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Risk of infection in MPN patients in the era of Covid-19: A prospective multicenter study of 257 patients from the CML-MPN Quebec Research Group

To the Editor:

Recent studies have disclosed higher rates of infection in patients with the classic Philadelphia-negative myeloproliferative neoplasms (MPN).[1-3] Importantly, this increased propensity to infections appears to be inherent to the disease itself, irrespective of cytoreductive therapy.[2,3] The risk of death due to infection is also increased in the MPN population compared to controls.[2,4] From a real-world vantage point, an informative large-scale European study recently found relatively high rates of infection (50.5%) in their MPN cohort, more pronounced in those patients with myelofibrosis (MF) and/or receiving ruxolitinib (RUX) therapy.[1] However, further contemporary data examining the direct impact of MPN subtype, driver mutation, disease-directed therapy, prophylaxis and vaccination, and select concurrent medication on infection rates in MPN remain scarce. No such studies have been conducted, to our knowledge, in Canada, and few – if any, in North America. Moreover, the rates of Covid-19 infection and associated clinical consequences in a large unselected, real-world MPN cohort have not previously been assessed. The objectives of this pan-provincial population-based study were accordingly to evaluate: (i) infection frequency and types; (ii) common prophylactic measures; and (iii) influence of molecular background, disease-directed therapy, and concomitant medications, on infection outcomes in patients with Philadelphia-negative MPN included in an extensive Quebec registry.

The current prospective study included five academic centers across Quebec, Canada. The diagnosis of polycythemia vera (PV), essential thrombocythemia (ET) and MF were in concordance with the 2016 WHO criteria.[5] All patients, having given prior informed consent, were participants in the chronic myeloid leukemia-MPN Quebec Research Group (GQR LMC-NMP) registry and database. Data was collected between June 29, 2020 and August 3, 2020 and consisted of patient-reported details, via structured telephone and/or email questionnaires, with subsequent physician review of the nature/frequency of infection, vaccination and drug prophylaxis, and MPN-directed drug exposure in the past 12 months. The MPN-specific data (for example, subtype, driver mutations status,) were abstracted from database records. Infection-associated data related exclusively to the previous 12-month time period. Standard statistical methods were used to compare variables across groups with p values < .05 considered significant. Differences in the distribution of continuous variables between categories were compared using the Mann–Whitney or Kruskal–Wallis test. Categorical variables were compared using the χ^2 test. The JMP Pro 14.1.0 software package was used for all analyses (SAS Institute, Cary, NC, USA).

The clinical characteristics and infection types and severity for 257 informative MPN cases stratified by disease subtype are presented in Table 1. The cohort included 95 PV, 125 ET, and 37 MF patients with overall median age of 70 years (range 26–93 years) and a 40:60 male to female distribution. Driver mutation status for 235 evaluable cases was as follows: *JAK2* (84%), *CALR* (12%), *MPL* (2%), and triple negative (2%). In the previous 12 months, the majority of patients had been exposed to hydroxyurea (HU) (n = 155; 68%), followed by RUX (n = 32; 14%), multiple cytoreductive drugs or combinations (n = 18; 8%), anagrelide (n = 8; 3%), interferon (n = 4; 2%), or busulfan (n = 2; 1%), while 10 patients (4%) had not received any MPN-specific therapy. Most subjects had received low-dose aspirin (n = 201; 78%), with skewing towards PV/ET versus MF cohorts (p < .001). Overall, 86 patients (33%) reported at least one infectious episode over the past 12 months. For those treated on an outpatient basis, 48 (19%) reported a single episode while 29 (11%) had more than one episode, with relatively balanced distribution across MPN subtypes (p = .6). In total, 12 patients (5%) required inpatient treatment, represented primarily by MF patients (n = 5; 14%) versus those with PV (n = 3; 3%) and ET (n = 4; 3%) (p = .06). Infection types overall

