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ORIGINAL RESEARCH

Internal Psychometric Validation of an International Burden of Illness Survey for Idiopathic Multicentric Castleman Disease

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ABSTRACT

***Introduction*:** Idiopathic multicentric Castleman disease (iMCD) is a rare, chronic, debilitating lymphoproliferative disorder where the mainstay of treatment is symptom management. Our recent international patient survey showed that patients with iMCD have a high symptom burden that has a significant negative patient-reported impact on several aspects of daily life. As part of our ongoing work towards the development of an iMCD symptom burden scale, assessing the survey's psychometric properties is a critical step in understanding its adequacy, relevance, and usefulness. As iMCD is a rare disease, there are challenges to conducting such psychometric analyses which we describe.

***Methods*:** As part of the exploratory psychometric analysis, three a priori hypothesis sets (HS) were generated by interviewing an iMCD-experienced clinician, a patient, and a caregiver to explore the iMCD patient survey's internal construct validity, given no gold standard iMCD measure exists for external construct validation. HS-1 hypothesized that a convergent or discriminant relationship exists with the patients' self-assessment of symptom effect on daily life between two potentially related or unrelated symptoms, respectively. HS-2 hypothesized that having a greater number of symptoms has a positive convergent relationship with the patients' assessment of symptoms' effect on daily life. Finally, HS-3 hypothesized that patients receiving treatment versus no treatment was associated with patients reporting less effect of symptom burden on their daily life. Spearman's rank absolute correlation strength (ACS) was used for HS-1 and HS-2 (convergent relationship, ACS ≥ 0.3 and p value < 0.05; divergent relationship, ACS < 0.3), and Cohen's d to quantify standardized absolute effect sizes (AES) for HS-3 (AES ≥ 0.5 and p value < 0.05).

***Results*:** Our analyses partially supported HS-1. None of the three positive convergent

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relationships were supported. Of the six discriminant relationships, only dizziness with impaired cognitive function and tiredness with dizziness were supported. HS-2 analyses showed there was convergent validity between the number of symptoms and their effect on aspects of daily life. HS-3 analyses did not provide evidence to support the hypothesis.

***Conclusion*:** These internal psychometric construct analyses provide initial support for the bespoke iMCD patient survey and will guide additional work towards the development of the first iMCD-specific symptom burden scale.

Keywords: Exploratory analysis; Quality of life impact; Symptom burden; Quality of life survey

Key Summary Points

Internal construct validity analyses further elucidate a survey's value. A key aspect of psychometric validation is testing a priori hypotheses. Conducting analyses, based on a priori hypotheses, and assessing whether the measure matches these, provides confidence that the measure is capturing what it is intended to capture.

Idiopathic multicentric Castleman disease (iMCD) is a rare disease with an incidence of 3.1–3.4 cases per million in the USA. The initial iMCD survey was designed to gather information on the symptom burden imposed on patients and caregivers.

Three hypothesis sets were explored and of these it was determined that, as reported by patients, the number of symptoms impacted the daily lives of patients.

Small patient numbers hindered the appropriate testing of the hypotheses, a common issue with rare diseases. Therefore, it cannot be definitively concluded that the unmet hypotheses were incorrect, but rather may be due to other factors such as the sample size which hindered the testing of these for statistical significance.

These analyses will guide the development of an iMCD-specific symptom burden patient-reported outcome measure (PROM).

INTRODUCTION

Idiopathic multicentric Castleman disease (iMCD) is a rare lymphoproliferative disorder characterized by a cytokine-driven chronic hyperinflammatory state and is usually associated with a high prevalence of morbidities, high symptom burden, and, in severe cases, multiorgan failure and death [1–5]. Symptomatology in patients with iMCD can be improved with interleukin-6 (IL-6)-directed therapy as evidenced in a phase 2 randomized controlled trial (RCT), where patients with MCD treated with siltuximab compared to placebo-treated group reported significant durable improvement in several symptom domains such as physical health, mental health, emotional health, pain, and vitality [6, 7]. Despite RCT data and contrary to the international evidence-based treatment guidelines that recommend siltuximab as first-line therapy in iMCD, population-level analyses of treatment patterns in the USA show a disturbing trend [7–9]. A high proportion of patients with iMCD (>50%) were either managed with a watch-and-wait strategy or did not receive the recommended IL-6-directed therapy [8, 9]. One of several plausible explanations for this observation is the incomplete understanding of iMCD symptomatology and its natural history.

Our recently completed international iMCD patient survey demonstrated a high symptom burden with varied symptomatology in these patients that was previously unrecognized and unappreciated [3]. Additionally, we showed the debilitating effect of the high symptom burden on several aspects of patient's daily life encompassing physical health, mental health, social well-being, financial well-being, sexual functioning, and work/employment [3]. Considering the chronicity and multiplicity of iMCD symptoms, lack of curative options, and demonstrated symptom benefit with IL-6-directed therapy [6], it is important to consider improvement in patient-reported health-related quality of life (HRQoL) as an important endpoint in iMCD management. Despite the high symptomatology and its adverse global impact on daily life, there exists no standardized disease-specific instruments to measure symptom burden in patients with iMCD. As a result of the fluctuating nature of patients' symptoms and unpredictable clinical trajectory, having an iMCD-specific symptom burden scale as a patient-reported outcome measure (PROM) will enable better monitoring of disease features for timely intervention. Accumulating evidence indicates that routine PROM collection and analysis in rare diseases improves patient-centered care [10, 11]. Condition-specific PROMs can provide sensitive measurements of dynamic changes in health status including disease severity, response to treatment, or treatment toxicities [12]. The European Medicines Agency and the US Food and Drug Administration recognize and require that for a condition-specific PROM to have content validity, it needs to have input from stakeholders with experience living or managing the condition [12–15]. PROMs can be used in clinical trials and daily practice and can assist with the development of value-based assessments required by health technology assessment (HTA) authorities.

Following survey completion, exploratory analyses were designed to better understand the survey's psychometric properties. The primary objective of these analyses was to assess prespecified hypotheses generated through external clinical and patient consultation to explore internal construct validity of the patient-reported iMCD symptom burden survey. We focused on internal construct validity given that no gold standard iMCD measure exists for external construct validation. The psychometric analyses focused on a priori hypothesized relationships between symptoms (specific combinations) or number of symptoms and patient-reported effects on daily life from such symptoms, and additionally, overall impact of treatment on patient-reported effect of iMCD on daily life.

