Original Research Article

The Prognostic Value of Thrombocytopenia in COVID-19 Pneumonia, Gezira Isolation Centers, Sudan.

Abstract

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes novel coronavirus disease 2019 (COVID-19), is spreading rapidly around the world. Thrombocytopenia in patients with COVID-19 has not been fully studied. To date no published works in Sudan describe thrombocytopenia among COVID-19 patients.

Objective: To study the prognostic value of thrombocytopenia in COVID-19 Pneumonia

Methods: A prospective cross-sectional study enrolled 140 COVID-19 patients in Gezira Isolation Centers during the period from November 2020 to February 2021. Data regarding demographics, clinical presentation, laboratory investigation, mode of oxygen therapy and outcomes were collected. Thrombocytopenia defined when platelets counts less than 150 x 10^3 cell/cumm.

Results: Among 140 patients, 86(61%) were males and 54(39%) were females, their mean age was 66.5±13.5 years. In outcomes, 91(65%) patients were recovered and 49(35%) were deceased. The mean of platelets count was 246±124 x 10^3 cell/cumm and 38(27.1%) patients had thrombocytopenia, among them 37(26.4%) patients had platelet count ranged from 51-149 x 10^3 cell/cumm and one (0.7%) patients had platelet count below 50 x 10^3 cell/cumm. Thrombocytopenic patients were significantly older than those without thrombocytopenia (70.9±9.1 years vs 64.8±14.4 years; P. value= 0.017). Also, thrombocytopenic patients were more tended to have hypertension (63.2% vs 44.1%; P. value= 0.025), diabetes mellitus (DM~~(~~; 63.2% vs 43.1%; P. value= 0.024), renal disease (65.8% vs 16.7%; P. value= 0.001), and lung disease (10.5% vs 0%; P. value= 0.041). Moreover, thrombocytopenic patients were more inclined to received mechanical ventilation (100%) and CPAP (81.8%) more than more than those without thrombocytopenia (P. value= 0.000). Thrombocytopenia was significantly correlated with mortality (67.3% vs 5.5%; P. value= 0.000). The AUC of thrombocytopenia (platelets count below 140 x ~~x~~ 10^3 cell/cumm) in detecting mortality was 0.830 (95% CI: 0.748-0.913; P. value= 0.000), with sensitivity of 86.8% and specificity of 84.3%.

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Conclusion: ~~the~~ The frequency of thrombocytopenia in Sudanese COVID-19 patients was high. The development of thrombocytopenia was significantly associated with older age, DM, hypertension, renal diseases and lung disease and invasive ventilation. Moreover, thrombocytopenia was significantly correlated with mortality

Keywords: COVID-19 patients, thrombocytopenia, Sudanese,

Introduction

In early December 2019, the first pneumonia cases of unknown origin were identified in Wuhan, the capital city of Hubei province. The pathogen has been identified as a novel enveloped RNA beta corona virus that has currently been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has a phylogenetic similarity to SARS-CoV. Patients with the infection have been documented both in hospitals and in family settings (1).

The World Health Organization (WHO) has recently declared coronavirus disease 2019 (COVID-19) a public health emergency of international concern. As of February 25, 2020, a total of 81,109 laboratory-confirmed cases had been documented globally and WHO recognized COVID-19 as pandemic (2)

The clinical syndrome is nonspecific and characterized by fever, headache and dry cough in the majority of patients, with about a third experiencing shortness of breath. Some patients have other symptoms such as myalgias, sore throat, and diarrhea. A complete or partial loss of the sense of smell (anosmia) has been reported as a potential history finding in patients eventually diagnosed with COVID-19, but this has not been a distinguishing feature in published studies. The median age of patients is between 49 and 56 years, median duration of 20 days. Cases in children have been rare. Although most cases appear to be mild, all patients admitted to the hospital have pneumonia with infiltrates on chest x-ray and ground glass opacities on chest computed tomography. About a third of patients subsequently developed acute respiratory distress syndrome and required care in the intensive care unit. This is particularly true for patients with comorbid conditions such as diabetes or hypertension (1).

