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ORIGINAL ARTICLE

Pain in individuals with idiopathic inflammatory myopathies, other systemic autoimmune rheumatic diseases, and without rheumatic diseases: A report from the COVAD study

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Abstract

Objectives: To compare pain intensity among individuals with idiopathic inflammatory myopathies (IIMs), other systemic autoimmune rheumatic diseases (AIRDs), and without rheumatic disease (wAIDs).

Methods: Data were collected from the COVID-19 Vaccination in Autoimmune Diseases (COVAD) study, an international cross-sectional online survey, from December 2020 to August 2021. Pain experienced in the preceding week was assessed using numeral rating scale (NRS). We performed a negative binomial regression analysis to assess pain in IIMs subtypes and whether demographics, disease activity, general health status, and physical function had an impact on pain scores.

Results: Of 6988 participants included, 15.1% had IIMs, 27.9% had other AIRDs, and 57.0% were wAIDs. The median pain NRS in patients with IIMs, other AIRDs, and wAIDs were 2.0 (interquartile range [IQR] = 1.0–5.0), 3.0 (IQR = 1.0–6.0), and 1.0 (IQR = 0–2.0), respectively ($P < 0.001$). Regression analysis adjusted for gender, age, and ethnicity revealed that overlap myositis and antisynthetase syndrome had the highest pain (NRS = 4.0, 95% CI = 3.5–4.5, and NRS = 3.6, 95% CI = 3.1–4.1, respectively). An additional association between pain and poor functional status was observed in all groups. Female gender was associated with higher pain scores in almost all scenarios. Increasing age was associated with higher pain NRS scores in some scenarios of disease activity, and Asian and Hispanic ethnicities had reduced pain scores in some functional status scenarios.

Conclusion: Patients with IIMs reported higher pain levels than wAIDs, but less than patients with other AIRDs. Pain is a disabling manifestation of IIMs and is associated with a poor functional status.

KEYWORDS
autoimmune diseases, functional status, myositis, pain, rheumatic diseases

1 | INTRODUCTION

Idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of rare systemic autoimmune diseases characterized by a predilection for skeletal muscle inflammation and a variety of extra-muscular manifestations. Muscle symptoms along with extra-muscular involvement may limit activities of daily living and negatively affect health-related quality of life (HRQoL).[1-3]

HRQoL is a multidimensional and complex concept which involves physical and psychological domains as well as social functioning and relationship with the environment.[4,5] Patients with systemic autoimmune rheumatic diseases (AIRDs) have impaired HRQoL compared to the general population.[1-3] Importantly, pain is commonly reported by patients and is a major contributor to poor QoL in chronic rheumatic conditions. A large European multicenter study showed that pain was frequent among patients with systemic lupus erythematosus, despite apparent clinical remission.[6,7] Similarly, while previously underplayed as a key clinical feature of IIM, recent qualitative data indicate pain as one of the most important aspects of their disease experience.[8]

Increasing recognition of the importance of pain in AIRDs and its negative effect on HRQoL has galvanized efforts to develop tools to reliably assess these symptoms and advance knowledge in the field. The Patient-Reported Outcomes Measurement Information System (PROMIS) set measures, funded by the National Institutes of Health (NIH), provides accurate and valid item banks related to various health domains, calibrated by the item response theory.[9] This flexible and reliable instrument can be used to capture the domains of physical and mental health and social well-being in a variety of conditions, facilitating patient status monitoring and the decision-making process.[9-11]

Although the importance of patient-reported outcomes has become increasingly recognized in AIRDs, studies on pain perceptions in patients with IIMs are scarce.[12] This study aims to compare pain intensity using PROMIS core set measures among a large sample of individuals with IIMs, other AIRDs, and those without rheumatic disease (wAIDs) as well as to understand the association of pain with disease activity, demographics, and functional status.

2 | PATIENTS AND METHODS

2.1 | Study design

This is an international cross-sectional online patient survey, which is part of the COVID-19 Vaccination in Autoimmune Diseases (COVAD) protocol.[13] While COVAD focused on COVID-19 vaccination, a breadth of supporting data was collected. Here we report an analysis of data related to pain. Ethics approval was obtained from the Institutional Ethics Committee of Sanjay Gandhi Postgraduate Institute of Medical Sciences, Raebareli Road, Lucknow, India. It was obtained as per local guidelines and all participants electronically consented. There was no monetary or other compensation to the patient for participation in the study.

2.2 | Study population

Survey participants (patients and wAIDs) were recruited in 94 countries as described elsewhere.[13] Adults (≥18 years old) with a self-reported diagnosis of IIMs (antisynthetase syndrome, dermatomyositis, immune-mediated necrotizing myopathy, inclusion body myositis, overlap myositis mixed connective tissue disorder, and polymyositis), other AIRDs (ankylosing spondylitis, mixed connective tissue disease, polymyalgia rheumatica, primary Sjögren's syndrome, psoriatic arthritis, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, and systemic vasculitis), and wAIDs were invited to complete the electronic survey from December 2020 to August 2021. Patients' self-reported diagnoses were considered valid only when they reported that their diagnosis was confirmed by a rheumatologist, neurologist, or any other physician.