METHODS

iMCD Burden of Illness Patient Survey: Data Source and Collection

These analyses are based on responses to the "International Survey to Elicit the Burden of Illness of Idiopathic Multicentric Castleman Disease—Patient Survey" [3], and permission for use of this data has been granted by the funder and the researchers. The online survey conducted between 14 April 2021 and 8 November 2021 was administered to patients with iMCD registered with the Castleman Disease Collaborative Network (CDCN), a USA-based organization which, among other objectives, aims to support patients with Castleman Disease (CD) worldwide. This survey included patients registered with the CDCN and residing in Australia, Canada, UK, and USA (see Fig. 1). Patients were recruited via the CDCN using a variety of methods including postings on the CDCN website, communication via the CDCN social media (Facebook), and direct mailing to CDCN patient-members. There were no specific recruiting sites or investigators involved in direct recruitment in any of the countries. This was a non-targeted dissemination of the survey through CDCN and recruitment was primarily based on voluntary participation of the patients and caregivers provided they met the eligibility criteria and signed the consent form. In preparing to conduct the Symptom Burden Study, a non-therapeutic, non-interventional online survey, the researchers followed advice and guidance on ethics approval from each country where

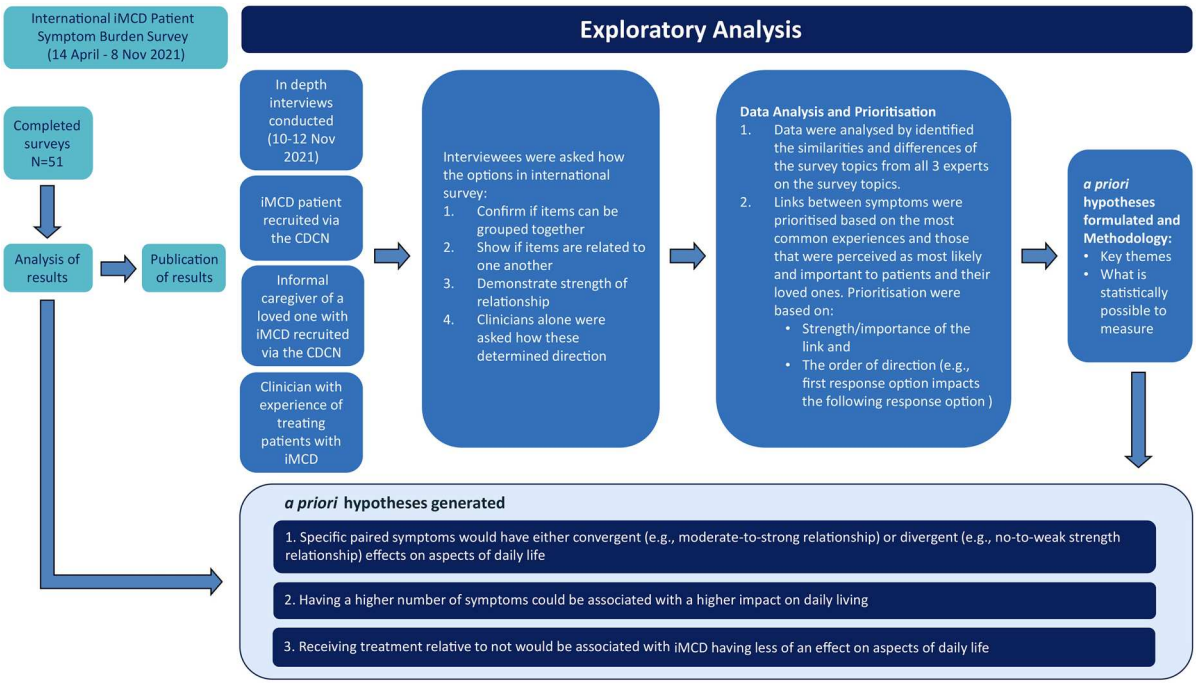

Fig. 1 Hypothesis generation process. *CDCN* Castleman Disease Collaborative Network, *iMCD* idiopathic multicentric Castleman's disease

it was anticipated that the participants would reside. We undertook this research following the WMA Declaration of Helsinki. All patients were recruited from the Castleman Disease Collborative Network (CDCN, based in the USA) via communication to their members, who reside all over the world. The advertisement of this survey was limited to CDCN members only, irrespective of their resident country, but the participation was limited to four English-speaking countries. These countries were Australia, Canada, the UK, and the USA given similarities in the consent and approval process, proportional representation of patients with iMCD from these countries in the CDCN, and the likelihood of recruiting an adequate number of respondents. Approval was granted by the following Ethics Committees: Advarra for Canada: Pro00049277 granted 4/04/2021; Australia: Bellberry 2021–05-507, 26/07/2021. Guided by Advarra it was concluded (and communicated to BresMed) that the study met the US criteria (at the time of submission) for exemption from ethics approval/IRB oversight. To assess the need for ethics approvial in the UK, the online NHS portal assessment questions were complemented and it was determined that ethics approval was not required. Therefore waivers were obtained for England, Wales, Scotland, and Northern Ireland. Of note, there were no designated clinical sites, centres, nor investigators in any of the four countries for direct recruitment of the study patients as it was an international online survey and recruitment of all patients was done via the CDCN. Informed consent was obtained from all individual participants included in the study before they could participate in the online survey. Study participants were able to withdraw from the study at any point. Consent to publish was obtained from all individual participants included in the study.

Eligibility criteria included English-speaking patients aged ≥ 18 years with a self-reported healthcare practitioner-confirmed iMCD diagnosis. Patients enrolled in a clinical trial 6 months prior to the survey were excluded. Written consent was obtained from all respondents before they were permitted to participate in the survey.

The survey methodology including the development of the questionnaire, its validation, and administration have been extensively elucidated elsewhere [3]. Patients were asked what symptoms they had experienced over the past week and the severity impact of symptoms was explored on several domains of daily life which included pain/discomfort, mobility, diet, sexual functioning, emotional and psychological well-being, work/education, social life, general routine, personal relationships, financial well-being, and ability to travel. Questions related to patient-reported effects on daily life (e.g., due to symptoms or treatment) were assigned a Likert, ordinal scale numerical value from 0 to 4 for the following severity categories: 0, does not affect my daily life; 1, slightly affects my daily life; 2, moderately affects my daily life; 3, severely affects my daily life; 4, very severely affects my daily life. A higher number on the ordinal scale suggested worse severity in terms of patient-reported effect on daily life. An overview of the survey's sections and specific questions and associated responses used for the psychometric analyses are provided in the Supplementary Appendix (SA)-S1.

