

The association between severe COVID-19 and low platelet count: evidence from 31 observational studies involving 7613 participants

A novel coronavirus disease broke out in 2019 (COVID-19). This disease was found to be a result of infection from the 2019 novel coronavirus (2019-nCoV).¹ The severity of COVID-19 disease ranges from asymptomatic to critically severe; clinical research reported that 10–15% of the patients were in the severe category and required a great deal of medical treatment and nursing care.² Indicators are needed to evaluate and predict the severity of the disease. We conducted the present meta-analysis to clarify whether platelet count might be a potential indicator to evaluate and predict the severity of COVID-19 in patients.

Relevant studies published in English up to 30 April 2020 were searched through PubMed Scopus, EMBASE, Web of Science and Cochrane Library. Keywords included “COVID-19”, “platelet count”, “severe” and “thrombocytopenia”. To be included in the analysis, the studies had to report the mean and (\pm standard deviation, SD) of the platelet count in both severe and non-severe COVID-19 patients, or report the median and interquartile range (IQR) or median and range of platelet count, from which we could extract information about the mean (\pm SD).^{3,4} The studies that reported the proportions of patients with thrombocytopenia in both severe and non-severe COVID-19 were also included. Studies were excluded when the participants might have a large overlap with other included studies. Study quality was evaluated by a checklist from the Agency for Healthcare Research and Quality. The pooled standardized mean difference (SMD) and odds ratio (OR) with 95% confidence interval (CI) were worked out by STATA 12.0 software (StataCorp LCC, College Station Texas, USA), and shown in the forms of forest plots figures. The detailed statement of materials and methods is shown in Data S1.

After a comprehensive search and review (Figure S1), 31 studies with 7613 participants were included. Twenty-five of the included studies reported the platelet count of both severe and non-severe COVID-19 patients and 15 of the included studies reported the proportion of thrombocytopenia in both severe and non-severe COVID-19 patients. Detailed information and the reference list of included studies are shown in Tables SI and SII.

For the 25 studies that reported the platelet count of both severe and non-severe COVID-19 patients, the pooled SMD revealed a lower platelet count in severe patients than non-severe patients (SMD = -0.36 , 95% CI -0.48 to -0.23 ,

$I^2 = 56.9\%$; shown in Fig 1A). The results of a sensitivity analysis and test of publication bias are shown in Figures S2 and S3. Six of the 25 studies defined death as the severe state. The pooled SMD revealed a much lower platelet count in non-survivor COVID-19 patients than survivor patients (SMD = -0.60 , 95% CI -0.72 to -0.47 , $I^2 < 0.1\%$; shown in Fig 1B).

Fifteen of the 31 included studies reported the proportion of thrombocytopenia in both severe and non-severe COVID-19 patients. The pooled OR of thrombocytopenia for severe COVID-19 patients indicated a significant association between thrombocytopenia and severe COVID-19 (OR = 3.46 , 95% CI 1.72 – 6.94 , $I^2 = 91.8\%$; shown in Fig 2A). The results of a sensitivity analysis and test of publication bias are shown in Figures S4 and S5. Three of the 15 studies defined death as the severe state. The pooled OR suggested a stronger association between thrombocytopenia and death caused by COVID-19 (OR = 11.75 , 95% CI 3.51 – 39.31 , $I^2 = 88.9\%$; shown in Fig 2B).

Abnormal platelet count, especially thrombocytopenia, is quite common in patients in the intensive care unit (ICU).⁵ The decreasing platelet count usually indicates the dysfunction of organs or systems and leads to a disorder of homeostasis. Studies found that thrombocytopenia in the ICU tended to increase the risk of death.⁶ It has also been reported that 2019-nCoV infection might affect the blood coagulation mechanism resulting in a disorder of blood coagulation.⁷

