Section: Pathology

Original Research Article

COVID-19 INFECTION AND ITS EFFECT ON PLATELET COUNT AND MEAN PLATELET VOLUME - EVALUATION AT TERTIARY TEACHING HOSPITAL

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is a novel infectious viral disease, with insufficient well-established diagnostic laboratory parameters that could be used to evaluate disease severity and its complications which alters hemodynamics of the body which include thrombocytopenia, thromboembolism or other cardiovascular events and helps to predict clinical prognosis. It is known to cause serious respiratory symptoms and involvement of other body systems such as, neurological and the immune system. We aimed to explore the platelet count and Mean platelet volume (MPV)and related risk factors in patients with COVID-19.

Materials and Methods: This is a retrospective, hospital record based, longitudinal study patients who tested RT PCR positive with symptoms of COVID-19. We included both home quarantine and hospitalized patients for whom basic hematological investigations were done. We estimated the platelet count and Mean platelet volume of all the positive patients.

Results: Out of 2596 patients were diagnosed of COVID -19 infection 2553(98.34%) patients survived and43 (1.65%) patients died. There is male preponderance of 1609 (62%) and females were 987(38%). Moderate COVID-19 illness was present in 34.82% of all patients; severe illness was seen in 4.58%andmajority of patients were of mild symptoms of about 60.63%. Patients with severe thrombocytopenia were seen in146 patients of5.62%in the study. MPV in our study is increased in severe COVID 19 positive patients.

Conclusion: In conclusion, Low platelet count is associated with abnormal coagulation function and increased risk of DIC, severe disease manifestation and increased mortality in patients with COVID-19. In addition, the mean platelet volume may be used as an auxiliary test in predicting the mortality in COVID-19 patients. About 45.9% patients are above 60 years of age group.

Keywords: Corona virus disease (COVID- 19), Platelet count (PC), Mean platelet volume(MPV), thrombocytopenia.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a novel infectious viral disease, with insufficient well-established diagnostic laboratory parameters that could be used to evaluate disease severity and its complications which include thromboembolism or cardiovascular events and to predict clinical prognosis. Coagulation cascade and functions have not been well studied in the COVID-19 patients.[1]

The novel virus was named 2019 Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) by WHO; due to more than 79% homology with SARS-CoV, SARS-CoV-2 was responsible for coronavirus disease 2019 (COVID-19).This novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread globally and became pandemic since December 2019. In December 2019, a series of pneumonia cases of unknown etiology emerged in Wuhan, Central China with a population

of 11 million people and was thought to be related to an exposure from Huanan Seafood Wholesale Market. This condition was later confirmed to be the coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Different from normal pathogens, this virus is powerful and has extended rapidly to other Chinese cities and countries, thus leading to the widespread of pneumonia. The number of COVID-19 cases has sharply increased in China and outside China, and the number of affected countries increased. By its alarming levels of spread and severity, the World Health Organization characterized COVID-19 as a pandemic on March 11, 2020. COVID-19 poses a great public health and clinical burden worldwide. SARS-CoV-2 was quickly transmitted among humans, threatening human life and generating many financial losses. SARS-CoV-2 spread occurs by inhalation or ingestion of viral droplets. Thus, the main sources of human infection are contact with any contaminated surfaces, viral droplets can spread from one to two meters and settle on surfaces or with the respiratory droplets of infected people, e.g. through sneezing, coughing or physical contact. SARS-CoV-2 infection can also occur by touching the nose, eyes or mouth with hands contaminated with the virus Coronavirus disease 2019 (COVID-19) causes a spectrum of disease with severe proinflammatory state which can be associated with a unique coagulopathy and procoagulant endothelial phenotype.

Common symptoms include fever, dry cough/expectoration, fatigue, upper respiratory congestion, gastrointestinal symptoms, loss of smell, loss of taste,appetite and myalgia/arthralgia of both small and large joints. Most patients present mild symptoms, but it may progress to severe symptoms in some patients especially the elderly and/or patients with comorbidities like Diabetes, Heart and kidney problems.Severe patients develop rapidly into acute respiratory failure, acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis, and coagulation disorders leading to Multi Organ Failure and Sudden Cardiac arrest. The prognosis of patients with severe pneumonia of COVID- 19 is worse than that of patients with mild type. Early recognization of the risk factors of severe pneumonia contributes to antecedent intervention, which shows crucial clinical significance for the treatment and prognosis of patients.

