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Bleeding complications in *bcr-abl*-negative myeloproliferative neoplasms (MPN): A retrospective single-center study of 829 MPN patients

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Abstract

In patients with *bcr-abl*-negative myeloproliferative neoplasms (MPN), concerns are often raised about the use of anticoagulants because of an increased bleeding risk. However, there are few MPN studies focusing on bleeding. To investigate bleeding complications in MPN, we report our retrospective, single-center study of 829 patients with a median follow-up of 5.5 years (range: 0.1–35.6). A first bleeding event occurred in 143 of 829 patients (17.2%), corresponding to an incidence rate of 2.29% per patient/year. During the follow-up period, one out of 829 patients (0.1%) died due to bleeding. Regarding anticoagulation, most bleeding occurred in patients on antiplatelet therapies (60.1%), followed by patients on anticoagulation therapies (20.3%) and patients not on anticoagulation (19.6%). In multivariate analysis, administration of antiplatelet (HR 2.31 [1.43, 3.71]) and anticoagulation therapies (HR 4.06 [2.32, 7.09]), but not age, gender or mutation status, was associated with an increased bleeding risk. Comparing the "probability of bleeding-free survival" between the MPN subtypes, no significant difference was observed ($p = 0.91$, log-rank test). Our retrospective study shows that antiplatelet and anticoagulation therapies significantly increase the risk of bleeding in MPN patients without affecting mortality. However, there is no reason to refrain from guideline-conform primary or secondary anticoagulation in MPN patients.

KEYWORDS
anticoagulation, bleeding, myeloproliferative neoplasms

1 | INTRODUCTION

Bcr-abl-negative myeloproliferative neoplasms (MPN), including polycythemia vera (PV), essential thrombocythemia (ET) and primary or secondary myelofibrosis (MF), are clonal disorders of hematopoietic stem cells. They are associated with an increased risk of thromboembolic events, which is known to be a major contributor to higher morbidity and mortality compared to the healthy population. On the other hand, MPN patients are also at increased risk of bleeding, probably due to disease-related complications[1] or

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to antiplatelet and anticoagulation therapies which are frequently administered.[2,3]

With reference to the literature, in a retrospective multicenter study including 891 patients with ET and 180 patients with prefibrotic myelofibrosis (pre-MF), Finazzi et al.[4] observed a significantly increased incidence of major bleeding events in pre-MF patients (1.39% per pts/year) compared to ET (0.79% per pts/year). Independent predictors of bleeding in a multivariate analysis included acetylsalicylic acid (ASA) use and a diagnosis of pre-MF. In 2019, Rungjirajittranon et al.[5] published a large meta-analysis with over 13 000 MPN patients from 29 cohort studies. The pooled prevalence of bleeding complications at the time of MPN diagnosis was 6.2%, but data on bleeding in the further MPN course were not analyzed. In 2020, in a retrospective multicenter study of 442 MPN patients treated with direct oral anticoagulants (DOACs), Barbui et al.[6] observed an incidence of major bleeding events of 3.0% per patient/year in patients with atrial fibrillation and of 2.3% per patient/year in patients with venous thromboembolism. Of note, bleeding occurred significantly more often in MF patients, but bleeding under anticoagulants other than DOACs or under antiplatelet agents was not studied. Recently, Nicol et al.[7] reported an incidence for all bleeding events ranging from 0.1 to 6.6% and for major bleeding from 0.3 to 5.3% per patient/year in a comprehensive literature review that included 38 studies involving over 10 000 ET and over 5000 PV patients. A total of 39 different potential risk factors for hemorrhage were identified (including age, gender, MPN diagnosis, mutation status and anticoagulation therapies), but no data were presented for MF patients.

However, there are currently only a limited number of studies that include all MPN subtypes, analyze all bleeding events at the time of MPN diagnosis as well as in the further course of the disease and consider antiplatelet and anticoagulation treatments. In 2015, Kander et al.[8] observed 64 major and minor bleedings after a median time of two years after MPN diagnosis in a retrospective single-center study including 351 MPN patients. An increased risk of bleeding from antiplatelet therapy was not observed; however, DOACs were not administered in this trial. Kaifie et al.[9] conducted another retrospective multicenter study with 455 MPN patients in 2016. With regard to major bleeding events ($n = 36$), no association was found between ASA, vitamin K antagonists (VKA) or DOAC treatment and an increased risk of bleeding, but data on minor bleeding were not recorded in this analysis.

To provide further data on the frequency, risk factors and types of all bleeding complications at the time of MPN diagnosis and during the course of the disease, we report on our retrospective, single-center study of 829 MPN patients receiving various antiplatelet and anticoagulation therapies.

