CysC. The functional status of FM patients was evaluated using the Fibromyalgia Impact Questionnaire (FIQ).

Results: No statistically significant difference was determined between the patient and control groups in terms of age, gender, and BMI ($P > .05$). A comparison of the serum CatS and CysC levels of the FM and control groups revealed a statistically significant difference ($P = .001$). No correlation was determined between FIQ and serum CatS and CysC levels ($P > .05$).

Conclusion: Serum CatS and CysC levels were found to be higher in FM patients. However, there was no correlation between the functional status of FM patients and serum CatS and CysC levels. These results can be of guidance for further clinical studies of the etiopathogenesis and treatment of FM.

KEYWORDS

cathepsin S, cystatin C, fibromyalgia, pain

1 | INTRODUCTION

Fibromyalgia syndrome (FM) is a musculoskeletal disease characterized by chronic diffuse pain and increased pain sensitivity.[1] Although the etiopathogenesis of FM is not yet clear, genetic, environmental and immunological factors, and peripheral and central mechanisms are thought to play a role.[2] In clinical studies, central sensitization has been thought to be responsible for the pathogenesis of FM and it has been claimed that abnormalities in the perception and/or processing of pain in the central nervous system may play a role.[3,4]

Central sensitization can be defined as an incorrect and abnormal response of the central nervous system (CNS) due to neuronal hyperexcitability and hypersensitivity in the CNS as a result of a peripheral stimulation.[5] It is known that some chemokines, cytokines and neuromediators are involved in presynaptic and postsynaptic processing of peripheral nociceptive stimulation in the CNS.[6,7] Previous studies have suggested that in order to develop chronic neuropathic pain, microglial cell density should be increased and neural immune interaction should be present.[8,9] Adenosine triphosphate (ATP), which is released from sensory neurons in the dorsal horn as a result of peripheral stimulation, activates microglial cells, releases cathepsin S (CatS) from activated microglial cells and releases the inactive fractalkine (CX3CL1) in the dorsal horn.[8,10] Released CX3CL1 binds to the CX3CR1 receptor on the microglial cell, resulting in the release of inflammatory mediators from microglial cells via p38 mitogen-activated protein kinase.[8] Therefore, it has been said that CX3CL1 may be an important signaling pathway in neuropathic pain.[8,11]

CatS is an important member of the cathepsin family, which can be expressed in a limited number of tissues. It is a protease responsible for the breakdown of damaged proteins, and also has different functions such as protein signal transduction, chemokine/cytokine processing, antigen presentation.[12,13] However, CatS function is known to be regulated by cystatin C (CysC), an endogenous protease inhibitor. CysC controls the intracellular and extracellular activities of lysosomal cysteine proteinases such as CatB, H, K, L, S in neurons and microglial cells.[12,13]

FM is a disease characterized by chronic pain, therefore it can be considered that CatS, which has been shown to have an impact on chronic pain, may play a role in the pathogenesis of FM. However, to the best of our knowledge, there is no study in the literature evaluating serum CatS levels in FM. However, assessing only serum CatS levels in FM may not be enough to understand the role of CatS in FM pathogenesis. Therefore, evaluation of serum CysC level, which is an endogenous inhibitor of CatS in FM, may be important for better understanding of FM pathogenesis. The aim of this study was to compare serum CatS and CysC levels in FM patients and healthy subjects.

2 | PATIENTS AND METHODS

This cross-sectional study was conducted in the Physical Medicine and Rehabilitation Clinic of Sivas Cumhuriyet University Medical Faculty between January 2019 and October 2019. The study included 145 patients who were newly diagnosed with primary FM according to the 2010 American College of Rheumatology[14] criteria and 129 healthy control subjects. FM patients with malignancy, rheumatic disease (osteoarthritis, Behçet's disease, rheumatoid arthritis, etc), those with a known history of systemic disease (hypertension, diabetes mellitus, neurological or psychiatric disease, etc) and those with a history of regular drug use for any disease, were excluded. The functional status of FM patients was evaluated using the Fibromyalgia Impact Questionnaire (FIQ). The control group was formed of subjects with no known disease and no medication use, recruited from hospital personnel and the relatives of patients. The age, gender, and body mass index (BMI) of the participants were recorded.

The study protocol was approved by the Cumhuriyet University Clinical Research Ethics Committee (approval: 2019-02/19, dated: 20.02.2019). Written informed consent was obtained from each participant. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Venous blood was collected from the patient and control groups. Venous blood samples were taken at 08:00-10:00 after an 8-hour fast. The samples in anticoagulant tubes were centrifuged at 2000 *g* for 5 minutes at +4°C, then the separated serum was stored at −30°C until the measurements of serum CatS and CysC levels. Human CatS and CysC levels were measured with enzyme-linked immunosorbent assay kits (Biont, catalog nos: YLA1443HU, YLA1444HU, respectively) according to the manufacturer's instructions (Shangai YL Biotech Co., Ltd).

2.1 | FIQ

A 20-item FIQ was used to assess the patients' physical function, occupational status, depression, anxiety, sleep, pain, stiffness, fatigue and general health as a means of evaluating the functional status of the patients and the progression and outcomes of the disease.[15] The validity and reliability of the FIQ was demonstrated in Turkey by Sarmer et al.[16]

2.2 | Statistical analysis

Data obtained in the study were analyzed statistically using the IBM SPSS Statistics version 22.0 software (IBM Corp., Armonk, NY, USA). Conformity of the data to normal distribution was analyzed using the Kolmogorov-Smirnov test. Student's *t* test was applied when the parametric test assumptions were met. Mann-Whitney *U* test and Spearman's correlation test were used when the parametric test assumptions could not be met, and a Chi-square test was used to evaluate the categorical data. A correlation of 0.10 to 0.29 was considered slight, 0.30 to 0.49 moderate, and 0.50 to 1.0 as good in the interpretation of the results. Data were expressed as number and percentage or as mean/median ± standard deviation values. A value of $P < .05$ was considered statistically significant. Considering the 3.6% prevalence rate of FM in Turkey[17] and the total population of the province, 145 patients were included in the study within a 95% confidence interval. The power of the study was calculated post hoc as 91.31%.

3 | RESULTS

The study was conducted on 145 FM patients (7 male, 138 female; mean age 43.7 ± 10.4 years; range, 18 to 75 years) and 129 healthy

TABLE 1 Comparison of serum cathepsin S and cystatin C levels between patients and controls

	Patients (n = 145)	Controls (n = 129)	*P*
Cathepsin S, mg/L	538.6 (255.7-961.4)	360 (157.1-675.7)	.001*
Cystatin C, mg/L	2.88 (1.38-4.33)	1.97 (1.15-2.91)	.001*

Note: Results are given as median 1st and 3th quartiles.

*$P < .05$ was regarded as significant.

control subjects (4 male, 125 female; mean age 44.2 ± 8.5 years; range, 18 to 72 years). No statistically significant difference was determined between the patient and control groups in terms of age and gender ($P > .05$). There was no statistical difference between the FM patients (mean 25.8 ± 4.21) and control group (mean 25.03 ± 3.96) in terms of BMI values ($P > .05$). When the serum CatS and CysC levels of the FM patients and the control group were compared, the serum CatS and CysC levels were statistically significantly higher in the FM group than in the control group ($P = .001$) (Table 1). The mean FIQ score was 62.1 ± 12.3 (range 23.6-89.4) in patients with FM. There was no statistically significant correlation between serum CatS, CysC and the FIQ score in the patients with FM (*P*-0.218, $P = .424$, respectively) (r = −0.65, r = 0.16, respectively).

4 | DISCUSSION

In this study, serum CatS and CysC levels were compared in patients with FM and healthy control subjects. According to the results of the study, serum CatS and CysC levels were found to be higher in patients with FM than in the healthy control group. However, no correlation was determined between serum CatS and CysC levels and functional status in patients with FM. To the best of our knowledge, these results are presented here for the first time in the literature.

Cysteine cathepsins are important proteases involved in many physiological processes. Cathepsins are overexpressed in pathological conditions and released into the extracellular space, suggesting that cathepsins may be valuable diagnostic and therapeutic markers.[18] Cathepsin S has been shown to play an important role in the pathogenesis of various diseases such as cancer, asthma, cardiovascular diseases, diabetes, and cystic fibrosis.[12,19] There are also studies which have evaluated the level of CatS in some rheumatological diseases. In a study of patients with rheumatoid arthritis (RA), Weitof et al[20] showed that patients with seropositive RA had higher levels of CatS in serum and synovial fluid compared to control groups. In another study, serum CatS levels were found to be higher in RA patients than in healthy control subjects.[21] In a study of patients with lupus, it was shown that serum CatS levels were high and that CatS inhibition might be important in the treatment of lupus.[22] It has also been shown that FM patients had elevated levels of CX3CL1 activated by CatS in serum and cerebrospinal fluid.[11] The results of the study by Backryd et al[11] showed that the levels of CatS, known to release CX3CL1 in FM, may also be high. In the current study, high serum CatS levels were determined in FM patients, and this finding was similar to those of previous studies evaluating the level of CatS in different diseases.

CysC is an endogenous inhibitor of cysteine proteases. Although CysC was first identified in the cerebrospinal fluid (CSF), it was later shown in other body fluids and tissues.[23] It has been claimed that serum CysC level can be used as a biomarker for some diseases because it is not affected by factors such as diet, age and gender.[24] In particular, the association of CysC with renal, cardiovascular and nervous system diseases is well known.[25-27] There are few studies evaluating the relationship between CysC and pain in the literature. Mannes et al[28] in a study conducted on pregnant women, showed that the CysC expressions in CSF are higher in pregnant women with labor pain than in pregnant women with painless births. An experimental study in rats suggested that CysC may be a biomarker for pain.[29] In another study of different disease groups, Akbas et al[30] found high levels of CysC in the CSF of patients with pain. Guo et al[24] reported that patients with osteoarthritis had higher CysC levels in CSF in a different study of patients with chronic painful osteoarthritis. In the current study, serum CysC levels were found to be higher in patients with FM than in the healthy control group. These results are consistent with previous findings in the literature. It can be considered that the increase in CysC levels may be due to increased CatS enzyme activity, because increased enzyme activity is thought to cause increased endogenous inhibitors of enzymes.[31]

Limitations of this study included the lack of objective pain level measurement, lack of correlation between pain levels and CatS and CysC levels, and that the number of male patients was low in both groups.

