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Frequency of thrombocytopenia in severe COVID-19 pneumonia and its effects on clinical outcomes

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Abstract: To aim of the study was to determine the frequency of thrombocytopenia and its effect on clinical outcomes in South Asian patients admitted with severe COVID-19. It was a cross-sectional study conducted at the COVID intensive care unit of tertiary care government hospital of Karachi, Pakistan. 190 patients admitted in five months from 1/2/2021 till 30/6/2021 were included in the study. Platelet counts were recorded at presentation and all patients were also followed to observe if they develop thrombocytopenia during the course of hospital stay. The patient outcome and need for mechanical ventilation was assessed 28 days after admission and compared with the frequency of thrombocytopenia. Thrombocytopenia was seen in 26.8% (n=51) admitted patients. Among these, 68.6% patients had thrombocytopenia at presentation and 31.4% patients developed thrombocytopenia during the course of hospital stay. The range of platelet count in thrombocytopenic patients was $11x10^9$ - $150x10^9$. Mean platelets count in thrombocytopenic patients was $110x10^9$ (SD 33). Mortality in patients who developed thrombocytopenia was 73.6% and 56.9.2% in patients without thrombocytopenia (p 0.034). Patients with thrombocytopenia were more likely to require mechanical ventilation (p 0.024). Thrombocytopenia is frequently observed in patients with severe COVID-19and can be used as a tool for risk stratification.

Keywords: Thrombocytopenia, COVID 19, mortality rate, mechanical ventilation.

INTRODUCTION

The spectrum of Covid-19 ranges from asymptomatic to symptomatic infection (Mizumoto *et al*., 2020, Huang *et al*., 2020). The disease is characterized by SpO2 <94% at room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg, respiratory frequency >30 breaths/min, or lung infiltrates >50% (Roy *et al*., 2019). The presence of thrombocytopenia has been seen as an initial manifestation of COVID-19infection (Ahmed *et al*., 2020). There are many mechanisms thought to be responsible for development of the thrombocytopenia in COVID19 patients including direct infection of bone marrow precursor cells, destruction of bone marrow precursors during cytokine release storm, immune destruction of platelets and platelet consumption in the lungs in microthrombi (Xu *et al*., 2020).

Considering the of severity of condition and unpredictable outcome several prediction tools based on clinical and laboratory parameters have been proposed to identify the patients who are more likely to develop severe illness and adverse clinical outcomes (Wynants *et al*., 2020).

Mild thrombocytopenia ($100\text{-}150x10^9$/L) has been identified in severe cases of COVID-19 and patients with severe disease have been reported with lower platelet counts when compared those with non-severe disease (Wool and Miller, 2021). Furthermore, data have shown that patients who did not survive had a significantly lower platelet count than survivors and that is highlighting that the substantial decrease in platelet count may be a marker of worsening illness (Lippi *et al*., 2020). In this regard the study was designed to determine the incidence of thrombocytopenia in severe covid-19 infection and its effect on clinical outcomes.

MATERIALS AND METHODS

This was a cross-sectional study conducted at the COVID isolation ward of tertiary care government hospitals of Karachi, Pakistan. Patients admitted over a period of five months from 1/2/2021-30/6/2021 were included in the study. The total number of SARS cov2 positive patients admitted during the period of study was 372. However, after application of inclusion and exclusion criteria, the data of 190 patients were recorded. The study was approved by the ethical committee of tertiary care hospital (No.F.2-81/2021/GENL/Conf9/JPMC).

The set inclusion criteria were adult patients aged >18years and positive PCR test for Covid-19. Exclusion criteria were previous respiratory pathologies including interstitial lung disease, chronic pulmonary disease and pulmonary tuberculosis; heart failure; chronic liver disease or chronic kidney disease; history of malignancy; use of immunosuppressive drugs including long term steroids; sepsis; recent major surgical procedures and other causes of thrombocytopenia including DIC and drug induced thrombocytopenia.

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The thrombocytopenia was defined as platelet count less than $150x10^9$/L. Severe infection was defined as SpO2 <94% on room air at sea level or a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300mm Hg or respiratory frequency >30 breaths/min >50% Lung infiltrates on imaging.