Hypotheses

These exploratory analyses are used to investigate the strength of the relationships between patient-reported symptoms and their perceived impact on daily life. A priori hypotheses were generated on the basis of an IMCD clinician's expert opinion, one patient with iMCD, and one informal caregiver representative via in-depth interviews conducted between 10 and 12 November 2021 (Fig. 1). The interviews explored whether specific questions and response options could be grouped together as potentially related, e.g., if responses to one item would be related to responses on another item. For the interviews, a hypothesis inferring a positive relationship with a strong strength of relationship was posed, e.g., "if tiredness has a big impact on daily life for patients with iMCD, then so would physical weakness", alongside which the responder would suggest if they thought this positive relationship would be of strong, weak, or no strength; this example relationship between tiredness and physical weakness was suggested to be strong. Hypothesized relationships were prioritized on the basis of the most common experiences and those that were perceived as most likely and important to patients and their caregiver, as well as those noted to be the strongest by the clinical expert; these hypotheses were subsequently grouped into three hypotheses sets.

Hypotheses Set 1 (HS-1): Specific Paired Symptoms' Related Patient-Reported Effect on Daily Life

It was hypothesized that specific paired symptoms would have either convergent (e.g., strength of relationship moderate to strong) or discriminant (strength of relationship none to weak) relationship with patient-reported effects on aspects of daily life (see Symptoms Q13 in SA-S1).

Three positive convergent relationships were hypothesized to exist, i.e., one symptom's negative patient-reported effect on daily life would be related to the other symptoms' negative patient-reported effect on daily life (SA-Fig. S1):

- C1. Tiredness and weakness (physical).
- C2. Tiredness and impaired cognitive function.
- C3. Loss of appetite and weight loss.

Six discriminant relationships were hypothesized to exist (SA-Fig. S2):

- D1. Dizziness and impaired cognitive function.
- D2. Dizziness and loss of appetite.
- D3. Dizziness and tiredness.
- D4. Depression and tiredness.
- D5. Loss of appetite and anxiety.
- D6 Loss of appetite and weight loss.

Hypotheses Set 2 (HS-2): Number of Symptoms and Patient-Reported Effect of Symptoms on Aspects of Daily Life

It was hypothesized that having a greater number of symptoms (Symptoms Q12, SA-S1) would have a positive convergent relationship with worse severity in terms of patient-reported impact of overall symptoms on specific aspects of daily life (i.e., Symptoms Q15, SA-Fig. S3).

Hypotheses Set 3 (HS-3): Receiving iMCD Treatment or Not and Patient-Reported Effect of Treatment on Aspects of Daily Life

It was hypothesized that receiving treatment for iMCD [intravenous, oral, both oral and intravenous, or just for symptom management] (Treatment Q19, SA-S1) would be associated with less of a patient-reported effect of iMCD on aspects of daily living compared to those not on treatment (Impact of iMCD on your daily life Q33; SA-Fig. S4).

Statistical Analyses

The analyses include all observed cases from the cohort ($N=51$); whilst, the analytical sample size (n) varies dependent on the analysis being performed with relevant n values presented in the result tables. Construct validity assesses how well a measure represents the construct it was designed to represent whereby our construct of interest is iMCD burden, particularly in relation to patient-reported effect on aspects of daily life. We assessed internal construct validity (i.e., utilizing responses to different questions within the same questionnaire) in relation to internal convergent, discriminant, and known-group validity. All analyses were conducted in Stata 17.

Convergent and discriminant validity assesses the strength and direction of relationship between questions, based here on correlation analyses. Convergent validity here refers to the extent to which responses on a test or instrument exhibit a moderate to strong relationship with responses on conceptually similar tests or instruments. In contrast, discriminant validity here refers to the degree to which a test or measure has a weak to no correlation with another measure, whose underlying construct is conceptually unrelated. Given that the severity rating options common across hypotheses are considered categorical and ordinal, Spearman's rank absolute correlation strength (ACS) and associated p value are used to indicate the degree to which questions are measuring related (i.e., convergent as for HS-1 and HS-2) or unrelated (i.e., discriminant for HS-1) factors. Correlation strength is described on the basis of Cohen's ACS cutoffs: weak, <0.3; moderate, $0.3<0.5$; strong, ≥ 0.5. On the basis of these ACS values:

- Convergent validity is suggested to be supported when there is an estimated moderate to strong and statistically significant relationship: ACS ≥ 0.3 and p value <0.05.
- Discriminant validity is suggested to be supported when there is an estimated weak to no relationship which need not be statistically significant: ACS <0.3.

Known-group validity assesses the extent to which question scores differ between groups that are expected to differ, i.e., between treatment and no treatment groups for HS-3. Known-group differences are quantified using Cohen's d standardized absolute effect sizes (AES; i.e., the difference in mean scores between the two subgroups divided by the standard deviation of the score for the no treatment group), where AES are defined as trivial, <0.2; small, $0.2<0.5$; medium, $0.5<0.8$; large, ≥ 0.8. A positive effect size suggests the mean value of the no treatment group is higher than the treatment group (i.e., a more severe score); a negative effect size suggests the mean value of the treatment group is higher than the no treatment group. The p value is based on the Wilcoxon–Mann–Whitney test as a non-parametric test for statistical significance between independent sample distributions when assuming the data is at least ordinal. On the basis of these AES values, the known-group validity is suggested to be supported when there is an estimated medium

Table 1 Descriptive statistics of patient cohort

Demographic value	Patient sample
Number of people, *N*	51
Female, *N* (%)	29 (56.9%)
Age-related factors, mean (SD, min–max), years	
Age at the time of survey	47.4 (11.9, 22–78)
Age experienced first symptoms	41.3 (12.8, 14–76)
Age at the time of diagnosis of iMCD	41.3 (11.9, 17–67)
Country, *N* (%)	
Australia	4 (7.8%)
Canada	4 (7.8%)
UK	3 (5.9%)
USA	40 (78.4%)
Ethnic group, *N* (%)	
Asian	7 (13.7%)
Black or African American	1 (2.0%)
Native Hawaiian or Other Pacific Islander	2 (3.9%)
White	38 (74.5%)
Prefer not to answer	3 (5.9%)
Employment status, *N* (%)	
Disabled	13 (25.5%)
Employed full time	21 (41.2%)
Employed part time	4 (7.8%)
Homemaker	3 (5.9%)
Retired	3 (5.9%)
Unemployed/seeking opportunities	6 (11.8%)
Prefer not to say	1 (2.0%)
Subtype, *n* (%)	
iMCD NOS	40 (78.4%)
TAFRO	11 (21.6%)

