Original Article

Disease and Clinical Characteristics of Patients with Chronic Myeloproliferative Neoplasms: 11-year Single Center Experience

Kronik Myeloproliferatif Neoplazi Tanılı Hastalarda Klinik Özellikler ve Hastalık Karakteristikleri: 11 Yıllık Tek Merkez Deneyimi

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ABSTRACT

Introductıon: BCR/ABL-negative myeloproliferative neoplasms are characterized by over-production myeloid lineages in the bone marrow. Polycythemia vera, essential thrombocythemia and primary myelofibrosis are the most common myeloproliferative neoplasms. The aim of this study was to analyse patient demographic characteristics, laboratory findings, mutational status together with complications, clinical course and survival.

Methods: This study was conducted on patients diagnosed with myeloproliferative neoplasms between 2008 and 2019. Blood parameters, demographic information, mutation analysis, management, complications and follow-up periods were recorded. Survival rates were calculated and the effect of the parameters on overall survival was analyzed.

Results: Evaluation was made of 247 patients, comprising 105 polycythemia vera, 126 essential thrombocythemia and 16 primary myelofibrosis patients. During follow-up, 11 polycythemia vera, 14 essential thrombocythemia and 2 primary myelofibrosis patients developed thromboembolic complications. Median overall survival could not be reached in polycythemia vera and essential thrombocythemia patient and determined as 70.3 months in primary myelofibrosis patients. Age, LDH, ferritin and platelet/lymphocyte ratio at the time of diagnosis and thromboembolic complications were determined to have a statistically significant effect on survival in all patients. Lower survival rates were seen in the primary myelofibrosis patients although thromboembolic complications were observed at similar rates in all 3 disease subgroups.

Discussion and conclusion: In addition to known risk factors such as age and thromboembolic complications, parameters such as LDH, ferritin and PLR, which may be considered to indicate disease activity and inflammation, can also be used as prognostic markers.

Keywords: myeloproliferative neoplasia, prognosis, thrombosis

ÖZET

Giriş ve amaç: BCR / ABL-negatif miyeloproliferatif neoplaziler, kemik iliğindeki miyeloid öncül hücrelerin aşırı üretimi ile karakterizedir. Polisitemi vera, esansiyel trombositemi ve primer miyelofibrozis en sık görülen miyeloproliferatif neoplazilerdir. Bu çalışmanın amacı hastaların demografik özelliklerini, klinik seyir ve laboratuvar bulgularını komplikasyonlar ve sağkalım ile birlikte analiz etmektir.

Yöntem ve gereçler: Bu çalışmaya 2008-2019 yılları arasında miyeloproliferatif neoplazi tanısı alan hastalar dahil edildi. Kan parametreleri, demografik bilgiler, mutasyon analizi, tedavi, komplikasyonlar ve takip süreleri kaydedildi. Sağkalım oranları hesaplandı ve parametrelerin genel sağkalım üzerindeki etkisi analiz edildi.

Bulgular: 105 Polisitemi vera, 126 esansiyel trombositemi ve 16 primer miyelofibrozis olmak üzere oluşan toplam 247 hasta değerlendirildi. Takip sırasında 11 polisitemi vera, 14 esansiyel trombositemi ve 2 primer miyelofibrozis hastasında tromboembolik komplikasyon gelişti. Polisitemi vera ve esansiyel trombositemi hastalarında ortalama genel sağkalıma ulaşılamadı, ancak primer miyelofibrozis

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hastalarında 70.3 ay olarak belirlendi. Tanı anında yaş, LDH, ferritin ve trombosit / lenfosit oranı ve tromboembolik komplikasyonlarının tüm miyeloproliferatif neoplazi hastalarında sağkalım üzerinde istatistiksel olarak anlamlı bir etkisi olduğu belirlenmiştir. Primer miyelofibrozis hastalarında daha düşük sağkalım oranları görülmesine rağmen, tromboembolik komplikasyon oranı 3 hasta alt grubunun hepsinde benzer oranlarda izlenmiştir.
Tartışma ve sonuç: Yaş ve tromboembolik komplikasyonlar gibi bilinen risk faktörlerine ek olarak, LDH, ferritin ve PLR gibi hastalık aktivitesini ve inflamasyonu gösteren parametreler de bu hastalıkların takibinde prognostik belirteç olarak kullanılabilir.

