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Understanding the experience of fatigue in adolescent and young adults with myeloproliferative neoplasms: a mixed methods study

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Abstract

Background: This study explores fatigue in adolescents and young adults (AYAs) diagnosed with myeloproliferative neoplasms (MPNs), a population facing unique developmental and psychosocial challenges. The objectives were to examine age-related differences in fatigue among patients with MPNs (QUAN), explore its manifestations, impact on daily life, and management among AYAs (QUAL), and integrate these findings to provide a comprehensive understanding of fatigue in this population (QUAN+QUAL).

Methods: A convergent mixed methods design was employed, integrating quantitative data from medical records, including fatigue scores from the Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score, with qualitative data gathered through semi-structured interviews with AYA patients.

Results: Quantitative analysis revealed that AYAs reported significantly higher fatigue levels than older adults (57 % vs. 43 %; $p = 0,027$). Moreover, fatigue was significantly associated with early satiety ($p = 0.0036$), inactivity ($p = 0.034$), and pruritus ($p = 0.014$), suggesting that targeted management of these symptoms may help alleviate fatigue in this population. In contrast, fatigue in older adults correlated broadly with all subitems, indicating its association with overall symptom burden rather than specific symptom clusters. Qualitative findings underscored fatigue as a multidimensional and pervasive symptom, frequently impairing AYAs' ability to work and engage in daily activities. Pharmacologic treatments, including those targeting MPN biomarkers, were commonly viewed as ineffective for managing fatigue. In contrast, regular physical activity emerged as the most beneficial strategy, often enhanced by structured sleep routines, healthy eating habits, and restorative napping.

Conclusion: These findings highlight the need for age-specific, non-pharmacological approaches to fatigue management in AYA patients with MPNs. Tailored interventions, particularly those promoting physical activity, may improve symptom control and overall quality of life in this understudied and vulnerable patient population.

Background

Myeloproliferative neoplasms (MPN) are chronic hematologic malignancies that classically include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (MF) [1,2]. The median age at diagnosis falls within the sixth decade of life, varying by MPN subtype [3]. While most cases occur in older adults, about 10% of patients are diagnosed before the age of 40 [4]. This younger cohort, referred to as adolescent and young adults (AYA), represents a distinct patient subset with reportedly less aggressive phenotypic, cytogenetic, and mutational profiles compared to older patients [4,5]. More indolent disease features and younger age systematically place AYA patients into lower MPN risk stratification groups [6,7]. This can lead to the mistaken assumption that younger age means milder symptoms, despite evidence showing that symptoms and quality of life (QoL) are independent of risk level [8]. This is particularly relevant in AYAs, where severe symptoms justify initiating therapy rather than opting for surveillance.

Given the chronic nature of MPNs, AYA patients face a lifelong burden of symptoms, compounded by longer life expectancy and ongoing exposure to disease- and treatment-related complications [9,10]. Fatigue is the most common and burdensome symptom, affecting 81–95% of patients regardless of MPN subtype [10–15] and is associated with impaired physical functioning, emotional well-being, social participation, and overall QoL [16]. The

pathophysiology of fatigue in MPNs is multifactorial and includes inflammatory cytokine dysregulation, impaired hematopoiesis, cachexia, physical deconditioning, thrombosis, hemorrhage, and microvascular dysfunction [17]. An international survey also identified several modifiable contributors to fatigue, including alcohol and tobacco use, medical comorbidities, medication use, and depressive symptoms, highlighting the need for a comprehensive, multidimensional management approach [18].

Despite the central role of fatigue in MPNs, most studies have evaluated patients across the entire adult age spectrum [16,18,19]. In a previous study, our group demonstrated that although overall Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) scores were similar between AYAs and older patients with PV and ET, AYAs exhibited distinct symptom patterns, including a higher prevalence of clinically significant fatigue [20]. However, little is known about how fatigue is experienced by AYAs, whose unique developmental stage and life challenges, including education, career development, relationships, family planning, and identity formation, may influence both the expression and impact of this symptom. Building on these findings, we conducted a mixed methods study to examine age-related differences in fatigue among patients with MPNs (QUAN), explore how fatigue is experienced by AYAs, including its manifestations, impact on daily life, and management strategies (QUAL), and integrate quantitative and qualitative findings to provide a comprehensive understanding of fatigue in the lives of AYA patients with MPNs (QUAN+QUAL).

Methods

Design

A concurrent mixed methods design [21] was used to integrate quantitative and qualitative data on fatigue in patients with MPNs (Figure 1). By integrating objective clinical assessments with patients' subjective experiences, this approach provided a more comprehensive understanding of the multidimensional nature of fatigue, capturing both its clinical manifestations and its psychosocial impact.

The study was approved by the Research Ethics Committee of the Montreal East Island Integrated University Health and Social Services Centre serving Maisonneuve-Rosemont Hospital (approval no. 2024-3457). All procedures complied with the Declaration of Helsinki and its subsequent amendments. Written informed consent was obtained from all participants prior to study participation. Participants were informed that participation was voluntary and that they could withdraw at any time without affecting their care.