Hematological changes such as thrombocytopenia and coagulation disorder in COVID-19 patients are not rare and thrombocytopenia was detected in 5–41.7% of the patients with COVID-19 (3)

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Currently, the possible mechanisms by which SARS-CoV-2 causes thrombocytopenia are speculated to involve the following: (A) an impaired haematopoietic microenvironment caused by systemic inflammation or cytokine storm, for example, elevated IL-1β, IL-1RA, IL-6, IL-8, IL-18, and TNF-α which ~~is~~ are a common phenomenon in SARS-CoV-2 infection (Wilson et al., 2020, PMID: 32706339; Chen et al., 2021, PMID: 34367188) and in radiation injury (Kiang et al., 2020 PMID: 32426105), could suppress haematopoiesis. (B) SARS-CoV-2 might directly infect haematopoietic stem cells or megakaryocytes through angiotensin-converting enzyme 2 (ACE2), CD13 or CD66a, as in other coronavirus infections that elicit thrombocytopenia. (C) antiviral antibodies cross-reacting with haematopoietic cells and (or) platelets, e.g. anti-adenovirus antibodies, can cross-react with platelet integrin GPIIb/IIIa. Indeed, Chen et al. (ref no.) showed that delayed-phase thrombocytopenia was the result of impaired maturation of megakaryocytes in COVID-19 patients. (D) An autopsy of nonsurvivors revealed thrombotic microangiopathy and disseminated intravascular coagulation, which lead to the increased consumption of platelets (reference needed). (E) Activated platelets can be scavenged via splenic/hepatic macrophages. In fact, two separate teams independently provided evidence that platelets are hyperactivated in COVID-19 patients. The activation of the Mitogen-activated protein kinase (MAPK) pathway could partially explain this platelet hyperreactivity (4).

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It has also been reported that decreased numbers of platelets may serve as a surrogate marker for poor prognosis in a wide range of infectious diseases, including rapidly evolving β-coronaviruses, and COVID-19 shall not be considered an exception to this rule. Taking advantage of this fact and bearing in mind that the results of several studies reported that low platelet count is associated with increased risk of having severe disease, it is reasonable to assume that thrombocytopenic COVID-19 patients will experience disease with a higher risk of adverse outcome (5)

Up to date and according to our best knowledge there ~~is~~ are no published works in Sudan ~~describe~~ describing the prognostic value of thrombocytopenia in COVID-19 patients, therefore in this study we aimed to assess the frequency and associates of thrombocytopenia among Sudanese COVID-19 patients

Material and methods

In ~~this is~~ a nonexperimental, cross-sectional study, a total of 140 COVID-19 patients diagnosed by defined reverse-transcriptase polymerase chain reaction (RT-PCR) test by nasopharyngeal swab were recruited from ~~in~~ Socotra Isolation Center and Mycetoma Isolation Center in Gezira State. These two isolation centers cover COVID-19 patients in Gezira state and near neighboring states. Patients with pre-existing thrombocytopenia or previously on drugs that cause thrombocytopenia were excluded.

At admission, the tests of complete blood count, including the platelet count, was conducted and repeated afterwards on the discretions of treating physicians. Thrombocytopenia was defined when platelets counts were less than 150 x 10^3 cell/cumm

The study was approved by the institutional ethics committee. Informed written consent to participate in the study was obtained from the study participants.

Data analysis

Data was analyzed by using a computer program Statistical Package for Social Sciences (SPSS V. 21.0). The analyzed data presented in tables and figures designed by Microsoft Excel 2010. ANOVA test was used as significance test for continuous variables and Chi-Square for categorical variable. Multiple receiver operating characteristic curve (ROC) was drawn to evaluate prognostic value of thrombocytopenia in detecting the mortality. P. value is significant at the level of 0.05 or less.