Table 1 continued

Demographic value	Patient sample
Treatment for iMCD, *N* (%)	
Not receiving treatment	8 (15.7%)
Patients receiving treatment	39 (79.5%)
Both IV and oral treatment	13 (25.5%)
IV treatment only	23 (45.1%)
Treatment for iMCD symptoms, not iMCD itself	3 (5.9%)
Missing data	4 (7.8%)
Number of symptoms, mean (SD, IQR, min–max)	6.7 (4.9, 2–9, 0–20)

iMCD idiopathic multicentric Castleman's disease; *iMCD NOS* idiopathic multicentric Castleman's disease not otherwise specified; *IQR* interquartile range; *SD* standard deviation; *TAFRO* thrombocytopenia, anasarca, fever, bone marrow reticulin fibrosis or renal dysfunction and organomegaly

Source: Adapted with permission and based on Table 1 in [3]

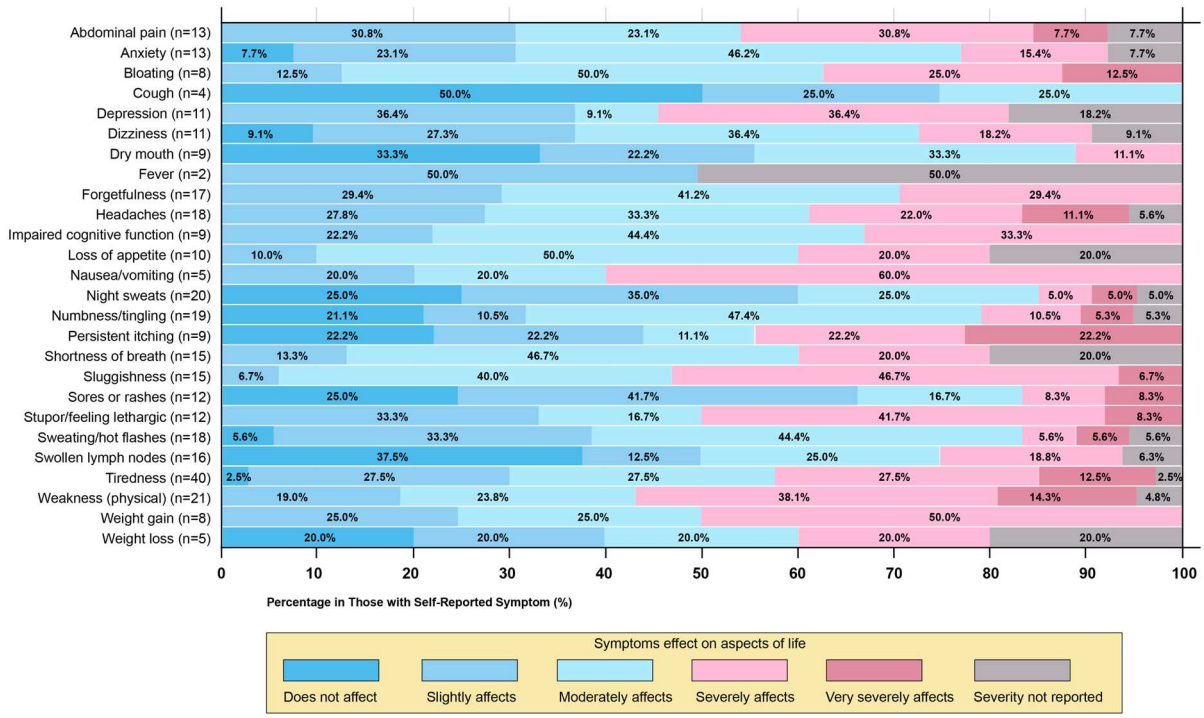

Fig. 2 Patient-reported severity of symptom effect on daily life. Sample size of symptoms corresponds to the number of patients who reported experiencing the relevant symptom 1 week prior to completing the survey. Source: Adapted with permission and based on Fig. 2 in [3]

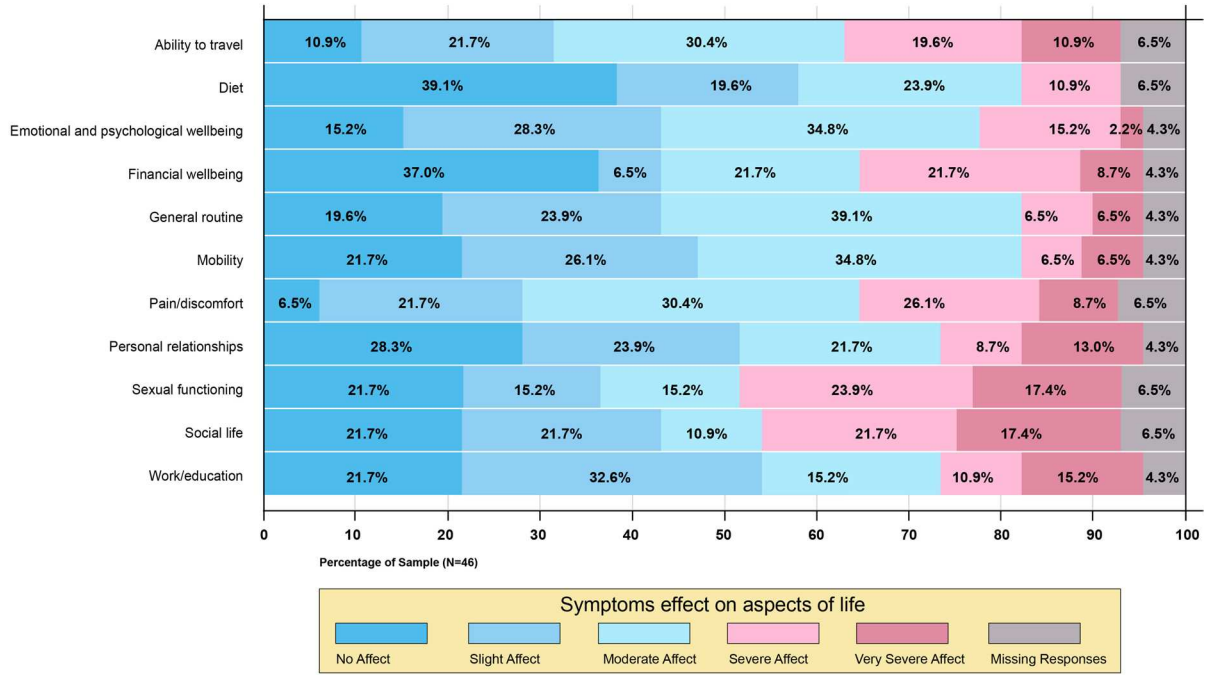

Fig. 3 Patient-reported symptom effect on aspects of life. Sample size of $N = 46$ accounts for only those patients who reported experiencing symptoms, with five patients having reported not experiencing any iMCD symptoms. Source: Adapted with permission and based on Fig. 4 in [3]

to large effect size with a statistically significant difference between groups' score distributions: AES ≥ 0.5 and p value < 0.05.

