Health-related quality of life improvements and response thresholds of myositis outcome measures and response criteria

M. Almackenzie[1], A. Aggarwal[2], S. Keret[3], T. Chandra[4], R. Lomanto Silva[5], E. Gkiaouraki[4], N. Pongtarakulpanit[4,6], S. Moghadam-Kia[4], C.V. Oddis[4], R. Aggarwal[4]

[1]Division of Rheumatology, Medical Cities of the Ministry of the Interior, Riyadh, Saudi Arabia; [2]Department of Rheumatology, Indraprastha Apollo Hospital, New Delhi, India; [3]Rheumatology Unit, Bnai-Zion Medical Center, Faculty of Medicine, Technion, Haifa, Israel; [4]Division of Rheumatology and Clinical Immunology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; [5]Department of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Boston, MA, USA; [6]Division of Allergy, Immunology and Rheumatology, Department of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

Abstract

Objective

Limited data exist on the clinical associations and responsiveness of myositis core set measures (CSMs) and response criteria using health-related quality of life (HRQoL) assessments like the Short Form Health Survey (SF-36). This study evaluates the associations and improvement thresholds of CSMs and Total Improvement Score (TIS) using SF-36 in idiopathic inflammatory myopathies (IIM).

Methods

Adults with IIM enrolled in two clinical trials and one observational study were assessed. Demographics and myositis CSMs including patient-global assessment (PtGA), physician-global assessment (PhGA), extra global disease activity score (EXGLB), manual muscle testing (MMT-8), Health Assessment Questionnaire (HAQ), creatine kinase (CK), and SF-36 were collected longitudinally. TIS was calculated at 6 months. Spearman's correlation assessed associations between SF-36 domains and summary scores for physical health (PCS) and mental health (MCS) with all CSMs and TIS. A mixed linear model examined longitudinal association. Minimal clinically important difference (MCID) was determined using the anchor method.

Results

The study included 105 IIM patients. Most SF-36 domains showed moderate to strong correlations with all CSMs at baseline as well as 6-month changes (delta change), except CK levels at baseline. TIS exhibited significant correlations with delta changes in most SF-36 domains. Longitudinally, significant associations were observed between SF-36 and most CSMs (except MMT-8). Higher thresholds in CSMs and TIS aligned with incremental improvements in PCS. MCIDs for PhGA, PtGA, EXGLB, HAQ, MMT-8 and TIS were 1.1, 1.84, 0.85, 0.65, 5.6, 23.7, respectively.

Conclusion

Most CSMs and TIS in IIM significantly correlated with SF-36 domains, reflecting concurrent HRQoL improvements.

Key words

myositis, inflammatory myopathies, core set measures, clinical meaningfulness, quality of life, SF-36

Maha Almackenzie, MBBS
Anushka Aggarwal, MD
Shiri Keret, MD
Tanya Chandra, MD
Raisa Lomanto Silva, MD
Eugenia Gkiaouraki, MD
Nantakarn Pongtarakulpanit, MD
Siamak Moghadam-Kia, MD, MS
Chester V. Oddis, MD
Rohit Aggarwal, MD, MS

Please address correspondence to:
Rohit Aggarwal
Division of Rheumatology and Clinical Immunology,
University of Pittsburgh School of Medicine,
3601 Fifth Ave., Suite 2B,
Pittsburgh, PA 15213, USA.
E-mail: aggarwalr@upmc.edu

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Introduction

Idiopathic inflammatory myopathies (IIM) encompass a rare group of systemic autoimmune rheumatic diseases (SARDs), characterised by muscle inflammation leading to progressive muscle weakness and substantial impairment in health-related quality of life (HRQoL) (1-4). Accurate assessment of disease activity and damage is crucial for managing IIM effectively and are critically important in clinical trials (5). The International Myositis Assessment and Clinical Studies (IMACS) Group validated six myositis core set measures (CSMs) for evaluating disease activity in patients with IIM. These CSMs include patient-global disease activity (PtGA), physician-global disease activity (PhGA), extra-muscular global disease activity score (EXGLB), manual muscle testing (MMT-8), the Health Assessment Questionnaire (HAQ), and the serum level of muscle enzymes (6, 7). The Total Improvement Score (TIS) is a composite metric encompassing these CSMs, formulated as part of the 2016 ACR/EULAR (American College of Rheumatology/European League Against Rheumatism) response criteria for myositis (8). Given the heterogeneity of myositis, where no single measure can adequately capture the diverse range of affected domains, the TIS was developed to provide a more comprehensive assessment of disease response to treatment.

Despite the widespread use of CSMs and the 2016 ACR/EULAR TIS in clinical trials, there is limited data on the clinical associations, validity, and responsiveness of these CSMs with respect to HRQoL and functional measures in IIM patients. Moreover, the clinical meaningfulness of various thresholds of improvement in CSMs and TIS, particularly in relation to improvement in HRQoL remains underexplored. Previous studies have indicated that worsening HAQ scores are associated with increased disease activity and longer disease duration (9, 10). In a study of the juvenile dermatomyositis population, improvement in at least one patient-reported outcome was observed in 71-77% of patients with minimal TIS improvement (11). Another study showed that 84% of adult IIM subjects had improvement in patient-reported outcome measures (PROM) along with at least minimal improvement in their TIS (12). However, the association of TIS with HRQoL remains unclear.

