SYSTEMATIC REVIEW

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Heparin-induced thrombocytopenia in patients with COVID-19: a systematic review and meta-analysis

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Heparin thromboprophylaxis is routinely administered during hospitalization for COVID-19. Because of 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 patients with COVID-19. The primary aim was to systematically review the clinical features and outcomes of patients with COVID-19 with confirmed HIT. The secondary objective was to perform a meta-analysis to estimate the incidence of HIT in hospitalized patients with COVID-19. A meta-analysis of 7 studies including 5849 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%; $I^2 = 65\%$) vs 0.1% (95% CI, 0.0%-0.4%; $I^2 = 0\%$) in therapeutic vs prophylactic heparin subgroups, respectively. The pooled incidences of HIT were higher in critically ill patients with COVID-19 (2.2%; 95% CI, 0.6%-8.3%; $I^2 = 72.5\%$) compared with noncritically ill patients (0.1%; 95% CI, 0.0%-0.4%: $I^2 = 0\%$). There were 19 cases of confirmed HIT and 1 with autoimmune HIT for clinical and laboratory characterization. The median time from heparin initiation to HIT diagnosis was 13.5 days (interquartile range, 10.75-16.25 days). Twelve (63%) developed thromboembolism after heparin therapy. In conclusion, the incidence of HIT in patients with COVID-19 was comparable to patients without COVID-19, 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.[1] 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.[2-5] The early report from China suggested a potential survival benefit of anticoagulation in patients with COVID-19.[6]

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Shortly after its spread to Europe, there were several cohorts that identified the high incidence of thromboembolism in hospitalized patients with COVID-19.[7-9] Therefore, several international guidelines recommended anticoagulants for the management of COVID-19–associated coagulopathy and routine pharmacologic thromboprophylaxis for all hospitalized patients with COVID-19 without contraindications.[10-13] However, a significant proportion of patients, especially in the intensive care unit (ICU), developed both arterial and venous thromboembolism despite standard-dose thromboprophylaxis.[7,14,15] Consequently, many medical centers have implemented intermediate-dose or therapeutic-dose anticoagulants to prevent thromboembolic complications.[16] Currently, there are several randomized controlled trials evaluating the efficacy and safety of different intensities of thromboprophylaxis in hospitalized patients with COVID-19.[17,18] In a recently published INSPIRATION randomized controlled trial, intermediate-dose prophylactic anticoagulation did not provide additional benefits over standard-dose prophylaxis.[19]

Heparin-induced thrombocytopenia (HIT) is an uncommon but serious immunologic complication from heparin leading to transient thrombocytopenia accompanied by highly prothrombotic state.[20] Diagnosis of HIT, especially in critically ill patients, is challenging because there are many alternative causes of thrombocytopenia.[21,22] Nonpathologic antiplatelet 4/heparin antibodies (anti-PF4/H Abs) may also be present in this population.[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,[10-13] unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) are indicated for hospitalized patients with COVID-19. 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 are critical for proper management (ie, initiation of nonheparin anticoagulants and avoiding platelet transfusion).[20,21]

To date, the incidence, clinical characteristics, and impacts of HIT on hospitalized patients with COVID-19 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 patients with COVID-19.

Methods

The protocol for this review was prespecified and registered in PROSPERO (CRD42021240788). The study was subsequently conducted following Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[23] 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 patients with COVID-19. 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 prespecified subgroup analyses including types of heparin (UFH vs LMWH), intensities of heparins (prophylactic vs therapeutic), and severity of patients with COVID-19 (critically ill vs 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 8 March 2021 and was updated on 14 June 2021 to identify studies reporting cases with confirmed HIT using platelet activation assays and/or incidence of HIT in patients with COVID-19. 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 $\geq$ 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. Nonoriginal 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 prespecified 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 patients with COVID-19 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 patients with COVID-19.

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 nonheparin anticoagulants, bleeding events, platelet transfusion, platelet recovery after nonheparin anticoagulants, patient's outcomes, the incidence of confirmed HIT, and the frequency of anti-PF4/H Ab detection.

Quality assessment

The methodologic quality of included studies for meta-analysis was performed independently by 2 authors (N.U. and N.T.) using a validated tool for assessing studies reporting prevalence data.[24] 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