RESULTS

Symptom Burden and Its Patient-Reported Impact on Daily Life

Table 1 shows the demographics, disease subtypes, and treatment information of the patients with iMCD who participated in the international online survey. Of the 51 respondents, the majority were female (56.9%), from the USA (78.4%), and of white ethnicity (74.5%). A total of 27 unique symptoms were self-reported by patients with iMCD and the mean number of symptoms experienced by a patient was 6–7 (range 0–22) [3]. Approximately 70% of patients with iMCD reported having ≥ 4 symptoms, with a third reporting ≥ 10 symptoms [3]. The most frequently reported symptoms were tiredness (78.4%), weakness (41.2%), night sweats (39.2%), and numbness/tingling (37.3%) (SA-Fig. S5). Other identified symptoms affecting patients with iMCD included abdominal pain (25.5%), anxiety (25.5%), depression (21.6%), dizziness (21.6%), forgetfulness (33.3%), headaches (35.3%), shortness of breath (29.4%), rash (23.5%), lethargy (23.5%), sweating (35.3%), and palpable lymph nodes (31.4%). Although not all patients experienced every symptom, patients in general reported experiencing multiple distinct symptom types. At the time of survey, 36 patients (70.6%) reported receiving iMCD-directed treatment: 45.1% received an intravenous treatment and 25.5% received a combination of intravenous and oral treatment.

The symptoms with at least moderate or higher (severe to very severe) patient-reported impact on daily life and affecting at least 70% of the patients with iMCD included sluggishness

Table 2 Convergent and discriminant validity between paired symptoms and their reported effect on daily life

Pairing	Paired symptoms		*n* (%*N*)	Symptom severity[a] Mean (SD)		Correlation coefficient[b]	*p* value	Supports hypothesis?
	Symptom 1	Symptom 2		Symptom 1	Symptom 2			
Convergent validity (ACS ≥ 0.3, $p < 0.05$)								
C1	Tiredness	Weakness (physical)	19 (37.3%)	2.63 (0.83)	2.47 (1.02)	0.37*	0.115	No
C2	Tiredness	Impaired cognitive function	9 (17.6%)	2.67 (0.87)	2.11 (0.78)	− 0.50*	0.175	No
C3	Loss of appetite	Weight loss	4 (7.8%)	2.00 (0.82)	1.50 (1.29)	0.63*	0.368	No
Discriminant validity (ACS < 0.3)								
D1	Dizziness	Impaired cognitive function	4 (7.8%)	2.00 (1.41)	2.75 (0.50)	0.27	0.728	Yes
D2	Loss of appetite	Dizziness	4 (7.8%)	2.00 (0.00)	2.00 (0.00)	0.00	N/A[c]	Omitted[c]
D3	Tiredness	Dizziness	9 (17.6%)	2.44 (0.88)	1.67 (1.00)	0.14	0.714	Yes
D4	Tiredness	Depression	9 (17.6%)	2.33 (0.87)	2.00 (1.00)	0.56*	0.120	No
D5	Anxiety	Loss of appetite	3 (5.9%)	1.67 (1.53)	2.33 (0.58)	0.87*	0.333	No
D6	Depression	Loss of appetite	2 (3.9%)	2.50 (0.71)	2.50 (0.71)	1.00*	N/A[c]	Omitted[c]

ACS absolute correlation strength (i.e., when ignoring the positive or negative correlation sign)

*ACS ≥ 0.3 signifies a moderate to strong relationship, with a statistically significant relationship defined as a *p* value < 0.05

[a]"Symptom severity" is "symptom effect on daily life" as perceived by the patient and is based on question 13: "Please rate how the symptoms you currently experience affect your daily life". Please note, symptom severity is based on a Likert scale from 0 (Does not affect my daily life) to 4 (Very severely affects my daily life); therefore, a higher mean number means worse severity on average

[b]Spearman's rank correlation coefficient strength defined on the basis of Cohen's ACS cutoffs: weak, < 0.3; moderate, 0.3 < 0.5; strong, ≥ 0.5. Convergent validity is suggested to be supported when there is an estimated moderate to strong and statistically significant relationship: ACS ≥ 0.3 and *p* value < 0.05; Discriminant validity is suggested to be supported when there is an estimated weak to no relationship which need not be statistically significant: ACS < 0.3

[c]Pairings D2 and D6 have perfect correlation; this is potentially due to the small sample

(93.3%), bloating (87.5%), nausea/vomiting (80.0%), impaired cognitive function (77.8%), physical weakness (76.2%), weight gain (75.0%), forgetfulness (70.6%), and loss of appetite (70.0%) (Fig. 2).

Of the 11 specific aspects of daily life explored in the survey, moderate to very severe patient-reported impact on daily life was reported by > 50% of patients with iMCD on their pain/discomfort (65.2%), ability to travel (60.9%), sexual function (56.5%), emotional/psychological well-being (52.2%), financial well-being (52.2%), general routine (52.2%), and social life (50.0%) (Fig. 3).

Table 3 Convergent validity between number of symptoms and overall symptoms effect on specific aspects of life

Aspects of life	*n* (%*N*)	Number of symptoms[a] Mean (SD)	Symptom severity[b] Mean (SD)	Correlation coefficient[c]	*p* value	Supports hypothesis?
Pain/discomfort	43 (84.3%)	6.84 (4.74)	2.09 (1.09)	0.52*	< 0.001*	Yes
Mobility	44 (86.3%)	6.95 (4.75)	1.48 (1.13)	0.53*	< 0.001*	Yes
Diet	43 (84.3%)	6.98 (4.80)	1.07 (1.08)	0.57*	< 0.001*	Yes
Sexual functioning	43 (84.3%)	7.02 (4.78)	2.00 (1.46)	0.50*	< 0.001*	Yes
Emotional and psychological well-being	44 (86.3%)	6.95 (4.75)	1.59 (1.02)	0.60*	< 0.001*	Yes
Work/education	44 (86.3%)	6.95 (4.75)	1.64 (1.38)	0.42*	0.005*	Yes
Social life	43 (84.3%)	6.98 (4.80)	1.91 (1.48)	0.67*	< 0.001*	Yes
General routine	44 (86.3%)	6.95 (4.75)	1.55 (1.11)	0.65*	< 0.001*	Yes
Personal relationships	44 (86.3%)	6.95 (4.75)	1.52 (1.37)	0.55*	< 0.001*	Yes
Financial well-being	44 (86.3%)	6.95 (4.75)	1.57 (1.44)	0.54*	< 0.001*	Yes
Ability to travel	43 (84.3%)	6.98 (4.80)	1.98 (1.18)	0.52*	< 0.001*	Yes
Other	13 (25.5%)	6.69 (5.38)	0.92 (1.38)	0.57*	0.043*	Yes