5 | CONCLUSION

Serum CatS and CysC levels were found to be higher in patients with FM than in healthy subjects. The results of this study may contribute to a better understanding of the pathogenesis of FM, and can serve as a guide for future clinical studies investigating the pathogenesis and treatment of FM. Nonetheless, there is a need for further clinical studies to evaluate the levels of serum CatS and CycS in FM.

CONFLICT OF INTEREST

The authors have no conflict of interests to declare in respect of the authorship and/or publication of this article.

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ORIGINAL ARTICLE

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Fibromyalgia in a rheumatology clinic in north-central Nigeria: An audit of the characteristics of the syndrome and the sensitivities of 4 sets of American College of Rheumatology criteria

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Abstract

Objectives: To describe the characteristics of fibromyalgia among Nigerian patients and assess the sensitivities of the American College of Rheumatology (ACR) criteria of 1990, 2010, 2011, and 2016 for making the diagnosis of fibromyalgia.

Methods: Consecutive patients diagnosed clinically with fibromyalgia by a rheumatologist were assessed. ACR criteria for fibromyalgia of 1990, 2010, 2011, and 2016 were applied to each patient. Polysymptomatic distress scores (PSD) were calculated from the Widespread Pain Index and Symptom Severity Scores. Sleep was assessed using the Pittsburgh Sleep Quality Index; fatigue by the Fatigue Severity Scale and the severity of fibromyalgia was determined using the Revised Fibromyalgia Impact Questionnaire (FIQR).

Results: A total of 660 new patients were seen out of which a diagnosis of fibromyalgia was made in 114 (17.3%). The mean age of the patients was 44.6 ± 15.6 years and females accounted for 84.2%. Twenty-one (18.4%) patients had changed or quit their jobs due to fibromyalgia. Problematic fatigue was present in 80 (70.2%), and sleep disturbance was reported in 83 (72.8%) patients. The severity of fibromyalgia, poor sleep, severe or very severe PSD, and male gender were associated with problematic fatigue, but only moderate/severe fibromyalgia independently predicted problematic fatigue (P = .004). The number of tender points (P = .001) and FIQR score (P = .038) were associated with changing or quitting jobs. The sensitivities of the ACR1990, ACR2010, ACR2011 and ACR2016 were 38.5%, 68.2%, 76.7% and 76.7%, respectively.

Conclusion: The ACR1990 had low sensitivity when used to diagnose fibromyalgia in this population and the ACR2010 encounters problems while applying the somatic symptom list.

KEYWORDS

assessment of sleep, criteria sensitivities, fatigue, fibromyalgia, severity, spiritual beliefs

1 | INTRODUCTION

Fibromyalgia is a chronic widespread pain disorder that is characterized by fatigue, non-restorative sleep, cognitive difficulties, and various somatic symptoms. It has been described all over the world at a prevalence ranging between 2% and 4% in the general populace.[1] It is a poorly understood disorder about which little is known on the African continent. The tendency to present with chronic widespread pain and a myriad of somatic symptoms makes for frequent difficulty in arriving at an early and reliable diagnosis. The lack of a diagnostic test for fibromyalgia further compounds the problem. Rheumatologists are very few in sub-Saharan Africa. Nigeria, a country of nearly 200 million people, currently has fewer than 40 practicing rheumatologists. Ethiopia, the second-most populous African nation with about 110 million residents, has no single rheumatologist. Fibromyalgia often proves to be frustrating for both patients and healthcare providers, and the poor knowledge of the syndrome in many sub-Saharan African countries means that patients may live with it for years without any understanding of the problem. Many of these individuals may never be diagnosed.

Since the development of the 1990 American College of Rheumatology (ACR) Classification Criteria for fibromyalgia (ACR1990), medical practitioners have often used it while assessing patients.[2] However, the ACR1990 only assesses tender points without any consideration for the somatic symptoms. While the ACR1990 is not a diagnostic test, it has been shown to have a sensitivity of 88.4% and specificity of 81.1%.[2] Other criteria have since emerged which also give consideration to the somatic symptoms of fibromyalgia and have been shown to have superior sensitivities. These include the 2010 ACR criteria (ACR2010), the 2011 modification of the 2010 ACR criteria (ACR2011), and the 2016 ACR criteria (ACR2016).[3-5] While the more recent criteria are supposed to be more sensitive, the real-world performances of these classification methods are not always as remarkable. Results from a national health interview survey in the USA showed that only about a quarter of patients with a clinical diagnosis of fibromyalgia satisfied the ACR2016 criteria.[6]

Fibromyalgia has been linked with a perception of mysteriousness among patients.[7] Understandably, a lack of knowledge of the nature and process of the disorder fuels this notion. Many religious and traditional beliefs influence the perceptions and attitudes of African patients toward their health challenges. Fibromyalgia, a seemingly bizarre condition for which there is often nobody around the sub-Saharan African patient who understands the disorder, is the quintessential health problem to blame on spirits and demonic attacks. We aim to describe the characteristics of fibromyalgia among the patients diagnosed in the first 20 months of operation of the rheumatology service of the University of Ilorin Teaching Hospital (UITH). We also seek to assess the sensitivities of the 4 sets of ACR criteria in diagnosing this condition among our patients.

2 | METHODS

This research is an audit of the cases of fibromyalgia diagnosed at the rheumatology unit of the UITH between August 2016 and March 2018. UITH serves as a referral center for patients from adjourning states.

Patients were prospectively recruited based on the presence of widespread pain defined as pain in all 4 quadrants of the body and over the axial skeleton. Case-by-case exclusion of other diagnoses was done.

The inclusion criteria were a clinical diagnosis of fibromyalgia by a rheumatologist based on widespread pain, fatigue, sleep disturbance, cognitive disturbance and typical somatic symptoms seen in fibromyalgia after excluding alternative diagnoses as the cause. No predetermined minimum tender point count was required for diagnosis. All patients were of age 16 years or older. All patients were diagnosed for the first time in UITH by the same rheumatologist within the study period. Patients with fibromyalgia with a background of a primary rheumatic disease such as rheumatoid arthritis or systemic lupus erythematosus were excluded. All patients had routine blood tests, full blood count, electrolytes and urea, thyroid function test, erythrocyte sedimentation rate and other tailored investigations. Others included serology and imaging as required. Ethical approval was obtained from the UITH Ethics Review Committee.

We applied each of the 4 sets of ACR criteria for fibromyalgia on each patient. These are the ACR1990, ACR2010, ACR2011, and ACR2016 criteria. These were administered by a trained research assistant in a separate room from the rheumatologist. Tender points were assessed with finger pressure enough to blanch the nail bed and these points were recorded in a body chart. The reported sites of pain were also recorded in a separate body chart. Demographic and clinical characteristics, as well as the beliefs of the patients regarding fibromyalgia, were obtained. The Polysymptomatic Distress (PSD) scores were calculated from adding up the Widespread Pain Index (WPI) and Symptom Severity Scores of the ACR2010.[8] PSD represents an objective way to grade how fibromyalgic a patient comes across. Fibromyalgianess was classified based on PSD as none (0-3), mild (4-7), moderate (8-11), severe (12-19), and very severe (20-31).[9] The functional status of each patient was determined using pragmatic but non-validated functional classification as follows.[10]

I - Complete ability to carry out all the usual duties without handicaps.

II - Adequate for normal activities despite the handicap of discomfort or limited motion of one of the joints.

III - Limited to little or none of the duties of usual occupation or self-care.

IV - Incapacitated, largely or wholly bed-ridden or confined to a wheelchair with little or no self-care.

TABLE 1 Characteristics of patients

	Number	Percentage
Age		
16-25	11	9.6
26-35	23	20.2
36-45	24	21.1
46-55	37	32.5
56-65	8	7.0
66-75	9	7.9
76-85	0	0
86-95	2	1.8
Gender		
Male	18	15.8
Female	96	84.2
Duration of symptoms		
Less than 1 year	23	20.2
1-5 years	62	54.4
More than 5 years	29	25.4
Level of education		
None	13	11.9
Primary	14	12.4
Secondary	14	12.4
Tertiary	65	59.6
Postgraduate	3	2.7
Marital status		
Single	26	22.8
Married	75	65.8
Widowed	13	11.4
Functional class		
I	71	62.3
II	19	16.7
III	24	21.1
IV	0	0
Changed or stopped occupation		
Yes	21	18.4
No	93	81.6
Family history of CWP		
Yes	30	26.3
No	31	27.2
Unable to say	53	46.5
Sleep disturbance		
Yes	83	72.8
No	31	27.2
Fibromyalgianess (PSD)		
Mild	7	6.5
Moderate	6	5.6
Severe	68	63.6
Very severe	26	2.4
Fatigue		
No problematic fatigue	34	29.8
Problematic fatigue	80	70.2

Abbreviations: CWP, chronic widespread pain; PSD, polysymptomatic distress.

