# ***Original Research Article***

Clinical significance and outcome of COVID-19 patients with thrombocytopenia in Intensive care unit: A single centre study


**Abstract**

Introduction

SARS-CoV-2 infection can cause manifestations in multiple systems in the body.[1] Haematological system can also be affected by both SARS-CoV-2 infection and critical illness. There are studies that shows that thrombocytopaenia can be associated in patients with SARS-CoV-2 infection.[2] The data on its prevalence and outcome on critically ill COVID-19 patients are scarce. Some studies have shown that thrombocytopaenia is associated with worsening of respiratory parameters and unfavourable outcome of the critically ill patients.[3] Identifying the presence of thrombocytopaenia and its consequences is important to manage critically ill COVID-19 patients.

Aims

To identify the prevalence and consequences of thrombocytopaenia, the presence of other causes of thrombocytopaenia and association of thrombocytopenia with the outcome in critically ill COVID-19 patients.

Study design

A retrospective clinical analysis

Study set up

This was done in COVID designated Intensive care unit and High dependency unit in Base Hospital-Teldeniya, Sri Lanka.

Methodology

A retrospective study was done at COVID designated intensive care unit- Base Hospital ,Teldeniya, Sri Lanka. All patients with positive SARS-CoV-2 testing who later develops pneumonia with oxygen dependency and requiring ICU or HDU care were included in the study. Data was collected from patient records for the duration from 1$^{st}$ of January 2021 to 30$^{th}$ of June 2021. Their demographic data, data related to platelet counts, complications, outcome and other causes leading to thrombocytopaenia were collected. Thrombocytopaenia was categorised as mild (platelet count 100-150× $10^9$/L), Moderate (50-100×$10^9$/L) and severe (less than 50×$10^9$/L)

Results

Total of 189 patients were admitted to either ICU or HDU requiring oxygen therapy due to COVID pneumonia during the study period. The mean age was 60.59 years with SD of 14.9. Age range was 16 to 94 years. 63 patients (33.33%) had thrombocytopenia with 8 (12.69%), 19 (30.15%) and 36 (57.14%) had severe, moderate and mild thrombocytopenia respectively. 28 (44.4%) of the patients had low platelets at the time of admission. 31.7% of the patients had another cause that could contribute for thrombocytopenia. In thombocytapanic patients, there were significantly elevated levels of C- reactive protein and serum creatinine. Out of the patents who had thrombocytopenia 20


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(31.7%) patients died. This was equal to 48.7% of all critical care deaths. The proportion of death among patients with thrombocytopenia was found to be significant compared to that of patients with a normal platelet count. (p=0.045)

Conclusions

Thrombocytopenia may arise due to multiple aetiologies in critically ill patients. Our study shows that at least 1/3 of the critically ill patients with COVID-19 infection develop thrombocytopenia at some point of their course of illness. The mortality is high in this group. It is important to have an insight on the progression of the illness and the outcome in order to plan discharge and follow up for these patients.

Keywords : Thrombocytopenia, COVID-19, Critically ill patients, Platelets

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## Introduction

SARS-CoV-2 infection was declared a pandemic in March 2020 by the world health organisation. Since the beginning of the pandemic there are more than 263 million cases recorded worldwide.[1] Sri Lanka was also badly affected by the pandemic recording 565000 cases with nearly 14000 deaths by end of November 2021.[1] SARS-CoV 2 infection causes a spectrum of diseases with most individuals suffering only from asymptomatic or mild infection. About 10-20% of hospitalised patients requires Intensive care unit admission.[2] The mortality is high in patients who ends up in ICU. The most common cause of death in the ICU is the severe respiratory failure related to COVID-19 pneumonia. SARS-CoV- 2 infection also affects systems other than respiratory system. One such system is the haematological system and all cell lines may be affected due to that.[3]

Thrombocytopenia is found to be the commonest laboratory abnormality in non-COVID intensive care unit patients.[4] The incidence of thrombocytopenia in non-COVID critically ill patients is between 13% and 60%.[5,6,7] It has been associated with an increased risk of blood product transfusions, bleeding, length of stay, and mortality.[8,9] In non-COVID set up thrombocytopenia can be a result of decreased platelet production, increased destruction, increased aggregation, dilution, and sequestration.[10] The cause of thrombocytopenia in ICU may be difficult to determine and is often multifactorial.