Anahtar Kelimeler: miyeloproliferatif neoplazi, prognoz, sağkalım, tromboz

Introduction

BCR/ABL-negative chronic myeloproliferative neoplasms (MPNs) are a group of diseases associated with hematopoiesis and over-production of one or more myeloid lineages in the bone marrow (BM). Polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) are the most common MPNs. Although they share common clinical and hematological features, the disease course and therapeutic requirements are different for the different forms [1].

Recent studies have reported that JAK2 (Janus kinase 2; located on chromosome 9p24) mutations are found in virtually all patients with PV and approximately half of ET and PMF patients [2, 3]. Mutations in the MPL (myeloproliferative leukemia virus oncogene; located on chromosome 1p34) and CALR (calreticulin; located on chromosome 19p13.2) have also been described, and are usually somatic [4].

Over-proliferation of all myeloid lineages is seen in PV. In ET, the main problem is megakaryocyte proliferation and thrombocytosis [5]. In the clinical course of both diseases, fibrosis may develop in the BM, and PV and ET may transform to post-PV and post-ET myelofibrosis, which is associated with anemia, splenomegaly and shortened survival [6]. Unlike PV and ET, the main problems of PMF, in addition to clonal proliferation, are BM fibrosis and extramedullary hematopoiesis [7].

When all MPNs are considered, the most common symptoms are fatigue, abdominal pain or discomfort, headache, night sweats and itching [8]. Microcirculatory disorders such as erythromelalgia, visual and neurological symptoms may be seen due to activation of leukocytes, endothelium, platelets or coagulation cascade [9].

Assessments of the survival of these diseases have shown that life expectancy is shorter in PMF. ET affects the quality of life of patients more than survival whereas PV is associated with both impaired quality of life and a reduction in life expectancy [10-13]. The most important complications of MPNs are thromboembolism (TE), bleeding or progression to myelofibrosis or acute myeloid leukemia (AML). Thrombosis is a major cause of mortality and morbidity in PV and ET [14, 15], with a reported incidence of 7-39% and 7–22%, respectively [16-18].

The aim of this study was to analyze the demographic characteristics, clinical features, and the mutational status of MPN patients together with complications, clinical course and survival.

Patients and Methods

This retrospective study was conducted on patients diagnosed with BCR-ABL negative chronic MPN in the Hematology Department of Diskapi Yildirim Beyazit Training and Research Hospital between 2008 and 2019. The diagnosis of MPN was made according to the WHO diagnostic criteria of myeloid neoplasms [5, 19]. The date of diagnosis, demographic information, mutation analysis, treatment management, complications and follow-up periods were recorded for all patients. At the time of diagnosis, hematological parameters were examined, including hemoglobin (Hb) level, hematocrit (Hct) level, platelet count, white blood cell

Table1. Distribution of demographic and disease characteristics of patient subgroups

Parameters (n=247)	PV (n=105)	PMF (n=16)	ET (n=126)
Age,median(ranges),years	64 (20-86)	66.5 (39-85)	65 (22-91)
Cardiovascular risk factor			
Yes	68 (%64.8)	7 (%43.8)	69 (%54.8)
No	37 (%35.2)	9 (%56.2)	57 (%45.2)
Bone marrow fibrosis at diagnosis			
Yes	6 (%5.7)	16 (%100.0)	20 (%15.9)
No	99 (%94.3)	-	106 (%84.1)
Risk score			
Low	44 (%44.8)	3 (%18.8)	48(%38.1)
Int-1	-	5 (%31.2)	-
Int-2	-	4 (%25.0)	-
High	58 (%55.2)	4 (%25.0)	78 (%61.9)
Mutational frequency (%)	96.1	*75*	*71.4*
Driver mutations			
JAK2 V617F (+)	101/105	10/16	81/126
Exon 12 (+)	0/1	0/2	0/11
CALR (+)	0/1	2/4	7/23
MPL (+)	0/1	0/4	0/23
Splenomegaly			
Yes	49 (%47.6)	15 (%93.8)	35 (%27.8)
No	54 (%52.4)	1 (%6.2)	91 (%72.2)
Thromboembolic complication			
Yes	11 (%10.5)	2 (%12.5)	14 (%11.1)
No	94 (%89.5)	14 (%87.5)	112 (%88.9)
Median follow-up, month	28.1[0.0-265.7]	14.0[1.0-93.4]	45.0[0.8-190.2]
Final status			
Nonsurvivor	1 (%1.0)	5 (%31.2)	10 (%7.9)
Survivor	104 (%99.0)	11 (%68.8)	116 (%92.1)

