MIJELOPROLIFERATIVNE NEOPLAZME KOD BOLESNIKA MLAĐIH OD 40 GODINA: RETROSPEKTIVNA ANALIZA KLINIČKIH KARAKTERISTIKA

ORIGINALNI RAD

ORIGINAL ARTICLE

MYELOPROLIFERATIVE NEOPLASMS IN PATIENTS YOUNGER THAN 40 YEARS: A RETROSPECTIVE ANALYSIS OF CLINICAL CHARACTERISTICS

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SAŽETAK

Uvod: Mijeloproliferativne neoplazme (MNP) se obično dijagnostikuju kod bolesnika starosti oko 60 godina, međutim, u kliničkoj praksi se često sreću bolesnici mlađi <40 godina.

Cilj: Procena kliničko-laboratorijskih karakteristika, učestalost tromboza i analiza terapijskog pristupa kod bolesnika sa MPN <40 godina.

Metode: Retrospektivna studija obuhvatila je 84 bolesnika, dijagnostikovanih prema SZO kriterijumima, lečenih na Klinici za hematologiju UKCS od 2000. do 2024. godine.

Rezultati: Medijana starosti iznosila je 33 godine, sa većom učestalošću žena (60,7%). Policitemija vera (PV) je nađena kod 61,9%, esencijalna trombocitemija (ET) kod 25%, a prefibrotična faza primarne mijelofibroze (prePMF) kod 13.1% ispitanika. Mutacija *JAK2V617F* je detektovana je kod 46,5% bolesnika. Mikrovaskularne simptome imalo je 27.4%, svrab 14,3%, konstitucionalne simptome 7,1%, a splenomegaliju 45,2% bolesnika. Najviši hemoglobin i hematokrit su imali bolesnici sa PV (170 g/L,50%). Broj trombocita bio je najveći kod bolesnika sa prePMF ($1007x10^9$/L), zatim kod ET ($856x10^9$/L) i PV ($737,5x10^9$/L). Raspodela prema stepenu fibroze koštane srži bile je sledeća: MF0 - 28,5%, MF1 - 54,8%, MF2 - 4,8%. Ukupno, 41,7% bolesnika imalo je bar jedan kardiovaskularni faktor rizika, najčešće pušenje (23,8%). Prethodne tromboze imalo je 16,7% bolesnika, a tromboze tokom praćenja (8,3%) imali su samo bolesnici sa PV. Aspirin je koristilo 86,9% bolesnika, dok su flebotomije primenjene kod skoro svih bolesnika sa PV. Citoreduktivnom terapijom lečeno je 43,9% bolesnika, 39,1% jednom TL, najčešće hidroksiurea (HU). Prema European LeukemiaNET (ELN) skoru, 82,1% bolesnika pripadalo je grupi niskog rizika. Medijana praćenja bila je 72 meseca, a dva bolesnika su preminula (2,45%).

Zaključak: Većina mlađih bolesnika sa MPN pripada ELN grupi niskog rizika. Međutim zbog razvoja tromboze (25%), prisutnih tegoba, stepena trombocitoze i splenomegalije > 18 cm, skoro 1/2 prima citoreduktivnu terapiju. To ukazuje na potrebu bolje stratifikacije, kao i upotrebu drugačijih metoda za procenu rizika bolesti, kao što je sekvencioniranje sledeće generacije (NGS).

Ključne reči: mijeloproliferativne neoplazme, tromboze, adolescenti, mlađi uzrast

ABSTRACT

Introduction: Myeloproliferative neoplasms (MPN) are typically diagnosed in patients around 60 years of age; however, in clinical practice, patients <40 years are often encountered.

Aim: Assessment of clinical-laboratory characteristics, thrombosis incidence, and therapeutic approaches in patients with MPN<40 years.

Methods: This retrospective study included 84 patients diagnosed according to WHO criteria who were treated at the Clinic of Hematology, UCCS, from 2000 to 2024.

Results: The median age was 33 years, with a higher prevalence in females (60.7%). Polycythemia vera (PV) was found in 61.9%, essential thrombocythemia (ET) in 25%, and pre-primary myelofibrosis (prePMF) in 13.1% of participants. The JAK2V617F mutation was detected in 46.5% of patients. Microvascular symptoms were present in 27.4%, pruritus in 14.3%, constitutional symptoms in 7.1%, and splenomegaly in 45.2% of patients. The highest hemoglobin and hematocrit levels were found in PV patients (170 g/L, 50%). The platelet count was highest in patients with prePMF ($1007x10^9$/L), followed by ET ($856x10^9$/L) and PV ($737.5x10^9$/L). The distribution of bone marrow fibrosis was as follows: MF0 - 28.5%, MF1 - 54.8%, MF2 - 4.8%. Overall, 41.7% of patients had at least one cardiovascular risk factor, most commonly smoking (23.8%). The previous thrombosis occurred in 16.7% of patients, while thrombosis during follow-up (8.3%) was seen only in PV patients. Aspirin was used by 86.9% of patients, and phlebotomy was applied to almost all PV patients. Cytoreductive therapy was used in 43.9% of patients, with 39.1% receiving one line of treatment, most commonly hydroxyurea (HU). According to the European LeukemiaNET (ELN) score, 82.1% of patients were classified as low-risk. The median follow-up was 72 months, and two patients died (2.45%).

Conclusion: The majority of younger MPN patients belong to the low-risk ELN group. However, nearly half of the patients receive cytoreductive therapy due to the development of thrombosis (25%), the presence of symptoms, the degree of thrombocytosis, and splenomegaly > 18 cm. This indicates the need for better stratification and the use of different methods for disease risk assessment, such as next-generation sequencing (NGS).

Keywords: myeloproliferative neoplasms, thrombosis, adolescents, young age

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UVOD

Pacijenti mlađe životne dobi sa mijeloproliferativnim neoplazmama (MPN) predstavljaju posebnu subpopulaciju bolesnika čiji se broj stalno postepeno povećava [1]. Medijana starosti u trenutku postavljanja dijagnoze za klasične BCR-ABL1 negativne MPN, koje obuhvataju policitemiju veru (PV), esencijalnu trombocitemiju (ET) i primarnu mijelofibrozu (PMF), kreće se od 60-65 godina [2]. Prema podacima iz studija, pacijenti mlađi od 40 godina čine svega 10% ukupnog broja bolesnika sa MPN [3-6], dok neka druga istraživanja ukazuju da je taj udeo čak i 20% [7-9]. Od svih MPN entiteta, u populaciji mladih bolesnika, najčešća je ET sa 51%-72%, drugom mestu je PV, a najređe se javlja PMF [2,10-13]. ET se karakteriše megakariocitnom hiperplazijom i trombocitozom, bolesnici sa PV imaju značajnu eritrocitozu, dok oni sa PMF imaju fibrozu koštane srži, koja posledično kasnije dovodi do citopenija i ekstrameduarlne hematopoeze [14]. Kod sve tri bolesti postoji rizik od nastanka vaskularnih komplikacija, ali i akutne mijeloidne leukemije (AML), dok PV i ET mogu da se transformišu u mijelofibrozu (MF) [14].

Jedinstveno za mlade obolele od MPN je duži očekivani životni vek u odnosu na stariju populaciju, ali istovremeno, dugo trajanje bolesti pruža mogućnost za nastanak komplikacija povezanih sa bolešću i njenim lečenjem [2]. Takođe, postoje i dodatna pitanja koja se isključivo tiču ove starosne grupe, a odnose sa na psihosocijalne potrebe, fertilitet i trudnoću, kao i jedinstvenu biologiju MPN [11,15]. Većina dostupnih podataka, kao i aktuelni konvencionalni prognostički modeli, dobijeni su analizom starije populacije, te se postavlja pitanje u kojoj meri precizno odražavaju jedinstvene fenotipske obrasce ili prognostičke markere ove mlađe starosne grupe.

Tako, standardni *European LeukemiaNET (ELN)* prognostički skor je baziran na godinama života (> 60) i prethodnim trombozama, i služi za određivanje načina lečenja usmerenog na smanjenje rizika od krvarenja i tromboze [16]. Stoga je njegova primena kod mladih ograničena, jer se godine života tu ne pojavljuju kao faktor, pa jedino što ove bolesnike može da svrsta u visokorizičnu grupu jesu prethodne tromboze.

Cilj ove studije bio je evaluacija kliničko-laboratorijskih karakteristika, učestalosti tromboza i analiza terapijskog pristupa kod MPN bolesnika mlađih od 40 godina.