After informed consent, blood samples of all the patients were drawn for routine laboratory tests within 24 hours of admission. The routine tests include arterial blood gas analysis, complete blood count, liver function tests, renal function tests, coloring profile and inflammatory markers (C reactive protein, Lactate dehydrogenase, D Dimers and Ferritin). The Chest X-rays within 24 hours of admission was advised to determine the degree of lung involvement.

The demographic characteristics of patients; including age, gender and comorbidities were also recorded. Outcome variables were duration of hospital stay, total duration of oxygen therapy, total duration of invasive or non-invasive ventilation and clinical status of the patient on 28^{th} day of admission.

STATISTICAL ANALYSIS

Data was analyzed using SPSS version 26. Mean and Standard deviation were calculated for Hemoglobin, Total leukocyte count, Neutrophil lymphocyte ratio, Platelets, Urea, Creatinine, Glomerular filtration rate, CRP, LDH and D-Dimers. Frequencies and percentages were calculated for gender and comorbidities. The rest of the data was organized into categorical variables, including age range, presence or absence of thrombocytopenia, PiO2/FiO2 ratio, oxygen requirement, duration of hospital stay, duration of oxygen therapy and duration of invasive and non-invasive ventilation. Chi-square test was used to analyze categorical variables. P-value of less than 0.05 was considered as statistically significant.

RESULTS

There were 62.1% males and 37.9% females patients admitted during the study duration with covid-19 infection. The mean age of the patients was 57 (SD 12) years. The most common reported symptoms at the time of admission were fever, cough, shortness of breath, and fatigue or generalized weakness and most of the patients i.e. 51.6% had PO_2/FiO_2 ratio less than 100. Patient demographics, comorbidities and clinical manifestations are depicted in table 1.

Mean platelet count of the investigated patients was $238.0x10^3$ (SD 99.9). Thrombocytopenia was seen in 26.8% (n=51) admitted patients. Among these patients, 68.6% had thrombocytopenia at the time of presentation while 31.4% developed thrombocytopenia during the course of hospital stay. The range of platelet count in admitted patients was from $11x10^9$-$561x10^9$ and in those who developed thrombocytopenia was from $11x10^9$-$150x10^9$. Among the patients who developed thrombocytopenia 96% had platelet counts more than $53x10^9$ only two patients (4%) had platelets counts less than $50x10^9$. Mean duration of thrombocytopenia was 3.5 (SD 3.8) days. Thrombocytopenia was more commonly seen in males than females. The lab findings of the study participants are represented in table 2.

All patients received bolus doses of IV methylprednisolone followed by dexamethasone. Remdesivir was administered in 74.6% patients only 4.2% patients received Tocilizumab. Anticoagulant (enoxaparin/heparin) at treatment dose was administered in 73.0% patients while 26.5% received prophylactic dose of anticoagulants. Due to contraindications, anticoagulant was not administered in two patients. Furthermore, aspirin was administered to 58.2% patients who had a high cardiovascular disease risk score.

Most patients i.e. 38.1% stayed in the hospital for 0-7 days followed by 34.9% who stayed for 7-14 days and 6.3% who stayed for more than 28 days. Duration of oxygen therapy varied in the admitted patients 40.5% received it for 0-7 days (40.5%). Non-invasive ventilation was given to 65.3% patients and invasive ventilation was required by 41.6% of patients.

The outcome recorded by the 28th day of the admission for 61.6% patients was death. However, 28.4% were discharged on room air, 4.2% remained admitted with oxygen support and 3.7% remained admitted with non-invasive ventilation. The outcome of the studied population is shown in table 3.

Mortality in patients who developed thrombocytopenia was reported to be 73.6% while mortality in patients who did not develop thrombocytopenia was 56.9% (p 0.034). Patients who had thrombocytopenia were more likely to require mechanical ventilation (p 0.024). There were no significant differences in comparison in duration of hospital stay, duration of oxygen therapy, duration of invasive and non-invasive ventilation. Table 4 represents the Comparison of the incidence of thrombocytopenia in different groups of patients

DISCUSSION

The incidence of thrombocytopenia in patients with severe COVID-19 pneumonia and its effect on clinical outcomes and disease progression were studied in the current study. Many studies, have reported the incidence of thrombocytopenia in mild and severe COVID-19 cases. Some studies have also highlighted the predictive effect of thrombocytopenia on mortality. However, there is a lack of large cohort studies in the South Asian population.

