Moderate to Severe Thrombocytopenia and Survival Predictors in Pregnant Women During the Post-COVID-19 Pandemic ERA

Sofia Naz, Islam Bano*, Munnaza Andleeb, Zahra Waseem*, Zoha Nisar*

Department of Gynae & Obs, Quetta Institute of Medical Sciences/Combined Military Hospital Quetta /National University of Medical Sciences (NUMS) Pakistan, *Department of Gynae & Obs, Combined Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objective: To determine the moderate to severe thrombocytopenia (platelet count ≤100,000/ml) in pregnant women during routine follow-up visits and assess the associated risk of maternal death.

Study Design: Cross-sectional study.

Place and Duration of Study: Combined Military Hospital Rawalpindi and Combined Military Hospital, Quetta Pakistan, from May to Dec 2022.

Methodology: The study included ninety-four pregnant women who had a history of COVID-19 infection in their current pregnancy or in the past, had been vaccinated against the Sars-CoV-2 virus, and had a platelet count of less than 100,000/mL. Regression analysis was used to determine whether variables were significant predictors of survival, and appropriate statistical tests were used to evaluate significant relationships.

Results: During the study period, 2,104 patients gave birth vaginally or by caesarean section. For this duration, the frequency of pregnant women with platelet counts below 100,000/ml was calculated at 4.47%. Only four of the 94 patients died. Potential survival predictors identified were hemoglobin level, COVID-19 infection history, and COVID-19 infection during the current pregnancy.

Conclusions: The frequency of patients with moderate to severe thrombocytopenia has increased from 1% to 4.47 percent in the post-COVID-19 pandemic era. Pregnant women with moderate to severe thrombocytopenia have significant predictors of survival, including a history of COVID-19 infection, current COVID-19 infection, and haemoglobin levels.

Keywords: COVID-19 vaccines, COVID-19 infection during pregnancy, Gestational thrombocytopenia, Post-COVID-19 autoimmune phenomenon.

INTRODUCTION

In the second and third trimesters, 5-11% of pregnancies are affected by gestational thrombocytopenia; however, it affects approximately 31.6% of pregnant women with COVID-19.[1,2]Platelet counts range from 100,000 to 149,000/ml in mild thrombocytopenia, 50,000 to 100,000/ml in moderate thrombocytopenia, and less than 50,000/ml in severe thrombocytopenia.[3,4] One study evaluated the platelet counts of 7,351 pregnant women. According to their findings, a platelet count of less than 100,000/mm3 should prompt further investigation into possible causes other than pregnancy or associated complications. [5]

Thrombocytopenia is thought to be an autoimmune process in which antibodies against platelet factor 4 are made.[6] Platelets in COVID-19 patients become overactive, clot more easily through a mechanism dependent on the CD32 receptor, and die, which leads to thrombocytopenia. SARS-CoV-2 induces hypercoagulability due to endothelial dysfunction and excessive production of proinflammatory mediators.[6,7] This condition is characterized by an imbalance between pro- and anti-coagulant factors, as well as a decrease in platelet count. Patients with COVID-19 and thrombocytopenia have an increased risk of morbidity and mortality. [9,10]

The objectives of this study were to ascertain the moderate to severe thrombocytopenia (platelet count ≤100,000/ml) in pregnant women during routine follow-up visits and to assess the associated risk of maternal death. We hope that our findings will encourage the obstetrics community to monitor young pregnant women more closely for subclinical thrombocytopenia in order to detect it early and prevent complications.

METHODOLOGY

The cross-sectional study was conducted from May to December 2022 at the Department of Gynaecology and Obstetrics of Combined Military Hospital (CMH), Rawalpindi and CMH Quetta

Correspondence: Dr Islam Bano, Department of Obs & Gynae, Combined Military Hospital, Rawalpindi Pakistan
Received: 04 Jul 2023, revision received: 10 Jan 2024; accepted: 16 Jan 2024

Pakistan, after approval from the Hospital Ethical Committee (ERC No. 415/13/April/22). The sample size was determined assuming a 1% prevalence of thrombocytopenia.[11] The consecutive sampling technique was used to enroll ninety-nine hospitalized pregnant women who met the inclusion criteria after obtaining informed consent.

Inclusion Criteria: Pregnant women with moderate to severe thrombocytopenia (platelet count ≤ 100,000/ml) were included.

