TURKISH JOURNAL OF INTERNAL MEDICINE
ISSN:2687-4245
Original Article

Assessment of Relation between JAK2 Gene and Thrombosis in Myeloproliferative Neoplasms

Selda KAHRAMAN[1], Fatih DEMIRKAN[2]

[1]Department of Hematology, Medicana International Izmir Hospital, Izmir, Turkey
[2]Division of Hematology, Department of Internal Medicine, Dokuz Eylul University Izmir, Turkey

ABSTRACT

Background Thrombotic complications are the most considerable etiology causing morbidity and mortality in patients with philadelphia (Ph) negative myeloproliferative neoplasms (MPN). There are many studies evaluating the association of JAK2 mutation and risk of thrombosis in MPN with inconclusive results. We also investigated the relation between JAK2 mutation in all Ph negative MPN and thrombosis.

Material and Methods Thrombotic events and demographic features of 177 patients with Ph negative MPN were evaluated retrospectively.

Results JAK2 V617 F mutation was detected in 57% of patients with essential thrombocythemia (ET), %90.3 of pateints with polycythemia vera (PV), 100% of pateints with primary myelofibrosis (PMF). Thrombotic complications occured more frequently with JAK2 mutation in all MPN patients than without (p=0.014). In JAK 2 mutation positive groups, the median age, thrombosis risk scores and leucocyte values are higher, splenomegaly and arterial and/or venous thrombosis are detected more frequently (p<0.05). In subgroup analysis, there is a significant difference found in JAK 2 positive ET patients and negative group in case of thrombosis (p=0.023).

Conclusions JAK2 mutation and monitoring for thrombotic events should be performed in all MPN patients.

Turk J Int Med 2022;4(3):112-120
DOI: 10.46310/tjim.1055305

Keywords: *Thrombosis, myeloproliferative neoplasms, essential thrombocytemia, polycythemia vera.*

Received: January 13, 2022; Accepted: Aprik 21, 2022; Published Online: July 29, 2022

Address for Correspondence:
Selda Kahraman, MD

Department of Hematology, Medicana International Izmir Hospital, Izmir, Turkey
E-mail: sel_ad@yahoo.com

Introduction

Myeloproliferative neoplasms (MPN) include essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF).[1] These diseases have common clinical features, such as the high risk of vascular complications (especially in PV), progression to secondary myelofibrosis (especially in PV), and clonal evolution to the blast phase (especially in PMF).[2] From a biological point of view, 95% of patients with PV and 50-60% of patients with ET and PMF carried a common mutation of the JAK2 gene, the JAK2 (V617F).

The patients with PV and ET are currently stratified per thrombotic risk, and treatments are prescribed accordingly.[3] Patients older than 60 years old or with prior thrombosis attacks should be considered in a high-risk group, whereas those younger than 60 years old or with no history of thrombosis should be considered in a low-risk group. High-risk patients should be treated with cytoreductive agents, for example, hydroxyurea. Although this indication is valid for current practice, other parameters may be considered for patients with PV and ET in determining risk stratification, such as leukocyte count, the JAK2 (V617F) mutation, and bone marrow fibrosis grading. A higher leukocyte count has been shown to correlate with thrombosis in both PV and ET.[4,5] However, not all retrospective analyses accept a direct correlation between the leukocyte count and thrombosis.[6,7] Investigators supporting leukocytosis's role in predicting thrombosis in ET showed convincing data on patients with low-risk ET left untreated. In this setting, other investigators did not obtain the same results.[8]

The incidence of thrombosis detected in PV and ET are 12-39% and 11-25%, respectively.[9] Thrombosis is a critical prognostic criterion in MPN. Age over 60 and a history of thrombosis are two factors that increase thrombosis risk in MPN.[10] Cardiovascular risk factors promoting arterial thromboses like smoking, hypertension, diabetes and dyslipidemia are still controversial as a prognostic value.[11] In this group of diseases, thrombosis is usually identified in veins and/or large arteries.[12] By discovering clonal JAK2 mutation in PV patients, the definition and treatment of myeloproliferative neoplasms data is upgraded in 2020. JAK2 mutation forms by the switch between valine and phenylalanine in the 617th codon, the JAK2 pseudokinase piece. JAK2 mutation plays a fundamental role in the genetic description of myeloproliferative disease pathogenesis.[13-26] It is suggested that JAK2 differs the position and stability of thrombopoietin receptor MPL to affect thrombocyte activation.[14] As a result of a mutation in JAK2, the coagulation cascade is indirectly activated by alterations in apoptosis and transcription factors expressed in the activated JAK/STAT pathway.[15-29] Many studies evaluated the association of JAK2 mutation and risk of thrombosis in MPN with inconclusive results.[16] We also investigated the relation between JAK2 mutation in all Ph negative MPN and thrombosis and want to contribute Turkish data about the frequency of thrombosis in JAK2 positive, Ph negative patients.

