

Review

Thrombocytopenia Is Associated with COVID-19 Severity and Outcome: An Updated Meta-Analysis of 5637 Patients with Multiple Outcomes

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ABSTRACT

The COVID-19 pandemic is persistent worldwide. A prior meta-analysis suggested the association of thrombocytopenia (TCP) with more severe COVID-19 illness and high mortality. Considering newly published studies, we updated the previous meta-analysis to confirm and explain the association of TCP with COVID-19 severity and multiple outcomes. Twenty-four studies with 5637 patients with COVID-19 were included in this study. The weighted incidence of TCP in COVID-19 was 12.4% (95% confidence interval [CI], 7.9%–17.7%). Data synthesis showed that the platelet number was lower in patients with either more severe illness or poor outcomes and even lower in nonsurvivors, with weighted mean differences of $-24.56 \times 10^9/L$, $-22.48 \times 10^9/L$, and $-49.02 \times 10^9/L$, respectively. The meta-analysis of binary

outcomes (with and without TCP) indicated the association between TCP and 3-fold enhanced risk of a composite outcome of intensive care unit admission, progression to acute respiratory distress syndrome, and mortality (odds ratio [OR], 3.49; 95% CI, 1.57–7.78). Subgroup analysis by endpoint events suggested TCP to be significantly associated with mortality (OR, 7.37; 95% CI, 2.08–26.14). Overall, the present comprehensive meta-analysis indicated that approximately 12% of hospitalized patients with COVID-19 have TCP, which also represents a sign of more severe illness and poor outcomes.

Keywords: coronavirus disease 2019, COVID-19, SARS-CoV-2, platelet, thrombocytopenia, prognosis

The coronavirus disease 2019 (COVID-19) pandemic has affected more than 12 million people and caused more than 500,000 deaths worldwide.¹ Although most patients develop mild or uncomplicated illness, those with older age and pre-existing comorbidities are more susceptible to severe disease and have a higher risk of poor outcomes such

Abbreviations:

TCP, thrombocytopenia; CI, confidence interval; OR, odds ratio; ICU, intensive care unit; ARDS, acute respiratory distress syndrome; WMD, weighted mean difference; TPO, thrombopoietin; ITP, immune thrombocytopenia.

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as admission to the intensive care unit (ICU), progression to acute respiratory distress syndrome (ARDS), and even death.^{2,3} Thrombocytopenia (TCP) is commonly associated with viral infections and serves as a sign of sepsis progression and exacerbation.^{4,5} A prior meta-analysis suggested that low platelet count was associated with high mortality and more severe COVID-19 illness.⁶ Because new studies have been published, we conducted an update of the previous meta-analysis to confirm and explain the association of platelet number with COVID-19 severity and provide a direct comparison of the risk of multiple endpoints in patients with COVID-19 with and without TCP.

Materials and Methods

This systematic review was performed following the PRISMA statement (see [Supplemental Material 1](#)).⁷ The study protocol is provided in [Supplemental Material 2](#). Briefly, PubMed, Embase,

and Web of Science were searched to identify studies between December 1, 2019, and March 15, 2020, without language restriction. The following terms were used: “COVID-19” OR “Corona Virus Disease 2019” OR “coronavirus disease-19” OR “severe acute respiratory syndrome coronavirus 2” OR “SARS-COV-2” OR “2019 novel coronavirus” OR “2019-nCoV” OR “new coronavirus pneumonia.” Because new articles on COVID-19 are daily published, eligible articles published between March 15, 2020, and April 18, 2020, were also identified via PubMed using the aforementioned terms with AND for the following terms: “platelet” OR “thrombocytopenia” OR “thrombo*” OR “hemato*.” Studies were included in this meta-analysis if they met the following criteria: (i) adult population (older than 18), (ii) COVID-19 was confirmed by laboratory testing, (iii) platelet count or TCP frequency was reported, and (iv) English or Chinese full text was available. Studies involving patients with a particular illness or emergency conditions were excluded (eg, cancer and cardiovascular attack). When studies had significant overlapping data, the most comprehensive study was included.