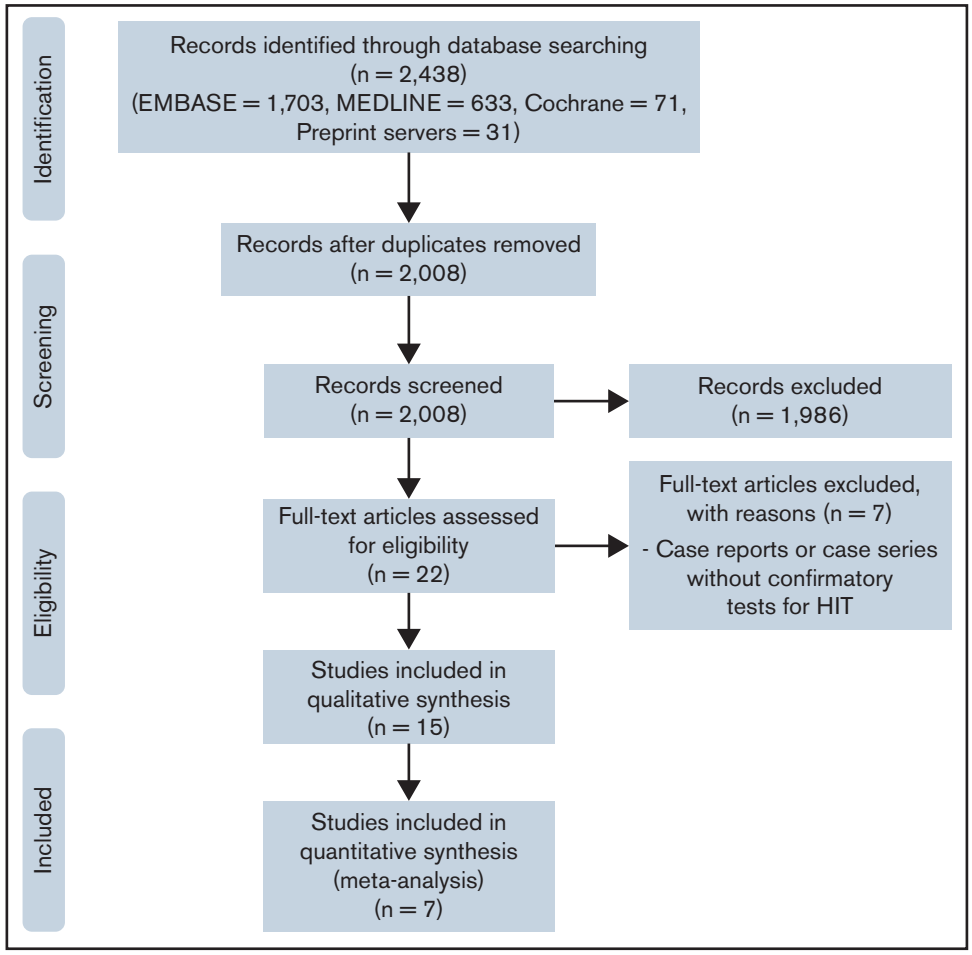

Figure 1. PRISMA flow diagram.

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). 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 I^2 statistic, which measured the inconsistency across study results. Interstudy heterogeneity was assigned as insignificant (I^2 = 0% to 25%), low (I^2 = 26% to 50%), moderate (I^2 = 51% to 75%), and high (I^2 > 75%).[25] The funnel plot for evaluation of publication bias was not performed because of the low number of studies included in the meta-analysis (<10 studies). For descriptive statistics, normality of the data was tested using the Shapiro-Wilk test. Continuous data were presented as means (±standard deviations) or medians with interquartile ranges (IQRs) as appropriate. All descriptive analyses were computed using SPSS version 22.0 for Window (SPSS Inc., Chicago, IL).

Results

The PRISMA flow diagram is shown in Figure 1. A total of 2008 unique studies were identified by literature search and were screened by titles and abstracts. Of these, 1986 were excluded, and 22 full texts were screened for eligibility. Eventually, 15 studies[26-40] met the eligibility criteria and were included in qualitative synthesis, and 7 studies[29,32-36,40] were sufficient for quantitative synthesis. Of 7 studies eligible for meta-analysis, the risks of bias were individually assessed. Four studies[33-35,40] were assigned as low risk of bias, whereas the other 3 studies[29,32,36] were classified as moderate risk of bias (supplemental Table 1).

Study characteristics

The main characteristics of the 15 included studies (12 published full-texts, 1 full-preprint report, and 2 abstracts)[26-40] are summarized in Table 1. Across 15 studies (8053 total patients), there were a total of 40 reported HIT patients. Of these, 19 HIT cases and 1 with autoimmune HIT who had diagnosis confirmed by SRA or HIPA were included for clinical and laboratory characterization.[26-33,37-39] 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.[26-29,33,37]

Table 1. Characteristics of included studies

Reference (first author and year)	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	Heparin administration in confirmed HIT
Riker[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%)	2 prophylactic UFH/LMWH and 1 therapeutic UFH
Lingamaneni[27] 2020	Case report	5	COVID-19 patients with HIT suspicion	4T score	ELISA	SRA	5/1	5 (100%)	All 5 received therapeutic heparin
May[28] 2020	Case report	7	Hospitalized COVID-19 patients with positive anti-platelet factor 4 Ab	4T score	ELISA	SRA	7/1	7 (100%)	3 prophylactic UFH, 3 prophylactic LMWH and 1 prophylactic LMWH/UFH
Patell[29] 2020	Retrospective cohort	88	patients hospitalized with Covid-19 and received intravenous UFH for ≥5 d	4T score	Latex immune turbidimetric assay	SRA	8/3	NR	All 3 confirmed HIT received therapeutic UFH
Bidar[30] 2020	Case report	2	Confirmed HIT in COVID-19 patients with severe ARDS on VVECMO	NR	ELISA	HIPA	2/2	2 (100%)	All 2 confirmed HIT received therapeutic UFH
Tran[31] 2020	Case report	1	A patient with SARS-CoV-2 pneumonitis and confirmed HIT	4T score	ELISA	HIPA	1/1	1	The patient with confirmed HIT received prophylactic LMWH
Daviet[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%)	All 7 confirmed HIT received therapeutic LMWH or UFH
Delrue[33] 2020	Retrospective cohort	626	All consecutive SARS-CoV-2-infected adults admitted to the ICU and medical wards	4T score	PaGIA, ELISA IgG	HIPLA, SRA	10/1	184 (29.4%)	Of 10 HIT suspicions, 2 received UFH, 1 received LMWH and 7 received LMWH followed by UFH
Helms[34] 2020	Prospective cohort	150	All patients with SARS-CoV-2 ARDS admitted to the ICU	NR	NR	NR	4/0	150 (100%)	150 (100%); 105 (70%) prophylactic doses; 45 (30%) therapeutic doses
Ionescu[35] 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%)	1156 with prophylactic LMWH; 699 with received prophylactic UFH; 424 with therapeutic LMWH and 295 with therapeutic UFH
Santi[36] 2020	Retrospective cohort	94	Hospitalized patients infected with COVID-19	NR	NR	NR	NR/2	NR	2 received therapeutic UFH
Warrior[37] 2020	Retrospective cohort	1265	Hospitalized COVID-19 positive patients	4T score	ELISA	SRA	8/1	NR	Of 8 HIT suspicions, 4 received LMWH, 2 received UFH and 2 received LMWH followed by UFH
Madala[38] 2021	Case report	1	A patient with SARS-CoV-2 pneumonia and ischemic stroke	4T score	ELISA	SRA	1/1	1	The patient with confirmed HIT received UFH followed by LMWH
Julian[39] 2021	Case report	1	A patient with COVID-19 positive and confirmed autoimmune HIT	N/A	ELISA	SRA	1/1	1	No heparin exposure before documented thrombosis and thrombocytopenia
Lawler[40] 2021	Randomized controlled trial	2231	Non-critically ill patients hospitalized for Covid-19	4T score	ELISA	SRA	NA/0	0	1181 received therapeutic- and 1050 received prophylactic-dose anticoagulation; no confirmed HIT