METODE

Retrospektivno istraživanje obuhvatilo je 84 bolesnika sa dijagnozom neke od bolesti iz grupe Filadelfija negativnih MPN, dijagnostikovanih, praćenih i lečenih na Klinici za hematologiju UKCS, u periodu od 2000. do

INTRODUCTION

Younger patients with myeloproliferative neoplasms (MPN) represent a special subpopulation of patients whose number is gradually increasing [1]. The median age at diagnosis for classic BCR-ABL1-negative MPNs, which include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), ranges from 60-65 years [2]. According to data from studies, patients younger than 40 make up only 10% of the total number of patients with MPN [3-6], while some other studies indicate that this proportion is even 20% [7-9]. Of all MPN entities, in the population of young patients, ET is the most common with 51%-72%, PV is second, and PMF is the least common [2,10-13]. ET is characterized by megakaryocyte hyperplasia and thrombocytosis, patients with PV have significant erythrocytosis, while those with PMF have bone marrow fibrosis, which subsequently leads to cytopenia and extramedullary hematopoiesis [14]. In all three diseases, there is a risk of vascular complications, but also of acute myeloid leukemia (AML), while PV and ET can transform into myelofibrosis (MF) [14].

Uniquely for young people with MPN is the longer life expectancy compared to the older population, but at the same time, the long duration of the disease provides the possibility for complications related to the disease and its treatment [2]. Also, there are additional questions that exclusively concern this age group and are related to psychosocial needs, fertility, and pregnancy, as well as the unique biology of MPN [11,15]. Most of the available data, as well as the current conventional prognostic models, have been obtained by analyzing the elderly population, and the question arises to what extent they accurately reflect the unique phenotypic patterns or predictive markers of this younger age group.

Thus, the standard European LeukemiaNET (ELN) prognostic score is based on years of life (> 60) and previous thromboses and serves to determine the treatment approach aimed at reducing the risk of bleeding and thrombosis [16]. Therefore, its application in young people is limited because age does not appear as a factor, so the only thing that can place these patients in the high-risk group is previous thromboses.

This study aimed to evaluate the clinical and laboratory characteristics, the frequency of thrombosis, and the analysis of the therapeutic approach in MPN patients under 40 years of age.

METHODS

The retrospective study included 84 patients diagnosed with one of the diseases from the Philadelphia group of negative MPNs who were diagnosed, monitored, and treated at the UKCS Hematology Clinic from

2024. godine. Dijagnoza je postavljena prema aktuelnim SZO kriterijumima [17].

Iz medicinske dokumentacije prikupljeni su sledeći podaci: 1) demografske karakteristike bolesnika; 2) prisustvo *JAK2V617F* mutacije; 3) simptomi; 4) prisustvo palpablne splenomegalije; 5) parametri krvne slike; 6) vrednosti laktat-dehidrogenaze; 7) stepen fibroze kostne srži; 8) kardiovaskularni (KV) faktori rizika; 9) prisustvo i vrsta prethodnih tromboza i tromboza u toku praćenja; 10) modaliteti lečenja; 11) prognostički skorovi (*ELN* skor, *International Prognostic Score of Thrombosis* in *WHO – ET* (*IPSET Thrombsis)*, *International Prognostic Score for ET: Predicts Survival (IPSET survival), International Prognostic Scoring System* (*IPSS*)); 12) dužina preživljavanja; 13) uzrok smrtnog ishoda.

Deskriptivnim statističkim parametrima, kategorijalni podaci su prikazani kao apsolutne i relativne učestalosti, a numerički podaci, s obzirom da nisu imali normalnu raspodelu, prikazani su kao medijana i opseg (Min-Max). Za testiranje razlika u učestalosti korišćen je hi-kvadrat test, a za testiranje razlika vrednosti numeričkih podataka korišćeni su Kruskal-Wallis-ov test i Mann-Whitney test. Kriterijum za statističku značajnost je bio $p < 0.05$. Podaci su obrađeni korišćenjem softverskog programa SPSS Statistics 22 (SPSS Inc., Chicago, IL, USA).

REZULTATI

Studija je obuhvatila 84 bolesnika uzrasta do 40 godina sa potvrđenom dijagnozom bolesti iz grupe Filadelfija negativnih mijeloproliferativnih neoplazmi (Ph- MPN). Policitemiju veru imalo je 52 bolesnika (61,9%), esencijalnu trombocitemiju 21 bolesnik (25%), prefibrotičnu fazu primarne mijelofibroze 11 (13,1%). Nijedan bolesnik nije imao manifestnu fazu PMF. Grupu su činile dominantno žene, 51 odnosno (60,7%), dok su 33 ispitanika, (39,3%) bili muškarci (odnos Ž : M=1,55:1). Medijana starosti bolesnika u trenutku postavljanja dijagnoze bila je 33 godine (od 14 do 40 godina) (Tabela 1).

Alel specifičnom PCR metodom kod 39 bolesnika (46,4%) nađena je *JAK2V617F* mutacija, dok je kod 24 bolesnika (28,6%) bila odsutna; kod 21 bolesnika (25%) ova analiza nije bila rađena (Tabela 1). U grupi sa PV, 31 bolesnik (59,6%) imao je JAK2V617F mutaciju, 5 bolesnika (9,6%) nije imalo, dok kod 16 bolesnika (30,7%) analiza nije bila sprovedena. Kod bolesnika sa ET, prisustvo JAK2V617F mutacije utrvđeno je kod 6 bolesnika (28,6%), dok je 10 bolesnika (47,6%) bilo negativno, a kod 5 bolesnika (23,8%) ova mutacije nije ispitivana. Svim bolesnicima sa prePMF je rađena ova analiza, pri čemu je kod 2 bolesnika (18,2%) dokazano prisustvo mutacije, dok je 9 bolesnika (81,8%) bilo negativno.

Mikrovaskularne simptome pri dijagnozi imalo je 23 bolesnika (27,4%), glavobolju 19 bolesnika (22,6%),

2000 to 2024. The diagnosis was made according to current WHO criteria [17].

The following data were collected from the medical documentation: 1) demographic characteristics of the patient; 2) presence of JAK2V617F mutation; 3) symptoms; 4) presence of palpable splenomegaly; 5) blood count parameters; 6) values of lactate dehydrogenase; 7) degree of bone marrow fibrosis; 8) cardiovascular (CVD) risk factors; 9) presence and type of previous thrombosis and thrombosis during follow-up; 10) treatment modalities; 11) prognostic scores (ELN score, International Prognostic Score of Thrombosis in WHO – ET (IPSET Thrombsis), International Prognostic Score for ET: Predicts Survival (IPSET survival), International Prognostic Scoring System (IPSS)); 12) length of survival; 13) cause of death.

Descriptive statistical parameters and categorical data are shown as absolute and relative frequencies, and numerical data, considering that they did not have a normal distribution, are shown as median and range (Min-Max). The chi-square test was used to test the differences in frequency, and the Kruskal-Wallis and Mann-Whitney tests were used to test the differences in numerical data values. The criterion for statistical significance was $p < 0.05$. Data were processed using the SPSS Statistics 22 software program (SPSS Inc., Chicago, IL, USA).

RESULTS

The study included 84 patients aged up to 40 years with a confirmed diagnosis of the disease from the Philadelphia group of negative myeloproliferative neoplasms (Ph-MPN). Polycythemia vera was present in 52 patients (61.9%), essential thrombocythemia in 21 patients (25%), and prefibrotic phase of primary myelofibrosis in 11 (13.1%). No patient had a manifest phase of PMF. The group consisted predominantly of women, 51 or so (60.7%), while 33 respondents (39.3%) were men (ratio F : M=1.55:1). The median age of the patients at the time of diagnosis was 33 years (from 14 to 40 years) (Table 1).

JAK2V617F mutation was found by the Allele-specific PCR method in 39 patients (46.4%), while it was absent in 24 patients (28.6%); this analysis was not performed in 21 patients (25%) (Table 1). In the group with PV, 31 patients (59.6%) had the JAK2V617F mutation, 5 patients (9.6%) did not, while in 16 patients (30.7%), the analysis was not performed. In patients with ET, the presence of the JAK2V617F mutation was confirmed in 6 patients (28.6%), while 10 patients (47.6%) were negative, and in 5 patients (23.8%), this mutation was not examined. This analysis was performed on all patients with prePMF, whereby the presence of the mutation was proven in 2 patients (18.2%), while 9 patients (81.8%) were negative.

