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Temporal relationship between thromboembolic events and myeloproliferative neoplasm diagnosis: is it associated with mortality risk?

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Abstract. – OBJECTIVE: The aim of this study is to investigate the temporal relationship between the first occurrence of thromboembolic events (TEE) and the timing of myeloproliferative neoplasm (MPN) diagnosis and to determine risk factors for TEE-related mortality in MPN.

PATIENTS AND METHODS: A total of 138 BCR-ABL-negative MPN patients with TEE, diagnosed from January 2010 to December 2019, were included in this retrospective cohort. Patients were compared according to mortality and subjects were classified into three groups with respect to having suffered index TEE before, during, or after MPN diagnosis.

RESULTS: The mean age of surviving patients was 57.5±13.8, while those who had died had a mean age of 72.0±9.0 (p<0.001). Males represented 56.5% of patients with mortality and 60.9% of those without mortality (p=0.876). TEE was detected in 26.0% of MPN patients, and TEE-related mortality rate was 16.7%. There was no relationship between mortality and the classification of patients according to index TEE (p =0.884). High age (p<0.001) and danazol use (p=0.014) were independently associated with TEE-related mortality.

CONCLUSIONS: The temporal relationship between TEE and MPN diagnosis was not found to influence mortality. Older patients and danazol recipients should be considered to have a higher risk of TEE-related mortality.

Key Words:
Myeloproliferative neoplasms, Thromboembolic event, Mortality, Danazol, Older age.

Introduction

Myeloproliferative neoplasms (MPNs) are hematological malignancies characterized by proliferation of bone marrow cells, often observed in one or more myeloid cell lines[1]. There are seven diseases in the MPN group: polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), chronic myeloid leukemia (CML), chronic neutrophilic leukemia, chronic eosinophilic leukemia and unclassifiable MPN[2]. Diseases other than CML are accepted to be negative for the *BCR-ABL* oncogene, also known as the Philadelphia chromosome[3]. The worldwide reported annual incidence of MPN ranges from 0.44 to 5.87 per 10,000 individuals[4].

Thromboembolic events (TEE) are common among patients and have an impact on MPN-related morbidity and mortality[5]. In a comprehensive meta-analysis, the frequency of thrombosis in patients with PV, ET, and PMF were reported as being 28.6%, 20.7%, and 9.5%, respectively[6]. Various studies[7-9] have reported that thrombosis-related deaths account for 45%, 26%, and 12% of deaths in patients with PV, ET, and PMF, respectively. TEE most frequently occur around the time of MPN diagnosis; however, they can also occur before or after diagnosis[10,11]. In a population-based study comparing MPN patients with controls, thrombosis hazard ratios were reported to be 4.0, 2.4, and 1.8 at 3 months, 1 year, and 5 years after the diagnosis, respectively[12]. TEE may also occur before MPN diagnosis, with a reported incidence of 14-41%[13,14], and we rarely had findings that would convincingly lead to MPN diagnosis at the time of TEE[10,15]. The negative impact of TEE on MPN prognosis is an undisputable issue[5,16]; however, it is unknown whether there is a relationship between MPN mortality and the timing of the index thrombosis event (before MPN diagnosis, at the time of diagnosis, or after diagnosis), particularly since this issue has not been adequately investigated.

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Considering the impact of thrombosis in MPN, it is evident that the influence of TEE and its characteristics must be addressed in every aspect. Therefore, in this study, we aimed to investigate the effect of the temporal relationship between the index TEE and MPN diagnosis. Additionally, a secondary focus was to identify risk factors associated with TEE-related mortality in MPN patients.

Patients and Methods

Ethical Statement and Study Design

The ethical approval required for this retrospective study was obtained from the University of Health Sciences Dr. Sadi Konuk Training and Research Hospital, Bakırköy, Istanbul, Turkey (date: April 4, 2022, no.: 2022-07-10). The study was conducted in compliance with the Helsinki declaration and its later amendments. This retrospective cohort study was carried out in the Department of Hematology of Dr. Sadi Konuk Training and Research Hospital.

Study Population and Data Collection

According to the descriptive statistics (effect size = 0.244) reported in the study by Næss et al[17], a sample size of 132 was found to achieve 80% power for a two-sided significance level of 0.05. Sample size was calculated by using the Chi-square test power analysis.

The data of a total of 530 patients diagnosed with *BCR-ABL*-negative MPN, from January 2010 to December 2019, who had been treated as outpatients or inpatients in the Hematology Department of our hospital were analyzed.