count (WBC), neutrophil count, lymphocyte count, monocyte count, platelet count, platelet distribution width, mean platelet volume (MPV), lactate dehydrogenase (LDH), ferritin and B12 vitamin levels. Survival rates were calculated and the effect of the parameters on overall survival (OS) was analyzed. High-risk and low-risk categories were evaluated in PV and ET patients according to age and previous thrombosis history [20]. The International Prognosis Scoring System (IPSS) was used for PMF patients [21].

Statistical analysis

Data obtained in the study were analysed statistically using SPSS Statistics 20 software (IBM, Armonk, NY, USA). Descriptive data were given as percentages. The Independent Samples t-test (t-table value) was used to compare two independent groups with normal distribution of measurement values, and the Mann-Whitney U test (Z-table value) was applied to data not showing normal distribution. $\chi 2$-cross tables were used to examine the relationship between qualitative variables. Only variables which were statistically significant in the univariate analysis were included in the multivariate Cox regression model. Two-sided p values<0.05 were accepted as statistically significant. Survival was estimated from Kaplan-Meier curves. Comparisons between the patient groups were made using the log-rank test.

Ethical approval and informed consent

All procedures performed in this study were conducted in accordance with the ethical standards of the institutional and / or national research committee and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards.

Approval for this study was given by the Local Ethics Committee (No: 86/14 Date: 20.04.2020).

Table 2. Distribution of some biochemical blood values according to diagnoses

Variable (N=247)	PV (n=105) Median [Min-Max]	PMF (n=16) Median [Min-Max]	ET (n=126) Median [Min-Max]
Hb, gr/dl	17.5[15.0-23.0]	11.5 [6.3-15.4]	13.5[8.3-17.4]
Hct	53.6[47.3-68.6]	34.1[19.2-48.8]	41.4[25.6-53.0]
WBCcount, $x10^9$/L	11.6[6.5-23.8]	21.9[4.8-43.3]	10.1[3.2-29.5]
Neutrophil count, $x10^9$/L	8.8[3.5-21.7]	17.7[2.5-37.5]	6.9[2.0-25.1]
Lymphocyte count, $x10^9$/L	2.1[0.6-4.6]	2.2[0.6-8.0]	1.9[0.7-7.1]
Monocyte count, $x10^9$/L	0.6[0.1-3.5]	0.8[0.1-1.7]	0.6[0.1-2.4]
PLT count $x10^9$/L	474.0[110.0-1932.0]	261.5[119.0-1074.0]	813.0[412.0-3199.0]
Pct %	0.4[0.1-1.5]	0.3[0.1-0.9]	0.6[0.2-2.7]
MPV	8.2[6.2-11.4]	8.5[6.6-10.0]	7.9[5.1-12.2]
LDH U/L	254.0[140.0-485.0]	663.0[212.0-1157.0]	255.5[152.0-625.0]
Ferritin ng/mL	21.3[4.8-349.0]	96.6[7.6-602.0]	42.5[2.0-454.0]
Vitamin B12 pg/mL	247.0[97.0-957.0]	482.0[228.0-1076.0]	301.0[79.0-1219.0]
PLR	241.8[48.4-685.7]	127.9[18.9-716.0]	457.1[95.9-1999.4]
NLR	4.2[1.1-27.1]	7.5[1.8-23.7]	3.5[1.1-12.9]
MLR	0.3[0.1-5.1]	0.3[0.1-1.1]	0.3[0.1-1.5]
Erythropoietin mlu/ml	2.0[0.5-11.1]	5.0[3.0-7.0]	7.4[1.0-99.0]