Results

In total this study included 140 COVID-19 patients, 86(61%) were males and 54(39%) were females, their mean age was 66.5±13.5 years and ranged from 20-90 years. Hypertension (n=69; 49.3) was the major commodities among our study patients. Most of the patients (n=106; 75.7%) presented with dyspnea. Out of 140 patients 99 received oxygen therapy, 33(23.6%) as CPAP, 27(19.3%) as non-rebreathing mask, 22(15.7%) as nasal mask and 11(7.9%) patients as simple face mask. Other detailed characteristics presented in table (1).

In outcomes, 91(65%) patients were recovered and normally discharged and 49(35%) were deceased (table 1)

Table (1): The baseline characteristics of COVID-19 patients

	N	%
Age (Yrs.); Mean ± SD	66.5±13.5	
Gender		
• Male	86	61.4
• Female	54	38.6
Comorbidities		
• Hypertension	69	49.3
• DM	68	48.6
• Renal disease	42	30
• CHF	5	3.6
• IHD	5	3.6
• Lung disease	4	2.9
• AF	2	1.4
Symptoms		
• Dyspnea	106	75.7
• Cough	93	66.4
• Fever	86	61.4
• Other	18	12.9
Oxygen therapy		
• None	41	29.3
• CPAP	33	23.6
• Non-rebreathing mask	27	19.3
• Nasal mask	22	15.7
• Simple face mask	11	7.9
• MV	6	4.3
Investigations		
Hemoglobin (g/dl); Mean ± SD	12.1±2.6	2.6
Leukocyte count (10^3 cell/cumm); Mean ± SD	13.5±6.7	6.7
Neutrophil (%); Mean ± SD	78.3±15.1	15.1
Lymphocyte (%); Mean ± SD	18±14.7	14.7
In-hospital outcomes		
• Discharge	91	65.0
• Death	49	35.0

DM; Diabetes Mellitus, CHF; Congestive Heart Failure, IHD; Ischemic Heart Disease, AF; Atrial Fibrillation, CPAP; Continuous Positive Airway Pressure, MV; mechanical ventilation

The mean of platelets count was found to be 246±124 x 10^3 cell/cumm and 38(27.1%) patients had thrombocytopenia, among them 37(26.4%) patients had platelet count ranged from 51-149 x 10^3 cell/cumm and one (0.7%) patients had platelet count below 50 x 10^3 cell/cumm (figure 1)