3 | MEASURES

Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), and individuals with a total PSQI score ≥5 were stratified as having poor sleep quality.[11] Fatigue was assessed using the Fatigue Severity Scale (FSS), a tool developed in 1987 by Krupp et al[12] A final score is calculated by adding up the rating for each statement and dividing it by 9. A final score of ≥4 is considered to represent severe (problematic) fatigue. The severity of fibromyalgia was assessed using the Revised Fibromyalgia Impact Questionnaire (FIQR). Fibromyalgia severity was categorized based on FIQR scores as mild (≤45), moderate (>46 and ≤65), and severe (>65).[13]

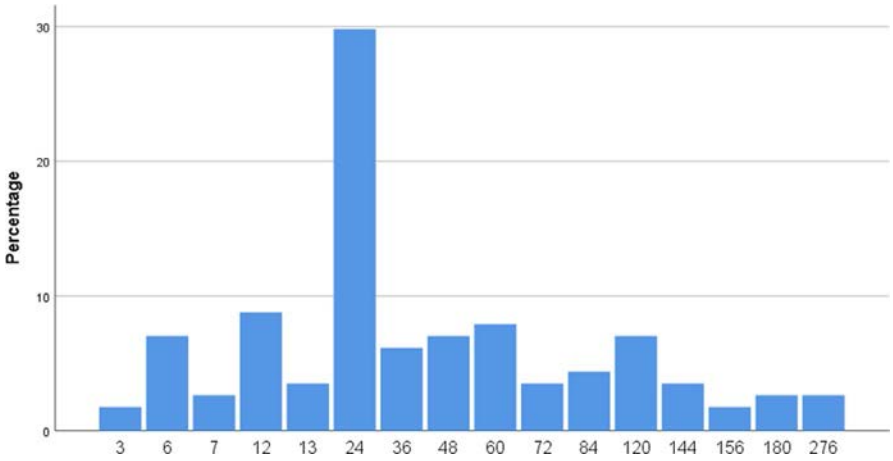
3.1 | Statistical analysis

All data were analyzed using SPSS version 21.0 for windows (IBM, Armonk, NY, USA). Demographic and clinical data were summarized using frequencies, percentages, and proportions. Tests of normality were performed using Shapiro-Wilk statistics. Sensitivities of ACR1990, ACR2010, ACR2011, and ACR2016 were determined against clinical diagnosis. Factors associated with problematic fatigue were determined using the Chi-square test, and a binary logistic regression analysis was done to predict problematic fatigue. t test and Mann-Whitney *U* tests were used as appropriate to determine associations between quitting or changing jobs due to fibromyalgia and each of the characteristics measured. Mann-Whitney *U* test was applied only for the duration of symptoms, which was not normally distributed. A *P* value <.05 was considered statistically significant.

4 | RESULTS

A total of 660 new rheumatology patients were seen over 20 months, out of which 136 patients had fibromyalgia. A total of 22 of the fibromyalgia patients also had an underlying diagnosis such as rheumatoid arthritis, systemic lupus erythematosus, and sarcoidosis while 114 patients representing 17.3% of the total seen in the period had "primary" fibromyalgia. These patients were referred to the rheumatology service from primary care centers, and specialties such as family medicine, gastroenterology, orthopedic surgery, urology, neurology, and psychiatry. The mean age of the patients was 44.6 ± 15.6 years,

FIGURE 1 Duration of symptoms (months)



and females accounted for 84.2% (96) (Table 1). The median duration of symptoms was 24 months (interquartile range = 48 months; Figure 1). Seventy-one (62.3%) of the patients fell into functional class I; 19 (16.7%), class II; and 24 (21.1%), class III. No patient was in functional class IV. A total of 21 (18.4%) patients had changed their job or stopped working due to fibromyalgia, and 30 (49.2%) of the 61 patients who were able to answer about the history of chronic widespread pain in their family confirmed it as positive. Problematic fatigue was present in 80 (70.2%), and sleep disturbance was reported in 83 (72.8%) patients.

There were more patients in the moderately severe disease category (53; 46.5%) than in the mild (32; 28.1%) or severe (29; 25.4%) groups. When the male and female patients were compared, as seen in Table 2, more females had moderate and severe fibromyalgia ($P < .001$). Women were also more polysymptomatic, with higher PSD scores ($P < .001$). However, problematic fatigue was universal among the males while it was found in only 62 (64.6%) females ($P = .001$). As seen in Table 3, problematic fatigue was significantly associated with the severity of fibromyalgia, poor sleep, severe or very severe fibromyalgianess, and male gender ($P < .05$ in each case). Following logistic regression analyses, moderate or severe fibromyalgia remained the only factor that independently predicted problematic fatigue (odds ratio = 6.6, $P = .004$) (Table 4).

As shown in Table 5, there is no statistically significant difference in the PSD, FSS, PSQI, or WPI scores of patients who have and who have not had to change or quit their jobs. Similarly, the duration of symptoms is comparable in the 2 groups. However, tender point count ($P = .001$) and overall FIQR score ($P = .038$) were significantly higher among those who have changed or quit their job. The

TABLE 2 Comparison of male and female patients

	Male N = 18 (%)	Female N = 96 (%)	*P*
Severity (FIQR)			
Mild	13 (72.2)	19 (19.8)	<.001
Moderate	2 (11.1)	51 (53.1)	
Severe	3 (16.7)	26 (27.1)	
Fatigue (FSS)			
No problematic fatigue	0 (0.0)	34 (35.4)	.001
Problematic fatigue	18 (100.0)	62 (64.6)	
Fibromyalgianess (PSD)			
Mild	5 (27.8)	2 (2.2)	<.001
Moderate	2 (11.1)	4 (4.5)	
Severe	3 (16.7)	65 (73.0)	
Very severe	8 (44.4)	18 (20.2)	
Sleep (PSQI)			
No sleep disturbance	2 (11.1)	29 (30.2)	.147
Sleep disturbed	16 (88.9)	67 (69.8)	

Abbreviations: FIQR, Revised Fibromyalgia Impact Questionnaire; FSS, Fatigue Severity Scale; PSD, polysymptomatic distress score; PSQI, Pittsburgh Sleep Quality Index

TABLE 3 Factors associated with problematic fatigue

	No problematic fatigue n (%)	Problematic fatigue n (%)	*P*
Severity (FIQR)			
Mild	15 (44.1)	17 (21.3)	<.001
Moderate	19 (55.9)	34 (42.5)	
Severe	0 (0.0)	29 (36.3)	
Sleep (PSQI)			
Normal sleep	16 (47.1)	15 (18.8)	.002
Poor sleep	18 (52.9)	65 (81.3)	
Fibromyalgianess (PSD)			
Mild or moderate	0 (0.0)	13 (17.1)	.018
Severe or very severe	31 (100.0)	63 (82.9)	
Gender			
Male	0 (0.0)	18 (22.5)	.003
Female	34 (100.0)	62 (77.5)	

Abbreviations: FIQR, Revised Fibromyalgia Impact Questionnaire; PSD, polysymptomatic distress score; PSQI, Pittsburgh Sleep Quality Index

TABLE 4 Logistic regression predicting problematic fatigue

	B	Wald	Adjusted odds ratio	P
Poor sleep	−0.732	1.843	–	.175
Severe or very severe fibromyalgianess	19.361	0.000	–	.998
Male gender	20.995	0.000	–	.998
Moderate or severe fibromyalgia	−1.887	8.464	6.601	**.004**

P values are considered statistically significant and indicated in bold

sensitivities of the ACR1990, ACR2010, ACR2011 and ACR2016 were 38.5%, 68.2%, 76.7% and 76.7% respectively. Almost half of the patients (48.2%) have been told at some point that their fibromyalgia symptoms were due to some form of spiritual attack and 37% have had one form of religious ritual to appease the gods in an attempt to find a cure (Figure 2).

5 | DISCUSSION

Fibromyalgia is an infrequent diagnosis in West Africa. While the diagnosis of fibromyalgia can take time and be difficult,[14] there is often an agreement between the impression of the primary care physician and the rheumatologist.[1,15] There is no diagnostic test for fibromyalgia and for this and other arguments such as the possibility that the disorder is psychosocial rather than organic and not willing to legitimize a "made-up" clinical condition, many physicians do not believe in and refrain from diagnosing fibromyalgia.[1,16,17]

The mean age of 44.6 years of our patients is similar to that of French patients with a mean age of 44 years who were diagnosed based on a Fibromyalgia Rapid Screening Tool score of 5/6 or 6/6.[18] However, the French patients were all working women recruited via the internet. In a Belgian study of pain characteristics in fibromyalgia, patients' mean age of 46.9 years is also similar to our finding.[19] Relatively older populations of fibromyalgia patients have been described from Europe and the USA.[20,21] However, these reports did not confine their described populations to those with fibromyalgia as their only diagnosis. Problematic fatigue was found in four-fifths of our patients. This is similar to the findings of Overman and others in an international study of fibromyalgia across different rheumatic diseases.[22] Fatigue has been shown to correlate with pain in fibromyalgia and, on its own, can be very disabling for the patients.[23,24] We found that problematic fatigue was predicted by moderate to severe fibromyalgia. The pain in fibromyalgia has been suggested to lead to poor quality of sleep and following-day fatigue.[25]

Fibromyalgia is more common in women at a proportion ranging between 61% and more than 90%.[26,27] However, men with fibromyalgia suffer as much disability and poor quality of life from the disorder.[28,29] We found that 1/6 of our patients were men, a proportion that reflects the diagnostic approach to our cases. Traditionally, ACR1990 criteria tend to label substantially more females than males as compared to clinical diagnosis and the more recent ACR criteria.[30] Between 2.3:1.0 and 13.7:7.0 were reported as the female-male ratio of patients based on criteria methods, and this gap tends to be narrower when the newer ACR criteria are used.[30] In Kenya, 97.7% of the patients classified based on ACR1990 were female.[31] The men in our study had lower fibromyalgia severity, higher fatigue, and lower PSD than women. Women with fibromyalgia tend to have lower thresholds for reporting tenderness from the tender spot examination and they are more prone to catastrophizing, 2 features that may increase their self-report of fibromyalgia severity and PSD score.[32]

