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Marina Stal*

Northcentral University, USA

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***Corresponding author:** Marina Stal, Ph.D.Northcentral University, USA, ORCID: 0000-0002-2485-222X; Tel: 347-204-2050; E-mail: mstal3965@gmail.com

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Research Article

Myeloproliferative Neoplasms: Fatigue, depression & hemoglobin

Abstract

Objective: To evaluate existing relationships and differences in fatigue, depression, and hemoglobin value in individuals with Myeloproliferative Neoplasms.

Methods: This study utilized the Fatigue Severity Scale, Beck Depression Inventory-II, and self-report of MPN diagnosis and latest hemoglobin value to assess the dependent variables. To promote optimal opportunity for participation in this study, potential subjects were recruited through three online-based disease-specific support groups. A total of 125 individuals consented to participate in the study.

Results: Findings support prior findings including that fatigue is a prominent characteristic of MPNs and that depression within this population necessitates further study. Additionally, there is a need for further elucidation regarding underlying causes of fatigue that are not directly associated with hemoglobin value ($F(4, 134) = 5.306$, $p = .001$, Wilk's $\Lambda = 0.745$, partial $\eta^2 = .137$).

Conclusions: This study supports prior research that has demonstrated that individuals with MPNs manifest greater-than-expected intensity of fatigue as well as notable accounts of depression. Of particular interest is the average hemoglobin values did not demonstrate anemia, suggesting there is a need to investigate other potential underlying causes.

Cancer has been, and remains, a term associated with fear and a disease considered predominantly fatal [1]. Symptoms directly related to the cancer or its treatment may be understated, resulting in additional hardships [2,3]. Common symptoms discussed in relation to cancer include pain, fatigue, weight loss, and gastrointestinal distress [4]. The uncertainty of the cause of the symptoms prior to diagnosis may be a factor in concurrent psychiatric symptoms, such as anxiety and/or depression [5]. Furthermore, as the nature of the cancer is revealed and symptoms are further complicated with treatment-related side effects, the clinical picture becomes more complicated both physically and psychologically [6]. The ambivalent clinical picture is particularly relevant when discussing cancer diagnoses that do not fit the established mold of cancer in regard to symptomology and prognosis, yet that are equally devastating [7].

Myeloproliferative neoplasms (MPNs), colloquially termed *chronic leukemias*, defy much of what is believed about cancer, yet simultaneously exhibit the same characteristics [8,9]. Perhaps the first distinction of MPNs is the ability of afflicted individuals to live an accepted and normal life span, albeit with the potential for transformation to an acute condition [8,9]. MPN is an umbrella term consisting of several diagnoses: polycythemia vera (PV), essential thrombocytopenia (ET), and myelofibrosis [8], (MF). Patients with MPNs may live a full lifespan with little more than associated symptoms; those with MF harbor greatest potential for transformation to acute leukemia [7].

As with many chronic diseases, MPNs have the potential to diminish quality of life and also transform to an acute stage of the disease [10-12]. Consequently, patients with MPNs oftentimes use additional therapies to help control the current symptoms while slowing the progression of the disease [13]. Between the symptoms of the disease and the side effects of the various therapeutic options, patients experience reductions in quality of life as well as significant symptoms that may limit functionality [14]. In fact, researchers suggested there may be an underlying inflammatory process within cancer that may contribute to depressive symptoms [15-17].

In MPNs, fatigue is a symptom that is often seen in patients, commonly attributed to the reduced balance of appropriate blood cells that help transport oxygen [18]. Within the current literature regarding cancer, fatigue is primarily presented as a side effect of treatment rather than a symptom of the disease; this does not hold true for MPNs [19,20]. In MPNs, fatigue is

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identified as a fundamental symptom of the underlying disease [18]. Researchers have identified that patients with MPNs have severe symptom burdens that significantly impact quality of life and functionality, with fatigue being most prominent [22-26].

Another psychological component possibly contributing to decreased quality of life is the presence of depression [7]. The American Cancer Society [7], acknowledged depression in up to 1 in 4 cancer patients, and notes that it may be transient or chronic. Of particular interest is that increased fatigue is a component of depression according to the American Psychological Association, suggesting the reason cancer patients experience fatigue may be multidimensional [9]. Research within this area indicated 12.5% of a specific population was found to meet criteria for depression, suggesting a correspondence with disease-related symptom burden [21]. Specific to the MPN population, depression was identified as a significant potential side effect of a common therapy, pegylated interferon-a [30]. However, limited information exists regarding differences in fatigue and depression severity between the MPN diagnoses, restricting the understanding of its influence [21,31].