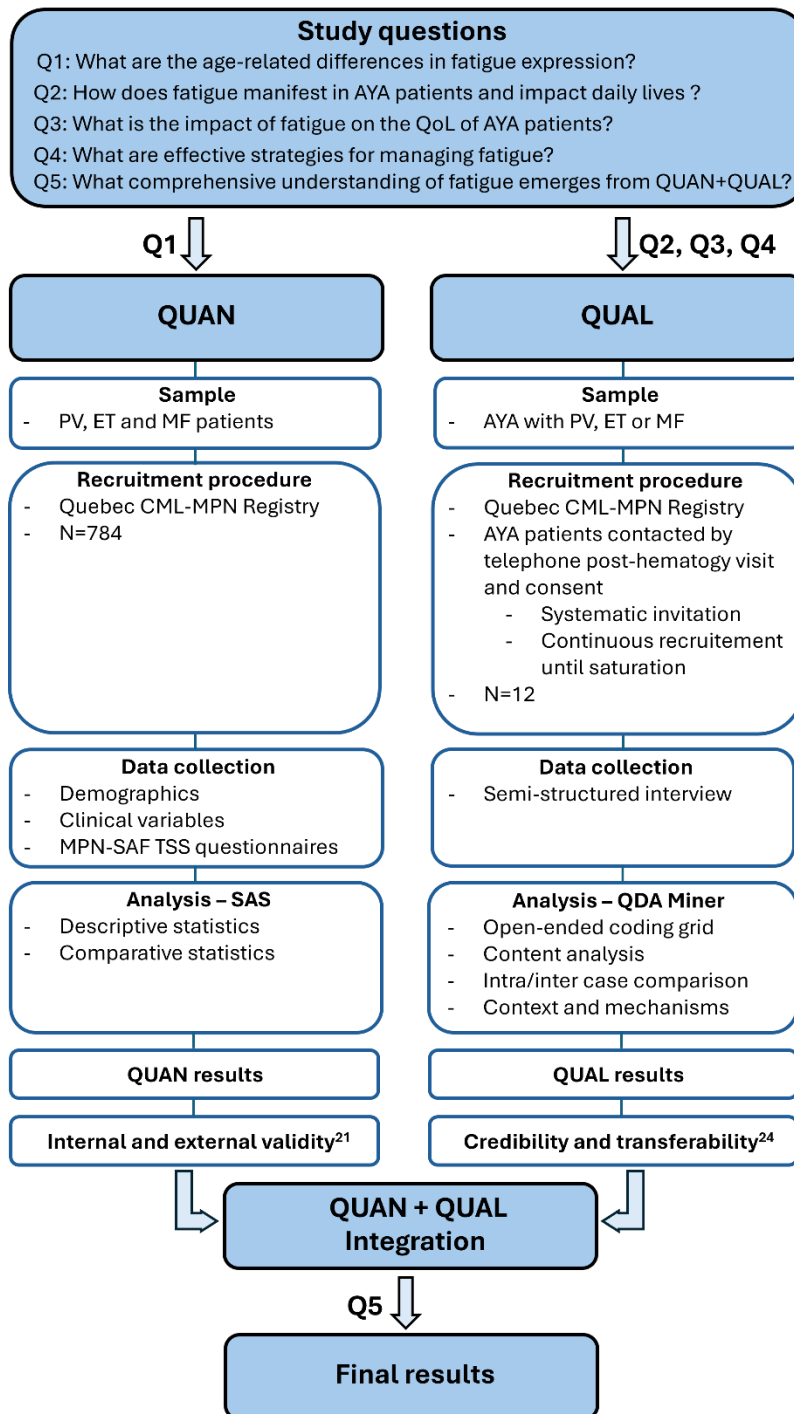


Figure 1: Study design: Multicenter prospective study using a parallel-concurrent mixed methods approach. Abbreviations: QUAN: quantitative data; QUAL: qualitative data; PV: Polycythemia vera; ET: Essential thrombocythemia; MF: Myelofibrosis; CML-MPN : Chronic Myeloid Leukemia and Myeloproliferative Neoplasm; AYA: adolescent and young adult. References [21, 24]

Quantitative data collection and analysis

Consecutive eligible patients diagnosed with PV, ET, or MF between August 1981 and June 2024, based on World Health Organization criteria [1] and enrolled in the Groupe québécois de recherche en LMC-NMP (GQR LMC-NMP) (Quebec CML-MPN research group), were included. The GQR LMC-NMP maintains a provincial MPN registry that includes patients from more than 20 academic and community centers across Quebec, with an estimated participation rate exceeding 90%. AYA patients were defined as those aged 18–40 years at diagnosis. Eligible patients were also required to have the capacity to provide written informed consent. Patients with a life expectancy of less than 3 months due to a medical condition unrelated to their MPN were excluded.

Registry data were collected prospectively and retrospectively and included demographic characteristics, medical history, lifestyle, medications, clinical variables, treatment, and treatment response. Fatigue and symptom burden were assessed using the MPN-SAF TSS, a validated (Cronbach's $\alpha = .83$) and highly reproducible instrument that measures the severity of 10 common MPN-related symptoms and correlates with QoL [9,10,22,23]. Patients rate each symptom from 0 (absent) to 10 (worst imaginable), yielding a total score ranging from 0 to 100. The questionnaire has been routinely administered in the GQR LMC-NMP registry since 2015, typically every six months, with some patients completing questionnaires more frequently.

Continuous variables are presented as means (range) or medians (range), as appropriate, whereas categorical variables are presented as frequencies. Group comparisons were performed using the Mann–Whitney U test or Kruskal-Wallis test for continuous variables and the χ^2 test for categorical variables. Pearson correlation coefficients were calculated to assess the relationship between fatigue intensity and clinical variables, as well as other subitems on the MPN-SAF TSS.

P values < 0.05 were considered statistically significant. Analyses were performed using JMP® Pro version 18.4.1.2 (SAS Institute, Cary, NC, USA).

Qualitative data collection and analysis

Semi-structured interviews were conducted with 12 AYA participants aged 19–41 years. The same inclusion and exclusion criteria used for the quantitative analysis were applied to interview recruitment. Purposive sampling was used to achieve variation in participant sex, age, and MPN subtype. Between July 2023 and June 2024, eligible participants were invited to participate during routine consultations or follow-up visits with their treating hematologist. Of the 13 patients approached, 12 agreed to participate. Recruitment continued until thematic saturation was achieved.

A semi-structured interview guide explored four broad domains related to fatigue: 1) patient experience and symptom manifestations, 2) perceived causes or contributing factors, 3) impact on daily life, and 4) management strategies (Supplemental materials). Example questions included: *"Thinking about the symptoms listed in the MPN-SAF TSS questionnaire, which ones have the greatest impact on you, and how do they relate to your fatigue?"*, *"Can you describe your experience of fatigue since being diagnosed with your MPN?"*, *"What do you think contributes to or worsens your fatigue?"*, *"How does fatigue affect your daily life, including work, school, relationships, and leisure activities?"*, and *"What strategies or treatments have you found helpful, or unhelpful, for managing your fatigue?"* Follow-up prompts were used to encourage participants to elaborate on the nature, progression, severity, and consequences of their fatigue. Field notes documenting non-verbal behaviours (e.g., facial expressions, tone of voice, and emotional responses) were taken throughout the interviews. Interviews were conducted individually by SDB, who had no therapeutic relationship with the participants, via

Zoom (Zoom Video Communications, San Jose, CA, USA). Interviews were audio-recorded and subsequently reviewed and discussed with the multidisciplinary research team (SDB, NS, and KB), which included expertise in hematology (MPN-specific care), oncology nursing, and qualitative and mixed methods research.

