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Thrombosis in Covid-19 Patients and Dilemma of Antithrombotic Choice: A Systematic Review

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Abstract Background: Coronavirus Disease 2019 (COVID-19) potentially deteriorates the immune system and triggers prothrombotic states in many patient scenarios. Clinical studies so far do not stratify the risk of thromboembolism in COVID-19 cases. Objective: This systematic review investigates the risks of thromboembolism and outcomes of anticoagulation therapy in COVID-19 patients. Methods: We searched PubMed, Cochrane Library, Embase, Web of Science, and Google Scholar to identify relevant studies assessing thromboembolism and anticoagulant therapy in COVID-19 patients. Study Selection, Data Extraction, and Synthesis: Two reviewers screened the titles and abstracts of the included studies in the context of COVID-19, thrombosis, and anticoagulant therapy. The reviewers also ascertained the elimination of duplicate articles. Results: We included eight studies based on the thromboembolism predisposition of COVID-19 (adult/elderly) patients with the status/history of cardiovascular disease, diabetes, hypertension, obesity, and hospital admission. Conclusion: Prospective studies need to explore the risks of thromboembolism in patients with COVID-19. The current body of evidence does not substantiate antithrombotic treatment for managing thromboembolism in the setting of COVID-19. The physicians must take preventive measures for reducing the incidence rate of thromboembolism in COVID-19 scenarios until the availability of definitive treatment.

Keywords: *thromboses, COVID-19, anticoagulants, incidence, SARS-CoV-2*

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1. Introduction

The World Health Organization reported SARS-CoV-2/COVID-19 (coronavirus disease) pandemic in 2020 [1]. However, the novel coronavirus disease was first recognized and reported by China in 2019. Coronavirus potentially impairs the respiratory system of the infected patients that eventually triggers breathing difficulty. Medical literature reveals substantial variations in the COVID-19 symptoms among individuals. Moderate flu and fever reportedly develop in a few of the infected individuals. The findings of Blagosklonny (2020) reveal the moderate impact of COVID-19 manifestations during the initial phase of the disease. The worsening of symptoms over time is dominated by a range of factors that vary across patient populations. The rate of mortality in COVID-19 scenarios, however, increases with age. Age proves to be the deterministic factor of COVID-19-related deaths in a variety of cases [2]. Evidence-based findings also affirm a higher mortality rate among COVID-19 infected men than women [3].

COVID-19 patients with chronic comorbidities experience a higher risk of death as compared to non-COVID-19 patients. These comorbidities majorly include hypertension, asthma, and diabetes [4]. Aged individuals with chronic disease conditions remain highly vulnerable to the deleterious manifestations of COVID-19. Age advancement gradually impacts the physiological growth and development of cells and tissues. Over time, incongruous cellular functioning elevates the risk of serious and life-threatening complications in COVID-19 patients [5]. The hyperfunction theory and its relationship with quasi-programmed aging provide some explanation for the age-dependent prognosis of COVID-19. Other factors impacting the COVID-19 susceptibility of individuals include immunosenescence, hyper-inflammation, thrombosis, hyper-thrombosis, inflammaging, and cytokine storms. [6].

COVID-19 substantially increases the risk of arteriovenous thromboembolism by triggering excessive inflammation, diffuse intravascular coagulation, and hypoxia. Clinical studies, however, do not elaborate on the mechanisms associated with the thrombosis-related predisposition of COVID-19 patients. Future studies need to investigate the impact of COVID-19 infection on thromboembolism's prognosis to inform the treatment decisions. Studies also report a high ICU (intensive care unit) admission rate among COVID-19 patients with serious comorbidities that elevate the risk of thromboembolism.

Clinical studies confirm a high incidence rate of venous thrombosis in COVID-19 scenarios. Thromboembolism in COVID-19 patients probably occurs due to the excessive activation of white blood cells and resultant immune responses [7]. COVID-19 patients with thrombosis require focussed care based on comprehensive treatment algorithms or surgical interventions to improve their treatment outcomes and recovery [8]. Clinical studies report variable results regarding the frequency of thrombosis in COVID-19 patients. Most of the studies, however, affirm the occurrence of thrombosis in 50% of COVID-19 cases.