Tabela 1. Kliničke i laboratorijske karakteristike mladih bolesnika sa MPN

Table 1. Clinical and laboratory characteristics of young MPN patients

Varijabla / *Variable*	***n (%)***
Uzrast (godine), medijana (opseg) / *Age (years), median (range)*	33 (14-40)
Pol (Ž/M) / *Gender (F/M)*	51 (60.7%) / 33 (39.3%)
Tip MPN / *MPN type*	
PV	52 (61.9%)
ET	21 (25.0%)
prePMF /	11 (13.1%)
JAK2V617F mutacija / *JAK2V617F mutation*	
Pozitivna / *Positive*	39 (46.4%)
Negativna / *Negative*	24 (28.6%)
Nije urađena / *Not done*	21 (25.0%)
Simptomi / Symptoms	
Svrab / *Itching*	12 (14.3%)
Mikrovaskularni simptomi / *Microvascular symptoms*	23 (27.4%)
Glavobolja / *Headache*	19 (22.6%)
Konstitucionalni simptomi / *Constitutional symptoms*	6 (7.1%)
Palpabilna splenomegalija / *Palpable splenomegaly*	38 (45.2%)
Povišen LDH / *High LDH, U/L*	43 (51.2%)
Stepen fibroze u koštanoj srži / *Bone marrow fibrosis*	
MF-0 / *MF-0*	24 (28.5%)
MF-1 / *MF-1*	46 (54.8%)
MF-2 / *MF-2*	4 (4.8%)
Nepoznato / *Unknown*	10 (11.9%)
Kardiovaskularni faktori rizika / *Cardiovascular risk factors*	
HT / *HT*	8 (9.5%)
Pušenje / *Smoking*	20 (23.8%)
HT+ HLP / *HT+ HLP*	2 (2.4%)
Pušenje, HT / *Smoking, HT*	4 (4.8%)
Pušenje HT, HLP / *Smoking, HT, HLP*	1 (1.2%)
Prethodne tromboze / *History of thrombosis*	14 (16.7%)
Tromboze u toku praćenja / *Thrombosis during follow-up*	7 (8.3%)
Praćenja (meseci) / *Follow-up (months)*	72 (3-288)
Smrtni ishod / *Death*	2 (2.4%)

Numerički podaci su prikazani kao medijana (opseg Min-Max) a kategorijalni podaci kao broj pacijenata i procenat, n (%)
MPN – mijeloproliferativna neoplazma, PV – policitemija vera, ET – esencijalna trombocitemija, prePMF – prefibrotična faza primarne mijelofibroze, LDH – laktat dehidrogenaza, HT – hipertenzija, HLP – hiperlipidemija

Numerical data are presented as median (Min-Max range) and categorical data as number of patients and percentage, n (%)
MPN - myeloproliferative neoplasm, PV - polycythemia vera, ET - essential thrombocythemia, prePMF - prefibrotic phase of primary myelofibrosis, LDH - lactate dehydrogenase, HT - hypertension, HLP - hyperlipidemia

svrab 12 bolesnika (14,3%), dok su konstitucione tegobe bile prisutne kod 6 bolesnika (7,1%). Palpabilna splenomegalija nađena je kod 38 bolesnika (45,2%) (Tabela 1).

U ispitivanoj grupi bolesnika vrednosti hemoglobina ($p < 0,001$), hematokrita ($p < 0,001$), MCV ($p = 0,016$)

Microvascular symptoms at diagnosis were present in 23 patients (27.4%), headache in 19 patients (22.6%), itching in 12 patients (14.3%), and constitutional complaints were present in 6 patients (7.1%). Palpable splenomegaly was found in 38 patients (45.2%) (Table 1).

Tabela 2. Parametri krvne slike po tipovima MPN kod mladih bolesnika

Table 2. Blood count parameters by types of MPN in young patients

Parametri / *Parameters* medijana (opseg) / *median (range)*	*Tip MNP / Type MNP*			*p*	*p*-vrednost između grupa / *p-value between groups*		
	PV	*ET*	*prePMF*		*PV-ET*	*PV-prePMF*	*ET- prePMF*
Hemoglobin / *Hemoglobin*	170.0 (140.0-316.0)	137.5 (123.0-165.0)	132.0 (98.0-161.0)	**<0.001**	**<0.001**	**<0.001**	0.670
Hematokrit / *Hematocrit*	50.0 (41.4-66.0)	41.7 (34.0-48.0)	38.8 (29.6-45.1)	**<0.001**	**<0.001**	**<0.001**	0.413
MCV / *MCV*	84.0 (68.0-100.0)	91.0 (70.0-98.0)	88.0 (65.0-92.0)	**0.016**	**0.007**	0.203	0.148
Br. Leukocita / *No. Leukocyte WBC count*	9.9 (5.5-22.3)	8.0 (5.4-67.0)	8.6 (7.2-15.1)	0.086	**0.042**	0.217	0.502
Br. Trombocita / *No. Thrombocytes PLT count*	737.5 (166-1122)	856.0 (553-1748)	1007.0 (461-1876)	**0.003**	**0.018**	**0.003**	0.381

Vrednosti su prikazane kao medijana i opseg (Min-Maks), boldirano- statistički značajna razlika ($p < 0.05$)
PV – policitemija vera, ET – esencijalna trombocitemija, prePMF – prefibrotična faza primarne mijelofibroze, MCV – prosečna zapremina eritrocita, WBC – leukociti, PLT – trombociti

Values are shown as median and range (Min-Max), bold - statistically significant difference ($p < 0.05$)
PV - polycythemia vera, ET - essential thrombocythemia, prePMF - prefibrotic phase of primary myelofibrosis, MCV – mean corpuscular volume, WBC - leukocytes, PLT - platelets
Hemoglobin (g/L), Hematocrit (%), MCV (f/L), No. Leukocyte (x10^9/L), No. Thrombocytes (x10^9/L)

i trombocita (p = 0,003) statistički su se značajno razlikovale prema grupama ispitanika, dok vrednosti leukocita nisu pokazale značajnu razliku (p = 0,086). Vrednosti hemoglobiona bile su značajno veće u grupi pacijenata sa PV, 170,0 g/L (opseg 140,0-316,0 g/L), u odnosu na grupu ET, 137,5 g/L (raspon 123,0-165,0 g/L), (p < 0,001), kao i u odnosu na grupu prePMF, 132,0 g/L (raspon 98,0-161,0 g/L), (p < 0,001), dok se vrednosti hemoglobina nisu razlikovale između ET i prePMF (p = 0,670). Vrednosti hematokrita takođe su bile značajno više u grupi pacijenata sa PV, 50,0% (raspon 41,4-66,0%), u odnosu na grupu ET, 41,7% (raspon 34,0-48,0%), (p < 0,001), kao i u odnosu na grupu prePMF, 38,8% (raspon 29,6-45,1%) (p < 0,001), dok se vrednosti hematokrita nisu razlikovale između ET i prePMF (p = 0,413).

Vrednosti MCV-a bile su statistički značajno veće kod pacijenata sa ET, 91,0 f/L (raspon 70,0-98,0 f/L), u odnosu na grupu sa PV, 84,0 f/L (raspon 68,0-100,0 f/L), (p < 0,001), dok između ispitanika ostalih grupa nije postojala značajna razlika. Vrednosti trombocita bile su značajno niže u grupi pacijenata sa PV, 737,5 x10^9/L (raspon 166,0-1122,0 x10^9/L), u odnosu na grupu ET, 856,0 x10^9/L (raspon 553,0-1748,0 x10^9/L), (p = 0,018), kao i u odnosu na grupu prePMF 1007,0 x10^9/L (raspon 461,0-1876,0 x10^9/L), (p = 0,003), dok se vrednosti trombocita nisu razlikovale između ET i prePMF (p = 0,381) (Tabela 2).

U celoj grupi bolesnika, vrednost laktat-dehidrogenaze (LDH) bila je povišena kod 43 (51,2%). Eritropoetin je bio snižen kod 25 bolesnika (29,8%), normalan kod

In the examined group of patients, the values of hemoglobin (p < 0.001), hematocrit (p < 0.001), MCV (p = 0.016), and platelets (p = 0.003) statistically significantly differed according to the groups of subjects, while the values of leukocytes did not show a significant difference (p = 0.086). Hemoglobin values were considerably higher in the group of PV patients, 170.0 g/L (range 140.0-316.0 g/L), compared to the ET group, 137.5 g/L (range 123.0- 165.0 g/L), (p < 0.001), as well as in relation to the prePMF group, 132.0 g/L (range 98.0-161.0 g/L), (p < 0.001), while the values hemoglobin did not differentiate between ET and prePMF (p = 0.670). Hematocrit values were also significantly higher in the PV group, 50.0% (range 41.4-66.0%), compared to the ET group, 41.7% (range 34.0-48.0%), (p < 0.001), as well as in relation to the prePMF group, 38.8% (range 29.6-45.1%) (p < 0.001), while hematocrit values did not differ between ET and prePMF (p = 0.413).