Ab, antibody; CIA, chemiluminescent immunoassay; ELISA (or EIA), enzyme-linked immunosorbent assay (or enzyme immunoassay); ICU, intensive care unit; NR, not reported; PaGIA, particle gel immunoassay.

Table 2. Clinical and laboratory characteristics of hospitalized patients with COVID-19 with confirmed HIT

Case	Age (y), sex	Severity of COVID-19	Indication of heparin	Type and dose of heparin	Duration of heparin to HIT diagnosis (d)	Initial platelet count (x10^9 /L)	Nadir platelet count (x10^9 /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[26]	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	Death
2[27]	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	Death
3[28]	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	N/A
4[29]	68, F	ICU	AF	UFH; therapeutic	7	416	<5	None	4	LITA (1.8 U/mL)	SRA, positive	Argatroban, bivalirudin	Platelet recovery	Alive
5[29]	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	Death
6[29]	49, M	ICU	COVID pneumonia	UFH; therapeutic	12	176	25	None	6	LITA (1.9 U/mL)	SRA, borderline positive	Argatroban	Platelet recovery	Alive
7[30]	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	Alive
8[30]	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	Alive
9[31]	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	Alive
10[32]	46, M	ICU (ARDS. MV, ECMO)	Clinical trial (COAG-COVID)[a]	LMWH and UFH; therapeutic	16	61	33	Multiple DVT	6	CIA (46 U/mL)	HIPA, positive	Argatroban	Platelet recovery/ discharge from ICU	Discharge from ICU
11[32]	50, M	ICU (ARDS, MV, ECMO)	Clinical trial (COAG-COVID)[a]	LMWH and UFH; therapeutic	13	243	73	Intracardiac thrombus, ECMO membrane thrombosis	6	CIA (11 U/mL)	HIPA, positive	Argatroban	Platelet recovery/ still in ICU	Still in ICU
12[32]	43, F	ICU (ARDS, MV, ECMO)	Clinical trial (COAG-COVID)[a]	LMWH and UFH; therapeutic	15	160	48	Multiple DVT, ECMO pump thrombosis	6	CIA (39 U/ML)	HIPA, positive	Argatroban	Platelet recovery/ still in ICU	Still in ICU
13[32]	63, M	ICU (ARDS, MV)	Clinical trial (COAG-COVID)[a]	LMWH and UFH; therapeutic	14	191	56	Stroke	4	CIA (60 U/mL)	HIPA, positive	Danaparoid	Platelet recovery, discharge from hospital	Alive
14[32]	59, M	ICU (ARDS, MV)	Clinical trial (COAG-COVID)[a]	LMWH and UFH; therapeutic	9	161	62	DVT	5	CIA (4 U/mL)	HIPA, positive	Danaparoid	Platelet recovery, discharge from ICU	Discharge from ICU

ARDS, acute respiratory distress syndrome; CIA, chemiluminescent immunoassay (cutoff < 1 U/mL); DVT, deep vein thrombosis; ECMO, extracorporeal membrane oxygenation; ELISA, enzyme-link immunosorbent assay; F, female; HIPLA, heparin-induced platelet activation assay (positivity threshold 13%); ICU, intensive care unit; LITA, latex immune turbidimetric assay; M, male; MV, mechanical ventilation; N/A, not available; PE, pulmonary embolism; RRT, renal replacement therapy; TE, thromboembolism; VTE, venous thromboembolism.

*COAG-COVID (Coagulopathy of COVID-19: A Pragmatic Randomized Controlled Trial of Therapeutic Anticoagulation Versus Standard Care).