Exclusion Criteria: Women with diabetes, liver disease, kidney disease, cardiac disease, cancer, ITP, or thrombocytopenia prior to pregnancy were excluded.

Given that gestational thrombocytopenia is a diagnosis of exclusion, we performed the following diagnostic tests to confirm it: a complete blood count (CBC) includes a peripheral smear to determine the number and morphology of platelets and red blood cells. A coagulation profile, including prothrombin time (PT) and activated partial thromboplastin time (aPTT), was performed to rule out coagulation abnormalities. Liver function tests (LFTs) are used to evaluate liver health. Viruses such as hepatitis B and C, HIV, and CMV can cause thrombocytopenia; therefore, serology tests to rule out such infections as a cause were requested. Through a comprehensive medical history and physical examination, all other potential causes of thrombocytopenia were ruled out. Five patients were ultimately excluded from the final analysis due to the ambiguous diagnosis of gestational thrombocytopenia. The patients' complete medical history was obtained, including their age, gravida, parity, gestational age, hypertension, and history of gestational thrombocytopenia. All of the afore-mentioned information was collected via a self-developed, structured questionnaire.

Statistical Package for Social Sciences (SPSS) version 26.0 was used for the data analysis. Quantitative variables were expressed as Mean±SD and qualitative variables were expressed as frequency and percentages. Chi-square test and independent sample t-test was applied to explore the inferential statistics. The logistic regression analysis was con-ducted to determine which variables were most pre-dictive of a positive outcome (survival of the mother). The p-value lower than or up to 0.05 was considered as significant.

RESULTS

A total of 2,104 pregnant patients were admitted to the obstetrics unit, undergoing either vaginal delivery or a caesarean section. The study included 94 patients with a platelet count below 100,000/mL. Within this group, 9.58% (9 out of 94) of patients experienced comp-lications, including acute renal failure, post-partum haemorrhage, and four fatalities, resulting in an adverse outcome rate of 4.25%. Notably, 4.30% of patients exhibited severe thrombocytopenia (platelet count ≥50,000), 7.45% required blood transfusions, and 19.15% necessitated emergency platelet trans-fusions, particularly in the context of caesarean sections. A notable majority of our study participants, 86(91.5%), were carrying a singleton pregnancy. All the participants had received at least one dose of the COVID-19 vaccine, with the most common vaccines being SinoPharm 46 (48.9%) and SinoVac 30(31.9%). Hypertension was observed in 8(8.5%) of the cases, and 14(14.9%) had a history of gestational throm-bocytopenia. The average age of the patients was 29.97±2.65 years, and the gestational age was 35.08±4.20 weeks (Table-I).

Table-I: Demographic Characteristics and Laboratory Parameters of the Study Participants (n= 94)

Parameters		Frequency(%)
Parity	Primiparous	39(41.5%)
	P2-P5	53(56.4%)
	P>5	2(2.1%)
Pregnancy	Singleton	86(91.5%)
	Twins	8(8.5%)
Hypertension	Not present	86(91.5%)
	Present	8(8.5%)
Name of COVID-19 Vaccine	Sino pharm	46(48.9%)
	SinoVac	30(31.9%)
	Pfizer	5(5.3%)
	AstraZeneca	1(1.1%)
	Moderna	6(6.4%)
	Cansino	6(6.4%)
History of COVID-19 Infection	No	69(73.4%)
	Yes	25(26.6%)
COVID-19 in current pregnancy	No	90(95.7%)
	Yes	4(4.3%)
History of Gestational Thrombocytopenia	No	80(85.1%)
	Yes	14(14.9%)
Outcome	Recovery	90(95.7%)
	Death	4(4.3%)
Quantitative Parameters	Mean±SD	Range
Age (years)	29.97±2.65	24-38
Gestational Age (weeks)	35.08±4.20	18-40
Hemoglobin Level (g/dl)	10.81±1.13	7.6-13.0
Platelets count (x 103 cells/μL)	83.63±13.77	40.00-99.00
Systolic BP (mmHg)	117.61±17.19	100-180
Diastolic BP (mmHg)	75.00±10.95	60-110

Table-II presents a detailed comparison of the means of quantitative variables categorised by the patients' outcomes, shedding light on potential predictors of survival in individuals with thrombocytopenia. Notably, the haemoglobin level and platelet count may be good indicators of survival.