MCV values were statistically significantly higher in ET patients, 91.0 f/L (range 70.0-98.0 f/L), compared to the PV group, 84.0 f/L (range 68,0-100.0 f/L), (p < 0.001), while there was no significant difference between the subjects of the other groups. Platelet values were significantly lower in the PV group, 737.5 x10^9/L (range 166.0-1122.0 x10^9/L), compared to the ET group, 856.0 x10^9/L (range 553.0- 1748.0 x10^9/L), (p = 0.018), as well as in relation to the prePMF group 1007.0 x10^9/L (range 461.0-1876.0 x10^9/L), (p = 0.003), while platelet values did not differentiate between ET and prePMF (p = 0.381) (Table 2).

In the entire group of patients, the value of lactate dehydrogenase (LDH) was elevated in 43 (51.2%).

Tabela 3. Tromboze i KV faktori rizika kod mladih bolesnika sa MPN

Table 3. Thrombosis and CV risk factors in young patients with MPN

	Dijagnoza MPN / *MPN diagnosis*			*p*
	PV	ET	prePMF	
Ukupan broj (%) / *Total number (%)*	**52 (61.9%)**	**21 (25.0%)**	**11 (13.1%)**	
Prethodne tromboze / *History of thrombosis*	11 (21.2%)	1 (4.8%)	2 (18.2%)	0.233
Arterijske / *Arterial*				
TIA /	0 (0)	1 (4.8%)	0 (0)	
AIM /	3 (5.8%)	0 (0)	0 (0)	
CVI /	2 (3.8%)	0 (0)	0 (0)	
Periferna arterijska tromboza / *Peripheral arterial thrombosis*	1 (1.9%)	0 (0)	0 (0)	
Venske / *Venous*				
DVT /	1 (1.9%)	0 (0)	0 (0)	
PE /	1 (1.9%)	0 (0)	0 (0)	
CVT /	1 (1.9%)	0 (0)	0 (0)	
PVT /	1 (1.9%)	0 (0)	2 (18.2)	
Budd-Chiari /	1 (1.9%)	0 (0)	0 (0)	
Tromboze tokom praćenja / *Thrombosis during follow-up*	7 (13.5%)	0 (0)	0 (0)	
Tromboza u levoj komori srca / *Left ventricle thrombosis*	1 (1.9%)	0 (0)	0 (0)	
AIM	2 (3.8%)	0 (0)	0 (0)	
CVI	1 (1.9%)	0 (0)	0 (0)	
Venske / Venous *Venous*				
DVT	3 (5.8%)	0 (0)	0 (0)	
Broj KV faktora rizika / *Number of CV risk factors*				
0	27 (51.9%)	14 (66.7%)	8 (72.8%)	
1	20 (38.5%)	5 (23.8%)	3 (27.3%)	0.293
2	4 (7.7%)	2 (9.5%)	0 (0)	
3	1 (1.9%)	0 (0)	0 (0)	

Kategorijalni podaci su prikazani kao broj pacijenata i procenat n (%)
TIA – tranzitorni ishemijski atak, AIM – akutni infarkt miokarda, CVI – cerebrovaskularni insult, DVT – duboka venska tromboza, PE – plućna embolija, CVT – centralna venska tromboza, PVT – tromboza vene porte, MPN – mijeloproliferativna neoplazma, PV – policitemija vera, ET – esencijalna trombocitemija, prePMF – prefibrotična faza primarne mijelofibroze

Categorical data are presented as the number of patients and percentage n (%)
TIA - transient ischemic attack, AMI - acute myocardial infarction, CVI - cerebrovascular insult, DVT - deep vein thrombosis, PE - pulmonary embolism, CVT - central venous thrombosis, PVT - portal vein thrombosis, MPN - myeloproliferative neoplasm, PV - polycythemia vera, ET - essential thrombocythemia, prePMF - prefibrotic phase of primary myelofibrosis

14 bolesnika (16,7%), dok kod 45 bolesnika (53,6%) nije rađen. Stepen fibroze u koštanoj srži je bio MF 0 kod 24 bolesnika (28,5%), MF 1 kod 46 bolesnika (54,8%), MF 2 kod 4 bolesnika (4,8%), a kod 10 bolesnika (11,9%) nisu bili dostupni podaci (Tabela 1).

Kardiovaskularne faktore rizika imalo je 35 bolesnika (41,7%), od čega je 8 bolesnika (9,5%) imalo hipertenziju, 20 bolesnika (23,8%) su bili pušači, udruženu pojavu hipertenzije i hiperlipidemije je imalo 2 bolesnika (2,4%), pušača koji su istovremeno imali i hipertenziju bilo je 4 (4,8%), dok su sva tri faktora rizika bila prisutna kod samo 1 bolesnika (1,2%). Raspodela prema dijagnozama u odnosu na broj kardiovaskularnih rizika bila je sledeća: 27 bolesnika sa PV (51,9%), 14 bolesnika sa ET (66,7%) i 8 bolesnika sa prePMF (72,8%)

Erythropoietin was decreased in 25 patients (29.8%), normal in 14 patients (16.7%), while in 45 patients (53.6%), it was not done. The degree of fibrosis in the bone marrow was MF 0 in 24 patients (28.5%), MF 1 in 46 patients (54.8%), MF 2 in 4 patients (4.8%), and in 10 patients (11.9%) no data were available (Table 1).

Cardiovascular risk factors were present in 35 patients (41.7%), of which 8 patients (9.5%) had hypertension, 20 patients (23.8%) were smokers, 2 patients had the combined occurrence of hypertension and hyperlipidemia (2.4%), there were 4 (4.8%) smokers who also had hypertension, while all three risk factors were present in only 1 patient (1.2%). The distribution according to diagnoses in relation to the number of cardiovascular risks was as follows: 27 patients with PV

Tabela 4. Terapijski pristup i stratifikacija prema ELN skoru mladih bolesnika sa MPN

Table 4. Therapeutic approach and stratification according to the ELN score of young MPN patients

	Dijagnoza MPN / *MPN diagnosis*			*p*
	PV	ET	prePMF	
Ukupan broj (%) / *Total number (%)*	**52 (61.9%)**	**21 (25.0%)**	**11 (13.1%)**	
Terapija / *Therapy*				
ASA / *ASA*	43 (82.7%)	20 (95.2%)	10 (90.9%)	0.325
VKA / *VKA*	1 (1.9%)	0 (0)	1 (9.1%)	
DOAK / *DOAC*	1 (1.9%)	0 (0)	0 (0)	
ASA+OAK / *ASA+ OAC*	3 (5.8%)	0 (0)	0 (0)	
Flebotomije / *Phlebotomy*	50 (96.2%)	3 (14.3%)	0 (0%)	**<0.001**
Citoreduktivna terapija / *Cytoreductive treatment*	24 (46.1%)	9 (42.9%)	4 (36.4%)	0.831
Standardni ELN skor / *Standard ELN score*				
Nizak rizik / *Low risk*	40 (76.9%)	20 (95.2%)	9 (81.8%)	0.181
Visok rizik / *High risk*	12 (23.1%)	1 (4.8%)	2 (18.2%)	
Prisutni KV faktori rizika / *CV risk factors*	25 (48.1%)	7 (33.0%)	3 (27.3%)	0.299

Kategorijalni podaci su prikazani kao broj pacijenata i procenat n (%), Podebljano- statistički značajna razlika učestalosti
ASA – acetilsalicilna kiselina, VKA – antagonisti vitamina K, DOAK – direktni oralni antikoagulanti, OAK – oralni antikoagulanti, ELN – European LeukemiaNet, KV – kardiovaskularni, PV – policitemija vera, ET – esencijalna trombocitemija, prePMF – prefibrotična faza primarne mijelofibroze

Categorical data are presented as number of patients and percentage n (%), Bold - statistically significant difference in frequency
ASA - acetylsalicylic acid, VKA - vitamin K antagonists, DOAC – direct oral anticoagulants, OAC - oral anticoagulants, ELN - European LeukemiaNet, CV - cardiovascular, PV - polycythemia vera, ET - essential thrombocythemia, prePMF - prefibrotic phase of primary myelofibrosis

nisu imali KV faktore rizika, jedan KV faktor rizika je imalo 20 bolesnika sa PV (28,5%), 5 sa ET (23,8%) i 3 sa prePMF (27,3%), 2 KV faktora rizika su imali 4 bolesnika sa PV (7,7%), 2 sa ET (9,5%) i ni jedan bolesnik sa prePMF, dok je jedan bolesnik sa PV je imao 3 KV faktora rizika (Tabela 1, Tabela 3).

