Heparin-induced Thrombocytopenia in Patients with Coronavirus Disease 2019: Systematic Review and Meta-analysis

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Noppacharn Uaprasert (Faculty of Medicine, Chulalongkorn University, Thailand) Nuanrat Tangcheewinsirikul (Faculty of Medicine, Chulalongkorn University, Thailand) Ponlapat Rojnuckarin (Faculty of Medicine, Chulalongkorn University, Thailand) Rushad Patell (Beth Israel Deaconess Medical Center, United States) Jeffrey Zwicker (Beth Israel Deaconess Medical Center, United States) Thita Chiasakul (Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red C, United States)

Abstract:
Heparin thromboprophylaxis is routinely administered during hospitalization for coronavirus disease 2019 (COVID-19). Due to the immune stimulation related to COVID-19, there is ongoing concern regarding a heightened incidence of heparin-induced thrombocytopenia (HIT). We performed a literature search using PubMed, EMBASE, Cochrane and, medRxiv database to identify studies that reported clinical and laboratory characteristics and/or the incidence of HIT in COVID-19 patients. The primary aim was to systematically review the clinical features and outcomes of COVID-19 patients with confirmed HIT. The secondary objective was to perform a meta-analysis to estimate the incidence of HIT in hospitalized COVID-19 patients. A meta-analysis of 7 studies including 5,849 patients revealed the pooled incidence of HIT in COVID-19 of 0.8% (95% confidence interval [CI], 0.2-3.2%; I² = 89%). The estimated incidences were 1.2% (95%CI, 0.3-3.9%; I² = 65%) versus 0.1% (95%CI, 0.0-0.4%; I² = 0%) in therapeutic versus prophylactic heparin subgroups, respectively. The pooled incidences of HIT were higher in critically ill COVID-19 patients (2.2%, 95%CI, 0.6-8.3%; I² = 72.5%) compared to non-critically ill patients (0.1%, 95%CI, 0.0-0.4%; I² = 0%). There were 19 cases of confirmed HIT and one with autoimmune HIT for clinical and laboratory characterization. The median time from heparin initiation to HIT diagnosis was 13.5 (interquartile range [IQR], 10.75, 16.25) days. Twelve (63%) developed thromboembolism after heparin therapy. In conclusion, the incidence of HIT in COVID-19 patients was comparable to non-COVID-19 medical patients, with higher incidences with therapeutic anticoagulation and in critically ill patients.

Conflict of interest:
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Noppacharn Uaprasert,¹,² Nuanrat Tangcheewinsirikul,¹,² Ponlapat Rojnuckarin,¹,² Rushad Patell,³ Jeffrey I Zwicker,³ Thita Chiasakul.¹,²

¹Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand.

²Research Unit in Translational Hematology, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand.

³Division of Hematology and Division of Hemostasis and Thrombosis, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Corresponding author: Noppacharn Uaprasert, MD
Division of Hematology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital Rama IV Rd, Pathumwan, Bangkok, 10330, Thailand, Email: drnoppacharn@yahoo.com

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**Abstract**

Heparin thromboprophylaxis is routinely administered during hospitalization for coronavirus disease 2019 (COVID-19). Due to the immune stimulation related to COVID-19, there is ongoing concern regarding a heightened incidence of heparin-induced thrombocytopenia (HIT). We performed a literature search using PubMed, EMBASE, Cochrane and, medRxiv database to identify studies that reported clinical and laboratory characteristics and/or the incidence of HIT in COVID-19 patients. The primary aim was to systematically review the clinical features and outcomes of COVID-19 patients with confirmed HIT. The secondary objective was to perform a meta-analysis to estimate the incidence of HIT in hospitalized COVID-19 patients. A meta-analysis of 7 studies including 5,849 patients revealed the pooled incidence of HIT in COVID-19 of 0.8% (95% confidence interval [CI], 0.2-3.2%; $I^2 = 89\%$). The estimated incidences were 1.2% (95%CI, 0.3-3.9%; $I^2 = 65\%$) versus 0.1% (95%CI, 0.0-0.4%; $I^2 = 0\%$) in therapeutic versus prophylactic heparin subgroups, respectively. The pooled incidences of HIT were higher in critically ill COVID-19 patients (2.2%, 95%CI, 0.6-8.3%; $I^2 = 72.5\%$) compared to non-critically ill patients (0.1%, 95%CI, 0.0-0.4%; $I^2 = 0\%$). There were 19 cases of confirmed HIT and one with autoimmune HIT for clinical and laboratory characterization. The median time from heparin initiation to HIT diagnosis was 13.5 (interquartile range [IQR], 10.75, 16.25) days. Twelve (63%) developed thromboembolism after heparin therapy. In conclusion, the incidence of HIT
in COVID-19 patients was comparable to non-COVID-19 medical patients, with higher incidences with therapeutic anticoagulation and in critically ill patients.
Introduction

Since the first emerging cluster of pneumonia in China in December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 170 million individuals and caused nearly 4 million deaths worldwide. Abnormal coagulation parameters, especially elevated D-dimer levels, were rapidly recognized as the key features of patients infected with SARS-CoV-2 and were associated with poor outcomes suggesting that hypercoagulation may play roles in the disease pathogenesis. The early report from China suggested a potential survival benefit of anticoagulation in coronavirus disease 2019 (COVID-19) patients.

Shortly after its spread to Europe, there were several cohorts that identified the high incidence of thromboembolism in hospitalized COVID-19 patients. Therefore, several international guidelines recommended anticoagulants for the management of COVID-19-associated coagulopathy and routine pharmacological thromboprophylaxis for all hospitalized COVID-19 patients without contraindications. However, a significant proportion of patients, especially in the intensive care unit (ICU), developed both arterial and venous thromboembolism despite standard-dose thromboprophylaxis. Consequently, many medical centers have implemented intermediate-dose or therapeutic-dose anticoagulants to prevent thromboembolic complications. Currently, there are several randomized controlled trials evaluating the efficacy and safety of different intensities of thromboprophylaxis in hospitalized COVID-19 patients. In a recently published INSPIRATION randomized controlled trials, intermediate-dose prophylactic anticoagulation did not provide additional benefits over standard-dose prophylaxis.
Heparin-induced thrombocytopenia (HIT) is an uncommon but serious immunologic complication from heparin leading to transient thrombocytopenia accompanied by highly prothrombotic state.\textsuperscript{20} Diagnosis of HIT, especially in critically-ill patients, is challenging since there are many alternative causes of thrombocytopenia.\textsuperscript{21,22} Non-pathologic anti-platelet 4/heparin antibodies (anti-PF4/H Abs) may also be present in this population.\textsuperscript{20} The diagnosis of HIT requires confirmatory tests that demonstrate platelet activation of anti-PF4/H Abs in the presence of heparin.

