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RESEARCH ARTICLE

The *JAK2*$_{V617F}$ mutation and the role of therapeutic agents in alleviating myeloproliferative neoplasm symptom burden

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Abstract

Alleviating symptom burden in patients with myeloproliferative neoplasms (MPNs) is imperative to achieving optimal management. Research remains to elucidate the relationship between the *JAK2*$_{V617F}$ (*Janus kinase 2*) mutation present in many MPN patients, and the symptomatology they experience. This retrospective study analysed data collected from MPN patients included in the Myeloproliferative Neoplasms: An In-depth Case–Control (MOSAICC) pilot study. The MPN Symptom Assessment Form was administered, and median symptom scores were compared between *JAK2*$_{V617F}$-positive and *JAK2*$_{V617F}$-negative groups. Multivariate logistic regression analysis adjusted for confounding variables. Overall, 106 MPN patients participated: 65.1% were *JAK2*$_{V617F}$ positive, 30.2% were *JAK2*$_{V617F}$ negative and 4.7% had an unknown status. Multivariate analysis revealed a low symptom burden for early satiety ($p < 0.01$), dizziness ($p < 0.05$), cough ($p < 0.05$) and bone pain ($p < 0.01$) in those receiving venesection alone. Interferon alpha was significantly associated ($p < 0.05$) with severe burden for 16 of the 27 symptoms. *JAK2*$_{V617F}$-positive females experienced a greater symptom burden than *JAK2*$_{V617F}$-positive males. There was no discernible relationship between the *JAK2*$_{V617F}$ mutation and symptom burden in MPN patients, unlike the therapeutic agents investigated. Larger studies are required to validate these results and identify mechanisms of symptom development and control in MPN patients.

KEYWORDS
essential thrombocythaemia, Janus kinase 2, management, myeloproliferative neoplasm, polycythaemia vera, primary myelofibrosis, treatment

1 | INTRODUCTION

Overproliferation of cells within the myeloid lineage, due to dysfunctional haematopoiesis, can result in the development of a group of haematological disorders known as myeloproliferative neoplasms (MPNs). The Philadelphia chromosome (*BCR:ABL*)-negative MPNs consist of essential thrombocythaemia (ET), polycythaemia vera (PV) and primary myelofibrosis (PMF) [1]. ET has the highest reported incidence rate worldwide, followed by PV and PMF [2].

Many patients with MPNs harbour an acquired driver mutation of either *Janus kinase 2 exon 14* (*JAK2*$_{V617F}$), the *calreticulin gene* (*CALR*), the *thrombopoietin receptor gene* (*MPL*) and/or exon 12 of the *JAK2*

gene [3]. The *JAK2*$_{V617F}$ mutation is most prevalent and is seen in approximately 99% of PV patients, 65% of PMF patients and 55% of ET patients [4]. This acquired gain-of-function mutation results in abnormal activation of the Janus kinase-signal transducer and activator of transcription (JAK–STAT) pathways, resulting in the over proliferation of myeloid cells seen in patients with MPNs [5, 6].

MPNs can have a great impact on an individual's quality of life (QoL), and patients may present with a wide range of symptoms. The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) was developed and validated to assess symptom burden to guide management of these patients [7].

An international study involving 699 MPN patients demonstrated the impact of MPNs on QoL. Using the Landmark health survey, results revealed that most patients felt a correlation between MPN-associated symptoms and a poorer QoL (83% in PMF, 74% in ET and 72% in PV). It was also shown that symptom severity did not always correlate with the stage of disease, illustrating the importance of utilising symptom scoring and QoL assessments when managing patients with MPNs [8].

Whilst MPN-SAF can be utilised for all MPN subtypes, current treatment guidelines remain MPN subtype specific. First-line therapy for PV includes aspirin and venesection, whilst initial management for many ET patients is aspirin only. *JAK* inhibitors are currently first-line treatments for patients with PMF, with therapies such as corticosteroids, androgens, erythropoiesis-stimulating agents, immunomodulators and/or splenectomy being used to correct anaemia [9]. Cytoreductive therapies are used depending on the risk level of the individual. Hydroxycarbamide is often used as first-line cytoreductive treatment in MPNs [9], but in the long term, it has been associated with increased risk of skin cancer [10] and in combination with other cytoreductive agents has been associated with leukaemic transformation [11]. Other therapies include ruxolitinib, interferon alpha (IFNα), anagrelide, busulfan, pipobroman and P32, with choice of drug depending on patient factors and disease state [9, 12].

The varying treatment options and associated impact on QoL have been studied amongst MPN subtypes; however, there appears to be a paucity of research into the influence of the *JAK2*$_{V617F}$ mutation on QoL and the effect that specific therapeutic agents might have on this. Considering this, a retrospective study was used to examine the data collected as part of the Myeloproliferative Neoplasms: An In-depth Case–Control (MOSAICC) pilot study [13]. The objective was to investigate whether there were differences in symptom severity and QoL by *JAK2*$_{V617F}$ status and to investigate the potential impact of therapeutic agents.

