Thrombocytopenia and Its Association with Mortality in Patients with COVID-19

Xiaobo Yang[1,2]*, Qingyu Yang[2]*, Yaxin Wang[1], Yongran Wu[1], Jiqian Xu[1], Yuan Yu[1], and You Shang[1,2†]

* Contributed equally

† Corresponding author

[1]Department of Critical Care Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

[2]Research Center for Translational Medicine, Jinyintan Hospital, Wuhan, China

Correspond to:

You Shang

Department of Critical Care Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

E-mail: you_shang@yahoo.com

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/JTH.14848

Summary

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.

Objective: To describe thrombocytopenia in patients with COVID-19.

Methods: For each of 1476 consecutive patients with COVID-19 from Jinyintan Hospital, Wuhan, China, nadir platelet count during hospitalization was retrospectively collected and categorized into (0, 50], (50, 100], (100 - 150] or (150 -) group after taking the unit ($\times 10^9$/L) away from the report of nadir platelet count. Nadir platelet counts and in-hospital mortality were analyzed.

Results: Among all patients, 238 (16.1%) patients deceased and 306 (20.7%) had thrombocytopenia. Compared with survivors, non-survivors were older, were more likely to have thrombocytopenia and had lower nadir platelet counts. The in-hospital mortality was 92.1%, 61.2%, 17.5% and 4.7% for (0, 50], (50, 100], (100 - 150] and (150 -) group, respectively. With (150 -) as the reference, nadir platelet counts of (100 - 150], (50, 100] and (0, 50] group had a relative risk of 3.42 (95% CI 2.36 - 4.96), 9.99 (95% CI 7.16 - 13.94) and 13.68 (95% CI 9.89 - 18.92), respectively.

Conclusions: Thrombocytopenia is common in patients with COVID-19, and it is associated with increased risk of in-hospital mortality. The lower the platelet count is, the higher the mortality becomes.

Keywords

SARS-CoV-2, COVID-19, thrombocytopenia, mortality, generalized linear model

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new highly transmittable coronavirus, is spreading rapidly around the world[1]. The virus causes a spectrum of diseases, named novel coronavirus disease 2019 (COVID-19) by WHO[2]. Among these diseases, pneumonia is studied most extensively[3–7]. Complications associated with COVID-19, including acute respiratory distress syndrome[3–7] and cardiac injury[8], were associated with increased mortality. One small sample-sized studies reported that the rate of thrombocytopenia was 12%.[4] Another study reported that 36.2% of patients had platelet count less than 150×10^9/L.[7] However, the degree of thrombocytopenia and its association with mortality have not been fully elucidated.

The present large sample-sized study from a single hospital of Wuhan, China, focused exclusively on thrombocytopenia. The objectives were to describe the epidemiology of thrombocytopenia and to explore the association between thrombocytopenia and mortality among patients with COVID-19.

Methods

Consecutive patients with confirmed COVID-19 admitted to Wuhan Jinyintan Hospital since late December 2019, who were either discharged or deceased by February 25th, 2020, were included. The diagnosis of COVID-19 was according to World Health Organization interim guidance and confirmed by RNA detection of SARS-CoV-2. This study was approved by the Ethics Committee of Jinyintan Hospital (KY-2020–06.01).

At admission, the tests of complete blood count, including platelet count, was conducted and repeated afterwards on the discretions of treating physicians. All data on laboratory tests of patients with COVID-19 were stored on a local server. After log files with information on hospital admission numbers being obtained, data on laboratory tests were retrieved and matched using admission numbers which were unique to each patient. For each patient, the nadir platelet count was identified and categorized into (0, 50], (50, 100], (100 - 150] or (150 -) group after taking the unit ($\times 10^9$/L) away from the report of nadir platelet count.

Data were expressed as median [interquartile range, IQR] for continuous variables and count (percentage) for categorical variables. The differences between survivors and non-survivors were explored using Wilcoxon test or Fisher's exact test. Generalized linear model was then used to analyze the relative risk (RR) of death in age, gender and groups of nadir platelet count. A

double-sided p-value < 0.05 indicated statistical significance. The Stata/IC 15·1 software (StataCorp, College Station, Texas, USA) was used for all analyses.

Results and Discussion

A total of 1476 patients, comprising of 1238 (83.9%) survivors and 238 (16.1%) non-survivors, were included. Their median [IQR] age was 57 [47 - 67] years and 776 (52.6%) patients were men. A total number of 4663 tests on platelet count were identified. The sequential changes in platelet counts in the first three weeks after admission were presented in Figure 1. With 125 × 10^9/L as the lower limit of normal range, thrombocytopenia occurred in 306 (20.7%) patients. As for nadir platelet counts, among predefined groups, the mortality decreased with the increasing of platelet counts (Figure 2).