Audio recordings were transcribed verbatim using Noota AI (Paris, France). Data were analyzed iteratively following the qualitative iterative analysis approach described by Miles, Huberman, and Saldaña [24]. Transcripts were read in their entirety then data condensed by assigning codes inductively to transcript sections based on meaning. Condensed data were organized into tables for presentation and iteration, the latter performed by shifting between condensed data (i.e., code) and organized data (i.e., table) to bring out themes. Team members discussed their hypotheses in relation to data throughout the analytical process, taking into account transcripts and field notes to interpret findings. Data were coded and managed using QDA Miner 6.0.16 (Provalis Research, Montreal, QC, Canada). Study quality was ensured with the following criteria: internal credibility and validity (cross-judge validation between team members), procedural accountability (documentation of the research process), and external transferability/validity (detailed description of context) [21,24].

Data integration

Quantitative and qualitative findings were integrated during data interpretation using a triangulation approach [21]. Following separate analyses of each dataset, results were compared through side-by-side juxtaposition to identify areas of convergence, complementarity, and divergence. Comparative tables were developed to align quantitative findings with participants' narratives, facilitating interpretation of how statistical associations corresponded to patients' reported experiences. Integration also enabled the generation of new hypotheses arising from

qualitative findings to explain quantitative results, including the interpretation of symptom clustering with fatigue. The integrated findings were synthesized to provide a comprehensive understanding of fatigue in AYA patients with MPNs.

Results

Quantitative results are presented first, followed by qualitative findings, which are contrasted with the quantitative results. Finally, an integrated QUAN+QUAL interpretation follows.

Quantitative results

Clinical characteristics and symptom burden of AYA and older (non-AYA) patients with MPN are presented in Table 1. The analysis included 399 MPN-SAF TSS assessments from 74 AYA patients (15 PV, 56 ET, 3 MF), and 3706 assessments from 710 non-AYA patients (270 PV, 366 ET, 74 MF). AYA patients had a median diagnosis age of 34 years (range, 19-40 years), completed a median of five questionnaires each (range, 1-16 questionnaires), and were predominantly female (68% vs. 55% in non-AYA, $p = 0.03$). This female predominance was accompanied by an expected higher prevalence of ET (76% vs. 52% in non-AYA) and a relative underrepresentation of PV and MF, which were more common in non-AYA patients ($p = 0.0002$). Consistent with ET enrichment, AYA patients were more likely to have platelet counts $>1000 \times 10^9/L$ (26% vs. 11%, $p = 0.009$) and *CALR* driver mutations (27% vs. 10%, $p = 0.009$). Non-AYA patients had significantly higher MPN disease-specific risk scores ($p < 0.0001$) and C-reactive protein levels ($p = 0.006$) compared to AYA patients. AYAs were also less likely to receive cytoreductive therapy (53% vs. 80%, $p < 0.0001$) and more likely to experience a delay in therapy initiation beyond 36 months (47% vs. 22%, $p = 0.0004$).

Mean aggregate and maximum MPN-SAF TSS scores did not differ between AYA and non-AYA patients, indicating a comparable overall symptom burden across age groups, irrespective of clinical characteristics or risk score. However, despite this similar overall symptom burden, AYA patients were more likely than their older counterparts to report significant fatigue (57% vs. 43%, $p = 0.027$). They also reported severe abdominal pain more frequently (7% vs. 1%, $p = 0.007$).

Table 1: Clinical characteristics and symptom burden patterns of AYA vs non-AYA patients with MPN

Variables	All patients (N=784)	AYA (n=74; 9%)	Non-AYA (n=710; 91%)	P value
Mean age at diagnosis; years (range)	63 (19-96)	34 (19-40)	65 (41-96)	<0.0001
Sex; n (%)				
- Females	440 (56)	50 (68)	390 (55)	0.03
MPN subtype; n (%)				
- PV	285 (36)	15 (20)	270 (38)	0.0002
- ET	422 (54)	56 (76)	366 (52)	
- MF	77 (10)	3 (4)	74 (10)	
Risk score; n (%)				
- Low	45 (22)	12 (71)	33 (17)	
- Intermediate	60 (28)	4 (23)	56 (29)	<0.0001
- High	106 (50)	1 (6)	105 (54)	
Leukocytes, x 10 ⁹ /L; median (range)	9.6 (1.8-48.7)	8.9 (5-17.6)	9.7 (1.8-48.7)	0.05
Leukocytes > 11 x 10 ⁹ /L; n (%)	210 (36)	11 (27)	199 (37)	0.18
Hemoglobin, g/L; median (range)	151 (55-230)	148 (91-203)	151 (55-230)	0.38
Hematocrit, %; median (range)	45 (16-70)	44 (27-64)	45 (16-70)	0.23
Platelets x10 ⁹ /L; median (range)	609 (51-2756)	655 (157-2695)	607 (51-2756)	0.06
Platelets > 1000 x10 ⁹ /L; n (%)	70 (12)	11 (26)	59 (11)	0.009
LDH > 240 U/L; n (%)	110 (52)	11 (65)	99 (51)	0.28
Ferritin > 150 ng/ml; n (%)	39 (29)	2 (15)	37 (31)	0.22
C-Reactive Protein > 5 mg/L; n (%)	35 (36)	0 (0)	35 (39)	0.006
JAK2V617F VAF 50%+; n (%)	149 (36)	7 (24)	142 (37)	0.15
CALR VAF 60%+; n (%)	3 (5)	0 (0)	3 (6)	0.34
Driver mutation; n (%)				
- JAK2V617F	545 (81)	40 (67)	505 (82)	
- CALR	78 (12)	16 (27)	62 (10)	0.009
- MPL	13 (2)	1 (2)	12 (2)	
- TN	38 (5)	3 (5)	35 (6)	
Active cytoreduction therapy; n (%)	605 (77)	39 (53)	566 (80)	<0.0001