2.3 | Data collection

All data were collected from the COVAD protocol survey which consisted originally of 37 items.[13] This included questions on COVID vaccination experience of patients (in retrospect, based on recall memory), although the e-survey also assessed pain, fatigue and PROMIS physical function using validated tools in a cross-section at the time of responding to the survey. This status of perceived physician health had nothing to do with COVID vaccine adverse events, and hence were explored in light of this as an independent data set from a cross-section of our study population. The survey was implemented using the web-based survey platform and followed the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) to report the data.[14]

2.4 | Study variables

The dependent variable was the level of pain in the last 7 days, measured using a numeral rating scale (NRS). Participants were asked to place a mark on a straight line anchored at the values from 0 to 10, in which 0 meant no pain and 10 meant very severe or maximum pain.

Independent variables considered in this study were: demographic data, including age, gender, ethnicity, and country of residence; specific subtype of autoimmune disease, and categories of physical function (general physical health status and ability to carry out routine activities).

2.5 | Functional status

General physical health was assessed using 5-category response scales extracted from the PROMIS 10 - a short form for physical function of the PROMIS Global Health instrument.[11,15] In summary, participants were asked, "In general, how would you rate your

physical health?", categorized as excellent, very good, good, fair, or poor. The ability to carry out everyday activities was assessed by the question "To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?", defined as completely, mostly, moderately, a little or not at all.

2.6 | Disease activity

Participants characterized their disease status in the last 4 weeks as active or inactive based on: (a) patient's own perception; (b) as per patients' self-reported physician's assessment of their disease activity status as informed to them by their physician; and (c) patients on a daily dose equivalent to ≥10 mg prednisone with either muscle weakness, active rash, or arthritis were also considered to have active disease.

2.7 | Statistical analysis

Qualitative variables were described using frequencies, and quantitative variables were described using mean and standard deviation if data were normally distributed or median and interquartile range (IQR) if the tested distribution was not assumable to a Gaussian normal curve. Kolmogorov–Smirnov test was used when testing for normality. Continuous variables were compared among ages by groups using analysis of variance or Kruskal-Wallis depending on data distribution. In the case of statistically significant results, Dunn's post hoc test was performed for multiple comparisons between groups. For categorical variables, groups were compared using the Chi-square test. To analyze the predicted pain NRS in multiple scenarios, we performed a negative binomial regression multivariate analysis clustering country of origin and adjusted for age, gender, and ethnicity. $P < 0.05$ was considered statistically significant and statistical analysis was conducted using STATA version 16.

3 | RESULTS

3.1 | Baseline demographics

A total of 7873 responses were initially available for analysis; however, 885 incomplete responses were excluded. Therefore, 6988 responses were analyzed: 1057 (15.1%) being from patients with IIM, 1950 (27.9%) those with other AIRDs, and 3981 (57.0%) wAIDs.

The respondents included in the analysis resided in 86 countries: 16.3% in Turkey, 14.6% in Mexico, 13.1% in India, 12.0% in the United Kingdom, 11.4% in the USA, 5.6% in Italy, and 27.0% in other countries (Table S1).

Among patients with IIMs, 338 (32.0%) had dermatomyositis, 247 (23.4%) had inclusion body myositis, 189 (17.9%) had polymyositis, 116 (11.0%) patients had antisynthetase syndrome, 111 (10.5%) had overlap myositis with other connective tissue disorders, and 56 (5.3%) had immune-mediated necrotizing myopathies. Among patients with other AIRDs, 869 (44.6%) had rheumatoid arthritis, 372 (19.1%) had systemic lupus erythematosus, 257 (13.2%) had ankylosing spondylitis or psoriatic arthritis, 252 (12.9%) had systemic sclerosis, 76 (3.9%) had primary Sjögren's syndrome, 67 (3.4%) had systemic vasculitis, and 23 (1.2%) had polymyalgia rheumatica.

The median age, gender, race/ethnicity characteristics, and mean pain NRS scores for each group are shown in Table 1.

3.2 | Pain in IIMs, wAIDs, and AIRDs

Overall, the median pain NRS score of patients with IIMs (2.0, IQR 1.0–5.0) was significantly higher than that of wAIDs (1.0, IQR 0.0–2.0) and significantly lower than that of other patients with other AIRDs (3.0, IQR 1.0–6.0), $P < 0.01$ (Table 1).

Among IIMs, patients with overlap myositis and anti-synthetase syndrome had the highest predicted pain NRS in a negative binomial regression analysis clustered by country of origin and adjusted for

TABLE 1 Demographic characteristics and self-reported pain intensity during the last week in patients with idiopathic inflammatory myopathies, other systemic autoimmune rheumatic diseases, and healthy controls.