2 | PATIENTS AND METHODS

Clinical data of all MPN patients who presented regularly at our university hospital were collected from June 2007 to April 2021 (time of last data cut off April 1st, 2021). MPNs were diagnosed according to the WHO 2016 criteria.[10] The main objective of this non-interventional, retrospective, single-center study was to investigate the frequency, risk factors and types of bleeding events before, at the time of and during clinical follow-up of MPN patients in a "real-world" setting. The data were collected in an electronic system. The institutional review board of our center approved the study. Briefly, the following information was collected for each patient: demographic data, mutation profile, method of objective diagnosis, history of bleeding complications and transformation. Follow-up time was defined as the time from MPN diagnosis to first bleeding event, death or the last visit to our center, whichever came first. A total of 829 MPN patients with at least two visits at our center were enrolled in our study.

In a next step, we identified those patients who had experienced at least one MPN-associated bleeding complication (identified in the medical record or by history). In line with previous studies, we defined a MPN-associated bleeding complication if it occurred within a period of 3 months before MPN diagnosis or afterwards.[1,9,11,12] If a bleeding event occurred within 3 months before MPN diagnosis, the date of MPN diagnosis was equated with the date of bleeding complication. The diagnosis of hemorrhage was accepted only if confirmed by clinical examination or a positive result using techniques such as ultrasonography, CT or NMR. Furthermore, bleeding details such as locations, total number and time of diagnosis, recurrences and treatments were recorded. Finally, data on cytoreductive, antiplatelet or anticoagulation treatment and the duration of these treatments were recorded. Cytoreductive MPN treatment was defined as the use of hydroxyurea, busulfan, anagrelide, interferon alpha and/or ruxolitinib. Antiplatelet therapies were defined as the use of acetylsalicylic acid (ASA), P2Y-antagonists (clopidogrel, ticagrelor) or dual antiplatelet therapy (DAPT) and anticoagulation therapies as the use of vitamin K antagonists (VKA), direct oral anticoagulants (DOAC), or low-molecular weight heparin (LMWH).

The severity of bleeding complications was defined according to the criteria of the International Society on Thrombosis and Hemostasis.[13] According to these criteria and to criteria used in other studies,[1,9,14] we considered bleeding greater than II° (e.g., transfusion-dependent anemia, central nervous system involvement, retroperitoneal hemorrhage or other life-threatening bleeding) as a "major" bleeding event.

Acquired von Willebrand disease (AvWD) was defined by ristocetin cofactor activity and/or von Willebrand (vW) antigen below the laboratory reference range for blood type (<40% for blood group 0 or <53% for non-blood group 0) and for type 2 VWD, based on discrepancy between the vW ristocetin activity to antigen ratio (typically a ratio close to 0.5 or less) and/or the availability of vW multimer analysis.[1,8,15] According to these criteria, 51 MPN patients were diagnosed with AvWD. In 31/51 (60.8%), a date of AvWD diagnosis was available. The exact number of patients in our cohort who were tested for AvWD is not known.

2.1 | Statistical methods

For continuous variables, the median and range were provided. The annual incidence of bleedings was calculated by dividing the number

of events by the total number of patient/years. Differences in the proportions were estimated using Fisher´s exact test, Chi-square test, Mann–Whitney *U*-test or log-rank test (Mantel–Haenszel test). Kaplan–Meier plots were used to compare bleeding-free survival between therapies, and pairwise comparisons are done using log-rank tests with correction for multiple testing by Holm.

The Cox regression model was used to account for the effects of multiple variables on bleeding. For all analyses, the significance level was set to $\alpha = 0.05$.

3 | RESULTS

Overall, 829 MPN patients were included with a higher proportion of women (60.8%). The median age at MPN diagnosis was 50.9 years (range: 11.0–88.9). Different MPN subtypes were polycythemia vera (PV), *n* = 279 (33.7%), essential thrombocythemia (ET), *n* = 266 (32.1%), myelofibrosis (MF) including primary and secondary myelofibrosis, *n* = 168 (20.3%), prefibrotic myelofibrosis (pre-MF), *n* = 93 (11.2%) and MPN unclassifiable (uMPN), *n* = 23 (2.8%). All MPN unclassifiable patients were diagnosed by bone marrow biopsy. The mutation status was distributed as follows: *JAK2* mutation, 571 (68.9%), *CALR* mutation, 120 (14.5%), *MPL* mutation, 20 (2.4%), "triple negative," 43 (5.2%) and unknown 75 (9.0%). During the median follow-up of 5.5 years (range: 0.0–35.6), 143 out of 829 MPN patients (17.2%) experienced a first MPN-associated bleeding complication. The overall incidence rate for a first bleed was 2.29% per patient/year. With regard to MPN subtypes, this incidence rate was 2.16% per patient/year for PV patients (*n* = 279), 2.21% per patient/year for ET patients (*n* = 266), 2.41% per patient/year for primary or secondary MF patients (*n* = 168) and 3.17% per patient/year for pre-MF patients (*n* = 93). As far as major bleeding events are concerned, a total of 47/143 (32.9%) first bleeding events were classified as major. This corresponds to a major bleeding rate of 5.7% (47/829) in the whole group of 829 MPN patients The overall incidence rate for major bleeding was 0.75% per patient/year, with *n* = 14 major bleedings in PV patients (incidence: 0.61% per patient/year), *n* = 16 major bleedings in ET patients (0.74% per patient/year), *n* = 14 major bleedings in primary or secondary MF (1.09% per patient/year) and one major bleeding in pre-MF (0.26% per patient/year). Two major bleedings (2/23, 8.7%) were observed in patients diagnosed with MPN unclassifiable. Among the 143 MPN patients with a first bleeding complication (minor or major), the median age at the time of the event was 54.8 years (range: 22.6–83.6). The median time between MPN diagnosis and the first bleeding event was 4.1 years (range: 0.1–27.6 years).