Inclusion criteria were: being older than 18 years and having developed TEE at one of the following time periods: before, at the time of, or after the diagnosis of *BCR-ABL*-negative MPN. Patients with a follow-up period shorter than 3 years after MPN diagnosis were excluded from the study. Also, those with very recent TEE at the time of study inclusion (still receiving treatment or close monitoring) and patients with missing data were excluded. A final total of 138 patients who met the inclusion/exclusion criteria were included in the study.

Demographic data, MPN sub-types, comorbidities, smoking status, drug use and treatments, spleen-related information, laboratory results, thrombosis and bleeding characteristics, and mortality status were obtained retrospectively from the hospital database and patient charts.

Grouping

The patients were divided into two groups with respect to TEE-related mortality (survivors and those with mortality). Additionally, subjects were divided into three groups according to the temporal relationship between index TEE and MPN diagnosis. Group 1: index TEE before MPN diagnosis, Group 2: diagnosed with MPN during index TEE, and Group 3: index TEE after MPN diagnosis.

Outcomes

The primary outcome of the study was to investigate whether the timing of the first TEE was associated with the risk of mortality in MPN patients. The secondary outcome of the study was to investigate other factors that may be associated with TEE-related mortality in MPN patients.

Laboratory Analysis

All laboratory parameters analyzed in the study were selected from variables obtained routinely during the diagnosis and treatment of MPN. Hematological and biochemical analyses were performed from venous blood with use of routine devices in the Clinical Chemistry Department of Dr. Sadi Konuk Training and Research Hospital (PM-8000; Mindray, China and Cobas 800; Roche, Indianapolis, IN, USA). Parameters included complete blood count (white blood cell, neutrophil, lymphocyte, platelet and eosinophil counts, hemoglobin and hematocrit levels, mean corpuscular volume), lactate dehydrogenase, and erythropoietin. Additionally, data concerning treatment and management were recorded.

Morphological, cytogenetic and molecular genetic assessments required for the diagnosis of MPN subtypes were performed in the hematology, pathology and genetics laboratories of our hospital. Mutations were studied by Real-Time Polymerase Chain Reaction using a CFX96™ system (Bio-Rad Laboratories; Munich, Germany) and commercial kits in accordance with the manufacturers' recommendations.

Bone marrow aspirates and biopsies were obtained by experienced hematologists and were cultured for 24-48 hours in a 10 μg/mL Colcemid solution without mitogen for conventional bone marrow cytogenetics[16]. Experienced hematologists and pathologists performed morphological examinations of bone marrow aspirates and biop-

sies in accordance with the classifications of the World Health Organization (WHO, tumors of hematopoietic and lymphoid tissues)[18,19].

The Classification and Management of MPNs

MPN classifications and follow-ups were performed according to WHO criteria and the recommendations for MPN published in 2008[20] (for patients diagnosed before the 2016 edition) and in 2016[2].

Overall patient management and the treatment of MPN and its complications were conducted in accordance with the 2015 ESMO clinical practice guidelines[4] and the revised version of recommendations from the 2011 guidelines of European LeukemiaNet[21].

The Management of TEE and Hemorrhagic Events

The occurrence of one or more of the following was defined as TEE: acute myocardial infarction, deep vein thrombosis, ischemic stroke, pulmonary embolism, peripheral arterial thrombosis, thrombosis of mesenteries and splanchnic veins, superficial thrombophlebitis, or transient ischemic attack. TEE diagnoses were confirmed by experienced radiologists with the aid of computed tomography scanning, magnetic resonance imaging, color Doppler ultrasonography or angiography. In patients with TEE before MPN diagnosis, TEE management was performed according to contemporary guidelines at the relevant time[22,23].

Information concerning all hemorrhagic events, such as epistaxis, gastric bleeding and cerebral bleeding, were also obtained. Diagnosis and management of patients who had bleeding complaints during their outpatient follow-up or inpatient treatment were carried out by the relevant departments with up-to-date approaches.

Other Definitions and Procedures

Patients in which the cause of death was recorded as one of the specified TEE were defined to have suffered TEE-related mortality. Peripheral blood leukoerythroblastosis was defined as the presence of nucleated red cells, immature granulocytes and dacryocytes in peripheral smear[24]. Splenomegaly was defined as clinical or radiological demonstration of spleen enlargement, which was measured *via* ultrasound or computed tomography.

