

Platelet Indices as Potential Monitoring Biomarkers in COVID-19: A New Hope

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Author's Contribution

¹ Conception of study

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Abstract

Objective: To investigate the relationship between established acute inflammatory markers in COVID-19 patients with Mean platelet volume (MPV) and Platelet large cell ratio (P-LCR).

Materials and Methods: This was a retrospective longitudinal study conducted at Fauji Foundation Hospital, Rawalpindi from 10th June to 10th August 2020. Biochemical parameters i.e. CRP, serum ferritin, LDH, and pro-BNP as well as hematological parameters (MPV and P-LCR) were noted once every week during admission of all the COVID-19 positive patients.

Data were analyzed using IBM-SPSS version 23. Repeated measure ANOVA using a generalized linear model was done to check the trend of values during the duration of their stay. Pearson Correlation analysis and regression models were estimated to check the relationship of MPV and P-LCR with C- reactive protein, serum Ferritin, LDH, and pro-BNP. P-values less than 0.05 were considered statistically significant.

Results: The mean age of the studied group was 55.47 (SD=±15.0) years with the female to male ratio being 2:1. Mean platelet volume showed a statistically significant positive correlation with the established set of inflammatory markers other than pro-BNP with a p-value of less than 0.05. P-LCR however showed a positive correlation with CRP (p-value of less than 0.05) only with no significant correlation with other biochemical markers.

Conclusion: MPV is reported on routine complete blood count report (CBC). It is readily available at even the most under-resourced health centers; therefore reporting the platelet indices does not require extra testing, sampling, or reagent cost. A statistically significant positive correlation amongst the established acute inflammatory markers and relatively understudied platelet indices (MPV) in COVID-19 provides a cost-effective, readily available, and time-efficient tool for marking disease progression.

Keywords: COVID-19, Mean Platelet Volume, Platelet large cell ratio.

Introduction

Beginning in Wuhan, China in December 2019, COVID-19 had quickly become a pandemic with a huge global impact.^{1,2} According to the report of the World Health Organization (WHO), published on 6th July 2020, 11,327,790 COVID-19 cases were confirmed worldwide, with 532,340 deaths.² In Pakistan, the first case of COVID-19 was reported from Karachi on February 26, 2020. The virus has been swiftly spreading all across the country since then leading to increase mortality and morbidity. Pakistan has most likely contracted cases through travel, by land, and air with neighboring countries.³ COVID-19 has a varied presentation, from asymptomatic carriers to symptomatic patients having fever, breathing difficulties, and pneumonia-like condition. More severe conditions with respiratory failure requiring mechanical ventilation, multi-organ failure, and DIC have also been observed.⁴

The diagnosis of COVID-19 is primarily done through RNA detection by PCR whereas serological surveillance is done through antibody testing. The role of diagnostics lab tests has extended far beyond disease detection. Many laboratory parameters are consistently being used for monitoring the disease and its severity.⁵

In COVID-19, symptomatic patients are monitored through various biochemical markers including LDH, CRP, Ferritin, interleukin-6, D-dimer, etc. at various stages of the disease process. The rising parameters indicate poor prognosis and worsening of the disease. These parameters along with the clinical behavior of the patient are the pertinent guide for the physician for further management.^{6,7,8} Other than biochemical markers, many hematological parameters exhibited on Complete blood count are considered helpful in understanding the disease process and its progression. Amongst these, lymphocyte count, platelet lymphocyte ratio, and neutrophil-lymphocyte ratio have been extensively studied.⁷ Platelet indices such as mean platelet volume (MPV) and platelet large cell ratio (P-LCR) are routinely used in clinical practice worldwide as the index of inflammation.⁸ Higher MPV and P-LCR have been found in sepsis to be a poor prognostic factor.⁹ In COVID-19 the role of these platelet indices has been under-investigated. There is a paucity of data that has assessed mean platelet volume and other platelet parameters in COVID-19. Furthermore, there is only scarce data documenting MPV and P-LCR to have an association with mortality, morbidity, or disease progression.¹⁰ No

correlation amongst the established biochemical markers like CRP, LDH, Ferritin, and platelet indices have been established.

In this study, we aimed to investigate the relationship between established acute inflammatory markers in COVID-19 and MPV, and P-LCR. Platelet and its indices are readily available, cost-effective, and time-efficient parameters for continuous monitoring even in the most under-resourced centers. The study of any correlation between routine monitoring markers, platelet indices, and disease process will help to devise a cost-efficient monitoring plan for COVID-19 affected patients globally especially in underdeveloped countries.