2 | METHODS

This retrospective case cohort study analysed the data collected from patients with MPNs as part of the MOSAICC pilot study following a previously described protocol [13]. The pilot study was carried out between 2013 and 2014. Ethical approval was granted by the Office for Research Ethics Committee, Northern Ireland (OREC-NI 12/NI/0165). Data were collected through a self-completed MPN-SAF questionnaire, telephone interviews with trained researchers and clinical report forms completed by their healthcare team.

The MPN-SAF questionnaire required participants to rate 27 MPN symptoms on a scale from 0 (absent or does not interfere) to 10 (worst imaginable or completely interferes) [7].

Data were categorised into presence or absence of comorbidity, classified as the presence of two or more medical diseases [14], with the MPN diagnosis accounting for one of these diseases. Body mass index (BMI) was dichotomised into underweight—normal (<25.0 kg/m^2) and overweight—obese (≥25.0 kg/m^2) [15]. Age and sex were categorised into <60 or ≥60 years and female or male, respectively, whilst smoking status (smoking at least one cigarette daily) was defined as current (yes or no) and alcohol intake defined by current consumption of alcohol (yes or no).

Comparisons of baseline characteristics and treatment data between *JAK2*$_{V617F}$-positive and *JAK2*$_{V617F}$-negative groups were analysed using Fisher's exact and chi-squared tests. Treatment data were categorised into current use (yes or no), and treatment groups containing a sample size of less than five were merged into an 'other' group. Overall median and interquartile ranges (IQRs) were calculated for each symptom on the MPN-SAF. Symptom prevalence was calculated for the overall cohort as well as the *JAK2*$_{V617F}$-positive and *JAK2*$_{V617F}$-negative groups by taking all those who reported a score of ≥1 and dividing this by the total number of participants in each group. Nonparametric data were initially analysed using the Mann–Whitney *U* and Kruskal–Wallis tests. An ordinal logistic regression model was used to analyse the relationship between therapeutic agents and each MPN-SAF variable by calculating adjusted odds ratios (AORs) and 95% confidence intervals (CIs). The regression model was adjusted for concurrent medical therapies, age, gender, *JAK2*$_{V617F}$ status, BMI, comorbidity, smoking status and alcohol intake. Statistical analysis was conducted using R (version 4.1.2) [16], with *p*-values <0.05 considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics

A total of 106 MPN patients participated in the MOSAICC pilot study, of which 65.1% were *JAK2*$_{V617F}$ positive ($n = 69$), 30.2% were *JAK2*$_{V617F}$ negative ($n = 32$) and 4.7% had unknown *JAK2*$_{V617F}$ status ($n = 5$). Overall, this resulted in a patient participation rate of 66.7%. Baseline characteristics were distributed similarly across *JAK2*$_{V617F}$ cohorts and there were no significant differences in characteristics between the groups (Table 1).

3.2 | Treatment groups

Overall, the most prescribed therapy was aspirin (74.5%), followed by hydroxycarbamide (66.0%), venesection (17.0%) and IFNα (11.3%). For all therapeutic agents analysed, *JAK2*$_{V617F}$-positive patients accounted

TABLE 1 Baseline characteristics.

	Overall ($n = 106$)[a], n (%)	$JAK2_{V617F}$ positive ($n = 69$), n (%)	$JAK2_{V617F}$ negative ($n = 32$), n (%)	$JAK2_{V617F}$ positive versus $JAK2_{V617F}$ negative, p-value[b]
Age				0.634
<60 years	33 (31.1)	21 (30.4)	12 (37.5)	
≥60 years	73 (68.9)	48 (69.6)	20 (62.5)	
Gender				1.000
Female	64 (60.4)	43 (62.3)	20 (62.5)	
Male	42 (39.6)	26 (37.7)	12 (37.5)	
Body mass index (kg/m^2)				0.413
Underweight—normal (<25.0)	46 (43.4)	33 (47.8)	12 (37.5)	
Overweight—obese (≥25.0)	59 (55.7)	35 (50.7)	20 (62.5)	
Current cigarette smoker				0.715
Yes	9 (8.5)	7 (10.1)	2 (6.3)	
No	97 (91.5)	62 (89.9)	30 (93.8)	
Currently consumes alcohol				0.950
Yes	65 (61.3)	43 (62.3)	19 (59.4)	
No	41 (38.7)	26 (37.7)	13 (40.6)	
Comorbidity[c]				0.428
Yes	83 (78.3)	56 (81.2)	23 (71.9)	
No	23 (21.7)	13 (18.8)	9 (28.1)	

[a]Overall cohort ($n = 106$) contains five participants with unknown JAK2 status.
[b]Chi-squared/Fisher's exact test used to compare groups between $JAK2_{V617F}$-positive and $JAK2_{V617F}$-negative cohort.
[c]Self-reported comorbidity, defined as presence of ≥2 conditions including myeloproliferative neoplasm diagnosis [14].

for the largest proportion of users and were significantly higher for aspirin ($p = 0.003$), hydroxycarbamide ($p < 0.001$) and IFNα ($p = 0.021$). Furthermore, females accounted for the greatest proportion of medication users in comparison to males across all treatment groups (data not shown).