Material and Methods

This study evaluated the clinical and demographic characteristics of 177 Ph negative chronic MPN patients according to classic and updated diagnostic criteria from 1994 to 2011 in Dokuz Eylul Hematology Clinic. All thrombotic events were recorded in MPN patients before and/or after diagnosis. Thrombotic events proven with clinic, laboratory and/or imaging were accepted for assessment. Thrombotic events were evaluated under two titles: 1. Thrombosis related to venous system: Events with venous thromboembolism (VTE) (deep venous thrombosis [DVT], pulmonary embolism [PE], portal venous thrombosis, and splenic venous thrombosis); 2. Thrombosis related to arterial system: Proceeds with atherosclerosis and/or arterial thrombosis (atherothrombotic vessel disease-related myocardial infarction, coronary artery disease, cerebrovascular disease, peripheral arterial disease). The thrombosis risk scores for every patient were calculated.

Statistical Analysis

The retrospective study was evaluated by SPSS 15.0 for Windows Software Program. The odds ratio and Chi-square test determined the relation between JAK2 mutation and thrombosis. The odds ratio was 95%. Thrombosis risk factors other than JAK2 mutation in JAK2 (+) and (-) groups

were established by the Student t-test and Mann-Whitney U test. The statistically significant difference was p<0.05 for the Student-t-test, Mann-Whitey U and Chi-square test.

Results

The mean age of the MPN patients was 60 years (range: 18-90), and the male/female ratio was 1.1 (53.7% of the patients were male and 46.3% female). Most patients were diagnosed with ET (63.3%, 62 patients). Of the others, 62 had PV (35%), and 3 had PMF (1.7%). JAK2 mutation was positive in 107 patients (60.5%) and negative in 70 patients (39.5%). JAK2 V617 F mutation was detected in 57% of patients with ET, 90.3% of patients with PV, and 100% of patients with PMF. Thromboembolic events were detected in 71 patients (41%). Venous thrombosis was detected in 22 patients (12.4%) and arterial thrombosis in 49 patients (27.7%). The region of thromboembolisms was summarized in Table 1.

When we evaluated the patient's history, there were hypertension in 60 patients (33.9%), diabetes mellitus in 25 patients (14.1%), dyslipidemia in 27 patients (15.3%), and smoking in 27 patients (15.3%). Forty patients (22.6%) were considered high, 55 (31.1%) moderate, and 82 (46.3%) low risk for thrombosis. The characteristics of 177 MPN patients (with PV, ET, and MF) were showed in Table 2. At diagnosis, haemoglobin value was 14.83±2.61 g/dL hematocrit value was 44.25±8.08%, leucocyte count was 10,300 mm^3 (880-38,000), thrombocyte count was 702,000 mm^3 (57,000-2,285,000). Splenomegaly existed in 32.8% (n: 58) patients however 119 patients did not have splenomegaly (67.2%). Assessment of thrombosis risk score of PV, ET and PMF patients according to age at diagnosis, sex, JAK 2 mutation, laboratory values, splenomegaly, other diseases, arterial and venous thrombosis was presented in Table 2. There were significant differences detected in sex, age, haemoglobin, hematocrit and thrombocyte values between PV and ET (p<0.05) (*Table 2*). The effect of JAK2 mutation in venous and/or arterial thrombotic events was investigated in all MPN groups and PV, ET and PMF subgroups. All statistical analysis of the retrospective study was done by odds ratio (*Table 3*). In JAK 2 mutation-positive groups, the median age, thrombosis risk scores, and leucocyte values were higher, and splenomegaly and arterial and/or venous thrombosis were detected more frequently (p<0.05). Venous thromboembolic events in JAK (+) MPN patients were detected higher than JAK2 (-) patients (odds ratio: 4.82, p=0.014). In subgroup analysis, a significant difference was found in JAK 2 positive ET patients (p=0.023). No significant difference was detected between JAK 2 positive PV patients and VTE (p=0.562).