Hb: Hemoglobin, Hct: Hematocrite, Plt:Platelet, WBC: White blood cell, PCT: Plateletcrit, MPV: Mean platelet volume LDH: Lactate dehydrogenase, PLR: Platelet to lymphocyte ratio, NLR: Neutrophil to lymphocyte ratio, MLR: Monocyte to lymphocyte ratio

Table 3. Treatment characteristics in disease subgroups

	PV (n=105)	PMF (n=16)	ET (n=126)
First linetreatment			
Hydroxyurea	76 (%72.4)	13 (%81.2)	102 (%81.0)
Anagrelide	-	-	6 (%4.7)
Interferon	-	-	2 (%1.6)
Ruxolitinib	-	3 (%18.8)	-
No treatmentindications	29 (%27.6)	-	16 (%12.7)
1th linetreatmentduration[median, month]	28.5[1.0-222.0]	13.5[1.0-92.0]	36.0[1.0-187.0]
Indication of 2nd linetreatment			
Unresponsivetomedication			
Inadequate	-	-	2 (%6.9)
Side effect, intolerance	1 (%50.0)	2 (%28.6)	7 (%24.1)
Loss of response	1 (%50.0)	3 (%42.8)	9 (%31.1)
Other	-	1 (%14.3)	11 (%37.9)
	-	1 (%14.3)	-
Second line treatment			
Hydroxyurea	-	-	5 (%16.7)
Anagrelide	2 (%100.0)	1 (%16.7)	23 (%76.8)
Ruxolitinib	-	5 (%83.3)	-
Interferon	-	-	2 (%6.7)
2th line treatment duration, [median, month]	23.5[15.0-32.0]	12.0[1.0-28.0]	20.5[1.0-128.0]

Table 4. Examination of factors affecting overall survival in all patients with Cox-Regression model

All patients	B	Standart error	Wald	df	Sig.	OR	95.0% confidenceinterval OR	
							Lower	Upper
Age at diagnosis	0.062	0.029	4.595	1	0.032	1.064	1.005	1.127
Thromboembolism	2.237	0.656	11.618	1	0.001	9.367	2.588	33.905
LDH	0.005	0.001	15.759	1	0.000	1.005	1.003	1.008
Ferritin	0.006	0.002	7.532	1	0.006	1.006	1.002	1.010
PLR	0.003	0.001	11.220	1	0.001	1.003	1.001	0.004

Results:

Evaluation was made of 247 patients, comprising 105 PVR, 126 ET and 16 PMF. The median age was 64 years (20-86) for PV, 66.5 years (39-85) for MF and 65 years (22-91) for ET patients. Of the total 247 patients, 51.6% were female (35.3% of PV patients; 58% of ET patients and 43.8% of PMF patients). The overall frequency of driver mutations was 96.1% for PV, 71.4% for ET and 75% for PMF patients. The demographic and clinical characteristics of the patients are given in Table 1. The hematological and biochemical parameters of the patients are given in Table 2.

Hydroxyurea (HU) was administered as first-line treatment to 76 (72.4%) patients with PV for a median duration of 28.5 months. The most common indications for switching to the second-line treatment were inadequate response (50%) and side-effects (50%). There were no indications for treatment in 29 (27.6%) PV patients, so they were followed up with anti-aggregant agents. HU was administered as the first line treatment to 102 (81.0%) ET patients for a duration of median 36.0 months. The most important indication for switching to the second-line treatment was side-effects (37.9%). In 23 ET patients (76.8%), anagralide was administered as the second-line treatment for a median of 20.5 months, and 16 (12.7%) ET patients had no indication for treatment and were followed up with anti-aggregant agents. Of the patients diagnosed with PMF, the first-line treatment of HU was administered to 13 (81.2%) for a median of 13.5 months, and second-line treatment of ruxolitinib was administered to 5 (83.3%) for median 12 months. Indications for second-line treatment wee mainly side-effects (42.8%). The treatment characteristics of the disease subgroups are given in Table 3.