Mild thrombocytopenia has been observed in approximately 5–10% of patients with symptomatic SARS-CoV-2 infection.[11] The incidence of thrombocytopenia in Intensive car unit (ICU) patients are not known. But there are many case reports reporting thrombocytopenia in these patients. Various mechanisms have been suggested, including decreased platelet production and enhanced platelet destruction, as for other viral infections.

Several case reports have shown that SARS-CoV-2 can be associated with immune mediated thrombocytopenia often presenting as Immune thrombocytopenic purpura. Some of the cases were severe, requiring platelet transfusions. There are some cases of thrombocytopenia associated with thrombosis. Thrombosis has also been reported commonly in COVID-19 patients. There are many cases of diagnosed heparin induced thrombocytopenia with the presentation of thrombosis and thrombocytopenia.

Meta analysis done by Pranata etal has shown that thrombocytopenia in COVID 19 patients is associated with a poor prognosis. The same analysis has shown that it has a high specificity but low sensitivity in determining prognosis.[12]

When considering the above factors, thrombocytopenia is an important clinical finding in critically ill COVID -19 patients. No data related to thrombocytopenia and their outcome in ICU patients are available in Sri Lankan population. Therefore this study was planned in order to identify the incidence and clinical outcome of critically ill COVID 19 patients in a single centre in Sri Lanka.

**Methodology**

A retrospective cohort study was conducted in COVID designated Intensive care unit, Base Hospital, Teldeniya. The study was approved by the Institutional Review Board of National Hospital Kandy, Sri Lanka. Adult patients (age ≥ 18 years) admitted to the 24-bed medical ICU with a diagnosis of positive SARS-CoV-2 status between 1st of January 2021 to 30th of June 2021 were included in the study. Only the first admission was included for patients who had multiple ICU admissions. Patients with known disorders associated with thrombocytopaenia were excluded from the study. These includes haematological disorders (e.g., idiopathic thrombocytopenia purpura, congenital thrombocytopenia, hypersplenism), hematologic malignancies, use of chemotherapy (in the last 30 days prior to admission), mechanical heart valves, hepatic cirrhosis and alcohol abuse. In addition pregnant patients and patients who had doubtful SARS-CoV-2 testing status were also excluded from the study.

The following data were obtained from the patients' medical records: age, gender, co-morbidities, Investigation profiles, severity of SARS-CoV-2 infection, Investigations related to platelet count, duration of mechanical ventilation, vasopressor use, major bleeding episodes, transfusion requirements, duration of ICU stay, and outcome in the ICU. The following laboratory values were collected for all patients when available: Platelet count (daily count for 14 days ), hemoglobin, creatinine, lactate, prothrombin time, activated partial thromboplastin time, D-dimer assay, fibrinogen level, peripheral blood smear evidence of haemolysis, serum lactate dehydrogenase and liver function tests. Data about the usage of medications that are commonly associated with thrombocytopenia in critically ill patients was recorded. These includes, beta-lactam antibiotics, vancomycin, linezolid, trimethoprim-sulfamethoxazole, H2 receptor blockers and heparin.

Thrombocytopenia will be diagnosed using full blood count (FBC). FBC is done in all patients routinely on admission and then daily to every other day depending on the clinical condition during the ICU stay. Thrombocytopenia will be categorised as follows,

1- Mild – platelet count from 100-150000 /ml
2- Moderate – Platelet count from 50-100000/ml
3- Severe – Platelet count less than 50000/ml

Statistical analysis

Data were summarized as mean (standard deviation (SD)), median (interquartile range (IQR)) or percentages. Continuous variables with normal distribution were compared with student t test and Mann-Whitney U test was used for skewed distribution. For comparison of categorical variables, we used chi-square test. To determine the impact of thrombocytopenia on outcome, a multivariate logistic regression analysis using the mortality as the dependent factor. When appropriate, the odds ratio (OR) and 95% confidence intervals (CI) were calculated. A P value of <0.05 was considered statistically significant.