Almost a fifth of our patients have either changed their jobs to a less demanding one or stopped working entirely. In the USA, a third of fibromyalgia patients receive the Social Security Disability and Supplemental Security Income.[33] Similarly, the prevalence of disability as a result of fibromyalgia in a Canadian cohort was reported to be 30.8%.[34] Unsurprisingly, these figures are higher in North America than the proportion of our patients who are occupationally impacted at least for one reason: there is no social welfare payment scheme in Nigeria. However, as it was among our patients, fibromyalgia severity was associated with occupational functioning in the Canadian study.[34]

Clinical diagnosis tends to identify more patients than the criteria-based diagnosis.[6,35] While the ACR1990 is a set of classification criteria originally developed for defining the minimum characteristics of patients for research purposes, the ACR2010, ACR2011, and ACR2016 are all preliminary diagnostic criteria.[2,30] Tender point assessment is not a component of the more recent 3 criteria sets, and they all consider the somatic symptoms that may accompany

TABLE 5 Comparison of characteristics of patients in terms of occupational functioning

	Quit/changed job	Did not quit/ changed job	P
PSD	17.5 ± 6.1	20.3 ± 6.5	.120
FSS	4.5 ± 1.4	4.7.7 ± 1.4	.565
PSQI	6.2 ± 3.4	6.5 ± 3.5	.715
WPI	9.8 ± 4.3	10.7 ± 4.2	.405
Tender points	14.8 ± 4.1	9.5 ± 4.7	**.001**
FIQR	57.1 ± 17.0	49.5 ± 14.4	**.038**
Duration of symptoms, mo	24 (12-120)	24 (3-276)	.662

Abbreviations: FIQR, Revised Fibromyalgia Impact Questionnaire; FSS, Fatigue Severity Scale; PSD, polysymptomatic distress score; PSQI, Pittsburgh Sleep Quality Index; WPI, Widespread Pain Index

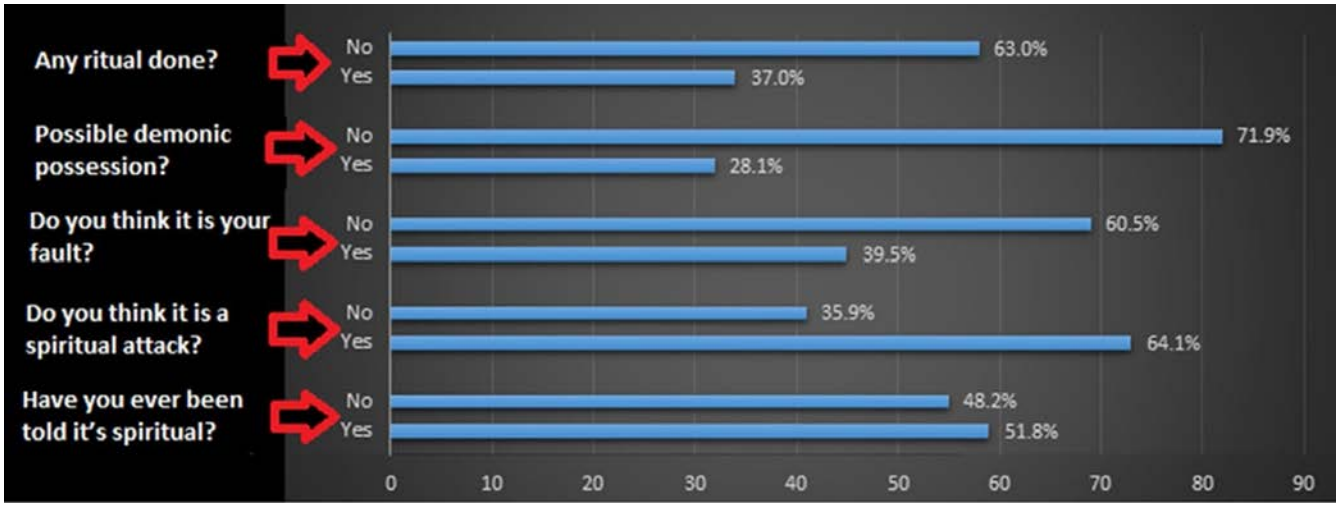


FIGURE 2 Spiritual perception of fibromyalgia among patients

the clinical presentation, an aspect lacking in the ACR1990. As the ACR1990, ACR2010, ACR2011, and ACR2016 diagnosed 38.5%, 68.2%, 76.7%, and 76.7% of our patients, respectively, it would appear that relying on the tender point assessment only is a weak method to diagnose our patients. Also, only the ACR2016 recognizes that fibromyalgia may be diagnosed in the presence of an alternative condition, effectively implying that fibromyalgia is not a diagnosis of exclusion as was required in all the other criteria. Although to satisfy the conditions for all criteria, we recruited only patients without other conditions for this study, in reality, multimorbidity is very common among patients with fibromyalgia.[36-38]

Furthermore, the list of permissible somatic symptoms that was introduced in the 2010 criteria has aspects that are generally less likely to be found in a Black African with or without fibromyalgia. Photosensitivity, Raynaud's, and easy bruising all fall into this category. Photosensitivity is rare among sub-Saharan Blacks who have not been on skin-lightening creams or have background connective tissue diseases. Similarly, primary Raynaud's is almost unheard of in tropical Africa. Black patients are unlikely to exhibit the typical white, blue, and red color changes that are characteristic of Raynaud's phenomenon. Other contents of this list present different issues. Bladder spasm is a difficult symptom to obtain from Nigerians in whom the local languages do not have equivalent words for the human bladder, nor are many of the patients familiar enough with their own anatomy to know that their pain is coming from the bladder. Lastly, fever is almost always attributed to malaria in this part of the world until otherwise proven. Due to the high prevalence of the immunity to malaria, many Nigerian adults will have trophozoites in their blood when they are not symptomatic for malaria. Therefore, asking a patient if they have had a fever can hardly be taken as a somatic symptom of fibromyalgia since many Nigerians have a fever every now and then.

The west African culture of explaining poorly understood health problems as a manifestation of spiritual forces abundantly favors fibromyalgia. This is particularly reinforced among the patients who have sought the help of healthcare professionals repeatedly but are not closer to the solution or even explanation. About half of our patients have been told by relatives and spiritualists that their symptoms are due to some form of bewitchment or demonic attack and more than a third of them are convinced this is the case. Similar beliefs have been reported regarding psychiatric disorders, epilepsy and ear, nose and throat-related disorders among patients in Nigeria.[39-41] The limitations of this study include the likelihood that the cases captured fall into the more severe spectrum as patients were assessed in a tertiary care center. Also, using physician's diagnosis as a reference of assessment of the criteria sets could not be considered as a gold standard. However, this would represent the real-world scenario and the true ground for diagnosis of the vast majority of fibromyalgia sufferers.

In conclusion, fibromyalgia occurs among Nigerians, and the majority of patients have a moderately severe disorder. Female patients seem to have more severe fibromyalgia and also come across as more fibromyalgic due to their higher polysymptomatism while problematic fatigue is more prevalent among males. Tender point assessment using ACR1990 has low sensitivity in diagnosing these patients, and there are specific challenges with using the standard somatic symptom list in Nigerian patients. Fibromyalgia is also poorly understood by patients, leading them to attribute it to bewitchment.

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ORIGINAL ARTICLE

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Effect of anti-interleukin-1 treatment on quality of life in children with colchicine-resistant familial Mediterranean fever: A single-center experience

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Abstract

Aim: The aim of this study is to evaluate the clinical parameters, acute-phase reactants, side effects, genetic mutations among colchicine-resistant Familial Mediterranean fever (FMF) patients who received anti-interleukin-1 (anti-IL-1) treatment. We also evaluate the quality of life and school attendance among colchicine-resistant FMF patients, in relation to treatment with anti-IL-1.

Introductıon: Familial Mediterranean fever is the most common inherited autoinflammatory disorder. Although the main treatment of FMF is colchicine, a small group of patients are resistant to colchicine treatment. Anti-IL-1 treatment is promising in colchicine-resistant patients due to excessive IL-1β production in pathogenesis. The aim of this study is to evaluate the quality of life and school attendance rates among colchicine-resistant FMF patients after anti-IL-1 treatment.

Methods: This is a single center retrospective study of 25 pediatric colchicine-resistant FMF patients treated with anti-IL-1 treatment. Autoinflammatory Disease Activity Index (AIDAI) was used for disease activity assessment. School attendance rates were evaluated before and after treatment.

Results: There were 25 patients with FMF (11 M/14 F) who were treated with anakinra or canakinumab for various indications (colchicine-resistant recurrent febrile attacks in 20, colchicine-related side effects in 2, subclinical inflammation in 3 patients). Only 3 patients developed side effects with anakinra (2 headache, 1 urticarial rash). There was a significant decrease in the frequency of attacks, acute-phase reactants (erythrocyte sedimentation rate and C-reactive protein), AIDAI and physician's and patient's global assessment scores and improvement in school attendance rates. At the last follow-up, all patients were in remission, and only 3 had subclinical inflammation.

Conclusıon: Anti-IL-1 treatment is quite effective in children with colchicine-resistant FMF patients, proven with improved AIDAI scores and school attendance rates. In the long term by lowering disease activation even development of amyloidosis may be prevented.