Specific proinflammatory cytokines, including interleukin-1 beta (IL-1β), tumor necrosis factor–alpha (TNF-α), and interleukin 6 (IL-6) have been identified as possibly leading to symptoms of fatigue and behavioral changes [19,39,40]. In patients with ovarian cancer, Schrepf et al. (2016) reported elevations in the pro-inflammatory cytokine interleukin-6 (IL-6) and alternations in cortisol, which have been associated with depression [41]. Other researchers reported similar findings in patients with pancreatic cancer, highlighting an association between depression and elevation of IL-6 [42].

Much of MPN-directed research is focused on development and evaluation of therapies, a component of the patient population remains isolated in regard to their needs. Greater understanding of the significance of fatigue and depressive symptoms within this population can assist in enhancing their quality of life and promoting further research [22-26]. Investigating the relationship between depression and symptoms of fatigue in the MPN population can assist in identifying optimal therapeutic options that may also enhance quality of life [22-26].

Methods

Ethical approval

Consent and study procedures designed in strict accordance with all human subject protections and good clinical practices. Authorization to conduct the study were received by both the IRB at Northcentral University (2018-017-SMM) and through agreements with the research sites (i.e., support groups) prior to initiation of the study.

Research methodology and design

The research methodology and design for this study was a quantitative, causal comparative, and prospective. To achieve utmost impact for a rare disease group by maximizing the sample pool, online disease-specific support groups were selected as the medium for recruiting participants.

Population and sample

Power analysis for a multivariate analysis of variance (MANOVA) with three levels and three dependent variables was conducted in G*Power to determine a sufficient sample size using an alpha of 0.05, a power of 0.80, and a large effect size (f^2 = 0.15). Based on the aforementioned assumptions, the desired sample size was 24. To ensure all MPN diagnoses were equally represented, at least 8 patients within each diagnostic group (ET, PV, MF) were recruited for participation.

Materials/Instrumentation

The Fatigue Severity Scale (FSS) was used to evaluate individual experiences of fatigue [32]. The FSS is a 9-item self-report questionnaire assessing various aspects of fatigue on a scale of 1 (strongly disagree) to 7 (strongly agree). The total score ranges from 9 to 63, with a higher score indicating greater fatigue severity.

The Beck Depression Inventory II (BDI-II) was used to evaluate individual experiences of depressive symptoms [33]. The BDI-II consists of 21 statements used to assess the nature and intensity of depression; each item is rated on a scale from 0-3 (arranged in increasing severity). A higher score is indicative of more symptomology, with a score of 20 and higher indicating moderate to severe depression.

The American Cancer Society identifies anemia as the condition of having low hemoglobin, therefore participants were asked to report their last known hemoglobin value from their most recent laboratory evaluation [4]. ACS reports hemoglobin between the lower limit of normal and 10 g/dL as mild anemia, between 8 to 10 g/dL as moderate, 6.5 to 8 g/dL as severe, and less than 6.5 as life-threatening [4].

Data collection and analysis

All components of the study, consisting of the consent, screening questions, surveys, and specific questions, were hosted on the website www.SurveyMonkey.com. Any questions that were answered were stored on the site within the respective study, with access limited to the researcher; no identifying information was collected. The study remained opened until all three disease groups had congruent numbers of participants (N = 125). Once the appropriate number of participants was reached, all recruitment posts were removed, the study was disabled on www.SurveyMonkey.com, and all data was downloaded and imported directly into IBM SPSS 24.0.

Results

Descriptive statistics

125 individuals consented to participate in the study; 26 were found to be ineligible when completing the screening process. A total of 76 MPN diagnoses were documented: 21 myelofibrosis, 32 polycythemia vera, and 23 essential thrombocythemia. 48 participants did not disclose an MPN diagnosis.

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Fatigue severity scale

The Fatigue Severity Scale was completed by 83 participants and skipped by 42. The questions were answered on a Likert scale of 1-7 with 7 indicating greatest severity. The average score of the FSS was 15.07 (SD = 6.92, range = 1-30), and was normally distributed with skewness of .094 (SE = .264) and kurtosis of -.599 (SE .523). The statement "my motivation is lower when I am fatigued" was found to have the highest intensity (N = 18, M = 6.167, SD = .923). The statement "fatigue interferes with my work, family, or social life" was found to have the greatest frequency (N = 66, M = 5.37 SD = 2.10) (Table 1).

Table 1: Fatigue severity scale average by diagnosis.