were as follows: urinary tract (11%), ears nose throat (ENT) (9%), other – including dental, vaginal, and epididymal (7%), cutaneous (6%), herpes zoster (5%), bronchitis (4%), pneumonia (3%), gastrointestinal (GI) (2%), and Covid-19 (1%). Infection types were proportional across MPN subtypes with the exception of a trend towards higher rates of zoster infection in the MF sub-group (14% vs. 3% PV and 4% ET; p = .08). Antibiotic, antiviral, and antifungal prophylaxis had been received by 3 (1%), 3 (1%), and 1 (<1%) patient, respectively, with the majority consisting of MF patients. Vaccinations for influenza, herpes zoster, and pneumococcal pneumonia had been reported in 115 (45%), 16 (6%), and 19 (7%) patients, respectively, with no bias in MPN type.

Clinical parameters of MPN patients stratified according to occurrence of infectious complications are detailed in Table S1. No appreciable differences were detected on the basis of age (>65 years old vs. younger; p = .4), MPN subtype (p = .6), driver mutation (p = .9), or concurrent aspirin therapy (p = .3). Analysis by gender disclosed a higher frequency of infections in females versus males (38% vs. 26%; p = .04). From a treatment standpoint, most of the patients treated with ruxolitinib in the past 12 months presented at least one infectious event (n = 18; 56%), while events were reported in 39%, 30%, and 13% of those having received multiple/combination therapies, hydroxyurea, and anagrelide, respectively. As 18 patients (8%) had received either multiple agents or combinations thereof, specification of *any* RUX use in the past 12 months disclosed a significant association with infectious events (p = .001), while none were observed with hydroxyurea use (p = .2). Of note, none of the four patients treated with interferon and, conversely, both patients treated with busulfan, reported an infectious episode. While only a minority of patients were exempt from any cytoreductive therapy in the previous year (n = 10), 20% of them reported being treated for an infection. Vaccination status for influenza and herpes zoster showed no significant association with infection rate (p = .2 and .4, respectively), though none of the 16 patients vaccinated against zoster reported zoster infections in the timeframe of interest. In contrast, the majority of patients having received the pneumococcal vaccine (n = 11; 58%) declared having had an infectious event in the past year (p = .02). Of the entire cohort, only two patients reported having contracted the Covid-19 virus, one of which required hospitalization without intensive care support.

This multicenter prospective, patient-reported study of infection outcomes in MPN confirms clinically relevant rates of infection in all MPN subtypes, though somewhat lower than those previously described (33% vs. previously reported 45–50%).[1,3] Though limited by factors including potential recall and regional biases, as well as logistics beyond the scope of this report, such as disease and therapy duration, co-morbidities, complete drug history, or infection grade, the current study critically represents a large dataset derived from an "all-comers" highly inclusive MPN registry, circumventing the bias towards reporting solely severe infections/hospitalizations, and addresses fundamental questions about the prevalent phenomenon of infections in MPN from a practical, real-world standpoint. Interestingly, our data did not disclose a significant association between infection risk and advanced age, a finding which concurs with some,[1] though not other reports,[2] suggesting an uncertain role for age as a substantive, isolated risk factor for infections in MPN. The apparent increase in infection rate in women versus men in this study is challenging to interpret, but may be due to gender differences in adverse event reporting, known to occur in some patient-reported study settings, and possibly disproportionate representation of UTI in the range of infections. Importantly, in contrast with another similarly-designed study,[1] while more MF patients experienced infectious events compared to their PV/ET counterparts, this did not meet statistical significance, suggesting that in our cohorts, other variables (e.g., disease duration, risk category, or perhaps newly-instituted public health pandemic restrictions and practices) may have more markedly influenced outcomes. Consistent with previous reports, exposure to RUX significantly increased the risk of infection in MPN patients, with a specific predilection towards herpes infections,[6] while exposure to hydroxyurea had no impact, conceivably due, in part, to its use primarily in PV/ET populations. The former observation should sensitize physicians and patients to the infectious risks associated with RUX and advocates for potentially accrued infection surveillance of MPN patients treated with this agent. Interestingly, while uncommonly utilized, individuals treated with busulfan experienced the second highest rate of infection, while those having been exposed to multiple or combination therapies were the third most affected, serving as a potential warning when considering multidrug regimens in these patients. Finally, patients who were vaccinated for pneumococcus in the last 12 months had a significant increase in infectious events, possibly reflecting an impetus for vaccination driven by recent infections or perhaps greater inherent susceptibility of these patients rationalizing the vaccination event.