3.3 | MPN subtype

Of the 106 MPN patients, 55 (51.9%) were diagnosed with ET, 37 (34.9%) with PV and 14 (13.2%) with PMF. The $JAK2_{V617F}$ mutation was observed in 89.2% of the PV cohort, 56.4% of the ET patients and 35.7% of PMF participants. Analysis of symptom severity between subtypes (PV, ET and PMF) demonstrated significant differences for fever only ($p = 0.025$), which was more common in PMF patients than in PV patients ($p = 0.017$) (data not shown).

3.4 | Symptom prevalence

Amongst the MPN-SAF categories, fatigue was found to be the most prevalent symptom across both $JAK2_{V617F}$ groups, with 90.3% of the overall cohort experiencing fatigue during the 24-h period prior to completion of the questionnaire. All the remaining MPN-SAF symptoms were prevalent amongst more than 50% of the study population. The least prevalent symptom was found to be fever (13.0% and 15.6%, $JAK2_{V617F}$-positive and $JAK2_{V617F}$-negative groups, respectively).

3.5 | Severity of symptoms

Comparison of median symptom scores found that the $JAK2_{V617F}$-positive cohort reported a significantly greater severity of abdominal pain ($p = 0.008$), abdominal discomfort ($p = 0.015$), early satiety ($p = 0.036$) and pruritus ($p = 0.023$) in comparison to their $JAK2_{V617F}$-negative counterparts (Table 2). Once adjusted for potential confounding variables through regression analysis, there were no significant differences in symptom severity between $JAK2_{V617F}$-positive and $JAK2_{V617F}$-negative participants (Table S1).

3.6 | Overall QoL

Overall QoL was impaired in 78.3% and 71.9% of $JAK2_{V617F}$-positive and $JAK2_{V617F}$-negative patients, respectively, with no statistically significant difference between the cohorts ($p = 0.357$) (Table 2).

TABLE 2 Median scores for Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) symptom variables.