Arterial thromboembolic events were evaluated higher in JAK2 (+) MPN patients (odds ratio: 2.954, p=0.005). It was confirmed that there was a statistically significant increase in arterial thrombotic events in JAK 2 positive patients rather than JAK2 negative patients with ET (p=0.011). On the other hand, there was no relation between JAK2 mutation and arterial thrombosis development in PV patients (p=0.277). If all vascular diseases were included, JAK 2 positive MPN patients had a higher probability of thromboembolic events than JAK2 negative patients detected in our study (odds ratio: 3.376, p=0.001). In the subgroup analysis of all vascular diseases, JAK2-positive ET patients had a significantly higher affinity to thrombosis (p=0.001). On the other hand, there was no statistically significant relation between affinity to thrombosis in JAK2 positive PV patients (p=0.359).

Venous thrombosis was statistically significant with a high-risk score, presence of splenomegaly, hypertension and JAK2 mutation in simple variable regression analysis (p values <0.034-0.062-0.014). Venous thrombosis was increased in patients with JAK2 mutation, splenomegaly and hypertension (p values as follows <0.030-0.065-0.041, according to multiple variable regression analysis) (*Table 4*).

In simple variable regression analysis, arterial thrombosis was detected more frequent in old, hypertensive, dyslipidemic patients and with the presence of high leucocyte count, smoking and JAK2 positiveness (p<0.05) (*Table 5*). According to arterial thrombosis predictors in multiple variable regression analysis, smoking, leucocyte value, and JAK2 positiveness increased arterial thrombosis development (*Table 5*).

Table 1. Frequency of venous and arterial thromboembolic events and distribution.

Venous thromboembolism 12.4% (n: 22)		Arterial thromboembolism 27.7% (n: 49)	
Region	Number of patients	Region	Number of patients
Deep venous thrombosis	17	Myocardial infarction	12
Pulmonary embolism	4	Coronary artery disease	25
Portal venous thrombosis	4	Cerebrovascular disease	23
Splenic venous thrombosis	2	Periferic arterial disease	4

*In 22 patients only venous, in 49 patients only arterial; in 15 patients both venous and arterial thromboembolic event are existed.

Table 2. Patients characteristics due to diagnostic groups.

	PV (n: 62)	ET (n: 122)	MF (n: 3)	p value†
Age	67 (18-85)	61 (27-90)	61 (53-63)	0.018
Sex (female/male)	21/41	60/52	1/2	0.013
JAK 2 mutatation	56/6 (90.3%)	66/46 (58.9%)	3/3 (100%)	0.042
Hypertension	25/37 (40.3%)	34/78 (30.4%)	1/3 (33.3%)	0.184
Dsylipidemia	8/54 (12.9%)	19/93 (17%)	0/3 (0%)	0.479
Smoking	12/50 (19.4%)	14/98 (12.5%)	0/3 (0%)	0.224
Diabetes mellitus	8/54 (12.9%)	17/95 (15.2%)	0/3 (0%)	0.682
Thrombosis risk score	L: 24 (38.7%) I: 24 (38.7%) H: 14 (22.6%)	L: 57 (50.9%) I: 30 (26.8%) H: 25 (22.3%)	L: 1 (33.3%) I: 1 (33.3%) H: 1 (33.3%)	0.212
Hemoglobine (g/dL)	17.14±2.03	13.68±1.91	10.30±1.41	<0.001*
Hematocrit (%)	51.08±6.23	40.81±6.30	31.77±3.96	<0.001*
Leucocyte (/10^3 mm^3)	10.4 (3.9-26.4)	10.2 (0.88-38)	16.4 (15.4-19.5)	0.492
Thrombocyte (/10^3 mm^3)	359 (127-1,143)	814 (162-2,285)	370 (57-2,027)	<0.001*
Splenomegaly	21/41 (33.9%)	34/78 (30.4%)	3/3 (100%)	0.633
Venous thrombosis	7/55 (11.3%)	14/98 (12.5%)	1/3 (33.3%)	0.815
Arterial thromboembolism	15/47 (24.2%)	32/80 (28.6%)	2/3 (66.7%)	0.533
Venous or arterial thromboembolism	17/45 (27.4%)	37/75 (33%)	2/3 (66.7%)	0.443

† Evaluation between difference in PV and ET groups.
*p<0.05.
EV: essential thrombocythemia, PV: polycythemia vera, PMF: primary myelofibrosis, L: low risk, I: intermediate risk, H: high risk.