For pooled analysis, data on platelet count and TCP frequency in the overall population and subgroups based on disease severity or outcomes were extracted by 2 independent investigators. COVID-19 severity was defined as per the World Health Organization or local interim guidance, and studies without definite criteria were excluded. We used a composite of admission to ICU, progression to ARDS, or all-cause mortality to define adverse outcomes of COVID-19. Double-arcsine-transformed proportion, weighted mean difference (WMD), and odds ratio (OR) with 95% confidence interval (CI) were calculated and pooled in the meta-analysis as appropriate. In their absence, the mean and standard deviation of the platelet count were estimated from sample size, median, and interquartile range.⁸ A random-effects model was selected to account for clinical heterogeneity. Subgroup analyses were conducted based on endpoint events and TCP definition. The quality of the included studies was evaluated by 2 independent reviewers following the Newcastle-Ottawa scale (see [Supplemental Material 3: Table 1](#)). Discrepancies in data extraction and quality assessment were resolved through discussion with a third author. Statistical analyses were performed using the RStudio software.

Results and Discussion

After initial screening and full-text review, 24 studies^{2,3,9-30} with 5637 patients with COVID-19 were included in this

systematic review. The study selection procedure is illustrated in [Supplemental Material 3: Figure 1](#); the excluded studies and reasons for exclusion are detailed in [Supplemental Material 3: Table 2](#). **Table 1** shows the quality and general characteristics of the included studies. Seventeen studies^{2,3,9-13,15,17-19,21,24,26-29} including 4671 patients reported the incidence of TCP in hospitalized patients with COVID-19 (see [Supplemental Material 3: Figure 2](#)). Our meta-analysis indicated a weighted incidence of 12.4% ($I^2 = 95%$; 95% CI, 7.9%–17.7%; **Table 2** and [Supplemental Material 3: Figure 3](#)). This result was consistent with that of a previous meta-analysis of 218 patients that reported a combined estimation of 11.5%.³¹ Notably, the TCP frequency across included studies is inconsistent, with a wide range from 0% to 36.5%. This inconsistency may be attributed to different criteria applied for defining TCP and the heterogeneous disease severity spectrum among study populations. The results of subgroup analysis by cutoff values of 150, 125, and $100 \times 10^9/L$ for TCP were 28.7% (95% CI, 15.6%–43.9%), 17.3% (95% CI, 14.9%–19.9%), and 3.1% (95% CI, 0.4%–8.4%), respectively, as detailed in **Table 2** and [Supplemental Material 3: Figure 4](#).

Seven studies^{11,14,20,23,25,26,30} with 389 patients with severe COVID-19 and 1399 control patients with nonsevere COVID-19 showed a combined WMD of -24.56 ($I^2 = 53%$; 95% CI, -33.73 to -15.39), indicating that the platelet number was lower in patients with more severe COVID-19 (**Table 2** and [Supplemental Material 3: Figure 5](#)). Consistent with these results, a meta-analysis of 8 studies^{2,3,11,12,16,21,22,24} including 510 patients with adverse events (including admission to ICU, progression to ARDS, or death) and 1950 patients without adverse events revealed a combined WMD of -22.48 ($I^2 = 78%$; 95% CI, -40.97 to -3.99 ; **Table 2** and [Supplemental Material 3: Figure 6](#)). Subgroup analysis indicated the platelet count to be even lower in patients who succumbed to the disease (WMD, -49.02 ; $I^2 = 0%$; 95% CI, -60.26 to -37.78); however, no significant difference was observed between patients admitted to the ICU and those who were not (WMD, 0.41 ; $I^2 = 0%$; 95% CI, -20.04 to 20.87); **Table 2** and [Supplemental Material 3: Figure 7](#)). Taken together, these results highlight the lower platelet number in patients with either more severe COVID-19 or poor outcomes. These findings are consistent with those reported by Lippi et al,⁶ who first conducted a meta-analysis on 1779 patients to investigate the association between TCP and COVID-19 severity.

