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Platelet Indices as a Predict Markers of Thrombocytopenia Associated with Acute Lymphoblastic Leukemia and Acute Myeloid Leukemia

Rafie S. Al Khafaji[1], Intisar R. Sharba[2], Asma'a H. Mohamed[3]
[1,2] Department of Biology, Faculty of science, University of Kufa, Iraq,
[3] Department of Radiology techniques, Al-Mustaqbal University College/ Iraq
Corresponding author: Rafie S. Alkhafaji
Email: rafie.alkhafaji@uokufa.edu.iq
intisar.sharba@uokufa.edu.iq
Asmaa_Hassan@mustaqbal-college.edu.iq

Abstract

Thrombocytopenia is a condition characterized by abnormal decrease of platelet count in the blood; leukemia is one of its causes. This study dealt with platelet indicators that are not commonly used in pathological fields. In addition to the platelet count (PLT), the indicators included: mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), and platelet large cell ratio (P-LCR). This study verified the importance of the indicators by estimating ineffective platelet production in patients with Acute lymphoblastic leukemia (ALL) and Acute myeloid leukemia (AML). The study included 28 patients with acute leukemia, they were 11 with ALL (age: 25.64±14.76 years old) and 17 with AML (age: 31.59 ±13.49 years old), in addition 15 normal individuals as control. The blood samples were collected from them. The patients were significantly ($p<0.0001$) decreased in WBC, RBC, Hb, MPV, PLT, PCT, while significantly higher ($p<0.05$) in P-LCR, and PDW as compared with the control. Also, these parameters a higher significant when compared between ALL and AML patients, except WBC, PLCR, and PDW showed no significant differences between these patients. ROC test showed that MPV and PLC have higher area under curve (0.763, sensitivity=0.65, specificity=0.36 ($p<0.005$), and 0.940, sensitivity=0.82, specificity=0.18 ($p<0.0001$) respectively, for discriminating the leukemia and control. A negative ($p <0.001$) correlation among platelet counts with MPV (r= -0.670), PLC (r= -0.666), PLCR (r= -0.701), and PDW (r= -0.705), also a positive correlation between them of platelet indices in leukemia patients.

Conclusion: MPV and PLC, a potential marker more than P-LCR and PDW help in predicting leukemia patients as severing thrombocytopenia.

Keywords: Thrombocytopenia**,** Platelet Indices**,** Acute Leukemia, ALL, AML.

Introduction

In the medicine, Thrombocytopenia is one of the common hematologic disease causes, and it may be life-threatening. Multiple conditions can lead to thrombocytopenia. The four mechanisms can be divided into: reducing platelet output (hypoproductive thrombocytopenia) is accompanied with a number of bone marrow disorders increasing consumption/destruction (hyperdestructive) platelet production; and irregular platelet distribution and dilutional loss (Di Paola et al., 2002). Platelets have a vital role in the initiation of blood clotting (clot formation) by adhesion to injured blood vessels in addition to provide coagulation factors activation by their membranal phospholipids (Sekhon et al., 2006). In humans, the normal platelets count (150– 400 x 109/L) is upper than the required level to avert bleeding which is less than 50 x 10^9/L, and as long as PLT are higher than 20 x 10^9/L, the mild clinical signs and usually excludes to simple bruises. Lower than 10 x 10^9/L, rapidly increase the risk of