Table 3. Patient characteristics due to JAK 2 mutation.

	Positive (n: 125)	Negative (n: 52)	p value†
Age	65 (27-90)	57 (18-84)	0.003*
Sex (female/male)	65/60	30/27	0.895
Diagnosis	PV: 56 ET: 66 MF: 3	PV: 6 ET: 46	0.761
Hypertension	40/85	17/35	0.813
Dsylipidemia	16/109	6/46	0.252
Smoking	20/105	7/45	0.772
Diabetes mellitus	33/92	6/46	0.695
Thrombosis risk score	L: 37 I: 42 H: 46	L: 32 I: 14 H: 6	0.002*
Hemoglobine (g/dL)	14.84±2.41	14.83±2.92	0.976
Hematocrit (%)	44.81±8.01	43.41±8.18	0.264
Leucocyte (/10^3 mm^3)	11.1 (3.9-34.2)	9.55 (0.88-38)	0.002*
Thrombocyte (/10^3 mm^3)	702 (57-2,285)	695.5 (139-2,175)	0.739
Splenomegaly	51/74	10/42	0.003*
Venous thrombosis	22/103	2/50	0.008*
Arterial thromboembolism	42/83	7/45	0.004*
Venous or arterial thromboembolism	50/75	6/46	0.001*

† Evalutation of differance in PV and ET groups
*p<0.05
PV: polycythemia vera, ET: essential thrombocytosis, MF: myelofibrosis.

Table 4. Venous thrombosis predictors (simple-multiple variable logistic regression analysis, n: 177)

Venous thromboembolic events	OR	p value	OR*	p value*
JAK2 mutation	4.82 (1.34-16.97)	0.014	4.17 (1.15-15.14)	0.030
Age	1.02 (0.99-1.06)	0.195		
Sex (male/female)	0.85 (0.35-2.07)	0.712		
Diagnosis (PV/ET)	1.22 (0.43-2.95)	0.815		
Splenomegaly	2.73 (1.08-6.87)	0.034	2.50 (0.94-6.59)	0.065
Leucocyte (/10^3 mm^3)	1.00 (1.01-1.11)	0.524		
Hemoglobine (g/dL)	0.88 (0.74-1.06)	0.880		
Thrombocyte (/10^3 mm^3)	1.00 (0.99-1.01)	0.840		
Smoking	0.94 (0.26-3.48)	0.930		
Dyslipidemia	2.51 (0.88-7.21)	0.086		
Diabetes mellitus	0.99 (0.27-3.65)	0.991		
Hypertension	2.41 (0.96-6.05)	0.062	2.75 (1.04-7.25)	0.041

*OR (CI), was defined as p value.
Multiple variable regression analysis (R^2=0.152, p=0.002).

Table 5. Arterial thrombosis predictors (simple-multiple variable logistic regression analysis n: 177)†

Arterial thromboembolic events	OR	p value	OR *	p value*
JAK2 mutation	2.84 (1.33-6.07)	0.007	2.54 (1.06-6.08)	0.037
Age	1.03 (1.01-1.06)	0.009	1.01 (0.98-1.04)	0.465
Sex (male/female)	1.10 (0.57-2.17)	0.763		
Diagnosis (PV/ET)	1.25 (0.62-2.55)	0.534		
Splenomegaly	1.72 (0.85-3.45)	0.130		
Leucocyte (/10^3 mm^3)	1.01 (0.99-1.10)	0.006	1.00 (0.99-1.02)	0.049
Hemoglobine (g/dL)	0.97 (0.85-1.11)	0.689		
Thrombocyte (/10^3 mm^3)	1.00 (0.99-1.01)	0.057	0.99 (0.97-1.03)	0.063
Smoking	4.94 (2.07-11.81)	0.001	3.86 (1.33-11.22)	0.013
Dyslipidemia	5.44 (2.29-12.91)	0.001	2.15 (0.72-6.44)	0.173
Diabetes mellitus	1.64 (0.67-4.03)	0.277		
Hypertension	4.01 (1.98-8.10)	0.001	2.24 (0.72-6.44)	0.079

*OR (CI), was defined as p value.

