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Thrombocytopenia and Predicting the Severity of Coronavirus 2019

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Abstract

Background: The novel coronavirus, SARS-COV-2, that has emerged as pneumonia (COVID-19), is raising global concern. The current study aimed to quantify the diagnostic value of platelet count for the disease severity assessment.

Methods: This retrospective study was conducted at Imam Reza Hospital of Mashhad, Iran (February to March 2020) and included 738 hospitalized patients with confirmed COVID-19. We utilized the Hospital Information System to extract demographic data and laboratory indices collected on admission and middle of hospitalization.

Results: The participants' mean age was 59.0 years, 64.6% male. As revealed by the first and second tests, thrombocytopenia (platelet count ≤ 150×10^9 per L) respectively occurred in 215 (29.1%) and 175 (23.7%) persons. Of thrombocytopenic patients, 71.6% were male, and 21.9% had severe forms of the disease on admission, while the proportions were raised to 72.6% and 26.3% in the middle, accordingly. The level of Lactate dehydrogenase (LDH) and Serum creatinine (SCr) were significantly increased in thrombocytopenic patients compared with regular groups, either on admission or in the middle of hospitalization.

Conclusion: Durable thrombocytopenia during hospitalization can be a potential prognostic value for COVID-19 patients.

Keywords: COVID-19; Thrombocytopenia; Severity

Introduction

During the past five months of novel Coronavirus Disease 2019 (COVID-19) outbreak until April 19, 2020, it has infected an estimated 2.2 million individuals. It has been responsible for more than 146 thousand deaths worldwide [1]. "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)" causes COVID-19 may lead to extremely contagious pneumonia [2,3]. The clinical spectrum of COVID-19 may vary from asymptomatic infection or moderate illness to severe viral pneumonia with respiratory failure [2,4,5]. Furthermore, severe COVID-19 cases is associated with a critical illness, such as acute respiratory distress syndrome (ARDS), multi-organ failure (MOF), and is eventually followed by intravascular coagulopathy [6].

A growing number evidence demonstrated that biomarkers are vital targets for evaluating the patient's condition and illness severity. Low platelet count as a biomarker is readily and simply available, and thrombocytopenia is described to represent a predictive factor for recovery and recognized risks as well [7,8]. Thrombocytopenia may be more potent than other leading risk groups such as severe conditions such as multiple organ dysfunction score (MODS) and acute physiology and chronic health evaluation (APACHE) II [9]. In 55% of patients with acute respiratory syndrome (SARS) thrombocytopenia were seen and was considered as a notable mortality risk factor [10,11].

However, the link between thrombocytopenia and clinical features in COVID-19 infected patients has been poorly studied so far. Considering that thrombocytosis bears an essential role in antimicrobial defenses as well as coagulation cascade, we hypothesized that the severity of COVID-19 might be correlate with irregular platelet count. In this study, we attempted to address the question of whether the platelet count could discriminate between COVID-19 patients with or without severe condition.

Patients and Methods

This single-center retrospective study was conducted at Imam Reza Hospital (Mashhad, Iran). We enrolled a total of 738 adult patients with a confirmation of SARS-CoV-2 infection, who admitted to the Imam Reza Covid center from February to March 2020. The definite diagnosis was based on real-time Polymerase Chain Reaction tests, or alteration in chest CT scan and laboratory assay(s). One hundred and thirty participants, who met the WHO criteria for severe signs of the disease, were transferred to the intensive care unit (ICU). The severe form of the infection was considered at the presence of any of the following conditions: respiratory rate (RR) above 30 breaths/min, oxygen saturation (SpO2) below 90% [12]. Most patients were taking Hydroxychloqune and Azythromycin or ciprofloxacin, and based on their clinical course other medication such as Kaletra, corticosteroid IVIG and supportive care were added.

We extracted data from medical data recorded on hospital Information System. Laboratory indices of the patients, including erythrocyte sedimentation rate, C-reactive protein, lactate dehydrogenase, as well as platelet count.

All serum samples have been collected on admission and during hospitalization. Coagulation functions such as prothrombin time (PT) and activated partial thromboplastin time (APTT) were also detected. The statistical analyses of the records were carried out using Statistical Package for Social Science (SPSS, Chicago, IL, USA), version 16, and P.value less than 0.05 was considered significant.

This study received the ethics approval from Mashhad University of Medical Science Ethics Committee (No: 981800).

