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Significance of heparin induced thrombocytopenia (HIT) in COVID-19: a systematic review and meta-analysis

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Abstract
Heparin-induced thrombocytopenia (HIT) occurs in approximately 3% of patients receiving heparinoids. About 30–75% of patients with type 2 of HIT develop thrombosis as a result of platelet activation. The most important clinical symptom is thrombocytopenia. Patients with severe COVID-19 are among those receiving heparinoids. This meta-analysis performed to picture the current knowledge and results of published studies in this field. Three search engines were searched and 575 papers were found. After evaluation, 37 articles were finally selected of which 13 studies were quantitatively analyzed. The pooled frequency rate of suspected cases with HIT in 13 studies with 11,241 patients was 1.7%. The frequency of HIT was 8.2% in the extracorporeal membrane oxygenation subgroup with 268 patients and 0.8% in the hospitalization subgroup with 10,887 patients. The coincidence of these two conditions may increase the risk of thrombosis. Of the 37 patients with COVID-19 and confirmed HIT, 30 patients (81%) were treated in the intensive care unit or had severe COVID-19. The most commonly used anticoagulants were UFH in 22 cases (59.4%). The median platelet count before treatment was 237 (176–290) x 10^3/µl and the median nadir platelet count was 52 (31–90.5) x 10^3/µl.

Keywords COVID-19 · Heparin induced thrombocytopenia (HIT) · SARS-CoV-2 · Heparinoids · Thrombocytopenia · Thrombosis

Introduction

Heparin-induced thrombocytopenia (HIT) is a virtually proven side effect of fractionated and unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) use when thrombosis can lead to severe morbidity and mortality [1]. It is a major health challenge in intensive care units, cardiac surgery units, and cardiac catheterization laboratories because there are numerous causes of thrombocytopenia [2]. HIT occurs as a non-immunologic type (type 1) or as drug-induced and immune-mediated thrombocytopenia (type 2). Type 2 usually occurs 4–10 days after heparinoid use. HIT is rarely associated with bleeding manifestations, despite other drug induced thrombocytopenias. Nearly 30–75% of patients with undiagnosed and untreated HIT develop thrombosis. It occurs in about 3% of patients receiving unfractionated heparin (UFH) for about two weeks [3]. HIT mortality rate is about 20%, and amputation may occur in 10% of affected patients with HIT [4]. HIT usually involves IgG antibodies, rarely IgM or IgA antibodies. These antibodies recognize complexes of heparin and platelet factor 4 [5]. After the antibodies adhere to the PF4/heparin complex, platelet activation occurs, resulting in a procoagulant reaction (release of microparticles) [6, 7]. In general, HIT is classified to two types [8, 9]. Clinical symptoms such petechial, purpura, rash, skin necrosis are nonspecific, so heparin should not be replaced unnecessarily because it has a favorable risk-benefit ratio [10].

Since the first outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 2019, multiple waves of COVID-19 have spread to all corners of the world. COVID-19 has caused approximately 6,681,433 deaths worldwide as of 6 January 2023 [11]. SARS-C0V-2 is considered one of the most dangerous viruses in the coronavirus

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family [12]. The development of thrombosis, especially venous thromboembolism in COVID19, which can be a trigger for failure of many organs, is a major cause of mortality and morbidity in COVID-19 [13, 14]. Thrombosis in COVID-19 is a multifactorial process, and SARS-Co-V-2 can cause fluctuation of many prothrombotic and coagulation factors [15–18]. Heparin and heparin-like molecules as anticoagulant and anti-inflammatory drugs with direct antiviral properties have multiple effects in COVID-19 [19, 20]. One study has shown that non-critically ill patients with COVID-19 who received heparin had longer survival [21]. On the other hand, patients treated in the intensive care unit (ICU) have been shown to develop venous thromboembolism (VTE), pulmonary embolism (PE), or deep vein thrombosis (DVT) [22]. In patients requiring ICU hospitalization, VTE or PE may be present on ICU admission or may develop during the ICU stay [23, 24]. Therefore, patients in the ICU receive a prophylactic dose of an anticoagulant, including LMWH [25]. In patients with COVID-19 admitted to the ICU, the therapeutic dose of heparin was more beneficial than the prophylactic dose of heparin in moderately ill patients [26].

It seems that patients with severe COVID-19 treated in the intensive care unit have two potential factors for thrombophilia: COVID-19 and platelet activation by heparin. Therefore, the present systematic review and meta-analysis attempted to investigate the frequency of HIT in COVID-19 and related aspects.

Materials and methods

Data source and search strategy

The authors did a systematic search in three electronic medical databases (PubMed, Scopus, and Web of Science) separately to collect relevant papers examining HIT in COVID-19 patients. The following keywords were used as part of the search strategy in each database: "heparin-induced thrombocytopenia" OR "heparin-dependent IgG antibodies" OR "platelet factor 4 heparin-induced thrombocytopenia" OR "immune heparin-induced thrombocytopenia" OR "antibody-PF4-heparin complex" OR "Antiplatelet factor 4" OR "Heparin-dependent IgG (HIT-IgG) antibodies" OR "IgG against platelet factor 4" OR "IgM against platelet factor 4" AND "COVID-19" OR "SARS-CoV-2" OR "2019-nCoV". Two independent authors (M. R. and H. M.) searched July 26, 2022, reviewed the full text to select eligible studies, entered all articles into EndNote X7 reference manager software for screening, and deleted duplicate articles. All discrepancies in each section (screening, study selection and data extraction) were resolved in a joint meeting after each section of the research.