Table-II: Comparison of Quantitative Parameters with Respect to Outcome (n=94)

Parameters	Study Groups		*p*-value
	Survived Mean±SD (n=90)	Died Mean±SD (n=4)	
Age in years	30.0±2.7	29.5±3.1	0.714
Gestational Age (weeks)	35.0±4.37	36.5±1.9	0.494
Hemoglobin Level (g/dl)	10.9±1.0	8.7±1.0	<0.001
Platelets count (x 103 cells/µL)	84.2±13.1	70.0±22.4	0.042
Systolic Blood Pressure (mmHg)	117.0±16.8	131.3±23.2	0.105
Diastolic Blood Pressure (mmHg)	74.6±10.5	85.0±17.3	0.315

Table-III shows a comprehensive examination of the association between various categorical variables and maternal outcomes within our study cohort. Notably, women with a history of COVID-19 infection during the current pregnancy exhibited a markedly higher mortality rate compared to those without such a history (*p*<0.001).

Table-III: Comparison of the Categorical Variables with Respect to Outcome (n=94)

Parameters	Study Groups		*p*-value
	Survived (n=90)	Died (n=4)	
Pregnancy			
Single	83(92.2%)	3(75.0%)	0.227
Multiple	7(7.8%)	1(25.0%)	
History of COVID-19 Infection			
Negative	68(75.6%)	1(25.0%)	0.025
Positive	22(24.4%)	3(75.0%)	
COVID-19 in current pregnancy			
Not present	88(97.8%)	2(50.0%)	<0.001
Present	2(2.2%)	2(50.0%)	
Hypertension Not present	84(93.3%)	2(50.0%)	0.002
Present	6(6.7%)	2(50.0%)	
History of Gestational Thrombocytopenia			
Negative	77(85.6%)	3(75.0%)	0.562
Positive	13(14.4%)	1(25.0%)	
Parity Primiparous	38(42.2%)	1(25.0%)	<0.001
P2-P5	51(56.7%)	3(75.0%)	
P>5	2(2.2%)	0(0.0%)	

To identify the effect of independent variables on the outcome, regression analysis was performed as shown in Table-IV. Lower haemoglobin levels exhibit a significant association with increased mortality, supported by the unadjusted odds ratio (UOR) of 0.103 on univariate analysis. However, it fails to maintain statistical importance in a multivariate context. In the same way, the other factors—including platelet count, history of COVID-19 infection, current pregnancy with COVID-19 infection, and high blood pressure—showed a possibly significant negative relationship with survival in univariate analysis but lost their statistical significance in multivariate analysis.

DISCUSSION

COVID-19 affects various systems within the human body, including the immune system, coagulation system, and even certain cell types. This multi-faceted impact potentially contributes to thrombocytopenia in pregnant patients. In contrast to research conducted prior to the COVID-19 era, which estimated a prevalence of 0.5% to 1% for a platelet count of <100,000/ml, 94/2104 (4.47%) of participants in this study had moderate to severe thrombo-cytopenia. [11,13] Recent research supports our findings, indicating an increase in the prevalence of moderate to severe thrombocytopenia among pregnant patients, suggesting a potential association between the disease and this condition.[5,9,14]

When dividing patients into two groups based on their outcomes (survival and non-survival), Haemoglobin and platelet counts emerged as potential significant predictors of survival in our analysis. Similar studies have demonstrated that low haemoglobin levels are associated with adverse outcomes in COVID-19 patients, including pregnant women.[15,16]

Furthermore, our Chi-Square test identified several categorical characteristics that showed strong associations with increased mortality rates. These results align with previous research, which also found an increased risk of adverse outcomes in pregnant women with COVID-19 who have comorbidities such as hypertension, COVID-19 during the current pregnancy, and a history of COVID-19 infection during pregnancy [18,19]

Table-IV: Parameter Estimates for Maternal Outcome using Logistic Regression Analysis (n=94)