Materials and Methods

It is a retrospective study carried out at Fauji Foundation Hospital Rawalpindi. After informed consent from patients for using their data, the data was noted for all the patients admitted in Fauji Foundation Hospital, Rawalpindi with positive PCR for COVID-19 from 10th June till 10th August 2020. Amongst these, the patients with short hospital stays (less than one week) were not included in the study to avoid errors or bias in the data analysis. The data of all the patients with significant medical stays (more than one week) was recorded. Categorical variables like age and gender were noted. Biochemical parameters like CRP, serum ferritin, LDH, and pro-BNP as well as hematological parameters (MPV and P-LCR) were noted on the day of admission and once every week during their admission. Serum ferritin and pro-BNP were performed on Siemen's ADVIA CENTAUR XP. The assay is a fully automated two-site sandwich immunoassay using direct chemiluminescent technology. Serum LDH was performed on Beckmen coulter DxC 700AU by enzymatic method IFCC (international federation for clinical chemistry). CRP qualitative was performed by Latex agglutination slide test on Huma Tex CRP kits. MPV and P-LCR were reported on the routine CBC performed on Sysmex XN-1000 series.

Statistical Analysis: Data were stored and analyzed using IBM-SPSS version 23.0, Mean with standard deviation were reported for platelet indices and other studied parameters, Repeated measure ANOVA using the generalized linear model was done to check the trend of values during the duration of their stay. Pearson Correlation analysis was done to check the relationship of MPV and platelet large cell ratio with C-reactive protein, serum Ferritin, LDH, and pro-BNP.

Further regression models were estimated to measure the effect of studied parameters on platelet indices after adjusting with age and gender. P-values less than 0.05 were considered statistically significant. A pie chart was used to show the distribution of gender and scatter plots were also used to represent the trend of MPV with serum Ferritin and LDH.

Results

In the present study, fifty-five patients were admitted to Fauji Foundation Hospital, Rawalpindi from 10th June to 10th August 2020 with a positive PCR for COVID-19. Of these, forty patients had a hospital stay of more than one week. Fifteen patients were either discharged early in their stay or left against medical advice. The data of the forty patients with a hospital stay of more than one week was recorded, analyzed, and reported weekly.

The mean age of the studied group was 55.47 (SD=±15.0) years. There was a female preponderance with a percentage of 67.5% (n=27) whereas male patients were 32.5% (n=13). Results showed the mean serum Ferritin levels at week-I were 625.7 ng/ml (SD=±653.8), at week-II 802.6ng/ml (SD=±802.6) and

week-III 945.3 ng/ml (SD=±784.5) increasing significantly with p<0.05. (Table 1)

The correlation analysis of platelet indices with the established set of inflammatory markers other than pro-BNP done at each week of hospital stay showed statistical significance with a p-value of less than 0.05. The correlation analysis of MPV and P-LCR with Pro-BNP was statistically insignificant. (Table 2)

The outcome of regression analysis to study the effect on MPV of studied parameters among COVID patients showed that at week-I one unit increase in serum Ferritin causes 0.1 times to increase in MPV with a p-value of 0.04. At week -II among patients with positive C-reactive protein MPV increased 2.1 times on average (p<0.01), and one unit increase in LDH gives a 0.1 unit increase in MPV on average (p<0.01). Models were adjusted for age and gender. (Table 3).

Similarly, the effect on P-LCR of established parameters in COVID-19 patients showed that only at week-II CRP gives a positive association with an increase in platelet large cell ratio, (p<0.01), all other parameters also give positive effect except pro-BNP but found statistically insignificant. The models were adjusted for age and gender. (Table 4)

Table 1: Platelet Indices and other studied parameters of COVID Samples

Parameters	Week-I	Week-II	Week-III	P-value
Serum Ferritin (ng/ml)	625.7	802.6	945.3	0.01*
LDH (U/L)	512.5	623.3	714.1	0.18
Pro-BNP (pg./ml)	3794.6	4486.9	4760.8	0.06
Mean Platelet Volume	11.5	12.0	12.7	0.06
Platelet Large Cell Ratio	32.3	34.5	37.4	0.17
C-reactive Protein a	0.90	0.77	0.90	0.33