Platelets are the smallest and extremely reactive blood components. Many studies have provided abundant evidence for their multifunctional nature. Blood platelets are the first to accumulate at the site of damage, where they change in shape and show formation of pseudopodia, local release of cytoplasmic granular content, and aggregation, when activated by classical agonists, such as ADP, TXA2, PAF, and inflammatory cytokines, e.g., IL-1, IL-6, and TNF alpha. They are first to be involved in the processes of fibrosis and maintenance of normal hemostasis.

Mean platelet volume (MPV) gives important information on the course and prognosis in many pathological conditions, such as cardiovascular diseases, respiratory diseases, Crohn's disease, rheumatoid arthritis, juvenile systemic lupus erythematous, diabetes mellitus, and the majority of neoplastic diseases.[20]

Hematological parameters have recently gained more attention due to reports of thrombocytopenia, impaired oxygen transport, and hypercoagulable state in Covid patients. Currently, research work is been carried out by many institutions on literature of COVID-19, while it prevailing all around the world. It remains crucial for us to understand its symptoms and various presentations to assist with early identification and help in disease containment. In the diagnosis of COVID-19, the platelet count and platelet indices are easily accessible, inexpensive, and important parameters in terms of differential diagnosis and can help in the differentiation of COVID-19 from influenza during seasonal outbreaks of the latter. 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.

Complex pathophysiology involves infection and systemic inflammatory response, causing a series of reactions such as coagulation activation, liver damage, myocardial damage, and kidney damage. Platelets play a significant role in the procedure of inflammation and coagulation, activated platelets release a great number of substances, which belong to the key factors of inflammation. Mean platelet volume (MPV) has been regarded as a surrogate marker of platelet activation. Mean platelet volume was a useful prognostic indicator for critical patients. Mean platelet volume ranges between 7.5 and 12.0 fl. PC ranges from 1.5 lakh cells /cmm to 4 lakh cells/cmm. The combination of MPV and Platelet count could be more clinically significant than MPV or PC alone.3,4,5Mean platelet volume/platelet count ratio (MPR) is considered to be a crucial marker of inflammatory and infectious diseases.[10]

Initially, COVID-19 infection produces a prominent elevation of fibrinogen and D-dimer/fibrin degradation products. This is associated with systemic hypercoagulability and frequent venous thromboembolic events. The degree of D-dimer elevation positively correlates with mortality in COVID-19 patients. It is known to cause serious respiratory symptoms and involvement of other body systems such as, neurological and the immune system.[2,11] Moreover, recent postmortem studies have shown evidence of widespread thrombosis in pulmonary vasculature and other organs.

MPV is inversely proportional to the platelet count, which is associated with hemostasis maintenance and preservation of constant platelet mass. This means that the increased production of platelets is accompanied by a reduction in their mean volume. Markedly enhanced or abnormal thrombocytopoiesis,

increased wear, or the effect of activating factors on blood platelets may lead to changes in the proportions between Mean platelet volume and Platelet count. Mean platelet volume correlates with platelet activity and is thus considered a marker of platelet activity. Elevated Mean platelet volume correlates with increased platelet aggregation, enhanced synthesis, and release of thromboxane TXA2 and β-thromboglobulin.Increased mean platelet volume (MPV), a sensitive indicator of circulating platelet activity and a prognostic marker in thrombo inflammation, has also been reported in association with specific viral infections. Nowadays, determination of platelet count and Mean platelet volume is commonly accepted and recommended by the International Committee for Standardization in Hematology (ICSH), can provide important information on the course and prognosis in many inflammatory conditions.[19]

The present study is a hospital record -based retrospective study conducted in all patients with laboratory-confirmed COVID-19 to evaluate the association between Platelet Count and Mean Platelet Volume and mortality, particularly the dynamic changes of circulating platelets and its role in the disease progression.