Discussion

Thrombosis is the most considerable aetiology causing morbidity and mortality in myeloproliferative diseases.[17] The thrombosis is declared mostly in veins and/or large arteries.[18] In 2005, clonal JAK2 mutation was defined in PV patients, upgrading the data on diagnosis and treatment of myeloproliferative diseases. JAK2 mutations are detected in 90-95% of PV patients and 50-60% of ET and PMF patients.[19-27] In our study, the frequency of JAK2 mutations was 90.3%, 57% and 100% in PV, ET and PMF patients, respectively. The major problem in our study was numerical inhomogeneity in our patients.[28] There is a consideration about the relation between JAK2 mutation and the development of thrombosis due to increased thrombotic vascular events detected in JAK2 positive MPN patients or thrombotic diseases such as Budd-Chiari syndrome without MPN.[20,30,31]

The incidence of thrombosis in MPN is 10% to 30%.[19] We included all atherosclerotic vascular changes in our study. Thus, isolated venous thromboembolic events were detected in 12.4% of all MPN patients, isolated arterial events in 27.7%, and both arterial and venous events in 8.47%. The higher frequency in our study may be due to the inhomogeneity of our patient population.

The relation between JAK2 mutation in MPN and thrombosis was first mentioned in a 2005 publication. Kralovic et al.[20] investigated a total of 244 patients (128 PV, 93 ET and 23 PMF) in the study and found the frequency of the JAK2 positivity as 48%. Among 177 follow-up patients in our study, 60.5% of the patients had JAK2 mutation. Campbell et al.[21] mentioned the statistically significant increment of frequency in venous thromboembolism in JAK2 positive ET patients (n: 776). However, there was no difference in arterial thrombosis in 2005. Evaluation of ET patients in Wolanskyj et al.[13] studies showed no relation between thrombosis and JAK2 mutation. Cheung (n: 60) and FInazzi (n: 179) analyzed patients with ET, and they declared the increased thrombosis risk in the JAK2 positive group (62% vs. 26% and 46% vs. 4%, respectively), similar to our study.[22] In our study, totally thrombosis risk in JAK2 positive patients was significantly higher than in JAK2 negative patients, and arterial thrombosis frequency was 21.46%, venous thrombosis frequency 10.73%, venous and/or arterial thrombosis frequency is 24.85%. In subgroup analysis, JAK2 mutation-positive PV

patients had 5% of arterial thrombosis and 17.7% of venous thrombosis, which was not statistically significant between the JAK2 negative group. The arterial thrombosis frequency was 22.3%, and venous thrombosis frequency was 11.6% in JAK2 mutation-positive ET patients, significantly higher than in JAK 2 negative ET patients.

As a result, there is a positive correlation between arterial and venous thrombosis and JAK2 positiveness in ET patients rather than PV patients. Smoking, advanced age, and splenomegaly were significantly associated with an increased risk of thrombosis in the JAK2 positive and negative MPN groups. In general, it is possible to prove that JAK2 mutation increases the risk of thrombosis in MPN patients. This condition is due to patient population heterogeneity and various factors contributing to thrombosis. On the other hand, no proven data shows simultaneous different thrombophilic mutations in JAK2 positive patients. Although JAK 2 mutations are correlated with thrombosis in MPN patients, JAK2 positivity is not detected in arterial and venous thrombosis rather than in MPN. There aren't enough appropriate data to include routine JAK2 mutation investigation in idiopathic venous thrombosis or early age and/or unexpected areas with venous/arterial thrombosis. The only exclusion of this can be splanchnic venous thrombosis.[23] Proven in several trials, isolated splanchnic thrombosis at diagnosis is related to increased JAK2 positiveness (17-58%). Further studies have discovered that almost all patients have MPN. In a retrospective study, Bayraktar et al.[24] found JAK2 positivity in 24% of 25 patients with chronic isolated non-cirrhotic portal vein thrombosis and found the frequency of MPN to be 44% in JAK2 positive and negative patients. They also showed at least one thrombophilic factor positivity in 19 of 25 patients. However, 3 out of 5 JAK2-negative MPN patients had no other clinically thrombophilic risk factors. The other two patients were diagnosed with protein C and antithrombin deficiency. 3 of 6 JAK2-positive patients had a homozygous methylene tetrahydrofolic acid reductase (MTHFR) C677T mutation.[24] Kahraman et al.[32] evaluated 143 JAK2-positive patients diagnosed with PV, PMF and ET. There was no significant relationship between JAK2 mutation burden and vascular complications such as thrombosis and bleeding.[32] After splenic vein thrombosis was first detected in our patient group, two patients were diagnosed with MPN in further evaluation. Both patients were JAK2 positive. However, this does not reflect the current prevalence of JAK2 positivity in splanchnic venous thrombosis because patients are referred to the haematology clinic after diagnosing MPN. Until recent data, it has been suggested that JAK2 mutation analysis is sufficient to screen for thrombophilia in splanchnic vein thrombosis. In the study of Fouassier et al.[25], none of the 11 paroxysmal nocturnal hemoglobinuria patients had a JAK2 mutation. The increased frequency of JAK2 mutations in other thrombotic diseases is controversial, but a direct relationship has not yet been proven. We found an association between arterial and venous thrombosis in JAK2 positive and negative ET patients. However, the exclusion of patients with insufficient data and progress in evaluating our study should be considered.