	N	Mean	Std. Deviation
Myelofibrosis	21	13.667	6.18
Polycythemia Vera	32	15.968	6.34
Essential Thrombocythemia	23	16.391	7.32

Beck depression Inventory II

The Beck Depression Inventory (BDI) was completed by 78 participants and skipped by 48. The questions were answered on a Likert scale of 0-3, each question having discrete answers for each option; higher scores indicate greater intensity. The average score of the BDI was 15.01 (SD = 9.57, range = 0-41), and was normally distributed with skewness of .629 (SE = .264) and kurtosis of .120 (SE .523). Severity is categorized as minimal (0-13), mild (14-19), moderate (20-28), and severe (29-63). presents the frequencies for the categorization of BDI results. The majority of respondents fell into the minimal category (27.4%, N = 34). The score with the greatest frequency was 6.0 (N = 8), followed by 16.0 (N = 7).

Statistical analyses

An ANOVA was conducted to compare the intensity of fatigue across different MPN diagnoses. The variable was normally distributed with skewness of -.354 (*SE* = .264) and kurtosis of -.349 (*SE* = .523). There were no significant differences in fatigue intensity at the p<.05 level for the three MPN diagnoses [$F(2, 73) = 0.961$, $p = 0.387$].

An ANOVA was conducted to compare the intensity of depressive symptoms across different myeloproliferative neoplasm diagnoses. The variable was normally distributed with skewness of .726 (*SE* = .271) and kurtosis of .228 (*SE* = .535). There was no significant differences in depressive symptom intensity at the $p < .05$ level for the three MPN diagnoses [$F(2, 73) = 0.148$, $p = 0.863$].

Hemoglobin levels (Table 2) were not normally distributed with skewness of 2.293 (*SE* = .285) and kurtosis of 4.616 (*SE* = .563). Fatigue severity as assessed with total fatigue score of the FSS was normally distributed with skewness of .094 (*SE* = .264) and kurtosis of -.599 (*SE* = .523). An ANOVA found a statistically significant difference in total fatigue score and hemoglobin value based on MPN diagnosis, $F(4, 134) = 5.306$, $p = .001$, Wilk's $\Lambda = 0.745$, partial $\eta^2 = .137$. Tukey HSD post-hoc analyses shows that mean scores for hemoglobin were statistically different between myelofibrosis and polycythemia vera ($p = .001$) and polycythemia vera and essential thrombocythemia ($p = .005$).

An ANOVA was conducted to evaluate differences in the relationship between the intensity of depressive symptoms (measured as total BDI-II score) and fatigue severity across different myeloproliferative neoplasm diagnoses. There was no significant relationship between the intensity of depressive symptoms and fatigue intensity [$F(4, 144) = 0.683$, $p = .605$, Wilk's $\Lambda = 0.963$, partial $\eta^2 = .0.19$] (Table 3).

Limitations

Noted limitations included: the restricted sample size, the use of the internet as a medium, the use of questionnaires that have not been validated for this population, the use of self-reported assessments, the partial completion of the self-reported questionnaires, and the choice to concurrently evaluate both fatigue and depression.

Discussion

Based on the results of the statistical analyses, there are no statistically significant differences in fatigue intensity between the MPN diagnoses. It is notable that the majority symptoms identified in the FSS had an average intensity > 4 (Range 0 – 7), with 6 symptoms rating > 5 (Table 2). This supports the previous findings identified in the literature review that fatigue is a prominent characteristic of these diseases. In particular, this study replicated the mean fatigue score as being ~50% of the maximum possible score that was recorded using the BFI in a prior study of 1179 patients [34]. Furthermore, the current study supports findings that fatigue is one of the most prominent symptoms (Table 2, $N = 30$, $M = 5.667$) and is evident across all MPN diagnoses [35] (Table 3).

Although there were no statistically significant differences in depressive symptom intensity between the MPN diagnoses, the results support prior findings that reported that 12.5% of MPN patients in a sample ($N = 119$) met depression screening criteria. The majority of respondents fell into the minimal category (27.4%, $N = 34$). The score with the greatest frequency was 6.0 ($N = 8$), followed by 16.0 ($N = 7$). This is a particularly important finding as it supports studies that claim depression in advanced hematologic disease (i.e., MPNs) requires attention and further investigation[21,36].

Table 2: Hemoglobin value average by diagnosis.

		Hemoglobin			
	N	Mean	Std. Deviation	Minimum	Maximum
Myelofibrosis	20	11.6	4.83	7.2	30
Polycythemia Vera	32	22.85	14.92	12.1	63.0
Essential Thrombocythemia	19	12.96	3.53	1.4*	16.3

*Self-reported, cannot be validated.