Table 2. (continued)

Case	Age (y), sex	Severity of COVID-19	Indication of heparin	Type and dose of heparin	Duration of heparin to HIT diagnosis (d)	Initial platelet count (x10^9 /L)	Nadir platelet count (x10^9 /L)	Thrombosis after heparin initiation	4T score	Screening test	Confirmatory test	Non-heparin anticoagulants	Platelet response after HIT treatment	Outcomes of patients as reported
15[32]	57, M	ICU (ARDS)	Clinical trial (COAG-COVID)[a]	UFH; therapeutic	11	159	39	None	5	CIA (21 U/mL)	HIPA, positive	Danaparoid	Platelet recovery, discharge from hospital	Alive
16[32]	69, M	ICU (ARDS, MV)	Clinical trial (COAG-COVID)[a]	UFH; therapeutic	16	215	107	None	4	CIA (2 U/mL)	HIPA, positive	Danaparoid	Platelet recovery, discharge from hospital	Alive
17[33]	64, M	ICU	VTE prophylaxis	LMWH; prophylactic	18	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 d), danaparoid (19 d), apixaban at discharge	Platelet recovery, discharge from hospital	Alive
18[37]	63, M	ICU (RRT)	RRT	LMWH and UFH; NA	N/A	N/A	67	PE	≥4	ELISA IgG (OD 0.62)	SRA, positive	Argatroban	N/A	Death
19[38]	65, F	Non-ICU	AF	LMWH and UFH; therapeutic	12	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[39]	65, M	Non-ICU	N/A	N/A	N/A (8 d after diagnosis of COVID-19)	N/A	6	DVT, PE (at presentation)	N/A	NR, positive	SRA, positive	Argatroban, apixaban, IVIG	Platele recovery, discharge from hospital	Alive

ARDS, acute respiratory distress syndrome; CIA, chemiluminescent immunoassay (cutoff < 1 U/mL); DVT, deep vein thrombosis; ECMO, extracorporeal membrane oxygenation; ELISA, enzyme-link immunosorbent assay; F, female; HIPLA, heparin-induced platelet activation assay (positivity threshold 13%); ICU, intensive care unit; LITA, latex immune turbidimetric assay; M, male; MV, mechanical ventilation; N/A, not available; PE, pulmonary embolism; RRT, renal replacement therapy; TE, thromboembolism; VTE, venous thromboembolism.

*COAG-COVID (Coagulopathy of COVID-19: A Pragmatic Randomized Controlled Trial of Therapeutic Anticoagulation Versus Standard Care).

Table 3. Clinical and laboratory characteristics of hospitalized patients with COVID-19 with negative confirmatory tests for heparin-induced thrombocytopenia

Case	Age (y), sex	Severity of COVID-19	Indication of heparin	Type and dose of heparin during HIT diagnosis	Duration of heparin when tested for HIT (d)	Initial platelet count (x10^9 /L)	Nadir platelet count (x10^9 /L)	Thrombosis after heparin initiation	4T score	Screening test	Confirmatory test	Non-heparin anticoagulants	Platelet recovery after HIT treatment	Patients' outcomes as reported
1[26]	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[26]	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[27]	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	N/A
4[27]	61. F	ICU (ARDS)	DVT	N/A	6	N/A	N/A	DVT	7	ELISA (OD 0.77)	SRA, negative	N/A	N/A	N/A
5[27]	68, F	ICU (ARDS)	DVT	N/A	8	N/A	N/A	DVT	7	ELISA (OD 0.42)	SRA, negative	N/A	N/A	N/A
6[27]	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	N/A
7[28]	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[28]	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[28]	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[28]	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	N/A
11[28]	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[28]	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	N/A
13[29]	49, M	ICU	COVID pneumonia	UFH; therapeutic	6	211	47	None	6	LITA (1.1 U/mL)	SRA, negative	Argatroban	None	Death
14[33]	77, M	ICU	VTE prophylaxis	LMWH and UFH; prophylactic	11	136	59	None	5	PaGIA, negative	HIPLA, negative	None	N/A	Death
15[33]	63, M	ICU	VTE prophylaxis	LMWH and UFH; therapeutic	14	250	11	None	4	PaGIA, negative	HIPLA, negative	None	N/A	Alive
16[33]	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
17[33]	63, M	ICU	AF	LMWH and UFH; therapeutic	12	177	38	None	4	PaGIA, negative	HIPLA, negative	None	N/A	Death
18[33]	71, M	ICU	AF	LMWH and UFH; therapeutic	21	240	77	None	4	PaGIA, negative	HIPLA, negative	None	N/A	Death
19[33]	66, M	ICU	PE	UFH; therapeutic	2	121	59	PE and DVT	4	PaGIA, negative	HIPLA, negative	None	N/A	Alive
20[33]	50, M	ICU	VTE prophylaxis	LMWH; prophylactic	12	227	136	Stroke	6	PaGIA negative	HIPLA, negative	None	N/A	Alive
21[33]	67, M	ICU	AF	UFH; therapeutic	23	363	138	DVT	6	PaGIA, negative	HIPLA, negative	None	N/A	Death

ARDS, acute respiratory distress syndrome; CIA, chemiluminescent immunoassay (cutoff < 1 U/mL); DVT, deep vein thrombosis; ECMO, extracorporeal membrane oxygenation; ELISA, enzyme-link immunosorbent assay; F, female; HIPLA, heparin-induced platelet activation assay (positivity threshold 13%); ICU, intensive care unit; LITA, latex immune turbidimetric assay; M, male; MV, mechanical ventilation; N/A, not available; PE, pulmonary embolism; RRT, renal replacement therapy; TE, thromboembolism; VTE, venous thromboembolism.