According to the guidelines,\textsuperscript{10-13} unfractionated heparin (UFH) or low molecular weight heparin (LMWH) are indicated for hospitalized COVID-19 patients. The wide use of heparin may lead to increasing incidence of HIT, complicating patient care by aggravating thrombocytopenia and intensifying thrombotic risks. Awareness and early recognition is critical for proper management (i.e., initiation of non-heparin anticoagulants and avoiding platelet transfusion).\textsuperscript{20,21}

To date, the incidence, clinical characteristics and impacts of HIT on hospitalized COVID-19 patients remain largely unknown. We conducted a systematic review to characterize clinical manifestations, laboratory profiles, management and clinical outcomes of HIT and performed a meta-analysis to estimate the incidence of HIT in hospitalized COVID-19 patients.

**Methods**

The protocol for this review was pre-specified and registered in PROSPERO (CRD42021240788). The study was subsequently conducted following Preferred
Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. The primary objective of this study was to systematically characterize clinical and laboratory presentations, diagnosis, management and clinical outcomes of HIT and HIT with thrombosis in hospitalized COVID-19 patients. The meta-analysis of the incidence of HIT, the incidence of anti-PF4/H Abs and risks associated with HIT development were planned if there were sufficient data for analysis. The pre-specified subgroup analyses including types of heparin (unfractionated heparin versus low molecular weight heparin), intensities of heparins (prophylactic versus therapeutic) and severity of patients with COVID-19 (critically ill versus non-critically ill) would be performed if there were sufficient data.

**Data source, search strategy and study selection**

A systematic search of electronic databases was performed using PubMed, EMBASE, Cochrane Library Database and the preprint server (medRxiv) from inception to March 8th, 2021 and was updated on June 14th, 2021 to identify studies reporting cases with confirmed HIT using platelet activation assays and/or incidence of HIT in COVID-19 patients. The following search terms were used: heparin, anticoagulant, anticoagulation, antithrombotic, thrombocytopenia, platelet, platelet factor 4, HIT, immune, coagulopathy, thrombosis, novel coronavirus 2019, COVID-19, SARS-CoV-2 and 2019-nCoV.

The inclusion criteria for eligible studies were as follows: (1) individual case reports or case series including less than 20 adult patients (age ≥ 18 years) who were hospitalized for COVID-19 and confirmed HIT using the following platelet activation assays: serotonin release assay (SRA), heparin-induced platelet activation (HIPA) test, platelet
aggregation test or flow cytometric assay; or (2) randomized controlled trials, retrospective or prospective observational studies enrolling at least 20 adult patients who were hospitalized for COVID-19 with reported incidence of HIT or sufficient data for computing the incidence of HIT. Non-original articles (such as reviews, commentaries, or guidelines) and duplicated studies were excluded. Two authors (N.U. and N.T.) independently searched the literature, screened titles and abstracts, and reviewed full texts to identify potentially eligible studies. Disagreements were resolved by consensus or a third reviewer (T.C.) when necessary. The selection result was reported according to the PRISMA flowchart.

Data extraction

Two authors (N.U. and N.T.) independently reviewed full data from individual selected studies including supplementary materials and independently extracted pre-specified data. Disagreements of extracted data were resolved by consensus or a third reviewer (T.C.) when necessary. The primary outcome was clinical and laboratory characteristics and clinical outcomes of COVID-19 patients with confirmed HIT. The secondary outcomes were the incidence of HIT, the incidence of anti-PF4/H Ab detection, and risks associated with HIT development in hospitalized COVID-19 patients.

For each study, the following data were extracted: study design, study population, number of participants, baseline characteristics of patients (age, sex, and severity), heparin administration (indications, types, intensity, and duration of heparin exposure before HIT diagnosis), initial platelet counts, nadir platelet counts, thromboembolic events after heparin initiation, clinical scoring systems, screening immunoassays for HIT, confirmatory assays for HIT, alternative non-heparin anticoagulants, bleeding
Quality Assessment

The methodological quality of included studies for meta-analysis was performed independently by two authors (N.U. and N.T.) using a validated tool for assessing studies reporting prevalence data. The tool contains 10 items assessing the external validity and internal validity of the study. For each item, a score of 0 or 1 was assigned to the answers yes or no, respectively. The summary assessment of overall risk of bias was rated according to the responses to the 10 items and included studies were classified based on the total score as low (0-3), moderate (4-6), or high risk (7-10) of bias.

Data analysis

The meta-analysis was performed using Comprehensive Meta-analysis (Version 2; Biostat, Englewood, NJ, USA). The pooled incidence of each outcome was calculated using DerSimonian and Laird method with random-effects model and were reported as the pooled incidence with 95% confidence interval (CI). Statistical heterogeneity was assessed using I² statistic, which measured the inconsistency across study results. Inter-study heterogeneity was assigned as insignificant (I² = 0-25%), low (I² = 26-50%), moderate (I² = 51-75%), and high (I² >75%). The funnel plot for evaluation of publication bias was not performed due to the low number of studies included in the meta-analysis (less than 10 studies). For descriptive statistics, normality of the data was
tested using Shapiro-Wilk test. Continuous data were presented as means (± standard deviations, SD) or medians with interquartile ranges as appropriate. All descriptive analyses were computed using SPSS version 22.0 for Window (Chicago, SPSS Inc.).

Results

The PRISMA flow diagram was shown in Figure 1. A total of 2,008 unique studies were identified by literature search and were screened by titles and abstracts. Of these, 1,986 were excluded, and 22 full texts were screened for eligibility. Eventually, 15 studies were assigned as low risk of bias, while the other 3 studies were classified as moderate risk of bias. (Supplementary data, Table S1).

Study Characteristics

The main characteristics of the 15 included studies (12 published full-texts, 1 full-preprint report and 2 abstracts) were summarized in Table 1. Across 15 studies (8,053 total patients), there were a total of 40 reported HIT patients. Of these, 19 HIT cases and one with autoimmune HIT who had diagnosis confirmed by SRA or HIPA were included for clinical and laboratory characterization. From 6 concurrent cohorts, clinical and laboratory data of 26 patients who were suspected to have HIT but had negative confirmatory tests were available for comparison.
A total of 7 studies were included for the estimation of the pooled incidence of HIT.\textsuperscript{29,32-36,40} These 7 studies collectively included a total of 5,849 patients, ranging from 86 to 2,574 patients.