The 36-Item Short Form Health Survey (SF-36), recommended by IMACS, is a widely utilised instrument that assesses HRQoL, functional health, and well-being across various medical conditions (13-15). Studies have shown that myositis patients typically score lower in SF-36 domains compared to the general population (4, 14), underscoring the significant impact of the disease on HRQoL and functional health. Conversely, patients who exhibit improvements in disease activity also show significant improvement in HRQoL and physical function correlating with changes in SF-36 domains (16-18).

First introduced in 1989, the minimal clinically important difference (MCID) quantifies the smallest change that is perceived as meaningful by the patient (19). The significance of measuring the MCID lies in its ability to define the threshold of improvement that is clinically relevant, providing a benchmark for evaluating treatment efficacy and guiding clinical decision-making (20). The currently established thresholds for TIS were developed through physician consensus, whereas MCIDs should be determined based on the level of improvement that is meaningful to patients.

The aim of this study was to evaluate the clinical associations, meaningfulness and improvement thresholds of various CSMs and TIS using the HRQoL and functional measure (SF-36) in patients with IIM. We also aimed to establish the MCID for each CSM and TIS to inform improved management strategies to enhance HRQoL and functional outcomes in myositis patients.

Methods

Study participants

Patients meeting the 2016 EULAR/ACR classification criteria for IIM (21) were included from three previously reported clinical trials or myositis cohorts: 1. the Tocilizumab in Myositis (TIM) clinical trial (22), 2. a prospec-

tive observational cohort [from the Physical Activity Monitor and Patient-Reported Outcome (PAMPRO) study] (23) and 3. interstitial lung disease (ILD) patients with anti-synthetase autoantibodies with or without myositis enrolled in the Abatacept for the Treatment of Myositis-associated Interstitial Lung Disease (Attack My-ILD) clinical trial (24). These three trials were chosen as there was prospective CSM determination as well as data collection encompassing the aforementioned metrics necessary to assess the quality of life and MCID.

The TIM trial studied the efficacy, safety, and tolerability of tocilizumab in 36 patients with dermatomyositis (DM) and polymyositis (PM) (22). PAMPRO enrolled 50 IIM (excluding IBM) patients (23) and Attack My-ILD enrolled 20 patients with anti-synthetase syndrome-associated interstitial lung disease (ASyS-ILD) (24). All subjects signed informed consent, and all studies were approved by the institutional review board of the University of Pittsburgh.

Study design and measures

Data collection included baseline patient demographics, SF-36 domains (Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, Mental Health) and two summary scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). The PCS is derived from four domains: Physical Functioning, Role Physical, Bodily Pain, and General Health, while the MCS incorporates the domains of Vitality, Social Functioning, Role Emotional, and Mental Health (25). Data were collected at baseline, 12 and 24 weeks with SF-36 scores ranging from 0 (poor health) to 100 (best health) (15).

Additionally, all six CSMs including manual muscle testing (MMT-8), physician-global disease activity (PhGA), patient-global disease activity (PtGA), extra-muscular global disease activity (EXGLB), health assessment question naire (HAQ), and creatine kinase (CK) were assessed at baseline, 12 and 24 weeks. To standardise results across different studies and enrolling centres, the MMT-8 scores were standardised by calculating the ratio of the measured MMT-8 to the normal score (0-100) in individual patients at each time point. Similarly, CK results were normalised according to the upper limit of normal for each respective laboratory.

Clinical responsiveness was assessed using the TIS at 12 and 24 weeks which includes criteria for minimal (≥20), moderate (≥40) and major (≥60) improvement (8).

A priori hypotheses

We hypothesised that various CSMs and the TIS will significantly correlate with HRQoL domains, as measured by the SF-36 in IIM patients. We expected reductions in disease activity and improvements in CSMs to be linked to better HRQoL outcomes. Specifically, MMT-8 and HAQ will be moderate to strongly associated with PCS, Physical Functioning, Role Physical, and Vitality; patient and physician global will be associated with both summary scores and most domains; CK may be associated with physical functioning and other physical domains, whereas extra-muscular may be associated with general health. Additionally, determining MCIDs for each CSM and TIS will provide valuable thresholds for assessing patient improvement and guide more effective management strategies.

Statistical analysis

Patient characteristics were described using simple descriptive statistics. Baseline CSMs and SF-36 domains were summarised as mean ± standard deviation (SD). Kruskal-Wallis and Mann-Whitney tests were used to compare mean in different domains among the group. Spearman correlation coefficients and corresponding *p*-values were calculated to assess the relationships between SF-36 domain scores and various CSMs at baseline. Additionally, the Spearman correlations for delta change of SF-36 domains and CSMs from baseline to 6 months, and TIS at 6 months, were analysed. Correlation coefficients were interpreted as follows: poor (0 to ±0.2), weak (0.2 to ±0.35), moderate (0.35 to ±0.5), and strong (0.5 to±1) (26).

- Responsiveness

The mixed linear analysis was employed to identify significant relationships between the independent variables (CSMs) and the dependent variables (SF-36 domains). The model was adjusted for sex, age, and race, with included data from all visits.