Conclusions

In conclusion, in the subgroup analysis of MPN patients, we proved the statistically significant relation between JAK2 mutation and arterial and/or venous thrombosis frequency in ET patients. However, there is no significant relation in PV patients. Multicenter prospective studies with long-term follow-up should be designed to determine the link between the JAK2 gene and thrombosis in MPN.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding Sources

There is no financial or other relationship that might lead to a conflict of interest.

Ethical Approval

For this study, approval was obtained local ethics committee.

Authors' Contribution

Study Conception, Literature Review, Critical Review, Data Collection and/or Processing, Statistical Analysis and/or Data Interpretation, Manuscript preparing held by all authors.

References

1. Yönal İ, Dağlar-Aday A, Akadam-Teker B, Yılmaz C, Nalçacı M, Yavuz AS, Sargın FD. Impact of JAK2V617F mutational status on phenotypic features in essential thrombocythemia and primary myelofibrosis. Turk J Haematol. 2016 Jun 5;33(2):94-101. doi: 10.4274/tjh.2014.0136.
2. Passamonti F, Rumi E, Pungolino E, Malabarba L, Bertazzoni P, Valentini M, Orlandi E, Arcaini L, Brusamolino E, Pascutto C, Cazzola M, Morra E, Lazzarino M. Life expectancy and prognostic factors for survival in patients with polycythemia vera and essential thrombocythemia. Am J Med. 2004 Nov 15;117(10):755-61. doi: 10.1016/j.amjmed.2004.06.032.
3. Cervantes F, Passamonti F, Barosi G. Life expectancy and prognostic factors in the classic BCR/ABL-negative myeloproliferative disorders. Leukemia. 2008 May;22(5):905-14. doi: 10.1038/leu.2008.72.
4. Carobbio A, Finazzi G, Guerini V, Spinelli O, Delaini F, Marchioli R, Borrelli G, Rambaldi A, Barbui T. Leukocytosis is a risk factor for thrombosis in essential thrombocythemia: interaction with treatment, standard risk factors, and Jak2 mutation status. Blood. 2007 Mar 15;109(6):2310-3. doi: 10.1182/blood-2006-09-046342.
5. Carobbio A, Antonioli E, Guglielmelli P, Vannucchi AM, Delaini F, Guerini V, Finazzi G, Rambaldi A, Barbui T. Leukocytosis and risk stratification assessment in essential thrombocythemia. J Clin Oncol. 2008 Jun 1;26(16):2732-6. doi: 10.1200/JCO.2007.15.3569.
6. Passamonti F, Rumi E, Arcaini L, Boveri E, Elena C, Pietra D, Boggi S, Astori C, Bernasconi P, Varettoni M, Brusamolino E, Pascutto C, Lazzarino M. Prognostic factors for thrombosis, myelofibrosis, and leukemia in essential thrombocythemia: a study of 605 patients. Haematologica. 2008 Nov;93(11):1645-51. doi: 10.3324/haematol.13346.
7. Palandri F, Catani L, Testoni N, Ottaviani E, Polverelli N, Fiacchini M, De Vivo A, Salmi F, Lucchesi A, Baccarani M, Vianelli N. Long-term follow-up of 386 consecutive patients with essential thrombocythemia: safety of cytoreductive therapy. Am J Hematol. 2009 Apr;84(4):215-20. doi: 10.1002/ajh.21360.
8. Gangat N, Wolanskyj AP, Schwager SM, Hanson CA, Tefferi A. Leukocytosis at diagnosis and the risk of subsequent thrombosis in patients with low-risk essential thrombocythemia and polycythemia vera. Cancer. 2009 Dec 15;115(24):5740-5. doi: 10.1002/cncr.24664.
9. Landolfi R, Di Gennaro L, Barbui T, De Stefano V, Finazzi G, Marfisi R, Tognoni G, Marchioli R; European Collaboration on Low-Dose Aspirin in Polycythemia Vera (ECLAP). Leukocytosis as a major thrombotic risk factor in patients with polycythemia vera. Blood. 2007 Mar 15;109(6):2446-52. doi: 10.1182/blood-2006-08-042515.