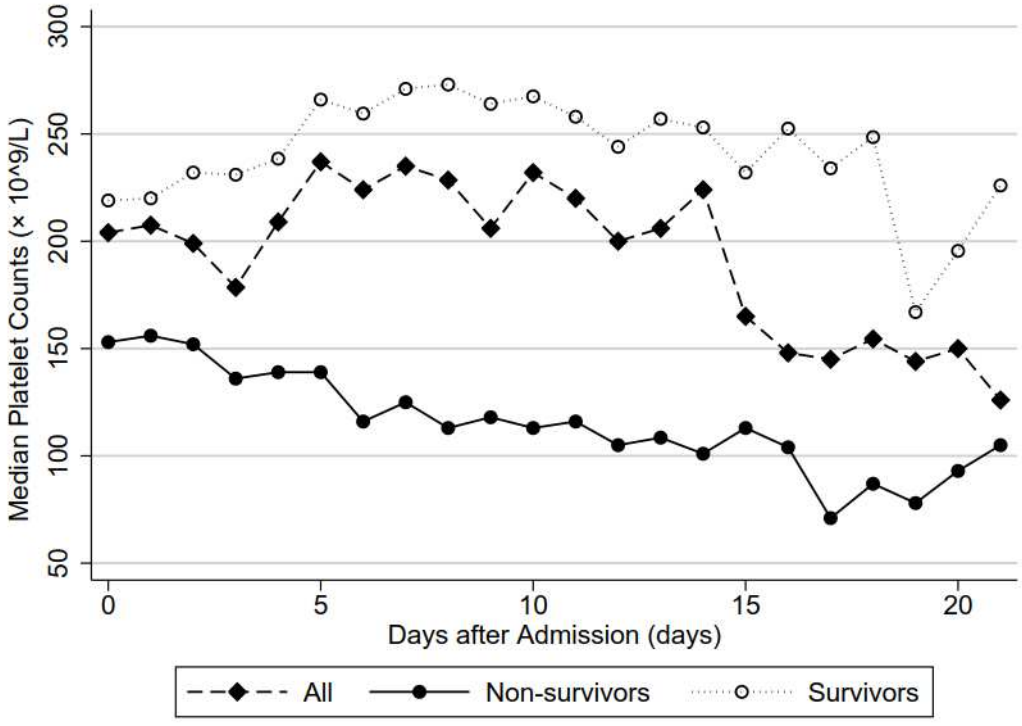

Figure 1. The sequential changes in platelet counts among 1476 patients with COVID-19 in the first three weeks after admission. The number of survivors was 1238 and the number of non-survivors was 238.

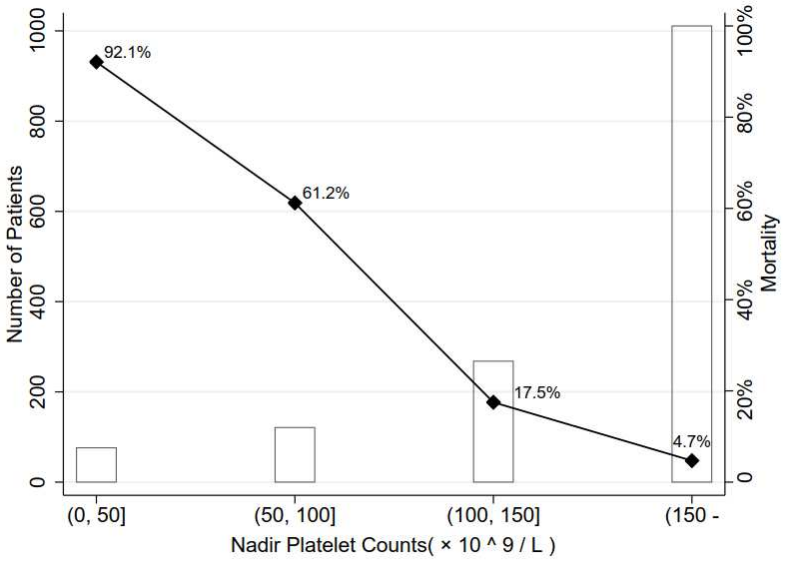

Figure 2. Number of patients and mortalities in 4 groups of patients with COVID-19 based on their nadir platelet counts.

Table 1. Differences on age, gender and tests on platelet count between survivors and non-survivors of patients with COVID-19.

Characteristics	Survivors (n = 1238)	Non-survivors (n = 238)	p
Age, years	56 [46 - 65]	67 [59 -75]	< 0.001
Male	620 (50.0%)	156 (65.5%)	< 0.001
Number of tests on platelet count	2 [2 - 3]	4 [2 - 8]	< 0.001
Number of patients with thrombocytopenia*	133 (10.7%)	173 (72.7%)	< 0.001
Nadir platelet count of each patient	203 [155 -257]	79 [43 - 129]	< 0.001

Data are expressed as median [IQR] or count (%).

* Normal range was 125 to 350 × 10^9/L.

Table 2. Relative risk of death in age, gender and groups of nadir platelet count in patients with COVID-19 obtained using a generalized linear model.

