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Standard blood parameters in anemic patients with cancer and with other diseases.

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Abstract

Introduction: In this study, we aimed to retrospectively investigate the relationship of the clinical and hematological parameters with malignancies in patients with anemia.
Patients and methods: Between January 2012 and February 2014, 54385 patients admitted to our emergency clinic. Of this population 1047 had anemia and were eligible for inclusion criterion to the study. Hematologic parameters of patients counted in an analyzer device (CELL-DYN 3700, Abbott Diagnostics, Abbott Park, IL, USA).
Results: According to the final diagnoses made in the admission clinics, the patients were grouped into malign and benign. One hundred and sixty-six (15.8%) patients were grouped as malign and 881 (84.2%) as benign. Malign group was older and had a greater male percentage than benign group. MPV and sedimentation rate were significantly higher in the malign group. Hemoglobin, hemotocrit, erythrocyte and platelet count were significantly lower in the malign group. In logistic regression analysis the independent predictors of malignancies were MPV (odds ratio (OR)=1.206; 95% confidence interval (CI)=1.050-1.386; p=0.008), age (OR=1.028; 95% CI=1.018-1.037; p<0.001), male gender (OR=1.835; 95% CI=1.197-2.814; p=0.005), and hemotocrit (OR=0.837; 95% CI=0.712-0.962; p=0.004).
Conclusion: Our study showed that age, male sex, hematocrit, and MPV were the on the population level statistically significant independent predictors of malignancies in patients diagnosed with anemia in emergency department.

Keywords: Anemia, Mean platelet volume (MPV), Platelet, Malignancy.

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Introduction

Anemia is a condition that hemoglobin (Hb) concentration is below than normal limits according to a subject's age and sex. The etiological factors of anemia include deficiencies of some minerals and vitamins, acute and chronic hemorrhages, chronic diseases, and various hematological and oncological conditions.

Many authors see Mean Platelet Volume (MPV) as a parameter of Platelet (PLT) activation and it is routinely measured in complete blood count analysis [1]. Platelets in addition to their role in coagulation cascade play an important role in tumor angiogenesis owing to their content of various proangiogenic and antiangiogenic molecules. Large platelets are metabolically and enzymatically more active than smaller ones [2,3].

Previous studies have shown a relationship among increased platelet count and renal, gastric, pancreatic, and colonic malignancies [4-7]. Additionally, it has been shown that MPV increases in pathologies of various systems, including chronic obstructive lung disease, venous thromboembolism, and chronic liver disease [8-10].

Although previous studies have shown that MPV and other hematological parameters are associated with some benign and malign disorders, in these studies patients having anemia was not separately evaluated and patients were not compared according to benign and malign conditions [11-13]. To our knowledge, there is no study comparing MPV in benign and malign conditions and also there is no study comparing MPV in patients with anemia. The aim of this study was to investigate the relationship of the clinical and hematological parameters, especially MPV, with malignancies in patients having anemia.

Patients and Methods

Totally 1784 patients were retrospectively identified out of 54385 patients who attended Dicle University Faculty of Medicine Emergency Department with any complaint between January 2012 and February 2014 as having anemia (Hb<12 g/dL for women and Hb<13 g/dL for men). Patients with anemia due to a primary oncologic and hematologic disease (such as acute and chronic leukemia, multiple myeloma, aplastic anemia, immune thrombocytopenia purpura,

megaloblastic anemia, myelodysplastic syndrome, thrombotic thrombocytopenic purpura), having thrombocytopenia, age below 17 y, trauma-induced anemia, upper and lower massive gastrointestinal bleeding, pregnancy, and missing medical records were excluded. Among 1784 patients with anemia, 1047 patients meet the inclusion criteria. The medical information of the study subjects were obtained from computer based data of the hospital medical automation system.

According to the final diagnoses, those are made in the admission clinics, the patients were grouped into two groups; one with anemic cancer patients (malign) and the other one anemic patient with some other disease (benign). Malign group patients were newly diagnosed and at the time of admission to hospital their diagnoses were not known by physicians of our emergency department.

Chronic disorders (inflammatory diseases, heart failure, chronic obstructive lung disease, rheumatoid arthritis etc.), benign gastrointestinal and genitourinary pathologies, and chronic renal disease were included in the benign group. But it was not examined whether patients in the benign group had previously received treatment for their diseases.

Age, sex, sedimentation rate, and hematological parameters including Hb, Hematocrit (Hct), Red Blood Cell (RBC) count, Mean Corpuscular Volume (MCV), Red blood cell Distribution Width (RDW), MPV, Platelet Distribution Width (PDW), White Blood cell Count (WBC), Platelet Count (PC), and Neutrophil/Lymphocyte Ratio (NLR) were recorded. Blood samples were taken into 1.8 cc EDTA-K containing standard hemogram tubes and studied only in same analyzer device (CELL-DYN 3700, Abbott Diagnostics, Abbott Park, IL, USA) within 30-60 min. The first results getting from patients in emergency department were included to the study. In addition, duration of hospital stay, erythrocyte transfusions and diagnosis made at the admission clinics were also investigated.