Prethodne tromboze su bile prisutne kod 14 bolesnika (16,7%), dok su tromboze u toku praćenja nastale kod 7 bolesnika (8,3%). Najviše tromboza pre dijagnoze MPN imali su bolesnici sa PV, 11 bolesnika (21,2%), dok su samo 1 bolesnik sa ET (4,8%) i 2 bolesnika sa prePMF (18,2%) imali prethodnu trombozu. Učestalost tromboza pre dijagnose MPN se nije statistički značajno razlikovala prema grupama ispitanika ($p = 0,233$). Od 11 bolesnika sa PV, 3 (5,8%) su imala akutni infarkt miokarda, 2 (3,8%) moždani udar, dok je po jedan (1,9%) bolesnik imao perifernu arterijsku trombozu, DVT, PE, CVT, PVT, Budd Chiari. Bolesnik sa dijagnozom ET je imao tranzitorni ishemijski atak, dok su oba bolesnika sa prePMF imala PVT. U toku praćenja tromboze su isključivo nađene kod bolesnika sa PV, od čega su 3 (5,8%) bolesnika imala DVT, 2 (3,8%) bolesnika AIM, dok je po jedan (1,9%) bolesnik imao CVI ili tromb u levoj komori srca. Broj KV faktora rizika se nije značajno razlikovao između dijagnostičkih grupa pacijenata, ($p = 0,293$) (Tabela 3).

U celoj grupi bolesnika, 73 (86,9%) su bili na terapiji ASA, 2 (2,4%) na terapiji VKA, jedan (1,2%) na DOAK, a 3 bolesnika (3,6%) na kombinaciji ASA i OAK. U okviru PV,

(51.9%), 14 patients with ET (66.7%) and 8 patients with prePMF (72.8%) had no CV risk factors, one CV risk factor was present in 20 patients with PV (28.5%), 5 with ET (23.8%) and 3 with prePMF (27.3%), 2 CV risk factors were present in 4 patients with PV (7 .7%), 2 with ET (9.5%) and no patient with prePMF, while one patient with PV had 3 CV risk factors (Table 1, Table 3).

Previous thromboses were present in 14 patients (16.7%), while thrombosis occurred during follow-up in 7 patients (8.3%). Patients with PV had the most thrombosis before the diagnosis of MPN, 11 patients (21.2%), while only 1 patient with ET (4.8%) and 2 patients with prePMF (18.2%) had previous thrombosis. The frequency of thrombosis before the diagnosis of MPN was not statistically significantly different according to the groups of subjects ($p = 0.233$). Out of 11 patients with PV, 3 (5.8%) had an acute myocardial infarction, 2 (3.8%) had a stroke, while one (1.9%) patient each had peripheral arterial thrombosis, DVT, PE, CVT, PVT, Budd Chiari. The patient diagnosed with ET had a transient ischemic attack, while both patients with prePMF had PVT. During follow-up, thromboses were exclusively found in patients with PV, of which 3 (5.8%) patients had DVT, 2 (3.8%) patients had AMI, while one (1.9%) patient had CVI or thrombus in the left ventricle of the heart. The number of CV risk factors did not differ significantly between diagnostic groups of patients ($p = 0.293$) (Table 3).

43 (82,7%) bolesnika je lečeno ASA, po jedan (1,9%) bolesnik sa VKA i DOAK, dok su tri bolesnika lečena prethodno pomenutom kombinacijom ASA i OAK. Među bolesnicima se ET, 20 (95,2%) je lečeno ASA i nije bilo bolesnika lečenih drugim tipom antitrombozne terapije. U grupi bolesnika sa prePMF, 10 (90,9%) je bilo na terapiji ASA, dok je jedan bio na terapiji VKA. Primena ASA u terapiji nije se značajno razlikovala između posmatranih grupa pacijenata ($p = 0,325$). Ukupno, 53 bolesnika (63,1%) je lečeno flebotomijama, od čega su 50 bili bolesnici sa PV, dok je 3 bolesnika imalo ET. Lečenje flebotomijom je značajno učestalije u grupi pacijenta sa PV ($p < 0,001$). Citoreduktivnom terapijom je lečeno 37 bolesnika (43,9%), dok je raspodela prema dijagnozama bila: 24 bolesnika (46,1%) u grupi sa PV, 9 (42,9%) u grupi sa ET i 4 (36,4%) u grupi sa prePMF, bez značajne razlike u primeni citoreduktivne terapije između grupa pacijenata ($p = 0,831$). U celoj grupi bolesnika, 33 bolesnika (39,1%) je lečeno jednom terapijskom linijom, dok su 4 bolesnika (4,8%) primala dve terapijske linije. Hidroksurea (HU) je bila prva linija terapije kod 31 bolesnika (36,1%), dok je 6 bolesnika (7,2%) incijalno lečeno interferonom. U drugoj terapijskoj liniji, 3 bolesnika su dobijala HU (3,6%), dok su po dva bolesnika dobijala INF (2,4%) ili ruksolitinib (2,4%) (Tabela 4).

Od ukupnog broja bolesnika, prema standardnom ELN skoru, visokom riziku je pripadalo 15 (17,9%). Raspodela u okviru dijagnoza, u odnosu na ELN skor, bila je sledeća: 12 bolesnika (23,1%) sa PV, 1 bolesnik (4,8%) sa ET i 2 bolesnika (18,2%) sa prePMF pripadali su grupi visokog rizika. Učestalost visokorizičnih pacijenata prema standardnom ELN skoru nije se značajno razlikovala između dijagnoza ($p = 0,181$). Od ukupnog broja bolesnika koji su primali citoreduktivnu terapiju, njih 10 (26,7%) je bilo klasifikovano kao visokorizično. U grupi bolesnika sa ET, prema IPSET survival skoru, 16 bolesnika je pripadalo grupi niskog rizika, 4 bolesnika intermedijernoj grupi, a prema IPSET thrombosis skoru, 11 bolesnika je pripalo grupi niskog, a 7 bolesnika intermedijernoj grupi rizika. U grupi bolesnika sa prePMF, prema IPSS skoru, 8 bolesnika je pripadalo grupi niskog, a 3 bolesnika grupi intermedijernog-1 rizika. Prethodno navedeni skorovi korišteni za bolesnike sa ET i prePMF nisu identifikovali visokorizične bolesnike u našoj kohorti (Tabela 4).

Kod dve bolesnice (2,45%) postojala je pozitivna porodična anamneza u smislu porodičnog prisustva prethodne MPN. Kod jedne bolesnice sa PV, majka je tekođe imala PV, a kod druge bolesnice sa prePMF, stric je imao ET.

Transformacija u MF dogodila se kod dve bolesnice koje su imale PV (post-PV MF), što čini 2,45% od ukupnog broja bolesnika. Vreme do fibrotične progresije je iznosilo 6 i 11,5 godina.

In the entire group of patients, 73 (86.9%) were on ASA therapy, 2 (2.4%) on VKA therapy, one (1.2%) on DOAK, and 3 patients (3.6%) on a combination of ASA and OAK. Within PV, 43 (82.7%) patients were treated with ASA, one (1.9%) patient each with VKA and DOAC, and three patients were treated with the combination mentioned above of ASA and OAK. Among the patients with ET, 20 (95.2%) were treated with ASA, and no patients were treated with another type of antithrombotic therapy. In the group of patients with prePMF, 10 (90.9%) were on ASA therapy, while one was on VKA therapy. The use of ASA in treatment did not differ significantly between the observed groups of patients ($p = 0.325$). In total, 53 patients (63.1%) were treated with phlebotomies, of which 50 were patients with PV, while 3 patients had ET. Phlebotomy treatment was significantly more frequent in the group of patients with PV ($p < 0.001$). 37 patients (43.9%) were treated with cytoreductive therapy, while the distribution according to diagnosis was: 24 patients (46.1%) in the group with PV, 9 (42.9%) in the group with ET, and 4 (36.4%) in the group with prePMF, with no significant difference in the application of cytoreductive therapy between patient groups ($p = 0.831$). In the entire group of patients, 33 patients (39.1%) were treated with one therapeutic line, while 4 patients (4.8%) received two therapeutic lines. Hydroxyurea (HU) was the first line of therapy in 31 patients (36.1%), while 6 patients (7.2%) were initially treated with interferon. In the second therapeutic line, 3 patients received HU (3.6%), while two patients each received INF (2.4%) or ruxolitinib (2.4%) (Table 4).