Factors	Outcome (Survival)		Univariate logistic regression			Multivariate logistic regression		
	Survived	Died	*p*-value	Un-adjusted OR	95% CI for UOR	*p*-value	Adjusted OR	95% CI for AOR
Hemoglobin Level (g/dl)	10.9±1.0	8.7±1.0	0.003	0.103	−3.762−−0.782	0.205	0.247	0.29-2.14
Platelets count (x 10³/μL)	84.2±13.1	70.0±22.4	0.065	0.950	−0.107-0.003	0.846	0.980	0.797-1.20
History of COVID-19 Infection								
Yes	22(24.4)	3(75)	1			1		
No	68(75.6)	1(25)	0.059	0.108	−4.54−−0.92	0.991	4.72x10-10	0.000-
COVID-19 Infection in the current Pregnancy								
Yes	2(2.2)	2(50)	1			1		
No	88(97.8)	2(50)	0.002	0.023	−6.197−−1.371	0.990	2.58x10-11	0.000-
Hypertension								
Yes	6(6.7)	2(50)	1			1		
No	84(93.3)	2(50)	0.015	14.0	0.503-4.775	0.995	1.66x10-15	0.000-
Parity								
P= 1	38(42.2)	1(25)	The results cannot be interpreted due to lack of convergence			0.990	22.06 x10-15	0.000-
P= 2-5	51(56.7)	3(75)				.	0.001	0.001-0.001
P> 5	2(2.2)	0(0)				1		

Both past and present COVID-19 infections in our study were strongly correlated with maternal mortality, consistent with the findings of previous studies linking COVID-19 infection to maternal mortality and other adverse pregnancy outcomes.[18,20] In the case of hypertension, it is important to note that this condition is associated with severe complications during pregnancy, such as preeclampsia and maternal death.[19,20]. While our Chi-Square test yielded a significant association between hypertension and survival (*p*=0.002), the regression analysis did not confirm a significant relationship. We attribute this discrepancy to the relatively small sample size for regression analysis, which may have limited the model's accuracy.

Thrombocytopenia has been demonstrated to be a common complication among COVID-19 patients and may be associated with a more severe disease and worse outcomes, including mortality [17]. According to the guidelines, patients with COVID-19 thrombo-cytopenia should be closely monitored and swiftly treated to avoid complications [13]. If an expectant woman has no history of COVID-19 infection, is not currently infected with COVID-19, and does not have hypertension, her prognosis improves if she develops severe thrombocytopenia. Nevertheless, it is essential to monitor and manage gestational thrombocytopenia as it progresses during pregnancy. Vaccinating pregnant women against COVID-19 has been shown to reduce the virus's transmission and the severity of its potential consequences.[14] These findings can be used to prioritize the treatment of expectant women infected with COVID-19 and identify high-risk patients.

RECOMMENDATIONS

Immunisation should be done against the COVID-19 infection to prevent women from experiencing the adverse effects of COVID-19 during pregnancy, including moderate to severe gestational thrombocytopenia. Pregnant women who contract the COVID-19 infection should be closely monitored for complications. To validate these findings and identify new survival predictors in pregnant women with thrombocytopenia in the post-COVID-19 pandemic era, larger-scale studies are required.

ACKNOWLEDGEMENT

CONCLUSIONS

The frequency of patients with moderate to severe thrombocytopenia has increased from 1% to 4.47 percent in the post-COVID-19 pandemic era. Pregnant women with moderate to severe thrombocytopenia have significant predictors of

survival, including a history of COVID-19 infection, current COVID-19 infection, and haemoglobin levels.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

SN: Data acquisition, critical review, approval of the final version to be published.

IB, MA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

ZW, ZN: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Chen Y, Xu Z, Wang P, Li XM, Shuai ZW, Ye DQ, et al. New-onset autoimmune phenomena post-COVID-19 vaccination. Immunology 2022; 165(4): 386-401. https://doi.org/10.1111/imm.13443

2. Parums DV. Editorial: SARS-CoV-2 mRNA Vaccines and the Possible Mechanism of Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT). Med Sci Monit 2021; 27: e932899. https://doi.org/10.12659/MSM.932899

3. Montgomery J, Ryan M, Engler R, Hoffman D, McClenathan B, Collins L, et al. Myocarditis following immunization with mRNA COVID-19 vaccines in members of the US military. JAMA Cardiol 2021; 6(10): 1202-1206. https://doi.org/10.1001/jamacardio.2021.2833

4. Román GC, Gracia F, Torres A, Palacios A, Gracia K, Harris, D. Acute Transverse Myelitis (ATM): Clinical Review of 43 Patients With COVID-19-Associated ATM and 3 Post-Vaccination ATM Serious Adverse Events With the ChAdOx1 nCoV-19 Vaccine (AZD1222). Front Immunol 2021; 12: 653786. https://doi.org/10.3389/fimmu.2021.653786