Selection of studies and eligibility criteria

After removing duplicate articles, articles were screened using inclusion and exclusion criteria by each author separately. Any discrepancy resolved in a joint meeting. Inclusion criteria included reports of cases or frequencies of HIT cases in patients with COVID-19 who used heparin during treatment. HIT would be verified by one of the following laboratory tests: Chemiluminescent Immunoassay (CIA), Enzyme-linked Immunosorbent Assay (ELISA), Latex Immune Turbidimetric Assay (LITA), and Particle Gel Immunoassay (PaGIA). Confirmatory tests for confirmation HIT are Serotonin Release Assay (SRA) and Heparin Induced Platelet Activation (HIPA).

Exclusion criteria include review articles, case reports, commentaries, guidelines, non-English language texts, and non-use of heparin during treatment, HIT post COVID-19 vaccine injection, and studies that did not have sufficient data. Case reports merely collected to have an imagination and estimation of frequency of HIT in COVID-19. They were not entered into the equation of meta-analysis to prevent bias. The severe COVID-19 patients are those require hospitalization, whereas the non-severe COVID-19 patients are those don't need hospitalized. Given that all patients with HIT are those had admitted in hospital, they would all be with severe COVID-19. Hence, we could not collect data on severity of patients with mild and moderate COVID-19.

Data extraction and quality assessment

To avoid bias, two reviewers (M. R. and H. M.) independently extracted data from the finally included studies: first author's name, year of publication, country, number of patients, age and sex distribution of patients, severity of COVID-19, clinical and laboratory characteristics and outcomes of patients, frequency of HIT, if reported. To assess the quality of the studies, each study was scored 0–10. The risk of bias score was determined by summing the scores. The final score of 0–3 was low, 4–6 was moderate, and 6–10 was high risk. The Joanna Briggs Institute (JBI) Appraisal Tool was used to assess the quality of included studies. JBI critical appraisal checklist is one of the appraisal tools that can assess the different types of articles.

Data synthesis and analysis

Meta-analysis was performed using the comprehensive meta-analysis version 2 (CMA2). The pooled frequency of each outcome was estimated using a random-effects model

or a fixed-effects model based on heterogeneity between studies. It was expressed as pooled frequencies with a 95% confidence interval (CI). The I2 test was used to measure heterogeneity between studies; I2 > 50% was considered an increase in heterogeneity. A 2-tailed P < 0.05 was considered statistically significant. Continuous data were presented as means (standard deviations) or medians with interquartile ranges (IQRs). All descriptive analyzes were calculated using GraphPad Prism version 9 (version 9, GraphPad Inc).

Results

Selection and characteristics of the articles

Based on the established search strategy, we found 575 articles in the medical search engines, including 166 articles from PubMed, 265 from Scopus, and 144 from the Web of Science database. After we removed duplicate articles, 333 articles remained. Articles were then screened by title and abstract, and 85 articles remained at this stage. After reviewing the full texts of the remaining articles using the criteria, 37 articles were finally selected. In addition, two articles were collected by reviewing the bibliography of the screened articles. Thus, 39 articles were finally included in the study (Table 1), of which 13 studies were quantitatively analyzed. The flowchart of the study screening process is shown in Fig. 1. All included studies were published between May 2020 and July 2022.

Patients with HIT and COVID-19

Review of the publication date of studies on HIT in patients with COVID-19 has shown that this topic soon attracted attention. The first paper was published in May 2020, about five months after the disease outbreak in China. Various types of studies have been conducted to detect HIT in patients with COVID-19, including 23 case reports, 11 retrospective cohort studies, 4 prospective cohort studies, and 1 randomized controlled trial (up to the time of our search). Among the 39 studies reviewed, various laboratory methods were used to screen patients for the detection of HIT, including ELISA 16 times, LITA 4 times, CTA 4 times, both ELISA and PaGI 1 time, and 14 studies did not report the method used in their surveys. To confirm HIT in patients, various laboratory methods were used, including SRA (in 11 studies), HIPA (in 4 studies), both HIPA and SRA (in 1 study), and 23 studies did not mention the methods used (Table 1). The clinical and laboratory characteristics of patients with COVID-19 and confirmed HIT were extracted from the 39 articles included in the study. Review of the geographic location of the published studies revealed that 16 studies were published from the United States, 15 studies from Europe, 6 from East Asia, 1 from Africa, and 1 from West Asia.

Among 39 articles, 11,334 patients with concomitant COVID-19 and HIT have reported. Among them, HIT was merely confirmed in 123 patients. Our mined data revealed that the complete data of only 37 patients exist; the clinical and laboratory characteristics of patients with COVID-19 and confirmed HIT have shown in Table 2. Of the 37 patients with COVID-19 and confirmed HIT, 30 patients (81%) were treated in the intensive care unit or had severe COVID-19. Of the 37 studies, the type of heparin administered was reported in 33 studies. The most commonly used anticoagulants were UFH in 22 cases (59.4%), LMWH and then UFH in 6 cases (16.2%), LMWH in 5 cases (13.5%), and no information was provided in 4 cases. After the diagnosis HIT, heparin was discontinued and alternative anticoagulants such as argatroban, apixaban, fondaparinux, bivalirudin, danaparoid, and rivaroxaban were used. The most frequently used alternative anticoagulants after confirmation from HIT were argatroban in 15 cases, apixaban in 4 cases, danaparoid in 4 cases, fondaparinux in 4 cases, bivalirudin in 3 cases, rivaroxaban in 1 case, and argatroban with bivalirudin in 1 case. The outcome of patients was 26 alive (70.2%), 5 in limbo (13.5%), 5 dead (13.5%), and 1 (2.7%) with unknown outcome (Table 2). There were 11,311 patients with COVID-19, with HIT confirmed in 37 of them. The median age of the 37 patients was 62 (49.5–65) years, with a sex ratio of 28 men (75.6%) and nine women (24.3%). In addition, the median platelet count before treatment was 237(176–290) x 10^3/µl and the median nadir platelet count was 52 (31–90.5) x 10^3/µl, showing a significant decrease in platelet count in the patients with HIT. In addition, the median value of the 4T score in the patients was 6 (4–6) (Table 3).