Statistical Analysis

All analyses, with a significance threshold of ≤ 0.05 (p-value), were performed on SPSS for Windows Version 25 (IBM Corp., Armonk, NY, USA). For the normality check, the Kolmogorov-Smirnov test was used. Data are given as mean ± standard deviation or median (1st quartile – 3rd quartile) for continuous variables according to normality of distribution, while frequency (percentage) values were given for categorical variables. Normally distributed variables were analyzed with the independent samples t-test. Non-normally distributed variables were analyzed with the Mann-Whitney U test. Categorical variables were analyzed with the Chi-square tests, the Fisher's exact test or the Fisher-Freeman-Halton test. Multiple logistic regression (forward conditional) was performed to identify factors independently associated with TEE-related mortality.

Results

Survivors had a mean age of 57.54 ± 13.82, while those with mortality had a mean age of 72.04 ± 9.01 years ($p < 0.001$). Sex distribution was similar among survivors and those with mortality ($p = 0.876$). Comparisons concerning the survivor and mortality groups are summarized in Table I. TEE was diagnosed in 26.0% of all MPN patients, and TEE-related mortality rate was 16.7%. The distribution of patients into the temporal groups was as follows: group 1: 34.8%, group 2: 29.0%, group 3: 36.2%. The percentage of patients with PMF was significantly higher in the mortality group, and the percentage of patients with ET was significantly higher in survivors ($p = 0.025$). The percentage of patients using danazol treatment was significantly higher in the mortality group ($p = 0.003$). Mean hemoglobin ($p = 0.002$) and mean hematocrit ($p = 0.007$) levels were significantly lower among deceased patients compared to survivors.

We performed multiple logistic regression analysis to identify factors independently associated with TEE-related mortality. Higher age ($p < 0.001$) and danazol use ($p = 0.014$) were found to be independently associated with TEE-related mortality. Other variables included in the analysis, PMF ($p = 0.185$), ET ($p = 0.060$), hemoglobin ($p = 0.356$) and hematocrit ($p = 0.317$) were found to be non-significant (Table II).

Only two patients had prefibrotic PMF (both were survivors), and one patient had grade 1-2 fibrosis (deceased). No patients were found to have experienced leukemic transformation. These fac-

tors were not included in statistical evaluations due to the limited patient count.

Discussion

Due to its high prevalence and significant impact on morbidity and mortality, thrombosis is the main issue of concern among patients with MPN[5]. Previous research[15,16] has established that thrombotic events have a strong impact on survival in MPN, but the temporal relationship between index TEE and MPN prognosis/survival is an unexplored issue. The findings of this study demonstrate that the timing of index TEE is unassociated with TEE-related mortality in MPN. In the present study, TEE was seen in 26.0% of all MPN patients, and TEE-related mortality rate was 16.7%. Of note, the highest rates of TEE-related mortality were detected in patients with PMF and ET. However, only advanced age and danazol use were identified as independent risk factors for TEE-related mortality in our group of patients with MPN.

The risk of TEE is highest at the time of initial MPN diagnosis[25]. However, it is not uncommon for MPN to be missed during the index TEE and to be diagnosed during a subsequent bleeding or TEE attack. Furthermore, the first TEE may also occur after MPN diagnosis[5,11,12]. In the present study, the incidence of TEE was found to be 26.0% in all MPN patients. The majority of patients with TEE were PV patients (40.6%), followed by ET patients (34.1%). When assessed, 9.1% of all MPN patients had their first TEE before diagnosis, 7.5% during diagnosis, and 9.4% after diagnosis. In the literature, TEE rates before, at the time of, or after MPN diagnosis show a wide range. In general, the incidence of TEE before MPN diagnosis has been reported in the range of 14-41%[13,14]. Zhang et al[15] reported that the incidence of thrombosis at the time of diagnosis or before diagnosis was 63.9%, and it was noted that 52.4% of patients developed thrombosis after diagnosis. The Mayo Clinic's data from 3023 patients with *BCR-ABL*-negative MPN showed that the percentage of patients with a history of thrombosis before or during diagnosis was 20%, while 17% experienced thrombotic events after diagnosis[26].