ACS absolute correlation strength (i.e., when ignoring the positive or negative correlation sign)

*ACS ≥ 0.3 signifies a moderate to strong relationship, with a statistically significant relationship defined as a *p* value < 0.05

[a]Number of symptoms is based on the 26 pre-defined symptoms outlined in question 12: "Over the past week, what symptoms have you experienced that you attribute to your iMCD". The options of "no symptoms" or "other" are not included in the number of symptoms estimation

[b]"Symptom severity" is "overall symptoms effect on specific aspects of life" as perceived by the patient and is based on question 15: "How do the symptoms you attribute to your iMCD affect specific aspects of your life?" Please note, effect severity is based on a Likert scale from 0 (Does not affect my daily life) to 4 (Very severely affects my daily life); therefore, a higher mean number means worse severity on average

[c]Spearman's rank correlation coefficient strength defined on the basis of Cohen's ACS cutoffs: weak, < 0.3; moderate, 0.3 < 0.5; strong, ≥ 0.5. Convergent validity is suggested to be supported when there is an estimated moderate to strong and statistically significant relationship: ACS ≥ 0.3 and *p* value < 0.05; Discriminant validity is suggested to be supported when there is an estimated weak to no relationship which need not be statistically significant: ACS < 0.3

Internal Psychometric Validity Analyses

Hypotheses Set 1: Convergent and Discriminant Validity Between Paired iMCD Symptoms and Their Patient-Reported Effect on Daily Life

Table 2 presents HS-1 convergent and discriminant validity results, with the distribution of associated responses related to self-reported symptoms and patient-reported symptom effect on daily life as shown in Figs. 2 and 3. Related to convergent validity, none of our analyses supported our hypotheses: all ACS values were ≥ 0.3, but none were statistically significant.

Related to discriminant validity, D1 and D3 are supported by our analyses. Both D4

Table 4 Known-group validity between those receiving treatment or not and iMCD effect on daily life

Aspects of daily life	Total sample	*n* (%*N*)		Symptom severity, mean (SD)[b]		Cohen's *d*[c]	*p* value[d]	Supports hypothesis?
	n (%*N*)	Treatment[a]	No treatment[a]	Treatment	No treatment			
Pain/discomfort	45 (88.2%)	37 (82.2%)	8 (17.8%)	1.84 (1.09)	1.63 (1.60)	− 0.18	0.668	No
Mobility	45 (88.2%)	37 (82.2%)	8 (17.8%)	1.32 (0.94)	1.00 (1.20)	− 0.33	0.378	No
Diet	44 (86.3%)	37 (84.1%)	7 (15.9%)	0.73 (0.87)	0.86 (1.21)	0.14	0.915	No
Sexual functioning	44 (86.3%)	36 (81.8%)	8 (18.2%)	1.97 (1.63)	1.00 (1.07)	− 0.63*	0.141	No
Emotional and psychological well-being	43 (84.3%)	36 (83.7%)	7 (16.3%)	1.61 (1.18)	1.00 (1.00)	− 0.53*	0.173	No
Work/education	45 (88.2%)	37 (82.2%)	8 (17.8%)	1.84 (1.62)	1.13 (1.13)	− 0.46	0.292	No
Social life	45 (88.2%)	37 (82.2%)	8 (17.8%)	1.76 (1.40)	1.00 (0.93)	− 0.57*	0.190	No
General routine	45 (88.2%)	37 (82.2%)	8 (17.8%)	1.54 (1.12)	0.88 (0.99)	− 0.60*	0.103	No
Personal relationships	45 (88.2%)	37 (82.2%)	8 (17.8%)	1.46 (1.43)	0.88 (0.64)	− 0.44	0.431	No
Financial well-being	44 (86.3%)	36 (81.8%)	8 (18.2%)	1.53 (1.46)	1.13 (1.36)	− 0.28	0.477	No
Ability to travel	45 (88.2%)	37 (82.2%)	8 (17.8%)	1.89 (1.33)	1.25 (0.71)	− 0.51*	0.193	No
Other	11 (21.6%)	7 (63.6%)	4 (36.4%)	0.86 (1.57)	0.50 (1.00)	− 0.25	0.809	No

AES absolute effect size (i.e., based on Cohen's *d* but when ignoring the positive or negative effect size sign); *SD* standard deviation

*AES ≥ 0.5 denotes an effect size that is medium to large, with a statistically significant effect size defined as a *p* value < 0.05

[a]"Treatment" here is based on the combination of four groups from question 19: "I only receive intravenous (IV) treatment for my iMCD", "I only receive oral treatment for my iMCD", "I receive both IV and oral treatment for my iMCD", and "I only have treatment for my iMCD symptoms, not for iMCD itself". The "no treatment" group is based on question 19 response "I do not receive any treatment"

[b]"Symptom severity" is "iMCD effect currently on daily life" as perceived by the patient and is based on question 33: "How much of an effect does iMCD currently have on your daily life?" Please note, symptom severity is based on a Likert scale from 0 (Does not affect my daily life) to 4 (Very severely affects my daily life); therefore, a higher mean number means worse severity on average

[c]Cohen's *d* absolute effect size defined as: trivial, < 0.2; small, 0.2 < 0.5; medium, 0.5 < 0.8; large, ≥ 0.8

[d]*p* value based on Wilcoxon–Mann–Whitney non-parametric test for statistical significance between independent sample distributions when assuming the data is at least ordinal

and D5 indicated a stronger relationship than hypothesized, although these results were not statistically significant. Both D2 and D6 have been omitted from consideration because of an estimated perfect relationship (i.e., ACS = 1) or perfect "lack of a" relationship (i.e., ACS = 0), which could be due to the restricted variability in responses in a small sample size (i.e., D2, $n = 4$; D6, $n = 2$) artificially representing a perfect relationship relative to an actual perfect relationship.