The mechanism by which 2019-nCoV affects blood coagulation might be similar to that of severe acute respiratory syndrome (SARS) which broke out in 2002 to 2003. The possible mechanism of thrombocytopenia in the SARS disease might be due to damage to the lung. The damage to the lung caused by the SARS corona virus, or mechanical ventilation, might lead platelet activation and aggregation, resulting in platelet consumption and thrombocytopenia.⁸ The lung has also been found to be a site of platelet biogenesis.⁹ Fibrosis and other lung damage might affect the formation and releasing of platelets. Collins¹⁰ reported that infection of the human coronavirus strain 229E could cause apoptosis in human monocytes/macrophages, which suggested that 2019-nCoV might damage the hematopoietic cells or platelet directly. However, the exact mechanism of how 2019-nCoV affects platelet count still needs to be explored.

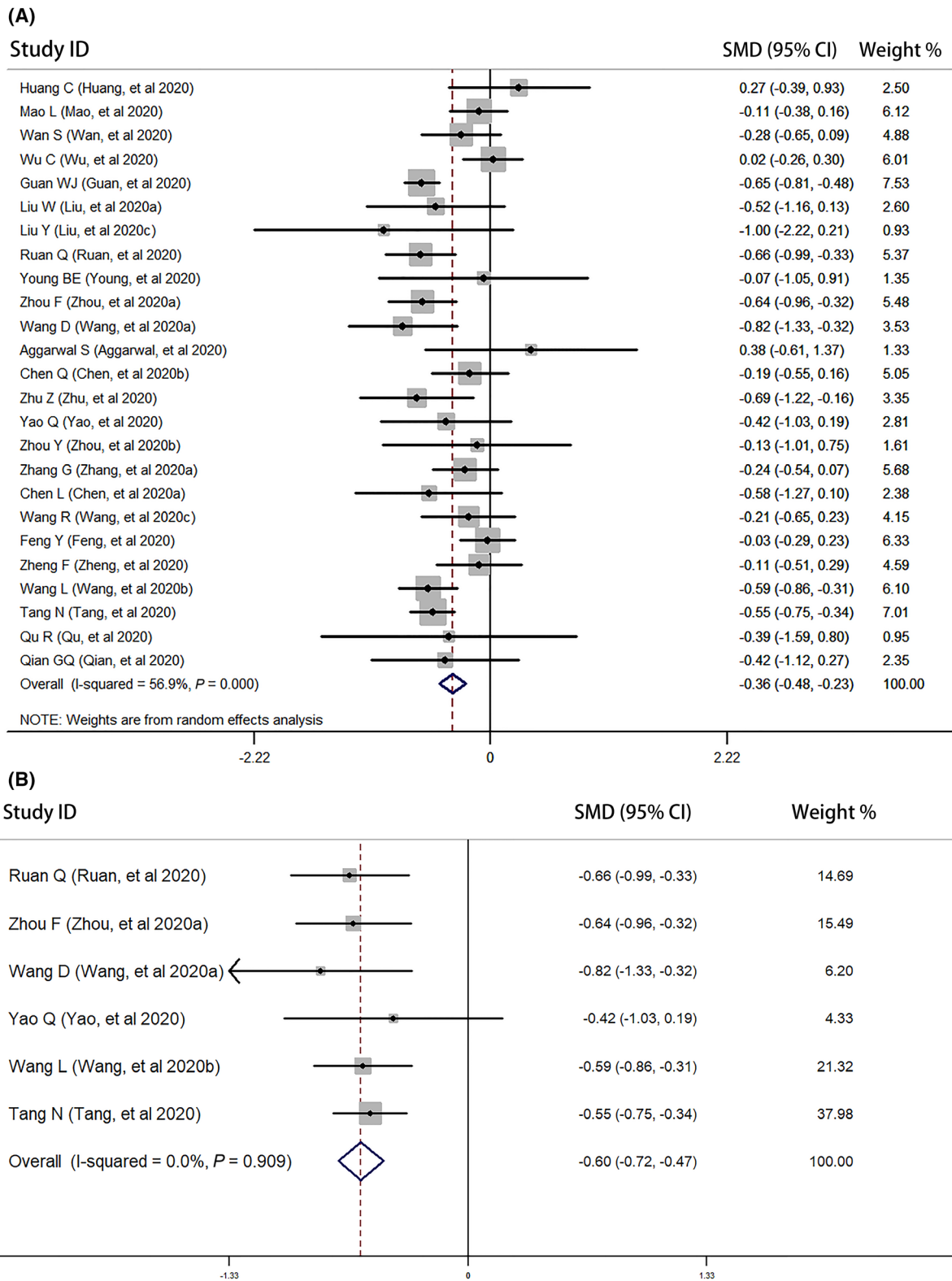


Fig 1. Result of meta-analysis on the standardized mean difference (SMD) of platelet count. The square in the forest plot denotes the SMD for the pooled effect with the corresponding 95% confidence interval (CI). (A) Result of pooled SMD between severe and non-severe COVID-19 patients, determined using a random-effect model. (B) Result of pooled SMD between non-survivor and survivor COVID-19 patients, determined using a fixed-effect model.