Frequency of HIT in patients with COVID-19

Thirty-nine studies examined the frequency of HIT in the population of patients with COVID-19, of which 13 had sufficient data to be included in the meta-analysis. The pooled frequency rate of suspected cases with HIT in 13 studies with 11,241 patients was 1.7% (95% CI, 0.6-4.9%; I2 95.24%) with a random-effects model. On the basis of the population studied, studies were divided into 3 subgroups: severe patients requiring support by extracorporeal membrane oxygenation (ECM subgroup), patients with suspected HIT (HIT suspected subgroup), and hospitalized patients (hospitalized subgroup). The frequency of HIT in the ECMO subgroup of 268 patients was 8.2% (95% CI, 6.5-14%; I2 36.14%) by the random-effects model, also one study with 86 patients reported the frequency of HIT in patients with

Table 1 Summary of included studies in the meta-analysis

Author(s)	Publication Date	Study Design	Patients/ HIT Confirmed (n)	Study Population	Clinical scoring system	HIT screening test	HIT confirmatory test	Quality assessment
Hemin S. Mohammed [35]	2022, May	CR	1/1	A COVID-19 patient with HIT suspicion	4T Score	NA	NA	7/10
Nabeel A. Siddiqui [36]	2021, July	CR	1/1	A Patient with ALI with HIT complicated by asymptomatic COVID-19	4T Score	NA	SRA	7/10
Yoshihiko Ogawa [37]	2020, Aug	CR	1/1	A COVID-19 patient admitted ICU (VA-ECMO)	4T Score	LITA	NA	7/10
* Filip Ionescu [38]	2020, Oct	RC	3119/12	Consecutive COVID-19 adult patients were hospitalized within eight hospitals located in Southeast Michigan	NA	NA	NA	9/11
Katherine Julian [39]	2021, May	CR	1/1	A patient with COVID-19 and confirmed autoimmune HIT	NA	ELISA	SRA	7/10
Kosaku Sasaki [40]	2022, May	CR	1/1	A Severe COVID-19 patient with pulmonary thromboembolism	4T Score	LITA	NA	7/10
Louisa Fadjri Kusuma Wardhani [41]	2022, Jul	CR	1/1	A COVID-19 patient with hypoxemic respiratory failure	4T Score & HEP Score	NA	NA	7/10
Jori E. May [42]	2020, Jun	CR	7/1	Hospitalized patients with COVID-19 and positive HIT	4T Score	ELISA	SRA	6/10
* Maxime Delrue [43]	2021, Jan	PC	626/1	COVID-19 adults patients admitted to the ICU and medical wards	4T Score	PaGIA, ELISA	HIPA, SRA	8/11
* Rushad Patell [44]	2020, Jul	RC	88/3	Patients hospitalized with COVID- 19 and received intravenous UFH	4T score	LITA	SRA	6/11
* Surbhi Warrior [45]	2020, Nov	RC	1265/1	Hospitalized COVID-19 patients	4T Score	ELISA	SRA	7/11
Michelangelo Sartori [46]	2020, Oct	CR	1/1	A COVID-19 patient with acute respiratory failure and acute renal failure	4T Score	CTA	NA	7/10
Ching-Tai Huang [47]	2020, Aug	CR	1/1	A COVID-19 patient with acute myocardial infarction and HIT suspicion	4T Score	ELISA	NA	7/10
Prasanth Lingamaneni [48]	2020, Jun	CR	5/1	COVID-19 patients with HIT suspicion	4T Score	ELISA	SRA	7/10
Frank Bidar [49]	2020, Aug	CR	2/2	Confirmed HIT in COVID-19 patients with severe ARDS	NA	ELISA	HIPA	7/10
* Florence Daviet [28]	2020, Nov	RC	86/7	COVID-19 ARDS patients with HIT	4T Score	CTA	HIPA	6/11
Richard R. Riker [50]	2020, May	CR	16/1	Thrombocytopenia with anti-PF4 Ab among intubated COVID-19 patients with ARDS	4T Score	ELISA	SRA	7/10
Paola S. Preti [51]	2021, Apr	CR	2/2	Severe COVID-19 with HIT	4T Score & HEP Score	ELISA	NA	7/10
Samragnyi Madala [52]	2021, Feb	CR	1/1	A COVID-19 patient	4T Score	NR	SRA	7/10
Sara Soliman [53]	2022, Feb	CR	1/1	Ischemic Stroke and Bilateral Pulmonary Embolism in COVID-19	4T Score	ELISA	SRA	7/10
Yasutaka Murakami [54]	2022, Jul	CR	1/1	A COVID-19 patient	4T Score	LITA	NA	7/10
Alberto Lázaro-García [55]	2022, Mar	CR	1/1	A COVID-19 patient with ventricular thrombus	4T Score	CTA	NA	7/10
Eileen Shiuan[56]	2022, Jun	CR	1/1	A COVID-19 patient with limb ischemia and HIT suspicion	4T Score	ELISA	SRA	7/10
A. Zyani [57]	2021, Nov	CR	1/1	A COVID-19 patient	4T Score	NA	NA	7/10
Alla Turshudzhyan [58]	2020, Jul	CR	2/1	COVID-19 patients with PE	NA	NR	NA	6/10
Michael Tran [59]	2020, Sep	CR	1/1	A patient with SARS-CoV-2 pneumonitis and confirmed HIT	4T Score	ELISA	HIPA	7/10