	Overall cohort ($n = 106$)			Aspirin ($n = 79$)			Hydroxycarbamide ($n = 70$)			IFNα ($n = 12$)		
Symptoms	$JAK2_{V617F}$ positive ($n = 69$), median score (IQR)	$JAK2_{V617F}$ negative ($n = 32$), median score (IQR)	p-Value[a]	$JAK2_{V617F}$ positive ($n = 51$), median score (IQR)	$JAK2_{V617F}$ negative ($n = 25$), median score (IQR)	p-Value[a]	$JAK2_{V617F}$ positive ($n = 47$), median score (IQR)	$JAK2_{V617F}$ negative ($n = 20$), median score (IQR)	p-Value[a]	$JAK2_{V617F}$ positive ($n = 10$), median score (IQR)	$JAK2_{V617F}$ negative ($n = 2$), median score (IQR)	p-Value[a]
Fatigue now	4.00 (4.50)	3.00 (4.25)	0.498	4.00 (4.00)	4.00 (4.00)	0.951	4.00 (4.00)	3.00 (4.25)	0.736	5.00 (3.50)	5.00 (5.00)	1.000
Fatigue usual 24 h	5.00 (4.50)	3.50 (4.00)	0.480	3.50 (4.00)	4.00 (4.00)	0.721	4.00 (4.00)	3.50 (4.25)	0.878	6.50 (2.00)	4.00 (2.00)	0.325
Fatigue worst 24 h	5.00 (6.00)	4.00 (5.00)	0.223	5.00 (5.00)	5.00 (5.00)	0.807	5.00 (5.00)	4.50 (5.25)	0.637	7.50 (3.50)	5.00 (4.00)	0.587
Fatigue affecting												
General activity	3.00 (5.00)	3.00 (5.00)	0.725	2.00 (5.00)	4.00 (4.00)	0.285	3.00 (5.00)	3.50 (5.00)	0.706	5.00 (3.75)	2.50 (2.50)	0.329
Mood	2.00 (4.00)	2.00 (5.00)	0.705	1.00 (4.00)	2.00 (4.00)	0.178	1.00 (4.00)	2.50 (3.50)	0.343	4.00 (3.50)	2.50 (2.50)	0.447
Walking	2.00 (5.50)	2.00 (5.00)	0.501	2.00 (5.00)	2.00 (5.00)	0.840	2.00 (5.00)	2.50 (5.00)	0.994	5.50 (5.00)	3.50 (3.50)	0.664
Normal work	2.50 (6.00)	3.50 (4.00)	0.872	2.00 (5.50)	4.00 (5.00)	0.479	2.00 (5.00)	4.00 (4.00)	0.385	6.00 (4.75)	3.00 (3.00)	0.331
Relations	1.00 (2.25)	0.00 (5.00)	0.895	1.00 (2.00)	1.00 (5.00)	0.521	1.00 (2.00)	1.00 (5.00)	0.528	2.50 (4.50)	2.50 (2.50)	0.913
Enjoyment	2.00 (5.00)	1.50 (5.00)	0.726	1.00 (4.00)	3.00 (5.00)	0.301	2.00 (4.00)	3.00 (5.25)	0.308	5.00 (3.50)	2.00 (2.00)	0.233
Early satiety	1.00 (4.00)	0.00 (2.00)	**0.036**	1.00 (4.00)	0.00 (2.00)	0.134	1.00 (3.00)	0.00 (1.25)	0.096	2.50 (6.25)	0.00 (0.00)	0.146
Abdominal pain	1.00 (2.25)	0.00 (0.00)	**0.008**	1.00 (2.00)	0.00 (0.00)	**0.039**	0.00 (1.00)	0.00 (0.25)	0.280	4.00 (3.00)	1.50 (1.50)	0.284
Abdominal discomfort	1.00 (3.00)	0.00 (2.00)	**0.015**	1.00 (3.00)	0.00 (2.00)	**0.038**	0.00 (3.00)	0.00 (2.00)	0.493	4.00 (4.25)	1.50 (1.50)	0.194
Inactivity	2.00 (5.00)	1.00 (3.25)	0.172	1.50 (4.00)	1.00 (3.00)	0.488	1.00 (4.00)	1.00 (3.25)	0.595	4.00 (4.00)	2.00 (2.00)	0.282
Headaches	0.00 (2.00)	0.00 (2.50)	0.811	0.00 (2.00)	0.50 (2.25)	0.791	0.00 (2.00)	0.00 (1.50)	0.950	3.50 (4.00)	4.00 (4.00)	0.913
Concentration	2.00 (5.00)	1.00 (4.00)	0.339	2.00 (5.00)	1.00 (4.00)	0.259	1.00 (2.75)	1.00 (4.25)	0.965	6.00 (5.00)	3.50 (3.50)	0.586
Dizziness	2.00 (5.00)	1.00 (3.00)	0.501	1.00 (3.00)	1.00 (3.00)	0.995	2.00 (4.00)	1.00 (3.25)	0.776	4.00 (3.75)	4.00 (1.00)	0.913
Numbness	1.00 (3.00)	0.00 (3.00)	0.070	1.00 (3.00)	0.00 (3.00)	0.252	1.00 (3.00)	0.00 (2.25)	0.352	3.00 (2.50)	3.00 (3.00)	0.829
Difficulty sleeping	3.00 (7.00)	1.00 (5.00)	0.190	3.00 (7.00)	1.00 (5.00)	0.301	3.00 (6.50)	2.50 (5.00)	0.626	5.50 (6.50)	2.50 (2.50)	0.440
Depression	1.00 (4.00)	2.00 (4.00)	0.991	1.00 (3.00)	2.00 (4.00)	0.296	2.00 (4.00)	2.50 (4.25)	0.490	2.00 (4.75)	3.00 (3.00)	0.740
Sexual problems	1.00 (5.00)	3.00 (5.00)	0.539	0.00 (5.00)	3.00 (5.00)	0.298	0.50 (5.00)	2.50 (5.25)	0.446	2.00 (5.75)	2.50 (2.50)	0.911
Cough	1.00 (3.00)	0.00 (2.00)	0.371	1.00 (2.50)	0.00 (2.00)	0.805	1.00 (2.50)	0.50 (2.25)	0.936	0.50 (3.00)	0.00 (0.00)	0.280
Night sweats	1.00 (4.00)	2.00 (5.25)	0.231	0.00 (4.50)	2.00 (6.00)	0.119	0.00 (3.00)	2.00 (5.00)	0.090	2.50 (6.00)	0.00 (0.00)	0.100
Pruritus	2.00 (5.00)	0.00 (2.25)	**0.023**	1.00 (5.00)	0.00 (2.00)	**0.025**	1.00 (4.00)	0.00 (3.00)	0.244	6.50 (4.00)	2.50 (2.50)	0.151

(Continues)

TABLE 2 (Continued)

Symptoms	Overall cohort ($n = 106$)			Aspirin ($n = 79$)			Hydroxycarbamide ($n = 70$)			IFNα ($n = 12$)		
	$JAK2_{V617F}$ positive ($n = 69$), median score (IQR)	**$JAK2_{V617F}$ negative ($n = 32$), median score (IQR)**	***p*-Value[a]**	**$JAK2_{V617F}$ positive ($n = 51$), median score (IQR)**	**$JAK2_{V617F}$ negative ($n = 25$), median score (IQR)**	***p*-Value[a]**	**$JAK2_{V617F}$ positive ($n = 47$), median score (IQR)**	**$JAK2_{V617F}$ negative ($n = 20$), median score (IQR)**	***p*-Value[a]**	**$JAK2_{V617F}$ positive ($n = 10$), median score (IQR)**	**$JAK2_{V617F}$ negative ($n = 2$), median score (IQR)**	***p*-Value[a]**
Bone pain	1.00 (4.00)	0.00 (2.00)	0.085	1.00 (4.00)	0.00 (2.00)	0.133	1.00 (3.00)	0.00 (1.50)	0.317	3.00 (6.25)	1.00 (1.00)	0.380
Fever	0.00 (0.00)	0.00 (0.00)	0.851	0.00 (0.00)	0.00 (0.00)	0.581	0.00 (0.00)	0.00 (0.00)	0.679	0.00 (0.75)	0.00 (0.00)	0.481
Weight loss	0.00 (1.00)	0.00 (0.00)	0.300	0.00 (0.50)	0.00 (0.00)	0.180	0.00 (0.50)	0.00 (0.00)	0.128	0.00 (2.75)	0.00 (0.00)	0.371
Overall QoL	2.00 (4.00)	1.50 (4.00)	0.357	2.00 (3.00)	2.00 (3.00)	0.866	2.00 (4.00)	2.50 (3.25)	0.451	5.00 (2.50)	2.00 (2.00)	0.158

Note: Severity of symptoms were rated on a scale from 0 (absent or does not interfere) to 10 (worst imaginable or completely interferes) [7].