**Clinical and laboratory characteristics of confirmed HIT in hospitalized patients with COVID-19**

From 11 studies, there were 19 confirmed HIT cases and one with autoimmune HIT, with sufficient data for characterization.\textsuperscript{26-33,37-39} Clinical and laboratory characteristics of individual cases were summarized in Table 2. Among the 19 documented cases of HIT, the median age was 62.0 (interquartile range [IQR], 51.0, 64.0) years. Males were the predominant proportion (74%). All but one patient (95%) were critically ill and were admitted to the ICU. Nine patients received UFH, 2 received LMWH and 8 received both LMWH and UFH. Of the 18 patients with available data on heparin intensity, 13 (72%) received therapeutic-intensity anticoagulation, while 5 (28%) received prophylactic anticoagulation. The median time from heparin initiation to HIT diagnosis was 13.5 (IQR, 10.75, 16.25) days. Median baseline platelet counts and median nadir platelet counts were 223 x 10\textsuperscript{9}/L (IQR, 160.5, 297) and 56 x 10\textsuperscript{9}/L (IQR, 37, 73), respectively. All but one patient had intermediate or high pre-test probability for HIT using the 4T scoring system with the median of 5.5 (IQR, 4, 6). Twelve patients (63%) developed thrombosis after heparin administration. A total 15 of 19 (79%) confirmed HIT cases demonstrated platelet recovery after heparin substitution with non-heparin anticoagulants. Of the 17 with known survival outcomes, 4 died shortly after HIT diagnosis.

Only one COVID-19 patient with autoimmune HIT was identified.\textsuperscript{39} He presented with pulmonary embolisms coexisting with severe thrombocytopenia 8 days after diagnosis.
of COVID-19 without previous heparin exposure, leading to a high suspicion of autoimmune HIT, which was confirmed by presence of functional anti-PF4/H Abs using SRA. He was successfully treated with intravenous immunoglobulin and argatroban followed by apixaban.

In 6 concurrent studies, hospitalized COVID-19 patients who were suspected to have HIT but had negative confirmatory tests were reported. Among these, 26 cases were reviewed for comparison with confirmed HIT (Table 3). Clinical and laboratory variables of patients with confirmed HIT and patients with negative HIT confirmatory tests were summarized (Table 4). The variables of both groups were closely similar.

Sixteen patients (61.5%) developed thromboembolic events after heparin therapy. Of patients with known survival outcomes, 13 of 20 (65%) patients died shortly after suspected HIT.

**Incidence of heparin-induced thrombocytopenia in hospitalized patients with COVID-19**

From 7 studies (N = 5,849 patients), the pooled incidence of HIT in hospitalized COVID-19 patients was 0.8% (95%CI, 0.2%, 3.2%; I² = 89%) (Figure 2). A sensitivity analysis of 4 studies (N = 3,031), in which the diagnostic criteria for HIT were specified, revealed the pooled incidence of 0.8% (95%CI, 0.1%, 6.4%; I² = 89%) (Supplementary figure S1).

A subgroup analysis according to the study’s risk of bias was performed (Figure 3). The pooled incidence of 3 small studies with moderate risk of bias, which included 268 patients mostly receiving UFH, was 4.5% (95%CI, 2.0%, 10.0%; I² = 46%). The pooled
incidence of 4 larger studies with low risk of bias (5,581 patients) was 0.2% (95%CI, 0.1%, 0.7%; \( I^2 = 43\% \)). There was a significant difference between the low risk and the moderate risk of bias (\( P < 0.001 \)).

Data on the incidence of HIT stratified by anticoagulation intensity were available in 4 studies. The pooled incidence of HIT in patients receiving prophylactic-intensity heparins was 0.1% (3 studies, \( N = 3,010 \), 95%CI, 0.0%, 0.4%; \( I^2 = 0\% \)), while the pooled incidence of HIT in patients receiving therapeutic heparins was 1.2% (4 studies, \( N = 2,033 \), 95%CI, 0.3%, 3.9%; \( I^2 = 65\% \)) (Figure 4). The pair-wise comparison revealed significant difference between prophylactic versus therapeutic heparins (\( P = 0.007 \)). We also analyzed the difference of HIT in the largest cohort including 2,574 patients receiving heparins. HIT development was higher in patients receiving therapeutic anticoagulation compared to prophylactic anticoagulation (odds ratio, 28.8, 95%CI, 3.7, 223.5, \( P = 0.001 \)).

A subgroup analysis to estimate pooled incidences of HIT in critically ill COVID-19 patients and non-critically ill COVID-19 patients was performed. A total of 3,169 patients from 5 studies were available for analysis. The pooled incidence of HIT in critically ill COVID-19 patients was 2.2% (4 studies, \( N = 508 \), 95%CI, 0.6%, 8.3%; \( I^2 = 73\% \)), while the pooled incidence of HIT in non-critically ill COVID-19 patients was 0.1% (2 studies, \( N = 2,661 \), 95%CI, 0.0%, 0.4%; \( I^2 = 0\% \)) (Figure 5). The pair-wise comparison revealed significant difference between critically ill and non-critically ill COVID-19 patients (\( P = 0.002 \)).
Although the pre-specified subgroup analysis to assess the risk for HIT between UFH and LMWH was planned, there were no sufficient data to compute the pooled incidences of HIT for UFH and LMWH.

**Incidence of anti-platelet factor 4/heparin antibody detection in hospitalized patients with COVID-19**

Existing data were not sufficient for estimating the pooled incidence of anti-PF4/H Abs (activating and non-activating) in all hospitalized COVID-19 patients receiving heparins, since the tests were only performed based on suspicion of HIT. In the only one study whereby anti-PF4/H Abs were screened in 172 consecutive patients (64 ICU and 108 non-ICU), the frequency of anti-PF4/H-associated polyspecific Abs (IgM, IgA and IgG; OD of > 0.5) was 33%, while the frequency of anti-PF4/H-associated monospecific IgG (OD of > 0.5) was 16%. Of the 19 cases with anti-PF4/H-associated polyspecific Abs OD of > 1.0, seven (37%) patients had thromboembolic events. However, all patients with positive anti-PF4/H Abs yielded negative HIT confirmatory tests.