The clinical parameters of the 143 MPN patients with a first bleeding event are summarized in Table 1. Most patients were female (*n* = 95, 66.4%) and were diagnosed at the time of the bleeding event with PV (*n* = 50, 35.0%), followed by ET (*n* = 48, 33.6%), primary or secondary MF (*n* = 31, 21.7%), prefibrotic myelofibrosis (*n* = 12, 8.4%) and MPN unclassifiable (*n* = 2, 1.4%). The *JAK2* V617F

TABLE 1 Overview of the demographic data and clinical characteristics of the 143 MPN patients with a first bleeding event

Male/female; *n* (%)	48/95 (33.6/66.4)
Median age at first bleeding event; years (range)	54.8 (22.6–83.6)
Median time from MPN diagnosis to first bleeding event; years (range)	4.1 (0.1–27.6)
MPN diagnosis at first bleeding event	
Polycythemia vera; *n* (%)	50 (35.0)
Essential thrombocythemia; *n* (%)	48 (33.6)
Primary or secondary myelofibrosis (MF); *n* (%)	31 (21.7)
Prefibrotic myelofibrosis (pre-MF); *n* (%)	12 (8.4)
MPN unclassifiable; *n* (%)	2 (1.4)
Driver mutations at MPN diagnosis	
JAK2; *n* (%)	102 (71.3)
CALR; *n* (%)	23 (16.1)
MPL; *n* (%)	2 (1.4)
"triple negative"; *n* (%)	10 (7.0)
Unknown; *n* (%)	6 (4.2)
Pts[a] with acquired von Willebrand disease (AvWD) at time of bleeding event, *n* (%)	11 (7.7)
Pts[a] with cytoreductive therapy[b] at time of bleeding event, *n* (%)	61 (42.7)
Median platelet count at time of bleeding event, G/l (range)[c]	455 (10–2096)
Median leucocyte count at time of bleeding event, G/l (range)[c]	9.0 (0.8–36.4)

[a]Pts = patients.

[b]Cytoreductive therapies: hydroxyurea (*n* = 26), anagrelide (*n* = 6), interferon (*n* = 4), ruxolitinib (*n* = 23), others (*n* = 2).

[c]Available in 86 patients.

mutation was the most common driver mutation detected in most bleeding patients ($n = 102$, 71.3%) followed by the *CALR* mutation in $n = 23$ patients (16.1%) and the *MPL* mutation in $n = 2$ patients (1.4%). In $n = 10$ patients (9.1%) none of these three main driver mutations ("triple negative") was detected, and in six patients the mutation status was unknown. At the time of the first bleeding event, 42.7% of bleeding MPN patients (61/143) were on cytoreductive treatment. Looking at the blood count at the time of bleeding event, the median platelet count (available in 86 patients) was 455 G/l (range 10–2096) and the median leucocyte count 9.0 G/l (range 0.8–36.4).

According to the above criteria, 51 (6.2%) patients were diagnosed with an acquired von Willebrand disease (AvWD). The median time between the diagnosis of an AvWD and MPN diagnosis was 1.3 years (range: 1.4 years before MPN diagnosis to 17.1 years after MPN diagnosis). Acquired von Willebrand disease (AvWD) was diagnosed in $n = 11$ (7.7%) of patients with bleeding events. In 6/11 patients (54.5%), AvWD was diagnosed at the same time as the bleeding event, and in five patients, AvWD was diagnosed before bleeding. Four patients with AvWD (36.4%) were receiving cytoreductive therapy at the time of AvWD diagnosis. Regarding MPN risk classifications, 8/11 (72.7%) patients with an AvWD (two PV patients, five ET patients and one MF patient, respectively) were classified as "low risk" ($n = 7$ according to ELN[16] and $n = 1$ according to International Prognostic Scoring System (IPSS)[17]). Only one patient with ET was classified as "high risk" according to ELN.

In a next step, an analysis was performed that considered the "probability of bleeding-free survival" focusing on the MPN subtypes entities of all 829 with 143 bleeding events. In this analysis, the difference in "probability of bleeding-free survival" between the patients diagnosed with PV, ET, primary or secondary myelofibrosis (MF), prefibrotic MF (pre-F) and MPN unclassifiable (uMPN) was not statistically different in the log-rank test ($p = 0.91$, Figure 1).