Abbreviations: IFNα, interferon alpha; IQR, interquartile range; QoL, quality of life.

Bold text highlights significant associations and refers to *p*-values < 0.05.

[a]Mann–Whitney *U*-test comparing symptom scores between $JAK2_{V617F}$-positive and $JAK2_{V617F}$-negative patients and between treatment groups for those prescribed either aspirin, hydroxycarbamide or IFNα.

Analysis of overall QoL scores for each treatment group revealed that the greatest impairment to overall QoL was reported by $JAK2_{V617F}$-positive patients receiving IFNα therapy (median, 5.00; IQR, 2.50) (Table 2). This was reinforced with the regression analysis where IFNα was associated with a significantly profound impairment to overall QoL when all potential confounding variables were held constant (AOR 7.08; 95% CI 1.53–32.81) (Figure 1).

3.7 | Symptom burden across treatment groups

For all three treatment groups (aspirin, hydroxycarbamide and IFNα) analysed in Table 2, significant differences in symptom severity between $JAK2_{V617F}$ cohorts were seen only in the aspirin treatment group. Statistical significance was observed for variation in abdominal pain ($p = 0.039$), abdominal discomfort ($p = 0.038$) and pruritus ($p = 0.025$), where the severity was greater within the $JAK2_{V617F}$-positive participants.

When potential confounding factors were adjusted for, a low symptom burden was observed in those receiving venesection compared to those not receiving venesection. This was statistically significant for early satiety (AOR 0.20; 95% CI 0.06–0.62), dizziness (AOR 0.32; 95% CI 0.10–0.94), cough (AOR 0.28; 95% CI 0.08–0.87) and bone pain (AOR 0.19; 95% CI 0.06–0.60) (Figure 1). As venesection is offered solely for patients with PV, it is unsurprising that the venesection cohort consisted entirely of $JAK2_{V617F}$-positive participants. Therefore, it was not possible to compare symptom severity between $JAK2_{V617F}$-positive and $JAK2_{V617F}$-negative participants for this therapy.

In contrast, a profound symptom burden across all variables, with the exception of cough (AOR 0.83; 95% CI 0.16–4.10), was found in patients who were undergoing IFNα therapy. Severe symptom burden in the IFNα cohort was especially significant for abdominal pain, with an AOR of 19.63 (95% CI 2.55–108.69).

Analysis of the hydroxycarbamide treatment group found the severity of abdominal discomfort to be significantly lower than those not receiving hydroxycarbamide (AOR 0.31; 95% CI 0.12–0.78). Finally, the aspirin treatment group was the only treatment group to demonstrate no significant association between aspirin treatment and symptom burden (Figure 1).

3.8 | Sex differences in symptom burden

Amongst patients with the $JAK2_{V617F}$ mutation, females reported a significantly greater severity of fatigue affecting their mood ($p = 0.046$), abdominal discomfort ($p = 0.034$), headaches ($p = 0.001$), depression ($p = 0.034$) and night sweats ($p = 0.049$) than males. In contrast, $JAK2_{V617F}$-positive male participants reported a significantly greater burden of sexual problems ($p = 0.034$) than females (Table 3).

Within the $JAK2_{V617F}$-negative cohort, symptom severity between males and females appeared to be similar for most symptoms, except for night sweats which were rated more severe in females ($p = 0.004$).