Table 3. (continued)

Case	Age (y), sex	Severity of COVID-19	Indication of heparin	Type and dose of heparin during HIT diagnosis	Duration of heparin when tested for HIT (d)	Initial platelet count ($\times 10^9$ /L)	Nadir platelet count ($\times 10^9$ /L)	Thrombosis after heparin initiation	4T score	Screening test	Confirmatory test	Non-heparin anticoagulants	Platelet recovery after HIT treatment	Patients' outcomes as reported
22[33]	65, M	ICU	PE suspicion	LMWH and UFH; therapeutic	24	317	138	PE and DVT	6	PaGIA, negative	HIPLA, negative	Argatroban	N/A	Death
23[37]	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
24[37]	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
25[37]	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
26[37]	34, M	N/A	N/A	LMWH; N/A	N/A	N/A	65	DVT	≥4	N/A	SRA, negative	Bivalirudin	N/A	Death

ARDS, acute respiratory distress syndrome; CIA, chemiluminescent immunoassay (cutoff < 1 U/mL); DVT, deep vein thrombosis; ECMO, extracorporeal membrane oxygenation; ELISA, enzyme-link immunosorbent assay; F, female; HIPLA, heparin-induced platelet activation assay (positivity threshold 13%); ICU, intensive care unit; LITA, latex immune turbidimetric assay; M, male; MV, mechanical ventilation; N/A, not available; PE, pulmonary embolism; RRT, renal replacement therapy; TE, thromboembolism; VTE, venous thromboembolism.

A total of 7 studies were included for the estimation of the pooled incidence of HIT.[29,32-36,40] These 7 studies collectively included a total of 5849 patients, ranging from 86 to 2574 patients.

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

From 11 studies, there were 19 confirmed HIT cases and 1 with autoimmune HIT, with sufficient data for characterization.[26-33,37-39] Clinical and laboratory characteristics of individual cases are summarized in Table 2. Among the 19 documented cases of HIT, the median age was 62.0 (IQR, 51.0, 64.0) years. Males were the predominant proportion (74%). All but 1 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, whereas 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 $\times$ 10^9/L (IQR, 160.5, 297) and 56 $\times$ 10^9/L (IQR, 37, 73), respectively. All but 1 patient had intermediate or high pretest probability for HIT using the 4T scoring system, with a median of 5.5 (IQR, 4, 6). Twelve patients (63%) developed thrombosis after heparin administration. A total of 15 of 19 (79%) confirmed HIT cases demonstrated platelet recovery after heparin substitution with nonheparin anticoagulants. Of the 17 with known survival outcomes, 4 died shortly after HIT diagnosis.

Only 1 patient with COVID-19 with autoimmune HIT was identified.[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 patients with COVID-19 who were suspected to have HIT but had negative confirmatory tests were reported.[26-29,33,37] 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 are 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 = 5849 patients),[29,32-36,40] the pooled incidence of HIT in hospitalized patients with COVID-19 was 0.8% (95% CI, 0.2%-3.2%; I^2 = 89%; Figure 2). A sensitivity analysis of 4 studies (N = 3031),[29,32,33,40] in which the diagnostic criteria for HIT were specified, revealed the pooled incidence of 0.8% (95% CI, 0.1%-6.4%; I^2 = 89%; supplemental Figure 1).

A subgroup analysis according to the study's risk of bias was performed (Figure 3). The pooled incidence of 3 small studies[29,32,36] with moderate risk of bias, which included 268 patients mostly receiving UFH, was 4.5% (95% CI, 2.0%-10.0%; I^2 = 46%). The

Table 4. Clinical characteristics and laboratory profiles of hospitalized patients with COVID-19 with confirmed HIT and patients with negative confirmatory tests

Variables	Patients with confirmed HIT (N = 19)	Patients with negative confirmatory tests (N = 26)
Age (y)	62.0 (50.0, 64.0)*	62 (50, 68.75)*
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 (d)	13.5 (10.75, 16.25)*	11 (6, 21)*
Initial platelet counts ($\times 10^9$/L)	223 (160.5, 297)*	209 (145.5, 247.5)*
Nadir platelet counts ($\times 10^9$/L)	56 (37, 73)*	59 (37.5, 91.75)*
Thrombosis after heparin administration	12 (63%)	16 (61.5%)
4T score	5.5 (4, 6)*	5 (4, 6)*

N/A, not available.
*Median (interquartile range).

pooled incidence of 4 larger studies[33-35,40] with low risk of bias (5581 patients) was 0.2% (95% CI, 0.1%-0.7%; I^2 = 43%). There was a significant difference between the low risk and moderate risk of bias ($P < .001$).

Data on the incidence of HIT stratified by anticoagulation intensity were available in 4 studies.[29,34,35,40] The pooled incidence of HIT in patients receiving prophylactic-intensity heparins was 0.1% (3 studies; N = 3010; 95% CI, 0.0%-0.4%; I^2 = 0%),[34,35,40] whereas the pooled incidence of HIT in patients receiving therapeutic heparins was 1.2% (4 studies; N = 2033; 95% CI, 0.3%, 3.9%; I^2 = 65%)[29,34,35,40] (Figure 4). The pairwise comparison revealed significant difference between prophylactic vs therapeutic heparins (P = .007). We also analyzed the difference of HIT in the largest cohort including 2574 patients receiving heparins.[35] HIT development was higher in patients receiving therapeutic anticoagulation compared with prophylactic anticoagulation (odds ratio, 28.8; 95% CI, 3.7-223.5; P = .001).

A subgroup analysis to estimate pooled incidences of HIT in critically ill patients with COVID-19 and non–critically ill patients with COVID-19 was performed. A total of 3169 patients from 5 studies[29,32-34,40] were available for analysis. The pooled incidence of HIT in critically ill patients with COVID-19 was 2.2% (4 studies; N = 508; 95% CI, 0.6%-8.3%; I^2 = 73%),[29,32-34] whereas the pooled incidence of HIT in non–critically ill patients with COVID-19 was 0.1% (2 studies; N = 2661; 95% CI, 0.0%-0.4%; I^2 = 0%)[33,40] (Figure 5). The pairwise comparison revealed significant difference between critically ill and non–critically ill patients with COVID-19 (P = .002).