**Results**

During the study period 189 patients were admitted to Intensive care unit requiring oxygen therapy due to COVID pneumonia. The mean age was 60.59 years with SD of 14.9. Age range was 16 to 94 years.

Out of 189 patients, 67 patients had thrombocytopaenia, but 5 patients were excluded due to pre-existing exclusion criteria. 63 patients (33.33%) had new onset thrombocytopenia at one point of critically ill period. Out of them 8 (12.69%), 19 (30.15%) and 36 (57.14%) had severe, moderate and mild thrombocytopenia respectively. 28 (44.4%) of the patients had low platelets at the time of admission. Figure 1 illustrates the study cohort.

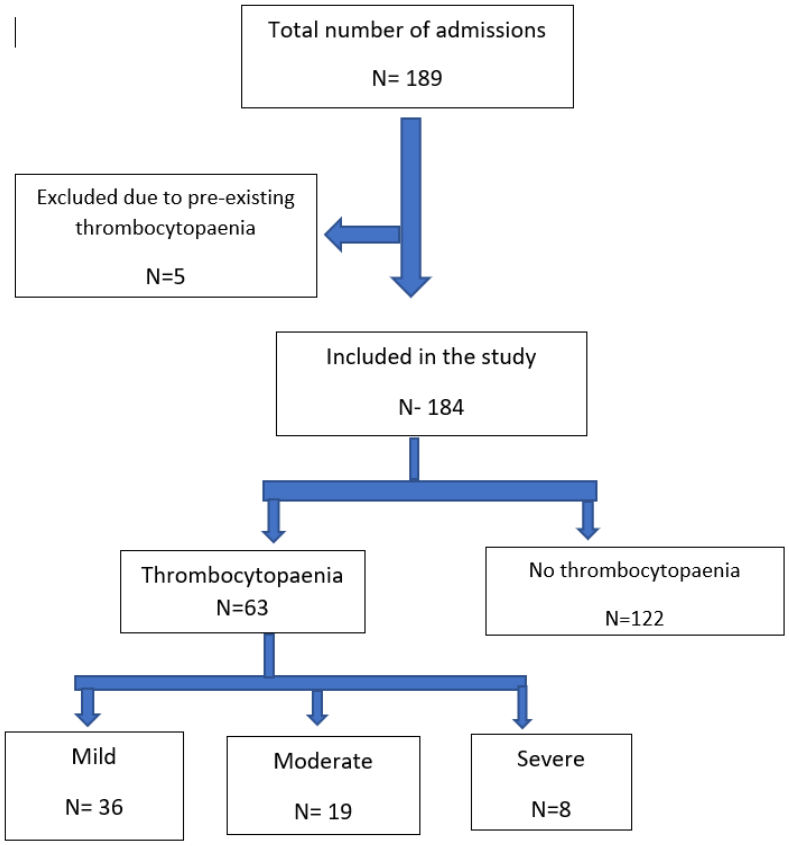


Figure 1: Summarises the pathway of patient inclusions and number of positive patients for thrombocytopaenia

Table 1 summarises the characteristics of patients who developed thrombocytopaenia associated with SARS_CoV-2 infection.

Table 1 shows baseline characteristics of patients with thrombocytopenia.

| Variables | Values |
|---|---|
| Total number with thrombocytopenia | 63 |
| Severity of Thrombocytopaenia<br>Mild<br>Moderate<br>Severe | <br>36(57.14%)<br>19 (30.15%)<br>8 (12.69%) |
| Age (mean) | 62.14 (SD 13.12) |
| Gender<br>Male<br>Female | <br>35 (55.5%)<br>28 (44.44%) |
| Co-morbidities<br>Diabetes mellitus<br>Hypertension<br>Cardiac disease<br>Chronic renal disease<br>Other | <br>33 (63%)<br>25 (38.6%)<br>10 (15.8%)<br>4 (6.3%)<br>3 (4.7%) |
| Outcome<br>Survived<br>Not- survied | <br>46 (73.01%)<br>17 (26.98%) |

The median (IQR) duration of thrombocytopenia was 7.9 (2.3-10.3) days. There were no significant differences in the severity of SARS-CoV-2 infection in patients with thrombocytopenia as compared to patients who did not develop thrombocytopenia.