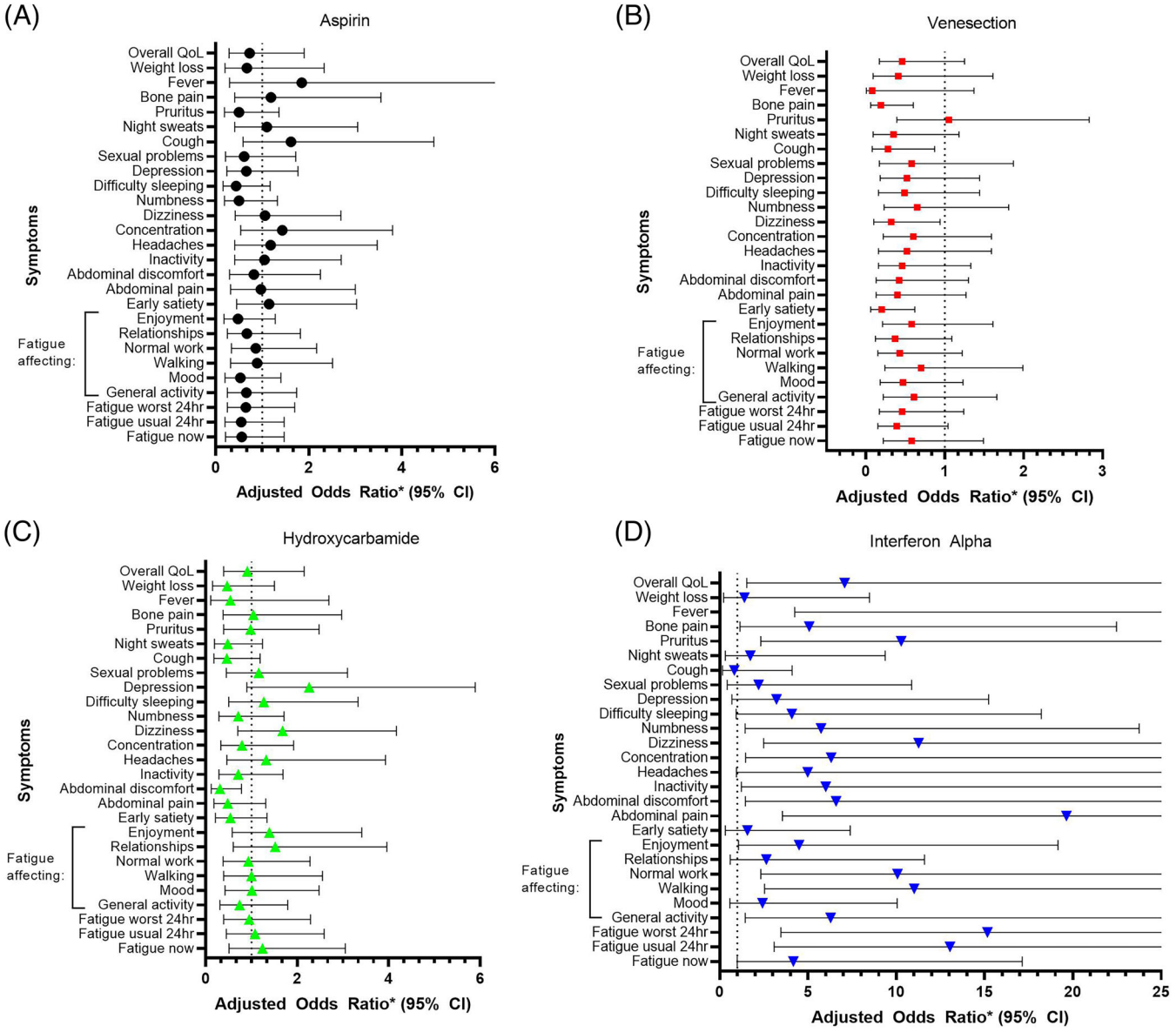

FIGURE 1 Treatment group regression analysis. Forest plots display results from ordinal logistic regression. Adjusted odds ratios (AORs) and 95% confidence intervals (CIs) were calculated to determine association between each treatment group and symptom severity. The results are shown for (A) aspirin, (B) venesection, (C) hydroxycarbamide and (D) interferon alpha (IFNα). The results not visible on graph (D) IFNα for fever (AOR 86.9; 95% CI 4.25–1777.55). *Adjusted for concurrent medication use, age, gender, baseline body mass index (BMI), comorbidity, smoking status, *JAK2*$_{V617F}$ status and current alcohol intake. AOR and 95% CI data are provided in Table S2. QoL, quality of life.

Furthermore, overall QoL was significantly poorer in female *JAK2*$_{V617F}$-negative participants than in their male counterparts ($p = 0.022$) (Table 3).

4 | DISCUSSION

To our knowledge, this is the first study to compare the symptom burden between *JAK2*$_{V617F}$-positive and *JAK2*$_{V617F}$-negative MPN patients. Results from regression analysis demonstrated no discernible association between the *JAK2*$_{V617F}$ mutation and symptom burden. This implies input from other factors contributing to the extensive symptom burden experienced by MPN patients. Analysis of the impact of therapeutic agents on symptom burden revealed a significantly lower symptom burden in the venesection treatment group, which contrasted with the profound symptom burden experienced by patients receiving IFNα. Amongst all the MPN participants fatigue was the most prevalent symptom, whilst fever was the least prevalent; a finding that has previously been reported in this group of patients [17].

In contrast to the low symptom burden seen in the MOSAICC MPN patients receiving venesection, other studies have demonstrated significant symptom burden in venesection patients compared to those

TABLE 3 Sex differences in symptom burden.