MATERIAL AND METHODS

In this hospital record -based retrospective study we studied patients from October 2020 to March 2021, at the Tertiary teaching hospital, Government General Hospital, Mahabubnagar District in Telangana, India. In this period, a total of 2596 patients were diagnosed as COVID-19. We screened all the symptomatic patients who attended Triage OP and of which patients who were tested RT PCR positive were included in the study. Complete blood count, C-reactive protein (CRP), D- dimer and biochemistry tests are routinely performed on patients who attended the Triage OP with complaints compatible with COVID-19 such as cough, cold, myalgia, loss of smell and taste, fever, headache, sore throat and shortness of breath. Samples of peripheral blood were collected into tubes with ethylenediaminetetraacetic acid. Mean platelet volume and platelet Count were determined using an automated blood cell analyzer (XN 1000-25152, Sysmex) together with examination of Leishman stained peripheral blood smears. Also, Lung Computed Tomography (CT) is performed on patients who have shortness of breath, after their examination by the doctor. Patients with oxygen saturation (SPO2) above 95% and with mild symptoms were advised home quarantine, these were categorised as mild cases. And patients were treated with oxygen support with SPO2 of 90 -95%, these were categorised as moderate cases. Oxygen saturation (SPO2) below 90% and with severe symptoms werecategorized as severe cases. We included all the patients of mild,moderate and severe cases in our study. Informed consent was taken from all the patients.

Statistical Analysis

The prevalence in this study was determined from the proposition of individuals and the total study population and is expressed as percentage. Descriptive statistics of variable and other characteristics of sampled population were calculated and tabulated and are expressed as percentages. All the statistical analysis was done using the Statistical Package for Social Sciences (SPSS) SOFTWARE PACKAGE VERSION 20.

RESULTS

Total of 2596 patients were diagnosed of COVID -19 infection from October 2020 to March 2021, at the Tertiary teaching hospital, Government General Hospital, Mahabubnagar were included in the study. Out of which 2553(98.34%) patients survived and 43 (1.65%) patients died, it is shown inpictorial representation in figure 1. There is male preponderance of 1609 (62%) and females were 987(38%) which is depicted in figure 2. Majority of the patients in our study were above 60yrs of age group which constitute of about 45.9%. Age distribution of covid infected persons in the study is shown in the table 1.

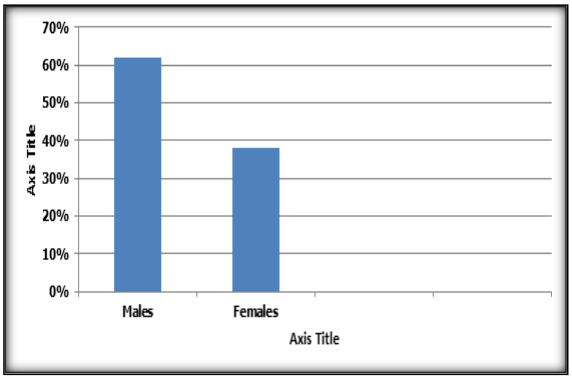

Figure 1: Showing Percentage of Male Preponderance

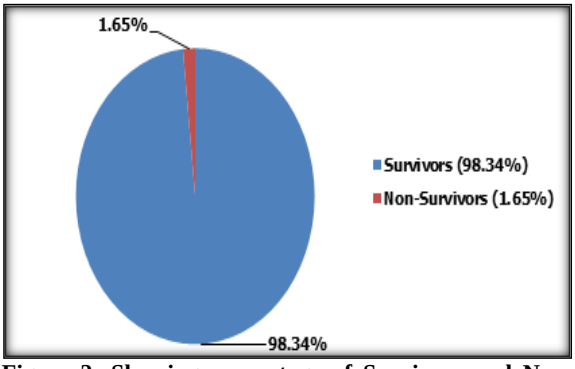

Figure 2: Showing percentage of Survivors and Non survivors

Majority of the study population had wide range of comorbidities. Moderate COVID-19 illness was present in 34.82% of all patients; severe illness was seen in 4.58%andmajority of patients were ofmild

symptomsof60.63%were reported. Categorization of covid patients in the study based on symptoms is shown in table 2.