The occurrence of TEE is the primary prognostic marker in MPN, and it is considered to be a preventable risk factor[5,12]. Therefore, much of the current treatment paradigms for MPN focus on preventing TEE and its recurrence[25]. Many risk factors have been identified to increase thrombosis risk[10,12,15] and mortality[15,16]. All factors that increase the risk of TEE can also be expected to have an effect on mortality. The results of the present study showed that TEE-related mortality rates were similar among patients who had their first TEE before, at the time of, or after MPN diagnosis. In the study of Pereira et al[27], it was stated that no significant excess mortality attributable to ET and PV was detected at 20 years and 18 years from diagnosis, respectively. However, in both diseases, excess mortality significantly increased after the first recorded TEE. One study showed that, for both PV and ET patients, those with TEE before and after MPN diagnosis had a greater risk of mortality compared to patients without TEE. Also, patients who experienced TEE within the first year after MPN diagnosis had shorter median survival than those without TEE[28]. These studies showed that TEE significantly increases the risk of mortality whether it is experienced before or after the diagnosis of MPN; however, these studies did not compare mortality risks between patients who experienced TEE before or after MPN diagnosis.

In the current study, the effect of the timing of index TEE on mortality was examined. This relationship may have been influenced by various factors, including treatment before and after thrombosis, other possible causes of death, the number of TEE, and the time between thrombosis and MPN. Most of these factors could not be investigated in this study due to missing data or the difficulty of collecting data. Despite our results showing the absence of a temporal relationship, more comprehensive studies that will take these factors into account may be able to clarify potential relationships. We hope that the present study will inspire further studies on this subject.

Other risk factors may also affect the risk of mortality in MPN. Apart from TEE, factors such as leukemic transformation, advanced age, anemia, and MPN sub-types are widely recognized to increase the risk of mortality in MPN patients[15,16]. In the present study, PV patients constituted the majority of patients who developed TEE. PV was present in 43.5% of survivors and 26.1% of those with mortality; however, a significant difference was not identified between these groups. The results of univariate analysis showed that only the ET and PMF diagnoses were associated with significantly increased mortality. Similarly, the hemoglobin and hematocrit levels of non-survivors were significantly lower than that of survivors.

Table I. Summary of mortality related variables and analysis results.

