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Mean Platelet Volume to Platelet Ratio as an Early Predictor of ICU Admission in Hematological Malignancies

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Abstract

Background & objective: The development of rapidly progressive complications and the high fatality rate in COVID-19 patients with hematological malignancies make it urgently needed to use readily available markers for early predicting of patients who need ICU admission. For these reasons, we aimed at identifying the usefulness of mean platelet volume to platelet ratio (MPR) and other indexes of inflammation as early predictors for the need of ICU admission in COVID-19 patients with hematological malignancies.

Methods: This study included 2 groups of hospitalized hematological malignancies patients: confirmed COVID-19 (18 patients) and COVID-19 negative (18 patients) of matched age, sex and bone marrow suppressive chemotherapy. Seven COVID-19 positive health care providers were included to determine MPR cutoff point of disease severity. MPR; Neutrophil to lymphocyte ratio; derived neutrophil to lymphocyte ratio; platelet to lymphocyte ratio; monocyte to lymphocyte ratio; neutrophil to lymphocyte x platelet ratio; systemic inflammation response index; systemic immune-inflammation index (SII) and aggregate index of systemic inflammation were calculated.

Results: Thirteen COVID-19 hematological malignancies cases were intermediate to severe and five cases were critical. Myeloid malignancies represent 55.56% of the cases. Acute leukemias constituted 72.22% (13 patients). ICU admission and deaths were more among acute leukemia. MPR was the only significantly different ratio between both hematological groups (p=0.001) and between ICU admitted and non-ICU admitted COVID-19 positive cases (p=0.010). MPR ≤ 0.0339 was an early indicator for ICU admission (sensitivity: 88.9%, specificity: 75%).

Interpretation & conclusion: MPR is the only reliable marker for the need of ICU admission in COVID-19 hematological malignancies. Mean platelet volume to platelet ratio must be calculated at COVID-19 diagnosis and at regular intervals to predict early need for ICU admission

Keywords: COVID-19; Hematological malignancies; Mean platelet volume to platelet ratio; Critical cases; Early biomarker

Introduction

COVID-19 positive cancer patients develop serious complications rapidly [1] and have higher fatality rate than the general population [2]. Patients with hematological malignancies are of concern for several reasons: a. they may have underlying immune system cancer, b. they develop chemotherapy induced bone marrow suppression with increased susceptibility to infections, c. there is similarity between their disease symptoms and COVID-19 infection symptoms [3] and, d. there is high rate of false negative SARS-CoV-2 RT-PCR in hematological malignancies either due to inability of the weakened adaptive immune system to respond to infection or the development of symptoms with smaller viral load below PCR detection limit [4].

For these reasons, it is urgently needed to use readily available markers for early assessment of COVID-19 associated inflammatory processes. CBC parameters can aid in early diagnosis of COVID-19 [5] and predicting its severity [6]. The lymphocyte count [7], the platelet count [8], red cell distribution width (RDW) [9], and neutrophil to lymphocyte ratio are all of prognostic value in COVID-19 infected patients [10]. This study aimed at evaluating the usefulness of mean platelet volume to platelet ratio (MPR) and

other blood cell index of inflammation as early predictors for the need of ICU admission in COVID-19 hospitalized hematological malignancies patients.

Patients

Study population

The hematological data of 18 hospitalized patients with confirmed COVID-19 infection hematological malignancies were compared with that of 18 comparable COVID-19 negative patients of matched age, sex and bone marrow suppressive chemotherapy. Patients' data were collected during the period from 5 September to 20 December 2020. Seven COVID-19 positive health care providers (6 mild and 1 moderate) were included to determine mean platelet volume to platelet ratio (MPR) cutoff point in relation to disease severity.

Data collection

Data were collected from the patient file system at the time of developing symptoms. COVID-19 diagnosis was based on lung CT and VIASURE SARS-CoV Real Time PCR of nasopharyngeal swab (CerTestBiotec, Spain) in all cases. Cases with clinical or radiological suspicious of COVID-19 without COVID-19 RT-PCR positive test were excluded. The disease severity was based on the National Health Committee of China clinical Classification [3].

Methods

Blood cell count inflammation parameters

Complete blood counts were measured in aseptic venous blood sample using automated counter ADVIA 2120 hematology system (Siemens Healthcare Diagnostics, USA).

