Original Article

Association of Thrombocytopenia and C-reactive Protein in COVID-19 Patients Attending a Tertiary Care Hospital

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ABSTRACT

OBJECTIVE: This study evaluates the frequency and relationship between Thrombocytopenia and CRP levels in Covid-19 patients.

METHODOLOGY: The cross-sectional retrospective study was conducted at Dr. Ishrat ul Ebad Khan Institute of Blood Diseases from October 2021 to September 2022. Data was collected from existing data from the blood bank and hematology laboratory. *C reactive protein (*CRP) and complete blood count (CBC) levels were observed in Covid-19 patients. Both genders, all age groups, COVID-19 patients and patients having Thrombocytopenia and raised levels of CRP were included in this study. At the same time, other bone marrow transplant patients and other infectious diseases such as Hepatitis B, Hepatitis C, Dengue, and Malaria were excluded from this study. *Statistical analysis was done by using the SPSS 20.0 version.*

RESULTS: Out of 844 patients, the mean age was 50 years, and the male proportion was high at 70% (n=590). Most patients, 95% (n=803) had grade 1 thrombocytopenia. The mean age was found to be higher (>50 years) in Grades 1 and 2 as compared to Grades 3 and 4, where we found (<40 years). A significant (p=0.002) mean age difference among grades was found. No significant (p=0.749) median difference in CRP among Grades were found.

CONCLUSION: The current study shows that COVID-19 significantly increases C-reactive protein levels. While treating and managing the patients of COVID-19, it is essential to detect the biomarkers that can predict the severity and prognosis of this disease.

KEYWORDS: Thrombocytopenia, Bleeding, C-reactive Protein, COVID-19

INTRODUCTION

Thrombocytopenia has been reported in up to 36% of individuals infected with the coronavirus responsible for coronavirus disease 2019 (COVID-19), the severe acute respiratory syndrome coronavirus 2 (SARSCoV2)[1]. Thrombocytopenia is usually modest in this context, produced by platelet activation and consumption[2,3]. The clinical importance of Thrombocytopenia varies depending on the clinical presentation. A primary hemostasis deficit accompanies Thrombocytopenia because platelets are necessary to maintain vessel wall integrity[4]. Clinically significant spontaneous bleeding does not often occur until the platelet count drops below 10-20 109/L. Thrombocytopenia, on the other hand, can increase surgical or traumatic bleeding or limit the administration of appropriate treatment for various illnesses (e.g., Antiviral therapy for chronic hepatitis C virus infection or cancer chemotherapy. In some circumstances, Thrombocytopenia is the only early indication of a more hazardous underlying problem (e.g., HIV infection or myelodysplastic syndromes), or it is a crucial sign of disease activity. Recognizing the cause of Thrombocytopenia has obvious clinical implications, but it can be challenging at times. Because of the potential consequences for the fetus, Thrombocytopenia in pregnancy deserves special attention. A structured approach to thrombocytopenia diagnosis includes the integration of clinical findings as well as appropriate support from the laboratory and other medical disciplines[4].

Low platelet counts are caused primarily by decreased production and increased platelet breakdown. Aplastic anemia, myelodysplastic syndromes, and chemotherapy-induced Thrombocytopenia are examples of bone marrow failure syndrome, whereas disorders, like disseminated intravascular coagulation (DIC) and thrombotic microangiopathies demonstrate more significant destruction. Platelet sequestration and hemodilution are two less common processes. Platelet sequestration is evident in portal hypertension -induced congestive splenomegaly, defined as platelet redistribution from the circulation pool to the splenic pool[5].

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Hemodilution occurs in individuals who have had significant blood loss and have received supportive treatment like Ringer lactate, Dextrose water or blood products. Multiple processes may contribute to the development of Thrombocytopenia in various types, such as primary immunological Thrombocytopenia (ITP), etc. Thrombocytopenia can complicate the hospitalization of individuals with several medical and surgical issues. Thrombocytopenia was seen in about 1% of adult inpatients[6]. However, only around a third of these patients had bleeding symptoms. Thrombocytopenia is substantially more common in intensive care units, where it is identified in 8%-68% of patients on admission and 13%-44% of patients during their stay[7]. Many distinct pathologies are frequently present in acute care situations (for example, sepsis, DIC, medications, and cardiac bypass surgery), and determining the source of Thrombocytopenia is not always possible. Because of its high infectiousness and high fatality in critically ill patients, Coronavirus Pneumonia (COVID-19) is a public health emergency. COVID-19 pathogenic and physiological processes, as well as diagnostic approaches, are still in the exploratory stage[8]. Clinical monitoring and effective treatment measures were required to reduce case fatality. It was necessary to investigate sensitive markers that reflect lung lesion changes and disease severity. C-reactive protein (CRP) levels can clinically recognize pneumonia, and patients with severe pneumonia had elevated CRP levels[9].