The localizations of 143 bleeding events and the corresponding classification into minor ($n = 96$, 67.1%) or major ($n = 47$, 32.9%) events are summarized in Table 2. Overall, most bleeding was mucocutaneous bleeding ($n = 56$, 39.2%), followed by postoperative bleeding ($n = 21$, 14.7%), epistaxis ($n = 22$, 15.4%) and gastrointestinal bleeding ($n = 17$, 11.9%). Considering only major bleeding, gastrointestinal bleeding ($n = 17$, 36.2%) was the most common, followed by postoperative bleeding ($n = 13$, 27.7%) and CNS bleeding ($n = 3$, 6.4%). The most common minor bleeds were mucocutaneous bleeding ($n = 52$, 54.2%), epistaxis ($n = 21$, 21.9%) and postoperative bleeding ($n = 8$, 8.3%). One patient died during the follow-up period as a result of a spontaneous retroperitoneal hematoma.

When considering different anticoagulation therapies, 438 of 829 patients (52.8%) received antiplatelet therapy during the follow-up period. Anticoagulants were given to 93 patients (11.2%), and in 298 (36.0%) patients neither anticoagulants nor antiplatelet therapy was used. The bleeding-free survival time for patients receiving antiplatelet drugs was 5.0 years (range 0.1–33.1), for

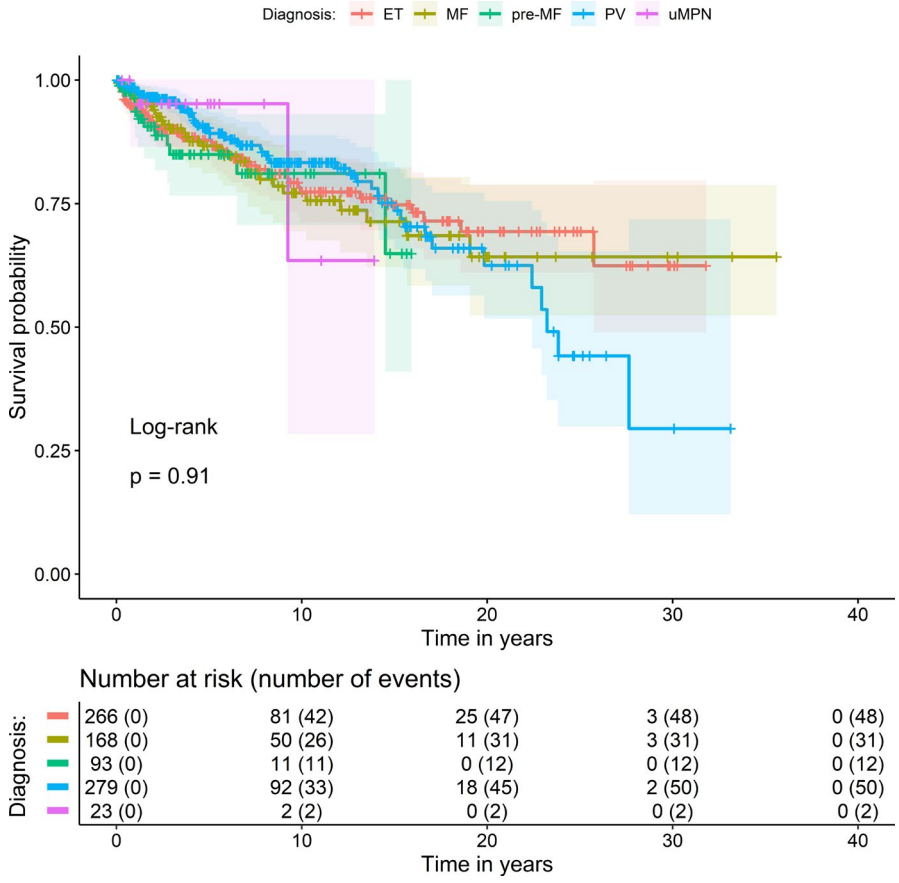

FIGURE 1 "Probability of bleeding-free survival" according to MPN subgroup: The cumulative "probability of bleeding-free survival" in 829 MPN patients according to subgroup with $n = 279$ PV patients (blue curve; $n = 50$ bleeding events), $n = 266$ ET patients (red curve; $n = 48$ bleeding events), $n = 168$ primary or secondary MF patients (olive green curve; $n = 31$ bleeding events), $n = 93$ pre-MF patients (green curve; $n = 12$ bleeding events) and $n = 23$ MPN unclassifiable patients (purple curve; $n = 2$ bleeding events). No statistically significant difference could be found with the log-rank test ($p = 0.91$)

TABLE 2 Localization of first bleeding events (n = 143) with n = 96 minor and n = 47 major events