- Minimal clinically important difference (MCID)

Using anchor-based method, we defined a PCS improvement of 7.2 as an anchor for clinical improvement, based on prior studies in rheumatoid arthritis (RA) patients (27). Furthermore, we applied a within-person change over time approach to determine the score change that most accurately distinguishes individuals who experienced a meaningful improvement in HRQoL from those who did not (28, 29). This approach employed the Redelmeier MCID, which is based on the mean change method (30); this methodology provides a solid benchmark for understanding the magnitude of change required in specific clinical measures to achieve meaningful improvements in patients' HRQoL, particularly in terms of disability (29, 31).

CSMs and TIS were categorised based on whether PCS improved. The mean change, SD, and TIS at 6 months were calculated and analysed using Mann-Whitney tests. The MCID was determined by calculating the difference in the mean change of CSMs and TIS between the PCS improved and non-improved groups (30, 31).

- Absolute percent improvement thresholds for each CSMs

Since MCIDs based on absolute score changes, rather than relative changes, can vary depending on baseline symptom levels or the degree of abnormality in the measure, this variability underscores the significant influence of baseline values on the interpretation of meaningful change (32, 33). Specifically, higher MCID values are typically observed in patients with more severe symptoms, which can be attributed to ceiling and floor effects. These effects limit the ability to detect meaningful changes due to the boundaries of the

Table I. Patients characteristics, baseline SF-36 domains, core set measures (CSMs) and total improvement score (TIS) at 6 months with mean ± SD.

Patient characteristics	**n (%)**
IIM subtype	
Dermatomyositis	46 (44.2%)
Anti-synthetase syndrome	31 (29.8%)
Polymyositis	19 (18.3%)
Necrotising myopathy	8 (7.7%)
Sex	
Male	38 (36.2%)
Female	67 (63.8%)
Race	
White	89 (84.8%)
Black	10 (9.5%)
Asian	6 (5.7%)
Age (years) (mean± SD)	52.31 ± 13.62
SF-36 domain scores	**Mean ± SD**
Physical functioning	46.01± 30.78
Role physical	33.52 ± 41.5
Role emotional	56.76 ± 44.41
Vitality	43.86 ± 24.4
Mental health	73.85 ± 17.65
Social functioning	63.98 ± 25.49
Bodily pain	61.10 ± 28.90
General health	46.91 ± 21.48
PCS	34.22 ± 12.04
MCS	48.61 ± 9.44
CSM scores	**Mean ± SD**
EXGLB	2.54 ± 1.98
PhGA	3.76 ± 2.19
PtGA	4.42 ± 2.50
HAQ	0.86 ± 0.73
MMT-8	92 ± 9.79
CK	608 ± 1248

TIS score (at 6 months)	**mean ± SD**	**n (%)**
< 20 (no improvement)	3.75 ± 4.7	30 (28.6%)
≥ 20 (minimal improvement)	43.62 ± 16.7	29 (27.6%)
≥ 40 (moderate improvement)	56.56 ± 9.2	16 (15.3%)
≥ 60 (major improvement)	65 ± 4.1	7 (0.07%)

IIM: idiopathic inflammatory myopathies; SF-36: short form 36; CSMs: core set measures; CK: creatine kinase; HAQ: health assessment questionnaire; MMT-8: manual muscle testing 8; EXGLB: extramuscular disease activity; PtGA: patient-global assessment; PhGA: physician-global assessment; TIS: total improvement score.

measurement scale (34). To address this, we calculated the absolute percent improvement threshold by calculating the absolute percentage change in each CSM from baseline to 6 months, using the formula: (6-month visit value minus baseline value) divided by the CSM range. Then, we calculated the mean change for the PCS improved and non-improved groups. The absolute percent improvement threshold was determined by finding the difference between the mean changes in the improved *versus* non-improved groups.

- *Assessing the effect of incremental improvements in CSMs and TIS on quality of life*

The meaningfulness of incremental improvements in CSMs and the TIS was evaluated by calculating the absolute percentage change for each CSM from baseline to six months. These changes were grouped according to the level of improvement. An absolute percentage change greater than 5% was classified as improvement or worsening for most CSMs, while a threshold of >2% was applied for MMT-8, following the Myositis Response Criteria (8). The corresponding mean change in the PCS score, along with the standard deviation, was also calculated.

All data were analysed using SPSS statistical software. Analyses were conducted under the assumption that missing values occurred at random, and no imputation methods were employed. The analysis proceeded with available observations only, and statistical significance was defined as a *p*-value of less than 0.05.

Results

The study consisted of 105 patients with IIM with a mean age of 52±13.6 years. Most patients were female (63.8%) and predominantly white (84.8%), 44.2% with DM, 29.8% with anti-synthetase syndrome, 18.3% with PM and 7.7% with immune mediated necrotising myopathy (IMNM). Patients' characteristics, baseline SF-36 domains, CSMs and TIS are summarised in Table I.