The severity of COVID-19 manifestations reciprocates with the incidence of thromboembolism. Old age, thrombophilia, and oncological manifestations include some potential factors that trigger thrombosis development in COVID-19 patients [9]. COVID-19 scenarios often associate with the risk of life-threatening complications [10]. Our study investigates the incidence of thromboembolism in patients with a confirmed diagnosis of COVID-19. It also evaluates the scope of improving treatment outcomes (in COVID-19 patients) with anticoagulation.

2. Methodology

2.1. Data Collection

From January 2020 to December 2020, PubMed, Google Scholar**,** Web of Science, Embase, Cochrane database, and Science were searched directly for the published studies. Anticoagulation, thromboembolism, COVID-19, coagulation, and thrombosis terms were included in the keywords used for selecting the research articles.

2.2. Inclusion and Exclusion Criteria

The research papers, cases, reports, and peer-reviewed studies published in 2020 were considered for assessment. The inclusion criteria relied on PICOS (patients, intervention, comparisons, outcome, and study design type) principle. Articles that documented the risk of thromboembolism or anticoagulation outcomes in patients with COVID-19 were included in our study. Consensus documents, correspondences, editorials, letters to the editor, unpublished studies, commentaries, studies with ineligible populations, and studies with ethical concerns were summarily excluded from the assessment [11].

2.3. Review of Relevant Articles

Keywords in the present study were used to screen the selected articles. Eight articles with 5-30 citations were selected for analysis.

2.4. Study Selection and Data Abstraction

Two reviewers scanned and analyzed the selected studies' titles and abstracts to remove irrelevant research based on the inclusion and exclusion parameters. The data abstraction spreadsheet was created via2010 edition of Microsoft Excel. It comprehensively captured relevant details from each of the selected studies. The study table included the first author's name, the article title, the journal name, year of publication, country (where the research was conducted), the study design, and the sample size. The study also included various anticoagulants based on their therapeutic efficacies in COVID-19 scenarios. The selected anticoagulants included heparin, vitamin K antagonists, direct thrombin inhibitors, or direct factor Xa inhibitors [12]. The selected studies also included outcome factors based on the occurrence, effectiveness, and severity of adverse reactions. The systematic review of full-text articles and data abstraction spreadsheet helped excluding preprints and duplicate studies.

2.5. Quality Assessment

The quality assessment of case-control/cohort studies was undertaken by the quality assessment tool from the National Heart, Lung, and Blood Institute (NHLBI) [13]. The quality instrument for assessing the cohort studies consisted of 14 items, while the tool used for evaluating case series included nine items. The quality assessment questionnaire relied on objective parameters, including "no," "yes," "cannot determine," or "not applicable," or "not reported.". We performed scoring for each of the selected studies to rate the quality of their research interventions.

3. Results

We screened 363 articles out of 420 articles following the elimination of duplicities. The inclusion and exclusion parameters further directed the omission of 307 articles. Eight relevant studies with 38 valid citations were finally included for our analysis. These studies incorporated a case report, a prospective cohort, and six retrospective case series. A full PRISMA flow chart (Figure 1) summarizes the research outcomes and the study selection process. According to the NIH quality assessment tool [14], which was fair in quality, the selected cohort studies were classified as having a good standard and applicable to the subject (except one study).