Table 1: Patients demographics, comorbidities, and clinical characteristics

Demographic/ comorbidity Frequency(percentage)								
Gender	Male				Female			
	118 (62.1)				72 (37.9)			
Age Groups	20-30	30-40	40-50		50-60	60-70		>70
	4 (2.1)	11 (5.8)	38 (20.0)		41 (21.6)	50 (26.3)		46 (24.2)
Co-morbidities	Diabetes		Hypertension		Ischemic Heart Disease			Others
	95 (50.0)		84 (44.2)		18 (9.5)			12 (6.3%)
Clinical Manifestation	Fever	Cough	Sore Throat	Shortness of breath	Diarrhea	Nausea/ vomiting	Fatigue	Others
	147 (75.4%)	113 (57.9%)	8 (4.1%)	186 (95.4%)	7 (3.6%)	6 (3.1%)	12 (6.2%)	11 (5.6%)
Oxygen saturation at room temperature	90-93%	80-89%	70-79%		60-69%	50-59%		<50%
	4 (2.1%)	54 (28.6%)	49 (25.9%)		37 (19.6%)	31 (16.4%)		14 (7.4%)
Need of oxygen in liters during admission	1-5L/min		6-10L/min		11-15L/min		>15L/min	
	21 (10.8%)		35 (17.9%)		27 (13.8%)		107 (54.9%)	
PO2/FiO2 ratio	<100		100-200		200-300		>300	
	98 (51.6%)		54 (28.4%)		37 (19.5%)		1 (0.5%)	
Mechanical ventilation during hospital stay	Non-invasive ventilation				Invasive ventilation			
	128 (67.4%)				76 (40.0%)			

Table 2: Patients' Laboratory findings at presentation

Laboratory value at presentation	Mean +/- Standard deviation
Hemoglobin	12.4± 1.9
Total leukocyte count	11.9 ± 5.0
Neutrophil lymphocyte ratio	11.1 ± 8.2
Platelets	238.5±99.9
Blood Urea Nitrogen	29.1±19.8
Creatinine	1.4±1.5
Glomerular filtration rate	69.7±30.6
C Reactive Protein	126.6±148.7
D Dimers	4.4±5.9
Lactate Dehydrogenase	825.3±486.8
Ferritin	903.1±573.9
International Normalized ratio	1.1±0.8
Serum sodium	137.4±6.0
Serum potassium	3.9±0.7
Total bilirubin	0.6±0.4
Alkaline phosphatase	150.5±110.4
Alanine aminotransferase	65.9±138.4

Table 3: Outcome of the studied population

	Outcome	Number of cases/(percentages)
Outcome after 28 days	Death	117 (61.6%)
	Discharged on room air	54 (28.4%)
	Discharged on home oxygen	4 (2.1%)
	Admitted with oxygen support via mask/nasal canula	186 (97.9%)
	Admitted with non-invasive ventilation	7 (3.7%)
	Admitted with invasive ventilation	1 (0.5%)
Duration of hospital stay	0-7 days	73(38.4%)
	More than 7 days	117 (61.6%)
Duration of oxygen therapy	0-7 days	76 (40%)
	More than 7 days	114 (60%)
Duration of non-invasive ventilation	0-7 days	84 (44.2%)
	More than 7 days	44 (23.1%)
Duration of invasive ventilation	0-7 days	68 (35.8%)
	More than 7 days	8 (4.2%)

Table 4: Chi square test - Comparison of the incidence of thrombocytopenia in different groups of patients

Grouping variable	Outcome	No. of cases	p-value
Need for mechanical ventilation	Yes	44	0.024*
	No	9	
Outcome at 28 days	Survivor	14	0.034*
	Non-Survivor	39	
Duration of hospital stay	0-7 days	20	0.904
	More than 7 days	33	
Duration of oxygen therapy	0-7days	20	0.692
	More than 7 days	33	
Duration of non-invasive ventilation	0-7 days	27	0.763
	More than 7 days	13	
Duration of invasive ventilation	0-7 days	20	0.638
	More than 7 days	3	

