

COVID-19 and heparin-induced thrombocytopenia: Is there a relationship?

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ABSTRACT

Objectives: The purpose of this study was to evaluate the literature in terms of heparin-induced thrombocytopenia (HIT) that develops in COVID-19 patients.

Materials and methods: Between March 2019 and March 2021, all published articles on the subject of the study formed the target population of the study. The keywords "COVID-19" or "SARS-CoV-2" and "heparin-induced thrombocytopenia" were searched in English in the most prestigious databases of PubMed, Scopus, and Web of Science (WoS).

Results: No publications on this subject were found in the SCOPUS database. Only 13 publications were found in the PubMed database, and 11 in the WoS database. Eleven (78.5%) were published in 2020, and three (21.5%) were published in the first three months of 2021. There were four (28.5%) letters to the editor, six (42.8%) case reports, and one each (7.2%) correspondence, review, research article, and a short report. The only research article is also a retrospective study, except that no large case series or research article other than this one was found. The United States was identified as the country with the highest number of publications on this subject (57.1%).

Conclusion: Prospective studies, we believe, are urgently needed to understand the effects of heparin-induced thrombocytopenia development on morbidity, mortality, and long-term outcomes, a condition that can contribute to COVID-19 patient mortality as well as increased risk for thromboembolic events.

Keywords: COVID-19, heparin-induced thrombocytopenia, heparin-induced thrombocytopenia.

More than 2.5 million people have died worldwide since the World Health Organization (WHO) declared a pandemic nearly a year ago. Aside from mortality, morbidity and rising healthcare costs are still on the agenda. Every day, new clinical presentations are reported as a result of global studies on this disease.^[1,2] It is now commonly recognized that a prothrombotic condition is one of the leading causes of COVID-19 infection-related

mortality. Therefore, low molecular weight heparin thromboprophylaxis is strongly advised for these patients.^[2] However, heparin-induced thrombocytopenia (HIT) may occur as a result of this treatment.^[3-6]

Heparin-induced thrombocytopenia is a transient, acquired clinical-pathological syndrome characterized by thrombocytopenia and thrombosis caused by antibody-mediated platelet activation and consumption as a result of a heparin-induced immune response. The presence of immunoglobulin (Ig) G antibodies that activate heparin-dependent platelets in the formation of thrombocytopenia and/or thrombosis confirms the diagnosis of HIT. Furthermore, in order to make a diagnosis, it is necessary to differentiate it from non-immune HIT.^[3,4] The pathophysiology of increased coagulopathy, thrombosis risk, or

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potentially increased HIT risk in COVID-19 patients is unidentified.^[5,6]

Since this complication is difficult to diagnose, its incidence is also unclear. The purpose of this study was to evaluate the literature on heparin-induced thrombocytopenia development in COVID-19 patients.

MATERIALS AND METHODS

Research model: The research model is a case study, which is one of the qualitative research methods. The main objective of a case study is to exhibit results for a specific situation. According to Creswell,^[7] a case study is a qualitative research method in which the researcher examines one or more limited-time situations using data collection tools (observations, interviews, audiovisuals, documents, reports) from multiple sources, identifying situations and situation-related themes.

The target population of the study: Between March 2019 and March 2021, all published articles on the subject of the study formed the target population of the study.

Method: The study aimed to assess the current situation of COVID-19 related HIT and linked academic publications. The objective of this

research was to evaluate the literature from this aspect. The keywords “COVID-19” or “SARS-CoV-2” and “heparin-induced thrombocytopenia” were searched in English in the most prestigious databases of PubMed, Scopus, and Web of Science (WoS). The data obtained were saved as Excel sheets so that the necessary analyses could be performed. Duplicated publications were included in the one-off review.