Table 1. General Characteristics of the Included Studies

Study	Region	N	Male (%)	Age (y)	Severity/ Outcome	Platelet Count		Incidence of TCP		NOS			
						Overall	SEV/PO	Non SEV/PO	Overall		With PO (%)	Without PO (%)	Cutoff
Chen, Liu, et al ⁹	Wuhan, China	29	72.0%	56 (median, 26–79)	48.3% severe disease	NR	—	—	—	<125	4		
Chen, Zhou, et al ¹⁰	Wuhan, China	99	68.0%	55.5 ± 13.1	23.0% in ICU	213.5 ± 79.1	—	—	—	<125	6		
Guan et al ¹¹	30 PRS ^b , China	1099	58.1%	47 (35–58)	15.7% severe disease	168 (132–207)	137 (99–179)	172 (139–212)	46.6	35.5	<150	7	
Huang, Wang, et al ¹²	Wuhan, China	41	73.0%	49 (41–58)	31.7% in ICU	165 (132–263)	196 (165–263)	149 (131–263)	4.9%	8.0	<100	7	
Huang, Tu, et al ¹³	Wuhan, China	34	41.2%	56.2 ± 17.1	23.5% in ICU	NR	—	—	—	NR	5		
Liu, Tao, et al ¹⁴	Wuhan, China	78	50.0%	38 (33–57)	14.1% deterioration	169.1 ± 57.3	143.90 ± 64.81	173.20 ± 55.37	NR	—	<100	7	
Shi et al ¹⁵	Wuhan, China	81	52.0%	49.5 ± 11.0	4% mortality	NR	—	—	0.0%	—	<100	6	
Wang et al ¹⁶	Wuhan, China	138	54.3%	56 (42–68)	26.1% in ICU	163 (123–191)	142 (119–202)	165 (125–188)	NR	—	<125	7	
Wu, Liu, et al ¹⁷	Jiangsu, China	80	48.8%	46.1 ± 15.4	3.8% severe disease	155 (116–188)	—	—	13.8%	—	<125	6	
Yang, Cao, et al ¹⁸	Zhejiang, China	149	54.4%	45.1 ± 13.4	No severe disease	174.5 ± 78.3	—	—	13.4%	—	<125	6	
Zhou et al ³	Wuhan, China	191	62.0%	56 (46–67)	28.3% mortality	206 (155–262)	166 (107–229)	220 (168–271)	7.0%	20.0	<100	8	
Xu et al ¹⁹	Zhejiang, China	62	56.0%	41 (32–52)	No severe disease	176 (136–216)	—	—	5.0%	—	<100	6	
Young et al ²⁰	Singapore	18	50.0%	47 (median, 31–73)	33.3% SaO ₂ ≤92%	159 (116–217)	159 (128–213)	156 (116–217)	NR	—	NR	7	
Fan et al ²¹	Singapore	67	55.2%	42 (35–54)	13.4% in ICU	NR	217 (154–301)	201 (157–263)	0.0%	—	<100	7	
Wu, Chen, et al ²	Wuhan, China	201	63.7%	51 (43–60)	26.4% in ICU	180 (137–242)	187 (125–253)	178 (140–240)	18.8%	—	<125	8	
Chen, Wu, et al ²²	Wuhan, China	274	62.0%	62 (44–70)	41.2% mortality	179 (133–235)	156 (112–219)	198 (160–256)	NR	—	<125	7	
Mo et al ²³	Wuhan, China	155	55.5%	54 (42–66)	54.8% refractory disease	170 (127–208)	159 (119–202)	179 (146–219)	NR	—	<125	7	
Tang et al ²⁴	Wuhan, China	449	59.7%	65.1 ± 12.0	29.8% mortality	215 ± 100	178 ± 92	231 ± 99	21.6%	—	<150	7	
Qu et al ²⁵	Guangzhou, China	30	53.3%	50.5 (median, 36–65)	10.0% severe disease	NR	169.7 ± 48.9	192.3 ± 58.1	NR	—	NR	6	
Wan et al ²⁶	Chongqing, China	135	53.3%	47 (36–55)	29.6% severe disease	158 (131–230)	147 (118–213)	170 (136–234)	17.0%	30.0	11.6	<125	6
Zhang, Zhang, et al ²⁷	Wuhan, China	95	55.8%	49 (39–58)	33.7% severe disease	NR	—	—	11.6%	20.0	8.6	<100	7
Liu, Sun, et al ²⁸	Wuhan, China	383	42.3%	46 (34–61)	12.8% mortality	174 (137–213)	—	—	17.8%	42.9	14.1	<125	8
Yang, Yang, et al ^{28a}	Wuhan, China	1476	52.6%	NR	16.1% mortality	NR	79 (43–129)	203 (155–257)	20.7%	72.7	10.7	<125	8
Yang, Shi, et al ³⁰	Shanghai, China	273	49.1%	49.1	26.0% CT scan progression	NR	176.0 ± 6.6	195.0 ± 5.1	NR	—	NR	6	