KEYWORDS
anti-IL-1 treatment, colchicine resistance, familial Mediterranean fever, life quality

1 | INTRODUCTION

Familial Mediterranean fever (FMF) is the most common inherited autoinflammatory disorder characterized by uncontrolled activation of the innate immune system.[1] The responsible gene *MEFV* is located on chromosome 16p and encodes a protein called "pyrin". Pyrin is involved in the activation of caspase-1 and the processing of active interleukin (IL)-1β.[2] Increased IL-1β production may explain the inflammatory phenotype of FMF patients.[3,4] Attacks usually last from 12-72 hours and are characterized by recurrent fever episodes, joint, skin and serosal involvement.[5] Chronic inflammation can lead to secondary amyloidosis by accumulation of extracellular amyloid protein at various tissues.[6] Standard treatment for FMF is colchicine.[6,7] Colchicine is effective both in controlling attacks and preventing the development of secondary amyloidosis, the most devastating complication of FMF. However, colchicine is ineffective or cannot be tolerated due to side effects in 5%-10% of patients.[8]

Mutations in *MEFV* genes undermine the innate immune response triggered by both endogenous and exogenous ligands. Depending on the exogenous stimuli, pyrin mutations causing FMF lead to enhanced IL-1β secretion by *NLRP3* or pyrin-inflammasome complex activation.[9] Since the role of IL-1β in spontaneous inflammation attacks is known, IL-1 blockade has become an alternative treatment option in colchicine-resistant FMF patients. These agents are anakinra, rilonacept and canakinumab. Several reports have pointed out the effectiveness of IL-1 blockade for preventing FMF attacks, in series with limited numbers of patients.[10,11]

The aim of this study is to evaluate the clinical parameters, acute-phase reactants, side effects, genetic mutations among colchicine-resistant FMF patients who received anti-IL-1 treatment. We also evaluate the quality of life and school attendance among colchicine-resistant FMF patients, in relation to treatment with anti-IL-1 treatment.

2 | METHODS

Four hundred and forty-five children were diagnosed with FMF between 2013-2019 in our center, and 25/445 were administered anti-IL-1 treatment (anakinra and/or canakinumab). Eight of these 25 children were reported previously in another study.[12] The diagnosis of FMF was made using Yalçinkaya-Ozen criteria. Fifteen patients had *M694V* homozygous, six patients had compound heterozygous and 4 patients had heterozygous mutations.

Colchicine resistance was defined as at least 1 attack per month for three consecutive months and elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) in between attacks despite taking adequate doses of colchicine.[13]

Clinical and laboratory data were obtained from the patients' records. Age, gender, clinical characteristics, MEFV1*MEFV* genotypes, acute-phase reactants (ESR, CRP and white blood cell counts [WBC]), average colchicine dose, disease duration, attack frequency, attack duration, accompanied diseases, and side effects of treatment were evaluated.

Anakinra (recombinant non-glycosylated homologous human IL-1 receptor antagonist) was started with a dose of 1 mg/kg/d and increased according to patient's clinical findings and laboratory results. Canakinumab (a human immunoglobulin G1 monoclonal antibody against IL-1β) was started with dose 2-4 mg/kg/4 wk. Frequency of drug administration was elongated according to clinical response. Colchicine treatment was continued in all patients, except patient 7.

We reviewed with regard to indication, effect on disease activity and acute-phase response, adverse events and Autoinflammatory Disease Activity Index (AIDAI) and physician's and patient's global assessments. Physician's and patient's global assessment score (visual analog scale [VAS]) indicated as 1 the best to 10 the worst.

AIDAI and VAS were evaluated in all patients before anti-IL-1 treatment and after 6 months of treatment. We asked all patients to complete a 1-month prospective diary. The AIDAI score comprised fever >38°C, abdominal pain, chest pain, arthralgia/myalgia, skin rash, pain relief taken. Serial disease activity measurement should be obtain at long enough intervals (3-6 months) for meaningful disease detection. The final activity score consists of the sum of all variables divided by the number of days over which the diary was completed.[14]

Efficacy of anti-IL1 treatment was evaluated >50% reduction of FMF attack frequencies, AIDAI score and VAS.

The school attendance of patients before and after anti-IL-1 treatment was recorded.

A signed informed consent form was obtained from each patient for whom anti-IL-1 treatment was planned. Ethics committee approval was received for this study, from the scientific and ethics committee of our hospital (approval number: 003; approval date: 12/31/2019).

2.1 | Statistical analysis

The values were analyzed using Statistical Package for Social Sciences (SPSS) software version 22. Quantitative variables were calculated as mean, ranges (minimum-maximum) or percentages. Wilcoxon test was used for evaluation of pre- and post-treatment AIDAI *P* values less than .05 were considered significant.

3 | RESULTS

There were 25 patients with FMF (11 M/14 F) who were treated with anakinra or canakinumab for various indications (colchicine-resistant

recurrent febrile attacks in 20, colchicine-related side effects in two patients, subclinical inflammation in 3). Eleven patients were treated with anakinra while 22 patients were treated with canakinumab. The mean age at onset of anti-IL-1 treatment was 14 ± 2 (8.5-16) years. The mean duration of the disease was 7.2 ± 3 years. All patients were taking adequate doses of colchicine with a median dosage of 0.031 ± 0.011 mg/kg/d before anti-IL-1 treatment (0.03-0.06 mg/kg/d). Demographic features, clinical findings, genotypes and indications of anti-IL-1 treatment are given in Table 1.

Two patients had juvenile idiopathic arthritis and were treated with non-steroidal anti-inflammatory drugs and methotrexate.

Two patients had sacroiliitis and also were treated with sulphasalazine. One of these patients (patient 8) had growth hormone deficiency and subclinical inflammation persisted even though there were no clinical attacks.

The attack frequency of the patients was mean 7.3 (3-15) times in the last 3 months before anti-IL-1 treatment.

Eleven patients were treated with anakinra with a median duration of 29.7 months (8-60), but 6 of them switched to canakinumab because of noncompliance and side effects (2 headache, 1 urticarial rash): all responded. After the initiation of anakinra treatment, six patients became attack-free, two patients reported more than 50% decrease, and three patients showed no change in the frequency of the attacks. The mean attack frequency was 7.3 (3-12) in the last 3 months before anakinra treatment, while it was 1.3 (0-4) in the 6 months after the anakinra. The mean attack frequency of the patients decreased significantly ($P = .003$).

Twenty-two patients were treated with canakinumab but 2 (13.3%) of them switched to anakinra for the increase in frequency of the attacks. One of the patients (patient 4, M) who switched from canakinumab to anakinra had a *M694V* homozygous mutation; the attacks of this patient included fever and abdominal-chest pain and, an increased incidence of attacks after 17 months of canakinumab use. After replacing it with anakinra, the number of attack significantly decreased.

The other patient (patient 18, M), was a patient with *M694V/M680I* mutation who developed renal amyloidosis at follow-up. After 6 months of canakinumab treatment, there was an increase in attack frequency and proteinuria. After switching to anakinra, a decrease in the number of attacks and improvement in proteinuria were observed.

The other patients completely responded to therapy and none of them had side effects.

The mean attack frequency was 7.36 (3-15) in the last 3 months before canakinumab treatment, while it was mean 0.81 (0-4) in the 6 months after canakinumab. The mean attack frequency of the patients decreased significantly ($P = .00$).

Anakinra was administered at a dose of 2-5 mg/kg/d and canakinumab at a dose 4 mg/kg/mo (max 150 mg).

A significant decrease was observed in the mean CRP (from 8.1 ± 7.8 mg/dL to 0.54 ± 0.67 mg/dL; $P < .01$), WBC (from 10 837 ± 3800/mm^3 to 7004 ± 1876.7/mm^3; $P < .01$) and ESR levels (from 44.4 ± 18.5 mm/h to 9.6 ± 76.5 mm/h $P < .01$).

TABLE 1 Demographic features, genotypes, and indications of anti-interleukin-1 treatment

Gender (N: 25)	
M	11
F	14
Age at diagnosis (mean)	6.8 (2-15) y
Age at biological treatment (mean)	14 ± 2 (8.5-16) y
Attack frequency/ 3 mo (mean)	7.3 (3-15)
Frequency of attacks after anakinra (mean, *P*)	1.3 (0-4), *P* = .003
Frequency of attacks after canakinumab (mean, *P*)	0.81 (0-6), *P* = .00
MEFV genotype, n (%)	
M694V homozygous	15 (60)
M694V heterozygous	2 (8)
Compound heterozygous	6 (24)
M694V/10. Exon mutation	3 (12)
M694V/The other exon mutations	3 (12)
M680I heterozygous	1 (4)
E148Q heterozygous	1 (4)
Treatment, n	
A	11
CAN	22
A to CAN	6
CAN to A	2
A side effect, n	
Headache	2
Urticarial rash	1
CAN side effect	None
Indications of anti-IL-1 treatment, n (%)	
CR	18 (72)
CR + subclinical inflammation	3 (12)
CR + colchicine side effect	2 (8)
CR + renal amyloidosis	2 (8)
Response to treatment, n	
Complete remission	22
Subclinical inflammation	3

Abbreviations: A, anakinra; CAN, canakinumab; CR, colchicine resistance; MEFV, Mediterranean Fever gene.

VAS and AIDAI scores were evaluated before and after the initiation of anti-IL-1 treatment. AIDAI score decreased from 27.2 ± 16.7 to 0.36 ± 1 and mean physician's global assessment 7.7 ± 1.5 to 1 ± 1.1, after anti-IL-1 treatment ($P < .01$, $P < .01$, respectively). The results were statistically significant.

Median number of days out of school after biological treatment significantly decreased (from 55.4 ± 19.9 to 2.28 ± 2.77; $P < .01$). Patient 4 was receiving home education because of frequent attacks. After anakinra there was no attack, quality of life and social life improved in all patients. The pre- and post-anti-IL-1 treatment VAS, AIDAI and school attendance are given in Table 2.

As for the adverse events, 1 patient (3.7%) had allergic reactions (severe disseminated rash) with anakinra treatment and 2 (7.4%) had headache which necessitated termination of treatment. There were no adverse events in the remaining patients during the course of treatment.