Baseline correlations of CSMs and TIS with SF-36

All physical and functional domains of SF-36 and PCS at baseline showed moderate to strong negative correlations with PhGA, PtGA, and HAQ as well as moderate positive correlation with MMT-8 indicating that higher disease activity is associated with lower physical function, whereas better muscle strength is linked to higher physical function. In addition, Pain, Role Emotional, Vitality, Social Functioning and MCS demonstrated moderate negative correlations with PhGA, PtGA, and HAQ, and weak positive correlations with MMT-8. CK did not show significant correlations with any SF-36 domains. (Fig. 1, Supplementary Table S1).

Correlations of CSMs delta changes with changes in SF-36

For the delta change of SF-36 domains and CSMs, as well as TIS at 6 months, the delta change in HAQ demonstrates strong negative correlations with delta changes in physical functioning and social functioning. Similarly, delta changes in PhGA and PtGA show moderate negative correlations with delta change in several SF-36 domains, particularly

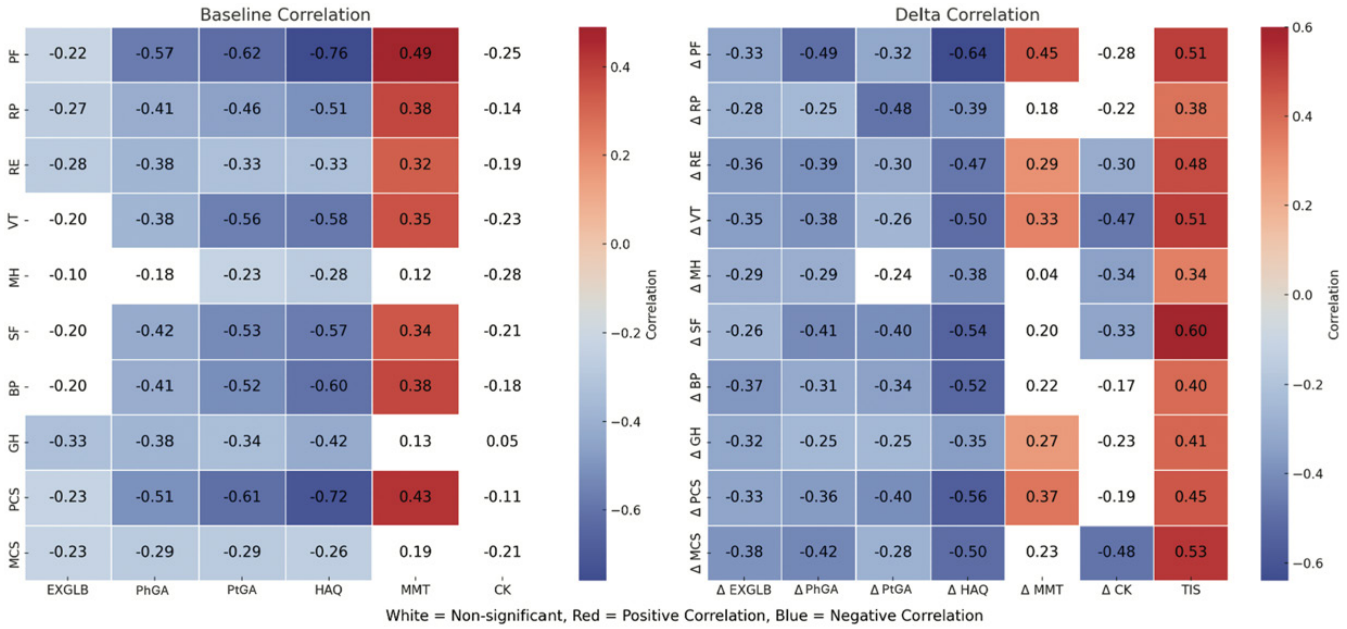

Fig. 1. Heatmap of Spearman correlation analysis Bbtween the SF-36 domains and core set measures at baseline and correlation of delta change of SF-36 domains, core set measures (CSMs), and total improvement score (TIS) at 6 months.
SF-36: short form 36; CSMs: core set measures; CK: creatine kinase; HAQ: health assessment questionnaire; MMT-8: manual muscle testing 8; EXGLB: extra-muscular disease activity; PtGA: patient-global assessment; PhGA: physician-global assessment; TIS: total improvement score; PF: physical functioning; RP: role physical; BP: bodily pain; GH: general health; VT: vitality; SF: social functioning; RE: role emotional; MH: mental health, PCS: physical component summary; MCS: mental component summary.