Hypotheses Set 2: Convergent Validity Between Number of iMCD Symptoms and Overall Patient-Reported Effect on Daily Life

Table 3 presents HS-2 convergent validity results, with the distribution of responses related to symptoms' effects on aspects of daily life as shown in Figs. 2 and 3. With a mean between 6 and 7 self-reported symptoms in patients with iMCD, the ACS was > 0.3 for all 11 domains of daily life that were explored in this survey. Our analyses supported HS-2 with a positive,

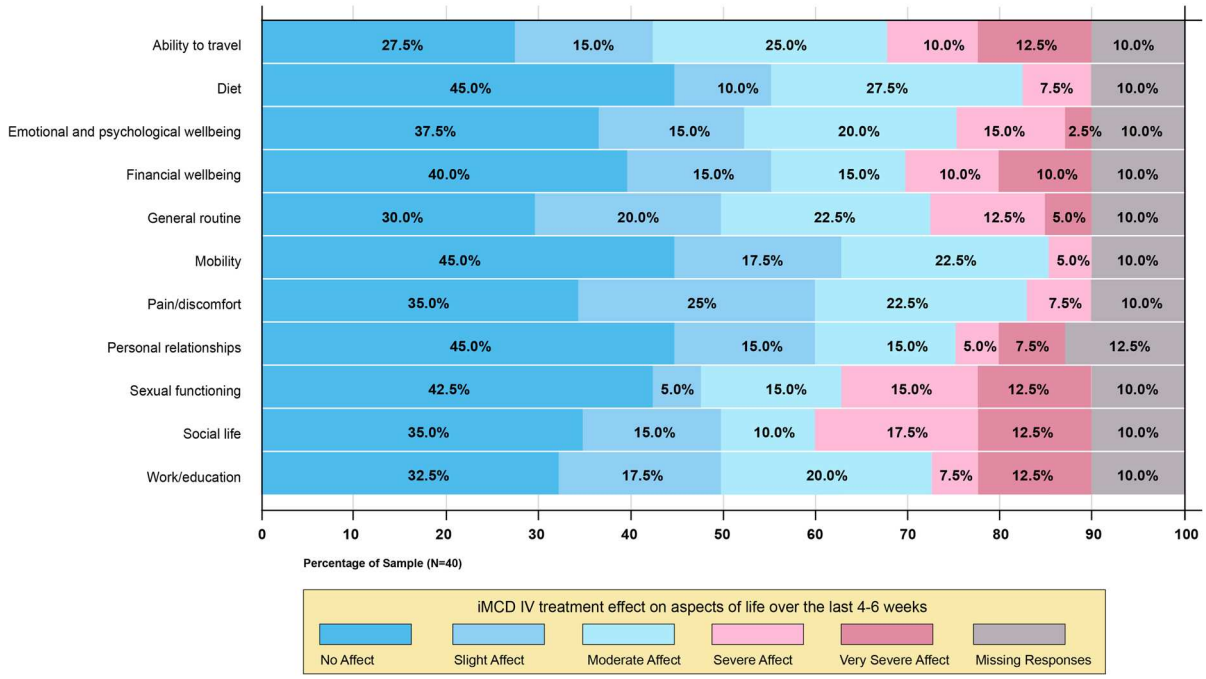

Fig. 4 Patient-reported iMCD treatment effect on aspects of life. Note: Sample size of $N = 40$ accounts for only those patients who reported receiving both IV and oral treatment for iMCD ($n = 13$), those receiving only intravenous (IV) treatment ($n = 23$), and those with missing data ($n = 4$). Patients not included in the figure are patients receiving no treatment ($n = 8$) and patients only receiving treatment for iMCD symptoms ($n = 3$). *iMCD* idiopathic multicentric Castleman disease

moderate to strong and statistically significant correlation estimated, i.e., a higher number of symptoms was associated with overall symptoms having a worse patient-reported effect on all aspects of daily life.

Hypotheses Set 3: Known-Group Validity Between Receiving iMCD Treatment (or Not) and Patient-Reported Effect of Treatment on Aspects of Daily Life

HS-3 known-group validity results (Table 4), with the distribution of responses related to iMCD's treatment patient-reported effects on aspects of daily life as shown in Fig. 4. Patient-reported aspects of daily life most impacted by treatment (moderately to very severely affected) were the patients' ability to travel (47.5%), sexual functioning (42.5%), general routine (40.0%), social life (40.0%), and work/education (40.0%). Across all aspects of daily life, except for diet, the treatment group had on an average a higher mean severity score than the no treatment group, indicating worse patient-reported iMCD effects on their daily life (opposite of what was hypothesized). Thus, our analyses do not support HS-3.

DISCUSSION

Our international iMCD patient survey assessed the range of symptoms experienced by patients with iMCD and evaluated the associated symptoms' relationship with patient-reported impact on their daily lives. In this study we conducted internal construct validity analyses to further elucidate the survey's value. Our goal was to incorporate the findings from the internal validity analyses to guide the development of an iMCD-specific symptom burden PROM; results were mixed in terms of support for the three prespecified hypotheses. Overall, the exploratory psychometric analyses findings provide a level

of confidence in the internal construct validity of the patient survey and offer valuable insights, potential developments, and interpretation of estimates.

A key aspect of psychometric validation is testing a priori hypotheses. Conducting analyses using the measure, and having the results match our a priori hypotheses, provides us with confidence that the measure is capturing what it is intended to capture. This has added complications though, such as having large enough sample sizes to detect differences between groups and post hoc realizations why the a priori hypothesis might be incorrect, or we do not have appropriate data to test the hypothesis. Our analyses are particularly hindered by small sample sizes, so hypotheses like those associated with HS-1 could be correct, but we do not have the sample size to test these hypotheses for statistical significance. Similarly for HS-3, a post hoc realization was that our cross-sectional data is not appropriate to test the hypothesis. For our analyses we have chosen not to change or censor our hypotheses, as this would be inappropriate. The approach taken is to report the hypotheses and results, then discuss the implications to inform future studies and more appropriate data collection (e.g., larger samples where possible, and longitudinal data) to better assess these or similar hypotheses in the future. Overall, what we have shown is twofold: we have provided assurance in the measure based on specific hypotheses being tested and shown to be true with confidence (i.e., for HS-2), but we have also recognized the limitations of our data and provided suggestions for future research.

HS-1 was largely not supported by our analyses, other than for tiredness which most of the sample reported. The other symptoms were reported by a small minority (< 50%) and specific pairings of symptoms required a further reduction in the sample size (e.g., only two people reported having both the symptom of depression and loss of appetite). Therefore, HS-1-associated analyses estimates need to be interpreted with caution given the small sample sizes for these specific analyses within a rare disease study already hindered by a naturally small population size. For the convergent relationships, another consideration was that although the links between symptoms explored were done in conjunction with patients, caregivers, and clinicians, there is paucity of literature to support the relationships explored (with the exception of loss of appetite and weight loss) [16]. For the divergent (weak to no) relationships, the hypothesis was supported between dizziness (vestibular function) and lower cognitive function [17–19], and between tiredness and dizziness.