Of note, the fact that data collection occurred during, and pertained to (in part), the period affected by the global Covid-19 pandemic, greater caution may have been exercised by these patients, potentially affecting infection endpoints. As certain of our observations challenge data from previous reports[1] (e.g., lower rates of infection, lack of association with MPN sub-type), highlighted by the fact that few patients in our cohort contracted Covid-19 (much less than would be expected given provincial infection rates and the median age of our cohort), the far-reaching impact of the pandemic and associated sanitary measures may at least be partially accountable, which in itself is a novel finding mandating further study. If rates of infections in patients with MPN have in fact been reduced since the onset of the Covid-19 outbreak, this data provide a clear signal to both patients and health care providers that current precautions are effective and warranted. Overall, the current observations provide additional significant insight into infection outcomes in MPN and represent the only such data from a large provincial registry reflecting a real-world setting.

TABLE 1 Descriptive statistics of MPN patients surveyed on infectious complications

Characteristics	All MPN patients (*n* = 257)	PV patients (*n* = 95)	ET patients (*n* = 125)	MF patients (*n* = 37)	*p* value
Age, years; median (range)	70 (26–93)	72 (36–93)	68 (26–92)	73 (47–86)	.08
Males; *n* (%)	103 (40)	46 (48)	36 (29)	21 (57)	**.001**
Driver mutation "N" evaluable = 235 (91%)					
JAK2; *n* (%)	197 (84)	91 (100)	85 (74)	21 (72)	
CALR; *n* (%)	28 (12)	—	24 (21)	4 (14)	**<.001**
MPL; *n* (%)	5 (2)	—	3 (2.5)	2 (7)	
Triple negative; *n* (%)	5 (2)	—	3 (2.5)	2 (7)	
MPN-related therapy, past 12 months "N" evaluable = 229 (89%)					
Hydroxyurea; *n* (%)	155 (68)	68 (78)	82 (75)	5 (15)	
Ruxolitinib; *n* (%)	32 (14)	10 (11)	3 (3)	19 (58)	
Anagrelide; *n* (%)	8 (3)	1 (1)	5 (5)	2 (6)	
Interferon; *n* (%)	4 (2)	1 (1)	3 (3)	0 (0)	**<.001**
Busulfan; *n* (%)	2 (1)	0 (0)	2 (2)	0 (0)	
Multiple/combinations[a]; *n* (%)	18 (8)	5 (6)	10 (9)	3 (9)	
None; *n* (%)	10 (4)	2 (2)	4 (4)	4 (12)	
Aspirin therapy; *n* (%)	201 (78)	77 (81)	107 (86)	17 (46)	**<.001**
Any infection requiring treatment in past 12 months; *n* (%)	86 (33)	32 (34)	39 (31)	15 (41)	.6
Outpatient treatment required for infection in past 12 months					
>1 infection; *n* (%)	29 (11)	14 (15)	10 (8)	5 (14)	
1 infection; *n* (%)	48 (19)	17 (18)	25 (20)	6 (16)	.6
None; *n* (%)	180 (70)	64 (67)	90 (72)	26 (70)	
Inpatient treatment required for infection in past 12 months					
1+ infection; *n* (%)	12 (5)	3 (3)	4 (3)	5 (14)	
None; *n* (%)	245 (95)	92 (97)	121 (97)	32 (86)	.06
Infection type					
ENT[b]; *n* (%)	23 (9)	10 (11)	10 (8)	3 (8)	.8
Bronchitis; *n* (%)	11 (4)	6 (6)	5 (4)	0 (0)	.1
Pneumonia; *n* (%)	7 (3)	2 (2)	5 (4)	0 (0)	.2
Gastrointestinal; *n* (%)	6 (2)	1 (1)	5 (4)	0 (0)	.1
Skin; *n* (%)	16 (6)	6 (6)	9 (7)	1 (3)	.6
Urinary tract; *n* (%)	27 (11)	9 (9)	14 (11)	4 (11)	.9
Herpes zoster; *n* (%)	13 (5)	3 (3)	5 (4)	5 (14)	.08
Covid-19; *n* (%)	2 (1)	1 (1)	1 (1)	0 (0)	.7
Other[c]; *n* (%)	18 (7)	9 (9)	7 (6)	2 (5)	.5
Prophylaxis					
Antibiotic; *n* (%)	3 (1)	0 (0)	1 (1)	2 (5)	.06
Antiviral; *n* (%)	3 (1)	1 (1)	1 (1)	1 (3)	.7
Antifungal; *n* (%)	1 (0.4)	0 (0)	1 (1)	0 (0)	.5
Vaccinations in past 12 months					
Influenza; *n* (%)	115 (45)	46 (48)	58 (46)	11 (29)	.1
Herpes zoster; *n* (%)	16 (6)	8 (8)	6 (5)	2 (5)	.5
Pneumococcal; *n* (%)	19 (7)	8 (8)	9 (7)	2 (5)	.8
Select concurrent medications Steroids; *n* (%)	11 (5)	3 (4)	5 (5)	3 (9)	.5