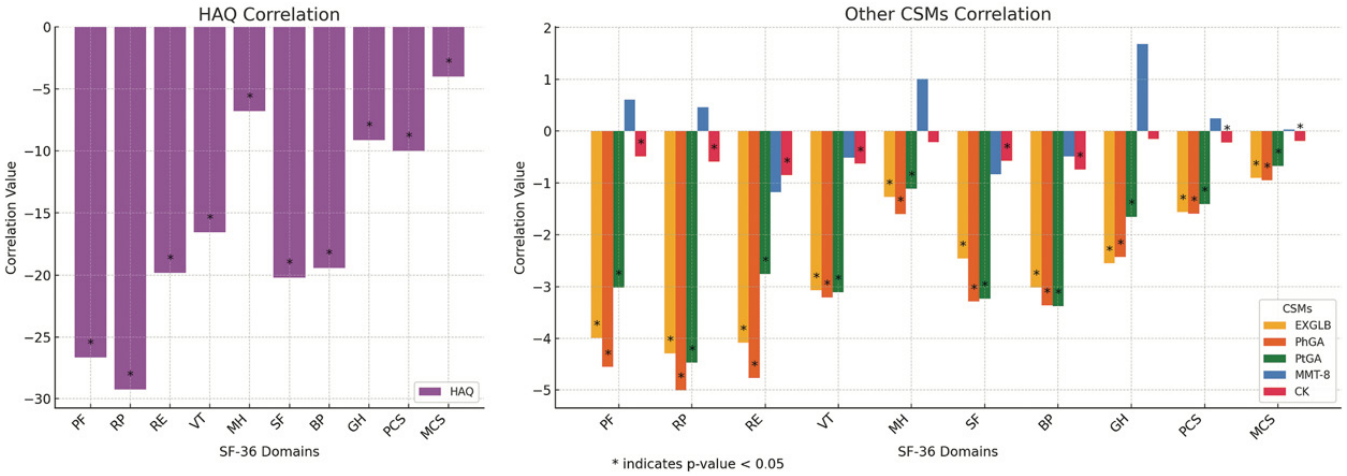

Fig. 2. Bar chart of mixed linear model results between core set measures (CSMs) and SF-36 domain changes over 6 months (adjusted for age, sex and race).
SF-36: short form 36; CSMs: core set measures; CK: creatine kinase; HAQ: health assessment questionnaire; MMT-8: manual muscle testing 8; EXGLB: extra-muscular disease activity; PtGA: patient-global assessment; PhGA: physician-global assessment; TIS: total improvement score; PF: physical functioning; RP: role physical; BP: bodily pain; GH: general health; VT: vitality; SF: social functioning; RE: role emotional; MH: mental health, PCS: physical component summary; MCS: mental component summary.

with social functioning and PCS. The delta change in CK shows moderate negative correlations with delta change in MCS and vitality. In contrast, the delta change in MMT-8 shows moderate positive correlations with delta changes in physical functioning and PCS, while TIS shows moderate to strong positive correlations with delta changes in all SF-36 domains. (Fig. 1, Suppl. Table S2).

Longitudinal association of CSMs with SF-36

Significant longitudinal associations were demonstrated between CSMs and changes in SF-36 domains and summary scores over 6 months, after adjusting for age, sex, and race (Fig. 2, Suppl. Table S3). Elevated CK, PtGA, PhGA, HAQ, and EXGLB were consistently linked to worse outcomes in physical functioning, role physical, vitality, and pain. HAQ had the strongest negative impact on physical domains. In contrast, MMT-8 did not show significant associations with any of SF-36 domains or summary scores in this analysis.

Known groups validity of CSMs and TIS

Significant improvements in most CSMs and TIS were observed among patients who achieved a PCS improve-

Table II. Core set measures mean at baseline, mean change over 6 months by PCS improvement *vs*. no improvement at 6 months. In addition, MCID for CSMs and TIS score at 6 months.

CSMs	PCS improved ≥7.2		PCS not improved ≤7.2			
	Baseline Mean ± SD	Mean change ± SD	Baseline Mean ± SD	Mean change ± SD	*p*-value of mean change	MCID (delta change)
EXGLB (0–10 cm VAS)	3.09 ± 1.85	-1.43 ± 0.41	2.6 ± 1.96	-0.58 ± 0.22	**0.03**	0.85
PhGA (0–10 cm VAS)	4.3 ± 2.24	-2.17 ± 0.52	3.73 ± 2.14	-1.07 ± 0.23	**0.02**	1.1
HAQ (0–3)	1.11 ± 0.65	-0.62 ± 0.10	0.75 ± 0.74	0.03 ± 0.05	**<0.01**	0.65
PtGA (0–10 cm VAS)	4.83 ± 2.66	-1.80 ± 0.72	3.88 ± 2.43	0.04 ± 0.33	**0.02**	1.84
MMT-8 (0-100)	90.65 ± 8.1	6.30 ± 1.6	93.3 ± 9.76	2.59 ± 1.14	**<0.01**	3.71
CK IU/L	633 ± 850	-264.8 ± 242.9	369 ± 1020	259.5 ± 115.5	0.18	524.3
TIS 6-months (0-100)		39.61 ± 24.90		15.87 ± 19.05	**<0.01**	23.74

SF-36: short form 36; CSMs: core set measures; CK: creatine kinase; HAQ: health assessment questionnaire; MMT-8: manual muscle testing 8; EXGLB: extra-muscular disease activity; PtGA: patient-global assessment; PhGA: physician-global assessment; TIS: total improvement score; PCS: physical component summary; MCID: minimal clinically important difference.

Table III. Absolute percentage (%) of core set measures (CSMs) mean change for PCS improvement *vs*. no improvement at 6 months and the delta changes.