	Bleeding events (n = 143)	Minor bleeding events (n = 96)	Major bleeding events (n = 47)
Localization n (%)			
Mucocutaneous bleedings	56 (39.2)	52 (54.2)	4 (8.5)
Postoperative bleeding	22 (15.4)	21 (21.9)	1 (2.1)
Epistaxis	21 (14.7)	8 (8.3)	13 (27.7)
Gastrointestinal bleeding excluding esophageal variceal bleeding	17 (11.9)	—	17 (36.2)
Other bleedings[a]	13 (9.1)	7 (7.3)	6 (12.8)
Menorrhagia	8 (5.6)	8 (8.3)	—
CNS bleeding	3 (2.1)	—	3 (6.4)
Esophageal variceal bleeding	3 (2.1)	—	3 (6.4)

[a]Major bleedings: intraoperative rupture of spleen (n = 1), macrohematuria (n = 1), spontaneous bleeding into musculus ileopsoas (n = 1), subcapsular intrasplenic hemorrhage (n = 1), bleeding of a corpus luteum cyst (n = 1), gastrointestinal bleeding of unknown localisation (n = 1) minor bleedings: hemorrhagic cystitis (n = 1), hemorrhoidal bleeding (n = 1), hemarthros of the knee (n = 1), vitreous bleeding (n = 1), gingival bleeding (n = 2), intraabdominal bleeding after TIPSS (n = 1)

patients receiving anticoagulants 4.7 years (0.1–23.9) and for the patients without any anticoagulation 6.2 years (0.1–35.6), respectively (Figure 2).

In terms of anticoagulation at the time of the 143 bleeding events, most bleeding occurred in patients on antiplatelet therapy (86/143, 60.1%), followed by patients on anticoagulants (n = 29, 20.3%) and patients with no anticoagulation at all (n = 28, 19.6%). ASA alone was used at the time of bleeding in 80/86 (93.0%) patients with antiplatelet therapy. Five patients were treated with P2Yantagonists due to ASA intolerance. In addition, one patient was treated with dual antiplatelet therapy (DAPT). Major bleeding occurred in 27/86 patients (31.4%) on antiplatelet therapy (three of them using P2Y antagonists; one patient received ASA in combination with low molecular weight heparin (LMWH)). It is noteworthy that 9/17 major gastrointestinal bleeding occurred with ASA and 2/17 with P2Y antagonists. One out of three esophageal variceal bleeds was observed under ASA.

VKAs were administered in 12/29 (41.4%) patients with anticoagulation therapy and bleeding, another ten patients (34.5%) received DOACs, and LMWHs were used in seven (24.1%). Of these 29 patients on anticoagulation therapy, eight (27.6%) experienced a major bleeding event (n = 4 with VKA and n = 4 with LMWH). No major bleeding occurred with the use of DOACs. Six out of 29 bleeding patients (20.7%) on anticoagulation therapy (VKA: n = 2; DOAC: n = 2; LMWH: n = 2) also received ASA. Out of the eight major bleeds observed during anticoagulation therapy, two (25%) occurred with the additional use of ASA.

For all 829 patients with 143 first bleeding events, an analysis of the "probability of bleeding-free survival" was performed depending on the use of antiplatelet or anticoagulation therapies (Figure 2). Difference between the three treatment groups was statistically different in the log-rank test ($p < 0.0001$). The pairwise comparison of the three curves shows significance at the $\alpha = 0.05$ level for anticoagulation therapies versus no anticoagulation and for anticoagulation therapies versus antiplatelet therapies. The curves without anticoagulation and with antiplatelet drugs were not significantly different.

In addition, an analysis was performed only for the 47 major bleeding events in 829 patients as a function of anticoagulation, considering the "probability of bleeding-free survival" (Figure 3). However, there was no statistical difference between these three groups in the log-rank test ($p = 0.061$).

To analyze further covariates that might influence the risk of bleeding in the 829 patients, we performed multivariate Cox regression with the variables age at MPN diagnosis, gender, MPN diagnosis, mutation status (presence of *JAK*-, *MPL*-, *CALR*-mutation, or "triple negative," respectively) and administration of antiplatelet or anticoagulation therapies. When performing Cox regression with these covariates, the proportionality assumption is violated. To solve this problem, the variable MPN diagnosis was used for stratification. In the analysis, 75 patients were excluded because no information on mutation status was available and the model was only applied to 774 patients. The estimated hazard ratios for the covariates are taken from Table 3. Overall, the model proved to be significant, i.e., the covariates were suitable to explain the dependent variable ($p = 0.00008$). To estimate the impact of the *CALR* mutation on the bleeding risk, this variable was considered as the reference category and the other mutation types (*JAK2*, *MPL* or "triple-negative") were compared to it. According to this analysis, only the use of antiplatelet drugs (HR 2.31) and the use of anticoagulation therapies (HR 4.06) were significant risk factors for bleeding.

In addition, another Cox regression was performed with the same variables, focusing on the n = 47 major bleeding events in 774 patients. Again, the use of antiplatelet therapies (HR 2.53) and the use of anticoagulation therapies (HR 4.34) were the only significant risk factors.

