



Association of Platelet Count and Mean Platelet Volume among Vaccinated and Unvaccinated Covid-19 Patients in the Riyadh Region, Kingdom of Saudi Arabia

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Abstract Background: COVID-19 has significantly influenced world health, with vaccinations essential in preventing severe illness and transmission. Platelet indices, such as platelet count and mean platelet volume (MPV), are valuable indicators for understanding inflammatory and coagulation processes in COVID-19 patients. However, the relationship between these characteristics and vaccination status is poorly understood. This study is set to investigate the association between platelet count, MPV, and COVID-19 vaccination status among COVID-19 patients in the Riyadh region of Saudi Arabia, focusing on variations in vaccine type and dosage number. **Material and Method:** This retrospective study involved 186 COVID-19 patients (vaccinated and unvaccinated) from King Fahd Medical City in Riyadh between April 2020 and February 2024. Demographic information, vaccination records, and platelet indices were obtained from patient medical records to examine relationships, statistical comparisons were made using Mann–Whitney U test, Kruskal–Wallis test, Chi-square test, and Fisher’s exact test. **Results:** The mean platelet count was $249.2 \pm 109.4 \times 10^3/\mu\text{L}$, whereas the MPV was $10.4 \pm 1.4 \text{ fL}$. There was no significant difference in platelet count or MPV between vaccinated and unvaccinated groups ($p = 0.064$ and $p = 0.029$, respectively). There was no significant variance in platelet count between dosages, while MPV varied significantly, especially in those who had received three doses of vaccinations. **Conclusion:** Our study found that COVID-19 vaccines had a negligible effect on platelet count, but MPV showed significant variations in dose-response. This suggests no potential regulatory influence of vaccination on platelet function in COVID-19 patients. These findings underscore the importance of considering hematologic parameters in the context of COVID-19 and vaccination status, and they provide valuable insights for future research in this area.

Key Words Platelets Count, Mean Platelet Volume, Vaccinated, Non-Vaccinated, Covid-19, Riyadh Region

INTRODUCTION

COVID-19, produced by SARS-CoV-2, has been an international health crisis since its inception in late 2019. It predominantly affects the respiratory system but has broad systemic consequences, including the hematologic system [1]. Platelets are small cell fragments in the blood, play an essential role in hemostasis and immunological response. They are involved in blood clotting and immune response to pathogens [2]. Recent studies show alterations in platelet indices such as platelet count and mean platelet volume (MPV) in COVID-19 patients, which might represent the virus's inflammatory state [3].

SARS-CoV-2 is a positive-sense, single-stranded RNA virus with an envelope, glycoprotein, and spike protein. SARS-CoV-2, a respiratory virus, enters an individual's body and infects the lungs, the primary and dominant organs. COVID-19 produces many symptoms, frequently involving the hemostatic system [4]. Severe pulmonary inflammation, characterized by a cytokine storm and immune system hyperactivation, activates and damages the vasculature, potentially leading to pulmonary thrombosis early in the illness course [4]. The SARS-CoV-2 virus does not appear to have intrinsic procoagulant properties, instead,

the coagulopathy is most likely a consequence of this severe COVID-19 inflammatory response and endothelial activation/damage [4].