CSMs (Absolute % change)	Mean change			
	PCS improved ≥7.2	PCS not improved ≤7.2	*p*-value	Delta change in CSMs (Absolute %)
EXGLB	-14% ± 17	-5.8% ± 16	**0.02**	8.2
PhGA	-21% ± 22	-10% ± 16	**0.02**	11
HAQ	-20% ± 14	1.1% ± 12	**<0.01**	**21**
PtGA	-18% ± 30	0.4% ± 23	**0.02**	**18.4**
MMT-8	6.3% ± 7	2.5% ± 8	**<0.01**	**3.8**
CK	-17% ± 58	1% ± 44	0.176	18

CSMs: core set measures; CK: creatine kinase; HAQ: health assessment questionnaire; MMT-8: manual muscle testing 8; EXGLB: extra-muscular disease activity; PtGA: patient-global assessment; PhGA: physician-global assessment; PCS: physical component summary.

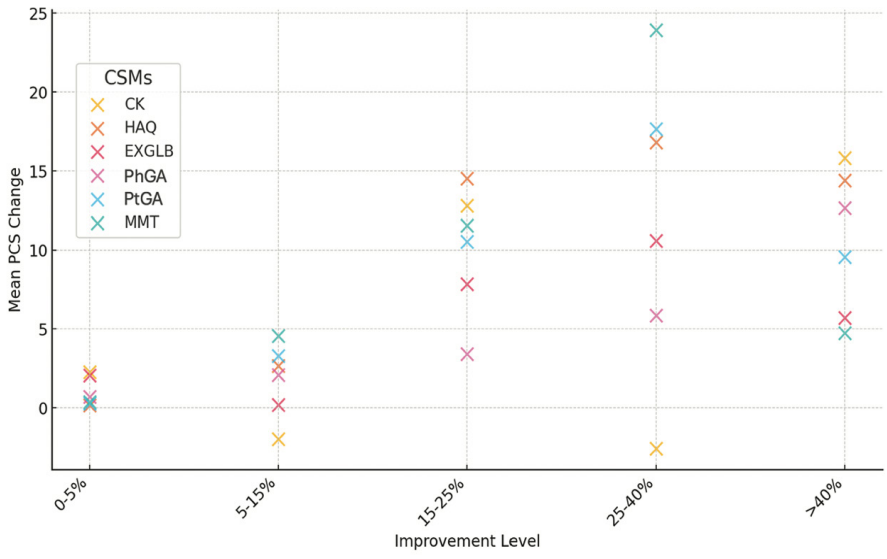

Fig. 3. Dot plot of core set measures absolute percentage changes and TIS *vs*. PCS improvement from baseline to 6 months.
CSMs: core set measures; CPK: creatine kinase; HAQ: health assessment questionnaire; MMT-8: manual muscle testing 8; EXGLB: extra-muscular disease activity; PtGA: patient-global assessment; PhGA: physician-global assessment; TIS: total improvement score; PCS: physical component summary.

ment of ≥7.2 compared to those who did not (Table II). Patients with PCS improvement of ≥7.2 showed greater reductions in EXGLB, PhGA, PtGA, and disability (HAQ), as well as notable enhancements in muscle strength (MMT-8) and TIS. In contrast, changes in CK levels were not statistically significant (p=0.18).

Minimal clinically important differences (MCIDs) for each CSMs

The MCID for each CSM and TIS is provided Table II, highlighting the meaningful improvement in their HRQoL is associated with improvements in CSMs and TIS. EXGLB had an MCID of 0.85, while PhGA and PtGA were 1.1 and 1.84, respectively, showing that a reduction of these scores by these thresholds on a 0-10 cm VAS is clinically meaningful. The HAQ's MCID was 0.65, with a scoring range of 0-3. The MMT-8 MCID was 3.71, indicating that an MMT-8 change of about 4 (standardised scale 0-100) correlated with a significant improvement in HRQoL (specifically the physical function-related domains). Given the actual MMT-8 range of 0-150, this translates to an MMT-8 MCID of approximately 6. The CK MCID was 524.3 which was not statistically significant while the TIS MCID of 23.74 correlated with significant PCS improvements.

Absolute percent improvement thresholds for each CSMs

The absolute percent improvement thresholds for each CSM are presented in Table III. A 21% improvement in the

HAQ from baseline is deemed clinically meaningful for HRQoL, indicating a substantial improvement in physical function. Similarly, an 8.2% improvement in EXGLB is considered clinically significant. For PhGA and PtGA, clinically meaningful improvements were found to be 11% and 18.4%, respectively. As for the MMT-8, a 3.8% improvement was identified as clinically significant in terms of HRQoL. Notably, CK did not show a statistically significant change between the two groups.

Incremental improvements in SF-36 physical component summary (PCS) with varying thresholds of change in CSMs and TIS

The improvement in absolute percentage change in CSMs, TIS at 6 months showed the corresponding trends of improvement in PCS. As patient- and physician-reported disease activity, disability, and muscle strength improve, as reflected by CSM absolute percentage changes and TIS thresholds, there were corresponding increases in PCS scores (Fig. 3, Table IV).

Table IV. Relationship between various thresholds of CSMs and TIS absolute % changes and corresponding mean (± SD) improvement in PCS change Over 6 months.