The next step was to compare various clinical and laboratory parameters between the MPN patients with a severe (n = 47), a mild

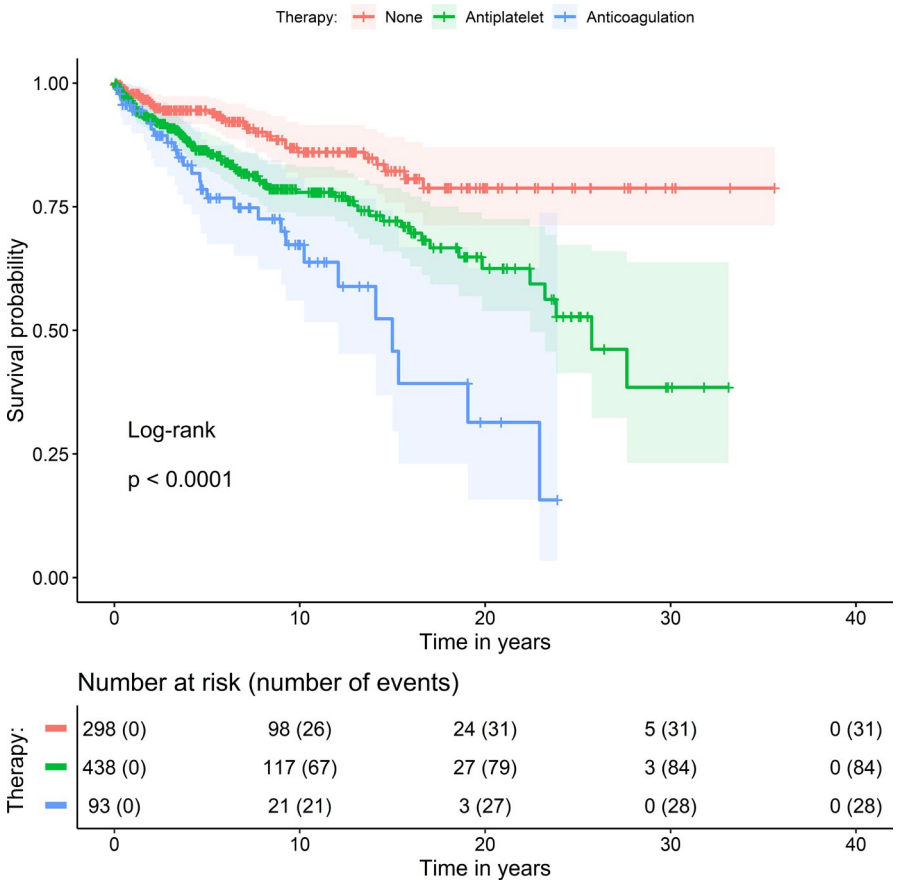

FIGURE 2 "Probability of bleeding-free survival" according to anticoagulation use: The cumulative "probability of the bleeding-free survival" in 829 MPN with 143 first bleeding events according to the use of antiplatelet or anticoagulation therapies with 438 patients receiving antiplatelet therapies (green curve; $n = 86$ bleeding events), $n = 93$ with anticoagulation therapies (blue curve; $n = 29$ bleeding events) and $n = 298$ without anticoagulation (red curve; $n = 28$ bleeding events). The difference between the three groups was statistically significant ($p < 0.0001$)