RESULTS

As a result of the study, no publications on this subject were found in the SCOPUS database. Only 13 publications were found in the PubMed database, and 11 in the WoS database. Eleven (78.5%) were published in 2020, and three (21.5%) were published in the first three months of 2021. There were four (28.5%) letters to the editor, six (42.8%) case reports, and one each (7.2%) correspondence, review, research article, and a short report. The only research article is also a retrospective study, except that no large case series or research article other than this one was found. The United States was identified as the country with the highest number of publications on this subject (57.1%). Riker was the author with the most articles on this subject. The journal with the most publications on this subject

Table 1. A detailed review of published articles on COVID-19 related heparin-induced thrombocytopenia

Journal name	Author	Country	Article types
Journal of Investigative Medicine High Impact Case Reports	Lingamaneni et al. ^[2]	United States of America	Case report
Circulation	Daviet et al. ^[4]	France	Letter to editor
Thrombosis Research	Huang et al. ^[6]	Taiwan	Letter to editor
American Journal of Hematology	Patell et al. ^[8]	United States of America	Correspondence
Antibodies (Basel)	Cai et al. ^[9]	United States of America	Review
Hematology Reports 2021	Sartori and Cosmi ^[10]	Italy	Case report
Research and Practice in Thrombosis and Haemostasis	Riker et al. ^[11]	United States of America	Case report
Journal of Artificial Organs: the official journal of the Japanese Society for Artificial Organs	Bidar et al. ^[5]	France	Case report
Thrombosis Journal	Phan et al. ^[12]	Vietnam	Case report
Research and Practice in Thrombosis and Haemostasis	Riker et al. ^[13]	United States of America	Letter to editor
Research and Practice in Thrombosis and Haemostasis	May et al. ^[14]	United States of America	Letter to editor
Journal of Thrombosis and Haemostasis	Nazy et al. ^[15]	Canada	Short report
Cureus	Madala et al. ^[16]	United States of America	Case report
Blood	Warrior et al. ^[17]	United States of America	Research article

was Research and Practice in Thrombosis and Hemostasis, which had two publications (Table 1).

DISCUSSION

The pathophysiology of increased coagulopathy, thrombosis risk, and potentially increased heparin-induced thrombocytopenia risk in COVID-19 patients is still unknown.^[4,5] Our study intends to guide future research by looking at the global situation.

However, it is worth noting that only one research article was found globally as a result of our research. The only research article on this subject was conducted by Warrior et al.^[17] The incidence of heparin-induced thrombocytopenia in COVID-19 patients was reported to be 0.6% in this study, which was higher than the general population. The small sample size and retrospective study of this research, which found that HIT development may contribute to COVID-19 patient mortality and increased risk of thromboembolic events, was noted as a study limitation.^[17]

Heparin-induced thrombocytopenia is a serious immune-mediated complication of heparin treatment that develops when pathogenic antibodies bind platelet factor 4 (PF4)-heparin complexes, causing platelet activation, platelet consumption, and thrombin formation. Paradoxically, HIT is characterized by both thrombocytopenia and prothrombotic status.^[5] The increased HIT prevalence in these patients could be attributed to severe immune reactions and possibly platelet activation as a result of increased PF4 release. Furthermore, critical patients with COVID-19 may develop life-threatening coagulopathy, requiring aggressive anticoagulation therapy to avoid thromboembolic complications. This increased incidence can be explained by the higher doses of heparin used for COVID-19.^[4]

During the COVID-19 pandemic, Daviet et al.^[4] from France reported an 8% incidence of heparin-induced thrombocytopenia in 86 severe COVID-19 patients in two intensive care units. Thrombocytopenia is common in critical patients, while the incidence of HIT is relatively rare (<1%).^[4] However, in patients receiving extracorporeal membrane oxygenation (ECMO), the rate can reach up to 3.7%.^[4] During the COVID-19 pandemic, the

incidence of HIT increased from 2 to 21% in a previously published cohort of 105 patients supported by veno-venous ECMO.^[18] COVID-19 and HIT, on the other hand, are extremely difficult to differentiate. Multiple instruments, including clinical scoring (the 4Ts score), enzyme immunoassays (EIAs), and serotonin release assay (SRA), all require sensitivity and specificity tests.^[19]

In conclusion, heparin-induced thrombocytopenia development, a condition that can contribute to COVID-19 patients' mortality as well as an increased risk of thromboembolic events; we believe that prospective studies are needed immediately to understand the effects on morbidity, mortality, and long-term outcomes.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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