*p<0.05 was considered significant using Repeated Measure ANOVA

a: Mean proportion of positive cases was reported

Table 2: Correlation analysis of Platelet Indices with Studied Parameters

Parameters		Mean	platelet	Mean	platelet	Mean	platelet
		Platelet	large cell	Platelet	large cell	Platelet	large cell
		Volume	ratio	Volume	ratio	Volume	ratio
		week-I	week-I	week-II	week-II	week-III	week-III
c-reactive protein	r-value	0.389	0.378	0.648	0.653	0.298	0.416
	p-value	0.01*	0.01*	<0.01*	<0.01*	0.202	0.068
Serum Ferritin	r-value	0.523	0.374	0.604	0.542	0.503	0.362
	p-value	<0.01*	0.01*	<0.01*	<0.01*	0.02*	0.117
LDH	r-value	0.410	0.284	0.631	0.502	0.564	0.464
	p-value	<0.01*	0.076	<0.01*	<0.01*	0.01*	0.03*
Pro-BNP	r-value	0.252	0.220	0.334	0.381	0.316	0.249
	p-value	0.116	0.173	0.03*	0.01*	0.175	0.289

*p<0.05 was considered statistically significant for Pearson correlation

Table 3: Effect of Studied Parameters on MPV in COVID patients

Parameters	MPV week-I		MPV week-II		MPV week-III	
	$\beta \pm$ S.E	p-value	$\beta \pm$ S.E	p-value	$\beta \pm$ S.E	p-value
c-reactive protein	(1.2 \pm 0.9)	0.16	(2.1 \pm 0.6)	<0.01*	(0.2 \pm 1.5)	0.92
Serum Ferritin	(0.1 \pm 0.1)	0.04*	(0.1 \pm 0.1)	0.07	(0.1 \pm 0.1)	0.55
LDH	(0.1 \pm 0.1)	0.15	(0.1 \pm 0.1)	<0.01*	(0.1 \pm 0.1)	0.14
Pro-BNP	(-0.1 \pm 0.1)	0.46	(-0.1 \pm 0.1)	0.11	(-0.1 \pm 0.1)	0.88
Adjusted R-square	0.30		0.63		0.26	

*p<0.05 was considered significant for Beta Coefficient
 Dependent Variables: Week-I MPV, Week-II MPV, Week-III MPV
 Independent variables C-reactive protein, serum Ferritin, LDH, Pro-BNP at respective weeks
 Model(s) were adjusted for age and gender

Table 4: Effect of Studied Parameters on Platelet Large Cell ratio in COVID patient

Parameters	Platelet Large Cell Ratio week-I		Platelet Large Cell Ratio week-II		Platelet Large Cell Ratio week-III	
	$\beta \pm$ S.E	p-value	$\beta \pm$ S.E	p-value	$\beta \pm$ S.E	p-value
c-reactive protein	(9.4 \pm 5.1)	0.07	(12.7 \pm 3.3)	<0.01*	(13.9 \pm 8.8)	0.13
Serum Ferritin	(0.1 \pm 0.1)	0.32	(0.1 \pm 0.1)	0.35	(0.1 \pm 0.1)	0.93
LDH	(0.1 \pm 0.1)	0.41	(0.1 \pm 0.1)	0.11	(0.1 \pm 0.1)	0.1
Pro-BNP	(-0.1 \pm 0.1)	0.88	(-0.1 \pm 0.1)	0.78	(-0.1 \pm 0.1)	0.64
Adjusted R-square	0.27		0.48		0.12	

*p<0.05 was considered significant for Beta Coefficient
 Dependent Variables: Platelet Large cell at week-I, week-II, and Week-III respectively
 Independent variables C-reactive protein, serum Ferritin, LDH, Pro-BNP at respective weeks
 Model(s) were adjusted for age and gender

Discussion

The present study was conducted to evaluate any correlation that exists between the relatively understudied platelet indices (MPV and P-LCR) and established prognostic biomarkers in COVID-19 patients. A statistically significant positive correlation will enable the clinicians to use the fairly cost-effective platelet indices provided in routine CBC to monitor disease progression in COVID-19 instead. This will not only be cost-effective but readily available at even the most under-resourced centers.

The study exhibited a statistically significant correlation (p-value<0.05) between MPV with the already established inflammatory markers i.e. serum ferritin, CRP, and LDH in patients with COVID-19. P-LCR showed a statistically significant (p-value<0.05) correlation with CRP only. A correlation of these platelet indices with pro-BNP was not found to be statistically significant.