10. Marchioli R, Finazzi G, Landolfi R, Kutti J, Gisslinger H, Patrono C, Marilus R, Villegas A, Tognoni G, Barbui T. Vascular and neoplastic risk in a large cohort of patients with polycythemia vera. J Clin Oncol. 2005 Apr 1;23(10):2224-32. doi: 10.1200/JCO.2005.07.062.
11. Royer Y, Staerk J, Costuleanu M, Courtoy PJ, Constantinescu SN. Janus kinases affect thrombopoietin receptor cell surface localization and stability. J Biol Chem. 2005 Jul 22;280(29):27251-61. doi: 10.1074/jbc.M501376200.
12. Sirhan S, Fairbanks VF, Tefferi A. Red cell mass and plasma volume measurements in polycythemia: evaluation of performance and practical utility. Cancer. 2005 Jul 1;104(1):213-5. doi: 10.1002/cncr.21105.
13. Wolanskyj AP, Lasho TL, Schwager SM, McClure RF, Wadleigh M, Lee SJ, Gilliland DG, Tefferi A. JAK2 mutation in essential thrombocythaemia: clinical associations and long-term prognostic relevance. Br J Haematol. 2005 Oct;131(2):208-13. doi: 10.1111/j.1365-2141.2005.05764.x.
14. Kralovics R, Teo SS, Buser AS, Brutsche M, Tiedt R, Tichelli A, Passamonti F, Pietra D, Cazzola M, Skoda RC. Altered gene expression in myeloproliferative disorders correlates with activation of signaling by the V617F mutation of Jak2. Blood. 2005 Nov 15;106(10):3374-6. doi: 10.1182/blood-2005-05-1889.
15. Robertson B, Urquhart C, Ford I, Townend J, Watson HG, Vickers MA, Greaves M. Platelet and coagulation activation markers in myeloproliferative diseases: relationships with JAK2 V6I7 F status, clonality, and antiphospholipid antibodies. J Thromb Haemost. 2007 Aug;5(8):1679-85. doi: 10.1111/j.1538-7836.2007.02626.x.
16. Lussana F, Caberlon S, Pagani C, Kamphuisen PW, Büller HR, Cattaneo M. Association of V617F Jak2 mutation with the risk of thrombosis among patients with essential thrombocythaemia or idiopathic myelofibrosis: a systematic review. Thromb Res. 2009 Sep;124(4):409-17. doi: 10.1016/j.thromres.2009.02.004.
17. Cervantes F, Passamonti F, Barosi G. Life expectancy and prognostic factors in the classic BCR/ABL-negative myeloproliferative disorders. Leukemia. 2008 May;22(5):905-14. doi: 10.1038/leu.2008.72.
18. Elliott MA, Tefferi A. Thrombosis and haemorrhage in polycythaemia vera and essential thrombocythaemia. Br J Haematol. 2005 Feb;128(3):275-90. doi: 10.1111/j.1365-2141.2004.05277.x.
19. Pietra D, Li S, Brisci A, Passamonti F, Rumi E, Theocharides A, Ferrari M, Gisslinger H, Kralovics R, Cremonesi L, Skoda R, Cazzola M. Somatic mutations of JAK2 exon 12 in patients with JAK2 (V617F)-negative myeloproliferative disorders. Blood. 2008 Feb 1;111(3):1686-9. doi: 10.1182/blood-2007-07-101576.
20. Patel RK, Lea NC, Heneghan MA, Westwood NB, Milojkovic D, Thanigaikumar M, Yallop D, Arya R, Pagliuca A, Gäken J, Wendon J, Heaton ND, Mufti GJ. Prevalence of the activating JAK2 tyrosine kinase mutation V617F in the Budd-Chiari syndrome. Gastroenterology. 2006 Jun;130(7):2031-8. doi: 10.1053/j.gastro.2006.04.008.
21. Campbell PJ, Scott LM, Buck G, Wheatley K, East CL, Marsden JT, Duffy A, Boyd EM, Bench AJ, Scott MA, Vassiliou GS, Milligan DW, Smith SR, Erber WN, Bareford D, Wilkins BS, Reilly JT, Harrison CN, Green AR; United Kingdom Myeloproliferative Disorders Study Group; Medical Research Council Adult Leukaemia Working Party; Australasian Leukaemia and Lymphoma Group. Definition of subtypes of essential