Variables	All (n = 6988)	IIMs (n = 1057)	Other AIRDs (n = 1950)	HCs (n = 3981)	*P* value
Age, y	42 (29, 56)	60 (49, 70)[a,b]	49 (39, 59)[a,c]	33 (25, 47)[b,c]	<0.001
Female	5031 (72.0)	776 (73.4)	1664 (85.3)	2591 (65.1)	<0.001
Ethnicity					
White	3853 (55.1)	879 (83.1)	1196 (61.4)	1778 (44.7)	<0.001
Asian	1716 (24.6)	73 (6.9)	480 (24.6)	1163 (29.2)	
Hispanic	968 (13.9)	49 (4.7)	174 (8.9)	745 (18.7)	
Others	451 (6.4)	56 (5.3)	100 (5.1)	295 (7.4)	
Pain VAS (0–10)	1 (0, 4)	2 (1, 5)[a,b]	3 (1, 6)[a,c]	1 (0, 2)[b,c]	<0.001

Note: Data showed as median (interquartile range) and frequency (%). Letters in the same line (a, b, c) indicate a significant difference ($P < 0.05$) between the means with the Dunn-Bonferroni post hoc test.

Abbreviations: AIRDs, systemic autoimmune rheumatic diseases; HC, healthy controls; IIMs, idiopathic inflammatory myopathies; IQR, interquartile range; VAS, visual analog scale.

age, gender, and ethnicity (Table 2, Table S2). Using patients with dermatomyositis as reference (mean of predicted pain NRS = 3.1), patients with overlap myositis had a statistically higher NRS score (difference of predicted pain NRS = 0.9, 95% CI = 0.3–1.6, $P = 0.007$), followed by antisynthetase syndrome (difference of predicted pain: NRS = 0.5, 95% CI = −0.2 to 1.2, $P = 0.170$), and patients with inclusion body myositis had a statistically lower NRS score (difference of predicted pain: NRS = −0.6, 95% CI = −0.8 to −0.4, $P < 0.001$) (Table 2).

3.3 | Association of pain NRS by disease activity, gender, age, and ethnicity

Predicted pain NRS score of patients with IIMs was higher than wAIDs but lower than patients with other AIRDs in almost all scenarios of disease activity, except for inactive disease based on the patient perception, in which patients with IIMs (NRS = 2.2, 95% CI = 1.7–2.8) and other AIRDs (NRS = 2.6, 95% CI = 2.3–2.9, $P = 0.299$) had a similar pain NRS score, with both being higher than wAIDs (NRS = 1.4, 95% CI = 1.3–1.6, $P = 0.003$) (Table 3).

Regardless of disease activity, female patients with IIMs reported more pain than their male counterparts. In general, increasing age was associated with more pain in active as well as inactive disease in IIMs. Hispanic patients reported less pain in some active disease categories in IIMs. Table 4 shows the coefficients of all covariates included in the multivariate binomial regression analysis.

3.4 | Association of pain with general health status

The predicted pain NRS score of patients with IIMs was higher than wAIDs but lower than patients with other AIRDs in case of good or fair general health status. However, there was no difference in pain if the subject reported very good or excellent health status. AIRDs had significantly higher pain than IIMs in subjects with poor health status, whereas IIMs were similar to wAIDs (Table 3).

The female gender was associated with higher pain in all scenarios of general health, except for patients with poor health status, where there was no difference between males and females. Being Asian was associated with lower pain in patients with fair general health, and being Hispanic was associated with lower pain in cases of fair and very good general health. Age had no impact on NRS scores concerning different health statuses (Table 4).

3.5 | Association of pain with the ability to carry out routine activities

Patients with IIMs who had an impaired ability to carry out routine activities experienced more intense pain than wAIDs, but less pain than patients with other AIRDs in most scenarios (Table 3).

The female gender was associated with higher pain, except for patients with extreme disability, where females and males had similar pain levels. Asian ethnicity was associated with lower pain NRS, except for patients with no disability (Table 4).

4 | DISCUSSION

In the present study, we showed that patients with IIMs had a higher pain NRS score than wAIDs, but a lower NRS score than patients with other AIRDs. This difference was observed across different levels of disease activity and functional status. An association between pain and poor functional status was seen in all groups, as well as an association between active disease and pain in patients with IIMs and AIRDs. Among IIMs, patients with overlap myositis and antisynthetase syndrome had the highest NRS scores. We hypothesized that this may be explained, at least in part, by the frequent association of antisynthetase syndrome and overlap myositis with arthritis.

An analysis of the covariates included in the multivariable models to predict NRS scores revealed that both male gender and being an wAID had a protective effect on pain scores in almost all scenarios while being female or having an AIRDs was associated with higher pain scores. Age was associated with higher pain NRS scores

TABLE 2 Multivariate negative binomial regression for self-reported pain intensity during the last week assessed by a VAS from 0 to 10 in the major subtypes of idiopathic inflammatory myositis.