Table 1 (continued)

Author(s)	Publication Date	Study Design	Patients/ HIT Confirmed (n)	Study Population	Clinical scoring system	HIT screening test	HIT confirmatory test	Quality assessment
Xuan T. Phan [60]	2020, Dec	CR	1/1	A COVID-19 patient on extracorporeal membrane oxygenation support with HIT suspicion	4T Score	CTA	NA	7/10
Elizabeth J. Benge [61]	2022, Jan	CR	1/1	A COVID-19 patient	NA	ELISA	NA	7/10
Justine Brodard [62]	2021, Feb	CS	12/3	COVID-19 patients with suspected HIT	4T Score	ELISA	HIPA	6/9
* Tiffany Pascreau [63]	2021, Jun	PC	119/21	Hospitalized patients with COVID-19	4T Score	NR	NA	7/11
* Deepa J. Arachchillage [64]	2021, Sep	RC	152/16	Patients with severe COVID-19 supported by ECMO	4T Score	ELISA	NA	8/11
* Florence Daviet[65]	2021, Nov	RC	76/3	Patients with severe COVID-19 supported by ECMO	NA	NA	NA	8/11
* Ali Tabatabai[66]	2020, Dec	RC	40/5	Patients with severe COVID-19 supported by ECMO	NA	NA	NA	6/11
* Paola Adele Lonati[67]	2021, Nov	PC	50/4	COVID-19 with moderate disease	NA	ELISA	NA	7/11
Koray Durak[68]	2021, Apr	RC	17/1	Patients with severe COVID-19 supported by ECMO	NA	NA	NA	9/11
* Hanny Al-Samkari[69]	2021, Jan	RC	3239/18	Critically ill adults with COVID-19 (ICU)	NA	NA	NA	9/11
Gabriel Parzy[70]	2020, Oct	RC	13/3	Patients with severe COVID-19 supported by ECMO	NA	NA	NA	7/11
* Julie Helms[71]	2020, May	PC	150/0	Patients with SARS-CoV-2 ARDS admitted to the ICU	NA	NA	NA	9/11
* Lawler[72]	2021, Aug	RCT	2231/0	Non-critically ill patients hospitalized for COVID-19	4T Score	ELISA	SRA	9/11

Abbreviations: ALI, Acute Limb Ischemia; ARDS, Acute respiratory distress syndrome; PE, Pulmonary Embolism; N, Number; NR, Not Reported; NA, Not Available; PC, Prospective Cohort; RC, Retrospective Cohort; CS, Cross-Sectional; CR, Case Report; RCT, Randomized Controlled Trials; CIA, Chemiluminescent Immunoassay; ELISA; Enzyme-linked Immunosorbent Assay; LITA, Latex Immune Turbidimetric Assay; PaGIA, Particle Gel Immunoassay. SRA, Serotonin Release Assay; ECMO, Extracorporeal Membrane Oxygenation; ICU, Intensive Care Unit; HIT, Heparin Induced Thrombocytopenia; HIPA, Heparin Induced Platelet Activation; *, the studies that entered the meta-analysis

HIT-suspected 8.1% (95% CI, 3.9-16.1%). and in the hospitalization subgroup with 10,887 patients, the frequency of HIT was 0.8% (95% CI, 0.2-2.7%; I2 95.91%) by the random effect model. Heterogeneity between subgroups was significantly different (p: 0.006) (Fig. 2). In order to investigate the publication bias between articles, used Begg's Funnel plot and Egger's test (Fig. 3). The Begg's test and Egger's test showed that there was no stable evidence of publication bias in the meta-analysis (P: 0.2 and P: 0.45 respectively). In order to measure the effect of each study on the analysis, each article was omitted from the analysis to quantify the frequency of HIT. We did not notice a significant change in the pooled frequency rate before and after extracting each sample. The sensitivity plot is shown in Fig. 4.

Discussion

The current systematic review evaluated information from 39 studies involving 11,334 patients with COVID-19 and HIT. Merely, 13 articles with 11,241 patients included in the meta-analysis. The pooled frequency of antiplatelet factor 4 antibodies (activating and nonactivating antibodies) was 1.7%. Current screening tests for the detection of HIT are based on the detection of antibodies (immunoassay) that detect both pathogenic and nonpathogenic antibodies to platelet factor 4. Therefore, HIT, a potentially life-threatening immunologic disorder, must be confirmed with a confirmatory heparin-dependent platelet activation assay such as SRA or HIPA. In total, there were 37 patients with HIT and COVID-19 in whom one of the confirmatory tests was performed. We hypothesis that If no confirmatory test is available, the rise in platelets after switching from heparin to non-heparin anticoagulants (argatroban, apixaban, fondaparinux, bivalirudin, danaparoid, and rivaroxaban)