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spontaneous mucocutaneous bleeding and menacing of life, gastrointestinal bleeding or spontaneous intracranial hemorrhage (Greenberg and Kaled, 2013). Common and potentially deadly consequences of acute myeloid leukemia are bleedings. Transfusion of preventive platelet is treatment standard for low platelet count patients to avoid bleeding (Franchini et al., 2013). The count of platelets has been the major cause of platelet transfusions for decades. Yet, platelet count isn't always a good indicator of bleeding risk, and bleeding can happen even with a high platelet count and despite platelet transfusions (Blajchman, 2008; Slichter et al., 2010). The platelet indicators like MPV , PDW (measured of width at 20 % of a platelet histogram) and P-LCR ,percentage of platelets size with upper than 12 fl, are often ready as portion of blood disease consequences of a lot of an automated analyzers (Wiwanitkit, 2004; Negash et al., 2016). Platelet activation causes changes in platelet shape, as well as an increase in platelet swelling and MPV (Boos & Lip, 2006; Boos & Lip, 2007). These platelet indices and platelet disorders have been the subject of several studies (Just Vinholt et al., 2019; Jeon et al., 2020). High MPV and PDW have been reported in idiopathic thrombocytopenic purpura patients. Nevertheless, PDW is a more accurate sign for distinguishing between hyperdestructive and hypoproductive thrombocytopenia. Furthermore, MPV has been shown to be a credible indicator of platelet function in concentration of stored platelets, with higher MPV indicating product decadence (Xu et al., 2013; Khan & Ullah, 2020). Only a few studies have looked into platelet activation's ability to predict a thrombocytopenia and bleeding phenotype in ALL and AML patients, and the current findings are contradictory. The patients with AML and thrombocytopenia have lower platelet activity, which raises the likelihood of bleeding. So, the purpose was to estimate the predictive value of platelet indices for thrombocytopenia future bleeding incidents in patients with ALL and AML.

Materials and Methods

This cross-sectional study has been conducted in Al-Najaf City's Tumor Center, from first January 2021 to March 2021. Ethical approval was obtained from the Ethical Committee of the Faculty of Science, Kufa University, after ensuring that the patients' data is anonymized and that the patients' demographics are strictly confidential. About Twenty-eight leukemia patients (because they limitation) divided into 11 had a diagnosis with ALL (mean age: 25.64±14.76, range: 12–49 years old) and 17 with AML (mean age: 31.59 ±13.49, range: 8–50 years old), were based on bone marrow examination (had been performed) were enrolled in the current study. Patients were selected on age > 12 years, who not having received antiplatelet drugs or platelet transfusions during the prior five days. On the day of the report, no cytotoxic chemotherapy was received by the patients. In this study, a case has been excluded which where platelet indicators were not present on the complete blood count clip and diagnosis could not be made on biopsy of the bone marrow. Blood was drawn from patients by antecubital venipuncture into 5 mL and collecting in tube with EDTA anti-coagulated. CBC analyses were measured according on the manufacturer’s protocol of a fully automatic Hematology analyzer (Sysmex, Xn-350; Germany) following the blood draw in

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less than 6 h. from collection, obtained RBC, WBC, Hb, PLT, PTC, MPV, RDW, and P-LCR values.

Statistical Analysis: All data were designed by SPSS software (V.25 Inc., Chicago, USA) and Microsoft Excel 2019. Kolmogorov-Smirnov test for variables distribution. The non-parametric Mann-Whitney U test was used to compare qualitative and quantitative values, data expressed as median with inter-quartile range (IQR), Nominal variables were presented as frequency and percentage (%) were compared between studied groups using the Chi-square test. Correlation coefficient analysis was completed with Pearson's or Spearman rank. The receiver operating characteristic curve (ROC) analytical curve has been used to estimate the diagnostic efficiency independent indicator of bleeding in thrombocytopenia groups of patients by assay the ratio of area under the curve (AUC). Significance of differences was detected at $p<0.05$.

Results

The result of the current study which were included leukemia patients (n=28, male 18 (64.3%), and female 10 (35.7%) were significantly ($p<0.0001$) decreased in WBC, RBC, Hb, MPV, PLT, PCT, while significantly higher ($p<0.05$) in P-LCR, and PDW as compared with the healthy controls (n=15). Also, these parameters a higher significant when compared between ALL and AML patients, except WBC, PLCR, and PDW showed no significant differences between these patients, **[Table-1]**. Receiver operative curve of sensitivity and specificity showed that MPV and PLC have higher area under curve (0.763, sensitivity=0.65, specificity=0.36, p=0.005, and 0.940, sensitivity=0.82, specificity=0.18, p=0.0001) respectively **[Figure-1 A and B]**, pointing a better predictive ability, specificity and sensitivity in distinguishing the leukemia and healthy control groups **[Table -2]**. A negative correlation ($p<0.001$) between platelet counts with MPV (r= -0.670), PLC (r= -0.666), PLCR (r= -0.701), and PDW (r= -0.705), also a positive correlation between them of platelet indices in leukemia patients **[Table-3].**

[Table-1] Demographic characteristic and clinical parameters in the patients with acute leukemia (ALL and AML).

