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Prognosis of COVID-19 in patients with vein thrombosis: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: SARS-CoV-2 is currently affecting millions of humans worldwide, thus contributing to the COVID-19 pandemic. Thromboembolic events have a higher incidence among patients with COVID-19, but there are few reports on the relationship between the prognosis of COVID-19 patients and thromboembolic events. The objectives of this meta-analysis were to explore the relationship between the prognosis of COVID-19 patients and thromboembolic events.

MATERIALS AND METHODS: Medline (PubMed), the Web of Science, Embase, and the Cochrane Library were searched for case-control studies that included data on vein thrombosis in patients with COVID-19 and were published in English, between January 1 and July 25, 2020. According to the inclusion and exclusion criteria, the included data were confirmed, the prognoses of patients with and without concurrent thromboembolic events were compared, and the odds ratio (OR) was used as the effect size.

RESULTS: Eighteen studies (2,030 patients) were included. Thromboembolic events complicated a total of 609 COVID-19 patients. The combined OR of the mortality of COVID-19 patients with thromboembolic events was 1.93 (95% CI: 1.13-3.27), that of ICU treatment rate was 2.63 (95% CI: 1.49-4.67), and that of treatment with invasive mechanical ventilation was 3.14 (95% CI: 1.97-5.02).

CONCLUSIONS: As compared with COVID-19 patients with and without thromboembolism, the mortality, ICU treatment rate, and invasive mechanical ventilation treatment rate of COVID-19 patients with thromboembolism were found to be increased significantly, and the prognosis was worse.

Key Words:
COVID-19, Prognosis, Vein thrombosis, Meta-analysis, SARS-CoV-2.

Introduction

In December 2019, a new type of viral pneumonia broke out in Wuhan City, Hubei Province, which quickly caused an epidemic in China. In February 2020, the World Health Organization defined it as COVID-19 and announced that the outbreak had caused a worldwide pandemic in March 2020[1]. As of July 25, 2,164,111 people have been infected and 146,198 people died worldwide[2]. COVID-19 is a respiratory disease caused by the SARS-CoV-2 virus and often has common clinical manifestations, such as fever, cough, nasal congestion, sore throat, fatigue, and headache[3]. Of the complications surrounding COVID-19, thromboembolism is a more common comorbidity. Thromboembolism can manifest as venous thrombosis of the extremities, deep vein thrombosis, and acute and chronic pulmonary embolism. At present, many articles have discussed the pathogenesis

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of thromboembolism. SARS-CoV-2 may cause damage or inflammation of the vascular endothelium, which leads to impaired regulation of the vascular endothelium and, ultimately, to the formation of thrombus[4]. However, the prognosis of COVID-19 patients with thromboembolic events has yet to be discussed. The present meta-analysis goal was to explore whether the clinical prognosis of COVID-19 patients complicated by thromboembolic events is worse than that of COVID-19 patients not complicated by thromboembolic events.

Materials and Methods

As this study is a meta-analysis, the approval of an institutional or Ethics Committee was not required. MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) were consulted during the design, analysis, and reporting stages of this meta-analysis[5,6].

Search Strategy and Study Selection

The search criteria keywords included "thrombosis" or "thromboses" or "thrombus" or "thromboembolism" or "embolisms" or "embolus" and "Novel coronavirus 2019" or "Wuhan pneumonia" or "COVID-19" or "SARS-CoV-2" or "Wuhan virus" or "Chinese virus" or "Novel coronavirus" or "2019 nCoV" or "Wuhan coronavirus" or "the 2019 coronavirus". Studies published between January 1 and the present day (July 25th, 2020) that included these keywords were searched in Medline (PubMed), the Web of Science, Embase, and the Cochrane Library. The titles, abstracts, and full texts of all documents identified using these search criteria were independently screened by the researchers. All reported COVID-19 patients with thromboembolism (venous thrombosis or pulmonary embolism) were included in the meta-analysis. Additionally, a detailed review of all reference lists was conducted to determine whether additional eligible articles met the research conditions. A total of 1037 potentially relevant articles were identified. After screening the titles and abstracts, 1019 research articles that did not satisfy the inclusion criteria were eliminated. Ultimately, there were 18 studies with a total of 2030 COVID-19 patients included in our present meta-analysis (Table I).

Statistical Analysis

The analysis software used in this study was RevMan 5.2. The odds ratio (OR) and 95% confidence interval (95% CI) of the deaths, ICU treatment, or invasive mechanical ventilation of patients with COVID-19 combined with thromboembolic events were calculated for meta-analysis. OR forest plots of whether patients with COVID-19 and thrombotic events had died, received ICU treatment, or received invasive mechanical ventilation were then drawn. According to the level of heterogeneity (I^2) of the included studies, random effects ($I^2 > 50\%$) or fixed effects ($I^2 < 50\%$) were used. The forest plots present the 95% CI, percentage weights, heterogeneity between studies, and p-values.