Results

A total of 738 patients were selected, the mean age was 59.0 years (range, 69.3-44.3 years) and 64.6% of them were men. Among all participants, 608 patients present with moderate disease (82.4%) and 130 with the severe-type (17.6%). Routine blood tests and serum biochemistry detection were performed on admission and re-examined during hospitalization about 5 days later. The initial test showed thrombocytopenia (platelet count ≤ 150×10^9 per L) in 215 individuals (29.1%), while 175 patients (23.7%) had thrombocytopenia according to the second test. Of all patients with thrombocytopenia, 71.6% and 72.6% were male on admission and during hospitalization, respectively. Based on the initial test, 21.9% and 19% of the patients with thrombocytopenia and normal platelet were transfer to the ICU respectively and there was no significant difference (p=0.074), but regarding the middle test during hospitalization, the scale raised by 26.3% in thrombocytopenic and decreased to15% in normal platelet count patients, so the difference became significant (p=0.002) (Table 1). Therefore, durable thrombocytopenia and male gender can be the risk factor for severity of covid 19.

As reported by both on admission and intermediate results, patients with thrombocytopenia showed considerably lower levels of Erythrocyte Sedimentation Rate (ESR) compared with those without thrombocytopenia, but patients with thrombocytosis (Plt>450×10^9 per L) had elevated ESR (*P*=0.000). Serum creatinine concentration (SCr) was comparable in the patients with normal platelet count and thrombocytopenia either in the initial tests or re-examination (*P*=0.001).The level of Lactate Dehydrogenase (LDH) was substantially higher in thrombocytopenic patients than with normal platelet count, measured by first (643.0 (453.5, 866.0) U/L *vs*. 571.0 (448.5, 786.5) U/L, P= 0.046) and middle tests (666.0 (467.0, 898.0) U/L *vs*. 571.0 (439.0, 771.0) U/L, *P*= 0.044). In the light of the analysis, no major differences were observed regarding the level of C-reactive protein (CRP) (Table 2).

	Categories of platelet count (10^9/L)			Total	P value
	≤150	150-450	>450		
First test					
Subjects, n	215	514	9	738	
Age (years), median (IQR)	60.4 (42.7, 70.1)	58.8 (45.5, 68.9)	57.1 (45.6, 67.0)	59.0 (44.3,69.1)	0.933
Sex (males), n (%)	154 (71.6)	319 (62.1)	4 (44.4)	477 (64.6)	0.016
Severe cases, n (%)	47 (21.9)	83 (16.1)	0 (0)	130 (17.6)	0.074
Middle test					
Subjects, n	175	545	18	738	
Age (years), median (IQR)	61.0 (42.1, 70.7)	58.4 (45.3, 68.1)	57.9 (50.0, 72.1)	59.0 (44.3,69.1)	0.996
Sex (males), n (%)	**127 (72.6)**	**339 (62.2)**	**11 (61.1)**	**477 (64.6)**	**0.038**
Severe cases, n (%)	46 (26.3)	83 (15.2)	1 (5.6)	130 (17.6)	0.002

Table 1: Demographic data of COVID-19 patients

Platelet count*	ESR	CRP	LDH	SCr	INR	PT	ATPP
First test							
≤150	44.0 (26.0, 61.0)	75.2 (30.3, 132.9)	643.0 (453.5, 866.0)	1.0 (.9, 1.3)	1.1 (1.0, 1.2)	12.9 (12.0, 13.9)	31.9 (29.5, 35.7)
150-450	54.0 (32.0, 85.0)	83.9 (35.4, 150.5)	571.0 (448.5, 786.5)	1.0 (.8, 1.1)	1.1 (1.0, 1.2)	12.8 (12.1, 13.7)	31.9 (29.2, 34.9)
>450	103.0 (77.0, 119.0)	55.8 (13.7, 137.5)	425.0 (321.0, 662.0)	0.8 (.8, 1.0)	1.1 (1.0, 1.2)	13.5 (12.4, 14.2)	30.3 (26.6, 33.8)
P value	0.000	0.216	0.046	0.001	0.641	0.579	0.273
Middle test							
≤150	41.0 (22.0, 57.0)	64.1 (25.5, 147.6)	666.0 (467.0, 898.0)	1.1 (.9, 1.4)	1.1 (1.0, 1.2)	13.1 (12.1, 14.5)	32.0 (29.5, 35.3)
150-450	54.0 (34.0, 84.0)	81.2 (34.7, 145.2)	571.0 (439.0, 771.0)	1.0 (.8, 1.2)	1.1 (1.0, 1.2)	12.8 (12.1, 13.7)	31.8 (29.2, 35.0)
>450	91.5 (56.8, 111.5)	71.0 (22.6, 203.0)	500.0 (364.5, 689.0)	0.9 (0.8, 1.1)	1.1 (1.0, 1.2)	12.9 (12.3, 13.5)	32.1 (29.5, 33.8)
P value	0.000	0.363	0.044	0.001	0.288	0.273	0.708