Table 2 summarises the comparison of laboratory findings on admissions of patients who had thrombocytopaenia vs patients without thrombocytopaenia. Patients with thrombocytopenia was found to have significantly elevated serum lactic acid levels at ICU admission (median value, 2.7 mmol/L vs. 1.7 mmol/L, $P < 0.01$). In addition patients with thrombocytopenia also had elevated serum creatinine and C- reactive protein levels compared to the patients without thrombocytopenia (Table 2). There were no statistically significant differences in serum haemoglobin and total WBC count between these two groups.

Table 2: Comparison of laboratory findings on admission

| Investigation | Thrombocytopaenia (N=63) | No thrombocytopaenia (N=122) | P value |
|---|---|---|---|
| Haemoglobin g/dl | 11.4 (2.1) | 11.3(2.2) | 0.81 |

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| | | | |
|---|---|---|---|
| (mean/SD) | | | |
| Total WBC count (/L) Mean/SD | $7.8x10^9$( 2.7) | 7.1 (2.9) | 0.73 |
| Lactate mmol/l (median/IQR) | 2.7 (1.4-4.2) (N= 44) | 1.7 (1.1-2.7) (N=98) | <0.001* |
| Serum Creatinine mg/dl (median/ IQR) | 1.5 (1.1-3.2) | 1.2 (0.8 – 2.2) | 0.02* |
| C- reactive protein mg/dl (mean / SD) | 34 (10.2) | 22 (8.3) | 0.01* |

(SD, standard deviation; IQR interquartile range. SI conversion factors: to convert hemoglobin values to g/L, multiply by 10; to convert creatinine values to µmol/L, multiply by 88.4; to convert total bilirubin values to µmol/L, multiply by 17.104. *Significant P values.)

Out of the patients who developed thrombocytopaenia in 20 (31.7%) patients , we could find another cause which can contribute to thrombocytopaenia. Figure 2 shows other causes contributed to thrombocytopenia. Sepsis and septic shock was the commonest cause that could have contributed to thrombocytopaenia other than SARS-CoV-2 infection.

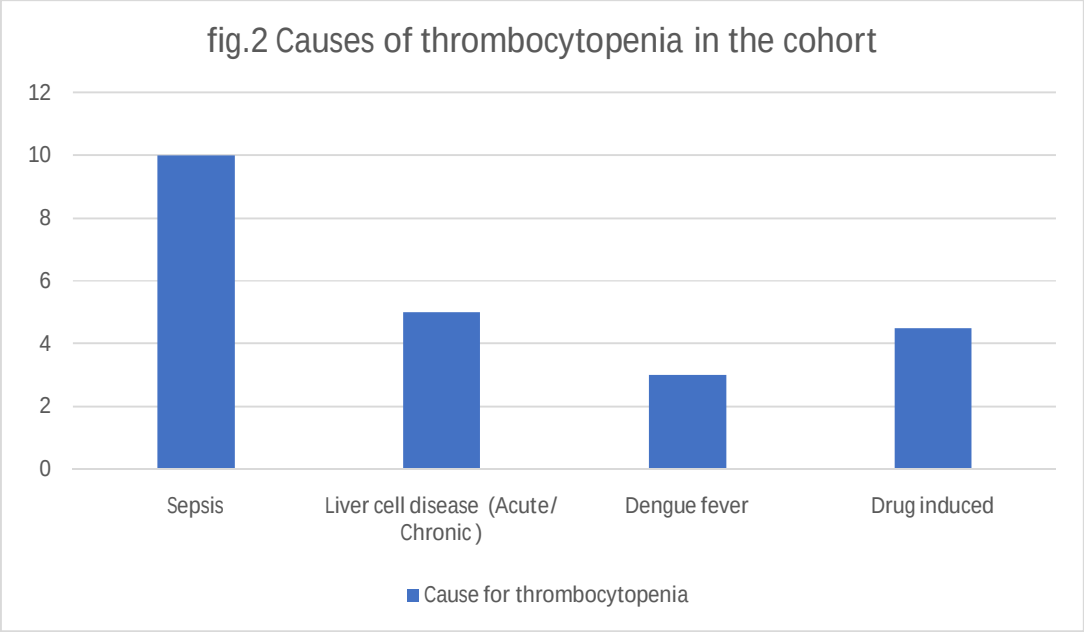


Figure 2: Showing co-existing conditions that can lead to thrombocytopaenia other than SARS-CoV-2 infection