	Relative Risk (95% confidence interval)	p
Age	1.03 (1.02 - 1.04)	< 0.001
Gender		
Male	1.29 (1.06 - 1.57)	0.012
Female	Reference	
Nadir platelet count		
(150 -	Reference	
(100 - 150]	3.42 (2.36 - 4.96)	< 0.001
(50, 100]	9.99 (7.16 - 13.94)	< 0.001
(0, 50]	13.68 (9.89 - 18.92)	< 0.001

Compared with survivors, non-survivors were older (67 [IQR, 59 - 75] years vs 56 [IQR, 46 - 65] years, $p < 0.001$), and more in male (65.5% vs 50.0%, $p < 0.001$) (Table 1). Thrombocytopenia was more likely to occur in non-survivors than in survivors (72.7% vs 10.7%, $p < 0.001$). Non-survivors had significantly lower nadir platelet counts than survivors (79 [43 - 129] vs 203 [155 -257], $p < 0.001$). When generalized linear modelling was used, the RR of death due to age was 1.03 (95% CI 1.02 - 1.04) with every one-year increase in age (Table 2). Compared with female, male patients had a RR of 1.29 (95% CI 1.06 - 1.57). With (150 -) as the reference, nadir platelet counts of (100 - 150], (50, 100] and (0, 50] had a RR of 3.42 (95% CI 2.36 - 4.96), 9.99 (95% CI 7.16 - 13.94) and 13.68 (95% CI 9.89 - 18.92), respectively.

In this large sample-sized study we found that 306 (20.7%) had thrombocytopenia and for patients categorized into (0, 50], (50, 100], (100 - 150] and (150 -) groups, the mortality was 92.1%, 61.2%, 17.5% and 4.7%, respectively. After adjusting age and gender, the trend that in-hospital mortalities corresponded positively to the magnitude of decrease in platelet count remained.

To our knowledge, this study is the first one specialized in the epidemiology of thrombocytopenia and the association between thrombocytopenia and in-hospital mortality in patients with COVID-19. The power of this study relies on its sample size. Even in the (0, 50] group, a total of 76 patients were identified. The cut-off values to group nadir platelet counts were derived from platelet criterion of sequential organ failure assessment score[9]. We did not use 20×10^9/L as a cut-off value because it would make the number of patients small in both (0, 20] group and (20, 50] group.

The proportion of patients with thrombocytopenia was smaller than that of patients with SARS. In patients infected by SARS-CoV, thrombocytopenia was found in 40% to 50% patients.[10–12] SARS-CoV can induce hematopoiesis after infecting cells in bone marrow. As a coronavirus sharing 79% genomic sequence to SARS-CoV and the same cell entry receptor of angiotensin-converting enzyme 2[13], it is possible that SARS-CoV-2 may cause thrombocytopenia in a similar way. In a study on coagulopathy associated with COVID-19, 71.4% (15 in 21) non-survivors met the International Society on Thrombosis and Haemostasis criteria of disseminated intravascular coagulopathy[14], which may cause increased consumption of platelets.

SARS-CoV-2 infects and causes diffuse alveolar damage, which entraps megakaryocytes and hinders the release platelets from megakaryocytes[15].

This study has limitations. First, it is a retrospective study and the tests on platelet count for each patient had different time intervals in between. Second, this study was focusing on exploring thrombocytopenia, so data on other organ damages were barely mentioned. Third, the medical source was relative short in the beginning of the COVID-19 outbreak in Wuhan, China, and this was a single centered study. Further studies are needed to confirm our findings.

Author Contributions

X.Yang drafted the manuscript, X.Yang, Q.Yang, X.Wang, Y.Wu, J.Xu and Y.Yu collected the data, Q.Yang analysed the data, X.Yang and Y.Shang designed the study.

Funding

None.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

Reference

1. World Health Organization. Situation report - 84. Published April 13th, 2020. Accessed April 13th, 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200413-sitrep-84-covid-19.pdf?sfvrsn=44f511ab_2.
2. World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it. Published February 11, 2020. Accessed March 31, 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it
3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506.
4. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507–513.
5. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China [published online ahead of print 7 February 2020]. JAMA. doi: 10.1001/jama.2020.1585.
6. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;2600(20):1–7.
7. Guan W-J, Ni Z-Y, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China [published online ahead of print 28 February 2020]. N Engl J Med. doi:10.1056/NEJMoa2002032.
8. Shi S, Qin M, Shen B, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China [published online ahead of print 25 March 2020]. JAMA Cardiol. doi: 10.1001/jamacardio.2020.0950.
9. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the working group on Sepsis-related problems of the European society of intensive care medicine. Intensive Care Med.

1996;22:707–710

10. Lee N, Hui D, Wu A, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. N Engl J Med. 2003;348(20):1986–94.
11. Wong RSM, Wu A, To KF, et al. Haematological manifestations in patients with severe acute respiratory syndrome: retrospective analysis. BMJ. 2003;326(7403):1358–62.
12. Choi KW, Chau TN, Tsang O, et al. Outcomes and Prognostic Factors in 267 Patients with Severe Acute Respiratory Syndrome in Hong Kong. Ann Intern Med. 2003;139(9):715.
13. Zhou P, Yang X-L, Wang X-G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270–273.
14. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia [published online ahead of print 19 February 2020]. J Thromb Haemost. doi: 10.1111/jth.14768.
15. Mandal R V., Mark EJ, Kradin RL. Megakaryocytes and platelet homeostasis in diffuse alveolar damage. Exp Mol Pathol. 2007;83(3):327–331.