Type of myositis	Predicted VAS (0–10), mean	95% CI		Difference	95% CI		*P* value
DM	3.1	2.7	3.5	Ref			Ref
OM	4.0	3.5	4.5	0.9	0.3	1.6	0.007
ASSD	3.6	3.1	4.1	0.5	-0.2	1.2	0.170
PM	3.1	2.7	3.5	0.0	−0.3	0.2	0.863
IMNM	3.0	1.8	4.2	−0.1	−1.0	0.8	0.831
IBM	2.5	2.2	2.8	−0.6	−0.8	−0.4	<0.001

Note: The model was clustered by country of origin and adjusted for age, gender, and ethnicity.

Abbreviations: ASSD, antisynthetase syndrome; DM, dermatomyositis; IBM, inclusion body myositis; IMNM, immune-mediated necrotizing myopathy; OM, overlap myositis; PM, polymyositis; Ref, reference; VAS, visual analog scale.

TABLE 3 Multivariate negative binomial regression scenarios for pain intensity during the last week assessed by a VAS from 0 to 10.

Sample	Disease status	Groups	Predicted pain VAS mean	95% CI	ΔGroups	95% CI	$P > \|z\|$
All (n = 6988)		IIM	2.9	2.5–3.2	Ref		
		AIRDs	3.4	3.2–3.6	0.5	0.1 to 1.0	0.018
		HC	1.5	1.3–1.6	−1.4	−1.7 to −1.1	<0.001
Based on physician assessment	Active + HC (n = 4519)	IIM	3.3	3.0–3.7	Ref		
		AIRDs	3.8	3.5–4.1	0.5	0.1 to 0.9	0.027
		HC	1.4	1.3–1.6	−1.9	−2.3 to −1.5	<0.001
	Inactive + HC (n = 6453)	IIM	2.6	2.3–3.0	Ref		
		AIRDs	3.2	3.0–3.4	0.6	0.1 to 1.0	0.008
		HC	1.5	1.3–1.6	−1.2	−1.5 to −0.9	<0.001
Based on patient assessment	Active + HC (n = 6361)	IIM	3.0	2.6–3.4	Ref		
		AIRDs	3.7	3.5–3.9	0.7	0.3 to 1.2	0.002
		HC	1.5	1.3–1.6	−1.5	−1.9 to −1.2	<0.001
	Inactive + HC (n = 4879)	IIM	2.2	1.7–2.8	Ref		
		AIRDs	2.6	2.3–2.9	0.3	−0.3 to 1.0	0.299
		HC	1.4	1.3–1.6	−0.8	−1.3 to −0.3	0.003
Based on glucocorticoid dose	Active + HC (n = 4951)	IIM	3.0	2.7–3.2	Ref		
		AIRDs	3.4	3.1–2.6	0.4	0.0 to 0.8	0.044
		HC	1.5	1.3–1.6	−1.5	−1.3 to −0.3	<0.001
	Inactive + HC (n = 6021)	IIM	2.6	2.1–3.0	Ref		
		AIRDs	3.3	3.1–2.5	0.7	0.2 to 1.2	0.006
		HC	1.5	1.3–1.6	−1.1	−1.5 to −0.7	<0.001
General health status	Poor (n = 242)	IIM	5.1	4.3–5.8	Ref		
		AIRDs	6.7	6.5–7.0	1.7	0.9 to 2.4	<0.001
		HC	4.1	2.9–5.4	−0.9	−2.3 to 0.4	0.173
	Fair (n = 1177)	IIM	4.1	3.8–4.4	Ref		
		AIRDs	4.7	4.4–4.9	0.5	0.2 to 0.9	0.002
		HC	2.7	2.3–3.1	−1.4	−2.0 to −0.9	<0.001
	Good (n = 2510)	IIM	2.5	2.2–2.7	Ref		
		AIRDs	3.2	2.9–3.6	0.8	0.3 to 1.2	0.001
		HC	1.9	1.8–2.1	−0.5	−0.8 to −0.3	<0.001
	Very good (n = 2142)	IIM	1.6	1.1–2.1	Ref		
		AIRDs	1.8	1.5–2.1	0.2	−0.4 to 0.8	0.491
		HC	1.1	10–1.3	−0.5	−0.9 to 0.0	0.053
	Excellent (n = 917)	IIM	1.1	0.0–3.1	Ref		
		AIRDs	1.3	0.7–1.9	0.3	−1.1 to 1.6	0.709
		HC	0.8	0.6–0.9	−0.3	−1.2 to 0.6	0.533
Ability to carry out routine activities	Not at all (n = 160)	IIM	2.4	1.5–3.4	Ref		
		AIRDs	4.2	2.8–5.6	1.8	0.3 to 3.3	0.021
		HC	2.6	1.7–3.6	0.2	−1.0 to 1.5	0.744
	A little (n = 482)	IIM	4.1	5.0–6.1	Ref		
		AIRDs	5.6	2.9–4.3	1.4	0.9 to 2.0	<0.001
		HC	3.6	3.1–4.3	−0.5	−1.3 to 0.3	0.251