Although the prespecified subgroup analysis to assess the risk for HIT between UFH and LMWH was planned, there were not sufficient data to compute the pooled incidences of HIT for UFH and LMWH.

Incidence of anti-PF4/H Abs detection in hospitalized patients with COVID-19

Existing data were not sufficient for estimating the pooled incidence of anti-PF4/H Abs (activating and nonactivating) in all hospitalized patients with COVID-19 receiving heparins, because the tests were

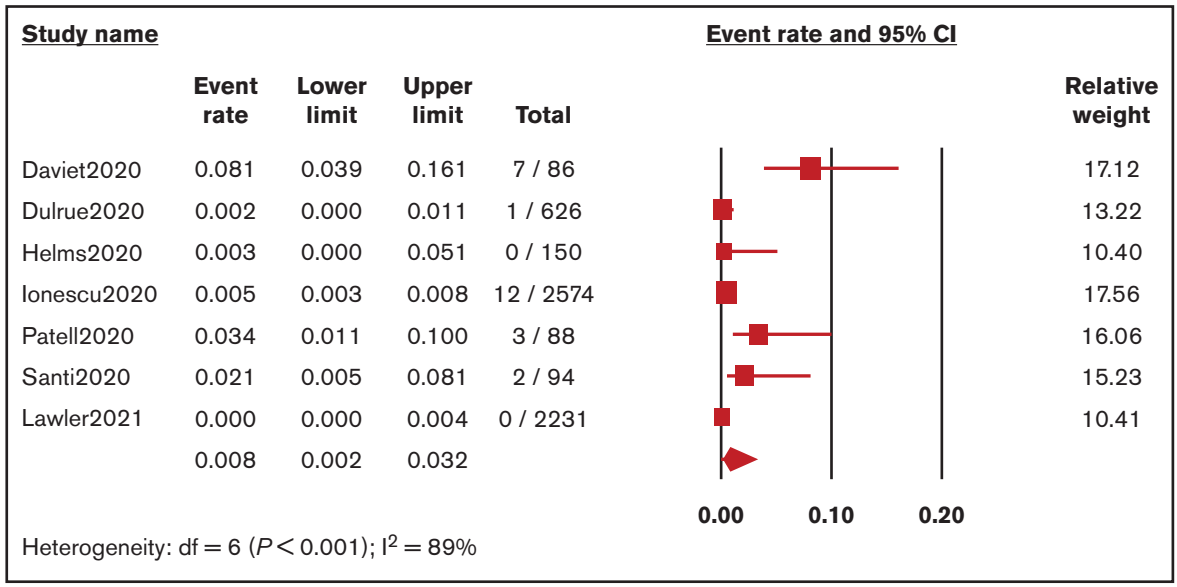

Figure 2. Forest plot showing pooled estimated incidence of HIT in hospitalized patients with COVID-19.

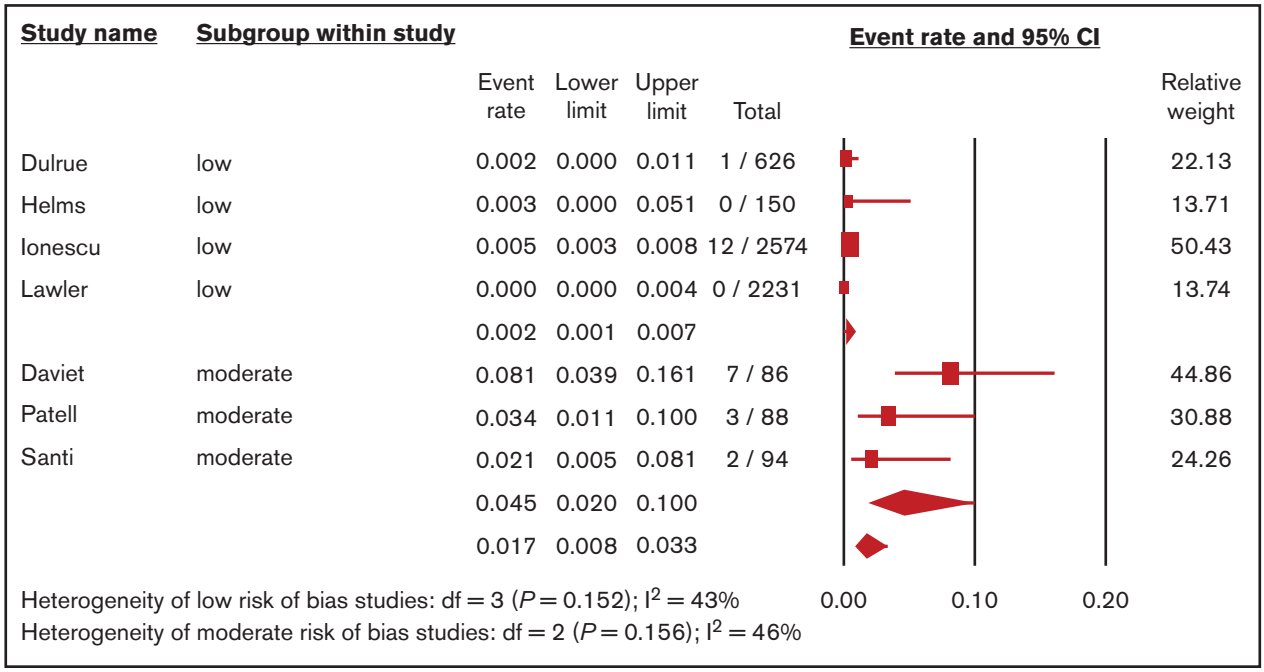

Figure 3. **Forest plot showing the pooled estimated incidence of HIT in hospitalized patients with COVID-19 according to the risks of bias.**

only performed based on suspicion of HIT. In the only 1 study whereby anti-PF4/H Abs were screened in 172 consecutive patients (64 ICU and 108 non-ICU),[33] the frequency of anti-PF4/H-associated polyspecific Abs (immunoglobulin M [IgM], IgA, and IgG; OD of >0.5) was 33%, whereas 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 with an OD of >1.0, 7 (37%) patients had thromboembolic events. However, all patients with positive anti-PF4/H Abs yielded negative HIT confirmatory tests.