thrombocythaemia and relation to polycythaemia vera based on JAK2 V617F mutation status: a prospective study. Lancet. 2005 Dec 3;366(9501):1945-53. doi: 10.1016/S0140-6736(05)67785-9.
22. Finazzi G, Caruso V, Marchioli R, Capnist G, Chisesi T, Finelli C, Gugliotta L, Landolfi R, Kutti J, Gisslinger H, Marilus R, Patrono C, Pogliani EM, Randi ML, Villegas A, Tognoni G, Barbui T; ECLAP Investigators. Acute leukemia in polycythemia vera: an analysis of 1638 patients enrolled in a prospective observational study. Blood. 2005 Apr 1;105(7):2664-70. doi: 10.1182/blood-2004-09-3426.
23. Levy DE, Darnell JE Jr. Stats: transcriptional control and biological impact. Nat Rev Mol Cell Biol. 2002 Sep;3(9):651-62. doi: 10.1038/nrm909.
24. Bayraktar Y, Harmanci O, Büyükasik Y, Shorbagi AI, Sungur AH, Boylu CA, Gürgey A, Balkanci F. JAK2V617F mutation in patients with portal vein thrombosis. Dig Dis Sci. 2008 Oct;53(10):2778-83. doi: 10.1007/s10620-008-0225-y.
25. Fouassier M, Girodon F, Cleyrat C, Robillard N, Garand R, Hermouet S. Absence of JAK2-V617F in paroxysmal nocturnal haemoglobinuria-associated thrombosis. Thromb Haemost. 2009 Jul;102(1):180-2. doi: 10.1160/TH09-03-0140.
26. Lee E, Lee KJ, Park H, Chung JY, Lee MN, Chang MH, Yoo J, Lee H, Kong SY, Eom HS. Clinical implications of quantitative JAK2 V617F analysis using droplet digital PCR in myeloproliferative neoplasms. Ann Lab Med. 2018 Mar;38(2):147-54. doi: 10.3343/alm.2018.38.2.147.
27. Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2021 update on diagnosis, risk-stratification and management. Am J Hematol. 2020 Dec;95(12):1599-613. doi: 10.1002/ajh.26008.
28. Tefferi A. Primary myelofibrosis: 2021 update on diagnosis, risk-stratification and management. Am J Hematol. 2021 Jan;96(1):145-62. doi: 10.1002/ajh.26050.
29. Moliterno AR, Kaizer H. Applied genomics in MPN presentation. Hematology Am Soc Hematol Educ Program. 2020 Dec 4;2020(1):434-9. doi: 10.1182/hematology.2020000128.
30. Zhang Y, Zhou Y, Wang Y, Teng G, Li D, Wang Y, Du C, Chen Y, Zhang H, Li Y, Fu L, Chen K, Bai J. Thrombosis among 1537 patients with JAK2V617F -mutated myeloproliferative neoplasms: Risk factors and development of a predictive model. Cancer Med. 2020 Mar;9(6):2096-105. doi: 10.1002/cam4.2886.
31. Iurlo A, Cattaneo D, Bucelli C, Baldini L. New perspectives on polycythemia vera: From diagnosis to therapy. Int J Mol Sci. 2020 Aug 13;21(16):5805. doi: 10.3390/ijms21165805.
32. Kahraman CY, Sincan G, Tatar A. Evaluation of the relationship between janus kinase 2 mutational burden and clinical findings in adult myeloproliferative neoplasm patients. Med Bull Haseki. 2022;60:26-32. doi: 10.4274/haseki.galenos.2021.7530.