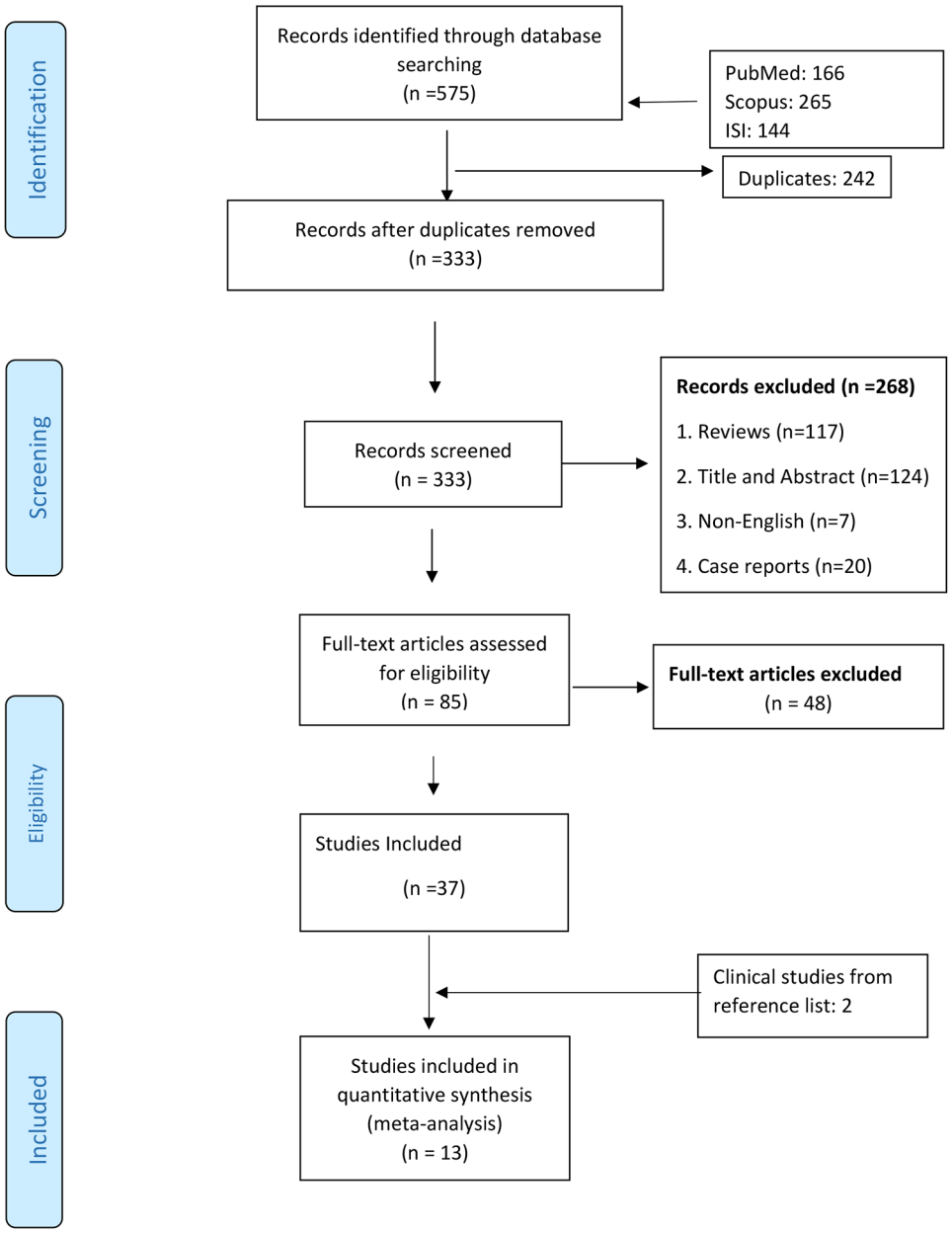


Fig. 1 Flowchart describing the process of literature study selection

may be helpful in establishing the diagnosis HIT. In a similar meta-analysis by Uapraserta N. et al. total of 15 of 19 (79%) confirmed HIT cases demonstrated platelet recovery after heparin substitution with non-heparin anticoagulants [27].

Men with COVID-19 were more susceptible to HIT (75.6%) than women with COVID-19 (28 men vs. 9 women). The more frequent occurrence of HIT in men with COVID-19 has been reported in other studies [28–30]. This may be because sex hormones influence SARS-CoV-2 penetration, priming, inflammatory process, and susceptibility to thrombosis. It seems that women are better protected against COVID-19 because of some factors, including more effective immune response and lower systemic inflammation [31]. This study showed that 67.5% of patients with HIT and COVID-19 were still alive. This may be due to several factors, including switching to a different anticoagulant, which leads to an increase in platelet count and prevents platelet activation.

Most publications on HIT in COVID-19 are from Western countries. This indicates that the topic of HIT may be neglected or receive little attention in developing countries. Since the mortality rate of HIT is considerable, clinicians concerned with the treatment of patients with COVID-19 in developing countries should take this into account.