Blood cell derived inflammation indexes were then calculated

Mean platelet volume to platelet ratio (MPR)= mean platelet volume/ platelet ratio; neutrophil to lymphocyte ratio (NLR) = neutrophil / lymphocyte ratio; derived neutrophil to lymphocyte ratio (dNLR)= neutrophils / (white blood cell- neutrophils); platelet to lymphocyte ratio (PLR)= platelet / lymphocyte ratio; monocyte to lymphocyte ratio (MLR)= monocyte / lymphocyte ratio); NLPR= neutrophils/(lymphocyte x platelet ratio); systemic inflammation response index (SIRI)= (neutrophils x monocytes)/ lymphocytes; systemic immune-inflammation index (SII) = (neutrophils x platelets)/lymphocytes, and aggregate index of systemic inflammation (AISI) = (neutrophils x monocytes x platelets)/lymphocytes [11].

Statistical Analysis

Data were analyzed using IBM-SPSS version 21 (SPSS, Inc., Chicago, IL, USA). The normality of data distribution was tested using single sample Kolmogorov-Smirnov test. For normally distributed data, continuous variables were expressed as mean ± SD and were compared using Student's t test. Categorical variables were expressed as number (%) and were compared using chi-square (X^2) or Fisher as appropriate. For non-normally distributed data, continuous variables were presented as median and interquartile range and compared using Mann-Whitney test. Correlation between MPR and different variables were done using Pearson's correlation. A receiver-operating characteristic curve (ROC) was generated. The area under the curve (AUC) and 95% CI were calculated. P value <0.05 was considered significant.

Results

Demographic and clinical data

Both hematological malignancies groups were age (p=0.798) and sex (p=0.738) matched. Seven patients (38.89%) were in the age group 20-30 years in both groups. Acute leukemias constituted 72.22% of COVID-19 positive cases (13 patients) (Table 1). All patients presented with acute nonspecific symptoms such as fever (38-38.5°C) and dyspnea. ICU admission (80%, 4 cases) and deaths (100%, 6 cases) were more in acute leukemia.

Table 1: Comparison of demographic and clinical data between COVID-19 positive versus negative hematological malignancies patients.

Parameter	Hematological malignancies		Test of Significance
	COVID-19 positive (n=18)	COVID-19 negative (n=18)	
Age (years)	39.11 ± 14.696	35.56±15.34	0.798
Gender (M/ F)	9 (50%) / 9 (50%)	11(61.11%)/ 7(38.89)	0.738
Comorbidity			0.261
Hypertension	2 (11.12%)	0	
Diabetes	0	1 (5.56%)	
IHD	0	1 (5.56%)	

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Diagnosis Lymphoid Myeloid	 8 (44.44%) 10 (55.56%)	 10 (55.56%) 8 (44.44%)	0.740
Diagnosis distribution NHL HD AML ALL CLL CMML	 4 (22.22%) - 10 (55.56%) 3 (16.67%) 1 (5.56%) -	 - 1(5.56%) 7 (38.88%) 6 (33.33%) 3 (16.67%) 1(5.56%)	0.129
CT findings	18 (100%)	7 (38.89%)	0.00*
ICU admission	5 (27.78%)	0	0.045*
Case death	6 (33.33%)	0	0.019*

M: Men; F: Women; IHD: Ischemic heart disease; NHL: Non-Hodgkin lymphoma; HD: Hodgkin's disease; AML: Acute myeloid leukemia; ALL: Acute lymphatic leukemia; CLL: Chronic lymphocytic leukemia; CMML: Chronic myelomonocytic leukemia; p is significant if <0.05.

Hematological profile and blood cell-derived inflammation indexes

Comparison of hematological profile and blood cell -derived inflammation indexes between COVID-19 positive versus negative patients with hematological malignancies are shown in Tables 2 & 3. MPR was the only significantly different ratio between both groups (p=0.001) (Table 3). MPR was inversely correlated with platelets (r=-0.655, p=0.021). The cut-off points for MPR value ≤ 0.0339 (AUC=0.806; p=0.034; 95%CI: 0.594 -1) was associated with ICU admission (sensitivity: 88.9%, specificity: 75%) (Figure 1).

Table 2: Comparison of hematology profile between COVID-19 positive versus negative hematological malignancies patients.

