

## THROMBOCYTOPENIA AND ITS ASSOCIATION WITH COVID-19 INFECTION

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### ABSTRACT

**Objective:** To analyze association of thrombocytopenia with severity of COVID-19 disease.

**Study Design:** Cross sectional study.

**Place and Duration of Study:** Department of Pathology, Pak Emirates Military Hospital, Rawalpindi during the month of Apr 2020.

**Methodology:** Study population consisted of 100 confirmed cases of COVID-19 infection admitted in Pak Emirates Military Hospital (PEMH), Rawalpindi. Cases were confirmed by real time polymerase chain reaction (RT-PCR) performed on pharyngeal swabs. Patients were divided into two groups critical and non critical after obtaining the informed consent and approval from the ethical committee. Platelet counts were collected and categorized as 0-50, 51-100, 101-150 and more than 150.

**Results:** Mean age of the study population was  $43.57 \pm 14.4$  years Thrombocytopenia was present in 33.33% of critical and 12.85% of non critical patients. Out of total 100 patients 4 deceased and 96 survived. Among all the patients with thrombocytopenia (n=19) there were 21.05% non survivors and 78.94% survivors. Significant thrombocytopenia was seen among 4 non survivor cases, 3 were placed in first category (PLT<50) and 1 was placed in second category (plt 51-100). Out of 10 critical patients with thrombocytopenia 40% could not survive.

**Conclusion:** Thrombocytopenia has a significant association with COVID-19 patients and is associated with high mortality rate. It is a reliable marker for clinicians as these patients have high mortality and are more prone to develop complications.

**Keywords:** Corona virus disease 2019 (COVID-19), Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Thrombocytopenia.

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### INTRODUCTION

Corona virus disease 2019 (CoVID-19) is a novel infectious disease which is rapidly spreading across the world and is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)<sup>1</sup>. The disease started in the form of an outbreak from Wuhan, Hubei province, China, in December 2019 extended globally and turned into a great pandemic that entered Pakistan on 26th February 2020<sup>2</sup>. WHO announced outbreak as a serious health emergency on 30 January and a global pandemic on 11 March<sup>3</sup>. The disease received its official name by WHO as COVID 19 on 11 February 2020<sup>4</sup>. The 2019 novel coronavirus is believed to be related to severe acute respiratory syndrome-like (SARS-like) bat viruses due to

its sequence identity to bat- CoV<sup>5</sup>.

Six coronaviruses have been identified so far that can cause infection in humans (HCoV-229E, HCoVOC43, HCoV-NL63, HCoV-HKU1, SARS-CoV, and MERS-CoV). The first four viruses cause common cold whereas the SARS-CoV and MERS-CoV were responsible for severe acute respiratory syndrome and Middle East respiratory syndrome (MERS) respectively that occurred in the past. The most commonly presenting symptoms observed in COVID-19 patients are fever, fatigue and dry cough followed by shortness of breath<sup>6</sup>. Person to person transmissions occurs via droplet and contact<sup>7</sup>. Common laboratory findings in patients with COVID-19 infection include lymphopenia, thrombocytopenia, raised LDH and inflammatory markers (eg, CRP, ESR and ferritin), deranged coagulation profile and raised D-Dimers<sup>8</sup>. There are no established laboratory markers for early detection and evaluation

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of the disease severity. The aim of the study was to detect thrombocytopenia in patients with COVID-19 disease and identify patients who are at a higher risk of developing severe disease and to prevent mortality and improve clinical outcome.

## METHODOLOGY

This cross sectional study was planned and carried out in the Department of Hematology, Army Medical College, National University of Medical Sciences, Rawalpindi in collaboration with Pak Emirates Military Hospital, Rawalpindi. The study was conducted during the first week of April, after the approval of Ethical Review Board/Committee, Army Medical College, NUMS, Rawalpindi.