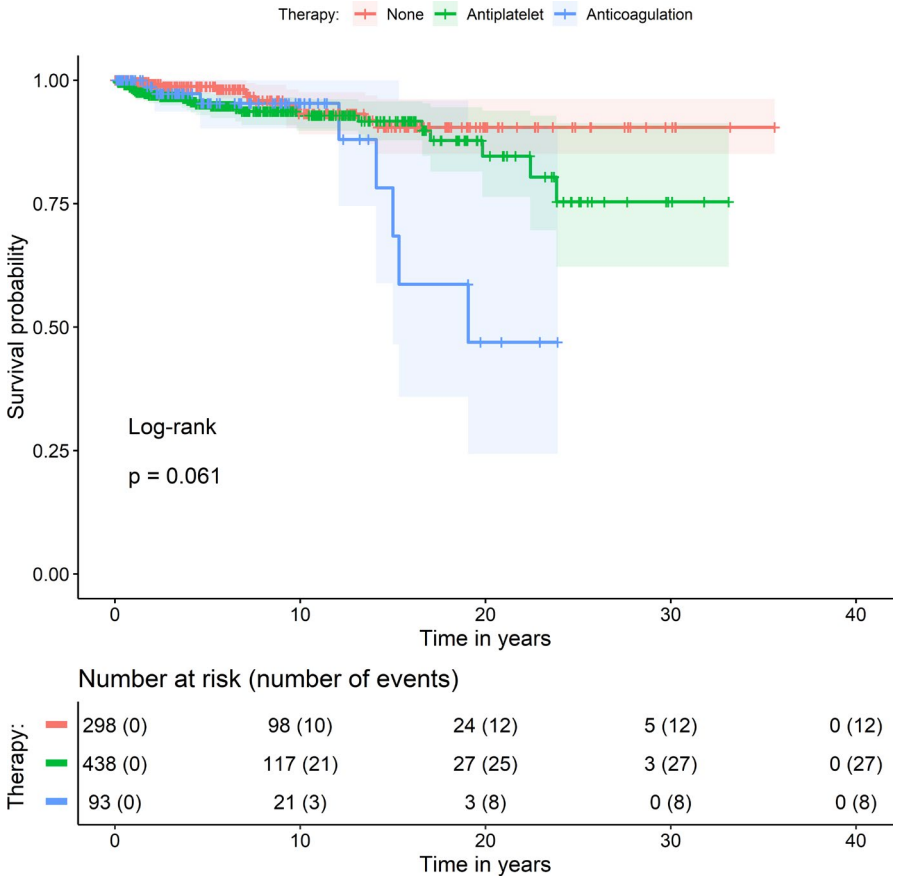

FIGURE 3 "Probability of bleeding-free survival" in relation to the use of anticoagulation, considering the 47 major bleeding events: The cumulative "probability of the bleeding-free survival" in 829 MPN with 47 major bleeding events according to the use of anticoagulation with 438 patients receiving antiplatelet therapies (green curve; $n = 27$ major bleeding events), $n = 93$ with anticoagulation therapies (blue curve; $n = 8$ major bleeding events) and $n = 298$ without anticoagulation (red curve; $n = 12$ bleeding events). The difference between the three groups was not statistically significant ($p = 0.061$)

($n = 96$) or no bleeding event ($n = 686$) (summarized in Table 4). The only significant difference was found in relation to the variable gender ($p = 0.011$). This may be explained by the fact that the gender ratio is balanced in patients with major bleedings, whereas in patients with minor bleedings and in patients without bleeding complications, the proportion of women is predominant.

4 | DISCUSSION

In MPN patients, thromboembolic complications are a major cause of increased morbidity and mortality, leading to the frequent use of antiplatelet and anticoagulant drugs as primary and secondary prophylaxis. On the other hand, MPN patients are also prone to bleeding.

TABLE 3 Hazard ratios from multivariate Cox regression of 774 MPN patients (with a known mutation status) with the variables age at MPN diagnosis, gender, administration of antiplatelet or anticoagulation therapies and mutation status

Multivariate Cox regression	
Variable	**HR [95% CI]**
Age at MPN diagnosis	1.01 [0.99, 1.02]
Gender	0.86 [0.59, 1.25]
Administration of antiplatelet drugs	2.31 [1.43, 3.71]*
Administration of anticoagulation therapy	4.06 [2.32, 7.09]*
Presence of *JAK2*	0.89 [0.53, 1.48]
Presence of *MPL*	0.46 [0.11, 1.98]
"Triple negative" mutational status	1.39 [0.64, 3.01]

Note: The 95% confidence intervals for the estimators are given in parentheses. Administration of antiplatelet drugs (HR 2.31) and administration of anticoagulation therapy were statistically significant (HR 4.06).

*Statistically significant.

Therefore, the potential for severe bleeding complications leading to premature discontinuation of anticoagulation is a concern. This in turn is associated with a significantly increased risk of recurrence of thromboembolism.[11,18,19] To date, many studies in MPN have focused only on bleeding events occurring concurrently with MPN diagnosis.[5] Other papers report only major bleeding events,[4,9,20] or only bleeding in certain MPN subtypes[3,4,19,20] or bleeding with the use of certain anticoagulants.[6,18]

Nicol et al.[7] identified 39 potential risk factors for bleeding events in their extensive literature review, which included over 15 000 patients with essential thrombocythemia (ET) and polycythemia vera (PV). Remarkably, only 37 fatal hemorrhages were recorded. Numerous studies on acetylsalicylic acid (ASA)/antiplatelet therapies and bleeding events in PV and ET patients were included in this review, although the data appeared contradictory to the authors. There were significantly fewer studies on vitamin K antagonists (VKA) and almost no data on anticoagulation with direct oral anticoagulants (DOACs). However, data on patients with myelofibrosis were not included in this review.

Remarkably, the only prospective study on this topic, the ECLAP study, found more bleeding events for PV patients in the ASA group (9.1% vs. 5.3%). However, this difference was not statistically significant ($p = 0.08$).[21] In contrast, in the retrospective multicenter study by Finazzi et al[4] with more than 1100 patients with ET and prefibrotic myelofibrosis (pre-MF), ASA use was an independent risk factor for bleeding in multivariate analysis.