Out of the patients who developed thrombocytopenia had more episodes of major bleeding compared to those patients who did not develop thrombocytopenia (7.9% vs. 4.01%, P < 0.01). Patients with thrombocytopenia also received more blood product transfusions. But this was statistically significant among the both groups. Although the patients with thrombocytopaenia had a relatively long ICU stay , this was not found to be statistically significant. Median length of stay was 10.1 days (IQR = 2.1) in thrombocytopaenic patients vs median length of stay of 9.1 days(IQR-2.3days) in non-thrombocytopaenic group accounted for this finding.

Out of the patents who had thrombocytopenia 20 (31.7%) patients died. This was equal to 48.7% of all critical care deaths. Figure 3 shows comparison of deaths between patients with thrombocytopenia and non-thrombocytopenia. The proportion of death among patients with thrombocytopenia was found to be significant compared to that of patients with a normal platelet count. (p=0.045)

Figure 3

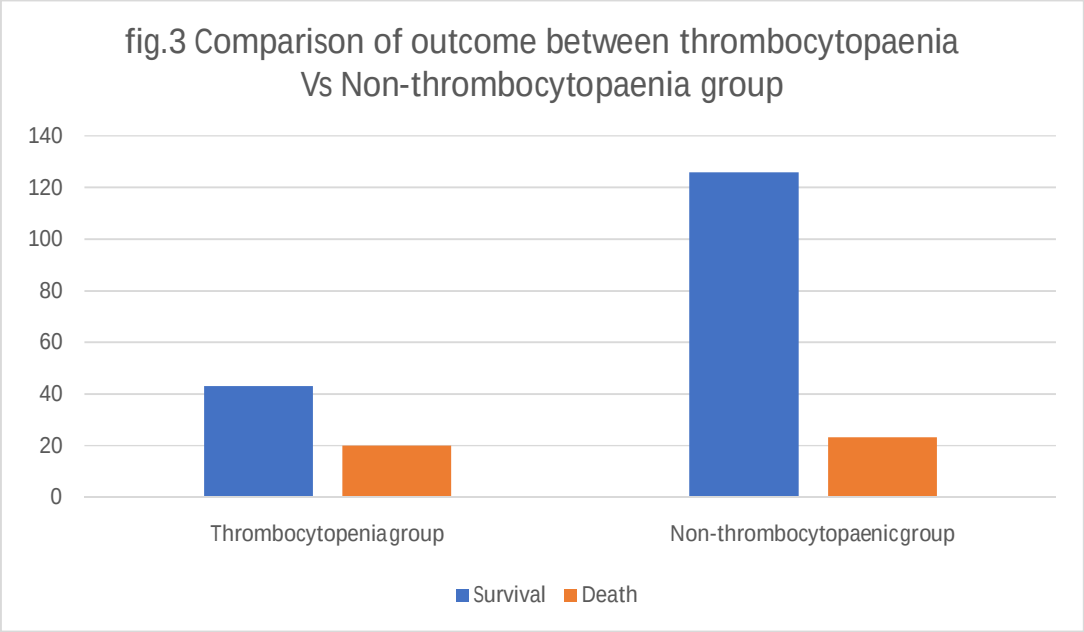


Figure 3: Showing comparison of ICU outcome in patients who are thrombocytopenic and non thrombocytopaenic

**Discussion**

With the onset of COVID-19 pandemic the burden to ICU was increased dramatically. Being a multi system disorder, SARS-CoV-2 infection affect almost all the systems in the body. The effect on the haematological system is variable. Lymphopenia is considered as a cardinal laboratory finding, with a prognostic value. Neutrophil/lymphocyte ratio and peak platelet/lymphocyte ratio has also been used in prognostication in severe cases.[13]