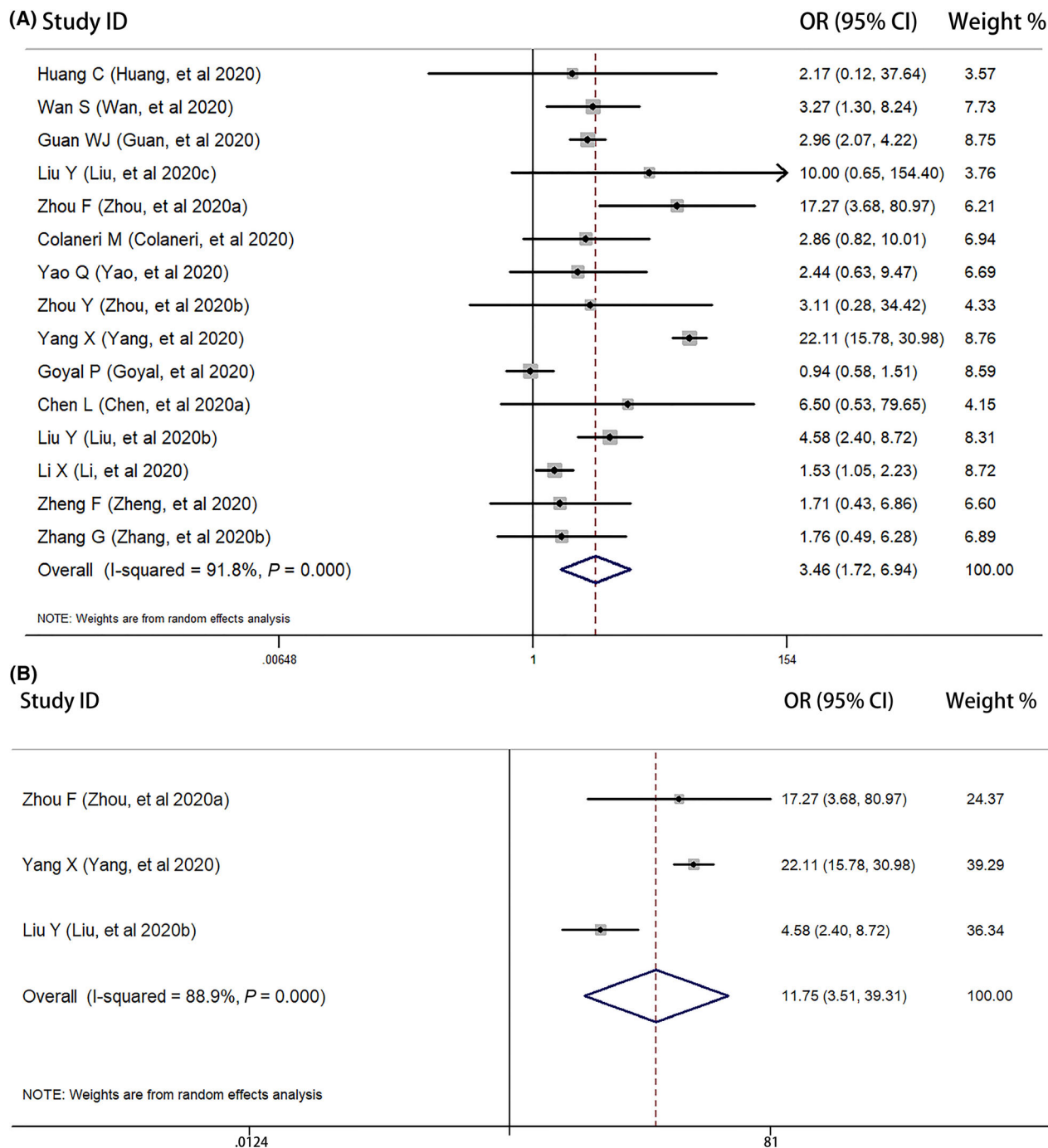


Fig 2. Result of meta-analysis on odds ratios (OR) of thrombocytopenia. The square in the forest plot denotes the OR for the pooled effect with the corresponding 95% confidence interval (CI). (A) Result of pooled OR for severe COVID-19 patients determined using a random-effect model. (B) Result of pooled OR for non-survivor COVID-19 patients determined using a random-effect model.

In conclusion, when compared to the non-severe COVID-19 patients, the patients with severe COVID-19 had a lower platelet count. The non-survivors had a much lower platelet

count than the survivors. Thrombocytopenia might be a risk factor for COVID-19 progressing into a more severe state. More studies about platelet count in COVID-19 are needed.

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Conflicts of interest

The authors declare no conflict of interest.

Author contributions

Shi-Qin Jiang, Qiu-Fen Huang and Wei-Ming Xie are joint first authors and contributed equally to the present meta-analysis; Shi-Qin Jiang, Wei-Ming Xie and Xiao-Qing Quan conceived the analysis; data was extracted by Qiu-Fen Huang and Wei-Ming Xie independently; Shi-Qin Jiang, Qiu-Fen Huang and Wei-Ming Xie analysed and interpreted the data; Shi-Qin Jiang and Chao Lv drafted the initial manuscript; the manuscript was critically revised by Xiao-Qing Quan for important intellectual content. All authors read and approved the final manuscript. All authors accept full responsibility for the content of the present article.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig S1. Flow diagram of literature search and study selection.

