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The association of mean platelet volume and platecrit and bone marrow fibrosis in patients with essential thrombocythemia: A cohort study

Esansiyel trombositemi hastalarında kemik iliği fibrozisi ile ortalama trombosit hacmi ve plateletkritin ilişkisi: Bir kohort çalışma

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Abstract

Aim: Essential thrombocythemia (ET) patients exhibit higher mean platelet volume (MPV) values compared to the healthy individuals. However, the association of degree of bone marrow fibrosis with either MPV or platecrit (PCT) has not been evaluated previously. The aim of this study was to investigate MPV and PCT values as predictive markers for evaluating bone marrow fibrosis (BMF) in ET patients.

Methods: We conducted a retrospective cohort study to analyze the data of ET patients, who were followed in out-patient clinic of our hematology department, between January 2015 and December 2016. Patients older than 18 years, who had bone marrow biopsy, CBC, biochemistry tests and an abdominal sonography performed at the time of diagnosis, JAK2 test ordered and were BCR-ABL negative were included in the study. The patients were divided into two groups according to the presence of BMF as "the BMF group" and "the non-BMF group". The cut-off value for MPV and PCT was determined according to the median value. Fisher's exact test and χ^2 were used for comparative statistical analysis.

Results: There were 22 males and 26 females with a median age of 56 years (range, 28–81). The BMF group included 35 (73%) patients while the non-BMF group included 13 (27%) patients. The median MPV was 8.8 fL (6.6-11.5) and median PCT was 0.69% (0.42-2.26), which was considered as the cut-off values for these parameters. There was no significant difference between the groups in patients with MPV ≤8.8 fL and MPV >8.8 fL (p=0.104) and also in patients with PCT ≤0.69% and PCT >0.69% (p=0.616).

Conclusion: There is no association between the BMF and MPV and PCT in ET patients. However this is the first study investigating the role of both MPV and PCT in BMF in ET patients.

Keywords: Essential thrombocythemia, Mean platelet volume, Platecrit, Bone marrow fibrosis

Öz

Amaç: Esansiyel trombositemi (ET) hastalarında ortalama trombosit hacmi (MPV) değerleri sağlıklı bireylere göre daha yüksek seyretmektedir. Ancak, ET'da MPV veya plateletkritin (PCT) kemik iliği fibrozisi (KİF) derecesi ile ilişkisi henüz araştırılmamıştır. Amacımız MPV ve PCT değerlerinin ET hastalarında kemik iliği fibrozisini değerlendirmede prediktif bir belirteç olarak rolünü araştırmaktır.

Yöntemler: Retrospektif bir kohort çalışması yaparak Ocak 2015 ile Aralık 2016 arasında hematoloji polikliniğimizden takip edilen ET hastalarının verilerini inceledik. 18 yaşından büyük, tanı anında kemik iliği biyopsisi, hemogram, biyokimya ve batın ultrasonu olan, JAK2 istenmiş olan ve BCR-ABL negatif hastalar çalışmaya dâhil edildi. Hastalar KİF varlığına göre "KİF grubu" ve "KİF olmayan grup" olarak iki gruba ayrıldı. MPV ve PCT için eşik değer için ortanca değer alındı. Karşılaştırmalı istatistiksel analizler için Fisher exact ve ki kare testi kullanıldı.

Bulgular: Hastaların 22'si erkek 26'sı kadın olup ortanca yaş 56 yaştı (Aralık 28-81). KİF grubunda 35 (%73) hasta varken KİF olmayan grupta 13 (%27) hasta mevcuttu. Medyan MPV 8,8 fL (6,6-11,5) iken medyan PCT %0,69 (0,42-2,26) idi ve bunlar iki parametre için eşik değer olarak kullanıldı. KİF varlığı ile MPV ≤8,8 fL ve MPV >8,8 fL olan hastalar arasında, PCT ≤%0,69 ve PCT >%0,69 olanlardaki gibi anlamlı fark bulunmamaktaydı (p=0,104 ve 0,616).

Sonuç: Çalışmamızda ET hastalarında KİF ile MPV veya PCT arasında ilişki bulamadık. Bununla birlikte çalışmamız ET hastalarında KİF'ni öngörmede MPV ve PCT'nin rolünü araştıran ilk çalışmadır.

Anahtar kelimeler: Esansiyel trombositemi, Ortalama trombosit hacmi, Plateletkrit, Kemik iliği fibrozisi

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Introduction

Essential thrombocythemia (ET), one of the Philadelphia-negative classical myeloproliferative neoplasms, is a stem cell disorder and characterized by the proliferation of exclusively megakaryocytes, leading to excessive platelet production without any abnormalities in erythroid and myeloid lineages in the bone marrow [1]. Although ET might be complicated particularly by thrombosis, it can also progress to fibrotic phase (post-ET myelofibrosis) and leukemia in long term, during the course of the disease [2-3].