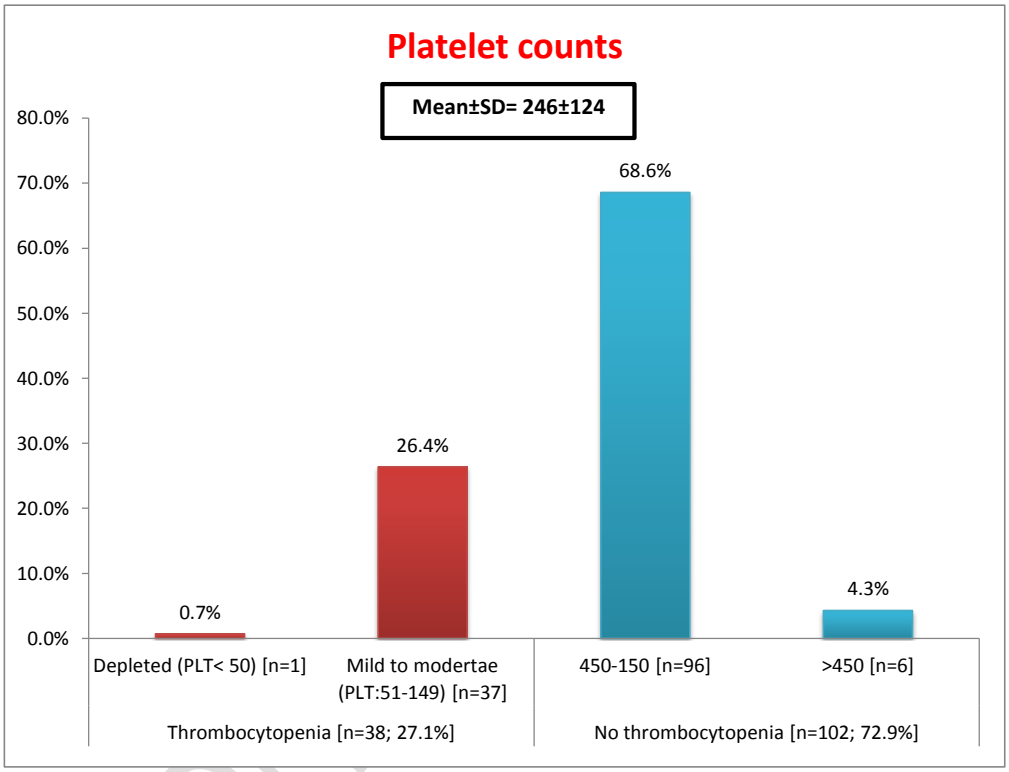

Figure 1: The platelets counts and thrombocytopenia among COVID-19 patients (N=140)

Table (2) revealed that, thrombocytopenia was significantly associated with advanced age (70.9±9.1 years vs 64.8±14.4 years; P. value= 0.017), hypertension (P. value= 0.025), DM (P. value= 0.024), renal diseases (P. value= 0.001), lung diseases (P. value= 0.041), MV and CPAP (P. value< 0.001)

Table (2): The factors associated with thrombocytopenia

	Thrombocytopenia	No Thrombocytopenia	P. value
Age (Yrs.); M±SD	70.9±9.1	64.8±14.4	0.017
Gender			
• Male	25(29.1%)	61(70.9%)	0.328
• Female	13(24.1%)	41(75.9%)	
Comorbidities			
• Hypertension	24(63.2%)	45(44.1%)	0.025
• DM	24(63.2%)	44(43.1%)	0.024
• Renal disease	25(65.8%)	17(16.7%)	0.001
• Lung disease	4(10.4%)	0(0%)	0.041
• CHF	2(5.3%)	3(2.9%)	0.413
• IHD	2(5.3%)	3(2.9%)	0.413
• AF	2(5.3%)	0(0%)	0.172
Symptoms			
• Dyspnea	32(84.2%)	74(72.5%)	0.110
• Cough	19(50%)	74(72.5%)	0.071
• Fever	19(50%)	67(65.7%)	0.065
• Other	7(18.4%)	11(10.7%)	0.296
Oxygen therapy			
• None	0(0%)	41(100%)	<0.001
• Nasal mask	0(0%)	22(100%)	
• Simple face mask	0(0%)	11(100%)	
• Non-rebreathing mask	5(18.5%)	22(81.5%)	
• CPAP	27(81.8%)	6(18.%)	
• MV	6(100%)	0(0%)	

DM; Diabetes Mellitus, CHF; Congestive Heart Failure, IHD; Ischemic Heart Disease, AF; Atrial Fibrillation, CPAP; Continuous Positive Airway Pressure, MV; mechanical ventilation

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Also, table (3) illustrated that, thrombocytopenia was significantly correlated with mortality (67.3% vs 5.5%; P. value= 0.000)

Table 3: The association between thrombocytopenia and outcomes

	Thrombocytopenia	No Thrombocytopenia	P. value
In-hospital outcomes			
• Discharge	5(5.5%)	86(94.5%)	<0.001
• Death	33(67.3%)	16(32.7%)	

Multiple receiver operating characteristic curve (ROC) was drawn to evaluate validity of platelets count in detecting mortality. As shown in figure (2); the AUC of thrombocytopenia (platelets count below 150 x x 10^3 cell/cumm) was 0.830 (95% CI: 0.748-0.913; P. value= 0.000), with sensitivity of 86.8% and specificity of 84.3%. Indicating thrombocytopenia is a significant prognostic indictor for mortality in COVID-19