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

No (Ref)	Age, Sex	Study location	Severity of COVID-19	Type and dose of heparin during HIT diagnosis	Duration of heparin (d)	Initial/Nadir platelet count ($x10^9$ /L)	Score	Screening test	Platelet activation assay for confirming HIT	Non-heparin anticoagulants	Outcome
1[35]	63, M	Iraq	Moderate to Severe COVID-19	UFH	3	258/111	4TScore; 6	NA	NA	Apixaban	Alive
2 [36]	49, M	USA, Caucasian	ICU	UFH	2	253/26	4TScore; 6	NA	SRA; Positive	Argatroban	Limbo
3 [37]	37, M	Japan	ICU-MV-ECMO	UFH;(5000 IU bolus and 300 IU/h initially)	10	210/90	4TScore; 6	LITA (3.1U/mL)	NA	Argatroban	Alive
4 [39]	65, F	USA	Non-ICU	NA	NA	NA/6	NA	Positive	SRA; Positive	Argatroban, Apixaban, IVIG	Alive
5 [40]	53, M	Japan	Severe COVID-19	UFH; 10,000 units	13	139/104	4TScore; 7	LITA (2.9 U/mL)	NA	Apixaban	Alive
6 [41]	71, M	Indonesia	COVID-19 with severe ARDS	UFH	9	NA/40	4TScore; 6 HEP; 5	NA	NA	NA	Alive
7 [42]	61, F	African American	ICU	UFH	NA	NA/37	4TScore; 4	ELISA (OD 0.95)	SRA; Positive	NA	Limbo
8 [43]	64, M	France	ICU	UFH 20,000 IU	18	223/67	4TScore; 6	PaGIA positive, ELISA (OD 2.4)	SRA; Positive, HIPA; Positive	Argatroban	Alive
9 [44]	68, F	USA	ICU	UFH	7	416/<5	4TScore; 4	LITA (1.8 U/mL)	SRA; Positive	Argatroban, bivalirudin	Alive
10 [44]	63, M	USA	ICU	UFH	6	154/52	4TScore; 8	LITA (1.6 U/mL)	SRA; Positive	Argatroban	Death
11 [44]	49, M	USA	ICU	UFH	12	176/25	4TScore; 6	LITA (1.9 U/mL)	SRA; Positive	Argatroban	Alive
12 [45]	63, M	USA	ICU	LMWH and UFH	12	290/63	4TScore > 4	ELISA (OD 0.62)	Positive	Argatroban	Death
13 [46]	78, M	Italy	ICU	UFH; 5000IU	18	305/41	4TScore; 6	CTA (9.44 U/ml)	NA	Argatroban	Alive
14 [47]	44, M	Taiwan	ICU-ECMO	NA	NA	200/74	4TScore; 6	Anti-PF4-heparin antibody (ng/mL); 17.14, ELISA;> 2.0 units	NA	NA	NA
15 [48]	63, M	USA	ICU	LMWH	12	304/96	4TScore; 6	ELISA (OD 1.2)	SRA; Positive	Argatroban	Death
16 [49]	62, F	France	ICU	UFH;	16	237/29	4TScore; 3	ELISA (OD 1.8)	HIPA; Positive	Argatroban	Alive
17 [49]	38, M	France	ICU	UFH;	21	248/93	4TScore; 4	ELISA (OD 1.6)	HIPA; Positive	Argatroban	Alive
18 [28]	46, M	France	ICU-MV-ECMO	LMWH, then UFH	16	61/33	4TScore; 6	CTA (46 U/mL)	HIPA; Positive	Argatroban	Alive
19 [28]	50, M	France	ICU-MV-ECMO	LMWH, then UFH	13	243/73	4TScore; 6	CTA (11 U/mL)	HIPA; Positive	Argatroban	Limbo
20 [28]	43, F	France	ICU-MV-ECMO	LMWH, then UFH	15	160/48	4TScore; 6	CTA (39 U/mL)	HIPA; Positive	Argatroban	Limbo
21 [28]	63, M	France	ICU-MV	LMWH, then UFH	14	191/56	4TScore; 4	CTA (60 U/mL)	HIPA; Positive	Danaparoid	Alive
22 [28]	59, M	France	ICU-MV	LMWH, then UFH	9	161/62	4TScore; 5	CTA (4 U/mL)	HIPA; Positive	Danaparoid	Alive
23 [28]	57, M	France	ICU	UFH	11	159/39	4TScore; 5	CTA (21 U/mL)	HIPA; Positive	Danaparoid	Alive
24 [28]	69, M	France	ICU-MV	UFH	16	215/107	4TScore; 4	CTA (2 U/mL)	HIPA; Positive	Danaparoid	Alive
25 [50]	70, M	USA	ICU	UFH	20	438/90	4TScore; 6	ELISA (OD 2.0)	Positive	Bivalirudin	Death

Table 2 (continued)

No (Ref)	Age, Sex	Study location	Severity of COVID-19	Type and dose of heparin during HIT diagnosis	Duration of heparin (d)	Initial/Nadir platelet count (x10^9 /L)	Score	Screening test	Platelet activation assay for confirming HIT	Non-heparin anticoagulants	Outcome
26 [51]	59, M	Italy	ICU-MV	LMWH	18	243/107	4TScore; 5 HEP: 6	ELISA (OD:0.81)	NA	Fondaparinux	Death
27 [51]	50, M	Italy	ICU	LMWH	16	324/28	4TScore; 4 HEP: 3	ELISA (OD:2.13)	NA	Fondaparinux	Alive
28 [52]	65, F	USA	NA	LMWH	12	290/63	4TScore; 6	Heparin-PF4 antibody 9.7 μ/mL (normal range: 0.0-0.9μ/mL)	SRA; Positive	Apixaban	Alive
29 [53]	69, F	USA	Severe COVID-19	UFH	13	120/43	4TScore; 6	ELISA (OD:1.345)	Positive	Fondaparinux	Alive
30 [54]	53, F	Japan	ICU-MV	UFH	8	243/121	4TScore; 7	LITA (> 5 U/mL)	NA	Argatroban	Alive
31 [55]	57, M	Spain,Caucasian	ICU	NA	NA	NA/51	4TScore; 6	CTA (2.28 U/mL)	NA	Fondaparinux	Alive
32 [56]	66, M	USA	NA	UFH	NA	NA/27	4TScore; 5	ELISA (OD: 2.056)	SRA; Positive	Bivalirudin	Alive
33 [57]	63, F	Morocco	ICU	LMWH	18	188/13	4TScore; 6	NA	NA	NA	Alive
34 [58]	65, M	USA	NA	NA	NA	NA/22	NA	Heparin PF4 antibody; Positive	NA	Argatroban	Limbo
35 [59]	62, M	USA	ICU	UFH	17	414/91	4TScore; 4	ELISA (OD: 1.08)	HIPA; Positive	Bivalirudin	Alive
36 [60]	43, M	Vietnam	ICU-ECMO	UFH	7	202/44	4TScore; 5	CTA (4 U/mL)	NA	Rivaroxaban	Alive
37 [61]	44, M	USA	ICU	UFH	13	295/115	NA	ELISA (OD: 1.960)	NA	Apixaban	Alive