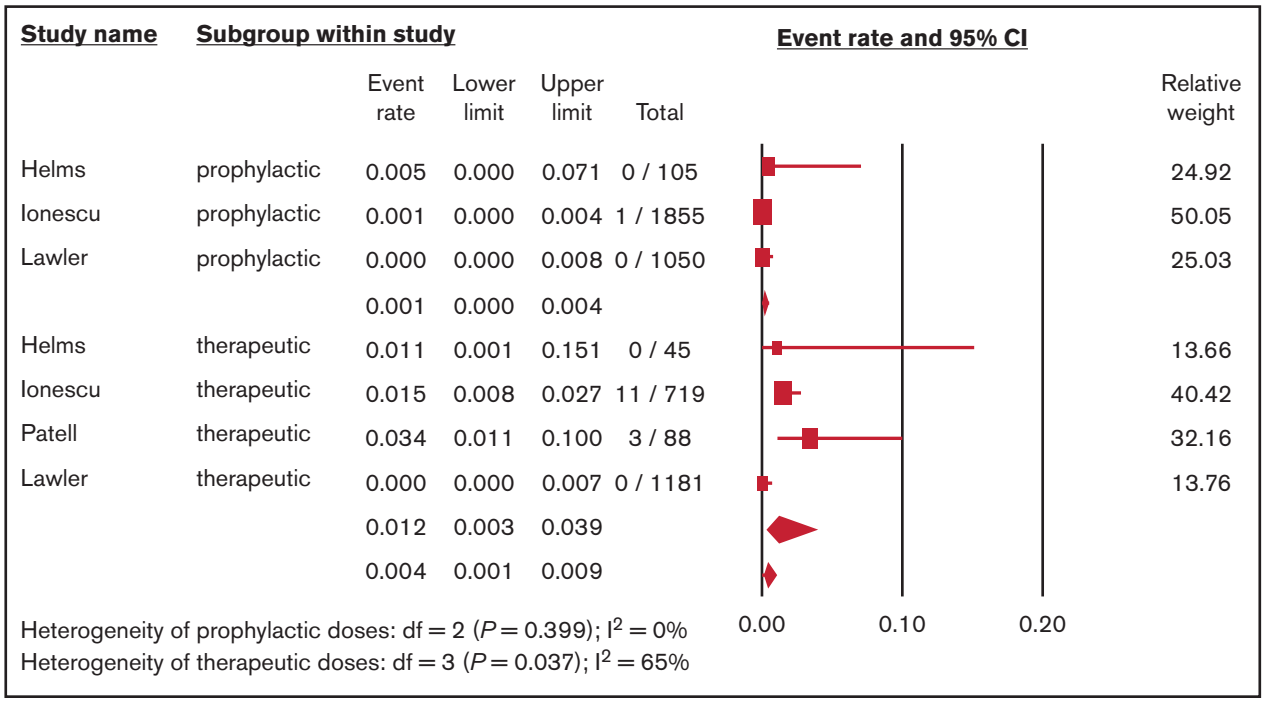

Figure 4. **Forest plot showing the pooled estimated incidence of HIT in hospitalized patients with COVID-19 according to the intensities of heparins.**