Data presented as median (interquartile range), median (range), or mean ± standard deviation. Poor outcomes included a composite of admission to ICU, progression to ARDS, and mortality.

^aThis study reported the nadir platelet count during hospitalization duration.

^bProvinces (PRS) include all provinces or provincial municipalities of China, except Hong Kong, Macau, and Tibet.

SEV, severe; PO, poor outcomes; PRS, provinces; NOS, Newcastle-Ottawa Scale; NR, not reported.

Table 2. Results Summary of Pooled Analyses and Subgroup Analysis

Combined Estimation Subgroup Analysis	Number of Studies (Patients)	I ²	Cochran's Q P Value	Effect Size
Incidence of TCP	17 (4671)	95%	.02	Proportion (95%CI) 12.4% (7.9% to 17.7%)
Cutoff <150	2 (1548)	97%	.00	28.7% (15.6% to 43.9%)
Cutoff <125	8 (2552)	43%	.09	17.3% (14.9% to 19.9%)
Cutoff <100	6 (537)	86%	.00	3.1% (0.4% to 8.4%)
Severe vs nonsevere	7 (1788)	53%	.05	WMD (95%CI) -24.56 (-33.73 to -15.39) ^a
With PO vs without PO	8 (2460)	78%	.00	-22.48 (-40.97 to -3.99) ^a
Mortality	3 (914)	0%	.67	-49.02 (-60.26 to -37.78) ^a
Admission to ICU	3 (246)	0%	.57	0.41 (-20.04 to 20.87)
ARDS	1 (201)	NA	NA	2.17 (-22.52 to 26.86)
Composite endpoint	1 (1099)	NA	NA	-14.67 (-29.74 to 0.40)
With TCP vs without TCP	5 (1578)	67%	.02	OR (95%CI) 3.49 (1.57 to 7.78) ^a
Mortality	2 (574)	60%	.11	7.37 (2.08 to 26.14) ^a
Admission to ICU	1 (40)	NA	NA	2.17 (0.12 to 37.64)
Composite endpoint	2 (964)	0%	.46	1.17 (1.04 to 2.80) ^a
Cutoff <150	1 (869)	NA	NA	1.58 (0.93 to 2.70)
Cutoff <125	1 (383)	NA	NA	4.58 (2.40 to 8.72) ^a
Cutoff <100	3 (326)	47%	.15	5.22 (1.30 to 20.93) ^a

^aZ test, P <.05. Composite endpoint included admission to ICU, the use of mechanical ventilation, and mortality.
PO, poor outcomes; NA, not applicable.

To investigate the association of TCP with COVID-19 outcome, 5 studies^{3,11,12,27,28} reporting a total of 199 adverse events (65 adverse events with TCP [15.9 per 100 participants] and 134 without TCP [11.5 per 100 participants]) were included. The combined OR of 3.49 ($I^2 = 67%$; 95% CI, 1.57–7.78) suggests TCP as a potential risk factor for poor outcomes in COVID-19 (Table 2 and Supplemental Material 3: Figure 8). Furthermore, the subgroup analysis by endpoint events showed that TCP was associated with a 7-fold enhanced risk of mortality in COVID-19 (OR, 7.37; $I^2 = 36%$; 95% CI, 2.08–26.14). A recent study indicated that platelet count was associated with in-hospital mortality in a dose-dependent manner.²⁸ Consistent with this finding, we found a stronger association between TCP and poor outcomes of COVID-19 when a lower cutoff TCP value was applied (Table 2 and Supplemental Material 3: Figure 9).