Symptoms	$JAK2_{V617F}$ positive ($n = 69$)			$JAK2_{V617F}$ negative ($n = 32$)		
	Female ($n = 43$), median score (IQR)	Male ($n = 26$), median score (IQR)	p-Value[a]	Female ($n = 20$), median score (IQR)	Male ($n = 12$), median score (IQR)	p-Value[a]
Fatigue now	4.50 (4.75)	3.00 (4.00)	0.105	4.00 (4.50)	2.00 (4.25)	0.223
Fatigue usual 24 h	5.00 (4.00)	3.00 (4.00)	0.138	4.00 (4.00)	2.00 (2.5)	0.316
Fatigue worst 24 h	6.00 (4.75)	4.00 (5.00)	0.124	5.00 (4.25)	3.00 (4.25)	0.176
Fatigue affecting						
General activity	3.00 (4.00)	3.00 (5.00)	0.570	4.00 (4.25)	1.00 (5.00)	0.321
Mood	3.00 (4.75)	1.00 (2.00)	**0.046**	3.00 (4.25)	1.50 (2.75)	0.213
Walking	3.00 (6.00)	2.00 (4.75)	0.510	2.50 (5.00)	0.50 (4.25)	0.545
Normal work	3.00 (5.00)	2.00 (4.75)	0.316	4.00 (4.25)	1.50 (5.00)	0.296
Relations	1.00 (3.00)	0.50 (2.00)	0.259	0.00 (5.00)	0.50 (2.50)	0.641
Enjoyment	2.50 (4.00)	2.00 (5.00)	0.352	3.50 (4.25)	0.50 (1.50)	0.064
Early satiety	2.00 (4.00)	1.00 (3.00)	0.243	0.00 (2.00)	0.00 (1.00)	0.438
Abdominal pain	1.00 (2.75)	0.00 (1.75)	0.060	0.00 (0.00)	0.00 (1.25)	0.282
Abdominal discomfort	2.00 (3.50)	0.00 (3.00)	**0.034**	0.00 (2.00)	0.00 (1.50)	0.911
Inactivity	2.00 (4.00)	1.00 (3.50)	0.086	1.00 (3.25)	1.00 (3.25)	1.000
Headaches	2.00 (5.00)	0.00 (0.00)	**0.001**	1.00 (3.50)	0.00 (0.25)	0.059
Concentration	2.00 (5.50)	1.00 (2.00)	0.050	2.00 (4.25)	0.50 (1.25)	0.328
Dizziness	2.00 (5.00)	1.00 (3.00)	0.071	1.50 (4.00)	0.00 (2.25)	0.085
Numbness	2.00 (4.50)	1.00 (3.00)	0.296	0.00 (3.00)	0.50 (2.25)	0.897
Difficulty sleeping	3.00 (6.00)	2.00 (3.75)	0.066	4.00 (5.25)	0.50 (1.50)	0.069
Depression	2.00 (4.50)	1.00 (2.00)	**0.034**	2.00 (5.00)	0.50 (3.00)	0.149
Sexual problems	0.00 (3.25)	3.50 (5.75)	**0.034**	2.50 (5.25)	3.00 (4.50)	0.594
Cough	1.00 (3.00)	0.50 (2.00)	0.442	0.00 (2.25)	1.00 (2.00)	0.465
Night sweats	2.00 (5.00)	0.00 (1.75)	**0.049**	4.50 (6.00)	0.00 (1.25)	**0.004**
Pruritus	2.50 (5.75)	1.00 (3.75)	0.256	0.00 (2.50)	0.00 (1.50)	0.591
Bone pain	1.00 (5.00)	1.00 (2.75)	0.316	0.00 (2.25)	0.00 (0.25)	0.253
Fever	0.00 (0.00)	0.00 (0.00)	0.759	0.00 (0.00)	0.00 (0.00)	0.926
Weight loss	0.00 (0.00)	0.00 (1.75)	0.366	0.00 (0.00)	0.00 (0.00)	0.864
Overall QoL	2.00 (3.50)	2.00 (4.50)	0.577	3.50 (3.25)	0.50 (2.00)	**0.022**

Note: Severity of symptoms were rated on a scale from 0 (absent or does not interfere) to 10 (worst imaginable or completely interferes) [7].
Abbreviations: IQR, interquartile range; QoL, quality of life.
Bold text highlights significant associations and refers to p-values < 0.05.
[a]Mann–Whitney U-test comparing symptom scores between females and males in both $JAK2_{V617F}$-positive and $JAK2_{V617F}$-negative cohorts.

receiving alternative therapies [19, 20]. This study corrected for concurrent medication use, which therefore enabled a more robust and comprehensive analysis of the relationship between individual therapeutic agents and symptom burden.

Hydroxycarbamide treatment has shown alleviation of MPN symptoms [21, 22]. Those taking hydroxycarbamide treatment in this study had lower AORs for many symptoms than those not taking hydroxycarbamide but there were no significant differences were detected.

IFNα therapy has been a controversial treatment option for MPNs, often associated with high levels of toxicity and an extensive side effect profile leading to high rates of discontinuation [23]. IFNα acts on many different pathways including activation of the JAK–STAT pathways. The binding of IFNα to receptors in turn results in activation and phosphorylation of Janus-activated kinases, resulting in activation of gene expression [24] and a reduction in $JAK2_{V617F}$ allele burden [25, 26]. In the current study patients receiving IFNα demonstrated a trend towards a more severe symptom profile in those harbouring the $JAK2_{V617F}$ mutation, suggesting that further investigation would be warranted.

A difference in symptom burden between females and males was most notable in the $JAK2_{V617F}$-positive group. In addition, the findings

showed that *JAK2*$_{V617F}$-negative females reported a significantly higher symptom burden than their male counterparts. Greater symptom burden in female MPN patients has been reported elsewhere [17, 27]. Interestingly, females have been reported to have a reduced *JAK2*$_{V617F}$ allele burden compared to their male counterparts, thus bringing into question the influence of the *JAK2*$_{V617F}$ mutation on symptom profile [28]. The causes attributing to the sex differences observed in symptom reporting are difficult to delineate and are most likely multifactorial and require further investigation.