**Discussion**

In this systematic review, we characterized 19 hospitalized COVID-19 patients with confirmed HIT using standard platelet activation assays. There were 26 patients who were suspected HIT but had negative confirmatory tests from concurrent cohorts for comparison. Some cases were assigned as HIT in their original cohorts due to strongly positive immunoassays. However, the recent study revealed that patients with COVID-19 frequently had strongly positive immunoassays without platelet
activating antibodies indicating non-pathogenic antibodies. Therefore, HIT diagnosis requires confirmatory heparin-dependent platelet activating tests despite the strongly positive immunoassays to avoid over-diagnosis and over-treatment of HIT.

Of the 19 confirmed cases of HIT, most patients were critically ill in the ICU, and males were predominant. The overrepresentation of males in COVID-19 patients with suspected HIT may be explained by the higher proportion of male patients admitted in the ICU and the higher probability to develop thrombocytopenia triggering investigation for HIT.

Half of patients were diagnosed after 14 days of heparin exposure, suggesting a delay in diagnoses of HIT in COVID-19 patients. Most of the patients with suspected HIT obtained a 4T score of ≥ 4. In addition, a similar proportion of confirmed HIT (12 of 19, 63%) and suspected HIT (16 of 26, 61.5%) cases developed thrombosis after heparin administration. Therefore, it is apparent that clinical features such as platelet counts and the presence of thrombosis cannot reliably predict the diagnosis of HIT in COVID-19 patients, and functional tests are required for the definitive diagnosis.

Almost all patients with confirmed HIT had platelet recovery shortly after switching to non-heparin anticoagulants. When the causes of thrombocytopenia are not obvious, immediate platelet response to alternative anticoagulant may be suggestive of HIT diagnosis. This observation may be helpful while waiting for a confirmatory assay, which may not be readily available for timely clinical management.

In this meta-analysis, we report the pooled incidence of HIT in hospitalized COVID-19 patients of 0.8% (95%CI, 0.2%, 3.2%) which was comparable to those reported from
large cohorts and meta-analysis of non-COVID-19 medical patients, which the incidences of HIT ranged from 0.08 to 0.94%. However, there was high heterogeneity among studies as 3 small cohorts with moderate risk of bias had very high incidence of HIT in COVID-19 patients (4.5%, 95%CI, 2%, 10%). All confirmed HIT in these 3 cohorts received therapeutic doses of UFH. In contrast, the pooled incidence of HIT from 4 larger cohorts with low risks of bias was 0.2% (95%CI, 0.1%, 0.7%) similar to non-COVID-19 patients. Therefore, prospective systematic studies are warranted to determine the incidence of HIT among different COVID-19 populations (based on disease severity, types of heparin and heparin dosing).

In critically ill patients, non-activating anti-PF4/H Abs may be present without causing HIT. In these cases, the screening immunologic assays are positive with negative confirmatory tests. In our review, there was only one study that screened anti-PF4/H Abs in consecutive hospitalized COVID-19 patients. Compared to the HIT incidence of 0.2% (95%CI, 0%, 1.1%), the frequency of patients with detected anti-PF4/H Abs was substantially higher (33%). Similarly to non-COVID-19 cases, HIT developed in less than 10% of patients with detectable anti-PF4/H Abs. Therefore, the routine screening for anti-PF4/H Abs in COVID-19 patients receiving heparin is probably not cost-efficient.

The pre-specified subgroup analysis was performed to assess the risk of heparin intensity and HIT development in COVID-19. Hospitalized COVID-19 patients who received therapeutic doses of heparins were at greater risk for HIT than those who received prophylactic doses of heparins. The recent INSPIRATION randomized controlled trial failed to demonstrate the benefits of intermediate-dose anticoagulation, compared with prophylactic-dose anticoagulation, to reduce thrombosis or mortality in
ICU patients with COVID-19.\textsuperscript{19} Notably, 7 thrombocytopenia of unspecified causes occurred only in patients assigned to the intermediate-dose group with the absolute risk difference of 2.2\% (95\%CI, 0.4\%, 3.8\%, \( P = 0.01 \)). Therefore, the risk of HIT in higher intensity anticoagulation should be considered.

The estimated incidence of HIT in critically ill COVID-19 patients was 2.2\%. This was relatively higher than those previously reported in non-COVID-19 patients (0.3-0.5\%).\textsuperscript{21,45} The hyperactivation of the immune system in COVID-19 may activate platelets to release of PF4 into circulation and stimulate anti-PF4/H Ab production.\textsuperscript{46} Severe endothelial injury, platelet hyperactivation and immune dysregulation after SARS-CoV-2 infection may involve in development of HIT in critically ill COVID-19 patients.\textsuperscript{47}

There are some limitations of this study. Most of studies were case reports, small case series or retrospective cohorts, which were prone to biases due to different HIT confirmatory tests and criteria, lack of central adjudication of HIT cases and incomplete data collection. In addition, all but one cohorts did not perform systematic surveillance, which may lead to either under- or overestimation of the incidences of HIT in COVID-19 patients due to case selection, as well as significant heterogeneity among studies. Finally, the number of studies included in both qualitative and quantitative were relatively small.

\textbf{Conclusions}
In this systematic review and meta-analysis, we reported a pooled incidence of HIT in COVID-19 patients of 0.8% which was similar to those previously reported in non-COVID-19 medical patients. However, the incidence of HIT in COVID-19 patients might be increased in patients receiving therapeutic-dose heparin and in critically ill patients. The clinical and laboratory profiles between COVID-19 patients with confirmed HIT and suspected HIT with negative confirmation were similar. A large prospective cohort with systematic surveillance of HIT is required to estimate the true incidence and determine risk factors for HIT in hospitalized COVID-19 patients.

Authorship

Contribution: N.U. was involved in conceptualization, database search, screening of abstracts and full texts, data extraction and analysis, quality appraisal, and writing the original draft and revision of manuscript; N.T. was involved in conceptualization, database search, screening of abstracts and full texts, and editing of the manuscript and the revised manuscript; P.R. was involved in data analysis, appraisal and editing of the manuscript and the revised manuscript; R.P. was involved in data analysis and editing of the manuscript and the revised manuscript; J.I.Z. was involved in appraisal and editing of the manuscript and the revised manuscript; and T.C. was involved in conceptualization, adjudication, data analysis and editing of the manuscript and the revised manuscript.

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The authors (NU, NT, PR, RP and TC) declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. J.I.Z. reports research funding from Incyte and Quercegen; consultancy services to Sanofi, CSL, and Parexel; and honoraria from/advisory board participation with Pfizer/Bristol Myers Squibb (BMS), Portola, Daiichi, Sanofi and CSL Behring.