Despite genetic and intensive molecular testing, examining the peripheral blood film remains the critical question driving our approach to thrombocytopenia diagnosis. Each of the three blood cell lineages should be examined thoroughly. When investigating Thrombocytopenia in a critically ill patient, we must first determine whether the cause is thrombotic microangiopathies or acute leukaemia (blasts). Even little delays in making these diagnoses might be fatal if adequate treatment is not started immediately. Given that a variety of non-exclusive pathogenic pathways can cause Thrombocytopenia and that there are various possible reasons for Thrombocytopenia, an essential laboratory evaluation should include liver and renal function testing, as well as a clotting screen with D-dimers[10] as well as lactate dehydrogenase measurement.

Clinical findings and peripheral blood smear results should prompt further investigation. There is no single hematologic or biochemical test that can be used to rule out a specific thrombocytopenia mechanism. A BM aspirate and biopsy are advised to rule out a primary BM disease if the source of the Thrombocytopenia is unknown. Reticulated platelets or a comparable immature platelet fraction can help distinguish Thrombocytopenia from destructive Thrombocytopenia (low percentages, high percentages)[11,12]. Thrombocytopenia usually does not cause bleeding until the platelet count falls below 50,000/L.

Furthermore, when platelet count decreases below 20,000/L, the danger of spontaneous life-threatening bleeding (for example, in the central nervous system) increases proportionally. Most clinicians use platelet transfusions to prevent spontaneous hemorrhage when counts are between 10,000/L and 20,000/L. Identifying the origin of Thrombocytopenia has obvious clinical implications, although it can be challenging at times.

Hematological alterations are typical in COVID-19 individuals, including a decreased platelet and lymphocyte count but an average white blood cell count, Prolonged APTT, increased D-dimer levels, and average prothrombin time in the majority of cases (PT). In most cases, the platelet count did not drop to the point where bleeding occurred. However, the processes through which this coronavirus interferes with the hematopoietic system are unknown. In this study, we will analyze the hematological changes of Thrombocytopenia and CRP in COVID-19 patients and provide possible routes by which COVID-19 generates Thrombocytopenia.

METHODOLOGY

This cross-sectional retrospective research design study was conducted in Dr. Ishrat ul Ebad Khan's Institute of Blood Diseases (DIEKIBD) from October 2021 to September 2022. Data was collected from existing data from the blood bank and hematology laboratory. Statistical analysis was done by using the SPSS 20.0 version. Ethical approval was obtained from the Institutional Review Board (IRB) of Dow University of Health Sciences (DUHS), Karachi. (IRB-2170/DUHS/Approval/2021). CRP and CBC (for Thrombocytopenia) levels were observed in COVID-19 patients. Differences in the CRP levels and degree of Thrombocytopenia were also assessed. Thrombocytopenia was often discovered when obtaining a complete blood count during an office visit[13]. Both genders, all age groups, COVID-19 patients and patients having Thrombocytopenia and raised levels of CRP were included in this study. In comparison, other bone marrow transplant patients and other infectious diseases such as Hepatitis B, Hepatitis C, Dengue, and Malaria were excluded from this study.

The thrombocytopenic cases were classified into the four grades below based on platelet count[14]

Grade 1: 75-150 10 3 /L
Grade 2: 50-75 10 3 /L
Grade 3: 25-50 10 3 /L
Grade 4: 25 10 3 /L

CRP level interpretation[15,16]**:** Less than 0.3 mg/dL: Normal (level seen in most healthy adults).

Detection of COVID-19[17]**:** RT-PCR was the preferred SARS-CoV testing method.

RESULTS

Out of 844 patients, the mean age was 50 years, and the male proportion was high at 70% (n=590). Most patients, 95% (n=803) had grade 1 thrombocytopenia. (**Table I**)

The most common grades in males and females were Grade 1 (n=237, 93%) and (n=566, 96%) respectively. The mean age was found to be higher (>50 years) in Grades 1 and 2 as compared to Grades 3 and 4, where we found (<40 years). A significant (p=0.002) mean age difference among grades was found. The median (IQR) CRP was high in Grade 4 (78 (22–258)), followed by Grade 1(65(17-158)), Grade 2(60 (27–133)), and Grade 3 (78 (22–258)). No significant (p=0.749) median difference in CRP among Grades were found. (**Table II**)

Table I: Demographics Characteristics

Characteristics	N = 844 (%)
Age (years), Mean±SD	50.1±16.8
Gender	
Female	254 (30.1)
Male	590 (69.9)
Thrombocytopenia (x10^3 /µL)	
Grade 1 (75 - 150)	803 (95.1)
Grade 2 (50 - 75)	15 (1.8)
Grade 3 (25 - 50)	9 (1.1)
Grade 4 (<25)	17 (2.0)

Table II: Relationship of age, gender with Thrombocytopenia

Characteristics	Grade 1 N = 803 (%)	Grade 2 N = 15 (%)	Grade 3 N = 9 (%)	Grade 4 N = 17 (%)	P-value
Gender					
Female	237(93.3)	8 (3.1)	5 (2.0)	4 (1.6)	0.069$^£$
Male	566(95.9)	7 (1.2)	4 (0.7)	13 (2.2)	
Age[a] (years)	50.4±16.5	53.9±15.0	35.9±18.4	39.4±22.6	0.002^α
CRP[b] (unit?)	65.3(17.0–158.2)	60.1 (27.0–133.1)	47.5 (22.5–239.6)	77.8(22.0–257.5)	0.749^β