In both the *JAK2*$_{V617F}$-positive and *JAK2*$_{V617F}$-negative groups, night sweats were rated significantly worse in females. MPNs tend to be a disease of older age [29], with most patients in this study aged 60 years and above. In the general population, females can commonly experience night sweats as part of a post-menopausal syndrome [30]. Whilst MPNs might increase the severity of night sweats the role of vasomotor symptoms in post-menopausal syndrome could account for the significant difference seen between males and females in both *JAK2*$_{V617F}$-positive and *JAK2*$_{V617F}$-negative groups. In addition, fewer males participated in the MOSAICC pilot study; therefore, it is possible that males experiencing a greater symptom burden did not participate. Likewise, patient-reported outcomes are a subjective measure of symptom severity and this consequently results in the potential for self-reporting bias when utilising these measures, perhaps contributing to the variance seen in this study.

The strengths of this study include the ability to adjust for potential confounders and concurrent medication use, which allowed for increased precision in analysis and adjustment for possible synergism between medications. This study appreciates the potential for self-reporting bias as a consequence of patient-reported symptom assessment, as well as the potential for participation bias due to the nonresponse of some of the recruited patients. Further studies including a larger cohort of MPN patients would be appropriate to fully elucidate the results reported here. Additionally, evaluating treatment duration and dose could provide a more thorough analysis of the treatment-related influence on symptomatology in MPN patients.

This study assessed symptom profile and severity variation between *JAK2*$_{V617F}$-positive and *JAK2*$_{V617F}$-negative patients. Whilst previous work has identified the effect of symptoms on QoL amongst MPN patients based on subtype, this study provides further insight into the impact of the *JAK2*$_{V617F}$ mutation on QoL. A greater understanding of the impact of the *JAK2*$_{V617F}$ mutation on patient QoL will help to guide therapeutic targets and shape development of future treatment options for the management of patients with MPNs. Furthermore, whilst this study focuses on the effect of the *JAK2*$_{V617F}$ mutation testing for other known mutations associated with MPNs, such as *CALR* and *MPL*, was not carried out in the study population, and therefore, the effect of these mutations on symptom severity remains unknown.

One limitation of this study was the failure to take into account the duration and stage of disease, which could influence symptom burden amongst MPN patients. Furthermore, the question remains as to whether the relatively low symptom burden observed with aspirin and venesection in comparison to hydroxycarbamide and IFNα is due to the action of the therapeutic agents themselves or whether those receiving the cytoreductive drugs have a greater disease burden. A further limitation is the relatively small cohort size, perhaps due in part to the rare nature of this group of diseases. It is hoped that the larger MOSAICC study will be able to further investigate the results reported here.

The results presented here reflect the therapies that were used in clinical practice at the time of data collection. Thus, since the time of data collection, newer drugs, such as ruxolitinib, have been licensed for use; therefore, this study was unable to analyse the therapeutic benefit of the most recent drugs on MPN-associated symptomatology, an analysis that could be included in the current ongoing study.

In conclusion, this contemporary study demonstrates that there is no discernible relationship between *JAK2*$_{V617F}$ status and symptom profile. Furthermore, when potential confounding variables were adjusted for, a low symptom burden was observed with venesection therapy which contrasted with the high symptom burden seen with IFNα therapy. Regardless of mutation, MPNs have a considerable impact on a patient's QoL, and thus, it is important for physicians to consider the presenting symptoms when managing patients.

AUTHOR CONTRIBUTIONS

The original pilot study design and data collection were carried out by the MOSAICC steering group; comprising of Lesley A Anderson; Andrew Duncombe; Mary Frances McMullin; Ruben Mesa and Glen James. Lai Yee Orbell analysed the data and wrote the paper. The MOSAICC steering group; Nouf Abutheraa and Charlene M McShane contributed to critically revising and approving the final research article.

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CONFLICT OF INTEREST STATEMENT

Mary Frances McMullin—BMS: advisory boards and clinical trial support; AbbVie: advisory boards and speaker bureau; CTI: advisory boards; Sierra oncology: advisory board. Ruben Mesa—Novartis/Sierra Onc/LaJolla/Pharma/Constellation: consultant; Celgene/Incyte/Abbvie/Samus/Genotech/Promedior/CTI/Constellation: research support.

DATA AVAILABILITY STATEMENT

Data access can be sought through submission of a data request to the MOSAICC steering group led by Prof Anderson (les-

ley.anderson@abdn.ac.uk). If approved a data transfer arrangement would be required.

ETHICS STATEMENT

Ethical approval was granted by the Office for Research Ethics Committee, Northern Ireland (OREC-NI 12/NI/0165). The study was performed in accordance with the Declaration of Helsinki.

PATIENT CONSENT STATEMENT

All participants provided written informed consent.

CLINICAL TRIAL REGISTRATION

NCT01831635.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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