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Table 1 Characteristics of included studies

| Authors        | Study design     | N   | Study population                                                                 | Pretest clinical scoring system | Immunoassay for screening HIT | Platelet activation assay for confirming HIT | Suspected HIT/confirmed HIT | Proportion of ICU or critical illness |
|----------------|------------------|-----|-----------------------------------------------------------------------------------|---------------------------------|-------------------------------|-----------------------------------------------|-----------------------------|---------------------------------------|
| Riker\textsuperscript{26} 2020 | Case report      | 16  | Thrombocytopenia with anti-PF4 Ab among intubated COVID-19 patients with ARDS       | 4T score                        | ELISA                         | SRA                                           | 3/1                         | 16 (100%)                             |
| Lingamaneni\textsuperscript{27} 2020 | Case report      | 5   | COVID-19 patients with HIT suspicion                                              | 4T score                        | ELISA                         | SRA                                           | 5/1                         | 5 (100%)                              |
| May\textsuperscript{26} 2020      | Case report      | 7   | Hospitalized COVID-19 patients with positive anti-platelet factor 4 Ab            | 4T score                        | ELISA                         | SRA                                           | 7/1                         | 7 (100%)                              |
| Patell\textsuperscript{28} 2020   | Retrospective cohort | 88  | patients hospitalized with Covid-19 and received intravenous UFH for ≥ 5 days     | 4T score                        | Latex immune turbidimetric assay | SRA                                           | 8/3                         | NR                                    |
| Bidar\textsuperscript{29} 2020    | Case report      | 2   | Confirmed HIT in COVID-19 patients with severe ARDS on VVECMO                    | NR                              | ELISA                         | HIPA                                          | 2/2                         | 2 (100%)                              |
| Tran\textsuperscript{31} 2020     | Case report      | 1   | A patient with SARS-CoV-2 pneumonitis and confirmed HIT                           | 4T score                        | ELISA                         | HIPA                                          | 1/1                         | 1                                     |
| Daviet\textsuperscript{32} 2020   | Retrospective cohort | 86  | COVID-19 ARDS in 2 ICUs enrolled in COAG-COVID trial                             | 4T score                        | Quantitative CIA; IgG specific | HIPA                                          | NR/7                        | 86 (100%)                             |
| Delrue\textsuperscript{33} 2020   | Retrospective cohort | 626 | All consecutive SARS-CoV-2-infected adults admitted to the ICU                   | 4T score                        | PaGIA, ELISA IgG               | HIPLA, SRA                                     | 10/1                        | 184 (29.4%)                          |
| Study | Design | Population | Intervention | Outcome | Treatment | Additional Details |
|-------|--------|------------|--------------|---------|-----------|--------------------|
| Helms et al. 2020 | Prospective cohort | 150 | All patients with SARS-CoV-2 ARDS admitted to the ICU | NR | NR | NR | 4/0 | 150 (100%) |
| Ionescu et al. 2020 | Retrospective cohort | 3480 (2574 receiving LMWH or UFH) | Consecutive COVID-19 adult patients hospitalized within 8 hospitals located in Southeast Michigan | NR | NR | NR | NR/12 | 642 (18.4%) |
| Santi et al. 2020 | Retrospective cohort | 94 | Hospitalized patients infected with COVID-19 | NR | NR | NR | NR/2 | NR |
| Warrior et al. 2020 | Retrospective cohort | 1265 | Hospitalized COVID-19 positive patients | 4T score | ELISA | SRA | 8/1 | NR |
| Madala et al. 2021 | Case report | 1 | A patient with SARS-CoV-2 pneumonia and ischemic stroke | 4T score | ELISA | SRA | 1/1 | 1 |
| Julian et al. 2021 | Case report | 1 | A patient with COVID-19 positive and confirmed autoimmune HIT | N/A | ELISA | SRA | 1/1 | 1 |
| Lawler et al. 2021 | Randomized controlled trial | 2231 | Non-critically ill patients hospitalized for Covid-19 | 4T score | ELISA | SRA | NA/0 | 0 |

Ab, antibody; HIT, heparin-induced thrombocytopenia; ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; NR, not reported; LMWH, low molecular weight heparin; UFH, unfractionated heparin; ELISA (or EIA): Enzyme-linked immunosorbent assay (or enzyme immunoassay);
Table 2 Clinical and laboratory characteristics of hospitalized COVID-19 patients with confirmed heparin-induced thrombocytopenia