Active antiplatelet therapy; <i>n</i> (%)	577 (74)	58 (78)	519 (73)	0.32
Therapy initiation > 36 months; <i>n</i> (%)	161 (24)	21 (47)	140 (22)	0.0004
Symptom burden scores				
Mean MPN-SAF TSS score				
Average (range)	14 (0-67.3)	16 (0-60)	14 (0-67)	0.31
Significant (>20); <i>n</i> (%)	261 (33)	29 (39)	232 (33)	0.26
Maximum MPN-SAF TSS Average (range)				
Significant (> 20); <i>n</i> (%)	22 (0-82)	25 (0-82)	22 (0-82)	0.32
	422 (54)	43 (58)	379 (53)	0.43
Subitem scores				
Fatigue				
Mean score (range)	3.8 (0-10)	4.5 (0-9)	3.7 (0-10)	0.06
Significant (>4); <i>n</i> (%)	343 (44.6)	41 (57)	302 (43)	0.027
Severe (>7); <i>n</i> (%)	73 (9.4)	10 (14)	63 (9)	0.2
Early satiety				
Mean score (range)	1.3 (0-9)	2 (0-8)	1.2 (0-9)	0.22
Significant (>4); <i>n</i> (%)	127 (16)	16 (22)	111 (16)	0.19
Severe (>7); <i>n</i> (%)	25 (3)	2 (3)	23 (3)	0.79
Abdominal pain				
Mean score (range)	0.6 (0-9.5)	1.2 (0-9.5)	0.6 (0-8)	0.07
Significant (>4); <i>n</i> (%)	85 (11)	13 (18)	72 (10)	0.06
Severe (>7); <i>n</i> (%)	14 (2)	5 (7)	9 (1)	0.007
Inactivity				
Mean score (range)	1.3 (0-10)	1 (0-9)	1.3 (0-10)	0.54
Significant (>4); <i>n</i> (%)	117 (15)	12 (16)	105 (15)	0.75
Severe (>7); <i>n</i> (%)	32 (4)	3 (4)	29 (4)	0.98
Difficulty concentrating				
Mean score (range)	1 (0-10)	1.2 (0-9)	1 (0-10)	0.31
Significant (>4); <i>n</i> (%)	108 (14)	14 (19)	94 (13)	0.18
Severe (>7); <i>n</i> (%)	22 (3)	2 (3)	20 (3)	0.97
Night sweats				
Mean score (range)	0.8 (0-9)	1 (0-9)	0.8 (0-9)	0.54
Significant (>4); <i>n</i> (%)	111 (14)	10 (14)	101 (14)	0.87
Pruritus				
Mean score (range)	0.8 (0-10)	0.9 (0-8.8)	0.8 (0-10)	0.5
Significant (>4); <i>n</i> (%)	96 (12)	11 (15)	85 (12)	0.48
Bone pain				
Mean score (range)	1 (0-10)	0.8 (0-9)	1 (0-10)	0.48
Significant (>4); <i>n</i> (%)	129 (16)	11 (15)	118 (17)	0.69
Weight loss				
Mean score (range)	0 (0-10)	0 (0-7)	0 (0-10)	0.26
Significant (>4); <i>n</i> (%)	38 (5)	3 (4)	35 (5)	0.72
Fever				
Mean score (range)	0 (0-7)	0 (0-7)	0 (0-7)	0.19
Significant (>4); <i>n</i> (%)	6 (1)	1 (1)	5 (1)	0.58

Abbreviations: *AYA*: adolescents and young adults; *MPN-SAF TSS*: MPN-Symptom Assessment Form Total Symptom Score; *MPN*: myeloproliferative neoplasms; *LDH*: lactate dehydrogenase; *JAK2V617F*: janus kinase 2; *CALR*: calreticulin; *VAF*: variant allele frequency; *MPL*: myeloproliferative leukemia protein; *TN*: triple negative.

The distinguishing features between AYA and non-AYA patients experiencing high (score > 4) vs low (score ≤ 4) levels of fatigue were next investigated (Table 2). Among AYA patients, fatigue severity was independent of gender, whereas in non-AYA patients, females were significantly more likely to report high fatigue ($p < 0.0001$). In AYA, high fatigue did not correlate with any clinical characteristics, treatment initiation, or use of cytoreductive or antiplatelet therapies. In contrast, among non-AYA patients, high fatigue was associated with a higher (>50%) *JAK2V617F* variant allele frequency (44% vs. 32% low fatigue, $p = 0.02$) and a statistically significant, though clinically modest, reduction in hemoglobin and hematocrit levels. In the non-AYA group, high fatigue was linked to greater use of ruxolitinib over hydroxyurea ($p = 0.0013$), lower use of antiplatelet therapy ($p = 0.0002$), and more frequent delays in therapy initiation ($p = 0.0025$). In both age groups, high fatigue correlated with significantly higher mean and maximum MPN-SAF TSS scores (AYA: $p = 0.0008$ and $p < 0.0001$; non-AYA: $p < 0.0001$ for both). Among AYA patients, high fatigue clustered with specific MPN-SAF TSS subitems: early satiety ($p = 0.0036$), inactivity ($p = 0.034$), and pruritus ($p = 0.014$). In contrast, in the non-AYA group, high fatigue showed broad correlations across all MPN-SAF TSS subitems ($p = 0.0037$ to $p < 0.0001$).

Table 2: Clinical features and outcomes of AYA vs non-AYA presenting high (> 4) vs low (≤ 4) mean fatigue scores

Variables	AYA (n=74)	High fatigue (n=41; 57%)	Low fatigue (n=31; 43%)	<i>P</i> value	Non- AYA (n=710)	High fatigue (n=302; 43%)	Low fatigue (n=395; 57%)	<i>P</i> value
Median age at diagnosis; years (range)	34 (19-40)	35 (19-40)	33 (20-40)	0.53	65 (41-96)	65 (41-96)	65 (41-92)	0.50
Sex								
- Female; n (%)	50 (68)	30 (73)	18 (58)	0.18	390 (55)	192 (64)	192 (49)	<0.0001