Results

Study Processing

The sample sizes of the present study varied between 20-330 patients with COVID-19. The total number of confirmed COVID-19 cases considered in this study was 2030, of which 1259 (62.04%) were men. In the report, 609/2030 (30.00%) of the COVID-19 patients also had thromboembolic events, 12 of the 18 studies reported patient deaths, 7 studies reported that patients received ICU treatment, and 7 studies reported that patients received invasive mechanical ventilation treatment. The deaths, ICU treatment status, and invasive mechanical ventilation status of all patients with COVID-19 included in the study are reported in Table I.

Pooled Analysis

Mortality of COVID-19 Patients With and Without Thrombosis

Figure 1 presents a forest plot created in RevMan that includes the deaths of COVID-19 patients in 12 of the examined studies. A total of 1461 COVID-19 patients were included in the study. There were 443 cases complicated by thromboembolic events, of which 114 patients died (mortality rate: 25.73%). There were 1018 cases without thromboembolic events, of which 121 patients died (mortality rate:11.89%). The combined OR of the mortality of COVID-19 patients was 1.93 (95% CI: 1.13-3.27). The heterogeneity between studies was high ($I^2 = 54\%$, $p = 0.01$), and a random-effects model

Table I. Basic information and mortality, ICU treatment, and invasive mechanical ventilation in 18 included studies. "/" means that the data or information is not mentioned in the original papers.

				Mortality	ICU treatment	Invasive mechanical ventilation	Mortality	ICU treatment	Invasive mechanical ventilation
Fraissé et al 2020[12]	92/37	61 (55-70) (median)	73 (79.00%)	26 (70.27%)	/	36 (97.30%)	18 (32.73%)	/	46 (83.64%)
Faggiano et al 2020[13]	25/7	/	85 (84.00%)	1 (14.29%)	/	/	4 (22.22%)	/	/
Cui S et al 2020[14]	81/20	59.9 (14.1) (mean)	37 (46.00%)	8 (40.00%)	/	/	0 (0.00%)	/	/
Poyiadji et al 2020[15]	330/74	/	150 (45.73%)	6 (8.11%)	/	42 (66.67%)	10 (3.91%)	/	13 (65.00%)
Gervaise et al 2020[16]	72/13	62.3 (17.8) (mean)	54 (75.00%)	3 (23.08%)	/	/	8 (13.56%)	/	/
Zhang et al 2020[17]	143/66	63 (14) (mean)	74 (51.70%)	23 (34.85%)	12 (18.18%)	19 (28.79%)	9 (11.69%)	3 (3.90%)	4 (5.19%)
Ren et al 2020[18]	48/41	70 (62-80) (median)	26 (54.20%)	13 (31.71%)	/	/	2 (28.57%)	/	/
Chen et al 2020[19]	88/40	63 (55-71) (median)	54 (61.00%)	12 (30.00%)	/	19 (47.50%)	8 (16.67%)	/	14 (29.17%)
Hippensteel et al 2020[20]	91/24	/	53 (58.24%)	2 (8.33%)	/	22 (91.67%)	20 (29.85%)	/	55 (82.09%)
Fang et al 2020[21]	93/41	/	60 (64.51%)	6 (14.63%)	/		5 (9.62%)	/	/
Maatman et al 2020[22]	109/31	61 (16) (mean)	62 (57.00%)	8 (25.81%)	/		19 (24.36%)	/	/
Artifoni et al 2020[23]	71/16	64 (46-75) (median)	43 (60.60%)	/	8 (50.00%)	6 (37.50%)	/	5 (9.09%)	2 (3.64%)
Bompard et al 2020[24]	135/31	64 (54-76) (median)	94 (70.00%)	/	12 (37.50%)	/	/	12 (11.65%)	/
Whyte et al 2020[25]	214/80	/	129 (60.28%)	/	36 (45.00%)	/	/	42 (31.34%)	/
Bavaro et al 2020[26]	20/8	62 (56-80) (median)	8 (40.00%)	/	2 (25.00%)	/	/	4 (33.33%)	/
Stoneham et al 2020[27]	63/21	/	38 (60.32%)	/	6 (28.57%)	/	/	14 (33.33%)	/
Desborough et al 2020[28]	66/10	59 (49-66) (median)	48 (73.00%)	/	/	9 (90.00%)	/	/	43 (76.79%)
Trimaille et al 2020[29]	289/49	62.2 (17.0)							
(mean)	171 (59.2%)	6 (12.20%)	21 (43.8%)		18 (7.5%)	51 (21.3%)			
Total	2030/609		1259 (62.02%)	114 (25.73%)	97 (35.66%)	153 (59.76%)	121 (11.89%)	131 (19.76%)	177 (46.83%)