| Case | Age (years), Sex | Severity of COVID-19 | Indication of heparin | Type and dose of heparin | Duration of heparin to HIT diagnosis (days) | Initial platelet count (x 10^9/L) | Nadir platelet count (x 10^9/L) | Thrombosis after heparin initiation | 4T score | Screening test | Confirmatory test | Non-heparin anticoagulants | Platelet response after HIT treatment | Outcomes of patients as reported |
|------|-----------------|----------------------|-----------------------|--------------------------|-------------------------------------------|---------------------------------|---------------------------------|----------------------------------|----------|----------------|----------------|---------------------|-----------------------------|---------------------------------|
| 1<sup>st</sup> | 70, M | ICU (MV, ARDS) | DVT prophylaxis | UFH; prophylaxis | 20 | 438 | 90 | PE | 6 | ELISA (OD 2.0) | SRA, positive (48%) | Bivalirudin | Death shortly after HIT diagnosis |
| 2<sup>nd</sup> | 63, M | ICU (MV) | DVT prophylaxis | LMWH; prophylaxis | 12 | 304 | 96 | DVT | 6 | ELISA (OD 1.2) | SRA, positive (49%) | Argatroban | Death shortly after HIT diagnosis |
| 3<sup>rd</sup> | 61, F | ICU (RRT) | RRT | UFH; prophylactic | N/A | N/A | 37 | N/A | 4 | ELISA (OD 0.95) | SRA, positive | N/A | N/A |
| 4<sup>th</sup> | 68, F | ICU | AF | UFH; therapeutic | 7 | 416 | < 5 | None | 4 | LITA (1.8 U/mL) | SRA, positive | Argatroban, bivalirudin | Platelet recovery |
| 5<sup>th</sup> | 63, M | ICU | STEMI | UFH; therapeutic | 6 | 154 | 51 | Splenic infarct and cerebral infarct | 8 | LITA (1.6 U/mL) | SRA, borderline positive | Argatroban | Platelet recovery |
| 6<sup>th</sup> | 49, M | ICU | COVID pneumonia | UFH; therapeutic | 12 | 176 | 25 | None | 6 | LITA (1.9 U/mL) | SRA, borderline positive | Argatroban | Platelet recovery |
| 7<sup>th</sup> | 62, F | ICU (MV, ECMO) | PE, ECMO | UFH; therapeutic | 16 | 237 | 29 | None | 3 | ELISA (OD 1.8) | HiPA, positive | Argatroban | Platelet recovery, discharge from hospital |
| 8<sup>th</sup> | 38, M | ICU (MV, ECMO) | ECMO | UFH; therapeutic | 21 | 248 | 50 | None | 4 | ELISA (OD 1.6) | HiPA, positive | Argatroban | Platelet recovery, discharge from hospital |
| 9<sup>th</sup> | 62, M | ICU (MV) | VTE prophylaxis | LMWH and UFH flush; prophylactic | 17 | 412 | 91 | PE | 4 | ELISA (OD 1.1) | HiPA, positive | Bivalirudin | Platelet recovery |
| 10<sup>th</sup> | 46, M | ICU (ARDS, MV, Clinical trial (COAG- | LMWH and UFH; therapeutic | 16 | 61 | 33 | Multiple DVT | 6 | CIA (46 U/mL) | HiPA, positive | Argatroban | Discharge from ICU |
| #  | Sex | Age | ICU Present (Causes) | COVID**a** | Anticoagulant | ADW | CIA | HIPA | Argatroban | Platelet Recovery/Discharge | Status |
|----|-----|-----|---------------------|------------|---------------|-----|-----|------|------------|-----------------------------|--------|
| 11**1** | 50, M | 13 | ECMO (ARDS, MV, ECMO) | Clinical trial (COAG-COVID)**a** | LMWH and UFH; therapeutic | 243 | 73 | Intracardiac thrombus, ECMO membrane thrombosis | 6 | CIA (11 U/mL) | HIPA, positive | Argatroban | Still in ICU |
| 12**1** | 43, F | 15 | ICU (ARDS, MV, ECMO) | Clinical trial (COAG-COVID)**a** | LMWH and UFH; therapeutic | 160 | 48 | Multiple DVT, ECMO pump thrombosis | 6 | CIA (39 U/mL) | HIPA, positive | Argatroban | Still in ICU |
| 13**1** | 63, M | 14 | ICU (ARDS, MV) | Clinical trial (COAG-COVID)**a** | LMWH and UFH; therapeutic | 191 | 56 | Stroke | 4 | CIA (60 U/mL) | HIPA, positive | Danaparoid | Alive |
| 14**1** | 59, M | 9 | ICU (ARDS, MV) | Clinical trial (COAG-COVID)**a** | LMWH and UFH; therapeutic | 161 | 62 | DVT | 5 | CIA (4 U/mL) | HIPA, positive | Danaparoid | Discharge from ICU |
| 15**1** | 57, M | 11 | ICU (ARDS) | Clinical trial (COAG-COVID)**a** | UFH; therapeutic | 159 | 39 | None | 5 | CIA (21 U/mL) | HIPA, positive | Danaparoid | Alive |
| 16**1** | 69, M | 16 | ICU (ARDS, MV) | Clinical trial (COAG-COVID)**a** | UFH; therapeutic | 215 | 107 | None | 4 | CIA (2 U/mL) | HIPA, positive | Danaparoid | Alive |
| 17**1** | 64, M | 18 | ICU | VTE prophylaxis | LMWH; prophylactic | 223 | 67 | DVT | 6 | PaGIA positive, ELISA IgG (OD 2.4) | HIPLA, positive (75%), SRA, positive (94% at 0.1 U/mL and 103% at 0.5 U/mL heparin) | Argatroban (13 days), danaparoid (19 days), apixaban at discharge | Alive |
| 18**1** | 63, M | N/A | ICU (RRT) | RRT | LMWH and UFH; NA | N/A | N/A | PE | ≥ 4 | ELISA IgG (OD 0.62) | SRA, positive | Argatroban | N/A | Death |
| 19**1** | 65, F | 12 | Non-ICU | AF | LMWH and UFH; therapeutic | 290 | 63 | Stroke, PE, iliac and femoral artery thrombosis | 6 | CIA (9.7 U/mL) | SRA, positive (94%) | Argatroban, apixaban | Platelet recovery, discharge from hospital | Alive |
| 20**1** | 65, M | 6 | Non-ICU | N/A | N/A | N/A | N/A | DVT, PE (at | N/A | N/A | NR, SRA, positive | Argatroban, Platelet recovery, discharge from hospital | Alive |
Table 3 Clinical and laboratory characteristics of hospitalized COVID-19 patients with negative confirmatory tests for heparin-induced thrombocytopenia
| Case | Age (years), Sex | Severity of COVID-19 | Indication of heparin | Type and dose of heparin during HIT diagnosis | Duration of heparin when tested for HIT (days) | Initial platelet count (x 10^9/L) | Nadir platelet count (x 10^9/L) | Thrombosis after heparin initiation | 4T score | Screening test | Confirmatory test | Non-heparin anticoagulants | Platelet recovery after HIT treatment | Patients' outcome as reported |
|------|-----------------|----------------------|----------------------|---------------------------------------------|---------------------------------------------|-------------------------------|------------------------------|-----------------------------------|---------|----------------------------|-----------------------------|--------------------------------|-----------------------------------------------|-----------------------------------------|
| 1    | 74, M           | ICU (MV, ARDS)       | DVT prophylaxis      | LMWH and UFH; prophylactic                  | 12                                          | 143                           | 68                           | Upper extremity venous thrombosis | 4       | ELISA (OD 1.3)            | SRA, negative (0%)                  | Fondaparinux then bivalirudin        | None                                           | Death                                    |
| 2    | 53, M           | ICU (MV, ARDS)       | AF                   | UFH; therapeutic                            | 11                                          | 207                           | 22                           | Skin necrosis                    | 6       | ELISA (OD 0.48)           | SRA negative (0%)                    | Argatroban then apixaban             | Recovery                             | Alive                                   |