COVID-19 vaccines aim to produce immunological responses, especially neutralizing antibodies, by targeting SARS-CoV-2's spike (S) protein, which was obtained from the virus's original strain. These vaccines teach the immune system to detect and battle the virus using the spike protein or an inactivated form to stimulate antibody production and T cell activation, guaranteeing protection against infection [5]. Vaccines developed by pharmaceutical companies and research organizations worldwide have undergone rigorous testing in clinical trials, ensuring their safety and efficacy. The Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273) mRNA COVID-19 vaccines, which have demonstrated favorable safety profiles, have shown high effectiveness in reducing the risk of infection, severe disease, and COVID-19-related mortality, contributing substantially to efforts to control the pandemic [6]. Platelets participate not only in hemostasis but also in innate immune responses, and vaccination may temporarily influence platelet turnover and morphology. Following BNT162b2 mRNA vaccination, study by Flego *et al.* reported a minimal transient decrease in platelet count, accompanied by a significant increase in platelet size, including MPV, during the subsequent days, suggesting increased platelet turnover [7]. However, there is a need to investigate how vaccinations affect platelet indices, some concerns regarding their safety have been increased by reports of uncommon but substantial adverse outcomes, and these include myocarditis, lymphadenopathy, thrombocytopenia, pulmonary embolism, and myocardial infarction. Thrombocytopenia is directly characterized by a reduced platelet count and may result from immune-mediated platelet destruction, impaired platelet production, or increased platelet consumption. In contrast, myocardial infarction (MI) and pulmonary embolism (PE) are thrombotic disorders in which platelet activation and platelet size may be more informative than platelet count alone. Increased MPV, reflecting the presence of larger platelets that are generally more metabolically and functionally active, has been associated with acute MI, with meta-analytic evidence showing significantly higher MPV among patients with MI. Such studies highlight the necessity for more study to evaluate vaccination safety and its impact on platelet-related parameters [7-8].

While the short-term effects of mRNA vaccines on platelet-immune crosstalk have been studied, there is still much to learn. Pfizer, Moderna, and AstraZeneca are among the vaccines used in Saudi Arabia [9]. While these vaccines are primarily evaluated for their efficacy in preventing infection and severe illness, insufficient knowledge exists of how they may affect hematological parameters, particularly platelet count and MPV. This underscores the importance of ongoing research in this area and the need for healthcare professionals, researchers, and students to be actively involved in this scientific inquiry.

Objective

The primary objective of this study was to compare platelet count and mean platelet volume (MPV) between vaccinated and unvaccinated patients with PCR-confirmed COVID-19. The secondary objectives were to evaluate differences in platelet count and MPV according to the number of vaccine doses received; to compare platelet indices among homologous Pfizer-BioNTech, homologous AstraZeneca, and heterologous/mixed vaccination schedules; and to assess the correlation between platelet count and MPV within vaccination and dose groups. In addition, the study aimed to investigate whether demographic and clinical factors, including age, sex, COVID-19 disease severity, hospitalization status, comorbidities, and time since the most recent vaccination, influenced the relationship between vaccination status and platelet indices. Finally, the study aimed to assess whether increasing numbers of vaccine doses were associated with a dose-response pattern in platelet count or MPV.

Literature Review

The platelet abnormalities observed during acute COVID-19 should be interpreted with caution in previously vaccinated patients, as SARS-CoV-2 infection can substantially alter platelet number, size, maturity, and reactivity. In a large cohort of hospitalized patients, platelet count, mean platelet volume, and immature platelet fraction (IPF) were associated with critical illness and mortality, whereas platelets from patients with COVID-19 exhibited a hyperreactive, prothrombotic phenotype [9]. Consistently, higher IPF and immature platelet counts have been reported in severe COVID-19 and were associated with prolonged hospitalization and adverse outcomes [10,11]. A meta-analysis of 5,637 patients further demonstrated that thrombocytopenia occurs in acute COVID-19 and is associated with greater disease severity and mortality [12].

Other platelet parameters, such as platelet size and maturity, have also been linked to enhanced platelet reactivity and adverse clinical outcomes. Larger platelets generally exhibit greater metabolic activity and stronger prothrombotic properties. Accordingly, a higher mean platelet volume (MPV) has been associated with greater morbidity and increased overall mortality. The immature platelet fraction (IPF), which represents the proportion of newly released platelets in the circulation, has likewise been associated with unfavorable outcomes and increased mortality across several disease conditions [13-15].

Platelets are released into the bloodstream from megakaryocytes, which transfer part of their transcriptomic content to newly formed platelets during platelet production. After entering the circulation, platelets can respond dynamically to both local and systemic stimuli and interact with several cell types, including monocytes and endothelial cells. Platelet functional activity is closely related to platelet RNA expression patterns, and interactions between platelets and viruses can modify the platelet transcriptome. In COVID-19, platelets have been reported to display a hyperreactive

phenotype, characterized by increased expression of activation markers such as P-selectin and activated GP IIb/IIIa, together with distinct transcriptomic alterations compared with platelets from individuals without the disease [16-20].