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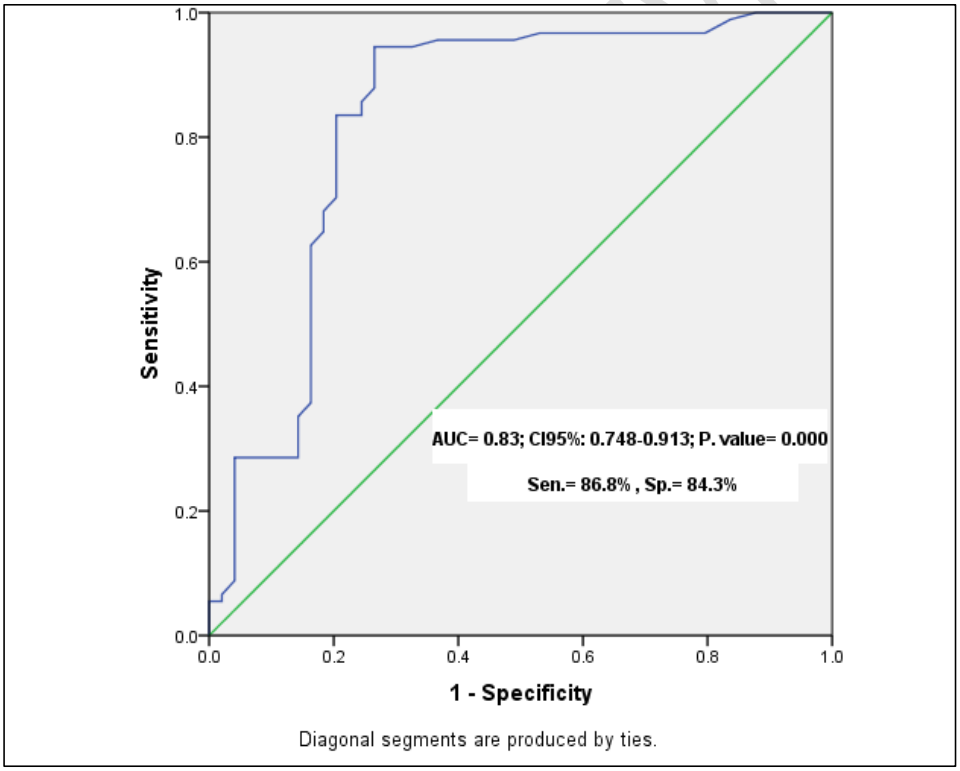

Figure 2: The multiple receiver operating characteristic curve (ROC) to evaluate prognostic value of thrombocytopenia in detecting the mortality

Discussion

This research, to the best of our knowledge, is the first study to describe the frequency, associates and prognostic value of thrombocytopenia in 140 Sudanese COVID-19 patients

In this study showed males were predominantly affected by COVID-19 more than females (61% vs 39%) with males to female ratio (1.5:1). Also several previous studies noticed that the incidence of SARS-CoV-2 infection is seen most often in adult male patients (1,6,7). In other side, many studies conducted by Li et al published in the New England Journal of Medicine (NEJM) (8) and Jian-Min J et al (9) observed similar susceptibility to SARS-CoV-2 between males and females. There is no clear explanation as to why men and women would be at different risk of infection; however some have proposed genetic mechanisms or sex-specific effects (10). Whether there are differences in risk of infection between men and women requires further research.

The mean age of study group was 66.5±13.5 years and ranged from 20-90 years. These results were comparable to Marta C et al in Italy (Median= 67.5 years) (11) and Jian-Min J et al in China (Medani= 62 years) (9). However, lowered means of age were reported by Chinese studies of Huang C et al (Median= 47 years) (1), Li et al. (Median= 49 years; 15-89 years) (8), and Chung et al (Median= 51 years) (12).