During follow-up, 11 (10.5%) PV patients, 14 (11.1%) ET patients and 2 (12.5%) PMF patients developed thromboembolic (TE) complications. When the survival rates of the patients were examined, OS of the whole sample could not be calculated because median survival could not be reached in the PV and ET subgroups. The median OS of the PMF patients was determined to be 70.3 (14.0-126.7) months. The survival rates of all the patients and disease subgroups are shown in Figure 1.

As a result of the Cox-Regression model for all patients, it was determined that age, LDH, ferritin and PLR values at the time of diagnosis and the development of TE had a statistically significant effect on survival for all MPN patients ($p < 0.05$). The Cox regression model and Odds Ratio values are shown in detail in Table 4. This analysis could not be performed for disease subgroups due to the low number of patients in the PMF group and the low number of non-survivors in the PV and ET groups.

Discussion

The main purpose of this study was to retrospectively examine our patients diagnosed with MPN that we followed up in our clinic and compare them with the literature.

The median age at diagnosis for PV and PMF has been reported to be 63-64 years, and 55 years for ET [22]. In the current study, the median age at diagnosis for PV, ET and PMF was 64, 65 and 66.5 years, respectively. In contrast to recent reports, the current study ET patients were older. In the ET subgroup, there was a predominance of female patients (58% F vs. 42% M), which was similar to findings of the International Prognostic Score of thrombosis in World Health Organization-Essential Thrombocythemia (IPSET) study [15]. Male predominance was determined in the PV group in accordance with the literature [23]. No gender difference was determined in the PMF patients.

JAK2 mutation has been found to be present in approximately 98% of PV, 60% of ET and 55% of PMF cases according to many recent studies [24-26]. In the current study the overall frequency of driver mutations was 96.1% for PV, 71.4% for ET and 75% for PMF patients. JAK V617F mutation was detected in 96% of PV patients and 64% of ET patients in accordance with current data in