Parameter	Hematological malignancies				Test of significance
	COVID-19 positive (n=18)		COVID-19 negative (n=18)		
	Mean±SD	No. (%)	Mean±SD	No. (%)	
WBCs (x10^9 /L) **<2** **2-4** **>4**	21.399±42.119	 8 1 9	47.438±137.039	 3 5 10	0.164 0.085
Platelets (x10^9 /L) **<100** **100-150** **>150**	90.89±95.41	 10 2 6	131.5±91.5	 7 4 7	0.599 0.529
Lymphocytes (x10^9 /L) **<0.5** **0.5-1** **>1**	3.997±8.532	 6 (50%) 6 (50%) 6 (50%)	38.197±135.064	 1 (5.56%) 5 (27.78%) 12 (66.67%)	0.065 0.078
Neutrophils (x10^9 /L) **<0.5** **0.5-1** **>1**	0.41 (0.06- 34.81)	 9 (50%) 1 (5.56%) 8 (44.44%)	2.81 (0.00- 0.56)	 3 (16.67%) 2 (11.11%) 13 (72.22%)	0.064 0.055

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Monocytes (x10^9/L) **≤ 0.3** **>0.3**	0.57±1.15	9 (50%) 9 (50%)	3.82±10.38	5 (27.78%) 13 (72.22%)	0.041* 0.085
RDW (%)	17.84±4.17		18.11 ±3.25		0.405
MPV (fL)	9.27±1.22		9.92±2.035		0.113

RDW: Red cell distribution width; MPV: Mean platelet volume; p is significant if <0.05

Table 3: Comparison of blood cell-derived inflammation indexes between COVID-19 positive versus negative hematological malignancies patients.

Parameter	Hematological Malignancies		Test of significance
	COVID-19 positive (n=18)	COVID-19 negative (n= 18)	
MPR	0.98±1.57	0.27±0.59	0.001*
SII	180.82±369.69	362.58 ±599.13	0.156
PLR	86.704±114.92	116.87±165.004	0.238
dNLR	1.04±1.18	1.38±1.597	0.340
MLR	0.29±0.39	0.55± 0.61	0.333
SIRI	3.38±12.07	4.62±14.30	0.834
AISI	134.01±301.57	476.96±1311.86	0.140
NLPR	0.10±0.12	0.07±0.16	0.956
NLR	1.87±3.03	1.93±2.11	0.470
NMR	9.89±11.54	4.77±5.14	0.080

NLR: neutrophil to lymphocyte ratio; dNLR: derived neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; MPR: mean platelet volume to platelet ratio; MLR: monocyte to lymphocyte ratio; NLPR= neutrophils/(lymphocyte x platelet ratio); SIRI: systemic inflammation response index; SII: systemic immune-inflammation index; AISI: aggregate index of systemic inflammation; p is significant if <0.05

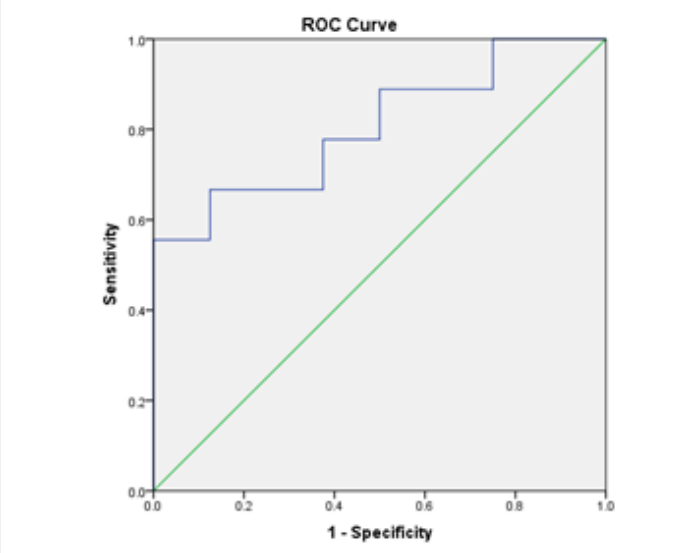

Figure 1: Receiver-operating characteristic curve showing MPR performance in predicting COVID-19 severity in COVID-19 positive patients.

Table 4 shows comparison between COVID-19 positive non-ICU admitted (13 intermediate/ severe cases, 72.22%) and ICU admitted (5 critical cases, 27.78%). Absolute lymphopenia (> 0.6 x10^9/L) was present in 3 (60%) of ICU admitted cases.