Variables	**Healthy controls n=15**	**Patients n=28**	**p-value**	**ALL n= 11**	**AML n=17**	**p-value ALL vs. AML**
Age (year) **Male n (/%)** **Female n (/%)**	39.13±10.89 8 (53.3%) 7 (46.7%)	29.25±14.05 18 (64.3%) 10 (35.7%)	0.023 *	25.64±14.76 8 (72.7%) 3 (27.3%)	31.59 ±13.49 10 (58.8 %) 7 (41.2 %)	0.115 ns
WBC ($x10^3$/ml) [A]	7.8 (7.0-8.3)	4.9 (1.8 - 20.8)	0.034 *	5.4 (3.4 - 81.6)	4.3 (0.8 -19.7)	0.589 ns
RBC ($x10^6$/ml)	4.45±0.53	3.33±0.78	0.0001 ***	3.78±0.76	3.04±0.67	0.009 **
Hb (g/dl)	12.95±1.28	9.56±2.15	0.0001 ***	10.94±1.75	8.66±1.93	0.006 **
MPV (fl)	10.63±0.88	9.30±1.51	0.001 ***	9.48±1.62	9.18±1.48	0.006 **
RDW %	12.64±0.59	14.82±2.87	0.001 **	15.73±2.56	14.24±2.99	0.086
PLT ($x10^3$/ml) [A]	200 (189-250)	43.5 (26.3 - 81.8)	0.0001 ***	91 (32 -127)	41 (18.5 - 50.5)	0.007 **

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PCT % [A]	0.23 (0.2 - 0.25)	0.05 (0.03-0.1)	0.0001 ***	0.12(0.07 - 0.21)	0.04(0.0 3 - 0.06)	0.007 **
P-LCR % [A]	24 (20- 28)	23.8 (17.9-36.8	0.012 *	23.3 (16 - 37)	24.2 (18 - 39)	0.556 ns
PDW % [A]	12.35±1.82	13.91±3.89	0.03 *	13.20±4.07	13.88±3.88	0.655 ns
mean ±SD, A median (IQR). *, **, *** p-value <0.05, <0.01, and <0.001 respectively.						

[Table -2] Specificity and Sensitivity of the platelet indices for diagnosis of thrombocytopenia in leukemia patients at different cut off points from ROC curve coordinate.

	MPV (fl)	**PCT %**	**PLCR %**	**PDW %**
AUC	0.763	0.940	0.605	0.554
SE	0.072	0.038	0.086	0.089
95% CI	0.623 to 0.904	0.885 to 1.000	0.437 to 0.773	0.380 to 0.727
p-value	0.005	0.0001	0.262	0.566
Cut off point	9.20	0.065	27.100	14.350
Sensitivity	0.65	0.82	0.393	0.286
1 - Specificity	0.36	0.18	0.000	0.000
Youden index	0.28	0.64	0.393	0.286

[Table -3]: Relationship between Platelet count and platelet indicators in patients with acute leukemia (ALL and AML).

		PLT	MPV (fl)	PCT (fl)	P-LCR %	PDW %
MPV (fl)	R	-0.670**	1			
	p-value	0.0001				
PCT (fl)	R	-0.666**	0.650**	1		
	p-value	0.0001	0.0001			
P-LCR %	R	-0.701**	0.662**	0.651**	1	
	p-value	0.0001	0.0001	0.0001		
PDW %	R	-0.705**	0.676**	0.678**	0.801**	1
	p-value	0.0001	0.0001	0.0001	0.0001	

*. Significant correlation at 0.05 levels (2-tailed).
**. Significant correlation at 0.01 levels (2-tailed).