TABLE 3 (Continued)

Sample	Disease status	Groups	Predicted pain VAS mean	95% CI	ΔGroups	95% CI	P > |z|
	Moderately (n = 964)	IIM	3.7	4.4–4.9	Ref		
		AIRDs	4.6	2.6–3.2	0.9	0.3 to 1.6	0.006
		HC	2.9	2.6–3.2	−0.8	−1.3 to −0.2	0.005
	Mostly (n = 1424)	IIM	2.9	3.6–4.0	Ref		
		AIRDs	3.8	2.0–2.3	0.9	0.6 to 1.2	<0.001
		HC	2.1	1.2–2.1	−0.7	−1.1 to −0.4	<0.001
	Completely (n = 3658)	IIM	1.6	1.2–2.1	Ref		
		AIRDs	1.9	1.6–2.3	0.3	−0.2 to 0.8	0.257
		HC	1.1	1.0–1.3	−0.5	−0.9 to −0.1	0.010

Note: The models were clustered by country of origin and adjusted for age, gender, and ethnicity.

Abbreviations: AIRDs, systemic autoimmune rheumatic diseases; CI, coefficient interval; HC, healthy controls; IIMs, idiopathic inflammatory myopathies; Ref, reference; VAS, visual analog scale; Δ, difference between 2 groups.

in some scenarios of disease activity, and Asian and Hispanic ethnicities had a protective effect on pain scores in some functional status scenarios.

As a main study strength point, we assessed a large number of patients with rare diseases and wAIDs, reducing the likelihood of type II errors, which are frequent when dealing with a small sample size. We also evaluated the potential confounding effects of clinical and demographic covariables. We assessed pain with patient-reported outcome measures via a structured e-survey questionnaire, allowing us to turn symptoms into quantifiable scores.

Previous studies with IIM patients have demonstrated an impaired HRQoL compared with wAIDs.[5,16,17,18,19,20] Emerging evidence has suggested a potential role of pain perception on HRQoL in diseases such as cancer, but few data exist in IIMs.[21-23] Most studies do not explore the factors which contribute to the experience of pain, focusing only on fatigue-related weakness, emotion, social activity, independence, physical activity, and body image.[21-23] Pain is a multidimensional experience that involves psychological, cognitive, and physical domains and may be influenced by factors such as therapy, age, gender, and disease status parameters.[24]

Despite receiving little research attention, pain is considered one of the most disabling symptoms in patients with AIRDs, including IIMs, and is one of the strongest predictors of poor QoL in these patients.[25] Pain may be linked to physical activity, even when the activity is of low intensity.[26] Likewise, in fatigue, patients with pain report difficulty carrying out their activities of daily living and, therefore, impairment in QoL.[25] Nonetheless, the contribution of physical activity to pain perception in IIM remains incompletely understood. In a recent systematic review, Misse et al[27] pointed out studies in which physical exercise was effective and safe in maintaining or improving IIM-related muscle strength and other parameters, pain, and perceived fatigue.[21,28,29]

According to a systematic review by Graham et al,[5] there is a direct influence of gender on the patients' impressions of their QoL, with males being less likely to report worse scores. A qualitative study that investigated QoL among patients with IIM and whose sample was 67% female, also showed pain as one of the main symptoms that impair QoL.[26]

Studies carried out in different Western populations have shown that the interpretation of pain varies according to gender,[22-24] and race.[30] According to a study of 1024 North American patients with chronic pain, women have more pain when compared to the opposite gender.[23] Conversely, a Turkish study that analyzed differences in gender-related perception did not show a statistical significance,[31] and a meta-analysis carried out in 2015 did not show a statistical significance for pain interpretation stratified by gender or race.[32]

In our study Hispanic patients reported less pain in some active disease categories in IIMs. In addition, Asian ethnicity was associated with lower pain NRS. Recent studies[33] have shown that Asian and Hispanic individuals report lower pain levels that other ethnic groups. These observations may be explained by potential differences in the coping mechanisms, perception of ill-health and other environmental and comorbidity-related variables on a background of chronic diseases.[34]

Interestingly, we observed that patients with IIMs and other AIRDs who reported their rheumatic disease to be inactive experienced more pain than wAIDs. This points to the importance of non-inflammatory factors in pain interpretation. Pain is known to be multifactorial[24] and depends on social,[22-24] constitutional,[25] and biological factors, such as increased cytokines, endothelial damage, and neurotransmitter imbalance.[35] Our findings reinforce the need for a multidisciplinary approach to pain in rheumatological patients.[24]

Saying et al[20] report that despite immunosuppressive treatment, approximately one-third of patients with IIMs require assistance for basic activities of daily living at a disease duration of 3 years and 7.5% at 5 years.[20] IIMs negatively impact basic functioning, social interactions, relationships, sleep, and self-esteem

TABLE 4 Coefficient of covariates in multiple scenarios of negative binomial regression analysis of pain, clustered by country of origin and adjusted for age, gender, and race/ethnicity.