A key finding, supporting HS-2, was the identification of a strong correlation between having a higher number of iMCD symptoms and worsening severity in patient-reported symptom burden on aspects of daily life. This finding highlights the need to integrate objective symptom assessment along with normalization of laboratory parameters and radiologic improvement for best assessment of treatment response to IL-6-directed therapy. This is supported by the findings of our iMCD symptom burden survey where a high proportion (approx. 80%) of patients, despite being on IL-6-directed therapy (approx. 70%), continued to experience high symptom burden that adversely impacted their daily lives [3].

For HS-3, an interesting result from our exploratory analysis was that the mean severity scores of iMCD on patient-reported aspects of daily life was more severe on average for the treatment than no treatment group, which was the opposite of our hypothesis (statistical significance not reached). Hypothesizing post hoc, this finding could be the outcome of preferential selection of more severely affected patients for treatment, thereby introducing confounding which is not accounted for within our psychometric analyses. This is supported by real-world analysis of iMCD treatment patterns in the USA where "decision to treat" favored patients presenting with either high symptom burden or those who were diagnosed as inpatient, both clinical surrogates of high disease severity [8]. Additionally, it is plausible that a proportion of treated patients had not spent enough time on therapy to notice symptomatic improvement in their daily lives. Conversely, the patients in the no treatment group could represent those

patients who were not on active treatment at the time of survey administration because of several reasons including not having severe enough disease (watch and wait) or in remission from prior therapy among others. Identifying such factors was beyond the scope of the cross-sectional dataset and potentially confounds our analysis. Analysis of a hypothesis such as this would require using prospective dataset with data collection time points before and after treatment or with a (randomized or matched) control group over the same time period, perhaps using regression analyses or other causal models.

Where symptomatic improvement is the primary objective, findings from our psychometric analyses extend support to incorporating a PROM into iMCD clinical management that is symptom-centric to adequately capture disease severity and treatment response using repeated measurements, thereby allowing real-time monitoring and timely intervention. This is particularly important as for some of the more commonly reported symptoms in the survey such as impaired cognition, forgetfulness, tiredness or fatigue, weakness, and lethargy, there may not be readily discernible radiologic or laboratory correlations. For future research, our exploratory findings indicate that the iMCD survey adequately captured the patient-reported impact and severity of iMCD-related symptoms on several aspects of daily life, even though the comprehensiveness of the survey (e.g., all aspects of daily life which could be potentially affected) cannot be ascertained on the basis of quantitative analysis of naturally small iMCD patient sampling.

In conducting the study, we observed a lack of clarity in the regulatory and ethical guidance in conducting non-interventional social/behavioral international online research that can potentially stymie research studies such as this [20]. Greater harmonization in international ethics procedures is warranted given the ever-growing importance of PROMs [15].

The study's strength lies in generating valuable insights and internal construct validity evidence for the iMCD survey that informs our ongoing work to continue towards development of the first-ever iMCD-specific symptom burden PROM (ClinicalTrials.gov, NCT05995834). This study has several inherent limitations. Small sample sizes, a recurring theme in rare disease studies including iMCD, limit rigorous statistical analyses and therefore the results need to be interpreted with caution. As a result of the small cohort size that limits drawing any meaningful comparisons among all individual specific iMCD entities, we grouped these entities under one broad iMCD group in our analysis. Another limitation is the cross-sectional nature of this study which does not allow measurement of symptoms with regards to treatment response and therefore the disease-related symptoms cannot be discriminated from treatment toxicities. While it is not surprising that the study of any rare disease including iMCD presents challenges due to difficulty in accruing sample sizes that are adequately powered to draw meaningful conclusions, this study brought forth an underappreciated challenge.

CONCLUSION

These internal construct validity analyses provide initial support for the bespoke iMCD patient survey and will guide additional work towards the development of the first iMCD-specific symptom burden PROM.

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Data Availability. The supplement to this manuscript and published manuscript provides additional information. Additional information can be made available upon request. Data availability and secondary use: the data controller for the survey data is Lumanity. As such, access for secondary use of the anonymised data should be discussed with Lumanity and EUSA UK; however, such use may require regulatory and ethics approvals, and updated patient consent.

Declarations

Conflict of Interest. Sudipto Mukherjee has served on an advisory board for EUSA. Sudipto Mukherjee has not received any funding for his contribution for this study but receives funding support from Velosano 2020 Impact Award for Rare Cancers and Blood Diseases (Cleveland Clinic Taussig Cancer Institute). Matthew Franklin and John Brazier received funding from Lumanity (Ex BresMed); Emily Jones and Nicola Mason received funding from EUSA Pharma. Francis Shupo and Grace Wayi-Wayi are employees of EUSA Pharma. Natasa Zibelnik was an employee of EUSA Pharma but is now employed by the Menarini Group.

Ethical Approval. In preparing to conduct the Symptom Burden Study, a non-therapeutic, non-interventional online survey, the researchers followed advice and guidance on ethics approval from each country where it was anticipated that the participants would reside. We undertook this research following the WMA Declaration of Helsinki. All patients were recruited from the Castleman Disease Collborative Network (CDCN, based in the USA) via communication to their members, who reside all over the world. The advertisement of this survey was limited to CDCN members only, irrespective of their resident country, but the participation was limited to four English-speaking countries. These countries were Australia, Canada, the UK, and the USA given similarities in the consent and approval process, proportional representation of patients with iMCD from these countries in the CDCN, and the likelihood of recruiting an adequate number of respondents. Approval was granted by the following Ethics Committees: Advarra for Canada: Pro00049277 granted 4/04/2021; Australia: Bellberry 2021–05-507, 26/07/2021. Guided by Advarra it was concluded (and communicated to BresMed) that the study met the US criteria (at the time of submission) for exemption from ethics approval/IRB oversight. To assess the need for ethics approval in the UK, the online NHS portal assessment questions were complemented and it was determined that ethics approval was not required. Therefore waivers were obtained for England, Wales, Scotland, and Northern Ireland. Of note, there were no designated clinical sites, centres, nor investigators in any of the four countries for direct

recruitment of the study patients as it was an international online survey and recruitment of all patients was done via the CDCN. Informed consent was obtained from all individual participants included in the study before they could participate in the online survey. Study participants were able to withdraw from the study at any point. Consent to publish was obtained from all individual participants included in the study.

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