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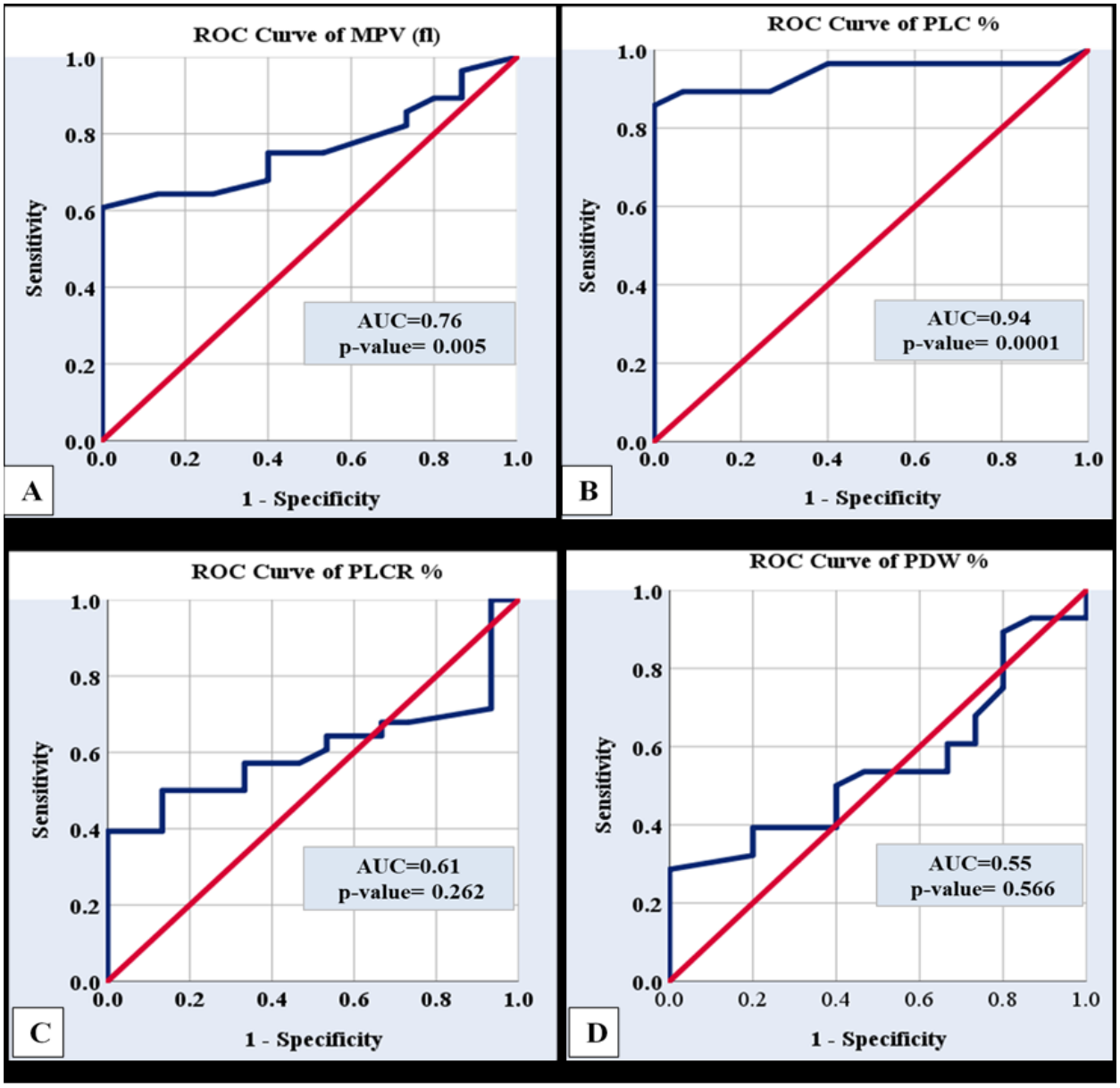

[Fig-1]: ROC curve coordinate of platelet indices of thrombocytopenia diagnostics in leukemia patients. "at different cut off points"

Discussion

Leukemia is a hematological disease that affects people all over the world. Leukemia is caused by mutations, ionizing radiation, exposure to contaminants, and infections (Bailey et al., 2014, Khan, 2016). In patients suspected of having leukemia, the first examination is a complete blood count (CBC), and the CBC findings are so distinctive that a successful doctor will confidently limit his differential diagnosis to a particular form of leukemia (Moussavi et al., 2014).

Early detection leads to prompt care, which reduces morbidity and mortality. The results in the current study showed a significant decreased in WBC, RBC, Hb, and PLT in ALL and AML patients when compared with controls, and a significant difference between two groups of patients, these finding conformed with study of (Munir & Khan, 2019) who reported that

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basic hematological parameters in cases of ALL were as raised total leukocytes count, low Hb and low PLT (in 52%, 82% and 88% cases of ALL. The CBC reflects the changes in the bone marrow caused by leukemic Cells (Jaime-Pérez et al., 2019).