The data of this study suggest that dyspnea (n=106; 75.5%), cough (n=93; 66.4%) and fever (n= 86; 61.4%) were the frequent encountered presenting symptoms among almost all our study's patients. These symptoms could be explained by, in normal lung tissue, ACE2 (receptor of SARS- CoV- 2) is mainly expressed by type I and type II alveolar epithelial cells. It was reported that 83% of II type alveolar cells expressed ACE2. Therefore, SARS- CoV- 2 infection causes damages to most II type alveolar cells (13). Correspondingly, meta-analysis of Leiwen F et al that included 43 studies involving 3600 patients reported among COVID-19 patients, fever (83.3% (95% CI 78.4–87.7)), cough (60.3% (54.2–66.3)), and fatigue (38.0% (29.8–46.5)) were the most common clinical symptoms (14). In another meta-analysis conducted by Pengfei S et al (included a total number of 50466 patients with SARS- CoV- 2 infection) showed that, fever 89.1% (95% CI: 81.8%, 94.5%), cough 72.2% (95% CI: 65.7%, 78.2%), and muscle soreness or

fatigue was 42.5% (95% CI: 21.3%, 65.2%) were the major symptoms (15). Centre for disease control (CDC) also listed these symptoms to be the major symptoms (16).

Remarkably, the most common comorbidities were hypertension (n=69; 49.3%) and diabetes mellitus (n=68; 48.6%). This could be attributing to chronic diseases (such as hypertension and DM) can weaken the immune system and make pro-inflammatory conditions. The high preponderance of hypertension among our study patients as the major comorbid endorsed to ACEI and ARBs which is generally used in hypertension management, as in ~~a~~ one experimental study with animal models, both angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been shown to up-regulate ACE2 (receptor of SARS- CoV- 2) expression in the lung and heart (17).

Our findings were consistent with systemic review conducted by Azin T et al who analyzed 8 articles included 417 patients in which hypertension, diabetes, cardiovascular disease, and pulmonary disease were the most common morbidities among COVID-19 patients (18). Also, Subodh S et al reported among 1786 COVID-19 patients, hypertension (15.8%) is the most common comorbidity (19).

Based on thrombocytopenia definition of platelets count less than 150 x 103 cell/cumm; this study revealed that the frequency of thrombocytopenia was found to be 27.1% (n=38), among them 26.4% (n=37) had mild to moderate thrombocytopenia and 0.7% (n=1) had depleted thrombocytopenia. The etiology of thrombocytopenia is likely to be diverse and multifactorial as well yet not fully understood, there are several possible mechanisms by which COVID-19 infection could affect the platelets count including; (A) an impaired haematopoietic microenvironment caused by systemic inflammation or cytokine storm, for example, elevated IL-6, which is a common phenomenon in SARS-CoV-2 infection, could suppress haematopoiesis. (B) SARS-CoV-2 might directly infect haematopoietic stem cells or megakaryocytes through angiotensin-converting enzyme 2 (ACE2), CD13 or CD66a, as in other coronavirus infections that elicit thrombocytopenia. (C) antiviral antibodies cross-reacting with haematopoietic cells and (or) platelets, e.g. anti-adenovirus antibodies, can cross-react with platelet integrin GPIIb/IIIa. Indeed, Chen et al. showed that delayed-phase thrombocytopenia was the result of impaired maturation of megakaryocytes in COVID-19 patients. (D) An autopsy of nonsurvivors

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revealed thrombotic microangiopathy and disseminated intravascular coagulation, which lead to the increased consumption of platelets. (E) Activated platelets can be scavenged via splenic/hepatic macrophages. In fact, two separate teams independently provided evidence that platelets are hyperactivated in COVID-19 patients. The activation of the Mitogen-activated protein kinase pathway could partially explain this platelet hyperreactivity (4).