A total of 354 COVID-19 patients with normal platelet count were included in the study who had COVID symptoms and were tested COVID positive.Majority of cases showed mild thrombocytopenia of about 1107 (42.64%). And patients with severe thrombocytopenia were of about146 (5.62%). Patients categorized based on platelet count is shown in the table 3.

Mean platelet volume is estimated in all the patients which is negatively correlated with Platelet count. In severely ill patients Mean platelet volume is high in the present study. All the patients who were with low platelet count coming under severe thrombocytopenia showedMPV >18fl. Patients with moderate thrombocytopenia showed Mean platelet volume of 15 – 18 fl and patients with mild thrombocytopenia showed Mean platelet volume of 12 – 15 fl which is depicted in table 3.

Variability of Platelet Count and their MPV Values in survivors and non survivors in the Present Study is Shown in table 4.

Table 1: Showing Age Distribution of Covid Infected Persons in the Study

Age Group	< 39 yrs	40 -59 yrs	> 60yrs
Total	591	812	1193
Percentage (%)	22.7	31.2	45.9

Table 2: Showing Symptomatic Categorization of Covid Patients in the Study based on Symptoms

Categorization	Mild	Moderate	Severe
Total no. of Patients	1574	904	118
Percentage	60.63%	34.82%	4.54%

Table 3: Showing Patients Categorized Based on Platelet Count and their MPV Values in the Present Study

Platelet Count	Mild Thrombocytopenia (1-1.5 lakh/ cmm)	Moderate Thrombocytopenia (50000-1 lakh/ cmm)	SevereThrombocytopenia(Less than 50000/cmm)	Normal count (1.5-4.0 lakh/ cmm)
Total no. of Patients	1107	989	146	354
Percentage	42.64%	38.09%	5.62%	13.63%
Range of Platelet Volume among patients	12– 15fl	15- 18fl	> 18fl	7.5 -12 fl

Table 4: Showing Variability of Platelet Count and their MPV Values in survivors and non survivors of the Present Study

Variables	Survivors	Non-survivors	t-value [95% CI]	P-value
Platelet Count in lakh/ cmm (Mean±SD)	124000± 12000	48000±6000	42.3	0.001*
MPV in fL (Mean±SD)	15±2	18±1.5	10.019	0.001*

DISCUSSION

In this study we investigated the change in platelet count among mild, moderate and severe cases suffering from COVID-19. An increase in MPV is correlated with thrombosis and inflammatory conditions. Therefore, MPV has always been considerедusefulprognosticindicatorforcritical patients.

Viral infection may affect hematopoiesis, in which SARS-CoV-2 may potentially impact megakaryocyte maturation and platelet production.6The mechanism behind could be abnormal megakaryocyte maturation in severe coronavirus infection.[7]

Possible mechanisms of COVID-19- associated thrombocytopenia –

A. Platelet activation and subsequent clearance by reticulo-endothelial system.

- Activation by increased thrombin generation and consumptive coagulopathy.
- Direct viral-platelet interaction activation.
- Associated with formation of platelet-leukocyte aggregates.

B. Platelet clearance due to increased endothelial damage.

- Pulmonary vasculature-specific.
- Widespread damage.

C. Platelet autoantibody formation, with subsequent platelet clearance bySplenic/ hepatic sequestration.

D. Marrow/ megakaryocyte suppression

- Due to inflammatory response.
- Due to direct viral infection.
- Due to reduced thrombopoietin.

Firstly, under the condition of inflammation, platelet production will increase owing to the increased

synthesis of thrombopoietin mediated by multifarious cytokines. Secondly, Mean platelet volume reflects the metabolism and proliferation of megakaryocytes and platelet production in bone marrow.In the beginning, when infection occurs, the release of many inflammatory cytokines (such as interleukin (IL-1,3,6),and tumor necrosis factor-α (TNF-α)) increases, leading to the increase of thrombopoietin and the expression of young platelets in the blood stream,which causes the increase of Mean platelet volume. Besides, after stress induced platelet destruction, the decrease of Platelet count further stimulates megakaryocyte to produce a large number of platelets, which also leads to an increase of Mean platelet volume. Thirdly, adverse prognosis in patients with decreased Platelet count and elevated MPV may be associated with increased risk of oxidative stress, thrombosis, and apoptosis in activated platelets.[10]