| 3    | 53, M           | ICU (ARDS)           | ACS and AF           | N/A                                         | 7                                           | N/A                           | N/A                          | None                              | 5       | ELISA (OD 0.71)           | SRA negative                        | Argatroban                          | N/A                                           |                             |
| 4    | 61, F           | ICU (ARDS)           | DVT                  | N/A                                         | 6                                           | N/A                           | N/A                          | DVT                               | 7       | ELISA (OD 0.77)           | SRA, negative                        | N/A                                  | N/A                                           |                             |
| 5    | 68, F           | ICU (ARDS)           | DVT                  | N/A                                         | 8                                           | N/A                           | N/A                          | DVT                               | 7       | ELISA (OD 0.42)           | SRA, negative                        | N/A                                  | N/A                                           |                             |
| 6    | 63, M           | ICU (ARDS)           | Suspected PE         | N/A                                         | 2                                           | N/A                           | N/A                          | Suspected PE                     | 4       | ELISA (OD 0.31)           | SRA, negative                        | N/A                                  | N/A                                           |                             |
| 7    | 50, M           | ICU (ECMO)           | ECMO                 | UFH; prophylactic                            | N/A                                         | N/A                           | 49                           | None                              | 5       | ELISA (OD 0.63)           | SRA, negative                        | N/A                                  | N/A                                           | Death                                    |
| 8    | 79, F           | N/A                  | VTE prophylaxis      | LMWH; prophylactic                           | N/A                                         | N/A                           | 155                          | None                              | 3       | ELISA (OD 1.89)           | SRA, negative                        | N/A                                  | N/A                                           | Alive                                   |
| 9    | 58, F           | N/A                  | VTE prophylaxis      | LMWH; prophylactic                           | N/A                                         | N/A                           | 305                          | PE                                | 3       | ELISA (OD 0.51)           | SRA, negative                        | N/A                                  | N/A                                           | Death                                    |
| 10   | 38, M           | ICU (ECMO)           | VTE prophylaxis, ECMO| LMWH and UFH; prophylactic                   | N/A                                         | N/A                           | 39                           | None                              | 3       | ELISA (OD 0.83)           | SRA, negative                        | N/A                                  | N/A                                           |                             |
| 11   | 71, F           | ICU (RRT)            | RRT                  | UFH; prophylactic                            | N/A                                         | N/A                           | 70                           | Stroke                            | 6       | ELISA (OD 0.47)           | SRA, negative                        | N/A                                  | N/A                                           | Death                                    |
| 12   | 46, M           | N/A                  | VTE prophylaxis      | LMWH; prophylactic                           | N/A                                         | N/A                           | 59                           | DVT                               | 5       | ELISA (OD 0.83)           | SRA, negative                        | N/A                                  | N/A                                           |                             |
| No. | Age | Gender | Location | Diagnosis | Prophylaxis | Mechanical Ventilation | ECMO | VTE Treatment | ELISA | SRA | HIPA | HLA | N/A | Outcome |
|-----|-----|--------|----------|-----------|-------------|------------------------|------|---------------|-------|-----|------|-----|-----|---------|
| 13th| 49, M | ICU | COVID pneumonia | UFH; therapeutic | 6 | 211 | 47 | None | 6 | LITA (1.1 U/mL) | SRA, negative | Argatroban | None | Death |
| 14th| 77, M | ICU | VTE prophylaxis | LMWH and UFH; prophylactic | 11 | 136 | 59 | None | 5 | PaGIA, negative | HIPLA, negative | None | N/A | Death |
| 15th| 63, M | ICU | VTE prophylaxis | LMWH and UFH; therapeutic | 14 | 250 | 11 | None | 4 | PaGIA, negative | HIPLA, negative | None | N/A | Alive |
| 16th| 60, M | ICU | VTE prophylaxis and DVT treatment | LMWH and UFH; therapeutic | 21 | 153 | 36 | DVT | 4 | PaGIA, negative | HIPLA, negative | None | N/A | Death |
| 17th| 63, M | ICU | AF | LMWH and UFH; therapeutic | 12 | 177 | 38 | None | 4 | PaGIA, negative | HIPLA, negative | None | N/A | Death |
| 18th| 71, M | ICU | AF | LMWH and UFH; therapeutic | 21 | 240 | 77 | None | 4 | PaGIA, negative | HIPLA, negative | None | N/A | Death |
| 19th| 66, M | ICU | PE | UFH; therapeutic | 2 | 121 | 59 | PE and DVT | 4 | PaGIA, negative | HIPLA, negative | None | N/A | Alive |
| 20th| 50, M | ICU | VTE prophylaxis | LMWH; prophylactic | 12 | 227 | 136 | Stroke | 6 | PaGIA, negative | HIPLA, negative | None | N/A | Alive |
| 21st| 67, M | ICU | AF | UFH; therapeutic | 23 | 363 | 138 | DVT | 6 | PaGIA, negative | HIPLA, negative | None | N/A | Death |
| 22st| 65, M | ICU | PE suspicion | LMWH and UFH; therapeutic | 24 | 317 | 138 | PE and DVT | 6 | PaGIA, negative | HIPLA, negative | Argatroban | N/A | Death |
| 23st| 58, M | N/A | N/A | LMWH; N/A | N/A | N/A | 60 | DVT | ≥ 4 | ELISA IgG (OD 1.68) | SRA, negative | Argatroban | N/A | Death |
| 24st| 77, M | ICU (RRT) | N/A | LMWH and UFH; N/A | N/A | N/A | 28 | Stroke | ≥ 4 | ELISA IgG (0.7) | SRA, negative | Argatroban | N/A | Alive |
| 25st| 36, M | N/A | N/A | LMWH; N/A | N/A | N/A | 2 | None | ≥ 4 | ELISA IgG (0.88) | SRA, negative | Argatroban | N/A | Alive |
| 26st| 34, M | N/A | N/A | LMWH; N/A | N/A | N/A | 65 | DVT | ≥ 4 | N/A | SRA, negative | Bivalirudin | N/A | Alive |