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Table 3: ANOVA post-hoc analyses: hemoglobin, fatigue, MPN diagnosis.

Dependent Variable	MPN Diagnosis		Mean Difference	Std. Error	*p*-value
Fatigue	Myelofibrosis	Polycythemia Vera	-2.268	1.914	.466
		Essential Thrombocythemia	-3.563	2.151	.229
	Polycythemia Vera	Myelofibrosis	2.269	1.914	.466
		Essential Thrombocythemia	-1.294	1.944	.784
	Essential Thrombocythemia	Myelofibrosis	3.563	2.151	.229
		Polycythemia Vera	1.294	1.944	.784
Hemoglobin	Myelofibrosis	Polycythemia Vera	-11.178	3.001	.001
		Essential Thrombocythemia	-1.291	3.381	.923
	Polycythemia Vera	Myelofibrosis	11.178	3.001	.001
		Essential Thrombocythemia	9.887	3.056	.005
	Essential Thrombocythemia	Myelofibrosis	1.291	3.381	.923
		Polycythemia Vera	-9.887	3.056	.005

Fatigue severity was not found to be significantly different with hemoglobin value, although fatigue severity and myeloproliferative diagnosis was found to be significant (r = .209, p = .042) when controlling for hemoglobin value. These are notable findings as prior research suggests that anemia (low hemoglobin) is a significant contributor to fatigue. A notable outcome is that the average hemoglobin values for MF and ET did not demonstrate anemia, thereby supporting the theory that the fatigue experience is not directly related to the hemoglobin value [15,26,34,37].

Lastly, while initial statistical analyses indicate no statistically significant relationships between depressive symptoms and fatigue severity for patients with MPNs, this supports prior research implicating a possible underlying factor [26,38]. Furthermore, due to the close interrelationship between fatigue and depression symptoms, it stands to reason that the current study supports the categorization of fatigue as residual symptoms of depression [38]. A more in-depth analysis focusing on specific symptoms indicated that there are relationships between depressive and fatigue symptoms, supporting the claim that the combination promotes a sedentary lifestyle further exacerbating symptoms [25].

Of note, existing studies regarding fatigue within the MPN population have primarily utilized the Myeloproliferative Neoplasm Symptom Assessment Form (*MPN-SAF*)[22-26]. While appropriate for the use in the population, the use of the FSS presents a different way of evaluating fatigue. Similarly, the evaluation of individual symptoms within the BDI-II emphasizes specific dimensions that may otherwise be missed due to focus on a total score.

Clinical implications

With limited information available regarding definitive etiology of fatigue and depression within the MPN population, this study provides evidence that both symptoms are markedly present, and are significantly impactful. Although fatigue and depression may not be independently or mutually life-threatening, both significantly impact quality of life and psychological well-being. This study supports prior research that has demonstrated that individuals with MPNs manifest greater-than-expected intensity of fatigue [22-26]. Moreover, while existing information regarding depression within this population is minimal, this study similarly espouses the salient presence of this symptom within the MPN population. This is a notable finding as it is also an established fact that fatigue is a common symptom of depression intrinsically suggesting that the presence of one signifies the existence of the other [29]. Furthermore, as the results from this studsy indicate that the average hemoglobin values did not demonstrate anemia, this is in support of prior research that suggest that the fatigue experience is not directly related to the hemoglobin value [22-26].

The culmination of said findings with the use of a non-targeted fatigue questionnaire and a limited sample indicates that this is a veritable topic of concern. This study has implications that may affect both future practice and research, as the subject being examined directly relates to individuals that may be offered alternative interventions. While biomedical advances are assisting in improving the mortality rate for afflicted individuals, the chronic nature of MPNs warrants equally determined attention toward improvement in quality of life.

Discussions regarding the presence and severity of subjective symptoms such as fatigue and depression can help identify interventions to improve quality of life as well as compliance with therapeutic modalities. This is particularly relevant in the MPN population, as one of the first-line therapies, pegylated-interferon-a, endorses the potential induction and worsening of depression and/or suicidality. Consequently, the revelation of notable mental health concerns merits a therapeutic collaboration with mental health professionals.

Conclusion

The significance of this study is that it explores an area not previously addressed in existing research. As life expectancy is not consistently impacted by MPNs, quality of life research is equally necessary. The results of this study showed that further understanding of the role of fatigue and potential underlying factors may assist in the development and implementation of interventions to improve quality of life within the MPN population.

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