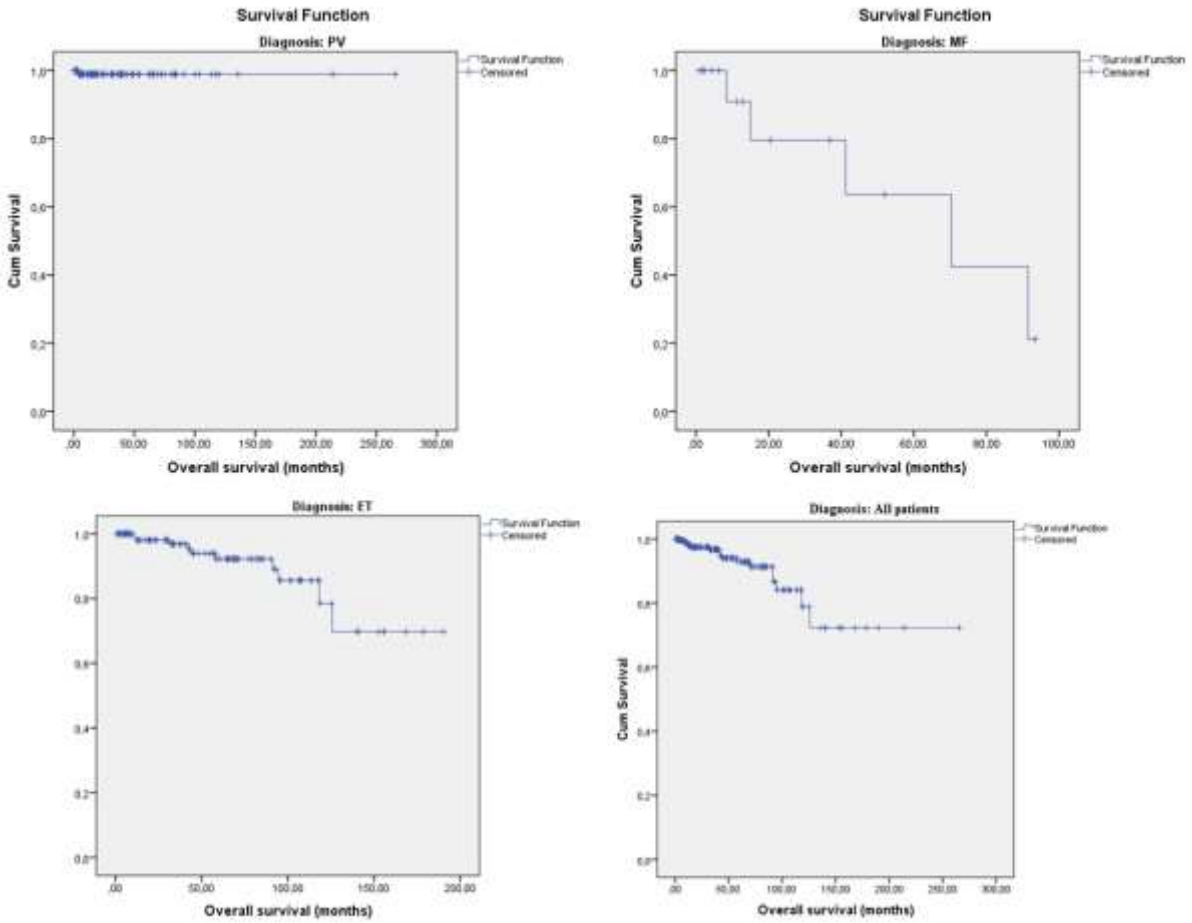

Figure 1: The survival rates of all the patients and disease subgroups

literature. However, in the current study PMF patients, JAK V617F mutation frequency was 62.5%, which was a higher rate than previously reported. The results of the current study supported that adding the analysis of JAK2 Exon 12, CALR and MPL to the JAK2 V617F mutation increased the overall mutational frequency. The CALR analysis in particular increased the frequency from 64.2% to 71.4% for ET patients and from 62.5% to 75% for PMF patients. Therefore, for patients with suspicion of ET or PMF, adding the CALR mutation analysis at the beginning of assessments rather than waiting for JAK2 results can be considered to increase diagnostic capability.

The major complication of Ph-negative MPNs was TE complications. The TE rates of PV patients was reported to be 38.4% in the European Collaboration on Low-dose Aspirin in Polycythemia Vera (ECLAP) study, which was a prospective study of 1638 patients [27]. Tefferi et al., found the incidence of thrombosis in PV patients to be 23.4% in an international study [28]. In the above-mentioned IPSET study, the incidence of thrombosis was 12% in ET patients [15]. In another study from Turkey, the frequency of thrombosis was seen to be 41.1% in ET, 35% in PV and 32% in PMF patients [29]. In the current study, thrombosis rates were 10.5%, 11.1%, and 12% in PV, ET, and PMF, respectively. With the exception of the IPSET study, the incidence of thromboembolism was lower in the current study compared to other studies. This may have been due to some missing data because of the retrospective design of the current study. Patient files may not have been processed and the follow-up time was not sufficient. Although it was

determined that the current study patients with ET developed TE more frequently than patients with PV, this result was not statistically significant.

The expected survival of PV and ET patients is almost the same as that of the general population. In a study from Sweden, the 8-year relative survival rate was 0.84 in PV patients and 0.91 in ET [30]. In a study by the Mayo Clinic Italian collaborative group with 826 patients, the median survival rates were ~20 years for ET, 14 years for PV and 6 years for PMF [22]. In the current study, similar to recent reports, OS was not reached for ET and PV patients, whereas it was determined to be 5.8 years for PMF patients.

In a large study of 1545 PV patients, advanced age (>67 years), leukocytosis ($\geq 15\times10^9$/L), history of thrombosis and abnormal karyotype were determined to be independent risk factors for survival [28]. When evaluated in terms of leukemic transformation and BM fibrosis in PV patients, which is very important for survival, advanced age, leukocytosis and abnormal karyotype have been shown to be related to leukemic transformation [28, 31].

In respect of ET, the IWGMRT study of 867 patients found that advanced age (>60 years), leukocytosis ($\geq 11\times10^9$/L), and a history of thrombosis were significant for survival [15].