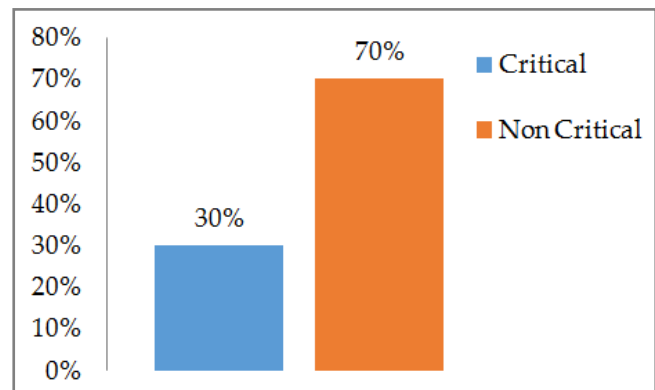
In this study we utilized consecutive samples of COVID 19 positive patients delivered to pathology lab of PEMH at the time of admission. A total of 100 patients were included in the study using the non probability consecutive sampling and informed consent was obtained from all patients. The sample size was calculated by WHO sample size calculator using a reference prevalence of thrombocytopenia as 8%, taking confidence Interval of 95%, margin of error 5% and power of test 80%. Our sample size came out to be 100. COVID positive patients of both genders and all ages were included in the study. Patients who were PCR positive for COVID 19 and refused to give informed consent were excluded from the study. None of the patients had a history of thrombocytopenia or taking any treatment for it. Brief history and demographics were recorded and participant's information was kept confidential. Every study subject was allotted a code number. Data was not accessible to anyone outside the research team.

Under sterile conditions 5.0ml of venous blood sample was drawn from COVID 19 positive patients, transferred to EDTA anticoagulated tube and submitted to lab. The sample was run on sysmex X P100 for complete blood picture inclusive of platelet counts. Patients were divided into two groups critical and non critical depend-

ing upon the severity of their symptoms. Samples of critical patients were received from ICU/HDU whereas samples of non critical patients were received from wards. Categorical variables were analyzed as frequencies and percentages and continuous variables were computed as means and Standard deviations. Chi square was used to determine variances among groups and categorical correlation. Data was entered and analyzed by using Statistical Package for Social Sciences (SPSS) version 22. The *p*-value of <0.05 was considered as significant.

## RESULTS

We analyzed the platelet counts of 100 consecutive COVID 19 infected patients during the month of April 2020. The critical patients admitted in ICU/HDU had respiratory failure, shock or multiorgan dysfunction while non critical patients had either none or mild respiratory symptoms. There were 30 patients in the critical group and 70 patients in non-critical



**Figure: Illness status of patients.**

group. Illness status of all admitted patients is represented in the figure.

Average age of COVID 19 patients was  $43.57 \pm 14.4$  years. The minimum and maximum age was observed as 20 and 75 years respectively (Age range = 55 years) (table-I).

Patients were categorized into four categories according to the grade of thrombocytopenia. group 1:  $\leq 50$ , group 2:  $\leq 100$ , group 3:  $\leq 150$  and group 4: More than  $>150$ . Chi square was used to assess the association of thrombocytopenia with

severity of disease and a significant *p*-value of 0.04 was obtained. Our statistics showed that out of total 100 patients 19 (19%) showed thrombocytopenia, 10 (33.3%) in ICU patients and 9 (12.85%) in non ICU patients respectively. Categorical outcome of all categories alongwith the frequency of thrombocytopenia in both groups is represented in table-II.

A higher frequency of thrombocytopenia was seen in critical group as compared to non-critical group. Moreover, patients with thrombocytopenia showed poor clinical outcome. Our results showed that out of total 100 patients 4 deceased and 96 survived. Among all the patients with thrombocytopenia in both groups there were 4 (21.05%) non survivors and 15 (78.94%)

platelet counts range from 150,000 to 450,000 platelets per microliter<sup>10</sup>. Thrombocytopenia is associated with an increased risk of sepsis and DIC<sup>11</sup>. It is frequently observed in many viral illnesses endemic to our region like dengue fever, HCV, HIV, CMV and human herpes-6 virus<sup>12</sup>. The relationship between viral infections and platelet counts has already been accepted in the past<sup>13</sup>. SARS-CoV-2 causes thrombocytopenia in the same way as is caused by SARS-CoV and HCoV229E viruses. It enters and invades the bone marrow cells and platelets through CD<sup>13</sup> receptors which leads to growth inhibition and induction of apoptosis in bone marrow. Thrombocytopenia occurs as a result of inhibition of haematopoiesis and reduced primary platelet formation<sup>14</sup>. Thrombocytopenia is a common

**Table-I: Descriptive statistics of age (years) of all patients (n=100).**

|             |         | COVID 19     | Critical       | Non-Critical  |
|-------------|---------|--------------|----------------|---------------|
| Age (years) | N       | 100          | 30             | 70            |
|             | Mean    | 43.57 ± 14.4 | 57.77 ± 14.019 | 37.49 ± 9.958 |
|             | Minimum | 20           | 20             | 21            |
|             | Maximum | 75           | 75             | 60            |