Statistical analyses were performed using SPSS for Windows 18.0 (SPSS Inc., Chicago, IL, USA). Data were tested for normally distributed using the Kolmogorov-Smirnov test. Continuous variables were shown as mean ± standard deviation or median Interquartile Ranges (IQR) as applicable. Continuous variables were compared with the Student's t-test, and the nominal variables with Chi-Square test. A logistic regression analysis was performed to evaluate the independent predictors of non-hematological malignancies. A p value below 0.05 was considered statistically significant.

Results

Our study included 1047 patients. One hundred and sixty-six (15.8%) patients were grouped as malign and 881 (84.2%) as benign. Malign group patients significantly have older age (63 (17-93) *vs.* 45 (17-92) y, p<0.001), and less female sex percentage (n=67 (40.3%) *vs.* n=398 (45.2%), p=0.003). Also, malign group patients significantly have higher chronic renal disease percentage 15.2% *vs.* 11.6%, p=0.002. The clinical demographics of both groups are presented in Table 1.

Table 1. *Clinical demographics of the study population.*

	Malignant n=166	Benign n=881	p value
Age (y, median (range))	63 (17-93)	45 (17-92)	<0.001
Duration of hospital stay (d)	23.1 ± 10.2	17.4 ± 13.6	0.56
Female gender	67 (40.3%)	398 (45.2%)	0.003
Erythrocyte transfusions, n (%)	86 (52.1%)	448 (50.9%)	0.8
Chronic renal disease, n (%)	25 (15.2%)	102 (11.6%)	0.002

In the malign group more than half of malignancies originate from 5 main organs that included, in descending order, stomach (15.9%), breast (13.4%), colon (12.6%), lung (10.9%), and liver (6.7%). The most common three symptoms at admission in the malign group were malaise-appetite-loss, weight loss (60.5%), nausea-vomiting (34.4%), and abdominal pain (32%). In the benign group, on the other hand, nausea-vomiting (29.5%), malaise-appetite loss-weight loss (27.3%), and impaired oral intake (15.1%) were the most common three symptoms.

The comparison of both groups in terms of hematological parameters revealed that the malign group had significantly lower Hb, Hct, and RBC count and PC compared to the benign group. Patients having malignancy had higher sedimentation rate (hour) than having benign diseases which were 67.2 ± 24.1 and 58.6 ± 14.9, respectively, p=0.001. MPV was also significantly high in the malign group (9.5 ± 1.8 fl *vs.* 7.8 ± 1.4 fl, p=0.01). Both groups were similar in terms of other hematological parameters including MCV, RDW, PDW, WBC, and NLR. The statistical comparisons of both groups with respect to mean hematological parameters are shown in Table 2.

Table 2. *Comparison of malign and benign study groups with respect to hematological parameters.*

Parameters	Reference range	Malign n=166	Benign n=881	p value
Hb (g/L)	(12.2-18.1)	8.4 ± 2.1	9.2 ± 1.8	<0.001
Hct (%)	(37.7-53.7)	25.3 ± 7.0	27.2 ± 6.6	0.005
WBC (109/L)	(4.6-10.2)	12.2 ± 7.8	12.6 ± 6.3	0.43
PLT (109/L)	(142-424)	255.2 ± 128.4	288.1 ± 179.7	0.04
MCV (fl)	(80-97)	79.1 ± 11.1	80.1 ± 9.3	0.28
RDW (%)	(11.6-16.8)	17.3 ± 3.5	16.8 ± 9.2	0.56
MPV (fl)	(7.2-11.5)	9.5 ± 1.8	7.8 ± 1.4	0.01
PDW	(9.6-15.2)	18.0 ± 1.6	17.9 ± 1.5	0.63
NLR	(0.4-15.0)	7.9 ± 8.0	7.4 ± 9.9	0.61
RBC × 10^{12}/L	(4.04-6.13)	3.1 ± 1.1	3.5 ± 0.8	<0.001

Sedimentation rate/h	(0-20)	67.2 ± 24.1	58.6 ± 14.9	0.001

Hb: Hemoglobin; Hct: Hematocrit; MCV: Mean Corpuscular Volume; MPV: Mean Platelet Volume; NLR: Neutrophil/Lymphocyte Ratio; PDW: Platelet Distribution Width; PLT: Platelet; RBC: Red Blood Cell; RDW: Red blood cell Distribution Width; WBC: White Blood Cell.

Independent predictors of malign patients in logistic regression analysis were MPV (odds ratio (OR)=2.506; 95% confidence interval (CI)=2.322-2.689; p=0.008), age (OR=1.028; 95% CI=1.018-1.037; p<0.001), male gender (OR=1.835; 95% CI=1.197-2.814; p=0.005), and degree of anemia (Hct) (OR=0.837; 95% CI=0.712-0.962; p=0.004) (Table 3).