Abbreviations: N, Number; NR, Not Reported; NA, Not Available; F, Female; M, Male; Ref, Reference; d, day; L, Liter; UFH, Unfractionated Heparin; LMWH, Low Molecular Weight Heparin; CIA, Chemiluminescent Immunoassay; ELISA; Enzyme-linked Immunosorbent Assay; LITA, Latex Immune Turbidimetric Assay; PaGIA, Particle Gel Immunoassay. SRA, Serotonin Release Assay; ECMO, Extracorporeal Membrane Oxygenation; MV, mechanical ventilation; ICU, Intensive Care Unit; HIT, Heparin Induced Thrombocytopenia; HIPA, Heparin Induced Platelet Activation

Table 3 The summary of Clinical and laboratory characteristics of hospitalized COVID-19 patients with confirmed HIT.

	Age	Initial platelet count (x10^9 /L)	Nadir platelet count (x10^9 /L)	Duration of heparin (d)	4T Score
N. Reports	37	31	37	31	34
Median	62	237	52	13	6
IQR	49.5–65	176–290	31–90.5	9–16	4–6

Abbreviations: N, Number; L, Liter; d, day; IQR, Interquartile range

Of the 37 confirmed cases with HIT and COVID-19, most patients (30 cases) were hospitalized in the intensive care unit or had severe COVID-19 (81%). This may be due to the tremendous release of cytokines and severe viral sepsis in COVID-19. This indicates that patients with severe COVID-19 are more susceptible to challenge with HIT compared with mild COVID-19. In addition, analysis of the HIT rate in the subgroups showed that HIT occurred more frequently in the HIT suspect group and then in the ECMO group of patients with COVID-19. This reflects that clinical suspicion of HIT by observing a decrease in platelet count is a robust sign of HIT that needs to be confirmed by rapid calculation of the 4Ts score and performance of a confirmatory laboratory test (33). Meanwhile, patients with severe COVID-19 who require oxygen supplementation therapy (which is a symptom of severe COVID-19) are vulnerable to HIT. Therefore, clinicians should keep an eye on the occurrence of HIT in patients with COVID-19 in the ICU. Reviewing the literature, we were able to find a similar meta-analysis across 7 studies involving 5849 patients [32]. The pooled incidence rate of HIT in this meta-analysis was

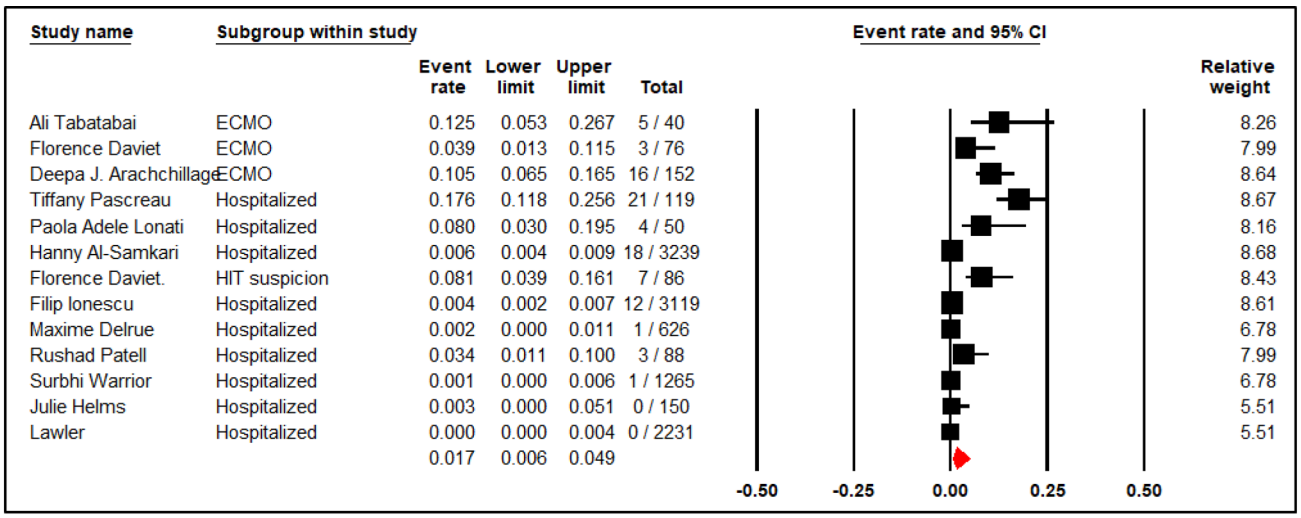
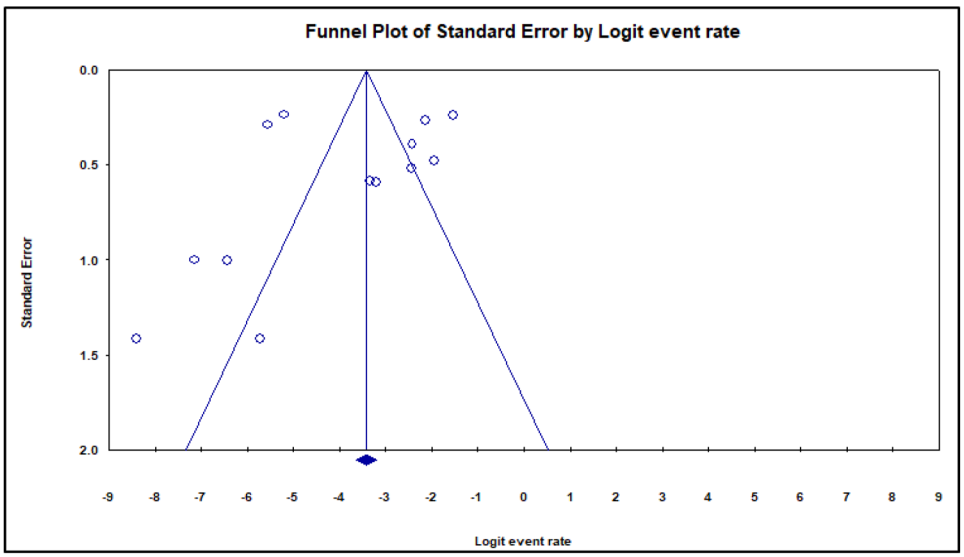