To some extent, ARDS onset, admission to ICU, and mortality can be considered as sequential events reflective of COVID-19 progression and deterioration.³ One advantage of the current study was the inclusion of many patients with multiple outcomes, allowing subgroup analysis to investigate the association of TCP with distinct endpoints. A surprising but interesting finding of the subgroup analysis is that TCP (both platelet number decrease and TCP rate) may not be significantly related to ICU admission (Table 2 and

Supplemental Material 3: Figures 7, 10) despite the trend of association between TCP and mortality and the composite endpoint (admission to ICU, use of mechanical ventilation, and mortality). A possible explanation for this result is that TCP tends to reach a significant level in the late clinical stage of COVID-19. This speculation can be supported by a prior study that reported a lower platelet number in patients hospitalized for more than 10 days after symptom onset than in those hospitalized within 10 days of symptom onset.¹⁹ Two recent studies that investigated the dynamic change in platelet count of patients with COVID-19 described a trend of persistent drop in platelet number for nonsurvivors, with a decline to $100 \times 10^9/L$ after approximately 2 weeks after admission.^{28,29} These results suggest that TCP is associated with COVID-19 progression and deterioration, highlighting the significance of monitoring platelet count. However, the results of the subgroup analysis may be limited by the small subgroup size and need further validation.

Although the role of TCP in COVID-19 has been well studied, the causal relationship between them is not yet established. Several possible mechanisms may be involved in platelet count fluctuations during the pathophysiological process of this viral disease. COVID-19 is a systemic infection characterized by hyperinflammation and hypercoagulable state in patients with severe disease.³²

Hence, TCP in COVID-19 may be explained by the irreversible consumption of platelets during the execution of procoagulant and immune modulation functions. Viral infection of megakaryocytes can increase their apoptosis and decrease maturation and ploidy.

Although there is no evidence that SARS-CoV-2 can directly infect the bone marrow or hematopoietic stem cells, the virus may modulate platelet production at other stages of development. For example, thrombopoietin (TPO), which is primarily produced in liver parenchymal cells, is a critical regulator of megakaryopoiesis and platelet production. Several reports have suggested that liver injury is a common complication of COVID-19.^{33,34} A drop in TPO production after parenchymal liver injury may at least in part explain TCP in COVID-19. Recently, a series of case reports suggested that COVID-19 is associated with the onset or reoccurrence of immune thrombocytopenia (ITP), which is characterized by isolated TCP, without thrombosis tendency and bone marrow abnormal cellularity.³⁵⁻³⁸ These findings suggested that the differential diagnosis of TCP in COVID-19 is indispensable; for SARS-CoV-2 infection-induced ITP, accurate diagnosis and specialized treatment are necessary to guarantee the prevention of bleeding episodes. Further investigation of the mechanisms of TCP can provide a more comprehensive understanding of this disease and provide a theoretical basis for clinical treatment.

In conclusion, this systematic review shows that TCP is common in COVID-19, as evident from a weighted incidence of 12.4%, and is associated with COVID-19 severity and outcome. Thus, TCP may serve as a potential biomarker to predict mortality in patients with COVID-19. A limitation of this study is that only 17 of the 24 included studies were available for synthesis for primary outcome, whereas all other subgroup analyses included data from <10 studies. Therefore, the results from subgroup analyses are uncertain and should be regarded with extreme caution. Further, most of the included studies were cross-sectional investigations, and the asymmetrical shape of the funnel plot (Supplemental Material 3: Figure 11) shows evidence of publication bias, suggestive of the high risk of bias involved in our meta-analysis. Because studies with strong quality evidence such as randomized controlled trials and case-control studies are not feasible or available in the context of the COVID-19 pandemic, individual patient data meta-analysis is warranted to address these questions in the future.

Supplementary Data

Supplemental figures and tables can be found in the online version of this article at www.labmedicine.com. **LM**

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