			Covariates									
			Groups			Age	Male	Ethnicity				κ
			IIMs	AIRDs	HCs			White	Asian	Hispanic	Others	
All		Coefficient	Ref	0.17	−0.66	0.00	−0.33	Ref	−0.08	−0.09	0.11	0.99
		95% CI		0.02 to 0.32	−0.78 to −0.54	0.00 to 0.01	−0.42 to −0.24		−0.20 to 0.03	−0.21 to 0.02	−0.01 to 0.22	0.81 to 1.18
		$P > \|z\|$		0.024	<0.001	0.064	<0.001		0.139	0.113	0.073	<0.001
Based on physician assessment	Active + HC	Coefficient	Ref	0.13	−0.85	0.01	−0.41	Ref	−0.05	−0.19	0.09	1.11
		95% CI		0.01 to 0.26	−0.98 to −0.72	0.00 to 0.01	−0.51 to −0.31		−0.18 to 0.8	−0.34 to −0.04	0.05 to 0.24	0.84 to 1.38
		$P > \|z\|$		0.031	<0.001	0.015	<0.001		0.426	0.016	0.193	<0.001
	Inactive + HC	Coefficient	Ref	0.19	−0.58	0.00	−0.33	Ref	−0.19	−0.21	−0.01	0.66
		95% CI		0.04 to 0.34	−0.70 to −0.47	0.00 to 0.01	−0.43 to −0.23		−0.19 to 0.03	−0.21 to 0.04	−0.01 to 0.26	0.66 to 1.09
		$P > \|z\|$		0.012	<0.001	0.027	<0.001		0.143	0.95	0.075	<0.001
Based on patient assessment	Active + HC	Coefficient	Ref	0.22	−0.71	0.00	−0.34	Ref	−0.09	−0.13	0.11	1.08
		95% CI		0.07 to 0.36	−0.84 to −0.59	0.00 to 0.01	−0.43 to −0.24		−0.21 to 0.02	−0.24 to −0.01	−0.02 to 0.24	0.89 to 1.27
		$P > \|z\|$		0.003	<0.001	0.121	<0.001		0.117	0.037	0.088	<0.001
	Inactive + HC	Coefficient	Ref	0.14	−0.44	0.01	−0.40	Ref	−0.03	−0.11	0.13	0.68
		95% CI		−0.14 to 0.41	−0.67 to −0.21	0.00 to 0.01	−0.49 to −0.30		−0.15 to 0.10	−0.26 to 0.05	−0.03 to 0.30	−0.03 to 0.30
		$P > \|z\|$		0.322	<0.001	0.016	<0.001		0.651	0.170	0.106	<0.001
Based on glucocorticoid dose	Active + HC	Coefficient	Ref	0.12	−0.72	0.01	−0.49	Ref	−0.21	−0.29	−0.04	0.73
		95% CI		0.00 to 0.24	−0.82 to −0.62	0.00 to 0.01	−0.49 to −0.30		0.05 to 0.43	−0.73 to −0.40	0.00 to 0.01	−0.44 to −0.25
		$P > \|z\|$		0.044	<0.001	0.011	<0.001		0.201	0.059	0.136	<0.001
	Inactive + HC	Coefficient	Ref	0.24	−0.56	0.00	−0.34	Ref	−0.16	−0.25	−0.01	0.63
		95% CI		0.05 to 0.43	−0.73 to −0.40	0.00 to 0.01	−0.44 to-0.25		−0.16 to 0.05	−0.25 to 0.00	−0.01 to 0.20	0.63 to 1.14
		$P > \|z\|$		0.013	<0.001	0.039	<0.001		0.287	0.050	0.085	<0.001

TABLE 4 (Continued)