Activated platelets tend to release many substances that play a role in inflammation.¹¹ This Platelet hyperactivity also occurs in COVID-19. Mean platelet volume (MPV) is considered a proxy marker of this

platelet activation. It is a depiction of platelet size. It ranges from 7.5 fL to 10.5fL.¹² An increase in MPV is correlated with thrombosis and inflammatory conditions. Therefore MPV has always been considered a useful prognostic indicator for critical patients.^{13,14,15}

Platelet larger cell ratio (P-LCR) is another marker of platelet activity. It gives a percentage of all platelets with a volume measuring over 12 fL circulating in the bloodstream. It normally ranges between 15-35%.¹⁴ P-LCR seems to be more susceptible to alterations in platelet size in comparison to MPV, despite their correlation.¹⁵

Our study depicted a female preponderance with 27 of 40 patients being females. In a study conducted locally in Pakistan, the gender division in patients with COVID-19 showed a male predominance of 89.7%.¹⁶ Similarly a study conducted in China had 31 of 40 infected patients of the male gender.¹⁷ This is in contrast to our study. The possible reason for the high female proportion in our study is most likely due to the fact that Fauji Foundation Hospital, Rawalpindi is a welfare hospital catering to the families of veteran armed personnel. The main bulk of patients being

catered here as out-patient as well in-patient are females.

To the best of our knowledge, there is no such study that has correlated mean platelet volume and platelet large cell ratio with established acute inflammatory markers in COVID-19 specifically.

Globally few such studies have been conducted that have depicted the significance of mean platelet volume in COVID-19 patients. Zhang et al.¹⁸ in their study showed that mean platelet volume is raised in the COVID-19 patients as compared to non-COVID-19. Furthermore, it tends to increase with the increasing severity of the disease. This is fairly comparable to our study since in our study, with the increasing trend of established biomarkers depicting the severity of the disease, mean platelet volume also tended to rise. Correlation with the acute inflammatory markers however was not done in the aforementioned study.

Numerous studies have however studied MPV as a biomarker in various systemic conditions.^{12,19,20} Since the pathophysiological aspect of some disease for example inflammation or tendency to develop a thrombotic complication is similar, therefore it could also be related to the disease progression in COVID-19.

MPV has been labeled and used as an inflammatory index in many conditions of systemic inflammation as well as diabetes, coronary heart disease, tumors, and connective tissue disorders. Ozder A²¹ in his study advocates MPV as an infection indicator in COVID-19 patients with diabetes as a comorbid. In his study, he established raised MPV in patients with diabetes that have contracted COVID-19. The present study included all patients irrespective of co-morbid. A progression in biochemical markers correlated with the changes in platelet indices irrespective of the presence of co-morbid.

In another study conducted in China, platelet and its parameters are studied in patients with COVID-19.²² Correlation of Platelet parameters with established inflammatory markers however were not studied. In the current study, platelet indices were correlated with established biomarkers.

In this study, P-LCR is positively correlated to CRP only whereas no statistically significant relationship is observed with other biochemical parameters. Since there is a scarcity of available data that has studies P-LCR in COVID-19, therefore, the results cannot be compared. In a study conducted by Mertoglu C²³ many hematological and biochemical markers were studied in COVID-19 and analysis was made between ICU and non-ICU patients. According to this study

platelet large cell ratio increases in COVID-19 and it positively correlates with the severity of the disease. A correlation amongst the various parameters however was not made.

To the best of our knowledge, this study is unique since it has attempted to trace a correlation between CRP, LDH, and serum Ferritin with MPV and P-LCR. Amongst the platelet indices, MPV can be used as a monitoring marker for COVID-19. Since MPV is a part of CBC, utilizing it as a monitoring tool will assist in cutting down the load on laboratories as CBC is performed in routine in all laboratories.

Conclusion

Mean platelet volume shows a statistically significant relationship with established acute inflammatory markers in COVID-19 whereas platelet large cell ratio correlates positively with CRP only. Since CBC analyzer is readily available at even the most under-resourced health centers; therefore reporting the platelet indices does not require extra testing, sampling, or reagent cost. A statistically significant positive correlation amongst the established acute inflammatory markers and relatively understudied platelet indices (MPV) in COVID-19 provides a cost-effective, readily available, and time-efficient tool for marking disease progression.

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