CSMs	Level of improvement based on percentage change	Mean PCS Change ± SD	Numbers
MMT8	Worsening to 2% improvement	0.37 ± 6.95	44
	>2% to 10% improvement	4.55 ± 6.69	15
	>10% to 20% improvement	11.57 ± 11.16	9
	>20% to 30% improvement	23.91	1
	>30% improvement	4.73	1
HAQ	Worsening to 5% improvement	0.17 ± 6.29	43
	>5% to 15% improvement	2.66 ± 7.04	13
	>15% to 25% improvement	14.52 ± 5.90	6
	>25% to 40% improvement	16.81 ± 14.07	3
	>40% improvement	14.38 ± 3.20	3
EXGLB	Worsening to 5% improvement	2.06 ± 7.93	38
	>5% to 15% improvement	0.18 ± 9.73	16
	>15% to 25% improvement	7.86 ± 3.10	7
	>25% to 40% improvement	10.60 ± 10.75	6
	>40% improvement	5.71 ± 5.61	3
PhGA	Worsening to 5% improvement	0.70 ± 6.94	29
	>5% to 15% improvement	2.10 ± 8.58	13
	>15% to 25% improvement	3.41 ± 7.68	8
	>25% to 40% improvement	5.87 ± 9.27	13
	>40% improvement	12.65 ± 9.55	6
PtGA	Worsening to 5% improvement	0.27 ± 7.42	37
	>5% to 15% improvement	3.30 ± 6.80	17
	>15% to 25% improvement	10.54 ± 10.14	6
	>25% to 40% improvement	17.66±7.51	2
	>40% improvement	9.57±8.51	6
CK	Worsening to 5% improvement	2.26±8.37	37
	>5% to 15% improvement	-1.98 ± 6.27	2
	>15% to 25% improvement	12.80 ± 5.40	3
	>25% to 40% improvement	-2.58	1
	>40% improvement	15.81 ± 13.22	3
TIS (6 months)	<20 (no improvement)	-0.11 ± 7.07	28
	≥ 20 (minimal improvement)	5.90 ± 9.61	25
	≥ 40 (moderate improvement)	9.64 ± 10.03	13
	≥ 60 (major improvement)	12.77 ± 15.32	5

CSMs: core set measures; CPK: creatine kinase; HAQ: health assessment questionnaire; MMT-8: manual muscle testing 8; EXGLB: extra-muscular disease activity; PtGA: patient-global assessment; PhGA: physician-global assessment; TIS: total improvement score; PCS: physical component summary.

Discussion

This study highlights the associations of disease activity and muscle weakness with the HRQoL of IIM patients, particularly in the physical health domains. Moderate to strong associations were observed between most CSMs, except CK, and various SF-36 domains as well as its summary scores (PCS and MCS). Importantly, we demonstrated the level of improvement in HRQoL with different thresholds of CSM and TIS improvement. The study also established the responsiveness of CSMs and TIS in predicting the impact of myositis on overall HRQoL, as well as determining the MCIDs for each CSM and TIS.

Among the CSMs, PhGA and PtGA exhibited strong negative correlations at baseline with physical functioning and PCS of the SF-36, and moderate correlation with other SF-36 domains reflecting the adverse effects of increased myositis disease activity on physical functioning and other HRQoL features. This correlation pattern aligns with that observed in adult DM, where PhGA correlates mildly to moderately with physical functioning, role physical, bodily pain, and general health (7). Furthermore, the longitudinal analysis reinforces these associations with HRQoL outcomes, supporting the sensitivity of PhGA and PtGA in capturing disease activity and their impact on overall HRQoL, particularly related to physical health domains.

EXGLB which encompasses extramuscular disease activity such as skin, joint and lung disease, showed significant but weaker negative correlations with most SF-36 domains, particularly with physical functioning, role physical and general health, indicating that higher levels of disease activity and systemic involvement were associated with worse HRQoL outcomes, though to a lesser extent. Furthermore, EXGLB delta changes demonstrated associations with SF-36 domains, primarily role emotional, vitality, bodily pain and MCS. This was confirmed longitudinally, highlighting the sensitivity of EXGLB disease activity along with HRQoL over time.

The HAQ proved to be a robust measure of disability, demonstrating strong negative correlations at baseline as well as longitudinally with most SF-36 domains particularly Physical Functioning, PCS, social functioning, vital-

ity and bodily pain. This finding aligns with a longitudinal cohort study involving a different subset of adult myositis patients, which similarly reported a strong negative correlation between the HAQ and the physical functioning domain of the SF-36, along with moderate correlations with role physical, bodily pain, and role emotional (2, 7). Among all CSMs, the HAQ demonstrated the strongest longitudinal associations, emphasising its sensitivity in reflecting the impact of disability on both physical and psychosocial aspects of HRQoL.