			Covariates									
			Groups			Age	Male	Ethnicity				κ
			IIMs	AIRDs	HCs			White	Asian	Hispanic	Others	
General health	Poor	Coefficient	Ref	0.28	−0.20	0.00	−0.05	Ref	−0.14	0.18	−0.07	1.81
		95% CI		0.13 to 0.44	−0.51 to 0.11	−0.01 to 0.00	−0.18 to 0.07		−0.31 to 0.04	0.02 to 0.35	−0.63 to 0.49	1.59 to 2.03
		$P > \|z\|$		<0.001	0.201	0.33	0.393		0.119	0.032	0.809	<0.001
	Fair	Coefficient	Ref	0.12	−0.42	0.00	−0.20	Ref	−0.20	−0.11	0.17	1.59
		95% CI		0.04 to 0.20	−060 to −0.25	0.00 to 0.00	−0.29 to −0.11		−0.35 to −0.06	−0.19 to −0.03	0.02 to 0.31	1.42 to 1.76
		$P > \|z\|$		0.003	<0.001	0.149	<0.001		0.006	0.007	0.002	<0.001
	Good	Coefficient	Ref	0.27	−0.25	0.00	−0.35	Ref	−0.04	0.01	0.04	0.698
		95% CI		0.11 to 0.43	−0.36 to −0.14	0.00 to 0.00	−0.49 to −0.21		−0.17 to 0.09	−0.10 to 0.12	−0.08 to 0.16	0.69 to 1.26
		$P > \|z\|$		0.001	<0.001	0.947	<0.001		0.531	0.899	0.517	<0.001
	Very good	Coefficient	Ref	0.12	−0.34	0.00	−0.33	Ref	−0.10	−0.18	−0.03	0.49
		95% CI		−0.23 to 0.47	−0.62 to −0.05	0.00 to 0.01	−0.48 to −0.18		−0.27 to 0.07	−0.35 to −0.02	−0.29 to 0.24	0.08 to 0.90
		$P > \|z\|$		0.506	0.021	0.081	<0.001		0.256	0.027	0.848	0.019
	Excellent	Coefficient	Ref	0.22	−0.33	−0.01	−0.26	Ref	0.047	−0.02	0.17	0.54
		95% CI		−0.98 to 1.41	−1.19 to 0.53	−0.03 to 0.00	−0.51 to −0.02		−0.12 to 0.26	−0.30 to 0.26	−0.37 to 0.70	0.64 to 1.72
		$P > \|z\|$		0.722	0.452	0.135	0.038		0.449	0.883	0.536	0.370

(Continues)

TABLE 4 (Continued)

			Covariates									
			Groups			Age	Male	Ethnicity				κ
			IIMs	AIRDs	HCs			White	Asian	Hispanic	Others	
Routine activities	Not at all	Coefficient	Ref	0.55	0.08	0.00	0.00	Ref	−0.68	−0.18	−0.42	0.95
		95% CI		0.09 to 1.00	−0.41 to 0.58	−0.01 to 0.02	−0.41 to 0.41		−1.37 to 0.00	−0.58 to 0.23	−0.98 to 0.14	0.21 to 1.70
		P > |z|		0.018	0.744	0.467	0.990		0.049	0.390	0.140	0.012
	A little	Coefficient	Ref	0.30	−0.12	0.00	−0.30	Ref	−0.30	−0.55	0.03	1.77
		95% CI		0.18 to 0.41	−0.34 to 0.09	−0.01 to 0.00	−0.44 to −0.16		−0.60 to −0.01	−0.75 to −0.34	−0.19 to 0.25	1.48 to 20.7
		P > |z|		<0.001	0.262	0.115	<0.001		0.043	<0.001	0.784	<0.001
	Moderately	Coefficient	Ref	0.22	−0.24	0.00	−0.16	Ref	−0.31	0.10	0.02	1.58
		95% CI		0.05 to 0.40	−0.40 to −0.09	−0.01 to 0.00	--0.25 to −0.06		−0.39 to −0.22	−0.05 to 0.25	−013 to 0.17	1.37 to 1.79
		P > |z|		0.011	0.002	0.114	0.001		<0.001	0.179	0.786	<0.001
	Mostly	Coefficient	Ref	0.28	−0.30	0.00	−0.26	Ref	−0.147	0.10	0.10	1.34
		95% CI		0.18 to 0.38	−0.45 to −0.15	−0.01 to 0.00	−0.36 to −0.15		−0.29 to −0.06	0.04 to 0.17	−0.03 to 0.22	1.15 to 1.54
		P > |z|		<0.001	<0.001	0.002	<0.001		0.004	0.002	0.120	<0.001
	Completely	Coefficient	Ref	0.17	−0.39	0.00	−0.36	Ref	−0.01	−0.01	0.07	0.51
		95% CI		−0.13 to 0.46	−0.64 to −0.14	−0.01 to 0.01	−0.51 to −0.21		−0.14 to 0.11	−0.18 to 0.16	−0.08 to 0.23	0.07 to 0.95
		P > |z|		0.276	0.002	0.557	<0.001		0.850	0.877	0.363	0.023

Note: Regarding all disease activity scenarios, male gender and HC were statistically associated with lower VAS than female sex and IIMs. AIRD was associated with higher VAS in all scenarios of disease activity, except for inactive disease based on the patient's perception. Age was associated with higher VAS in all scenarios of disease activity, except for active disease based on the patient perception. Being Hispanic was associated with lower VAS in patients with active disease either by their own or by their physician's perspective.