In the bone marrow, leukemic cells proliferate uncontrollably, displacing standard hematopoietic cells (Preethi, 2014; Naeem et al., 2017). The malignant cells replace the marrow, resulting in decreased erythropoiesis, which manifests as anemia or low Hb on a CBC (Munir & Khan, 2019, Jaime-Pérez et al., 2019).

Anemia is a common finding in almost all leukemias, including ALL and AML, and it has prognostic significance (Naeem et al., 2017; Amer et al., 2017). Thrombocytopenia, or a low platelet count, may occur as a result of blast cells replacing bone marrow or splenomegaly, it can be found in almost all types of leukemia, as a result, CBC results in leukemias correspond to the disease's underlying pathogenetic process [Munir & Khan, 2019; Amer et al., 2017).

The development of methods and tools to accurately estimate the number of platelets in many diseases has aroused a lot of interest among specialists and researchers (Negash et al., 2016). In this study, four platelet indicators: MPV, PCT, PDW and P-LCR were analyzed for their predictive capability in diagnostics of patients with leukemia, in agreement with some above studies (Bowles et al., 2005; Ntaios et al., 2008), there were a significant decreased in MPV, PLT, PCT, in ALL and AML patients as compared with the control.

Moreover, P-LCR, and PDW had significant increase between the studied groups and better discriminated potentials. Platelets are essential in normal hemostasis, thrombosis, and a variety of bleeding disorders (Mali et al., 2021). As a result, changes in platelet quantity (thrombocytopenia) are associated with a high level of morbidity. Thrombocytopenia may be caused by either peripheral damage (destructive thrombocytopenia) or insufficient development (hypoproliferative thrombocytopenia) (Khan & Ullah, 2020). Platelet indices, which include MPV, PDW, and PLCR, are tests taken on peripheral blood platelets. MPV means a platelet volume measurement that represents changes in the platelet stimulation or the synthesis rate of platelets. MPV result from dividing the plateletcrit (PCT) by the number of PLT (PCT= ratio of platelet volume to whole blood volume). PDW is a heterogeneity indicator of platelet. The platelet volume is called heterogeneous because platelets are aged or because the megakaryocytes are heterogeneously demarcated.

The large cell platelet ratio is the greater platelet measurement (12 fl in size). The platelet volume indicators differ according to the platelet count is well-known (Just Vinholt et al., 2019). In general, few papers indicated that MPV was elevated in thrombocytopenia patients; in addition to that the platelet size of thrombocytopenic patients is greater than average platelet size, as well as elevated PLCR levels (Babu & Basu, 2004). The study showed that MPV and PLC have higher sensitivity and specificity than PLCR and RDW in patients with ALL and ALM. In contrast, study of (Chandra et al., 2010), find that the MPV at a cut-off point of 8.15 fl had sensitivity 67.7% and specificity 65%, who proposed that instead of using MPV as a screening tool, bone marrow biopsy should be used. The recent study indicated that PDW proposed as a poor screening method for immune thrombocytopenia diagnosis (Tang et al., 2017). Another study, MPV and P-LCR have better specificity, sensitivity and predicative value in distinguishing the types of thrombocytopenia. An MPV of <10.75 fl can identify

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thrombocytopenic patients as hypoproductive with 70 % specificity, 74 % sensitivity, 64 % NPV and 79 % PPV. An MPV of >11.05 fl can distinguish patients with immune thrombocytopenia with 67 % sensitivity, 95 %, MPV is a good screening method for thrombocytopenia, according to this results (Negash et al., 2016). MPV and PDW had high diagnostic significance, while PLCR had low importance, according to a previous study (Norrasethada et al., 2019) proposed a specificity and sensitivity of 89 % and 77 % for MPV, respectively. This study agrees with some mentioned studies above in the platelet indicators PCT and MPV had high specificity and sensitivity for thrombocytopenia diagnosis.

Conclusion(s)

The study concluded that MPV and PLC, a potential marker more than P-LCR and PDW help in predicting a thrombocytopenia leukemia patients groups ALL and AML. The study suggested these indicators are utilized to suit with other clinical and laboratory information; these indications may be used to avoid bone marrow aspiration and biopsy in these patients.

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