Platelets, which are anucleated small cells with a volume of about 7 to 11 fL, play a crucial role in vascular homeostasis, furthermore in inflammation and atherogenesis. Platelets contain various granules, a microtubular system and an active membrane. Among them, granules contribute to the generation of inflammation and thrombosis by releasing their ingredients upon activation [4-6]. During those events, larger platelets are more potent in terms of thrombotic potential compared to the smaller ones [7]. Herein, mean platelet volume (MPV), representing the average platelet volume, has emerged as an indicator of platelet function and activation in various proinflammatory and prothrombotic clinical states [8]. Another MPV-related platelet index, which can be easily attained from complete blood count (CBC), is platecrit (PCT). It is the product of MPV multiplied by the platelet count and is stated as a percentage [9].It was demonstrated that ET patients exhibited higher MPV values compared to healthy individuals [10,11] and patients with reactive thrombocytosis [11]. However, the association of degree of bone marrow fibrosis with either MPV or PCT has not been previously evaluated. Therefore, the aim of this study is to investigate MPV and PCT values as predictive markers for evaluating bone marrow fibrosis in ET patients.

Materials and methods

We conducted a retrospective cohort study to analyze the data of ET patients, who were followed in out-patient clinic of our hematology department, between January 2015 and December 2016. Patients older than 18 years, who had bone marrow biopsy, CBC, biochemistry tests and an abdominal sonography performed at the time of diagnosis, JAK2 test ordered and were BCR-ABL negative were included in the study. All eligible patients with a diagnosis of ET were included in the study and thus no sample size analysis was performed.

The diagnosis of ET was based on 2008 World Health Organization criteria [12]. The data included gender, age, white blood cell count (WBC), hemoglobin (hb) level, platelet (plt) count, lactate dehydrogenase (LDH) level, disease age, MPV, PCT, splenomegaly status, Janus kinase 2 (JAK-2) mutation status and the degree of reticulin fibrosis. Thrombotic complications were evaluated at the time of entering the study. MPV and PCT values were gathered from the CBC measured on an EDTA tube at the time of diagnosis, on the same day with the bone marrow biopsy procedure.

Bone marrow fibrosis (BMF) degree was determined according to the reticulin and trichrome staining applied to the specimens and grading was done as follows [13]:

- Grade 0: Scattered linear reticulin with no intersections (cross-overs) corresponding to normal bone marrow
- Grade 1: Loose network of reticulin with many intersections, especially in perivascular areas
- Grade 2: Diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis
- Grade 3: Diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis

The patients were divided into two groups according to the presence of BMF as “the BMF group” and “the non-BMF group”. The cut-off value for MPV and PCT was determined according to the median value. This study protocol was approved by the institutional review board of the University of Health Sciences, Istanbul Training and Research Hospital (Number 939/2017).

Statistical analysis

The data were analyzed by using SPSS version 17.0 program. Data were presented as numbers and percentage or median and range, when appropriate. χ^2 and Fisher’s exact test was used for evaluating categorical values. All p-values were 2-sided with statistical significance at 0.05 alpha levels.

Results

The data of 48 ET patients are summarized in Table 1. There were 22 males and 26 females with the median age of 56 years (range, 28–81) at the time of diagnosis. The median WBC was 10110/mm^3 (3580-32520), hb was 13.6 g/dl (7.6-16.9), plt was 844500/mm^3 (484000-2637000), and LDH was 212 U/L (131-642). The median disease age was 22 months (5-105). Nine (18.8%) patients had splenomegaly. There were 26 (54.2%) patients who had JAK-2 mutation.

Table 1: Patient characteristics

Characteristic	n = 48
Gender, n, (%)	
Female	26 (54.2)
Male	22 (45.8)
Age, years, median, (range)	56 (28-81)
WBC, /10^3/mm^3, median (range)	10110 (3580-32520)
Hgb, /g/dl, median (range)	13.6 (7.6-16.9)
Plt, /10^3/mm^3, median (range)	844500 (484000-2637000)
PCT, %, median (range)	0.69 (0.42-2.26)
MPV, fL, median (range)	8.8 (6.6-11.5)
LDH, U/L, median (range)	212 (131-642)
Disease age, months, median (range)	22 (5-105)
Splenomegaly, n, (%)	
Present	9 (18.8)
Absent	39 (81.2)
JAK-2 mutation, n, (%)	
Present	26 (54.2)
Absent	22 (45.8)
Reticulin fiber, n, (%)	
Present	35 (73)
Absent	13 (27)

WBC: white blood cell count, Hgb: hemoglobin, Plt: platelet, PCT: Platecrit, MPV: mean platelet volume, LDH: lactate dehydrogenase

The BMF group included 35 (73%) patients while the non-BMF group included 13 (27%) patients. The median MPV was 8.8 fL (6.6-11.5) and median PCT was 0.69% (0.42-2.26), which was considered as the cut-off values for these parameters. There was no significant difference between the groups in patients with MPV ≤8.8 fL and MPV >8.8 fL (p=0.104) and also in patients with PCT ≤0.69% and PCT >0.69% (p=0.616) (Table 2).