M, male; F, female; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; MV, mechanical ventilation; ECMO, extracorporeal membrane oxygenation; RRT, renal replacement therapy; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; TE, thromboembolism; UFH, unfractionated heparin; LMWH, low molecular weight heparin; ELISA, enzyme-link immunosorbent assay; LITA, latex immune turbidimetric assay; PaGIA, particle gel immunoassay; HIPLA, heparin-induced platelet activation assay (positivity threshold 13%); SRA, serotonin release assay; HIPA, heparin-induced platelet activation assay; N/A, not available.
**Table 4** Clinical characteristics and laboratory profiles of hospitalized COVID-19 patients with confirmed heparin-induced thrombocytopenia and patients with negative confirmatory tests

| Variables                                | Patients with confirmed HIT (N = 19) | Patients with negative confirmatory tests (N = 26) |
|------------------------------------------|--------------------------------------|---------------------------------------------------|
| Age (years)                              | 62.0 (50.0, 64.0)<sup>a</sup>         | 62 (50, 68.75)<sup>a</sup>                        |
| Sex (male; female)                       | 14 (74%); 5 (26%)                    | 21 (81%); 5 (19%)                                 |
| Type of heparins (UFH; LMWH)             | 17 (63%); 10 (37%)                   | 15 (43%); 16 (46%) [4 N/A (11%)]                 |
| Intensity of anticoagulants (prophylactic; therapeutic) | 5 (26.3%); 13 (68.4%); [1 N/A (5.3%)] | 9 (34.6%); 9 (34.6%); [8 N/A (30.8%)]             |
| Duration of heparin to HIT diagnosis (days) | 13.5 (10.75, 16.25)<sup>a</sup>    | 11 (6, 21)<sup>a</sup>                            |
| Initial platelet counts (x 10<sup>9</sup>/L) | 223 (160.5, 297)<sup>a</sup>         | 209 (145.5, 247.5)<sup>a</sup>                    |
| Nadir platelet counts (x 10<sup>9</sup>/L)  | 56 (37, 73)<sup>a</sup>             | 59 (37.5, 91.75)<sup>a</sup>                      |
| Thrombosis after heparin administration  | 12 (63%)                             | 16 (61.5%)                                        |
| 4T score                                 | 5.5 (4, 6)<sup>a</sup>              | 5 (4, 6)<sup>a</sup>                              |

HIT, heparin-induced thrombocytopenia; UFH, unfractionated heparin; LMWH, low molecular weight heparin; N/A, not available; <sup>a</sup>Median (interquartile range)
Figure legend

**Figure 1** PRISMA Flow Diagram

**Figure 2** Forest plot showing pooled estimated incidence of heparin-induced thrombocytopenia in hospitalized COVID-19 patients

**Figure 3** Forest plot showing the pooled estimated incidence of heparin-induced thrombocytopenia in hospitalized COVID-19 patients according to the risks of bias

**Figure 4** Forest plot showing the pooled estimated incidence of heparin-induced thrombocytopenia in hospitalized COVID-19 patients according to the intensities of heparins

**Figure 5** Forest plot showing the pooled estimated incidence of heparin-induced thrombocytopenia in hospitalized COVID-19 patients according to severity of patients
Figure 1

Records identified through database searching (n = 2,438)  
(EMBASE = 1,703, MEDLINE = 633, Cochrane = 71, Preprint servers = 31)

Records after duplicates removed (n = 2,008)

Records screened (n = 2,008)

Records excluded (n = 1,986)

Full-text articles excluded, with reasons (n = 7)
- Case reports or case series without confirmatory tests for HIT

Full-text articles assessed for eligibility (n = 22)

Studies included in qualitative synthesis (n = 15)

Studies included in quantitative synthesis (meta-analysis) (n = 7)
| Study name     | Event rate | Lower limit | Upper limit | Total |
|---------------|------------|-------------|-------------|-------|
| Daviet2020    | 0.081      | 0.039       | 0.161       | 7 / 86|
| Dulrie2020    | 0.002      | 0.000       | 0.011       | 1 / 626|
| Helms2020     | 0.003      | 0.000       | 0.051       | 0 / 150|
| Ionescu2020   | 0.005      | 0.003       | 0.008       | 12 / 2574|
| Patell2020    | 0.034      | 0.011       | 0.100       | 3 / 88 |
| Santi2020     | 0.021      | 0.005       | 0.081       | 2 / 94 |
| Lawler2021    | 0.000      | 0.000       | 0.004       | 0 / 2231|
|               | 0.008      | 0.002       | 0.032       |       |

Heterogeneity: df = 6 (P < 0.001); $I^2 = 89\%$
| Study name | Subgroup within study | Event rate | Lower limit | Upper limit | Total |
|------------|-----------------------|------------|-------------|-------------|-------|
| Dulrue     | low                   | 0.002      | 0.000       | 0.011       | 1/626 |
| Helms      | low                   | 0.003      | 0.000       | 0.051       | 0/150 |
| Ionescu    | low                   | 0.005      | 0.003       | 0.008       | 12/2574 |
| Lawler     | low                   | 0.000      | 0.000       | 0.004       | 0/2231 |
| Daviet     | moderate              | 0.081      | 0.039       | 0.161       | 7/86  |
| Patell     | moderate              | 0.034      | 0.011       | 0.100       | 3/88  |
| Santi      | moderate              | 0.021      | 0.005       | 0.081       | 2/94  |

Heterogeneity of low risk of bias studies: df = 3 (P = 0.152); I² = 43%
Heterogeneity of moderate risk of bias studies: df = 2 (P = 0.156); I² = 46%
| Study name | Subgroup within study | Event rate | Lower limit | Upper limit | Total  | Relative weight |
|------------|-----------------------|------------|-------------|-------------|--------|-----------------|
| Helms      | prophylactic          | 0.005      | 0.000       | 0.071       | 0/105  | 24.92           |
| Ionescu    | prophylactic          | 0.001      | 0.000       | 0.004       | 1/1855 | 50.05           |
| Lawler     | prophylactic          | 0.000      | 0.000       | 0.008       | 0/1050 | 25.03           |
| Helms      | therapeutic           | 0.011      | 0.001       | 0.151       | 0/45   | 13.66           |
| Ionescu    | therapeutic           | 0.015      | 0.008       | 0.027       | 11/719 | 40.42           |
| Patell     | therapeutic           | 0.034      | 0.011       | 0.100       | 3/88   | 32.16           |
| Lawler     | therapeutic           | 0.000      | 0.000       | 0.007       | 0/1181 | 13.76           |
|            |                       | 0.012      | 0.003       | 0.039       |        |
|            |                       | 0.004      | 0.001       | 0.009       |        |

Heterogeneity of prophylactic doses: df = 2 (P = 0.399); I² = 0%

Heterogeneity of therapeutic doses: df = 3 (P = 0.037); I² = 65%
| Study name | Subgroup within study | Event rate and 95%CI | Relative weight |
|------------|-----------------------|----------------------|------------------|
|            |                       | Event Lower Upper    |                  |
|            |                       | rate limit limit     |                  |
|            |                       |                      |                  |
| Helms      | Critically ill        | 0.003 0.000 0.051 0/150 | 14.88            |
| Patell     | Critically ill        | 0.034 0.011 0.100 3/88 | 29.93            |
| Daviet     | Critically ill        | 0.081 0.039 0.161 7/86 | 33.88            |
| Delrue     | Critically ill        | 0.005 0.001 0.038 1/184 | 21.35            |
| Delrue     | Non-critically ill    | 0.001 0.000 0.018 0/442 | 49.98            |
| Lawler     | Non-critically ill    | 0.000 0.000 0.004 0/2219 | 50.02            |

Heterogeneity of critically ill patients: df = 3 (P = 0.012); I² = 73%
Heterogeneity of non-critically ill patients: df = 1 (P = 0.42); I² = 0%