[a]Values represented as mean±standard deviation, [b]Values represented as median (interquartile range), [£]Fisher Exact Test, [α]One Way ANOVA, [β]Kruskal Wallis, CRP: C-reactive protein

DISCUSSION

While treating and managing the patients of COVID-19 in this modern era of medicine, it is essential to detect the biomarkers that can predict the severity and prognosis of this disease. The detection of these biomarkers is essential for clinical care[18]. While dealing with COVID-19 patients, it is noted that there is a vast range in the severity of the disease, which ranges from asymptomatic to very severe symptoms. In the current series, it was observed that the platelet count and C-reactive protein count could be simple, inexpensive, familiar and readily available laboratory tests that can evaluate the seriousness of the disease in COVID-19-positive cases. It was established that Thrombocytopenia is associated with the severity of COVID-19. This prothrombotic condition is due to a hyper-inflammatory state and cytokine storm caused by the viral infection and is likely due to endothelial and platelet activation. This finding is based on the study conducted by Guan WJ et al. in China[19]. Multiple factors can cause Thrombocytopenia in critically ill patients. The cause of Thrombocytopenia is thrombin-mediated platelet activation, the use of antibiotics, antivirals, heparin, and other regularly used medicines, as well as hemodialysis.

Moreover, platelet production may become low due to the virus's direct effect on the bone marrow or the reduced impact of thrombopoietin. In very severe cases of COVID-19 infection, multi-organ failure may exacerbate Thrombocytopenia. Nine studies of 1779 COVID-19 patients concluded that very severe disease is associated with lower platelet count (P < 0.001)[20]. Therefore, a lower platelet count is associated with the worse prognosis of the patient. This was supported by a study from Wuhan in which 1,476 patients with COVID-19 showed that mortality was increasing with progressively lower platelet counts. Other studies have also demonstrated that Thrombocytopenia is a marker of poor clinical outcomes in critically ill patients[21]. Another study regarding COVID-19 and coagulopathies shows that 10.3% of patients showed platelet count <100 × 109/L, and 2.5% showed <50 × 109/L during their hospital stay. On the other hand, four patients had platelet count <50 × 109/L with bleeding events[22].

A systemic inflammatory response is observed in COVID-19. Elevated serum C-reactive protein levels are associated with severe disease in bacterial or viral infections. The current series shows that COVID-19 significantly increases C-reactive protein levels; this may be due to alveolar damage caused by the virus, also seen in the SARS epidemic in 2002. Systemic symptoms are enhanced in old patients (aged >60 years) with extensive radiological ground-glass lung changes, lymphopenia, Thrombocytopenia, and

increased C-reactive protein and lactate dehydrogenase levels[23]. According to some studies, the level of plasma C-reactive protein was directly associated with the severity of COVID-19 pneumonia, and it was found that C-reactive protein is an early indicator for severe illness[24].

CONCLUSION

The current study shows that COVID-19 significantly increases C-reactive protein levels, possibly due to alveolar damage caused by the virus; this alveolar damage was also seen in the SARS epidemic in 2002. While treating and managing the patients of COVID-19 in this modern era of medicine, it is essential to detect the biomarkers that can predict the severity and prognosis of this disease. Systemic symptoms are more enhanced in elderly patients (aged >60 years) with extensive radiological ground-glass lung changes, lymphopenia, Thrombocytopenia, and increased C-reactive protein.

LIMITATIONS OF THE STUDY

The limitations of the current series are that it is a retrospective observational study. The initial level of C -reactive protein, performed at the time of hospital admission, was used for the primary analyses. All the patients were hospitalized at a single hospital at Dow University Hospital in Karachi. However, Dow Hospital represents a diverse cohort of COVID-19 patients from all four provinces of Pakistan. Immunosuppression optimizes clinical outcomes in individuals with severe COVID-19, and steroids were given at the doctor's discretion. The admitting physician's knowledge of the initial C-reactive protein concentration may have benefited later patient treatment. Due to a lack of data on steroid use, few patients were anticipated to get steroids before the initial C-reactive protein measurement during hospitalization. Some critically ill individuals were given steroids or tocilizumab in some situations. However, the information regarding drug administration, its duration of use or dosing of these drugs was not recorded in this study. Finally, only in-hospital outcomes were recorded, and associations between Thrombocytopenia and C-reactive protein and long-term outcomes after the discharge of the patients were not determined.

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AUTHOR CONTRIBUTIONS

Kouser S: Conceptualization; Design methodology and supervised the findings of this work
Abbas FF: Design research study, concept making, Project administration; Writing IRB committee for approval of research study, publishing
Khan N: critically reviewed the manuscript to investigate the cases, Implementation of critical experimental protocols
Farooqui WA: Data analysis, data interpretation
Kamil S: Acquisition of Data, statistical analysis, verified the analytical methods
Khan R: Data collection, Statistical analysis

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