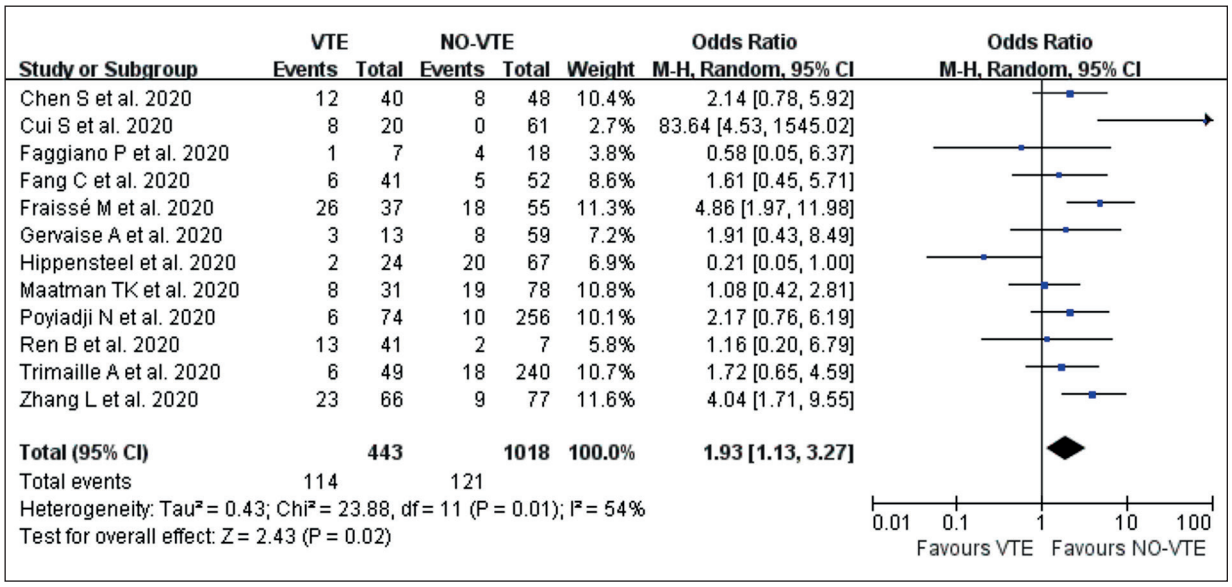

Figure 1. Forest plot of mortality of COVID-19 patients with or without venous thromboembolism.

was used. The funnel graph is symmetrically distributed, and no publication bias was found (Figure 2).

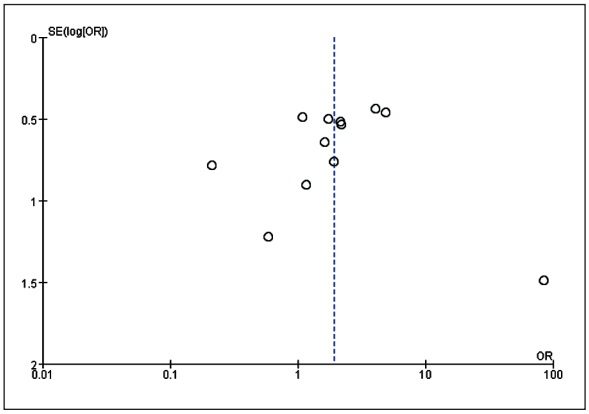

Figure 2. Forest plot of mortality of COVID-19 patients with or without venous thromboembolism.

ICU Treatment of COVID-19 Patients with and Without Thrombosis

Figure 3 presents a forest plot created in RevMan that includes patients who were reported to have received. ICU treatment in 7 of the examined studies. A total of 935 COVID-19 patients were included. There were 272 cases complicated by thromboembolic events, of which 97 patients received ICU treatment (treatment rate:

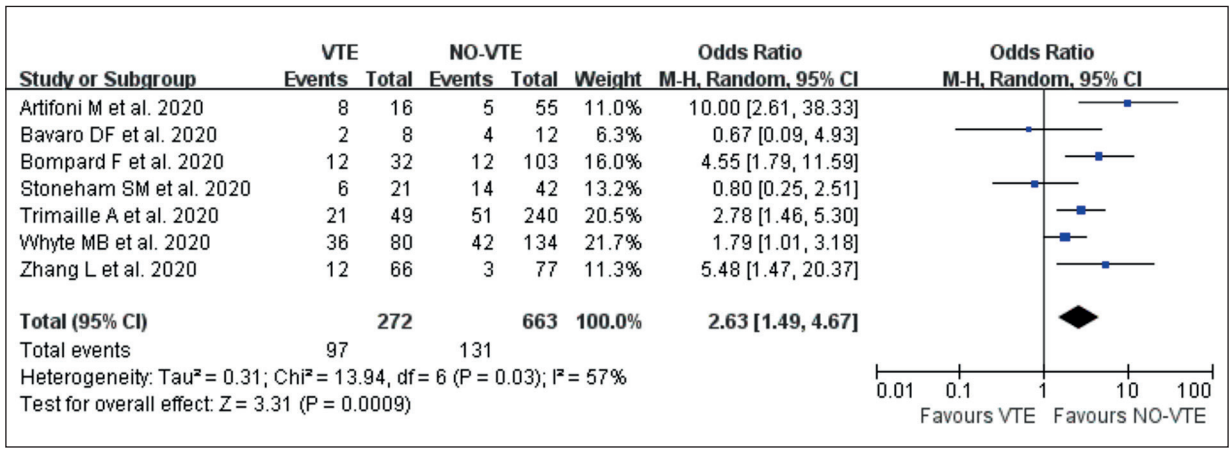

Figure 3. Forest plot of ICU treatment of COVID-19 patients with or without venous thromboembolism.

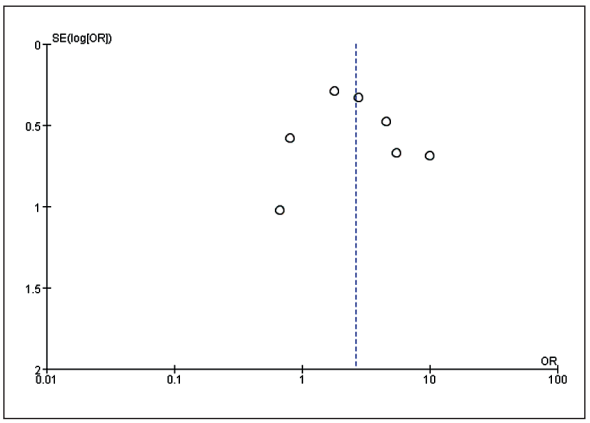

Figure 4. Forest plot of ICU treatment of COVID-19 patients with or without venous thromboembolism.

35.66%). There were 663 cases without thromboembolic events, of which 131 patients received ICU treatment (treatment rate: 19.76%). The OR of the ICU treatment of patients with COVID-19 was 2.63 (95% CI: 1.49-4.67). The heterogeneity between studies was high (I^2 = 57%, p = 0.03), and a random-effects model was used. The funnel graph is symmetrically distributed, and no publication bias was found (Figure 4).

Invasive Mechanical Ventilation Treatment of COVID-19 Patients with and Without Thrombosis

Figure 5 presents a forest plot created in RevMan that includes COVID-19 patients who were reported to have received invasive mechanical ventilation in 7 of the examined studies. A total of 634 COVID-19 patients were included. There were 256 cases complicated by thromboembolic events, of which 153 patients received invasive mechanical ventilation (treatment rate: 59.77%). There were 378 cases without thromboembolic events, of which 177 patients received invasive mechanical ventilation (treatment rate: 46.83%). The OR of the invasive mechanical ventilation treatment of patients with COVID-19 was 3.14 (95% CI: 1.97-5.02). The heterogeneity between studies was low (I^2 = 44%, p = 0.10), and a fixed-effects model was used. The funnel graph is symmetrically distributed, and no publication bias was found (Figure 6).

Discussion

The research results showed that the OR values of the mortality, ICU treatment rate, and invasive mechanical ventilation rate of COVID-19 patients complicated by thromboembolic events were 1.93, 2.63, and 3.37, respectively. It was found that the existence of thromboembolic events as a comorbidity in COVID-19 patients was related to poor prognosis, with high mortality and disease severity. COVID-19 is a serious respiratory disease caused by the SARS-CoV-2 virus. Severe viral infections can cause damage to the vascular endothelium[4], causing coagulation abnormalities that lead to bleeding and thromboembolic events[7,8]. Moreover, there is also evidence[9] that the levels of D-dimer in severe COVID-19 patients are significantly higher than those in