Genetic studies have also identified several genomic factors that regulate platelet count and size. Furthermore, platelet maturity appears to be associated with specific transcriptomic characteristics. Therefore, transcriptomic analysis of platelets from patients with SARS-CoV-2 infection may provide valuable insights into the molecular mechanisms underlying changes in platelet number, size, maturity, and functional activity during COVID-19 [21-23].

The first reports of thrombocytopenia accompanied by thrombosis in previously healthy individuals following administration of the ChAdOx1-S vaccine emerged in April 2021, as described by Greinacher *et al.*, Scully *et al.*, and Schultz *et al* [24-26]. These reports highlighted severe thrombotic complications and reduced platelet counts after vaccination [27]. In the index case reported by Greinacher *et al.*, the patient was admitted to the hospital 10 days after vaccination and received multiple therapeutic interventions, including anticoagulation with enoxaparin, red blood cell and platelet transfusions, prothrombin complex concentrate, and recombinant factor VIIa [24].

Importantly, preliminary data from fully vaccinated patients hospitalized with breakthrough COVID-19 showed IPF and platelet counts comparable to those of patients with acute COVID-19 in the pre-vaccine era, suggesting that these changes may remain attributable to active infection despite prior vaccination [25]. By contrast, vaccine-associated immune thrombocytopenia generally occurs shortly after vaccination, with most reported cases developing within approximately 12 days [26]. Likewise, vaccine-induced immune thrombotic thrombocytopenia is a distinct syndrome primarily associated with adenoviral vector vaccines and characterized by thrombocytopenia, thrombosis, and anti-PF4 antibodies within a characteristic post-vaccination interval [27]. Thus, in patients with remote vaccination and concurrent acute infection, infection-related platelet alterations are more biologically plausible unless a compatible temporal and clinical vaccine-associated syndrome is present [28-33].

METHODS

Study Design and Population

This is a retrospective record-based observational study with cross-sectional laboratory assessment involved data collected from King Fahd Medical City in Riyadh, Saudi Arabia from April 2020 to February 2024. Vaccination records were obtained from the national vaccination records in Saudi Arabia from the Sehaty program. Patient data, including platelet count, MPV, vaccine types and number of doses, was collected. A total of 186 participants, all with a history of COVID-19 infection, were included in the study. They were divided into two groups: those who had received at least one dose of the vaccine and those who had

not. Patients aged 10-85 years who were citizens and residents of Saudi Arabia and had COVID-19 confirmed with PCR were eligible for inclusion. Pregnant women, cancer patients, those with autoimmune diseases, and those using anticoagulants were all excluded due to their unique health conditions that could potentially confound the study's results.

Data Collection

PCR and CBC (platelets count and MPV) results data were obtained from medical records of COVID-19 patients admitted to King Fahd Medical city in Riyadh, vaccination data was collected from the national vaccination recodes in Saudi Arabia from Sehaty program. Notably, an ethical approval, signifying our commitment to research ethics, was obtained from the Riyadh Second Health Cluster with IRB number 24-285C.

Statistical Analysis

Data were analyzed using SPSS version 25.0 (IBM, Armonk, NY, USA). The distribution of continuous variables was assessed using the Shapiro–Wilk test and graphical inspection of histograms and Q–Q plots. As platelet count and MPV did not follow a normal distribution, non-parametric statistical methods were applied. Continuous variables were summarized using median and interquartile range (IQR), with mean±standard deviation (SD) additionally reported for descriptive purposes. The Mann–Whitney U test was used to compare continuous variables between vaccinated and unvaccinated groups, whereas the Kruskal–Wallis test was used to compare platelet indices across vaccination-dose categories. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant.

RESULTS

Demographic Characteristics

Initially 3915 patient data was collected and based on the inclusion and exclusion criteria a total of 186 patient data was included in this study. Out of 186 individuals, 104 were females (48.1% vaccinated, 61.9% unvaccinated), whereas 82 were males (51.9% vaccinated, 38.1% unvaccinated). The age varied from 10 to 85 years, with an average of 49.60±17.29 years (Table 1). Importantly, there was no significant difference in gender (p = 0.061) or age (p = 0.263) between the vaccinated and unvaccinated individuals, demonstrating the robustness of our study's methodology.