Leukocytes, x 10⁹/L; median (range)	8.9 (4.9-17.6)	8.9 (4.9-17.6)	8.7 (5.6-15.7)	0.96	9.7 (1.8-48.7)	9.6 (1.8-32.8)	9.9 (2.4-48.7)	0.31
Leukocytes > 11 x 10⁹/L; n (%)	11 (27)	8 (30)	3 (21)	0.57	199 (37)	77 (35)	119 (39)	0.27
Hemoglobin, g/L; median (range)	148 (91-203)	150 (91-203)	145 (130-173)	0.75	151 (55-230)	149 (55-226)	153 (68-230)	0.015
Hematocrit, %; median (range)	44 (27-64)	44 (27-64)	44 (38-56)	0.90	45 (16-70)	45 (16-66)	46 (19-70)	0.008
Platelets, x 10⁹/L; median (range)	655 (157-2695)	634 (157-2695)	727 (354-1403)	0.14	607 (51-2756)	581 (51-2756)	610 (60-1870)	0.29
Platelets > 1000 x 10⁹/L; n (%)	11 (26)	6 (21)	5 (36)	0.33	59 (11)	26 (12)	31 (10)	0.63
LDH > 240 U/L; n (%)	11 (65)	8 (67)	3 (60)	0.79	99 (51)	44 (51)	51 (51)	0.95
C-Reactive Protein > 5 mg/L; n (%)	0 (0)	0 (0)	0 (0)	NC	35 (39)	24 (48)	10 (28)	0.056
JAK2V617F VAF 50%+; n (%)	7 (24)	6 (33)	1 (10)	0.15	142 (37)	72 (44)	70 (32)	0.020
CALR VAF 60%+; n (%)	0 (0)	0 (0)	0 (0)	NC	3 (6)	2 (9)	1 (4)	0.44
Active cyto reduction therapy; n (%)	39 (53)	19 (46)	19 (61)	0.21	566 (80)	233 (77)	321 (81)	0.18
Cytoreductive agent; n (%)								
- Hydroxyurea	19 (76)	8 (67)	11 (85)	0.29	442 (85)	172 (78)	259 (89)	0.0013
- Ruxolitinib	6 (24)	4 (33)	2 (15)		81 (15)	48 (22)	33 (11)	
Active antiplatelet therapy; n (%)	58 (78)	31 (76)	26 (84)	0.39	519 (73)	198 (66)	310 (78)	0.0002
Therapy initiation > 36 months; n (%)	21 (47)	12 (55)	9 (43)	0.44	140 (22)	77 (28)	62 (18)	0.0025
Symptom burden scores								
Mean MPN-SAF TSS score > 20; n (%)	29 (39)	22 (54)	5 (16)	0.0008	232 (33)	196 (65)	34 (9)	<0.0001
Maximum MPN-SAF TSS score > 20; n (%)	43 (58)	32 (78)	9 (29)	<0.0001	379 (53)	245 (81)	131 (33)	<0.0001
Significant subitem scores								
Early satiety								
- Score > 4; n (%)	16 (22)	12 (29)	3 (10)	0.036	111 (16)	91 (30)	20 (5)	<0.0001
Abdominal pain								
- Score > 4; n (%)	13 (18)	7 (17)	4 (13)	0.62	72 (10)	56 (19)	14 (4)	<0.0001
Inactivity								
- Score > 4; n (%)	12 (16)	10 (24)	2 (6)	0.034	105 (15)	84 (28)	20 (5)	<0.0001
Difficulty concentrating								
- Score > 4; n (%)	14 (19)	10 (24)	4 (13)	0.21	93 (13)	79 (26)	13 (3)	<0.0001

Night sweats								
-	Score > 4; <i>n</i> (%)	10 (14)	7 (17)	2 (6)	0.16	101 (14)	74 (25)	26 (7) <0.0001
Pruritus								
-	Score > 4; <i>n</i> (%)	11 (15)	9 (22)	1 (3)	0.014	85 (12)	60 (20)	22 (6) <0.0001
Bone pain								
-	Score > 4; <i>n</i> (%)	11 (15)	7 (17)	3 (10)	0.36	118 (17)	96 (32)	19 (5) <0.0001
Weight loss								
-	Score > 4; <i>n</i> (%)	3 (4)	2 (5)	0 (0)	0.13	35 (5)	30 (10)	5 (1) <0.0001
Fever								
-	Score > 4; <i>n</i> (%)	1 (1)	0 (0)	0 (0)	NC	5 (1)	5 (2)	0 (0) 0.0037

Abbreviations: *AYA*: adolescents and young adults; *MPN-SAF TSS*: MPN-Symptom Assessment Form Total Symptom Score; *MPN*: myeloproliferative neoplasms; *LDH*: lactate dehydrogenase; *JAK2V617F*: janus kinase 2; *CALR*: calreticulin; *VAF*: variant allele frequency; NC: Non-computable

The clinical characteristics associated with a high overall symptom burden (MPN-SAF TSS > 20) were also examined (Table S1). In both AYA and non-AYA groups, women were more likely than men to report a high symptom burden ($p = 0.004$ and $p = 0.0003$, respectively). Among AYA patients specifically, elevated LDH was the only additional variable associated with a high symptom burden (100% vs. 50% low symptom burden, $p = 0.02$). In non-AYA patients, the clinical profile associated with a high symptom burden closely paralleled that observed for high fatigue, including greater use of ruxolitinib relative to hydroxyurea ($p = 0.0079$), lower use of antiplatelet therapy ($p = 0.0009$), more frequent delays in therapy initiation ($p = 0.0050$), and a statistically significant, although clinically modest, reduction in hematocrit levels.

Subgroup analyses for patients with ET and PV are presented in Tables S1 and S2 (Supplemental materials). Subgroup analysis was not feasible for AYA patients with MF because of the small sample size ($n = 3$). Overall, the subgroup analyses of clinical features and outcomes were consistent with the findings observed in the pooled MPN cohort.

Qualitative results

Twelve AYA patients participated in the qualitative study; their demographic and clinical characteristics are summarized in Table 3. Interviews lasted between 28 and 79 minutes (mean, 49 minutes). Analysis generated 24 condensed codes that were organized into five overarching themes: 1) fatigue as the predominant symptom and its interrelationships with other symptoms, 2) dimensions of fatigue, 3) perceived causes of fatigue, 4) impact of fatigue, and 5) effective fatigue management strategies.