At the last follow-up, all patients were in remission, and only 3 had subclinical inflammation. Canakinumab administration frequency was extended to 2 months only in 4 patients.

4 | DISCUSSION

In this study, we evaluated 25 patients with FMF who were treated with anti-IL-1 treatment because of colchicine resistance. As is known, colchicine is the standard treatment for FMF. Usage of colchicine led to complete remission in two-thirds of the patients and partial remission in one-third of the patients.[13] However, 5%-10% of patients are unresponsive to colchicine therapy.[8] The quality of life of these patients whose inflammation persists, decreases considerably and increases the risk for amyloidosis. The goal of FMF treatment is to prevent periodic attacks, suppress inflammation, and prevent the development of amyloidosis.[15] Therefore, anti-IL-1 treatment has been introduced in patients with ongoing clinical exacerbations with adequate doses of colchicine, or who continue to have subclinical inflammation without attacks.[16,17]

Inadequate response to colchicine in FMF patients may occur due to a higher inflammatory activity via IL-1β pathway and a stronger inflammatory activity exceeding anti-inflammatory effects of colchicine. The higher inflammatory activity may be associated with *MEFV* variations, environmental factors or accompanying inflammatory conditions.[18] The majority of colchicine-resistant FMF cases in the literature as well as in our study have homozygous *M694V* genotype which is associated with a more severe phenotype.[19] Moreover, 4 of 25 patients had another concomitant inflammatory disease. In our study, these factors are thought to contribute to increased inflammatory activity.

For FMF patients, scales are necessary to evaluate disease activation in follow-up and to determine risk groups for amyloidosis. AIDAI score was developed for autoinflammatory diseases and was modified for FMF patients.[20] Piram et al[14] demonstrated that the AIDAI score was a valid, easy and simple tool for assessing disease activity in FMF. It reflects the quality of life in a good way and also provides guidance in the evaluation of treatment response. Similarly, Eroglu et al[21] performed both treatment efficacy and treatment dose adjustment using AIDAI score in colchicine-resistant FMF patients. In our study, decrease in AIDAI score after anti-IL-1 blocking therapy is an indicator of the increase in quality of life.

Recently, studies have shown that anti-IL-1 treatment is effective and safe in children with FMF.[22] Köhler et al[23] demonstrated that anakinra and canakinumab treatment were effective and safe in colchicine-resistant FMF patients, and significant improvements in the modified FMF 50 score were demonstrated. Both agents have been shown to reduce acute-phase reactants and attack frequency in colchicine-resistant FMF. Local reactions with anakinra are reported in 25% of patients, which were transient and tolerable. In this study, the quality of life in patients treated with canakinumab was better than anakinra due to daily injection.[23] In our study, local reactions with anakinra and headache were more frequent, whereas these side effects were not observed in canakinumab. However, two patients receiving canakinumab were switched to anakinra because of increased frequency of attacks. Systemic complications did not occur in any patient. There was a significant increase in quality of life in both groups.

Colchicine-resistant FMF pediatric patients have poor quality of life, anti-IL-1 blockade treatment has been shown to have good results.[24] Thus, this treatment not only prevents attacks but also increases the quality of life of the patients. Anti-IL-1 treatment led to increased school attendance which was poor because of frequent attacks. In our study, significant improvements were observed in VAS levels after anti-IL-1 blocking treatment.

The AIDAI scale can be used to assess disease activity for FMF. Quality of life in patients with frequent exacerbations deteriorates and causes disruptions in education during childhood. With the help of biological treatment, attacks and subclinical inflammation are taken under control, while the quality of life of the patients increases. In the long term, the risk of amyloidosis due to subclinical inflammation is minimized with anti-IL-1 treatment.

TABLE 2 The pre- and post-anti-IL-1 treatment VAS, AIDAI and school attendance

	Pre IL-1 treatment	Post IL-1 treatment	*P*
AIDAI, median (min-max)	25 (6-71)	0 (0-4)	.00
VAS, median (min-max)	8 (5-10)	1 (0-4)	.00
No. of d out of school, d/y, median (min-max)	54 (27-105)[a]	2 (0-10)[a]	.00

Abbreviations: AIDAI, Autoinflammatory Disease Activity Index; IL, interleukin; VAS, physician's and patient's global assessment via visual analog scale.

[a]Wilcoxon test, ($P < .01$).

CONFLICT OF INTERESTS

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Tuba Kurt, MD: organization of the paper and substantial contribution to the acquisition of data. Fatma Aydın, P. Nilüfer Akpınar, Müge Sezer, Nermin Uncu, Banu Acar, MD: organization of the paper and revision critically for intellectual content.

ETHICAL APPROVAL

Ethics committee approval was received for this study, from the scientific and ethics committee of our hospital (approval number:003; approval date:12/31/2019).

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What is the effect of mixed exercise training for adults with fibromyalgia? A Cochrane Review summary with commentary

The aim of this commentary is to discuss in a rehabilitation perspective the published Cochrane Review "Mixed exercise training for adults with fibromyalgia[a]" by Bidonde J et al[1], under the direct supervision of Cochrane Musculoskeletal Group. This Cochrane Corner is produced in agreement with *International Journal of Rheumatic Diseases* by Cochrane Rehabilitation.

2 | BACKGROUND

Fibromyalgia is a chronic centralized pain disorder marked by widespread muscle tenderness.[2] It is a heterogeneous and complex condition. People with fibromyalgia also experience gastrointestinal and somatosensory symptoms, as well as fatigue, disturbances in sleep, memory, mood and cognition which have an important influence on their quality of life.[3-6]

The global mean prevalence of fibromyalgia is 2.7%.[7] Women are affected approximately 2 times more often than men,[8] although another study did not find any statistical difference in prevalence between males and females.[9] A variety of factors could influence the model of central amplification of pain perception. That is why recommendations and guidelines underline the importance of a multidisciplinary approach including pharmacological and non-pharmacological interventions (exercise, acupuncture, biofeedback, mind-body therapy).[10]

Previous studies and systematic reviews have assessed the effects of exercise in people with fibromyalgia and have found benefits in terms of improved health-related quality of life, reduced pain, decreased fatigue, enhanced physical function.[11-13] People with fibromyalgia often have decreased muscle strength and endurance and increased muscle fatigue. Resistance training may result in greater tolerance to muscle microtrauma and thus more successfully accomplish daily activities. A meta-analysis found improved muscle strength, pain tolerance, reduced muscle tenderness and improved health-related quality of life (HRQL) and physical function in women with fibromyalgia after moderate-to-high-intensity resistance training.[13]

It is important to identify the most efficacious exercise protocols and the type of exercise in order to achieve alleviation of the symptoms in persons with fibromyalgia, which is the objective of this updated Cochrane Review.[1]

3 | MIXED EXERCISE TRAINING FOR ADULTS WITH FIBROMYALGIA

Bidonde J, Busch AJ, Schachter CL, Webber SC, Musselman KE, Overend TJ, Góes SM, Dal Bello-Haas V, Boden C. 2019.

3.1 | What is the aim of this Cochrane review?

The aim of this Cochrane Review is to evaluate the benefits and harms of mixed exercise training protocols in adults with fibromyalgia.

3.2 | What was studied in the Cochrane review?

The population addressed in this review was adults with fibromyalgia. The interventions studied were mixed exercise interventions including at least 2 of the following: aerobic or cardiorespiratory (walking or cycling), resistance or muscle strengthening exercise (lifting weights or pulling against resistance bands), and flexibility (stretching) exercise. Interventions

[a]This summary is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2019, Issue 5, Art. No.: CD013340, DOI: 10.1002/14651858.CD013340 (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review. The views expressed in the summary with commentary are those of the Cochrane Corner authors and do not represent the Cochrane Library or Wiley. The views expressed in the summary with commentary are those of the Cochrane Corner authors and do not represent the Cochrane Library or Wiley.

that combined mixed exercise and self-management programs were also included. Exclusion criteria: interventions that combined mixed exercise with other non-exercise interventions, for example, massage; studies providing such exercise interventions as Pilates, yoga, Tai Chi, manual therapy, those focused on a single body region; studies with more than 50% of the time spent in aquatic exercise. The intervention was compared to: (a) controls (eg wait list, usual care, no intervention); (b) non-exercise (eg relaxation, cognitive behavioral therapy, biofeedback, medication); and (c) other exercise-only interventions. The outcomes studied were major outcomes (HRQL, pain intensity, fatigue, stiffness, physical function, adverse effects, withdrawals) and minor outcomes (submaximal cardiorespiratory function, muscle strength, improvement in pain greater than 30%). With the exception of withdrawals and adverse events, major outcome measures were self-reported and expressed on a 0-100 scale (lower values are best, negative mean differences indicate improvement; clinically important difference between groups of 15% relative difference was used). Health-related quality of life was assessed by Fibromyalgia Impact Questionnaire (FIQ), Short Form Questionnaire, EuroQol-5D. Pain intensity was assessed by visual analog scale (VAS), FIQ Pain, FIQ-Translated, McGill Pain VAS, Numerical Pain Rating Scale. Composite measures that include pain intensity and interference were extracted when studies did not report uni-dimensional measures on pain intensity (Short Form-36 [SF-36] or Rand 36 Bodily Pain Scale, Pain Severity Scale). Fatigue was assessed by fatigue VAS (FIQ/FIQ-Translated Fatigue, or single item fatigue VAS), followed by the SF-36 or Rand 36 Vitality subscale, the Chalder Fatigue Scale, the Fatigue Severity Scale, Multidimensional Fatigue Inventory. For assessment of stiffness the FIQ stiffness subscale was used. The tools used for assessment of physical function were FIQ physical impairment scale, followed by the Health Assessment Questionnaire (HAQ) disability scale, SF-36 or Rand 36 Physical Function Scale, the Sickness Impact Profile, and the Multidimensional Pain Inventory Household Chores Scale.