Thrombocytopenia is found to be the commonest laboratory abnormality in non-COVID intensive care unit patients.[4] The incidence of thrombocytopenia in non-COVID critically ill patients is between 13% and 60%.[5,6,7] Platelet count abnormalities has been studied as a marker of prognostication. There are studies that shows thrombocytopenia is associated with the severity of the disease. [14] Other studies have highlighted that patients with significantly elevated platelets had longer duration of hospitalization stays.[15]

Several mechanisms have been proposed as causative factors of thrombocytopaenia in SARS-CoV-2 infection. SARS-CoV- 2 is believed to reduce the production and increase the disruption of platelets

leading to thrombocytopaenia. [16] It has also been hypothesised that there is a correlation between the platelet count and the SARS-COV-2-associated cytokine storm, as the IL-6 promotes the generation of megakaryocytes by stimulating the increase of TPO levels. [17]

In our study, we found that about 1/3 of patients who are critically ill with SARS-CoV-2 infection develops thrombocytopenia during the critical care stay. This number is high considering the complications it can be associated with. In our study, we observed significant bleeding in patients with severe thrombocytopaenia. This is one of the serious conditions associated with low platelet counts. There are no actual target limits to commence transfusions of platelets in thrombocytopenic critically ill patients in non-COVID ICUs. The transfusion triggers can vary and follow unit protocols. A study conducted in 747 non-COVID ICU patients has shown that platelet transfusions have shown to reduce mortality in patients with severe thrombocytopaenia.[18] The transfusion practices and triggers in COVID-19 patients and its relation to mortality is not established. Authors would like to suggest this as a recommendation for future studies.

SARS-CoV-2 is associated with hypercoagulability state. This may manifest as thrombosis in deep veins, cerebro-vascular accidents, and myocardial infarctions. We also noticed that some of our patients developed deep vein thrombosis despite low platelet count. In such background one of the differential diagnosis would be Heparin Induced thrombocytopaenia.(HIT) Performing heparin–PF4 antibody testing would help in differentiating HIT and COVID induced hyercoagulability.[19] This testing is not available in Sri Lanka and therefore , differentiation was not possible.

According to our study, patients with thrombocytopaenia are likely to die, when compared to patients who have normal platelet count. Same has been shown in COVID-19 patients from other countries and this has been studied as a prognostic factor. An Egyptian study performed in COVID -19 patients has shown that platelet count is a simple and inexpensive method that can be used in predicting prognosis. [20]. Most studies shows that the presence of thrombocytopaenia is regarded as a poor prognostic factor in SARS-CoV-2 critically ill patients. This is compatible with the findings of our study as well.

However, one must think of causes of thrombocytopenia other than COVID-19 it self before coming into conclusions. 31.7% of patients had other identifiable cause for thrombocytopenia in our cohort. Most patients had sepsis co-existing with COVID-19. Thrombocytopania is a common finding in other viral infections. In a country like Sri Lanka, where dengue fever is prevalent, that needs to be excluded as the dengue it self can lead to lethal infections.

Considering the burden of critically ill patients with SARS-CoV-2 infection on the demand for ICU needs in a country, it is important to know the factors that could affect prognosis. This study can help by adding valuable information to the available literature in patients with thrombocytopaenia.

Our study has several limitations. This study contains data from a single centre and multi centre study should be done in order to develop this as a marker of prognosis. Our institute does not have facilities to check for HIT, and it was diagnosed clinically. This is also a disadvantage in a cohort where heparin is used widely in the back ground of high risk of thrombosis.

**Recommendations**

Considering all the factors, the future studies can be concentrated on developing these parameters as prognostication factors. It will help patient selection when the demand for the ICUs is high.

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## Conclusions

Thrombocytopenia is a common finding in critically ill COVID-19 patients. Our study shows that at least 1/3 of the critically ill patients with COVID-19 infection develop thrombocytopenia at some point of their course of illness. It is associated with increase morality , but does not increase the length of ICU stay. It is important to have an insight on the progression of the illness and the outcome in order to plan discharge and follow up for these patients.

## Consent

Not applicable, The study was done as a retrospective study .

## Ethical approval (where ever applicable)

Ethical review was obtained from ethical review committee of National Hospital Kandy- Sri Lanka. (NO NHK/ERC/17/2021)

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