Of the total number of patients, according to the standard ELN score, 15 (17.9%) were at high risk. The distribution within the diagnoses, in relation to the ELN score, was as follows: 12 patients (23.1%) with PV, 1 patient (4.8%) with ET, and 2 patients (18.2%) with prePMF belonged to the group high risk. The frequency of high-risk patients according to the standard ELN score did not differ significantly between diagnoses ($p = 0.181$). Of the total number of patients who received cytoreductive therapy, 10 of them (26.7%) were classified as high-risk. In the group of patients with ET, according to the IPSET survival score, 16 patients belonged to the low-risk group, 4 patients to the intermediate group, and according to the IPSET thrombosis score, 11 patients belonged to the low-risk group, and 7 patients to the intermediate risk group. In the group of patients with prePMF, according to the IPSS score, 8 patients belonged to the group of low, and 3 patients to the group of intermediate-1 risk. The aforementioned scores used for patients with ET and prePMF did not identify high-risk patients in our cohort (Table 4).

Medijana praćenja bolesnika je iznosila 72 meseca (3-288 meseci). Dva bolesnika (2,45%) su tokom praćenja preminula, a uzrok smrtnog ishoda kod jednog su bile posttransplatacione komplikacije nakon alogene tranplatacje matičnih ćelija hematopoeze, odnosno sekundarni malignitet, karcinom jetre kod drugog (Tabela 1).

DISKUSIJA

Najčešće dijagnostikovana Filadelfija negativna (Ph-) MPN kod mladih bolesnika je esencijalna trombocitemija (ET). Ovaj tip MPN najšešće se otkriva kod ispitanika ženskog pola, što objašnjava nalaz da su među mladim bolesnicima sa MPN pretežno žene (65-71%), dok je kod starijih zastupljenost ženskog pola manja i iznosi 46-58% [10,11]. U našoj kohorti, iako je češće nađena policitemija vera (PV), i dalje je dominantan ženski pol, jer žene čine skoro dve trećine ukupnog broja bolesnika.

Medijana starosti na dijagnozi u studijama sa mladim bolesnicima sa MPN kreće se između 20 i 36 godina, što je u skladu sa našim podacima gde je medijana bila 33 godine, sa rasponom od 14 do 40 godina. Ove studije su uključile bolesnike malđe od 45 godina starosti [10,18,19].

Pacijenti mlađe životne dobi sa MPN na dijagnozi su uglavnom bez tegoba (asimptomatski), slično kao i stariji [18]. Međutim, prema podacima Sobas i saradnika, više od jedne trećine bolesnika je imalo simptome zbog hiperviskoznosti [13]. U našoj studiji, skoro trećina bolesnika imala je mikrovaskularne tegobe, koje su bile najzastupljenije. Na drugom mestu je bio svrab, a manje od 10% bolesnika je imalo konstitucione tegobe. Prema podacima iz literature, koji su nisu brojni, bolesnici sa PV češće imaju na dijagnozi konstitucione simptome, 9,2% u odnosu na 3,9% kod bolesnika sa ET [13]. Splenomegalija je nađena kod skoro polovine naših ispitanika. Prema Szuber i saradnicima, povećan promer slezine bio je prisutan kod većeg procenta mlađih od 40 godina u odnosu na bolesnike starije od 60 godina [14]. Ovo je naročito značajno, uzimajući u obzir da je splenomegalija identifikovana kao faktor rizika za nastanak komplikacija i progresije bolesti, uključujući transformaciju, krvarenje i trombozu kod ove grupe bolesnika [12,13].

Kao što je i očekivano, bolesnici sa PV su na dijagnozi imali značajno više vrednosti hemoglobina i hematokrita u poređenju sa bolesnicima sa ET i prePMF ($p < 0,001$). Medijana hemoglobina kod PV bolesnika je bila 170 g/L, dok je kod bolesnika sa ET i prePMF ona iznosila 137,5 g/L i 132 g/L. Hematokrit je takođe bio najviši kod PV bolesnika, sa medijanom od 50,0%, u poređenju sa 41,7% kod ET i 38,8% kod prePMF. Trombociti

In two patients (2.45%), there was a positive family history in terms of family presence of previous MPN. In one patient with PV, the mother also had PV, and in another patient with prePMF, the uncle had ET.

Two patients with PV (post-PV MF) were transformed to MF, accounting for 2.45% of the total number of patients. The time to fibrotic progression was 6 and 11.5 years.

Median patient follow-up was 72 months (3-288 months). Two patients (2.45%) died during follow-up, and the cause of death in one was post-transplantation complications after allogeneic hematopoietic stem cell transplantation, i.e., secondary malignancy and liver cancer in the other (Table 1).

DISCUSSION

The most frequently diagnosed Philadelphia-negative (Ph-) MPN in young patients is essential thrombocythemia (ET). This type of MPN is most often detected in female respondents, which explains the finding that among young patients with MPN, women are predominantly female (65-71%), while in the elderly, the representation of the female gender is lower and amounts to 46-58% [10,11]. In our cohort, although polycythemia vera (PV) was found more often, the female gender is still dominant, as women make up almost two-thirds of the total number of patients.

The median age at diagnosis in studies with young patients with MPN ranges between 20 and 36 years, which is consistent with our data, where the median was 33 years, with a range of 14 to 40 years. These studies included patients younger than 45 years of age [10,18,19].

Younger patients diagnosed with MPN are generally asymptomatic, similar to the elderly [18]. However, according to the data of Sobas et al., more than one-third of patients had symptoms due to hyperviscosity [13]. In our study, almost a third of patients had microvascular problems, which were the most prevalent. In second place was itching; less than 10% of patients had constitutional complaints. According to data from the literature, which are not numerous, patients with PV more often have constitutional symptoms at diagnosis, 9.2% compared to 3.9% in patients with ET [13]. Splenomegaly was found in almost half of our subjects. According to Szuber et al., an increased spleen diameter was present in a higher percentage of patients younger than 40 years compared to patients older than 60 years [14]. This is particularly significant, considering that splenomegaly has been identified as a risk factor for complications and disease progression, including transformation, bleeding, and thrombosis in this group of patients [12,13].

toza je uočena kod svih ispitivanih MPN entiteta, ali su postojale značajne razlike u broju trombocita između pacijenata sa PV i ET (p = 0,018), kao i između PV i prePMF (p = 0,003). Najveći broj trombocita su imali bolesnici sa prePMF (medijana 1007x10^9/L), zatim bolesnici sa ET (medijana 856x10^9/L), dok su PV bolesnici imali najmanji stepen trombocitoze (medijana 737,5x10^9/L). Prema podacima iz literature, u grupi mladih bolesnika bila je zapažena trombocitoza većeg stepena u odnosu na starije što bi se moglo objasniti povećanom incidencom CALR mutacije u ovoj grupi, uzimajući u obzir da je ova mutacija povezana sa trombocitozom [2,11,18]. U našoj kohorti je isključivo ispitivana JAK2V617F mutacija, koja je bila pozitivna kod oko polovine bolesnika. LDH je bio povišen kod oko polovine bolesnika. Kod najvećeg broja bolesnika fibroza je odgovarala MF-1 sa više od 50%, dok su tek dva bolesnika su imali MF-2.

Prema podacima iz literature, približno 10% bolesnika sa MPN pokazuje familijarnu povezanost (klasterizaciju), što ukazuje na značaj naslednih komponenti u razvoju bolesti [14]. Učestalost familijarnih MPN je veća kod mlađih bolesnika u donosu na starije bolesnike (19% vs 9%) [10]. Ovo je takođe očekivano, s obzirom i na raniju pojavu bolesti u mlađoj grupi bolesnika. U našoj kohorti, kod dva bolesnika je uočena porodična pojava MPN (2,45%), što se može objasniti relativno malom grupom ispitanika.