Abbreviations: ET, essential thrombocythemia; ENT, ears nose and throat; MF, myelofibrosis; MPN, myeloproliferative neoplasms; PV, polycythemia vera.
Bold values denotes significant *p*-values.
[a]Multiple therapies included, either sequentially or in combination: ruxolitinib and anagrelide, ruxolitinib and busulfan, ruxolitinib and hydroxyurea, and hydroxyurea and anagrelide.
[b]ENT infections included sinusitis, common cold, and ear infections, among others.
[c]Other infections included: bacterial vaginosis, oral candida, dental infections, flu, and epididymitis.

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

Data available on request

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SUPPORTING INFORMATION

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

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The prognostic significance of del6q23 in chronic lymphocytic leukemia

To the Editor:

The clinical course of patients with newly-diagnosed chronic lymphocytic leukemia (CLL) is heterogeneous – an estimated 30% of patients never require treatment on long-term follow-up; on the other hand, a significant number of patients need therapy in the first few years after diagnosis.[1] The Dohner classification is the gold standard for cytogenetics-based risk stratification, and uses fluorescence in situ hybridization (FISH) to identify chromosomal abnormalities commonly associated with CLL, including del17p13, del13q14, del11q22, and trisomy 12.[1] Other less-common cytogenetic aberrations have also been noted, including deletion of 6q in 3–7% of CLL cases.[1,2] The prognostic significance of del6q23 remains controversial, likely due to its uncommon occurrence compared to the four other more routinely-noted FISH defects. Several studies have suggested an association of del6q23 with inferior outcomes including shorter overall survival (OS) and shorter treatment-free interval, although others have shown no difference in outcomes.[2,3] These studies are limited by small sample sizes, inclusion of both previously untreated and treated CLL patients, and lack of adequate accounting of other confounding factors. In this study, we comprehensively characterized clinical and cytogenetic profiles and outcomes in previously untreated CLL patients with del6q23 seen at Mayo Clinic over the past 25 years.

The Mayo Clinic CLL Database is comprised of CLL patients seen in the Division of Hematology at Mayo Clinic, Rochester, MN since 1995 who have granted permission for their records to be used for research. Clinical characteristics including age, sex, Rai stage, CD38 expression, ZAP70, CD49d, immunoglobulin heavy chain gene (*IGHV*) mutation status, and FISH findings of previously untreated CLL patients with del6q23 were compared to patients without del6q23. We also computed the CLL-International Prognostic score (CLL-IPI) for all patients where this information was available. FISH was performed on cell suspensions using standard