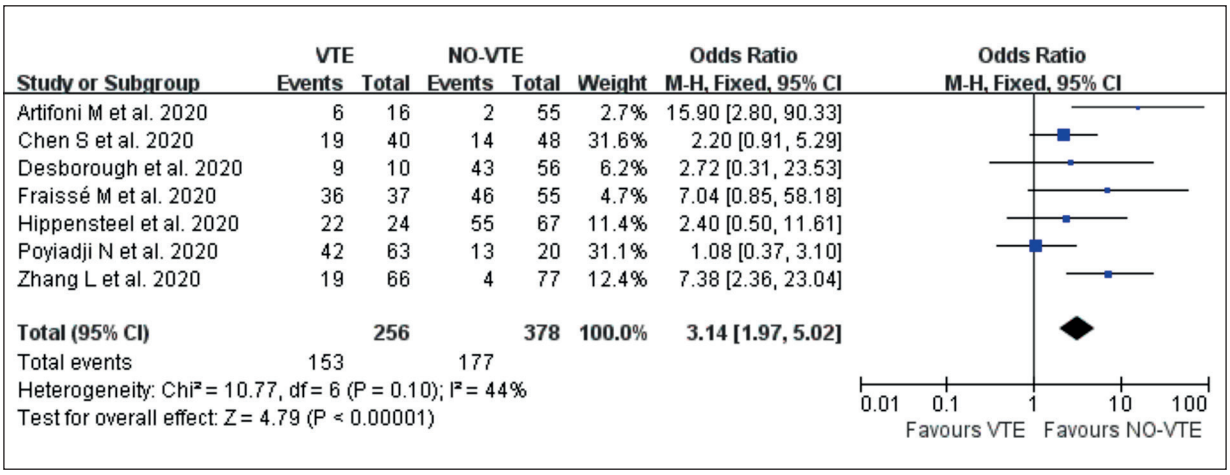

Figure 5. Forest plot of invasive mechanical ventilation treatment of COVID-19 patients with or without venous thromboembolism.

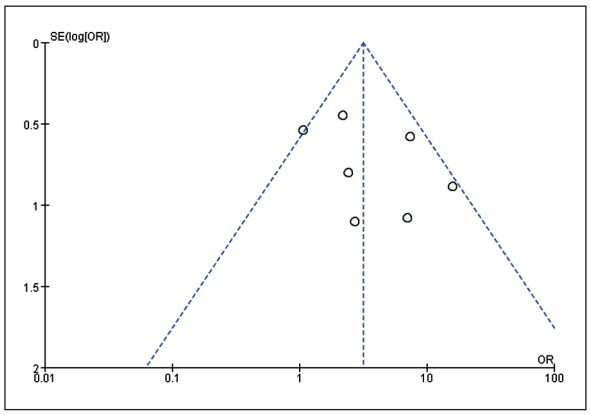

Figure 6. Forest plot of invasive mechanical ventilation treatment of COVID-19 patients with or without venous thromboembolism.

non-critical patients. For severe COVID-19 patients who have significantly increased D-dimer levels, the use of low-molecular-weight-heparin based anticoagulation therapy has been found to result in a better prognosis[10]. Therefore, current clinicians recommend the use of heparin to treat or prevent infection-related coagulopathy. Coupled with the results of this study, it is evident that clinical preventive anticoagulation is very necessary.

The present meta-analysis had three limitations. First, although 18 articles were examined, including a total of 2030 cases of COVID-19 patients, the sample size of each of the research indicators was small. Therefore, a large number of COVID-19 patients must be studied in the future to improve the accuracy of the research results. Second, subgroup analysis was not performed in this meta-analysis, e.g., the subgroup of COVID-19 patients with underlying disease. A previous meta-analysis article[11] has pointed out that blood pressure, diabetes, COPD, cardiovascular disease, and cerebrovascular disease are the main risk factors for COVID-19 patients. However, the present article did not clearly analyze the impacts of these underlying diseases on the final mortality or severity of COVID-19. Third, the research data in this article were retrospective studies; thus, the risk of thromboembolic events may, therefore, have been underestimated. Under the recommendation of preventive anticoagulation, the incidence of thrombotic events will have decreased, thus resulting in a decrease in the number of related reports or sample sizes; Moreover, some studies did not conduct systematic screening for thrombotic events.

Conclusions

The mortality and severity of COVID-19 patients with thrombotic events were found to be higher and more serious than those without thrombotic events, and the prognosis was worse. Of note, the present research results can provide recommendations for hospital doctors who are currently treating COVID-19 patients. In clinical treatment, attention should be paid to the risk of thrombotic events, thereby indirectly improving the prognosis of COVID-19.

Declaration of Interest

The authors have no conflicts of interest to disclose. All listed authors contributed to the planning, performing, and reporting of this work.

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