Vaskularne komplikacije su značajan rizik, naročito za bolesnike sa PV, a javljaju se kako pre postavljanja dijagnoze, tako i tokom daljeg prirodnog toka bolesti [11,20,21]. Dokazano je da su povezane sa dijagnozom MPN i da nekada mogu biti i prva manifestacija bolesti zbog koje se bolesnici javljaju hematologu [22,23]. U literaturni se nalazi da su prethodne tromboze bile prisutne kod 14-27% bolesnika sa PV, 6-13% bolesnika sa ET i 7-16% sa PMF [2,11,13,18,19]. Ovi podaci u velikoj meri odgovaraju zastupljenosti prethodnih tromboza u oviru različitih MPN dijagnoza i u našem istraživanju. Od svih prethodnih tromboza u našoj kohorti, najčešće su bile zastupljene tromboze splanhične cirkulacije sa 28,5% od ukupnog broja, dok je zastupljenost arterijskih i venskih tromboza bila jednaka. Drugi najšeći tip tromboze, odnosno tromboznih događaja, bio je akutni infarkt miokarda, koji se javio kod 21,4% bolesnika. Poznato je da MPN dovodi do tromboza na neuobičajenim lokalizacijama, kao što su tromboze splanhnične cirkulacije, uključujući Budd-Chiarijev sindrom (BCS), tromboza vene porte (PVT) i tromboza cerebralnih vena [11,22,24]. Tromboze u toku praćena isključivo su bile prisutne kod bolesnika sa PV sa predominacijom arterijskih tromboza koje su činile skoro 2/3. Prema literaturnim podacima kod bolesnika ove uzrasne grupe češće su bile prisutne venske tromboze u toku prać-

As expected, patients with PV had significantly higher hemoglobin and hematocrit values at diagnosis than patients with ET and prePMF (p < 0.001). Median hemoglobin in PV patients was 170 g/L, while in patients with ET and prePMF, it was 137.5 g/L and 132 g/L. Hematocrit was also highest in PV patients, with a median of 50.0%, compared to 41.7% in ET and 38.8% in prePMF. Thrombocytosis was observed in all MPN entities examined, but there were significant differences in platelet counts between PV and ET patients (p = 0.018) and between PV and prePMF (p = 0.003). Patients with prePMF had the highest number of platelets (median 1007x10^9/L), followed by patients with ET (median 856x10^9/L), while PV patients had the lowest degree of thrombocytosis (median 737.5x10^9/L). According to data from the literature, a higher degree of thrombocytosis was observed in the group of young patients compared to the elderly, which could be explained by the increased incidence of the CALR mutation in this group, taking into account that this mutation is associated with thrombocytosis [2,11,18]. In our cohort, the JAK2V617F mutation was exclusively examined, and it was positive in about half of the patients. LDH was elevated in about half of the patients. In the most significant number of patients, fibrosis corresponded to MF-1 with more than 50%, while only two patients had MF-2.

According to data from the literature, approximately 10% of patients with MPN show a familial connection (clustering), which indicates the importance of hereditary components in the development of the disease [14]. The frequency of familial MPN is higher in younger patients than in older patients (19% vs 9%) [10]. This is also expected, considering the earlier onset of the disease in the younger group of patients. In our cohort, a familial occurrence of MPN was observed in two patients (2.45%), which the relatively small group of subjects can explain.

Vascular complications are a significant risk, especially for patients with PV, and occur both before diagnosis and during the further natural course of the disease [11,20,21]. It has been proven that they are related to the diagnosis of MPN and that sometimes, they can be the first manifestation of the disease for which the patients consult a hematologist [22,23]. In the literature, previous thrombosis was present in 14-27% of patients with PV, 6-13% of patients with ET, and 7-16% with PMF [2,11,13,18,19]. These data correspond to previous thromboses' prevalence among different MPN diagnoses and in our research. Of all the previous thromboses in our cohort, the most common was thrombosis of the splanchnic circulation, with 28.5% of the total number, while the prevalence of arterial and venous thrombosis was equal. The second most com-

nja, pa čak češće i u odnosu na starije bolesnike [10]. Autori ovu pojavu objašnjavaju većim brojem tromboza splanhične cirkulacije u toku praćenja, sa 77% od ukupnog broja venskih tromboza [12]. S druge strane, arterijske tromboze su u toku praćenja uglavnom ređe zastupljene kod mlađih bolesnika. Smatra se da je ovo u vezi sa nižom incidencom kardiovaskularnih komorbiditeta i aterosklerotskih promena u krvnim sudovima [14]. Međutim, u našoj kohorti 41,7% bolesnika je imalo KV faktore rizika, pri čemu je pušenje bilo najčešće zastupljeno, a čak 8,3% bolesnika imalo je više od jednog faktora rizika. Taj nalaz može objasniti pojavu češćih arterijskih tromboza u našoj studiji.

Prema ELN preporukama, lečenje bolesnika sa PV je bazirano na riziku od tromboze. Grupi visokog rizika pripadaju bolesnici koji su imali prethodne tromboze ili su stariji od 60 godina, dok nizak rizik podrazumeva odsustvo oba navedena faktora. Primenom ovog skoring sistema, svi bolesnici u grupi mladih pripadaju grupi niskog rizika, osim ako nisu imali prethodne tromboze [16]. Lečenje niskorizičnih bolesnika sa PV podrazumeva primenu flebotomija sa ciljem da Hct bude < 45%, kao i primenu malih doza ASA [16,25]. Pre primene antitrombocitne terapije, bitno je testirati bolesnika na stečeni von Wilebrandov sindrom kako bi se identifikovali bolesnici sklon krvarenju, imajući u vidu da se on može da javi čak i u odsustvu izražene trombocitoze [26]. U našoj grupi bolesnika sa PV, većina je lečena niskim dozama ASA, sa svega par bolesnika je bilo na na oralnoj antikoagulantnoj terapiji (OAK). Razlog za uvođenje OAK kod skoro svih bolesnika bile su prethodne tromboze, osim kod jednog bolesnika kod koga je ova terapija uvedena zbog atrijalne fibrilacije. Bolesnici sa visokim rizikom, prema ELN preporukama, zahtevaju pored ove dve terapije i primenu citoreduktivne terapije [16]. Dok se HU standardno koristi kod starijih bolesnika, prema *ELN* i *NCCN (National Comperhensive Cancer Network)* preporukama, kod mladih prvi izbor citoreduktivne terapije je rekombinovani ili pegilovani INF-alfa [16,27]. U našoj grupi bolesnika, skoro polovina bolesnika sa PV lečena je primenom citoreduktivne terapije, uglavnom HU, dok je manji broj dobijao INF-alfa. Procenat lečenih je izuzetno visok, uzimajući u obzir da je manje od četvrtine bolesnika bilo svrstano u grupu sa visokim rizikom, a drugi razlozi za uvođenje terapije su bili visoka trombocitoza, splenomegalija, trudnoća ili značajne tegobe. Slično je i sa bolesnicima sa ET, gde su svi osim jednog pripadali grupi niskog rizika, pa a ipak je 42,9% bolesnika lečeno citoreduktivnom terapijom. ELN preporuke u smislu primene citoreduktivne terapije kod bolesnika sa ET ne razlikuju se mnogo u odnosu na PV, što se ne može reći i za primenu ASA [16]. Niske doze ASA su preporučene

mon type of thrombosis, or thrombotic events, was acute myocardial infarction, which occurred in 21.4% of patients. MPN is known to lead to thromboses in unusual locations, such as thromboses of the splanchnic circulation, including Budd-Chiari syndrome (BCS), portal vein thrombosis (PVT), and cerebral vein thrombosis [11,22,24]. Thrombosis during follow-up was exclusively present in patients with PV, with a predominance of arterial thrombosis, which accounted for almost 2/3. According to literature data in patients of this age group, venous thromboses were more likely to be present during follow-up and even more often compared to older patients [10]. The authors explain this phenomenon by the higher number of thromboses of the splanchnic circulation during follow-up, with 77% of the total number of venous thromboses [12]. On the other hand, arterial thrombosis during follow-up is generally less common in younger patients. This is thought to be related to lower cardiovascular comorbidities and atherosclerotic changes in blood vessels [14]. However, in our cohort, 41.7% of patients had CV risk factors, where smoking was the most common, and even 8.3% of patients had more than one risk factor. This finding may explain the occurrence of more frequent arterial thrombosis in our study.

According to ELN recommendations, treating patients with PV is based on the risk of thrombosis. Patients who have had previous thrombosis or are older than 60 years belong to the high-risk group, while low-risk implies the absence of both mentioned factors. By applying this scoring system, all patients in the youth group belong to the low-risk group unless they have had previous thrombosis [16]. The treatment of low-risk patients with PV involves the use of phlebotomy with the aim of Hct being < 45%, as well as the use of small doses of ASA [16,25]. Before applying antiplatelet therapy, it is crucial to test the patient for acquired von Willebrand syndrome to identify patients prone to bleeding, bearing in mind that it can occur even in the absence of pronounced thrombocytosis [26]. In our group of patients with PV, most were treated with low doses of ASA, with only a few patients on oral anticoagulant therapy (OAC). The reason for the introduction of OAC in almost all patients was previous thrombosis, except for one patient in whom this therapy was introduced due to atrial fibrillation. Patients with high risk, according to ELN recommendations, require cytoreductive therapy in addition to these two therapies [16]. While HU is standardly used in elderly patients, according to ELN and NCCN (National Comprehensive Cancer Network) recommendations, in young people, the first choice of cytoreductive therapy is recombined or pegylated INF-alpha [16,27]. In our group of patients, al-

kod bolesnika sa JAK2 mutacijom, dok kod CALR mutacije, s obzirom na veću sklonost ka krvarenju, treba biti oprezan [14]. Ipak, u našoj studiji svi, osim jednog bolesnika su dobijali ASA, a sama CALR mutacija nije bila rađena.