		Mortality		
	Total (n=138)	**No (n=115)**	**Yes (n=23)**	***p***
Age	59.96 ± 14.19	57.54 ± 13.82	72.04 ± 9.01	**<0.001**
Sex				
Male	83 (60.1%)	70 (60.9%)	13 (56.5%)	0.876
Female	55 (39.9%)	45 (39.1%)	10 (43.5%)	
Smoking status				
Non-smoker	81 (73.6%)	69 (74.2%)	12 (70.6%)	0.494
Ex-smoker	6 (5.5%)	6 (6.5%)	0 (0.0%)	
Smoker	23 (20.9%)	18 (19.4%)	5 (29.4%)	
Anticoagulant use	35 (25.4%)	30 (26.1%)	5 (21.7%)	0.861
Antiaggregant use	104 (75.4%)	86 (74.8%)	18 (78.3%)	0.930
Comorbidities				
Diabetes mellitus	32 (23.2%)	25 (21.7%)	7 (30.4%)	0.528
Hypertension	60 (43.5%)	50 (43.5%)	10 (43.5%)	1.000
Cerebrovascular disease	40 (29.0%)	32 (27.8%)	8 (34.8%)	0.675
Coronary artery disease	45 (32.6%)	36 (31.3%)	9 (39.1%)	0.626
Congestive heart failure	7 (5.1%)	4 (3.5%)	3 (13.0%)	0.090
Atrial fibrillation	7 (5.1%)	6 (5.2%)	1 (4.3%)	1.000
Chronic renal diseases	4 (2.9%)	2 (1.7%)	2 (8.7%)	0.129
Hyperlipidemia	8 (5.8%)	6 (5.2%)	2 (8.7%)	0.620
COPD/Asthma	6 (4.3%)	5 (4.3%)	1 (4.3%)	1.000
Malignancy	7 (5.1%)	4 (3.5%)	3 (13.0%)	0.090
Hypothyroidism	4 (2.9%)	4 (3.5%)	0 (0.0%)	1.000
Other	21 (15.2%)	19 (16.5%)	2 (8.7%)	0.527
Diagnosis				
Polycythemia vera	56 (40.6%)	50 (43.5%)	6 (26.1%)	**0.025**
Primary myelofibrosis	6 (4.3%)	3 (2.6%)	3 (13.0%)	
Essential thrombocythemia	47 (34.1%)	35 (30.4%)	12 (52.2%)	
Chronic eosinophilic leukemia	1 (0.7%)	1 (0.9%)	0 (0.0%)	
MPN-Unclassifiable	28 (20.3%)	26 (22.6%)	2 (8.7%)	
Treatment[1]	118 (85.5%)	97 (84.3%)	21 (91.3%)	0.527
Hydroxyurea	91 (65.9%)	77 (67.0%)	14 (60.9%)	0.748
Ruxolitinib	15 (10.9%)	10 (8.7%)	5 (21.7%)	0.133
Interferon alpha	8 (5.8%)	7 (6.1%)	1 (4.3%)	1.000
Anagrelide	4 (2.9%)	3 (2.6%)	1 (4.3%)	0.522
Danazol	5 (3.6%)	1 (0.9%)	4 (17.4%)	**0.003**
Spleen status				
Normal	100 (74.1%)	84 (74.3%)	16 (72.7%)	0.895
Splenomegaly	31 (23.0%)	25 (22.1%)	6 (27.3%)	
Splenectomy	4 (3.0%)	4 (3.5%)	0 (0.0%)	
Size of spleen	158 (140 - 190)	148 (140 - 179)	171 (158 - 190)	0.250
Leukoerythroblastosis	3 (2.2%)	2 (1.7%)	1 (4.3%)	0.424
WBC ($x10^3$)	10.39 (7.90 - 14.00)	10.43 (7.87 - 13.95)	9.78 (8.13 - 18.80)	0.547
Neutrophil ($x10^3$)	7.18 (4.79 - 10.34)	7.24 (4.71 - 9.76)	6.79 (4.87 - 14.10)	0.579
Lymphocyte ($x10^3$)	2.15 (1.71 - 2.49)	2.15 (1.73 - 2.48)	2.21 (1.61 - 2.57)	0.983
Eosinophil ($x10^3$)	0.25 (0.12 - 0.42)	0.25 (0.13 - 0.42)	0.25 (0.12 - 0.49)	0.759
Hemoglobin	14.80 ± 3.24	15.19 ± 3.04	12.92 ± 3.59	**0.002**
Hematocrit	46.24 ± 10.05	47.26 ± 9.56	41.03 ± 11.09	**0.007**
Platelet ($x10^3$)	617.97 ± 308.32	613.11 ± 303.60	642.04 ± 336.88	0.683
MCV (fL)	85.70 ± 10.53	85.81 ± 10.49	85.13 ± 10.97	0.777
LDH (U/L)	238 (192 - 315)	235 (191 - 305)	244 (210 - 548)	0.072
Ferritin (ng/mL)	40.55 (14.70 - 79.57)	35.02 (13.79 - 75.04)	62.00 (24.90 - 91.00)	0.116
Erythropoietin (IU/L)	3.6 (1.71 - 6.8)	3.5 (1.3 - 6.1)	10.4 (1.82 - 10.7)	0.259

Table continued

Table I *(Continued)*. Summary of mortality related variables and analysis results.

	Mortality			
	Total (n=138)	**No (n=115)**	**Yes (n=23)**	***p***
JAK-2				
Negative	45 (33.1%)	35 (30.7%)	10 (45.5%)	0.272
Positive	91 (66.9%)	79 (69.3%)	12 (54.5%)	
Index thromboembolic event				
Before diagnosis	48 (34.8%)	39 (33.9%)	9 (39.1%)	0.884
At diagnosis	40 (29.0%)	34 (29.6%)	6 (26.1%)	
During follow-up	50 (36.2%)	42 (36.5%)	8 (34.8%)	
Location of thrombosis(1)				
Coronary artery	62 (44.9%)	52 (45.2%)	10 (43.5%)	1.000
Cerebrovascular	55 (39.9%)	45 (39.1%)	10 (43.5%)	0.876
Deep vein	4 (2.9%)	3 (2.6%)	1 (4.3%)	0.522
Pulmonary	3 (2.2%)	2 (1.7%)	1 (4.3%)	0.424
Portal vein	13 (9.4%)	12 (10.4%)	1 (4.3%)	0.695
Other	12 (8.7%)	10 (8.7%)	2 (8.7%)	1.000
Bleeding	13 (9.4%)	10 (8.7%)	3 (13.0%)	0.455
Gastrointestinal tract	5 (3.6%)	3 (2.6%)	2 (8.7%)	0.411
Epistaxis	3 (2.2%)	3 (2.6%)	0 (0.0%)	
Cerebrovascular	2 (1.4%)	2 (1.7%)	0 (0.0%)	
Other	3 (2.2%)	2 (1.7%)	1 (4.3%)	

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. (1) Patients may have more than one of the followings. CEL: Chronic eosinophilic leukemia, COPD: Chronic obstructive pulmonary disease, *JAK*: Janus kinase, LDH: Lactate dehydrogenase, MCV: Mean corpuscular volume, MPN: Myeloproliferative neoplasms, WBC: White blood cell.