The mechanism of change in platelet indices in COVID-19 patients is probably multifactorial. Generally, platelet production increases as platelet count decreases. An increased number of young platelets is also functionally more active than older platelets. The large proplatelet fragments may indicate abnormal fragmentation of megakaryocytes. The lungs have been identified as a primary site of terminal platelet production, accounting for approximately 50% of total platelet production.[11]One could postulate that the damage to the lung results in disordered megakaryocyte fragmentation or disruption of the normal filtration of megakaryocytes in the pulmonary circulation, leaving increased megakaryocytes in the blood. Indeed, a large number of megakaryocytes have been found in the pulmonary capillaries at autopsy. Additionally, megakaryocytes are a rich source of cytokines and growth factors that have the potential to influence inflammatory or fibrotic lung diseases.[12]

We found that platelet count in severe cases decreased more than in the mild, moderate cases. Similar findings were observed in the studies done by ChangqianBao et al.,1Lippi Get al,[2]., Zhou M et al.,[3]Severe COVID-19 infection has been associated with thrombocytopenia in previous studies of Zhou Met al., Rodriguez-Morales AJ et al., Muhammad Asghar et al,[,6,12,13]Our results support these findings, the percentage of patients with thrombocytopenia was 86.37% in all COVID-19 patients and5.62% of patients have severe thrombocytopenia and most of the severe symptomatic covid cases have thrombocytopenia indicating thrombocytopenia to be a marker of severe disease.It might be considered that initial diagnosis of thrombocytopenia is associated with poor prognosis in COVID-19 patients.

Platelet counts upon admission were generally lower in severe compared to non-severe cases,[15,16] As well, low platelet numbers were identified as a prognostic factor in multiple smaller studies that included adults and the elderly.[17,18]

NumerousstudieshavehoweverstudiedMPVasabiomarkerinvarioussystemicconditions. Apart from low platelet numbers, increased mean platelet volume (MPV) has also been documented in COVID-19 patients in the study by Yu H et al,[18] Mean platelet volume is negatively correlated with Platelet Count in severe patients .Ranias et al,[14] have shown that if pneumonia occurs in patients with ischemic stroke, an increase in the MPV/PC ratio could predict 30 days mortality.Mean platelet volume in our study is increased in severe COVID 19 positive patients which is coinciding with finding of study done by Ertuğrulet al.[9]

CONCLUSION

In conclusion, coagulopathy is a non-negligible complication and potentially important cause of death in patients with critical COVID-19. Dynamically monitoring haematological and coagulation parameters, such as platelet count and D-dimer, might provide a reliable and convenient method for classifying and predicting the severity and outcomes of patients with COVID-19. In addition, the mean platelet volume may be used as an auxiliary test in predicting the mortality in COVID-19 patients. The widespread availability of automated hematologyanalyzers in hospitals and laboratories now permit accurate measurement of mean platelet volume and other indices. Bone marrow examination remains the gold standard for Thrombocytopenia, mean platelet volume is definitely a useful and reliable test. Thrombocytopenia in COVID-19 patients could be used as an effective biomarker to guide bone marrow damage, disease severity, possible deterioration of intravascular coagulation defect and vascular endothelial activation during viral sepsis induced biological catastrophic cascades. Thestudyofany correlationbetweenroutinemonitoring markers, platelet indices,and disease process will help to devise a cost-efficient monitoring plan for COVID-19 affected patients globally especiallyinunder developed countries.

Measures to prevent infection include frequent hand-washing and maintaining adequate social distancing and avoiding touching the face. Medical masks are recommended for those suspected of carrying the virus and for the people caring for them. Therefore, the correct hand hygiene, use of personal protective equipment's and social isolation are very important strategies in combating the transmission of SARS-CoV-2. Quarantine measures should be established to restrict the movement of uninfected people in regions where there is an epidemic outbreak and infected people, who can act as spreading the virus agents as long as the symptoms last until clinical recovery.[21]

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