Kod bolesnika sa PMF, lečenje se značajno razlikuje, i ukoliko nemaju citopeniju, prisutne visokorizične molekularne mutacije i imaju normalan kariotip, preporučuje se posmatranje, kliničke studije ili upotreba JAK inhibitora (JAKi) [14]. U suprotnom, za bolesnike visokog rizika, preporučuje se alogena transplatacija matićnih ćelija hematopoeze (TMĆH) [14]. U našoj grupi bolesnika isključivo je bila dijagnostikovana prePMF, pa je terapijski pristup bio sličan onom kod ET, s obzirom da ove dve bolesti karakteriše uporediv rizik od trombotičkih komplikacija [28]. Stoga je lečenje podrazumevalo primenu aspirina, a nešto više od trećine bolesnika je bilo lečeno i citoreduktivnom terapijom što je više u odnosu na procenat bolesnika sa trombozom (18.2%). Jedna bolesnica, sa progresijom u post-PV MF nakon 11,5 g od dijagnoze, transplantirana je, ali je preminula zbog nastanka posttransplatacionih komplikacija. Većina bolesnika u našoj grupi lečena je jednom linijom citoreduktivne terapije, a svega 4,8% bolesnika je zahtevalo drugu terapijsku liniju, i to HU, INF ili ruksolitinib.

Trenutno, ne postoje prognostički skorovi koji su specifično dizajnirani ili validirani za procenu mladih MPN bolesnika. U našoj kohorti za stratifikaciju rizika, kako je ranije pomenuto korišćen je standardni ELN skor, ali i IPSET srurvival i IPSET thrombosis za bolesnike sa ET i IPSS skor kod bolesnika sa prePMF [15,29,30]. Prema IPSET survival i IPSET thrombosis skorovima najveći broj bolesnika je pridao grupi niskog rizika, a ni jedan bolesnik nije pripadao grupi visokog rizika. Slično je i kod prePMF, gdje je IPSS identifikovao bolesnike uglavnom kao niskorizične.

Najčešći uzrok smrtnog ishoda u ovoj grupi bolesnika se pripisuje osnovnoj bolesti, transformaciji ili komplikacijama koje nastaju nakon TMĆH [10]. Literaturni podaci ukazuju na to da, iako ne postoji razlika u učestalosti transformacije u MF ili AML između mlađih i starijih bolesnika sa MPN, medijana dužine perioda do transformacije je značajno duža kod mlađih (< 45 g) u odnosu na starije (> 65 g) bolesnike (19-20 odnosno 7-8 godina) zbog veće dužne praćenja [11]. Samo kod dve bolesnice u našoj kohorti došlo je do progresije u post-PV MF, što se može objasniti kratkom medijanom praćenja koja je iznosila oko 3 godine. Podaci iz literature ukazuju da je > 45% transformacija zabeleženo nakon > 10 godina od postavljanja dijagnoze, pa stoga dužina praćenja predstavlja bitan faktor [13]. Smrtni ishod je nastupio kod dva bolesnika, i to, kako je ranije

most half of the patients with PV were treated with cytoreductive therapy, mainly HU, while a smaller number received INF-alpha. The percentage of those treated is exceptionally high, taking into account that less than a quarter of patients were classified as high-risk, and other reasons for the introduction of therapy were high thrombocytosis, splenomegaly, pregnancy, or significant complaints. It is similar to patients with ET, where all but one belonged to the low-risk group, and yet 42.9% of patients were treated with cytoreductive therapy. ELN recommendations regarding the application of cytoreductive therapy in patients with ET do not differ much compared to PV, which cannot be said for the application of ASA [16]. Low doses of ASA are recommended in patients with JAK2 mutation, while caution should be exercised in patients with CALR mutation, given the greater tendency to bleeding [14]. However, in our study, only one patient received ASA, and the CALR mutation was not performed.

In patients with PMF, treatment varies significantly, and if they do not have cytopenia, high-risk molecular mutations are present and have a normal karyotype; observation, clinical studies, or the use of JAK inhibitors (JAKi) are recommended [14]. Otherwise, for high-risk patients, allogeneic hematopoietic stem cell transplantation (HSCT) is recommended [14]. In our group of patients, only prePMF was diagnosed, so the therapeutic approach was similar to that of ET, considering that these two diseases are characterized by a comparable risk of thrombotic complications [28]. Therefore, the treatment involved the use of aspirin, and slightly more than a third of patients were treated with cytoreductive therapy, which is higher than the percentage of patients with thrombosis (18.2%). One patient, with progression to post-PV MF after 11.5 years from diagnosis, was transplanted but died due to post-transplantation complications. Most patients in our group were treated with one line of cytoreductive therapy, and only 4.8% of patients required a second line of treatment, namely HU, INF, or ruxolitinib.

Currently, no prognostic scores are specifically designed or validated for evaluating young MPN patients. In our risk stratification cohort, as previously mentioned, the standard ELN score was used for IPSET survival and IPSET thrombosis for patients with ET and IPSS score for patients with prePMF [15,29,30]. According to the IPSET survival and IPSET thrombosis scores, most patients belonged to the low-risk group, and not a single patient belonged to the high-risk group. It is similar to prePMF, where the IPSS identified patients primarily as low-risk.

The most common cause of death in this group of patients is attributed to the underlying disease, trans-

navedeno, kod bolesnice sa post PV PMF, usled komplikacija TMĆH, a kod drugog bolesnika razlog zbog sekundarnog maligneta.

ZAKLJUČAK

Adolescenti i mlade odrasle osobe čine posebnu subpopulaciju unutar MPN, pokazujući jedinstvene karakteristike po kojima se razlikuju od starijih bolesnika. Kao rezultat dugog trajanja bolesti u ovoj starosnoj grupi, postoji veći rizik od trombotičkih događaja, posebno tromboza splanhične cirkulacije, ali i veći rizik od transformacije u agresivniju formu bolesti zbog dužine praćenja. Naša studija pokazuje da većina mladih bolesnika sa MPN, prema standardnom ELN skoru, pripada grupi niskog rizika. Međutim, značajan broj njih razvija ozbiljne komplikacije, poput tromboza (25%), simptoma, trombocitoze i splenomegalije (> 18 cm), a kao rezultat, skoro polovina bolesnika se leči citoreduktivnom terapijom.

Ovi podaci ukazuju na potrebu za daljim istraživanjima kako bi se razvili prognostički modeli specifični za mlade MPN bolesnike, čime bi se omogućila preciznija stratifikacija rizika i optimalan terapijski pristup. Prisutnost familijarne pojave bolesti ukazuje na potrebu za sveobuhvatnim genetičkim testiranjem. Upotreba NGS (next-generation sequencing) u ispitivanju epigenetskih mutacija kod mladih bolesnika može značajno doprineti razumevanju genetskih promena koje utiču na tok bolesti i odgovor na terapiju.

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formation, or complications that occur after TMJ [10]. Literature data indicate that, although there is no difference in the frequency of transformation to MF or AML between younger and older patients with MPN, the median length of the period to transformation is significantly longer in younger (< 45 y) compared to older (> 65 y) patients. patients (19-20 or 7-8 years old) due to greater follow-up [11]. Only two patients in our cohort had progression to post-PV MF, which can be explained by the short median follow-up of about 3 years. Data from the literature indicate that > 45% of transformations were recorded after > 10 years from diagnosis, and therefore, the length of follow-up is an essential factor [13]. Death occurred in two patients, as previously stated, in a patient with post-PV PMF due to complications of TMJ and in the second patient due to secondary malignancy.

CONCLUSION

Adolescents and young adults form a particular subpopulation within MPN, showing unique characteristics distinguishing them from older patients. As a result of the long duration of the disease in this age group, there is a higher risk of thrombotic events, especially thrombosis of the splanchnic circulation, but also a higher risk of transformation into a more aggressive form of the disease due to the length of follow-up. Our study shows that most young patients with MPN, according to the standard ELN score, belong to the low-risk group. However, a significant number of them develop serious complications, such as thrombosis (25%), symptoms, thrombocytosis, and splenomegaly (> 18 cm), and as a result, almost half of the patients are treated with cytoreductive therapy.

These data indicate the need for further research to develop prognostic models specific to young MPN patients, enabling more precise risk stratification and an optimal therapeutic approach. The presence of a familial occurrence of the disease indicates the need for comprehensive genetic testing. The use of NGS (next-generation sequencing) in examining epigenetic mutations in young patients can significantly contribute to understanding genetic changes that affect the course of the disease and the response to therapy.

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