In the current study, Cox regression analysis could not be applied to the disease subgroups, but in the analysis of all the MPN patients, age at diagnosis and thrombosis history were found to have a significant effect on survival, which was consistent with recent reports. In addition, a higher platelet-to-lymphocyte ratio (PLR), serum LDH and serum ferritin levels were related to lower survival. Many studies have determined that eleveted PLR is associated with inflammatory, metabolic, prothrombotic and neoplastic diseases [32]. Morever, in many studies, it has been mentioned that PLR is a better inflammatory marker than WBC and is associated with poor prognosis and the risk of developing venous thrombosis [33]. In the current study, OS was lower in patients with higher PLR. In the literature, there is no study showing that PLR affects MPN or separately, ET and PV. Lucijanic et al demonstrated that the PLR was significantly higher in myelofibrosis than in healthy control subjects. They also found that higher PLR was associated with the absence of blast phase disease, constitutional symptoms, and massive splenomegaly, and this was attributed to PLR in MF being less related to inflammation than bone marrow fibrosis [34]. In the current study, a negative relationship was found between the serum ferritin levels and OS in patients with MPN. Although there is no information about this subject in the literature, it has been shown in a previous study that ferritin levels are higher in reactive thrombocytosis than in essential thrombocytosis [35]. High levels of ferritin in MF may be related to severe anemia and the need for blood transfusion. In addition to the known risk factors such as thrombosis and age, inflammatory markers such as ferritin and PLR are also associated with survival in MPN patients, which may indicate that inflammatory processes have a role in the pathogenesis of these diseases. On the other hand, low ferritin may be observed in PV patients as a secondary to phlebotomy. However, since ferritin at the time of diagnosis was evaluated in our study, the effect of low ferritin that may be observed after phlebotomy on overall survival could not be determined.

A previous study found that serum LDH levels were higher (89%) in PMF patients and elevated serum LDH levels were associated with disease burden [36]. In the current study, elevated serum LDH was related with shorter OS in all MPN patients.

Higher LDH levels, which indicate disease activity, may have had a negative effect on survival in this context.

The main goal of treatment in PV and ET is to reduce TE complications and secondarily, to control symptoms. In PMF, the aim is to decrease the patient's constitutional symptoms and improve the quality of life [37]. Acetylsalicylic acid to prevent cardiovascular complications is the main treatment for PV and ET. However, when the platelet count is $>1{,}000\text{x}10^9$/L in ET, aspirin should be

avoided due to acquired vWD. Phlebotomy should be kept in mind to keep the hemotocrit value <45 in PV. Cytoreductive agents such as HU, anagralide or interferon are indicated in patients at high risk of thrombosis. Ruxolitinib may be used when there is insufficient response to HU [38]. For the treatment of PMF, most patients are administered symptom-based therapy as blood transfusion, HU or ruxolitinib. Allogeneic stem cell transplantation should be considered in fit and young PMF patients with high risk features as a curable treatment option [20]. In the current study,72.4% of PV patients and 87.3% of ET patients had treatment indications. Hydroxyurea was the most commonly used first-line treatment agent, and the development of side-effects was the most common indication for switching to second-line treatment in all the disease subgroups. As second-line therapy in PV and ET, the most preferred agent was anagralide, whereas in MF, it was ruxolitinib. Limitations of this study were the Retrospective design and that the parameters associated with TE or prognosis were not evaluated due to insufficient data. Cox regression analysis could not be performed for the disease subgroups due to the low number of PMF patients and the low number of non-survivors in the PV and ET subgroups. The total follow-up period should be longer for diseases such as ET and PV, which have survival rates close to those of the normal population. There is a need for larger prospective studies to analysis TE complications.

In conclusion, the results of this study showed that PMF patients had lower survival rates than patients with other MPNs although TE was observed at similar rates in all 3 disease subgroups. In addition to the known risk factors such as age and TE complications, parameters such as LDH, ferritin and PLR indicating disease activity and inflammation can also be used as prognostic markers. There is a need for larger population-based epidemiological studies to be able to better understand the course of the diseases and to assist in their management.

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