Fig. 2 The forest plot of the frequency of the HIT in patients with COVID-19.

Fig. 3 Funnel plot of the frequency of HIT in patients with COVID-19



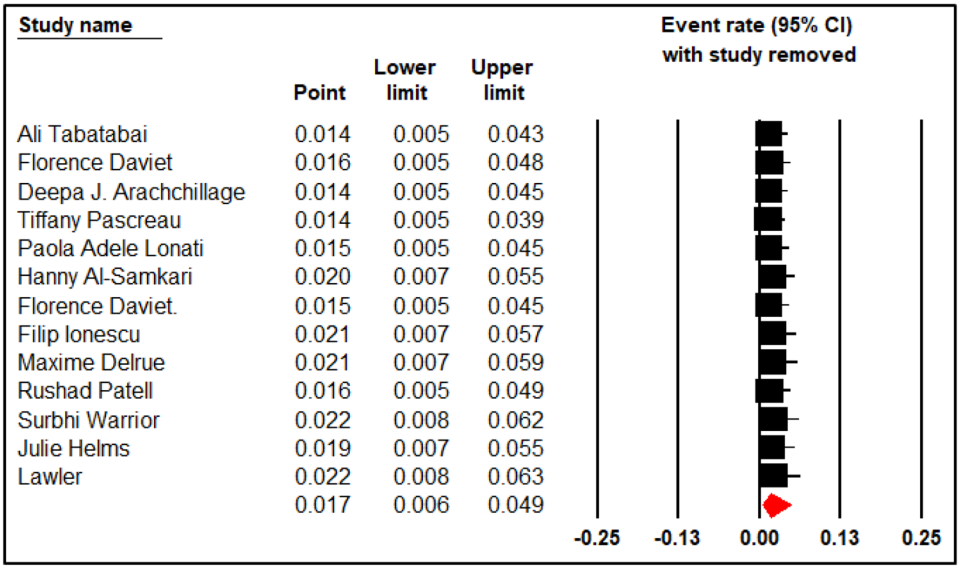


Fig. 4 Sensitivity analysis for pooled frequency rate with study removed

0.8%. The higher rate of HIT in our study may be due to the fact that we captured a larger number of papers and higher included patients, that HIT has received more attention in after primary reports, and that clinicians are paying more attention to HIT. In addition, the patients included in this meta-analysis had COVID-19, which is associated with a higher risk of thrombosis [15, 33, 34]. This may be attributed to the fact that patients with COVID-19 and HIT have a dual risk of thrombosis.

This study encountered some limitations. There were many cases with HIT, which were not confirmed by HIPA or SRA, while they were positive by screening tests. This may be one of the main causes of bias, reducing the true incidence of HIT. In addition, there were many case reports with incomplete information that did not meet the required criteria to be included in the meta-analysis. Dose of heparin was an interesting finding, but merely few studies have mentioned to it in their reports. This may be because thrombocytopenia is a multifactorial disease, so this complication may not be recognized and subsequently underreported in the medical literature.

Future studies are needed to investigate the impact of HIT on the morbidity and mortality of COVID-19. Another topic of interest in these patients is work on nonpathogenic anti-factor 4 platelet antibodies to show whether these patients are susceptible to developing pathologic antibodies to platelets in future. As for the widespread use of heparin and heparinoids in patients with COVID-19, the bottom line seems to be to keep an eye on thrombocytopenia and HIT in patients with COVID-19.

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Authors Contribution M.R. was involved in database searching, screening abstracts and full texts, data extraction, quality assessment, conducting meta-analysis, interpreting data, writing the first draft of the manuscript, and finalizing the manuscript. H.M. was involved in the conception, database search, screening of abstracts and full texts, writing the first draft of the manuscript, and finalizing the manuscript. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Mashhad University of Medical Sciences.

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