Regarding studies including all MPN subtypes and different types of antiplatelet and anticoagulation therapies, Kander et al.[8] included 351 MPN patients in a retrospective single-center study with a median follow-up of two years and a prevalence of bleeding (minor and major) of 15.6%. This is comparable to our analysis. A significantly increased risk of bleeding depending on the therapy with ASA or the mutation status was not observed. However, the influence of anticoagulation therapies such as VKA, low molecular

TABLE 4 Comparison of clinical parameters between MPN patients with a major bleeding event ($n = 47$), with a minor hemorrhage ($n = 96$) or with no bleeding at all ($n = 686$)

Parameters	Patients with a major bleeding event ($n = 47$)	Patients with a minor bleeding event ($n = 96$)	Patients with no bleeding at all ($n = 686$)	p
Median age at MPN diagnosis; years (range)	50.9 (11.0–78.1)	49.2 (17.7–79.7)	51.4 (11.8–88.9)	0.196
Gender (male/female)	23/24	25/71	275/411	**0.011***
Essential thrombocythemia (ET =	16	32	218	0.182
Polycythemia vera (PV)	14	36	229	
Myelofibrosis (MF)	14	17	137	
Prefibrotic myelofibrosis (pre-MF)	1	11	81	
MPN unclassified	2	0	21	
JAK2	33	69	469	0.769
CALR; *n* (%)	5	18	97	0.361
MPL; *n* (%)	1	1	18	0.725
Triple negative; *n* (%)	3	7	33	0.423

*Statistically significant.

weight heparin (LMWH) or DOACs on bleeding propensity was not included in the multivariate analysis. In 2016, Kaifie et al.[9] conducted a multicenter study investigating the risk of bleeding (and thrombosis) in a cohort of 455 MPN patients. Similar to our study, 8.2% major bleeding (n = 36) was observed. However, no significantly increased risk of bleeding was observed in patients receiving ASA, VKA or rivaroxaban therapy. Only treatment with heparin was associated with an increased risk of bleeding (OR = 5.64). However, minor bleeding was excluded in this study and an analysis of bleeding risk in *CALR* mutated or "triple-negative" patients was not performed.

Given this diversity of data on the risk of bleeding with the use of anticoagulation in MPN, and in order to obtain more "real-world" data on bleeding complications, we conducted our retrospective study of 829 MPN patients of all MPN subtypes. During a median follow-up of 5.5 years, we observed an incidence rate for all bleeding events of 2.29% per patient/year and for major bleeding of 0.75% per patient/year, which is comparable to other studies.[4,18] In terms of location, mucocutaneous hemorrhages were the most common, while among major bleedings, gastrointestinal, postoperative and CNS hemorrhages were the most common, which was also observed by Kaifie et al.[9] Over 2/3 of our MPN patients had no cytoreductive therapy at the time of the bleeding event, which may have contributed to increased bleeding propensity. Since only 11/143 (7.7%) MPN patients with bleeding had acquired von Willebrand disease (AvWD), the quantitative impact of this coagulation disorder on bleeding propensity appears to be small.

In contrast with the results of several studies,[8,9,21] our study suggests an increased risk of bleeding with antiplatelet and anticoagulation therapies, both for all bleeding and, in the multivariate analysis, only for major bleeding. However, it is clinically relevant that there was only one fatal bleeding event out of 829 MPN patients during the follow-up period. According to the Cox regression analysis, a 2.3-fold increased risk of the use of antiplatelet drugs and a 4.06-fold increased risk of the use of anticoagulation therapy compared to no anticoagulation was observed. One possible explanation for these results was the inclusion of all bleeding events (major and minor), all MPN subtypes and all kinds of anticoagulation, which has not been done before in comparable retrospective single-center studies. It should also be considered that prospective studies on the risk of bleeding with anticoagulation (antiplatelet drugs and/or anticoagulation therapies) in MPN patients are lacking. In contrast, prospective studies in the general population ("non-MPN") have shown an increased risk of bleeding with the use of ASA[22] and VKA[23] compared to no anticoagulation. It is noteworthy that one fifth (20.7%) of patients with a bleeding event under anticoagulation therapies in our cohort were also taking ASA, which could be another reason for the increased risk of bleeding. Overall, 34.5% of our patients on anticoagulation therapy received DOACs. Remarkably, not a single major bleeding event was recorded in this group. In contrast with anticoagulation, multivariate analysis and the log-rank test did not reveal an increased risk of bleeding associated with patient age, gender, MPN subtype or mutation status.

In summary, our study shows a significantly increased risk of bleeding complications in MPN patients treated with antiplatelet or anticoagulation therapies. It is clinically important to note that in our study there was no obvious evidence of increased bleeding-related mortality with the use of anticoagulation. Therefore, concerns about bleeding should still not be a reason to refrain from guideline-tailored primary prophylactic anticoagulation or to prematurely discontinue secondary prophylaxis in MPN patients. Ultimately, the indication for anticoagulation in MPN must be made carefully at the beginning and reviewed over the course of the disease.

CONFLICT OF INTEREST

All authors declare that they have no conflict of interest or competing interests.

ETHICS APPROVAL

The questionnaire and study protocol for this retrospective study were approved by the Ethics Committee of the Ruhr-Universität Bochum, based in Bad Oeynhausen.

CONSENT TO PARTICIPATE

Informed consent was obtained from all individual participants included in the study.

CONSENT FOR PUBLICATION

Patients gave informed consent regarding publication of their data.

CODE AVAILABILITY

Not applicable.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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