Table 2: The association of the reticulin fiber with MPV and PCT

	BMF	Non-BMF	p
Gender, n, (%)			
Female	8 (61%)	18 (51%)	0.746
Male	5 (39%)	17 (49%)	
Age, years, median, (range)	57 (40-81)	55 (28-80)	0.076
MPV			
≤ 8.8	4 (31%)	20 (57%)	0.104
> 8.8	9 (69%)	15 (43%)	
PCT			
≤ 0.69	7 (54%)	16 (46%)	0.616
> 0.69	6 (46%)	19 (54%)	
WBC, /10^3/mm^3, median (range)	11010 (8710-27780)	9470 (3580-32520)	0.214
Hgb, /g/dl, median (range)	13.6 (9.8-16.6)	13.6 (7.6-16.9)	0.141
Plt, /10^3/mm^3, median (range)	731000 (506000-2172000)	879000 (484000-2637000)	0.171
LDH, U/L, median (range)	203 (131-320)	218 (162-642)	0.113
Splenomegaly, n, (%)			
Present	1 (8%)	8 (23%)	0.418
Absent	12 (92%)	27 (77%)	
JAK-2 mutation, n, (%)			
Present	7 (54%)	19 (54%)	1.000
Absent	6 (46%)	16 (46%)	

MPV: mean platelet volume, PCT: Platecrit, Hgb: hemoglobin, LDH: lactate dehydrogenase, lym: lymphocyte, MPV: mean platelet volume, neu: neutrophil, plt: platelet, WBC: white blood cell count, BMF: bone marrow fibrosis

Discussion

Fibrotic transformation is a rare complication of ET, but it can lead to considerable morbidity and mortality in ET patients [3,14]. The diagnosis of fibrotic transformation requires the demonstration of bone marrow fibrosis ≥ grade 2 [15], which require performing a bone marrow biopsy, a procedure with a substantial discomfort. Although various risk factors such as anemia and advanced age were defined for the occurrence of fibrotic transformation in ET patients [16], a predictor, which notifies about the bone marrow fibrosis, has not yet been described. Accordingly, in the current study we evaluated the predictive role of MPV and PCT on BMF in ET patients, and did not find an association of BMF with MPV and PCT.

Mean platelet volume, a readily available parameter from CBC, provides significant clues about the megakaryocytic activity and platelet activation [8,17]. Mean platelet volume has been found to be increased in a number of diseases like heart disease [6,18-20], type 2 diabetes mellitus [21], nonalcoholic fatty liver disease [22], pancreatitis [23] and malignancies [24]. More importantly, higher MPV values were demonstrated to be associated with higher mortality in coronary artery disease [6,18,20], and increased risk of stroke in atrial fibrillation patients [19]. Another remarkable finding regarding the role of MPV is its decline with treatment in malignancies, which allows it to be a valuable parameter in the follow-up of malignancy patients [24]. Similar to MPV, PCT was also evaluated in heart diseases and shown to be an indicator of no-reflow [25] and adverse outcomes [26] in patients with myocardial infarction.

The role of both MPV and PCT has not been yet investigated comprehensively in hematological diseases. In a study including patients with the diagnosis of either immune thrombocytopenia (ITP) or acute myeloid leukemia (AML), MPV values were found to be higher in ITP patients compared to the AML patients and healthy subjects. Thus, MPV denotes the status of thrombopoiesis in the bone marrow, and higher MPV values are associated with increased bone marrow activity [27]. Mean platelet value was also increased in patients with heterozygous beta thalassemia, who had mild ineffective hematopoiesis and hemolysis [28]. Similar to the previous studies, MPV was increased in patients with the diagnosis of ET compared to the patients with reactive thrombocytosis [11] and healthy individuals [10,11]. Also MPV was higher in ET patients with a history of thrombosis [29]. Different from these issues, we evaluated the role of MPV together with PCT in estimating the BMF in ET patients; however, we were not able to demonstrate such an association.

The retrospective nature of the study, relatively low number of patients and also lack of a control group including patients with the diagnosis of myelofibrosis might have concealed the genuine association of BMF with MPV and PCT in ET patients, leading to limitation in this study. However, this is the first study investigating the role of both MPV and PCT in predicting BMF in ET patients.

Conclusion

Although MPV has been demonstrated to be high and a sign of hypercoagulability in ET, it seems that there is no association between BMF and MPV and PCT in ET. Further studies with larger sample sizes are warranted to verify this observation.

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