*Statistically significant

Similar to previously known causes of severe pneumonia, SARS (severe acute respiratory distress syndrome) and MERS (Middle East respiratory syndrome), thrombocytopenia has also been reported in patients infected with covid-19 (Petrosillo *et al*., 2020). It has been documented that the incidence of thrombocytopenia in COVID 19 patients varies according to the degree of disease severity (Wool and Miller, 2021). In the current study, 26.8% prevalence of thrombocytopenia was identified. According to documented studies from China the incidence of thrombocytopenia ranges from 4.9%-36.2% (Guan *et al*., 2020) and in Hong Kong it was reported as 44.8% which is highlights the importance of studying thrombocytopenia as a risk factor for worst outcome (Yang *et al*., 2005). A weighted incidence of 12.4% has been reported across the globe in a metanalysis of 24 studies (Xiaolong Z *et al*., 2021). A study carried out in a tertiary care hospital in Pakistan on 100 patients with COVID 19, revealed an incidence of 14% among admitted patients (Asghar *et al*., 2020). Studies carried out in India have revealed an incidence of 31.2% and 21.8% (Bhandary *et al*., 2020, Bansal *et al*., 2020). Cumulatively if we look at the reported figures of south Asian countries the incidence of thrombocytopenia lies between the range of 21-30%.

A study carried out on 170 patients in Pakistan revealed a platelet count of 147-331x10^9 with a mean of 198x10^9 among survivors and 239x10^9 among non-survivors (Sarfaraz *et al*., 2021). Another study carried out on 167 patients in China revealed a platelet count of 77x10^3 to 119x10^3 with a mean of 109x10^9 among COVID 19 patients who developed thrombocytopenia (Yuan *et al*., 2021). This was in parallel with our study which also revealed a platelet count of 53x10^9 till 150x10^9 in 96% of patients with thrombocytopenia. However, 2 patients had platelet counts less than 50x10^9.

Multiple cases of severe thrombocytopenia have been reported in COVID 19 patients secondary to a mechanism similar to immune thrombocytopenic purpura (ITP) (Bomhof *et al*., 2020, Lorenzo *et al*., (2020), Chen W *et al*., 2020, Deruelle *et al*., 2020, Hindilerden *et al* 2020). ITP usually occurs after the first week of infection with covid-19 (Mahévas *et al*., 2020, Bhattacharjee and Banerjee, 2020). Severe thrombocytopenia has also been reported in COVID 19 patients who develop disseminated intravascular coagulation (Terpos *et al*., 2020). In our study, out of 190 patients, 2 patients developed severe thrombocytopenia, i.e platelet counts less than 50x10^9. Both were male patients more than 60 years.

The current study revealed a significantly higher mortality in patients who developed thrombocytopenia then those who did not. Patients who developed thrombocytopenia were more likely to require mechanical ventilation. However, there were no significant differences in duration of hospital stay, duration of oxygen therapy, duration of invasive ventilation and duration of non-invasive ventilation. There was no significant correlation between nadir platelet counts and outcome of the patients. A large sample sized study, conducted in China, concluded that thrombocytopenia is common in patients with COVID-19, and it is associated with increased risk of in-hospital mortality. The lower the platelet count, the higher the chances of mortality (Yang *et al*., 2020). A meta-analysis of 9 studies from different parts of the world concluded similar results and suggested that low platelet counts in COVID 19 patients should serve as clinical indicator of worsening illness during hospitalization (Lippi *et al*., 2020).

The main limitation of our study was the wide clinical heterogeneity at presentation. Due to social taboos and lack of awareness, patients seek help at local inexperienced centers and present late in the course of disease at tertiary care government hospitals of Pakistan. Additionally, IL-6 inhibitors were not easily available at the hospital. All of these could have had an impact on the clinical course and outcome of patients. Thrombocytopenia has also been associated with

disseminated intravascular coagulation in COVID 19 patients (Bao *et al*., 2020). However, our patients with severe thrombocytopenia were not evaluated for it.

In summary, we concluded that the presence of thrombocytopenia is frequently seen at presentation in severe covid-19 patients and can be used for predicting the need for mechanical ventilation and mortality. However, it may not be a reliable marker in predicting long term outcomes of severe COVID-19 infections in resource limited settings. Larger multicentered trials are needed to further validate the results of current study.

CONCLUSION

Thrombocytopenia is frequently seen in patients with severe COVID-19 pneumonia, and is associated with a higher mortality rate and need for mechanical ventilation. The presence of thrombocytopenia can be used as a tool for risk stratification in COVID-19 patients.

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