Table 3: Demographics and clinical characteristics of interviewed AYA with MPN

No	Age-Range at Dx	Age-Range at interview	Educational level	MPN subtype	Fatigue Level	Number of children	Interview time (min)
1	15-19	15-19	High School	ET	Low	0	47
2	35-39	40-44	University	PV	High	0	58
3	25-29	30-34	University	ET	High	2	45
4	20-24	30-34	High School	ET	Low	1	63
5	35-39	40-44	College	ET	High	4	77
6	30-34	30-34	University	ET	Low	2	28
7	N/A	30-34	University	ET	Low	1	33
8	35-39	35-39	College	MF	Low	3	36
9	15-19	30-34	N/A	ET	High	3	43
10	30-34	35-39	College	PV	High	1	79
11	35-39	25-29	High School	ET	Low	1	40
12	35-39	40-44	University	MF	High	0	33

Abbreviations: AYA, adolescent and young adult; MPN, myeloproliferative neoplasms; PV, Polycythemia vera; ET, Essential thrombocythemia; MF, Myelofibrosis; N/A, not available

Theme 1: Fatigue as the predominant symptom and interrelationships with other symptoms

Although participants discussed a broad range of MPN-related symptoms, fatigue consistently emerged as the one with the greatest impact on their daily lives, despite considerable interindividual variability in its severity. One participant explained:

“Regarding fatigue, I’m not sure when the illness started, but I know that for many, many years, I always felt tired, always exhausted. Even in the morning, I struggled to get up. It was a bit like what someone with depression might experience.” (Participant 5)

Participants frequently described how fatigue interacted with other MPN-related symptoms, enabling comparison with the quantitative findings and the identification of areas of convergence and divergence (Table 4). Consistent with the quantitative analysis, fatigue was closely linked to inactivity. Conversely, abdominal pain, bone pain, fever, and weight loss were described as having little impact on daily life and were not perceived as contributors to fatigue. Divergence between the quantitative and qualitative findings was observed for early satiety and pruritus, which participants rarely associated with fatigue despite significant statistical associations in the quantitative analysis. In contrast, night sweats and concentration difficulties were frequently described as closely intertwined with fatigue.

Table 4: Mixed data analysis of MPN-SAF TSS subitems in AYA patients with high level of fatigue: illustrative quotes and interpretation on qualitative-quantitative data convergence and divergence

MPN-SAF subitems	High fatigue with high subitem <i>n</i> (%) (<i>n</i> =41)*	Participants reporting symptoms <i>n</i> (%) (N=12)	Quotes	Convergence/Divergence Comments
Early satiety	16 (29) <i>p</i> =0.036	0 (0)		Divergent None of the participants reported experiencing early satiety, and the correlation with fatigue observed in the quantitative analysis was not supported by the qualitative data.
Abdominal pain	7 (17) <i>p</i> =0.62	4 (33)	<i>“As for abdominal discomfort, there are definitely some positions, like when I was used to sleeping on my stomach, where I feel a little</i>	Convergent Participants reported that abdominal discomfort had minimal impact on QoL and did not perceive it as contributing to their fatigue.

			<i>uncomfortable. But nothing that really makes me think, "Oh, I'm sleeping poorly" or anything like that, no. It's more of an adjustment than anything else."</i> (Participant 8)	This finding was consistent with the quantitative results.
Inactivity	10 (24) <i>p=0.034</i>	5 (42)	<i>"On the personal side it's always the fatigue, which bothers me because it makes me less active, and it makes me less inclined to do things."</i> (Participant 2)	Convergent Four participants described inactivity as a consequence of their fatigue, while a fifth participant attributed her inactivity to the stress caused by living with an MPN. This association is supported by the quantitative analysis.
Difficulty concentrating	10 (24) <i>p=0.21</i>	4 (33)	<i>"Fatigue is like brain fog. [...] I'll be in a meeting, and I will be like, I have an idea and then it's...gone, but not, it's not like gone just for a few minutes, it's gone into the abyss of never coming back."</i> (Participant 10)	Divergent Most participants described problems with concentration as a manifestation of their fatigue. This association was not confirmed in the quantitative analysis.
Night sweats	7 (17) <i>p=0.16</i>	4 (33)	<i>"I wake up drenched in sweat, and I have nightmares when it happens too. When it happens, those nights are really not restful."</i> (Participant 2)	Divergent Participants who reported experiencing night sweats consistently described difficulty sleeping and increased fatigue as a result. This association was not supported by the quantitative analysis.
Pruritus	9 (22) <i>p=0.014</i>	3 (25)	<i>"The switch [from hydroxyurea] to interferon [to enable having a child]. That period was mentally, psychologically challenging, because of the pruritus I mentioned earlier, that was really tough. I think, in the entire journey with my illness since the diagnosis, that was the roughest part for me, and for my girlfriend</i>	Divergent Participants described pruritus episodes as particularly distressing. Some linked the symptom to treatment side effects (e.g., interferon), but none reported increased fatigue during these episodes. Therefore, the association between pruritus and fatigue observed in quantitative data was not supported qualitatively.

			<i>too, seeing me like that..." (Participant 4)</i>	
Bone pain	7 (17) <i>p</i> =0.36	2 (17)	<i>"The bones hurt as if they're about to dissolve, all over my body, but especially in my hands." (Participant 9)</i>	Convergent Some participants reported experiencing bone pain, but did not link it to fatigue. This finding was consistent with the quantitative results.
Weight loss	2 (5) <i>p</i> =0.13	0 (0)		Convergent None of the participants reported experiencing weight loss, and both methods agree that there is no correlation between weight loss and fatigue.
Fever	0 (0)	0 (0)		Convergent None of the participants reported experiencing fever. Both qualitative and quantitative findings indicated no correlation between fever and fatigue.

Abbreviations: AYA, adolescent and young adult; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; QoL: Quality of Life; NC: Non-computable

Theme 2: Dimensions of fatigue

Participants consistently described fatigue as a multidimensional experience characterized by physical exhaustion, lethargy, weakness, reduced motivation and impaired concentration. Fatigue was also commonly linked to non-restorative sleep, with many participants reporting persistent tiredness despite obtaining adequate sleep. One participant shared:

"It's like waking up in the morning and not feeling rested. That happens very often, even when I go to bed early, around 8:30-9:00 PM, trying to do the right thing and recover."
(Participant 3)

These findings expand the quantitative results by illustrating that fatigue encompasses cognitive, motivational, and sleep-related dimensions not captured by symptom severity scores alone.

Theme 3: Causes of fatigue

Although many AYA participants reported increased fatigue following their MPN diagnosis, the majority often struggled to discern whether their fatigue was attributable to the disease itself or to other factors such as work, family responsibilities, or the natural aging process. One participant explained:

“I’ve experienced a progression over the years. At the same time, you start wondering if it’s just the weight of those years that’s making you more tired. [...] We’re all buckling under the stress of a fast-paced life, where everything seems to overlap and intertwine. Add to that the kids, a partner, work, job changes, and life adjustments, it all piles on.” (Participant 5)

This theme provides context for the variability observed in fatigue scores by highlighting participants' uncertainty regarding the origins of their fatigue.