The mean platelet count was 249.15×10³/μL, comfortably within the normal range, indicating the good health of most participants. The mean platelet volume (MPV) is 10.38 fL, also within the normal range, further confirming the health status of most participants (Table 1). Platelet counts showed substantial inter-individual variability, ranging from 50 to 823 ×10³/μL (Table 1). Thus, although the overall mean platelet count was within the conventional reference interval, individual participants exhibited markedly

Table 1: The Descriptive Characteristics Among the Study Participants

Characteristic	Range	Mean	Std. Deviation
Age	10-85	49.60	17.286
Platelets count (100-450 x10 ³ /ul)	50-823	249.15	109.354
MPV (6.3-11.2) fl	7-14	10.38	1.433
Total	186	-	-

Table 2: The Distribution of Vaccine Types

Vaccine Type	n (%)
2 AstraZeneca, 1 Pfizer	8 (9.9)
2 Pfizer, 1 Moderna	1 (1.2)
AstraZeneca	14 (17.3)
AstraZeneca, Pfizer	1 (1.2)
Pfizer	56 (69.1)
Pfizer, Moderna, Pfizer	1 (1.2)

Table 3: Platelet Count and Mpv Comparison among Vaccinated and Non-Vaccinated Covid19 Patients

Characteristics	Discription	Vaccinated	Un vaccinated	Total	p-value
Platelets count (100–450 x 10 ³ /ul)	min - max	58–614	50–823	50–823	0.064
	Mean±SD	256.6±94.7	243.4±119.6	249.2±109.4	
	Median (P25 - P75)	250 (195–303)	217 (178–276)	227 (183–298)	
Mean platelet volume (MPV) 6.3–11.2 fl	min - max	6.6–13.6	6.9–13.7	6.6–13.7	0.029*
	Mean±SD	10.1±1.5	10.6±1.3	10.4±1.4	
	Median (P25 - P75)	10.1 (9.5–11.2)	10.5 (9.7–11.5)	10.3 (9.5–11.4)	

*Statistically significant at p<0.05

Table 4: Dose-response analysis

Characteristic	1 Dose	2 Doses	3 Doses	Unvaccinated	p- value
n (%)	35 (18.8%)	26 (14.0%)	20 (10.8%)	105 (56.5%)	
Platelets count (100-450 x10 ³ /ul)	263.77±83.5	242.19±83.32	262.65±125.35	243.43±119.59	0.727
Mean platelet volume (MPV) 6.3-11.2 fl	10.45±1.11	10.74±1.32	8.74±1.66	10.58±1.32	<0.001
Spearman's correlation coefficient (p)	-0.205	-0.325	-0.368	-0.36	
(p-value)	(0.237)	(0.105)	(0.111)	(<0.001)	

low or high platelet counts. Because the study was based on retrospective laboratory records and detailed clinical information explaining individual platelet abnormalities was not consistently available, these extreme observations were not assigned to specific clinical causes.

Vaccine Status and Types

The Pfizer vaccine was the most frequently used among vaccinated individuals (n=56, 69/1%), followed by AstraZeneca (n=14, 17.3%) and mixed-dose regimens (Table 2).

Comparison between Vaccinated and Unvaccinated COVID 19 Patients

The mean platelet count was highest among vaccinated participants (256.6±94.7 x¹⁰ 3/ul) than non-vaccinated (243.4±119.6 x¹⁰ 3/ul). The mean platelet volume (MPV) was less among vaccinated group (10.1±1.5 fl) than non- vaccinated ones (10.6±1.3 fl). Platelets count have no significant difference among vaccinated and non-vaccinated groups of participants (p = 0.064), while the mean platelet volume has a slight difference among vaccinated and non-vaccinated groups of participants (p = 0.029) (Table 3).

Dose-Response Analysis

The vaccination status reveals that 35 individuals (18.8%) received one dosage, 26 individuals received two doses

(14%), and 20 individuals received three doses (10.8%). There were 105 unvaccinated participants (56.5%).

