AN EXPLORATORY INTERNAL PSYCHOMETRIC VALIDATION OF A BURDEN OF ILLNESS INTERNATIONAL SURVEY FOR IDIOPATHIC MULTICENTRIC CASTLEMAN DISEASE

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Background

Idiopathic Multicentric Castleman disease (iMCD) is a subcategory of MCD, a rare lymphoproliferative disorder characterized by enlargement of the lymph nodes and lymphatic system. In a recent international survey involving iMCD patients, we identified substantial symptom burden owing to (or as a result of/resulting from) the wide of array of symptoms resulting in significant impact on various aspects of patients' daily lives. Currently, there is no established method for evaluating this symptom burden in this specific patient population. The development of an iMCD-specific symptom burden scale is essential to enable disease monitoring and management as well as it use in clinical trials.

To advance our goal of creating such a scale, we conducted an exploratory internal analysis of the symptoms identified and the patient-reported impact on their daily activities. This analysis aims to assess the psychometric properties of the survey, evaluating its adequacy, relevance, and utility in gauging the symptom burden experienced by iMCD patients.

In addition, this analysis aimed to assess the performance of certain pre-specified hypotheses, generated from external clinical and patient experts, against the psychometric properties of the survey with respect to its construct validity.

Methods

The iterative process of survey development has been described in a previous publication.[1] The survey was administered to adult iMCD patients in Australia, Canada, the UK and the US from April to November 2021, and registered with the Castleman Disease Collaborative Network (CDCN).

Questions related to patient-reported effect on daily life (e.g., due to symptoms or treatment) were assigned a Likert scale numerical value; in this case values were assigned on an ordinal scale 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 related to worse severity in terms of patient-reported effect on daily life.

Hypotheses (HS) were generated through collaboration between an iMCD clinician, a patient, and an informal caregiver representative via in-depth interviews (Fig. 1). The interviews explored whether questions and response options could be grouped together as the same or related to one another (e.g., responses to one item relating to responses on another item with a weak, moderate or strong association and the direction of that association).

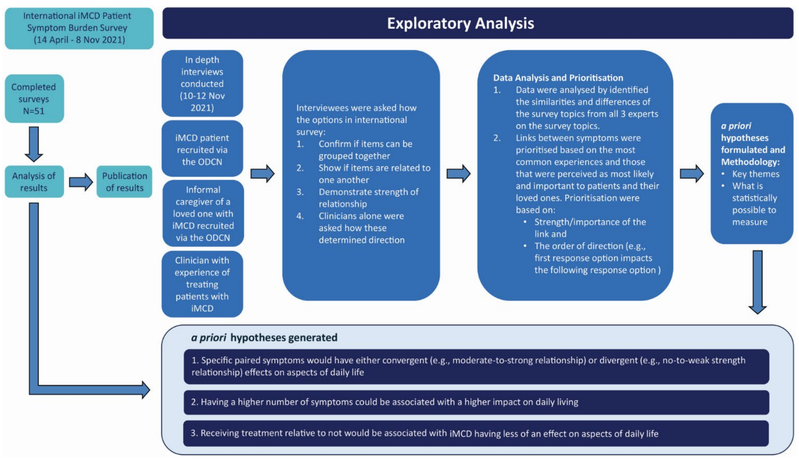
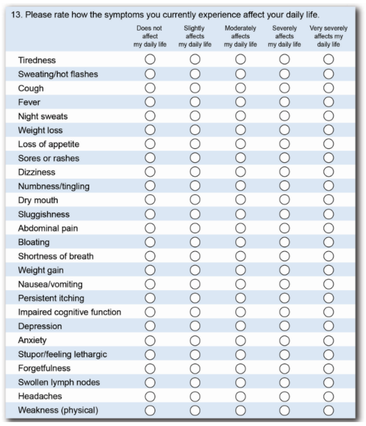


Fig. 1: Hypothesis Generation Process
CDCN: Castleman Disease Collaborative Network; iMCD: idiopathic Multicentric Castleman Disease

There were two parts to hypothesis set 1 (HS-1). HS-1 hypothesized that:
1. There were 3 positive convergent relationships (i.e., one symptom's negative patient-reported effect on daily life would be related to other symptoms' negative patient-reported effect on daily life).
2. There were 6 discriminant/divergent relationship (see Fig. 2). These were derived from symptoms prioritized based on the most common symptoms experienced and those links noted to be weakest by experts. Including where no link was perceived to exist.