Theme 4: Impacts of fatigue

The impact of fatigue varied considerably among participants. For some, it had little influence on daily functioning, whereas others described substantial disruptions to work and career trajectories, including modifying job responsibilities or changing careers altogether. Although fatigue occasionally limited social activities, most participants felt it did not substantially affect the quality of their interpersonal relationships. One participant explained:

“In terms of work, yes, it's certain that this isn't the job I would have chosen given my medical condition. I was involved in very engaging projects before. Now, I'm still in the same sector, but I took a position...that offers better working conditions. I opted for that stability, whereas the other projects I worked on were much more exciting and energizing.” (Participant 3)

These narratives illustrate the heterogeneous functional consequences of fatigue despite similar symptom scores. Nevertheless, only two participants explicitly described a marked reduction in overall QoL.

Theme 5: Effective fatigue management strategies

Participants described using multiple strategies to manage fatigue, although their perceived effectiveness varied considerably. Coffee often provided temporary improvements in alertness but did not prevent later energy decline. One participant explained:

“Usually, once the day gets started, things go fairly well, especially after one or two coffees. When I’m working, let’s say between 9:00 AM and 1:00 PM, I feel great and productive. But after that, my energy dips. It becomes harder to get motivated, and I struggle more with concentration.” (Participant 3)

In contrast, pharmacological treatments that successfully controlled hematologic parameters were generally not perceived to alleviate fatigue. As one participant noted:

“I have no idea whether [the treatments] are actually effective. It's mostly based on the blood test results. In principle, they're considered effective because, for example, my platelet count has gone down. [...] So yes, the medication is doing what it was intended to do. But beyond that, am I actually getting better? That's hard to say.” (Participant 5)

Regular physical activity emerged as the strategy most consistently perceived as beneficial, with all 12 participants describing exercise as an effective way to manage fatigue. Scheduled naps, healthy eating habits, and maintaining regular sleep routines were also commonly reported as helpful. One participant explained:

“I can’t go to the gym like I used to because I’m more fatigued, but I still do yoga four times a week and try to walk every day. Even if it’s just a brisk one-hour walk, I feel like it gives

me more energy the next day. I also pay attention to what I eat, drink less alcohol, and sleep better. When I eat well, exercise, drink less, and sleep well, I have more energy the following day, which makes it easier to stay active. I really think it has a positive impact.” (Participant 2)

Overall, participants distinguished between treatments that effectively controlled disease-related laboratory parameters and strategies that meaningfully alleviated fatigue, highlighting the complementary role of supportive non-pharmacological interventions as an adjunct to disease-directed pharmacological agents.

Data integration: Understanding fatigue in AYAs with MPN

Integration of QUAN+QUAL revealed fatigue as a predominant but heterogeneous symptom in AYAs with MPNs, with a distinct symptom profile compared with older patients. While quantitative analyses characterized fatigue severity and its associations with other MPN-related symptoms, qualitative findings expanded this understanding by revealing cognitive, motivational, and sleep-related dimensions not captured by symptom severity scores alone. Together, both datasets showed that similar fatigue scores could translate into markedly different functional consequences, particularly regarding work and career, while relatively few participants reported an overall reduction in QoL. Qualitative findings also contextualized the absence of associations between fatigue and clinical or treatment-related variables by highlighting the difficulty participants experienced in attributing fatigue specifically to their MPN and the limited perceived benefit of disease-directed therapies on fatigue. Finally, integration identified regular physical activity and other supportive non-pharmacological strategies as important components of fatigue management that were not captured by the quantitative analysis.

Discussion

Fatigue is a complex, multidimensional, and predominant symptom in patients with MPNs. Consistent with our previous findings [20], this mixed methods study confirmed that a greater proportion of AYAs experienced clinically significant fatigue compared with older adults with MPNs (Table 1). Importantly, this converged with the qualitative results, in which fatigue consistently emerged as the symptom with the greatest impact on participants' daily lives, despite considerable interindividual variability in its intensity. Interestingly, clinically significant fatigue was not associated with sex among AYAs, whereas older women were more likely than older men to report high fatigue (Table 2). This contrasts with the well-established observation that women generally report a greater overall symptom burden than men with MPNs, regardless of age (Table S1) [11,25,26]. The mechanisms underlying these sex differences remain incompletely understood but are thought to involve hormonal influences [26,27], differences in pain perception and symptom processing [26], and sex-related differences in symptom reporting and study participation [28]. The absence of sex differences in fatigue among AYAs, despite a similar overall MPN-SAF TSS symptom burden across age groups (Table 1), further suggests that fatigue plays a particularly prominent role in the symptom experience of younger patients and represents a key determinant of its impact on daily functioning. Additional factors, including postmenopausal hormonal changes, age-related comorbidities, and differences in social roles and symptom reference standards, may contribute to widening sex-based disparities in symptom burden with advancing age.

Beyond the observed age-related differences in fatigue, AYAs also exhibited unique epidemiological, biological, and clinical characteristics that provide important context for interpreting these findings. This population was characterized by a female predominance and a

higher prevalence of ET, concordant with known epidemiologic patterns [3], which was reflected by a greater proportion of patients with platelet counts $>1000 \times 10^9/L$ and an enrichment of *CALR* mutations (Table 1). Despite their younger age and lower-risk disease, AYAs remained significantly symptomatic compared with their older counterparts. These observations are consistent with a recent clinicopathological and epidemiological review of AYAs living with MPNs [29]. This apparent discrepancy may reflect a dissociation between conventional prognostic risk and symptom burden. While this remains hypothetical, risk stratification primarily captures the likelihood of adverse disease-related outcomes and may not adequately reflect the biological and functional determinants of symptoms such as fatigue. Moreover, the unique professional, family, and psychosocial demands faced by AYAs may amplify the impact of fatigue despite otherwise favorable disease characteristics.

Although its relationship to fatigue remains uncertain, AYAs also reported severe abdominal pain more frequently than non-AYAs (Table 1), a finding that may be partly explained by the higher proportion of females in this group, as young women, both in MPN and other disease contexts, have been shown to report more gastrointestinal symptoms than men [26,30]. Splenomegaly may represent an additional contributing factor, as it has been reported more frequently in younger patients with MPNs [4] and has been associated with abdominal discomfort, pain and early satiety [15,31]. A generally lower body mass index in younger patients could further increase the perceived intensity of these abdominal symptoms.