The analysis revealed the following platelet count means (± standard deviations) across the groups: after one dose, the mean platelet count was 263.77±83.5, after two doses 242.19±83.32, after three doses 262.65±125.35, and in the unvaccinated group 243.43±119.59. The p- value of 0.727 indicates no statistically significant difference in platelet counts between the groups. For mean platelet volume (MPV), the results were: 10.45±1.11 for one dose, 10.74±1.32 for two doses, 8.74±1.66 for three doses, and 10.58±1.32 for the unvaccinated group. The p-value of <0.001 demonstrates a statistically significant difference in MPV among the groups, with the group receiving three doses showing a notably lower MPV compared to the others.

MPV differed significantly across the vaccination-dose groups (p < 0.001), with the three-dose group showing the lowest mean MPV (8.74±1.66 fL). However, the three-dose subgroup included only 20 participants, and the observed difference should therefore be interpreted cautiously. The cross-sectional retrospective design does not permit determination of whether the observed MPV difference was attributable to the number of vaccine doses (Table 4).

A negative correlation between platelet count and MPV was observed in all vaccination-dose categories; however, the correlations were not statistically significant among

participants receiving one dose ($p = -0.205$, $p = 0.237$), two doses ($p = -0.325$, $p = 0.105$), or three doses ($p = -0.368$, $p = 0.111$). A statistically significant negative correlation was observed in the unvaccinated group ($p = -0.360$, $p < 0.001$). Given the small subgroup sizes, these subgroup correlations should be considered exploratory

DISCUSSION

COVID-19 vaccinations have significantly reduced the incidence and severity of COVID-19 infections and may offer protection against reinfections. Studies have shown that completing the basic vaccination series provides significant protection against reinfection compared to no vaccination [10]. This study focuses on platelet metrics and the comparison between vaccinated and unvaccinated patients, aimed to investigate the association between platelet count, mean platelet volume (MPV), and COVID-19 disease. 186 individuals with a history of COVID-19 infection, 104 of whom were female and 82 were male were included in the study. While there is no definitive evidence that COVID-19 infections preferentially affect women, while a study by Kopel *et al.*, reported that women may be more vulnerable to COVID-19 than men. This remains uncertain, as differences in COVID-19's impact on the lungs between genders have not yet been fully established [11].

The participants had a broad age range of 10–85 years, with a mean age of 49.60 ± 17.29 years. There was no statistically significant difference in age between vaccinated and unvaccinated participants ($p = 0.263$). Because age categories were not specifically analyzed in this study, comparisons with age-specific patterns reported in previous COVID-19 studies should be interpreted cautiously [34–38]. It is in contrast with the reports of Sobotka *et al.*, Starkeet. *et al.*, and Pezzullo *et al.* that identified older individuals were more susceptible to COVID-19. Our data emphasize the disease's broad impact across all age groups [11–13].

The clinical laboratory results showed a mean platelet count of $249.15 \pm 109.35 \times 10^3/\mu\text{L}$ and a mean MPV of 10.38 ± 1.43 fL. This contrasts the findings of Introcaso *et al.*, who found dysregulation in platelet count and MPV among COVID-19 patients, implying platelet changes even in vaccinated people [14]. Barrett *et al.* shed light on these dynamics, observing hyperactive platelets and increased megakaryopoiesis in COVID-19 patients with acute respiratory syndrome [15]. In the present study, vaccinated participants had a lower MPV than unvaccinated participants (10.1 ± 1.5 fL vs. 10.6 ± 1.3 fL; $p = 0.029$). Although MPV is commonly used as an indirect platelet index, the observed difference should not be interpreted as direct evidence of altered platelet activation, platelet stability, or thrombotic risk because platelet activation markers and clinical thrombotic outcomes were not assessed in this study. Therefore, the lower MPV observed among vaccinated participants represents an association that requires further investigation using direct platelet function and coagulation measurements. However, vaccinated patients with a third dosage had a lower MPV, indicating that vaccinations may