*10^9/L, ESR: Erythrocyte sedimentation rate (mm/h); CRP: C-reactive Protein (mg/L); LDH: Lactate dehydrogenase (U/L); SCr: Serum creatinine (mg/dL); INR: International normalized ratio; PT: Prothrombin time (s); APTT: Activated partial thromboplastin time (s)s

Table 2: Laboratory indices of COVID-19 patients

Discussion

In the presence of the accelerated rising of this new infection, identifying the biomarkers, which can predict the severity of the disease is vital to guide clinical care. As such, biomarkers play an essential role in distinguishing infected patients with the severe form of COVID-19. In our study, we found that platelet count could be an economical, rapid, and frequently available laboratory parameter that can easily discriminate between COVID-19 patients with and without the severe form of the disease. Lippi *et al.* also noted that thrombocytopenia is associated with a threefold enhanced risk of the severe form of COVID-19 [13]. Platelet expressed antimicrobial peptides are also identified as critical immune systems components by the defense against foreign pathogens [8]. As an illustration, thrombocytopenia is identified as a severity criterion and a predictive factor for mortality in hospitalized patients with community-acquired pneumonia (CAP) [14]. It is noteworthy that Zou *et al.* only utilized platelet count and hypoxemia as a prognostic model for SARS, and it represented 96.2% accuracy [15].

Various attempts have been performed to explain the underlying mechanism associated with thrombocytopenia in viral diseases. Thrombocytopenia may be due to microenvironment inflammation induced by coronaviruses and also cytokine storm, as well as platelets sequestration in lungs and liver. It is suggested that Coronavirus, such as SARS, may infect the cells of bone marrow and subsequently lead to growth inhibition, apoptosis induction, hematopoiesis, followed by reduced platelet generation along with raised platelets consumption in SARS- induced injured lungs [11,16,17]. The pulmonary tract may also be considered as a site of platelet releasing by mature megakaryocytes [18,19]. Besides, the damages to lung tissue following viral infection may cause platelet aggregation resulting in thrombocytopenia [11,18,19]. According to recent reports about the histopathological manifestation of COVID-19, widespread interstitial fibrosis was the predominant pathological pattern in the patient's lungs [20].

In demographic findings of our study, male participants showed a higher incidence of thrombocytopenia. As Zhou *et al.* reported in a study, the platelet count of non-survivor patients infected with COVID-19 in comparison with survivors was significantly lower, of which 70% were males [21]. Moreover, Zhao also showed that Asian males are at a more vulnerability to SARS-CoV-2 infection [22]. One possible explanation for male domination may rely on marked differences of immune responses between the adaptive immunity of males and females. Besides, the overall burden of viral infections, is evidently lower in fertility years of females [23].

In this study, we found that the thrombocytopenic population had elevated plasma creatinine levels (p.value=0.001). As Chen et al. described, the level of creatinine could progressively enhance as the clinical status of COVID-19 patients deteriorated [4]. So severe thrombocytopenia has been considered as a prognostic parameter, which may predict sequential and severe acute renal failure[24], and acute renal impairment in SARS may accompanied by high mortality [25].

Our results also demonstrated an increased serum LDH level in thrombocytopenic patients. Likewise, Pennell *et al.* declared that serum LDH activity has enhanced in most of the patients who were hospitalized for pneumocystis pneumonia, focal pulmonary tuberculosis, and bacterial pneumonia [26]. High LDH level represent damage of pulmonary endothelium and alveolar macrophages caused by various inflammation such as COVID 19.

In this study we cannot find the meaningful relation between ESR and CRP level with thrombocytopenia, but there was correlation between ESR and thrombocytosis, so it need study more about this relation.

There was no significant difference between level of coagulation tests like Pt, INR, PTT and thrombocytopenia, so the thrombocytopenia could not be a component of DIC.

Based on these correlations, when the virus induce thrombocytopenia because of bone marrow damage also can damage other organ such as lung, kidney and so on.

As a limitation of the current study, the underlying comorbidities of participants were not excluded. There was also incomplete laboratory testing of some cases, as well as the lack of exposure history.

Conclusion

In conclusion, durable thrombocytopenia during hospitalization in COVID-19 patients might be valuable prognostic factor for severe disease and other organ damage.

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