Fatigue in AYAs clustered specifically with inactivity, pruritus, and early satiety, whereas fatigue in non-AYAs was broadly associated with all MPN-SAF TSS subitems (Table 2). Taken together, these findings provide further evidence that AYAs represent a distinct population, characterized not only by unique epidemiological and biological features, but also by a distinct

symptom profile. The broader symptom clustering observed in older patients may partly reflect the cumulative effects of age-related comorbidities and reduced physiological reserve, which could amplify the interrelationships between fatigue and other symptoms. Alternatively, age-related differences in disease biology and inflammatory signaling may contribute to distinct patterns of symptom expression, but the mechanisms underlying these differences remain uncertain. Although the qualitative findings demonstrated both convergence and divergence with the quantitative analysis (Table 4), the integration of both datasets consistently supported this distinct symptom profile while providing a more nuanced understanding of how fatigue interacts with other symptoms in everyday life.

Beyond symptom recognition, these findings also raise important considerations regarding therapeutic management of AYAs with MPNs. Despite a comparable overall symptom burden, AYAs experienced a longer delay in the initiation of pharmacological therapy compared with older patients (Table 1); this is not unexpected given that practice guidelines conventionally recommend expectant management in younger (*de facto* lower risk) cases. In contrast, older patients were more frequently treated with cytoreductive therapies, likely reflecting the greater prevalence of higher risk scores in this group. Interestingly, however, even among non-AYAs, delays in treatment initiation were more frequent in patients with high fatigue than in those with low fatigue (28% vs. 18%, $p = 0.0025$), as well as in patients with high versus low overall symptom burden (29% vs. 19%, $p = 0.0050$). These findings suggest that traditional risk stratification may continue to take precedence over patient-perceived symptom burden in clinical decision-making. Although symptom severity is an established indication for treatment escalation with cytoreductive therapy, these findings highlight a potential gap between symptom

impact and therapeutic intervention suggesting that patient-reported symptoms may not always be fully captured or integrated into treatment decisions.

Interestingly, the specific symptom profile associated with fatigue in AYAs may also provide opportunities for alternative management approaches. Since fatigue was closely linked with a limited number of symptoms, including inactivity, pruritus, and early satiety, targeted management of these associated symptoms may represent a strategy to indirectly alleviate fatigue. Furthermore, non-pharmacological interventions may play an important role, particularly given the perception among many participants that pharmacological therapies were ineffective for fatigue management. Consistent with previous studies in MPNs [18,19], AYAs identified regular physical activity as the most beneficial strategy for improving fatigue. Supporting this perspective, a recent randomized controlled trial demonstrated that supervised exercise in patients with MPNs was feasible, accessible, and associated with potential improvements in inflammatory and disease-related markers [32]. Other strategies reported as beneficial by participants, including scheduled naps, healthy dietary habits, and maintaining regular sleep routines, may also represent accessible approaches to fatigue management.

Taken together, these observations suggest that management of fatigue in AYAs with MPNs requires a multidimensional approach integrating disease-directed therapy, symptom-specific interventions, and supportive non-pharmacological strategies. In patients with significant symptom burden, particularly when pharmacological approaches have limited perceived benefit or have not yet been initiated, early incorporation of lifestyle-based interventions may provide meaningful improvements in fatigue and QoL.

Study limitations

This study has several limitations. The quantitative component included both retrospective and prospective data and relied on patient-reported outcomes, which may be subject to reporting bias. Beyond the data interpretation discussed above, the relatively small number of AYAs may also have contributed to discrepancies between the quantitative and qualitative findings, such as the associations of fatigue with pruritus and early satiety observed in the quantitative analyses but not reflected in the qualitative interviews. In addition, subgroup analyses for patients with MF were not feasible because of the small sample size. The study may also be affected by survivorship and participation biases, though the latter is minimized through the highly inclusive recruitment strategy of the Quebec MPN registry.

Despite these limitations, several strengths should be noted. The systematic administration of the MPN-SAF TSS across the provincial registry minimized selection bias and enabled symptom assessment in a large, unselected real-world cohort. Furthermore, the high median number of completed questionnaires per participant reflects sustained patient engagement over time, supporting the robustness of symptom characterization. Finally, the mixed methods design provided complementary quantitative and qualitative perspectives, allowing a more comprehensive understanding of fatigue by integrating symptom patterns with patients' experiences.

Conclusions

This mixed methods study provides a comprehensive perspective on fatigue in AYA patients with MPN, revealing several key findings. Fatigue is the dominant symptom driving MPN-SAF TSS scores in this population and clusters with specific subitems in a pattern that differs from that observed in older patients. Fatigue in AYA patients is multidimensional and in some, can impair

their ability to work. These findings support the importance of complementary non-pharmacological interventions, particularly physical activity, in improving fatigue and QoL for AYA patients with MPN. Further studies are warranted to validate these findings in larger, prospective cohorts and to define the optimal approach for implementation of personalized management strategies.

Declarations

Abbreviations

MPN, myeloproliferative neoplasms; PV, polycythemia vera; ET, essential thrombocythemia; MF, myelofibrosis; AYA, adolescents and young adults; QoL, quality of life; GQR LMC-NMP, Groupe québécois de recherche en LMC-NMP (Quebec CML-MPN research group); MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score

Ethics approval and consent to participate

This study was approved by the research ethical committee of Montreal East Island Integrated University Health and Social Services Centre serving the Maisonneuve-Rosemont Hospital (approval number: 2024-3457). Written informed consent was obtained from all patients and interviewed participants.

Consent for publication

Written informed consent for publication was obtained from all study participants. Interviewed participants were specifically informed that anonymized statements and quotations from their interviews could be included in publications arising from the study. All potentially identifying information was removed to preserve participant anonymity.

Availability of data and materials

Study datasets and analyses are available from the corresponding author, upon reasonable request.

Competing interests

The authors declare no conflicts of interest.

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Author Contributions

SDB, KB, and NS designed the study. All authors contributed to data collection. SDB conducted the virtual interviews. SDB, KB, and NS performed the quantitative and qualitative analyses. SDB, KB, and NS drafted the manuscript, and all authors critically revised and approved the final version.

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