Methods


13. Please rate how the symptoms you currently experience affect your daily life.

	Does not affect my daily life	Slightly affects my daily life	Moderately affects my daily life	Severely affects my daily life	Very severely affects my daily life
Tiredness	○	○	○	○	○
Sweating/hot flashes	○	○	○	○	○
Cough	○	○	○	○	○
Fever	○	○	○	○	○
Night sweats	○	○	○	○	○
Weight loss	○	○	○	○	○
Loss of appetite	○	○	○	○	○
Sores or rashes	○	○	○	○	○
Dizziness	○	○	○	○	○
Numbness/tingling	○	○	○	○	○
Dry mouth	○	○	○	○	○
Sluggishness	○	○	○	○	○
Abdominal pain	○	○	○	○	○
Bloating	○	○	○	○	○
Shortness of breath	○	○	○	○	○
Weight gain	○	○	○	○	○
Nausea/vomiting	○	○	○	○	○
Persistent itching	○	○	○	○	○
Impaired cognitive function	○	○	○	○	○
Depression	○	○	○	○	○
Anxiety	○	○	○	○	○
Stupor/feeling lethargic	○	○	○	○	○
Forgetfulness	○	○	○	○	○
Swollen lymph nodes	○	○	○	○	○
Headaches	○	○	○	○	○
Weakness (physical)	○	○	○	○	○

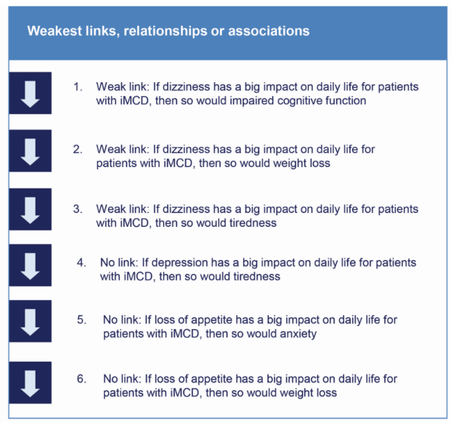
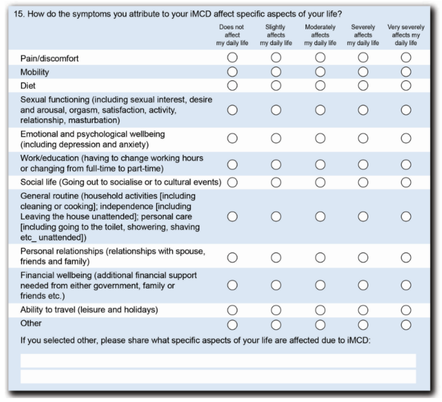


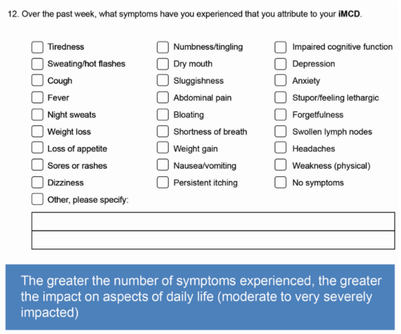
Fig. 2: Hypothesis set 1 – Divergent: specific paired symptoms' related patient-reported effect on daily life

Hypothesis set 2 (HS-2) hypothesized that having a greater number of symptoms has a negative convergent-relationship with how these symptoms are reported to affect daily life (Fig. 3). Hypothesis set 3 (HS-3) hypothesized that receiving treatment versus no treatment was associated with patients reporting less of a symptom burden on their daily life.


15. How do the symptoms you attribute to your iMCD affect specific aspects of your life?

	Does not affect my daily life	Slightly affects my daily life	Moderately affects my daily life	Severely affects my daily life	Very severely affects my daily life
Pain/discomfort	○	○	○	○	○
Mobility	○	○	○	○	○
Diet	○	○	○	○	○
Sexual functioning (including sexual interest, desire and arousal, orgasm, satisfaction, activity, relationship, masturbation)	○	○	○	○	○
Emotional and psychological wellbeing (including depression and anxiety)	○	○	○	○	○
Work/education (having to change working hours or changing from full-time to part-time)	○	○	○	○	○
Social life (Going out to socialise or to cultural events)	○	○	○	○	○
General routine (household activities [including cleaning or cooking]; independence [including Leaving the house unattended]; personal care [including going to the toilet, showering, shaving etc_ unattended])	○	○	○	○	○
Personal relationships (relationships with spouse, friends and family)	○	○	○	○	○
Financial wellbeing (additional financial support needed from either government, family or friends etc.)	○	○	○	○	○
Ability to travel (leisure and holidays)	○	○	○	○	○
Other	○	○	○	○	○

If you selected other, please share what specific aspects of your life are affected due to iMCD:


12. Over the past week, what symptoms have you experienced that you attribute to your **iMCD**.

- ☐ Tiredness
- ☐ Sweating/hot flashes
- ☐ Cough
- ☐ Fever
- ☐ Night sweats
- ☐ Weight loss
- ☐ Loss of appetite
- ☐ Sores or rashes
- ☐ Dizziness
- ☐ Numbness/tingling
- ☐ Dry mouth
- ☐ Sluggishness
- ☐ Abdominal pain
- ☐ Bloating
- ☐ Shortness of breath
- ☐ Weight gain
- ☐ Nausea/vomiting
- ☐ Persistent itching
- ☐ Impaired cognitive function
- ☐ Depression
- ☐ Anxiety
- ☐ Stupor/feeling lethargic
- ☐ Forgetfulness
- ☐ Swollen lymph nodes
- ☐ Headaches
- ☐ Weakness (physical)
- ☐ No symptoms
- ☐ Other, please specify:

The greater the number of symptoms experienced, the greater the impact on aspects of daily life (moderate to very severely impacted)

Fig. 3: Hypothesis set 3 - Number of symptoms and patient-reported effect of symptoms on aspects of daily life

Statistical Analysis

The analyses include all observed cases from the cohort (N=51); therefore, the observed case sample size (n) varies dependent on the analysis being performed with relevant n values presented in the result tables. All analyses were conducted in Stata 17. Spearman's rank absolute correlation strength (ACS) and associated p-value are used for HS-1 and HS-2. The strength of the correlation is described based on the ACS with a convergent validity statistically significant relationship defined by ACS ≥ 0.3 and p-value < 0.05 and discriminant defined by ACS < 0.3 (no need for statistical significance). For HS-3 Cohen's *d* was used to quantify standardized effect sizes for HS-3 with statistical significance determined by ACS>0.3 and p<0.05.

Results

Detailed participant characteristics have been published[1] and are shown in Poster 1 of this series. Fifty-one patients self-reported having clinician diagnosed iMCD.

Most patients (36/51; 70.6%) reported receiving iMCD-directed treatment and most of these reported receiving an anti-interleukin- 6 monoclonal antibody (31/36; 86.1%). The frequency of administration varied between once-a-week to once every six weeks.

A total of 27 unique symptoms were experienced by the 46 patients in the week prior to completing the survey; with 5 patients experienced no symptoms.

HS-1: In terms of convergent validity, none of the analyses supported the hypotheses; ACS for all relationships were higher than 0.3, but none were statistically significant. In terms of discriminant validity, two discriminant relationships (dizziness-impaired cognitive function and dizziness-tiredness; ACS<0.3) are supported by our analyses.

HS-2: Was supported by the analyses with a positive - moderate to strong relationship (p<0.01) i.e., a higher number of symptoms was associated with overall symptoms having a worse patient-reported effect on specific aspects of life (Table 1).

HS-3: Was not supported by the analysis.

Results

Table 1: 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] (*ACS > 0.3)	p-value (* < 0.05)	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 wellbeing	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 wellbeing	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).
Note: * ACS≥0.3 signifies a moderate to strong relationship, with a statistically significant relationship defined as a p-value < 0.05

Conclusions

The international iMCD survey[1] comprehensively assessed the range of symptoms experienced by iMCD patients and how patients reported these impacted their daily lives. This research provided exploratory internal construct validity analyses which, despites mixed results in term of support or not for the *a priori* hypotheses, provided useful and valuable insights for the survey and future research. The results for the analysis-supported aspects of the divergent HS-1 with two discriminant relationships (dizziness-impaired cognitive function and dizziness-tiredness; ACS<0.3). HS-2 supported the idea that treating iMCD associated symptoms could improve aspects of the patient's daily life.

An interesting outcome across all aspects of daily life (other than diet), is that patients in the 'treatment' group had on average worse patient-reported iMCD effects on their daily life; a somewhat paradoxical outcome. However, this finding could be the outcome of underlying treatment bias where the more severe patients were receiving treatment, thereby introducing confounding. When population-level analyses are considered showing iMCD treatment patterns in the US[2] this assumption is reasonable. In one such study, decisions to treat iMCD patients appear to be reserved for those presenting with either a high symptom burden or those who were diagnosed as inpatients; both clinical surrogates of disease severity.[2]

Limitations of this analysis across all hypotheses was the low sample sizes for each of the correlation analyses, and particularly in HS-1, impacting the generalizability and reliability of these results. Another limitation of this study is the presence of a potential confounding factor, where treatment may have functioned as a surrogate for disease severity; thereby questioning whether a regression-based longitudinal analysis rather than Cohen's *d* would have been a more reliable method of analysis.

These exploratory internal construct validity analyses provide support for the bespoke iMCD patient survey. It also highlighted where improvements can be made in the next phase of the research, the development of the iMCD disease burden scale (ISBUS: NCT05995834). This next phase incorporates methods that worked during the development of the survey, for example multistakeholder involvement, whilst being mindful of improvements that can be made, one being a larger sample size.

References:
[1] Mukherjee S, Shupo F, Wayi-Wayi G, et al. Symptom burden in patients with idiopathic multicentric Castleman disease and its impact on daily life: an international patient and caregiver survey. EClinicalMedicine. Oct 2023;64:102192. doi:10.1016/j.eclinm.2023.102192
[2] Cohen AB SA, Wang X, et al.,. Clinical characteristics, treatment patterns, and overall survival of real-world patients with idiopathic multicentric Castleman disease. *Journal of Clinical Oncology*. 2021;39(15)(7048)

Poster 2