**Table-II: Frequency of Thrombocytopenia In Critical And Non Critical Patients.**

| Thrombocytopenia                   | Critical   | Non Critical | <i>p</i> -value |
|------------------------------------|------------|--------------|-----------------|
|                                    | Frequency  | Frequency    |                 |
| Less Than 50 x 10 <sup>9</sup> /L  | 3 (10%)    | -            | 0.043           |
| Less Than 100 x 10 <sup>9</sup> /L | 3 (10%)    | 3 (4.3%)     |                 |
| Less Than 150 x 10 <sup>9</sup> /L | 4 (13.3%)  | 6 (8.6%)     |                 |
| More Than 150 x 10 <sup>9</sup> /L | 20 (66.7%) | 61 (87.1%)   |                 |

survivors. All the 4 non-survivors were older in age, belonged to critical group and were thrombocytopenic. Significantly, low platelet counts were observed among non-survivors. 3 of them were placed in category 1 (plt less than 50) and 1 was placed in category 2 (plt less than 100). Among the patients with thrombocytopenia in the critical group 10 (40%) of patients with thrombocytopenia could not survive.

Patients in the non-critical group recovered and were discharged with follow up advice. Remaining patients in the critical group were still under care.

## DISCUSSION

After erythrocytes, platelets are the second most abundant population in blood. Normal

finding in patients with COVID 19 disease and is considered as one of the important risk factors for an increased in hospital mortality<sup>15</sup>. The estimated mortality rate in this zoonotic disease is 2-5%<sup>16</sup>. Role of thrombocytopenia, an indicator of disease severity has not been established in patients with COVID-19 infection and attention is required to establish the the parameter of platelet counts in screening of critical and non critical cases. Platelet counts can be a useful parameter in predicting severe disease in COVID-19 positive patients and in discriminating them from non severe cases. Henry *et al* have recommended in their study close monitoring of platelet counts as a marker for potential progression to critical illness along with other hematological and

biochemical markers like WBC counts, IL-6 and serum ferritin<sup>17</sup>.

Our analysis revealed 19% of patients with thrombocytopenia in this study group i.e. platelet count less than  $150 \times 10^9/L$  with significant *p*-value of less than 0.05. Thrombocytopenia was most significant in severe cases even leading to death of some critical patients. In all the patients with thrombocytopenia there were 4 (21.05%) non survivors and 15 (78.94%) survivors. It was observed that all the 4 non survivors belonged to the critical group whereas remaining 15 survivors with thrombocytopenia belonged to both groups. Platelet count was low in both survivors and non survivors but in our study significantly low platelet counts were seen among non survivors. All non survivors were more than 60 years of age which indicated that older people are liable to become critically ill. Thrombocytopenia also remained significant in non critical group but patients remained asymptomatic and their platelet count did not decrease to a level at which bleeding occurs. These patients were recovered and were discharged with follow up advice. Patients with abnormal counts stayed in hospital longer than those with normal counts.

Thrombocytopenia shows significant correlation with critical and non critical group in lot of studies. Huang *et al* reported thrombocytopenia in 8% of ICU patients and 4% of non ICU patients, however, the frequencies observed in their study was less than ours and their *p*-value remained insignificant<sup>9</sup>. Wang *et al* also did not find any significant difference in platelet counts between ICU and non ICU groups and reported a *p*-value of 0.78 which is dissimilar to our study results<sup>18</sup>. Larsen *et al* found thrombocytopenia in 5-40% of COVID-19 patients and established significant association between thrombocytopenia at the time of admission and disease severity. There was no clinical and radiological remission in COVID-19 patients after 10 days suggesting disease progression<sup>19</sup>. Our results were comparable to Lippi *et al* results who reported more pronounced thrombocytopenia and a higher mortality rate in patients with severe

COVID-19 disease with substantially low platelet counts which was comparable to our study<sup>20</sup>.

### LIMITATION OF STUDY

The limitation of the study is that these are single time admission laboratory results. Therefore, thrombocytopenia was not reflected in the initial reports of many patients who dropped their counts later on and Could not be included in the study included in the study. As this is an ongoing process, further research is required to relate thrombocytopenia to COVID-19 infection and its severity for better clinical outcome of patients.

### CONCLUSION

Our findings suggest that platelet counts are a good predictor of disease severity and mortality and they can be used as a useful tool for timely discriminating patients with severe disease and thus improving the clinical outcome. It is a reliable marker for clinicians to be on guard in patients with thrombocytopenia and prevent complications and mortality.

### CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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