5. Moses ML, Kazzi NG, Lee L. Severe thrombocytopenia in a pregnant patient with asymptomatic COVID-19 infection: a case report. Cureus 2021; 13(1): e12904. https://doi.org/10.7759/cureus.12990

6. Kadir RA, Kobayashi T, Iba T, Erez O, Thachil J, Kazi S, et al. COVID-19 coagulopathy in pregnancy: Critical review, preliminary recommendations, and ISTH registry—Communication from the ISTH SSC for Women's Health. J Thromb Haemost 2020; 18(11): 3086-3098. https://doi.org/10.1111/jth.15072

7. Barsode S, Tarlekar V, Shora M, Mehendale S. Clinical profile of thrombocytopenia in pregnancy. Indian J ObstetGynecol Res 2019; 6(2): 192-195. http://doi.org/10.18231/j.ijogr.2019.044

8. Reese JA, Peck JD, Deschamps DR, McIntosh JJ, Knudtson EJ, Terrell DR, et al. Platelet counts during pregnancy. N Engl J Med 2018; 379(1): 32-43. http://doi.org/10.1056/NEJMoa1802897

9. Rabaan AA, Bakhrebah MA, Mutair AA, Alhumaid S, Al-Jishi JM, AlSihati J, et al. Systematic review on pathophysiological complications in severe COVID-19 among the non-vaccinated and vaccinated population. Vaccines 2022; 10(7): 985. https://doi.org/10.3390/vaccines10070985

10. Islam A, Bashir MS, Joyce K, Rashid H, Laher I, Elshazly S. An update on COVID-19 vaccine induced thrombotic thrombocytopenia syndrome and some management recommendations. Molecules 2021; 26(16): 5004. https://doi.org/10.3390/molecules26165004

11. Greinacher A, Langer F, Makris M, Pai M, Pavord S, Tran H, et al. Vaccine-induced immune thrombotic thrombocytopenia (VITT): update on diagnosis and management considering different resources. J Thromb Haemost 2022; 20(1): 149-156. https://doi.org/10.1111/jth.15572

12. Kotlyar A, Grechukhina O, Chen A. Vertical transmission of COVID-19: a systematic review and meta-analysis. Am J Obstet Gynecol 2021; 224(1): 35-53.e3. https://doi.org/10.1016/j.ajog.2020.07.049

13. Gernsheimer T, James AH, Stasi R. How I treat thrombocytopenia in pregnancy. Blood. 2013; 121(1): 38-47. https://doi.org/10.1182/blood-2012-08-448944

14. Bennett C, Chambers LM, Son J, Goje O. Newly diagnosed immune thrombocytopenia in a pregnant patient after coronavirus disease 2019 vaccination. J Obstet Gynaecol Res 2021; 47(11): 4077-4080. https://doi.org/10.1111/jog.14978

15. Mousavi SA, Rad S, Rostami T, Rostami M, Mousavi SA, Mirhoseini SA, et al. Hematologic predictors of mortality in hospitalized patients with COVID-19: a comparative study. Hematology 2020; 25(1): 383-8. https://doi.org/10.1080/16078454.2020.1833435

16. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020; 18(5): 1094-1099. https://doi.org/10.1111/jth.14817

17. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. Clin Chim Acta 2020; 506: 145-148. https://doi.org/10.1016/j.cca.2020.03.022

18. Allotey J, Fernandez S, Bonet M, Stallings E, Yap M, Kew T, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ 2020; 370. https://doi.org/10.1136/bmj.m3320

19. Pathirathna ML, Samarasekara BPP, Dasanayake TS, Saravanakumar P, Weerasekara I. Adverse Perinatal Outcomes in COVID-19 Infected Pregnant Women: A Systematic Review and Meta-Analysis. Healthcare 2022; 10(2): 203. https://doi.org/10.3390/healthcare10020203

20. Amirian A, Pakzad R, Hasanpour V, Mirzadeh N, Abdi F. Neonatal outcome among pregnant women with COVID-19: a systematic review and meta-analysis. J Matern Fetal Neonatal Med 2022; 35(25): 9234-9248. https://doi.org/10.1080/14767058.2021.2022648

....