3.3 | Search methodology and up-to-dateness of the Cochrane review?

The review authors searched for studies that had been published up to December 2017. It is one of a series of reviews about exercise training for fibromyalgia that will replace a previous Cochrane Review, first published in 2002.[14]

3.4 | What are the main results of the Cochrane review?

The review included 29 randomized controlled trials (2088 participants; 98% female; average age 51 years). The duration of disease or symptoms since diagnosis ranged from 4 to 19.4 years. The average exercise program was 14 weeks long with 3 sessions of 50-60 minutes per week. All exercise programs were fully or partially supervised. The settings: supervised group exercise with or without additional unsupervised home-based exercise.

The review shows the following major outcomes.

- Health-related quality of life (Moderate-Quality Evidence, 13 studies, 610 participants) - mean HRQL (FIQ Total) was 56 and 49 in control and exercise groups, respectively. Includes both clinically important and unimportant improvement with exercise with absolute improvement in the exercise group of 7% (3% better to 11% better) and relative improvement of 12% (6% better to 18% better).
- Pain (Moderate-Quality Evidence, 15 studies, 832 participants) - mean pain (FIQ Pain, VAS, and SF-36 Bodily Pain) was 58.6 and 53 in control and exercise groups, respectively. Clinically unimportant improvement with exercise with absolute improvement in the exercise group of 5% (1% better to 5% better) and relative improvement of 9% (3% better to 15% better).
- Fatigue (Moderate-Quality Evidence, 11 studies, 493 participants) - mean fatigue (FIQ Fatigue, VAS, and SF-36 Vitality Scale) was 72.3 and 59 points in control and exercise groups, respectively. Includes both clinically important and unimportant improvement with exercise with absolute improvement in the exercise group of 13% (8% better to 18% better) and relative improvement of 18% (11% better to 24% better).
- Stiffness (Low-Quality Evidence, 5 studies, 261 participants) - mean stiffness (FIQ stiffness and VAS) was 67.6 and 61 in control and exercise groups, respectively. Includes both clinically important and unimportant improvement with exercise with absolute improvement in the exercise group of 7% (1% better to 12% better) and relative improvement of 9% (1% better to 17% better).
- Physical function (Moderate-Quality Evidence, 9 studies, 477 participants) - mean physical function (FIQ Physical Function, SF-36 Physical Function, AIMS, and HAQ) was 49.2 and 38 in control and exercise groups, respectively. Includes both clinically important and unimportant improvement with exercise with absolute improvement in the exercise group of 11% (7% better to 15% better) and relative improvement of 22% (14% better to 30% better).
- All-cause withdrawal (Moderate-Quality Evidence, 19 studies, 1065 participants) - pooled analysis resulted in a not significant increased risk for all-cause withdrawals (relative risk 1.02 [0.69 to 1.51]) with an absolute change of 1% and relative change of 11%.
- Adverse events (Very Low-Quality Evidence, no reliable estimate) - no injuries or other adverse events were reported, some of the participants (in 8 of 21 studies) experienced increased fibromyalgia symptoms (pain, soreness or tiredness during or after exercise). Uncertainty in the precise risk of exercise due to low event rates.

Long-term effects (Very Low-Quality evidence, 8 studies) – HRQL, fatigue and physical function improvement persisted at 6 to 52 or more weeks after the intervention, but improvements in stiffness and pain did not persist.

3.5 | How did the authors conclude?

The authors concluded that compared to controls, moderate-quality evidence indicated that mixed exercise probably improves HRQL and fatigue, but this improvement may be small and clinically unimportant for some participants. Physical function showed improvement in all participants. Withdrawal was similar across groups. Low-quality evidence suggests that mixed exercise may slightly improve stiffness. Based on very low-quality evidence the authors are uncertain whether the long-term effects are maintained for all outcomes. Compared to other exercise or non-exercise interventions, the authors are uncertain about the effects of mixed exercise, because of the very low-quality evidence obtained from small, very heterogeneous trials. They are uncertain about the safety of mixed exercise although it appears they are well tolerated, but evidence on adverse events is scarce. The evidence was downgraded because of imprecision, selection bias, blinding of participants and care providers or outcome assessors, and selective reporting.

3.6 | What are the implications of the Cochrane evidence for practice in Rheumatology?

Fibromyalgia is a serious chronic condition marked by widespread pain and tenderness that deteriorates the quality of life of the affected persons. Regular exercise (mainly aerobic and strengthening) is usually recommended as part of the complex approach for management of the symptoms. People with fibromyalgia often associate exacerbations of symptoms with exercise. For practice in rehabilitation it is very important to identify for people with fibromyalgia both the effects they can expect of exercise training and define the most efficacious exercise program to achieve these effects and facilitate their adherence.

A previous Cochrane Review[11] suggested that moderate- and moderate-to-high-intensity resistance training improves function, pain, tenderness, and muscle strength in women with fibromyalgia, and that aerobic exercise was superior to moderate-intensity resistance training for improving pain, based on low-quality evidence. Low-intensity resistance training was found to be superior to flexibility exercise.

This Cochrane Review[1] found that mixed exercise interventions may be effective for individuals with fibromyalgia, although the evidence showed small to moderate effects. For some outcomes the improvements are small and possibly clinically unimportant. Participants in exercise interventions that include multiple forms of exercise (eg aerobic, resistance, and flexibility) obtained a benefit in physical fitness, which is very encouraging. No firm conclusion on specific intervention characteristics (eg type of mixed combination, duration of intervention, supervision) that may impact effectiveness could be made.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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CORRESPONDENCE

Paraneoplastic small vessel vasculitis and Takayasu arteritis associated with polycythemia rubra vera

Dear Editor,

Paraneoplastic vasculitis is a rare complication which can be associated with myeloproliferative disorders (MPD). Involvement of small and medium vessels and, very rarely, large vessels such as the aorta may be associated. Polycythemia vera (PV) complicated by a small and large-vessel vasculitis simultaneously has not been previously reported.

1 | CASE HISTORY

A 39-year-old man was admitted with sudden-onset left-sided weakness while attending a family function. He denied history of fever, weight loss, drug abuse, high-risk behavior and had no sick contacts. He had recurrent episodes of bilateral painful foot ulcers and intermittent claudication in both lower limbs for the last 4 years. He had no other significant medical history. He had multiple healed ulcers over the dorsum of foot and toes bilaterally. Few ulcers were active with central pallor, crusting and sloping edges. Peripheral pulsations were absent in the left upper limb and bilateral lower limbs (popliteal, posterior tibial and dorsalis pedis). Blood pressure was 110/70 mm Hg in the right upper and 90 /60 mm Hg in the left upper limbs. Nervous system examination showed left side hemiplegia with symmetrical sensorimotor peripheral neuropathy of upper and lower limbs.

Hemoglobin was 18.6 g/dL, packed cell volume 58%, total leucocyte count 8900/μL, platelet count 400 000/L, erythrocyte sedimentation rate 3 mm in 1 hour and C-reactive protein was high (15.6 mg/L). In the peripheral smear red blood cells were normocytic normochromic. Blood biochemistry was normal. Magnetic resonance imaging of the brain revealed infarcts in the bilateral frontal lobes, right lentiform nucleus, right caudate nucleus and left insular cortex. Trans-thoracic echocardiogram was normal. Ultrasonography of abdomen showed moderate splenomegaly. Arterial Doppler showed left proximal subclavian occlusion with bilateral superficial femoral artery occlusion. Digital subtraction angiography showed total occlusion of right internal carotid artery, left common carotid and left subclavian artery (Figure 1, upper panel A,B). There were extensive collaterals from posterior circulation on injecting dye to the vertebral artery and the left upper limb was receiving blood supply by subclavian steal (Figure 1, lower panel C-F). Nerve conduction study showed distal symmetrical axonal type sensory motor polyneuropathy of upper and lower limbs.

Serum erythropoietin level was low. Bone marrow examination showed hypercellularity with prominent erythroid, granulocytic and megakaryocytic proliferation (Figure 2, upper panel). The molecular biology analysis was positive for the *JAK2-V617F* mutation and qualitative analysis of BCR–ABL fusion gene was negative. Prothrombin time and partial thromboplastin time were normal. Human immunodeficiency virus, venereal disease research laboratory test, hepatitis B and hepatitis C serology were negative. Autoantibody profile including antinuclear antibody, rheumatoid factor, c-antineutrophil cytoplasmic antibody, p-antineutrophil cytoplasmic antibody and anti-phospholipid antibodies were all negative. Serum complement levels were normal. Skin biopsy from the ulcer and sural nerve biopsy showed vasculitis (Figure 2, lower panel). The procoagulant workup showed negative immunoglobulin G (IgG) and IgM anti-cardiolipin antibody, IgG and IgM β2 glycoprotein and lupus anticoagulant tests. Factor V Leiden, methylenetetrahydrofolate reductase (MTHFR) polymorphism, and prothrombin G20210A were not detected. Serum levels of homocysteine, protein C, and protein S were normal. The patient was diagnosed to have PV (2016 World Health Organization diagnostic criteria for PV) Takayasu arteritis (TA: 1990 American College of Rheumatology criteria) and small vessel vasculitis (skin and nerve biopsy). He was managed with aspirin, venesection, hydroxyurea and prednisolone 1 mg/kg. The patient was referred for endovascular revascularization to another center.