Table 3. *Logistic regression analysis for independent predictors of any malignancy in patients with anemia.*

	Odds ratio	95% CI	p value
Age	1.028	1.018-1.037	<0.001
Male Gender	1.835	1.197-2.814	0.005
Mean Platelet Volume	2.506	2.322-2.689	0.008
Hematocrit	0.837	0.712-0.962	0.004
Platelet count	0.968	0.934-1.002	0.055
Neutrophil-lymphocyte ratio	1.008	0.986-1.029	0.652
Sedimentation rate	0.998	0.882-1.114	0.08

Discussion

Anemia is a common finding in the course of malign diseases. Although our study was performed in an anemic overall population, malign group had a more profound anemia compared to the benign group. This suggests that the pathophysiology of anemia may be different in malign disorders than benign disorders. Anemia of malignancy is characterized by the production of certain cytokines such as interleukin, interferon gamma, and tumor necrosis factor alpha that leads to hemolysis, suppression of erythropoiesis, and inhibition of the response of erythroid progenitor cells to erythropoietin [14]. Anemia might also be resulted from bone marrow reactivity leading to the release of immature PLT which were hemostatically more active product of bone marrow. MPV is a parameter generated by full blood count analyzers as part of the routine Complete Blood Count (CBC) test cycle and it is usually overlooked by clinicians15. MPV correlates with the platelet function and activity [15,16]. Increased MPV has been also found to be associated with thrombotic conditions including acute coronary syndromes and deep vein thrombosis [17-19]. Recently, the relationship between MPV and malign disorders has been intensively investigated as a diagnostic parameter, which were malignancies of endometrium, liver, colon, stomach, and pancreas [11-13,20,21].

In our study, the mean MPV of both groups was within normal limits. Whereas the difference between MPV mean of both groups was statistically higher in the malignant group. Malign group patients had more age and more age is associated with more MPV. Verdoia et al. showed that MPV increase in elderly patients [22]. However in logistic regression analysis, we have found that MPV is an independent risk factor in determining malignancy. Therefore, age cannot be a confounding factor and we can state that increased MPV, independently from age, was a predictor of malign diseases in patients with anemia. It also determined that age, male sex, and Htc were the other independent predictors of malignancy. Our study showed that increased MPV were more associated with malignant than benign diseases.

Platelets may induce thrombophilic situations in patients having malignancy and they also play a role in metabolic functions of cancer cells *via* their angiogenic, metastatic, and proteolytic enzymes [23]. Vascular Endothelial Growth Factor (VEGF) and interleukins secreted by tumor cells. Therefore, malignant cells induce the production of cytokines by platelets, including interleukin-1 and other growth factors which promote metastasis and worsen prognosis [24]. Although PDW were similar in our patient groups, MPV and age were high in patients having malignancy. These results point that there is no significant association between PDW and MPV in patients having malignancy. Our study found also a lower mean PC in the malign group than the benign group and MPV was higher in the malign group. There is a negative correlation between MPV and PC due to compensation of the human organism to preserve total platelet mass [25]. Accordingly, platelet mass is the product of PC and MPV. As a result, a decrease in PC is compensated by an increase in MPV. Our study also detected a correlation between PC and MPV that was consistent with the above hypothesis [3,26-28]. However, PC was not found as an independent discriminative predictor in the logistic regression analysis. As a result, we can speculate that MPV is a more discriminative factor than PC.

Cancer patients had also a significantly higher rate of chronic kidney disease. MPV has been recently proposed as a prognostic biomarker of chronic kidney disease [29]. Therefore, theoretically more chronic renal disease in malign group patients might contribute the increase in MPV. However, in logistic regression analysis MPV was an independent significant factor. Because of logistic regression analysis results, we can state that MPV increase in malign group patients is independent from chronic renal failure.

Neutrophil-Lymphocyte Ratio (NLR) has also been investigated as an inflammation marker in several disorders including cardiovascular diseases and malignancies [30-32]. In our study NLR was similar in both groups. Furthermore, many disorders in the benign group, in which inflammatory processes are quite active, lead to similar elevation in NLR.

The limitations of our study were its retrospective and single-center design. Additionally we did not evaluate the stages of cancer patients in our study. Additionally, MPV measurement may yield slightly different results according to the type of automated analyzer used. However, we should consider that EDTA may induce changes in platelets over time and result in higher MPV [33]. This effect seems to be unpredictable and should be controlled by standardizing analysis. Therefore to

abolish this effect we used same analyzer device and determined MPV in patients within 30-60 min [34,35].

Conclusion

According to the results of the present study, age, male sex, hematocrit, and MPV were independent predictors of malignancies in patients presenting with anemia.

Conflict of Interest

There is no financial or potential conflict of interest.

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