These results were not confirmed by multivariable regression analysis. Only advanced age and danazol use were identified as independent risk factors for TEE-related mortality in our group of MPN patients. In a retrospective study, the survival of PMF patients was found to be significantly shorter than that of ET and PV patients. Also, in addition to the presence of TEE, leukemic transformation and hemoglobin (<13 g/dL) were found to be adversely associated with survival, whereas younger age (<60 years) was a good prognostic factor, in *BCR-ABL*-negative MPN[16]. Another study[15] showed that, in MPN patients positive for the $JAK2^{V617F}$ mutation, overall survival was significantly worse among those with PMF compared to patients diagnosed with PV or ET. However, the patient population in these studies included all patients with and without thrombosis, and no separate investigations were conducted regarding the timing of index TEE.

Danazol is a semisynthetic attenuated agent used in hematologic diseases[29-31]. It is recommended for the management of PMF-associated anemia and after discontinuation of ruxolitinib[29,32]. Although danazol therapy is generally well tolerated, some patients may experience side effects, such as cholestatic hepatitis, prostate adenocarcinoma, and elevated liver enzymes, leading to treatment discontinuation or dose reduction[33]. Danazol may also be associated with leukemic transformation of MPN[34]. Due to its positive effects on autoimmune mechanisms that

Table II. Significant factors independently associated with mortality, multiple logistic regression analysis.

	β coefficient	**Standard error**	***p***	**Exp (β)**	**95.0% CI for Exp (β)**	
Age	0.104	0.027	**<0.001**	1.110	1.053	1.169
Treatment, Danazol	3.006	1.224	**0.014**	20.215	1.836	222.574
Constant	-8.634	1.886	<0.001			

CI: Confidence Interval, Nagelkerke R^2=0.352.

cause reduced platelet levels, danazol is used in patients with thrombocytopenic purpura[31,35]. It was also reported that adding danazol to ruxolitinib treatment improved ruxolitinib-related outcomes, such as anemia and thrombocytopenia[36]. However, this effect of danazol may reverse the mechanism of action of therapy and may create an increased risk of thrombosis[30,37]. To the best of our knowledge, there are no other studies in which danazol has been associated with increased risk of mortality in MPN. Of note, danazol is suggested to increase the risk of TEE; however, the present study demonstrated that danazol could also increase TEE-related mortality in MPN patients. We therefore recommend cautious use of danazol in MPN patients, particularly the elderly. However, since the number of patients using danazol in our study was small, these results need to be confirmed in future studies.

Limitations

When interpreting the results of this study, some limitations should be considered. This is a single-center study, and the results only apply to MPN patients with TEE. We only investigated TEE-related deaths because (i) thrombosis is considered to be the main cause of mortality in MPN[15] and (ii) we wanted to investigate the effect of index TEE timing on solely TEE-related deaths to avoid bias. The retrospective collection of data resulted in a limited set of parameters; however, a respectable group of clinical and laboratory parameters were examined. Nonetheless, future studies should aim to include other parameters that could potentially affect TEE likelihood. Although the minimum follow-up period was 3 years, this limit may have reduced the number of patients that could have been included, particularly in the group including patients with TEE after MPN. Finally, since there are no other studies investigating this specific issue, results could not be directly compared.

Conclusions

The timing of the index TEE (before, during, or after the diagnosis of MPN) did not have a significant effect on TEE-related mortality. TEE-related mortality risk was found to be higher in patients with PMF and ET compared to other MPNs. Advanced age and danazol use were identified as independent risk factors for TEE-related mortality. We believe that patients with MPN who are older and those using danazol should be considered to have a higher risk of TEE-related mortality. However, these results need to be supported by more comprehensive studies.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

Ethical approval required for this retrospective study was obtained from the University of Health Sciences Dr. Sadi Konuk Training and Research Hospital, Bakırköy, Istanbul, Turkey (decision date: April 4, 2022, decision no.: 2022-07-10).

Informed Consent

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

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Authors' Contributions

EG: Planning, designing, data collection, literature survey, interpretation of the results, active intellectual support. DY: Designing, Data collection Collecting data of the work and statistical analysis. GBS: Collecting data of the work and statistical analysis. MD: Conception of the work.

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