MMT-8 offers a more targeted assessment of muscle strength and its specific contributions to physical function. At baseline MMT-8 scores demonstrated moderate positive correlations with the physical functioning domain, whereas correlations with psychosocial components were rather weak. This suggests that muscle strength alone may be insufficient to fully capture the broader spectrum of HRQoL impairments in myositis. Over six months, MMT-8 maintained moderate to strong positive correlations with changes in physical functioning and PCS, reflecting its role in tracking improvements specifically in physical health. These findings align with previous studies, which reported moderate correlations between MMT-8 scores and physical functioning (2, 7, 35). MMT-8 measures muscle strength, which does not comprehensively capture symptoms such as pain, fatigue, emotional distress, or limitations in social participation, all of which are integral to HRQoL while not directly correlating with muscle strength. Our study failed to show longitudinal associations between MMT-8 and most SF-36 domains. One potential explanation is the paucity of patients with moderate to severe muscle weakness in our study cohorts reflecting a "floor effect." That is, PAMPRO was an observational cohort of subjects with a broad range of muscle involvement, while the Attack-MyILD study required no muscle weakness as an inclusion criterion. Moreover, variations in muscle involvement across IIM subtypes may further explain the inconsistent associations observed, as patients with DM may exhibit preserved muscle strength, whereas those with IMNM or PM typically present with pronounced weakness (6, 36). This underscores that MMT-8 captures only part of the disease burden, emphasising the need for multidimensional outcome assessments that integrate both muscle and extra-muscular disease activity.

Interestingly, CK did not exhibit significant correlations with SF-36 domains at baseline, reflecting the predominance of DM patients in our cohorts, where the CK level is known to correlate poorly with disease activity (37). However, significant longitudinal correlations between CK and most SF-36 domains were observed, suggesting that CK may have longitudinal implications and may correlate with other CSMs regardless of baseline CK levels (38). The absence of a significant difference in CK levels between patients with or without PCS improvement further aligns with the known limitations of CK as a standalone marker in myositis. Previous literature has similarly noted that CK often shows poor concordance with patient-reported outcomes (6), supporting the notion that CK alone may insufficiently reflect the patient-perceived disease burden in IIM. Moreover, the heterogeneous subtype composition of our cohort, predominantly DM, may have contributed to the variability observed in CK associations with HRQoL (39). A recent longitudinal study demonstrated that the correlation between CK and PhGA varies considerably across IIM subtypes, being strongest in IMNM and weaker or absent in DM and IBM (40). This subtype-dependent inconsistency in CK's clinical relevance likely extends to patient-reported outcomes such as the SF-36, highlighting the complex interplay between biological markers and subjective measures of health status.

The TIS demonstrated the most integrative correlations, with significant moderate to strong positive associations longitudinally in almost all SF-36 domains over six months. The TIS accurately measures both clinical and functional improvement effectively capturing the effect of disease activity and treatment on HRQoL (41). Our study strongly supports the use of the TIS in evaluating the complexity of disease activity and disability in myositis patients. Moreover, higher improvement thresholds of TIS were associated with incremental improvements in SF-36 HRQoL, particularly the PCS.

The MCIDs for EXGLB, PhGA, and PtGA (Table II) provide valuable insights into the level of improvement needed to achieve significant changes in HRQoL, offering a critical tool for clinical trials and therapeutic monitoring. The MCID for MMT-8 suggests that an improvement of 6 points constitutes a clinically meaningful change in HRQoL, while the HAQ MCID of 0.65, emphasises the difference between RA and myositis where a higher MCID was seen in IIM (42).

Our study noted an MCID of 24 for TIS as the smallest change that patients perceive as meaningful in terms of HRQoL. This compares to the expert consensus metric of ≥20 reported in the 2016 ACR/EULAR criteria for minimal improvement. While this latter determination reflects improvement in many clinical trials, a change of ≥24 may better indicate a patient's perception of meaningful improvement related to HRQoL, and physical function. Although MCID is widely applied in clinical settings, its use in the context of IIM is underexplored. We addressed this knowledge gap by determining the MCID for CSMs and TIS in IIM related to HRQoL, providing novel insights into the meaningful thresholds for functional improvement in myositis. This finding offers a foundation for future research and clinical decision-making in IIM management.

Our study has several strengths and limitations. The majority of patients included in this analysis were of White, which may limit the generalisability of our findings to other racial or ethnic groups, as cultural and racial differences have been reported to influence responses to several SF-36 items (43, 44). Future studies with more ethnically diverse cohorts are needed to validate whether these relationships hold across populations. Another limitation is a relatively short six-month follow-up period, which may not have been sufficient to fully capture long-term changes in muscle strength and HRQoL. Addition-

ally, variability in disease subtypes may affect the generalizability of the results, as different forms of IIM, such as DM, may differ in the relative contributions of muscle involvement and biomarkers like CK. A strength of the study is that three prospective cohorts were used, two of which were clinical trials while the other was an observational study. This hybrid population increased our sample size and improved the generalizability of the results across both real world and clinical trial settings. Furthermore, we included the full spectrum of IIM patients, ranging from those with severe muscle weakness to those with no weakness, including subjects with ILD, a common manifestation of IIM and an important contributor to morbidity and mortality in myositis. Further, this study longitudinally evaluated the relationship between disease activity, muscle strength, and HRQoL in IIM patients, using well-established measures such as the SF-36 and CSMs and TIS. The inclusion of both physical and psychosocial dimensions of HRQoL offers a more holistic view of patient outcomes.

Conclusion

This study establishes the clinical meaningfulness of various CSMs and TIS in IIM. Significant associations were observed between SF-36 domain scores, CSMs and TIS, supporting the use of these measures in capturing patients' disease activity, disability, and HRQoL. Furthermore, by calculating the MCID for CSMs in IIM, our study provides novel insights into the clinically meaningful thresholds for improvement, offering valuable information for both clinical practice and future clinical trials in myositis.

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