Abbreviations: AIRDs, systemic autoimmune rheumatic disease; CI, coefficient interval; HCs, healthy controls; IIM, idiopathic inflammatory myopathies; κ, constant; Ref, reference; VAS, visual analog scale.

and hence have a profound effects on QoL.[5,17,18,26] However, it is poorly understood whether pain is a significant determinant of this poor HRQoL.

The present study has limitations: (i) the patients' diagnoses were self-reported, therefore prone to measurement bias; (ii) incidence of concomitant fibromyalgia, psychiatry disorders (eg, depression and anxiety)[36] or other factors which may impact pain perception, such as socioeconomic status and level of education;[37,38] (iii) matching of disease duration between different autoimmune diseases as varying elements of damage may influence the pain threshold; (iv) concomitant use of nonsteroidal anti-inflammatory drugs in several groups and matching; (v) the cross-sectional nature of this study prevents an evaluation of a causal relationship between the parameters and the potential role of a prospective behavior in many confounding covariables in this study; and (vi) this is a convenience sample prone to selection bias and the number of participants who had access to the e-survey questionnaire is unknown. Nonetheless, we believe that the multiple comparison groups and the adjustments performed to mitigate the effect of this bias contributed to the validity of our results. Finally, we did not explore aspects of pain other than intensity, such as location, duration, pain affect, and other manifestations that could be related and important to the pain experience that hopefully would be addressed in future studies.[39]

In conclusion, patients with IIMs experienced higher pain scores than individuals without a diagnosed autoimmune condition, albeit lower than individuals living with other rheumatic diseases. Individuals with active disease and moderate levels of physical disability experience higher pain levels. IIMs are traditionally conceptualized as painless conditions, but this large international study demonstrated pain is commonly experienced by patients with these conditions. This calls for further research into the understanding of the mechanisms of pain in IIMs and the complex interactions of pain perception with age, gender, ethnicity, socioeconomic construct, and other variables.

AUTHOR CONTRIBUTION

Conceptualization: SKS, MK, RFM, LSH, NR, JGJ, RAC, LG, VA. Data curation: all authors. Formal analysis: SKS, MK, NR, JGJ, JD, VA, LG. Funding acquisition: N/A. Investigation. Methodology: LG, MK, JBL, LSH, SKS, VA. Software: LG. Validation: all authors Visualization: all authors, Writing-original draft: SKS, RGM, LSH, NR, JGJ, RAC, LG, VA. Writing-review and editing: all authors.

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CONFLICT OF INTEREST STATEMENT

ALT has received honoraria for advisory boards and speaking for AbbVie, Gilead, Janssen, Lilly, Novartis, Pfizer, UCB. EN has received speaker honoraria/participated in advisory boards for Celltrion, Pfizer, Sanofi, Gilead, Galapagos, AbbVie, Lilly and holds research grants from Pfizer and Lilly. HC has received grant support from Eli Lilly and UCB; consulting fees from Novartis, Eli Lilly, Orphazyme, Astra Zeneca; speaker for UCB, Biogen. IP has received research funding and/or honoraria from Amgen, AstraZeneca, Aurinia Pharmaceuticals, Elli Lilly and Company, Gilead Sciences, GlaxoSmithKline, Janssen Pharmaceuticals, Novartis and F. Hoffmann-La Roche AG. JD has received research funding from CSL Limited. NZ has received speaker fees, advisory board fees and research grants from Pfizer, Roche, AbbVie, Eli Lilly, NewBridge, Sanofi-Aventis, Boehringer Ingelheim, Janssen, Pierre Fabre; none is related to this manuscript. OD has/had consultancy relationship with and/or has received research funding from or has served as a speaker for the following companies in the area of potential treatments for systemic sclerosis and its complications in the last 3 years: AbbVie, Acceleron, Alcimed, Amgen, AnaMar, Arxx, Baecon, Blade, Bayer, Boehringer Ingelheim, ChemomAb, Corbus, CSL Behring, Galapagos, Glenmark, GSK, Horizon (Curzion), Inventiva, iQvia, Kymera, Lupin, Medac, Medscape, Mitsubishi Tanabe, Novartis, Roche, Roivant, Sanofi, Serodapharm, Topadur and UCB. Patent issued "mir-29 for the treatment of systemic sclerosis" (US8247389, EP2331143). RA has/had a consultancy relationship with and/or has received research funding from the following companies: Bristol Myers-Squibb, Pfizer, Genentech, Octapharma, CSL Behring, Mallinckrodt, AstraZeneca, Corbus, Kezar, and AbbVie, Janssen, Alexion, Argenx, Q32, EMD-Serono, Boehringer Ingelheim, Roivant. LG and TG are Editorial Board members of *IJRD* and co-authors of this article. The remaining authors have no conflict of interest relevant to this manuscript.

DISCLAIMER

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ETHICS APPROVAL

Ethics approval was obtained from the Institutional Ethics Committee of Sanjay Gandhi Postgraduate Institute of Medical Sciences, Raebareli Road, Lucknow, 226014, India.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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