Our frequency of thrombocytopenia was in the range of literature as 5–41.7% of the patients with COVID-19 had thrombocytopenia (3), also our rate was sharply similar to Guan W et al who reported the rate of thrombocytopenia was 26.6% (20), lower than study of Chang D et al (21) and Liu Y et al (22) those found thrombocytopenia in 72.5% and 41.7%, respectively, and higher than study of Huang C et al who mention 5% of the patients with COVID-19 had thrombocytopenia (23).

This study showed that, thrombocytopenic patients were significantly older than those without thrombocytopenia (70.9±9.1 years vs 64.8±14.4 years; P. value= 0.017). Consistently the meta-analysis of Sukrita and Mainak~~et al~~ reported that older COVID-19 patients aged above 60 years (median= 62 years) were more tended to have immune thrombocytopenia secondary to COVID-19 (24). Also, the systemic review conducted by Heng M et al mentioned that advanced age is one of high-risk factors for thrombosis (those in arteries, veins or microthrombosis) and thus causing thrombocytopenia (4)

Remarkably, thrombocytopenic patients were more tended to have hypertension (63.2% vs 44.1%; P. value= 0.025), DM (63.2% vs 43.1%; P. value= 0.024), renal disease (65.8% vs 16.7%; P. value= 0.001), and lung disease (10.5% vs 0%; P. value= 0.041) more than those without thrombocytopenia. These findings were in agreement with the systemic review conducted by Heng M et al who reported that hypertension and DM are determinants of thrombosis and consequently ~~causing~~ leading to thrombocytopenia (4)

Fascinatingly, the current study demonstrated that thrombocytopenia was associated with severe forms of COVID-19 that required invasive ventilation, as thrombocytopenic patients were more tended to received mechanical ventilation (100%) and CPAP (81.8%) more than ~~more than~~ those without thrombocytopenia (P. value= 0.000). ~~these~~ These findings could be explained by invasive ventilation ~~worsen~~ exacerbating the haemodynamic effects and cause the ventilator-

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induced lung injury leading to further cytokine release and multi-organ dysfunction syndrome (24), and subsequently causing thrombocytopenia. Our findings were in accordance with meta-analysis of Li Q et al (25) and Jiang SQ (26) ~~those~~ which analyzed 613 COVID-19 patients and noticed that patients with severe disease had a lower platelet count than those with non-severe disease. Also, ~~in meta-analysis of~~ Giuseppe L et al ~~who~~ reviewed nine studies with 1779 COVID-19 patients and reported that thrombocytopenia is associated with an increased risk of severe disease (27).

One of the most ~~interested~~ interesting findings ~~of~~ in the present study is thrombocytopenia was significantly correlated with mortality (67.3% vs 5.5%; P. value= 0.000). Correspondingly, Thrombocytopenia at admission in COVID-19 patients was associated with a 4.24-fold increased risk of inpatient mortality in a study from Wuhan (28). Also, similar ~~ailr~~ to our findings, Li Q et al (25), Jiang SQ (26), Yang et al (29) and Xiaobo Y et al (30) reported Thrombocytopenia is common in patients with COVID-19, and it is associated with increased risk of in-hospital mortality.

Finally, through multiple receiver operating characteristic curve (ROC), the AUC of thrombocytopenia (platelet~~s~~ counts below 150 x ~~x~~ 10^3 cell/cumm) was 0.830 (95% CI: 0.748-0.913; P. value= 0.000), with sensitivity of 86.8% and specificity of 84.3%. Indicating thrombocytopenia is a significant prognostic indictor for mortality in COVID-19 patients.

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Conclusion

The present study concluded that, the frequency of thrombocytopenia in Sudanese COVID-19 patients was high. The development of thrombocytopenia was multifactorial. Moreover, thrombocytopenia was significantly correlated with the COVID-19-induced mortality.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms~~. Informed consent obtained for~~ from patients for studies within this publication~~participation~~.

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