alter platelet activity, perhaps preventing excessive thrombus formation. The vaccinated group had a slightly higher mean platelet count ($256.6 \pm 94.7 \times 10^3/\mu\text{L}$) than non-vaccinated individuals ($243.4 \pm 119.6 \times 10^3/\mu\text{L}$). This slight increase shows that vaccinations may affect platelet production or turnover slightly. The vaccinated group had lower MPV (10.1 ± 1.5 fL) than the non-vaccinated group (10.6 ± 1.3 fL), suggesting smaller and more stable platelets in vaccinated people. The lower MPV observed in vaccinated participants, particularly among those who had received three doses, may indicate differences in platelet indices according to vaccination status and dose number. However, the present study cannot determine whether these differences are attributable to vaccination itself. MPV can be influenced by several clinical and biological factors, including inflammation, infection severity, platelet production, and underlying disease. In addition, the study did not include direct measures of platelet activation, coagulation, or thrombotic events. Accordingly, the observed differences should be considered hypothesis-generating rather than evidence of a regulatory effect of vaccination on platelet function. Pfizer was the most frequently used vaccination among participants (69.1%), consistent with results by Francis *et al.* reported a global preference for Pfizer due to its effectiveness and comprehensive testing [16]. Most participants were unvaccinated ($n = 105$, 56.5%). However, the reasons for their vaccination status were not available in the medical records and therefore cannot be determined from the present study. The study found that MPV was consistently lower in vaccinated people, which supports the findings of Uzun *et al.* who discovered that vaccinations may reduce platelet hyperactivity and size [17]. Their investigation, which focused on adenoviral vaccines such as AstraZeneca and Johnson and Johnson, identified immune-mediated platelet activation as a role in vaccine-induced thrombotic events. Our data support their concept, as vaccinated individuals in our research had smaller, more stable platelets, which may reduce thrombo-inflammatory risks [39–42]. The dose-response analysis found that most individuals had only received one dosage, which might be explained by vaccination reluctance or an assumption that a single dose provided adequate protection [18]. The absence of a connection between gender and age with vaccination status ($p = 0.061$ and 0.263 , respectively) suggests that these demographic characteristics were not predictive of vaccine uptake in this population. Although platelet count did not change significantly across dosage groups ($p = 0.727$), MPV showed a significant decrease, particularly after three doses ($p < 0.001$). This is consistent with the findings of Gardellini *et al.* who discovered that MPV decreased in patients who received only one dosage [19]. Welsh *et al.* similarly observed decreased platelet size with each vaccine dosage, indicating that higher doses may further stabilize MPV and reduce thrombo-inflammatory risk [20]. A slight negative association (< 0.5), between dosage number, platelet count, and MPV suggests that as the number of

doses increases, MPV may decrease. This supports the concept that cumulative vaccination doses may affect platelet function.

CONCLUSIONS

This study investigated the association between platelet count and mean platelet volume (MPV) in COVID-19 individuals who had been vaccinated and those who had not, taking into account the type of vaccine used and the number of doses. Our data indicate that hematologic changes could develop in response to COVID-19 and vaccination status, with different platelet profiles among vaccinated patients, particularly those who got several doses, compared to non-vaccinated individuals. Some vaccinations were linked to higher platelet counts and MPV, suggesting an immune modulation impact that might offer a promising avenue for improving protection against COVID-19 consequences. These findings highlight the significance of continued hematologic monitoring in both vaccinated and unvaccinated COVID-19 patients. Small sample sizes and variations in the healthcare environment are some limitations of the study that can limit its broader application.

Future studies should strive to include larger, more diverse groups. This is crucial not only to better understand the impact of different vaccinations and dosages across various demographics, but also to ensure that all individuals feel included and valued in the research process. Many awareness and counseling sessions must be carried out among people to enhance the idea of vaccinating and get the full number of doses of COVID-19 vaccines. Additionally, reporting other laboratory markers can help identify any correlations between these markers and being vaccinated against COVID-19.

Ethical Approval

An ethical approval was obtained from Riyadh Second Health Cluster with IRB number 24-285C, 28 MAY 2024.

Conflict of Interest

No conflict of Interest

Data Availability Statement

The datasets presented in this study can be found with corresponding author.

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Author Contributions

Conceptualization, G.M.A, J.K and M.A.A.; methodology, G.M.A and J.K; software, T.A.W, R.H.H, and A.S.A.;

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