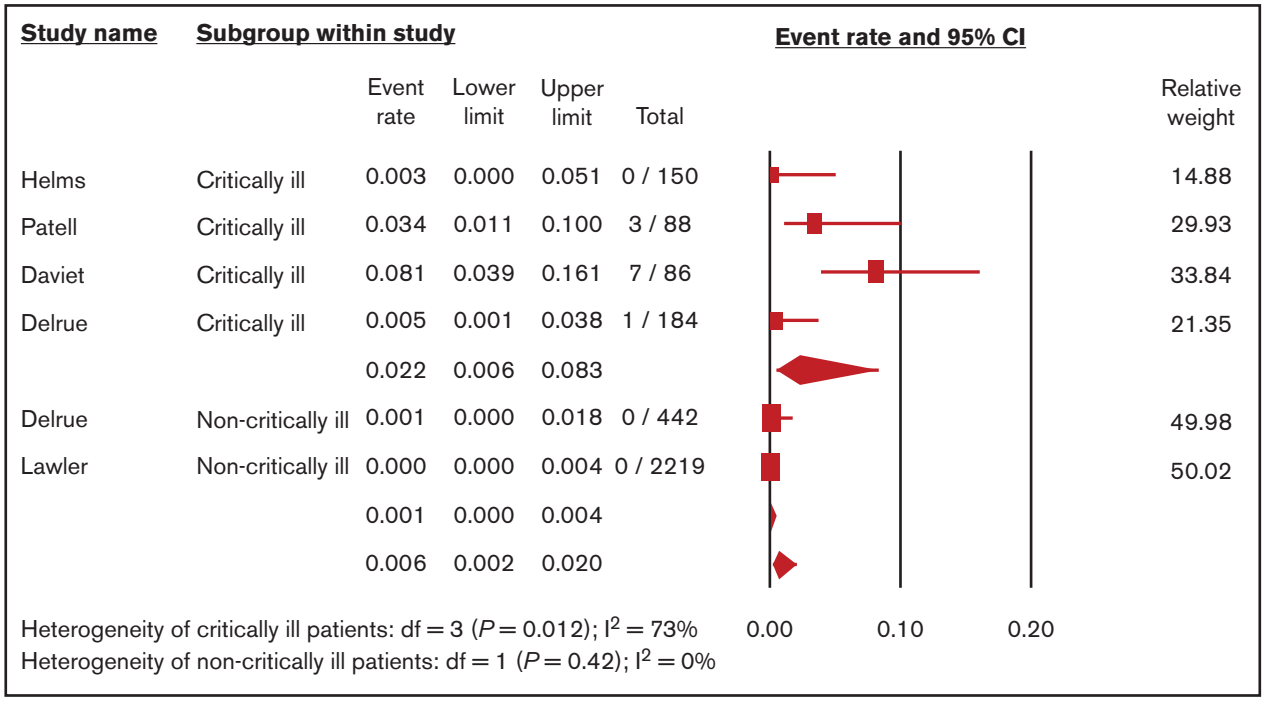

Figure 5. Forest plot showing the pooled estimated incidence of HIT in hospitalized patients with COVID-19 according to severity of patients.

Discussion

In this systematic review, we characterized 19 hospitalized patients with COVID-19 with confirmed HIT using standard platelet activation assays.[26-33,37,38] There were 26 patients who had suspected HIT but had negative confirmatory tests from concurrent cohorts for comparison. Some cases were assigned as HIT in their original cohorts because of strongly positive immunoassays.[26,29,37] However, a recent study revealed that patients with COVID-19 frequently had strongly positive immunoassays without platelet-activating antibodies indicating nonpathogenic antibodies.[41] Therefore, HIT diagnosis requires confirmatory heparin-dependent platelet-activating tests despite the strongly positive immunoassays to avoid overdiagnosis and overtreatment 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 patients with COVID-19 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.[42]

Half of patients were diagnosed after 14 days of heparin exposure, suggesting a delay in diagnoses of HIT in patients with COVID-19. 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 patients with COVID-19, and functional tests are required for definitive diagnosis.

Almost all patients with confirmed HIT had platelet recovery shortly after switching to nonheparin 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 patients with COVID-19 of 0.8% (95% CI, 0.2%-3.2%), which was comparable to those reported from large cohorts and meta-analysis of medical patients without COVID-19; the incidences of HIT ranged from 0.08% to 0.94%.[43] However, there was high heterogeneity among studies because 3 small cohorts with moderate risk of bias[29,32,36] had very high incidence of HIT in patients with COVID-19 (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[33-35,40] with low risks of bias was 0.2% (95% CI, 0.1%-0.7%) similar to patients without COVID-19. 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, nonactivating 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 1 study that screened anti-PF4/H Abs in consecutive hospitalized patients with COVID-19.[33] Compared with 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%).[33] Similarly to cases without COVID-19, HIT developed in less than 10% of patients with detectable anti-PF4/H Abs.[44] Therefore, the routine screening for anti-PF4/H Abs in patients with COVID-19 receiving heparin is probably not cost efficient.

The prespecified subgroup analysis was performed to assess the risk of heparin intensity and HIT development in COVID-19.

Hospitalized patients with COVID-19 who received therapeutic doses of heparins were at greater risk for HIT than those who received prophylactic doses of heparins.[29,34,35,40] 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 patients in the ICU with COVID-19.[19] Notably, 7 thrombocytopenias of unspecified causes occurred only in patients assigned to the intermediate-dose group, with an absolute risk difference of 2.2% (95% CI, 0.4%-3.8%; $P = .01$). Therefore, the risk of HIT in higher-intensity anticoagulation should be considered.

The estimated incidence of HIT in critically ill patients with COVID-19 was 2.2%. This was relatively higher than those previously reported in patients without COVID-19 (0.3%-0.5%).[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.[46] Severe endothelial injury, platelet hyperactivation, and immune dysregulation after SARS-CoV-2 infection may involve in development of HIT in critically ill patients with COVID-19.[47]

There are some limitations of this study. Most of studies were case reports, small case series, or retrospective cohorts, which are prone to biases because of different HIT confirmatory tests and criteria, lack of central adjudication of HIT cases, and incomplete data collection. In addition, all but 1 cohort did not perform systematic surveillance, which may lead to either under- or overestimation of the incidences of HIT in patients with COVID-19 because of case selection, as well as significant heterogeneity among studies. Finally, the number of studies included in both qualitative and quantitative analyses was relatively small.

Conclusions

In this systematic review and meta-analysis, we reported a pooled incidence of HIT in patients with COVID-19 of 0.8%, which was similar to those previously reported in medical patients without COVID-19. However, the incidence of HIT in patients with COVID-19 might be increased in patients receiving therapeutic-dose heparin and in critically ill patients. The clinical and laboratory profiles between patient with COVID-19 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 patients with COVID-19.

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 revised manuscript; P.R. was involved in data analysis, appraisal, and editing of the manuscript and revised manuscript; R.P. was involved in data analysis and editing of the manuscript and revised manuscript; J.I.Z. was involved in appraisal and editing of the manuscript and revised manuscript; and T.C. was involved in conceptualization, adjudication, data analysis, and editing of the manuscript and revised manuscript.

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