2 | DISCUSSION

Vasculitis may behave as a paraneoplastic syndrome associated with various hematological malignancies. Vasculitis associated with hematological malignancies predominantly present with cutaneous lesions, arthralgia, and neuropathy. Patients with MPD may have an increased risk of various autoimmune or autoinflammatory diseases. MPD may be preceded by or accompanied by chronic inflammation. Both humoral and cellular immunological abnormalities can be seen in patients with MPD.[1]

Concurrent association of malignancies with some forms of vasculitis raise the possibility that patients with certain types of vasculitis may be at increased risk of cancer. Vasculitis as a paraneoplastic

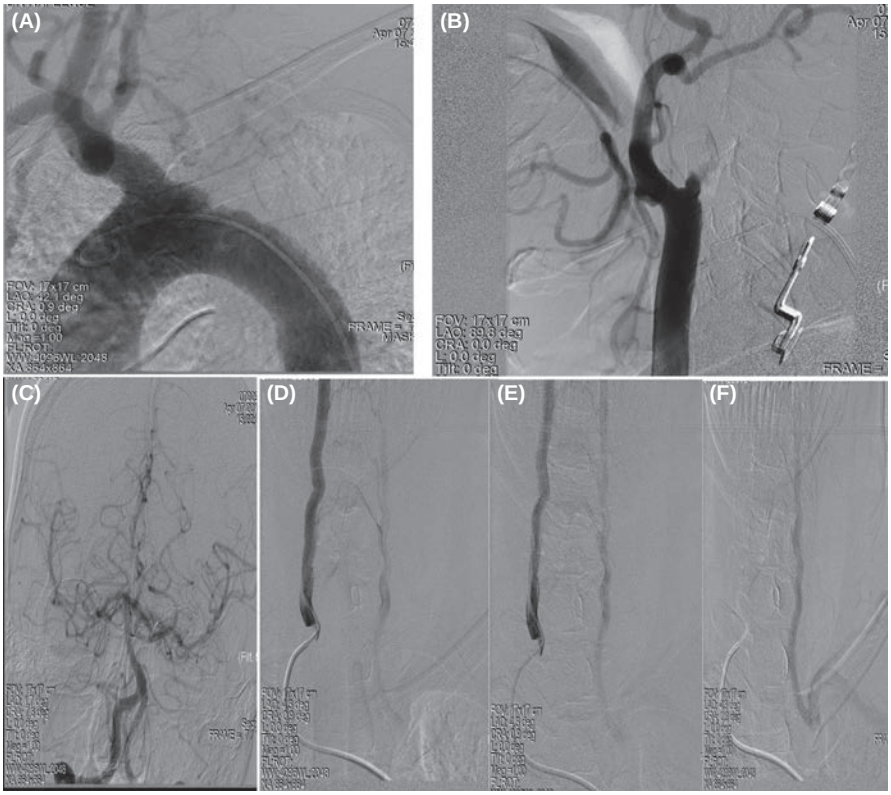

FIGURE 1 Digital subtraction angiography showing total occlusion of left common carotid, left subclavian artery and right internal carotid artery (upper panel, A, B). There were extensive collaterals from posterior circulation on injecting dye to the vertebral artery and the left upper limb was receiving blood supply by subclavian steal (lower panel, C-F)

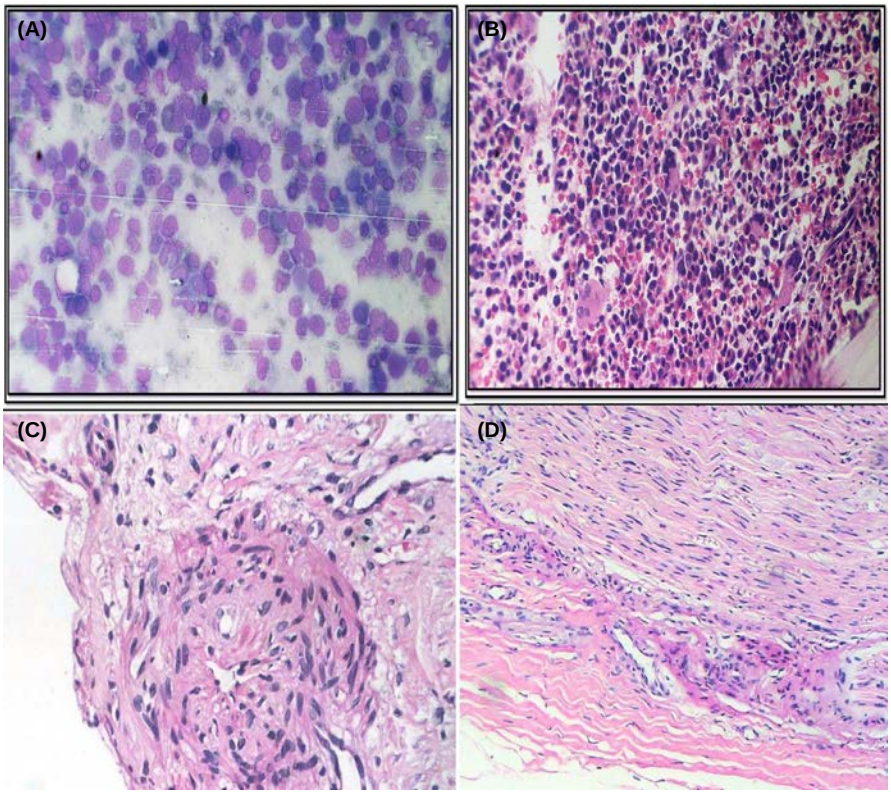

FIGURE 2 Upper panel. Bone marrow examination showing hypercellularity with prominent erythroid, granulocytic and megakaryocytic proliferation. Lower panel. Skin biopsy showing leukocytoclastic vasculitis and sural nerve biopsy showing lymphocytic vasculitis (hematoxylin and eosin staining) [Colour figure can be viewed at wileyonlinelibrary.com]

phenomenon is classically described with polyarteritis nodosa in association with hairy cell leukemia and the most common vasculitic manifestation of cancer is cutaneous vasculitis. Leukemias, lymphomas, myelodysplastic syndromes and chronic myelomonocytic leukemia are the hematological malignancies which are found to be more commonly associated with vasculitis.[2-5] Cutaneous leucocytoclastic vasculitis associated with PV was previously reported.[6,7] Two patients with PV-associated giant cell arteritis were reported in a previous study.[8] In a retrospective analysis of cancer risk in a cohort of patients with TA 1 patient had myelodysplastic syndrome;

however, the standardized incidence ratio (SIR) of myelodysplastic syndrome was found to be significantly increased (SIR: 51.3; 95% CI: 1.3-285.7) compared with that of the general population.[9] Our patient presented with sudden-onset left side hemiplegia and was found to have PV, TA and small vessel vasculitis. The small vessel vasculitis in our patient is likely to be paraneoplastic in etiology since other causes were ruled out by appropriate tests. The association between TA and PV might be by chance in our patient but paraneoplastic large-vessel vasculitis was previously reported in association with hematological malignancies.

To conclude we report a patient with PV complicated by a small and large-vessel vasculitis simultaneously which to our knowledge is the first such report.

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22nd Asia-Pacific League of Associations for Rheumatology Congress

14 - 17 November 2020

Kyoto International Conference Center, Japan

The 2020 congress has been postponed to new dates to be held on **14 November – 17 November 2020** in Kyoto International Conference Center, Japan. Please do look out for updates by visiting the website.

APLAR aims to improve standards of clinical practice, teaching, and research in rheumatology across Asia Pacific. We are recognising the long-term efforts and dedication of centers in the region with a similar goal for excellence in the field. The certification programme we have initiated will award leading centers in Asia Pacific as Centers of Excellence based on three pillars (research, clinical practice, academia), pre-defined by a list of criteria set by APLAR.

We hope the centers in the region with an excellent track record in any of these pillars will participate in this programme as our goal is to establish reference centers that are best in class models for practice, teaching, and research in rheumatology. We believe this will enhance and enrich the ‘best in class’ experience for our trainees involved in the APLAR Fellowship programme. Further, this will also help us build a strong network of reference centers for collaborations and consultation within and among countries in the region.

APLAR awarded Centers of Excellence have been updated and information about these centers can be found on the website. Center of Excellence 2020 application has been launched. Interested applicant may get in contact with APLAR's Member National Organisation for more information and application form. Application information has been made available through the Member National Organisations of APLAR. Application due date has been extended to **Tuesday, 30 June 2020.**

APLAR FELLOWSHIP GRANT

The Asia Pacific League of Associations for Rheumatology (APLAR) had awarded 1 applicant for the Fellowship Grant of 2020. They are embarking on their fellowship programme in the coming months. Successful candidates must have a long-term commitment to continue research or clinical work in his/her own country at the conclusion of the Fellowship. The grant is awarded to cover accommodation and subsistence costs. We congratulate the awardees and wish them a fruitful journey in their career paths.

APLAR RESEARCH GRANT

The Asia Pacific League of Associations for Rheumatology (APLAR) had awarded 1 applicant for the Research Grant of 2020. The grants are to assist the undertaking of research in either adult or paediatric rheumatology. The aims of the grant are to give the researcher an opportunity to start and do research within their own country of residence. In addition, we hope to promote and support basic and clinical research directed to the causes, prevention, and treatment of rheumatic diseases in the APLAR member society countries. This grant is to be used for consumables required for the research and not for salaries or fixed costs. It is expected that the research will be completed within one (1) year of the onset. The awarded candidates are encouraged to publish their work in the APLAR official journal – International Journal of Rheumatic Disease (IJRD) as part of their contribution.

APLAR-COPCORD GRANT

The Asia Pacific League of Associations for Rheumatology (APLAR) had awarded 2 applicants for COPCORD grant 2020. We encourage interested candidates to send in their application during the application period for COPCORD grant 2021. The aims of the grant are to give the researcher an opportunity to study rheumatic disease in the community of their own country of residence. This grant is to be used for consumables required for the research and not for salaries or fixed costs. It is expected that the research will be completed within one (1) year of the onset.

All APLAR Grants for 2020 has now been awarded. Interested applicants may look out for APLAR Grants 2021, which will launch for application in November later this year. APLAR Grants information on eligibility, criteria and application requirement can be found on the website.