Fig S2. Result of sensitivity analysis for standardized mean difference (SMD) of platelet count between severe and non-severe COVID-19 patients. The middle vertical line indicates

the pooled SMD of 25 studies, and the two side vertical lines represent the 95% confidence interval (CI) values. Every hollow round indicates the pooled SMD when the left study was omitted in a meta-analysis with a random-effect model.

Fig S3. Begg's funnel plot of the 25 studies reported the platelet count of both severe and non-severe COVID-19 patients. The horizontal line indicates the pooled standardized mean difference (SMD). The asymmetry of two oblique lines was tested by Egger's linear regression test ($P = 0.328$).

Fig S4. Result of sensitivity analysis on odds ratios (OR) of thrombocytopenia for severe COVID-19 patients. The middle vertical line indicates the pooled OR of 15 studies, and the two side vertical lines represent the 95% confidence interval (CI) values. Every hollow round indicates the pooled OR when the left study was omitted in a meta-analysis with a random-effect model.

Fig S5. Begg's funnel plot of the 15 studies reported the proportion of thrombocytopenia in both severe and non-severe COVID-19 patients. The horizontal line indicates the pooled odds ratio (OR). The asymmetry of two oblique lines was tested by Egger's linear regression test ($P = 0.735$).

Table S1. Characteristics of studies reported the platelet count in both severe and non-severe COVID-19 patients.

Table S2. Characteristics of studies reported the proportion of thrombocytopenia in both severe and non-severe COVID-19 patients.

Data S1. Materials and methods.

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