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Table 4: Comparison between ICU and non-ICU admitted COVID-19 positive hematological malignancies patients

Parameter	Non ICU admitted (n=13)	ICU admitted (n=5)	Test of significance
Age (years)	36.08±13.87	47±15.28	0.946
Sex (M/ F)	6/7	3/2	1
Hb (g/dL)	7.48±2.76	9.04±2.08	0.155
WBCs (x10^9 /L)	28.18±48.25	3.76±4.02	0.062
Neutrophils (x10^9 /L)	1.23 (0.06-34.81)	0.377 (0.21-5.70)	0.752
Lymphocytes (x10^9 /L	5.02±10.21	1.74±1.74	0.146
Monocytes (x10^9 /L)	0.69±1.38	0.2996±0.25	0.236
Platelets (x10^9 /L)	76.62±94.57	128±97.35	0.969
MPV (fL)	9.18±1.11	9.53±1.795	0.241
MPR	1.26±1.74	0.11±0.12	0.010*
SII	224.76±441.87	84.14±85.97	0.125

Hb: Hemoglobin; p is significant if <0.05.

Discussion

There is no association between COVID-19 infection and immune system cancer as more myeloid malignancies (55.56%) than lymphoid malignancies (44.44%) were COVID-19 positive in our cases. Acute leukemias comprise 72.22% of COVID-19 positive patients with the majority being AML (76.92%) perhaps due to more AML cases in this age group. COVID-19 associated hematological changes are indicators of systemic inflammatory response [12]. This inflammatory response is also common in cancer patients and is responsible for its progression [12]. This lessens the diagnostic significance of changes in some blood parameters in COVID-19 infected cancer patients. The main change in blood cell parameters in our COVID-19 positive patients are neutropenia, monocytopenia and higher MPR. Leucopenia, lymphopenia, and thrombocytopenia are present in nonmalignant COVID-19 positive cases [13] as well as in hematological malignancies due to several causes. Fifty percent of our COVID-19 cases had neutropenia (<0.5 X 10^9/L) which is mainly attributed to chemotherapy side effect and aggravated by neutrophil degranulation and lysis during severe infection [14]. Neutrophilia was present in only one patient with refractory acute monocytic leukemia. On the contrary, neutrophilia is a common finding in severe COVID-19 non-malignant cases due to immune dysregulation and superimposed bacterial infection [15].

Another important CBC parameter is RDW. Although RDW more than 14.5 at admission was associated with increase COVID-19 mortality risk from 11 to 31% in COVID-19 positive non-cancer patients [13], it is of less prognostic value in our COVID-19 positive cases. Insignificant increase in RDW was present in both hematological groups. This increase in RDW in cancer patients was explained by malnutrition, inhibition of gastrointestinal iron transport, the associated chronic inflammation [16] as well as anisocytosis resulting from decreased erythropoietin and increased cytokines and hepcidin [17].

The only significant blood cell-derived inflammation index between our groups was MPR. MPR is a combination of MPV and platelet counts. MPV was within the normal range (7.5-12 fl) [18] in both hematological groups. MPV value is variable in cancer patients being high in the majority and low in some cancers [18]. MPR was inversely correlated with the platelet counts in our COVID-19 cases. Thrombocytopenia (<100 X10^9/L) was present in 55.56% (10 cases) of our COVID-19 positive patients. Thrombocytopenia (as high as 57%) was present in non survivors COVID-19 positive non cancer patients [15]. Thrombocytopenia in our cases is explained by disease process, chemotherapy side effect, or COVID-19 complications including COVID-19 invasion of bone marrow hematopoietic cells or stromal cells [7].

Comparing ICU admitted and non-ICU admitted cases revealed presence of lymphopenia (>0.6 x10^9/L) in 60% of our ICU cases which is against its use as an early indicator of ICU admission as proposed by Fan et al in nonmalignant cases [19]. MPR was the only significantly different index between our COVID positive ICU admitted and non-ICU admitted cases. MPR value ≤ 0.0339 had sensitivity: 88.9% and specificity: 75% in early diagnosis of those in need for ICU admission.

Conclusion

Our findings indicate that MPR was the only reliable marker in COVID-19 positive cases. It must be calculated at COVID-19 diagnosis and at regular intervals to predict early need for ICU admission

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No funding was received by the authors for conducting this study.

Compliance with Ethical Standards

Conflict of Interest: the authors declare they have potential conflicts of interest, neither financial nor non-financial

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Human and animal Rights

The study was conducted using human blood samples and an approval by the Ethics Review Board of Alexandria University, Faculty of Medicine was obtained.

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