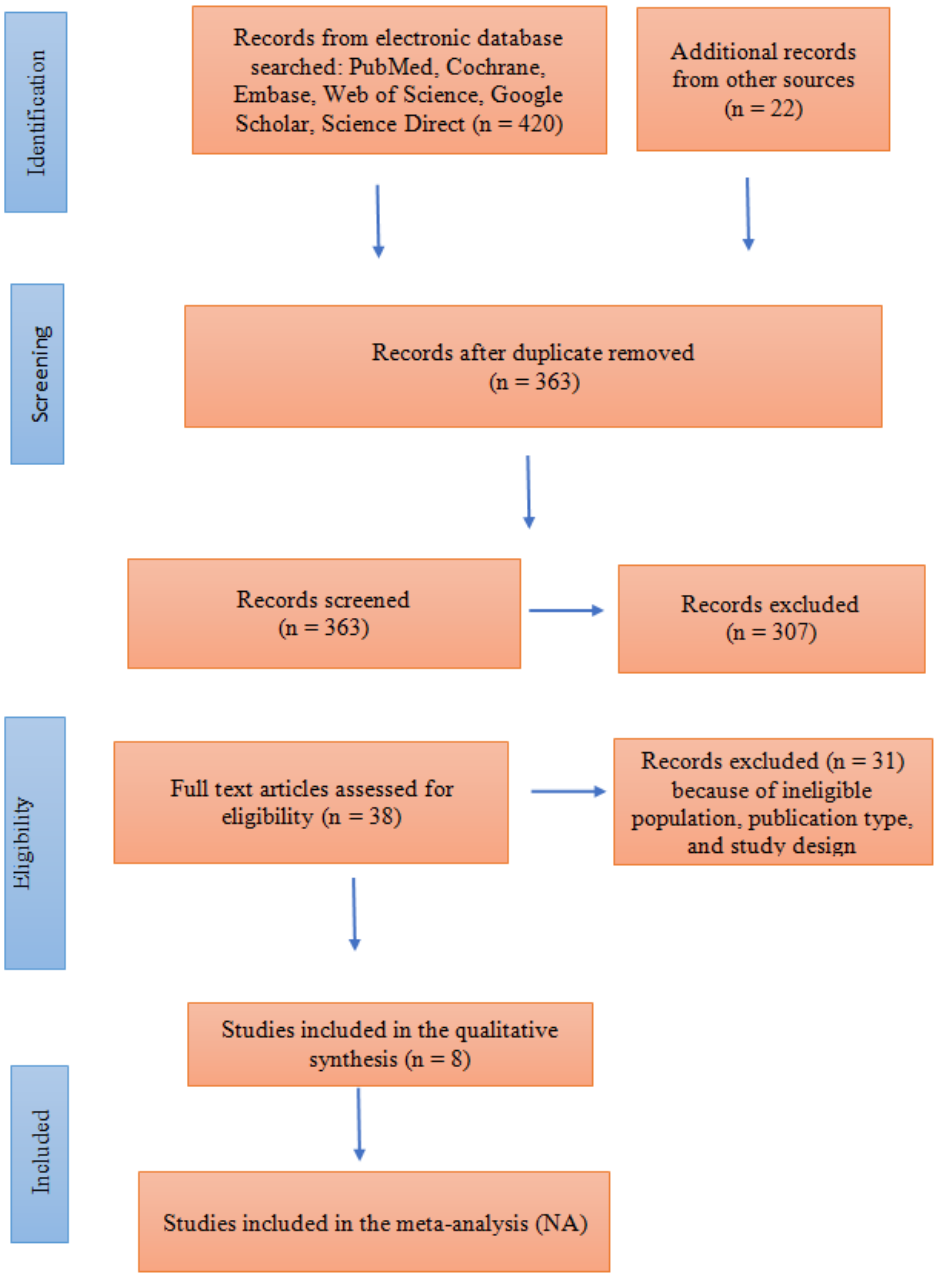

Figure 1. The PRISMA Flowchart

3.1. Incidence of Thromboembolism in COVID-19 Patients

The COVID-19 pandemic has triggered significant health problems around the world. The World Health Organization has so far reported2,082,745 deaths due to the coronavirus pandemic [15]. Few states reported a 15% fatality rate due to COVID-19 infection [16]. Several studies have recorded COVID-19 patients with episodes of thromboembolism. In Table 1, these studies are categorically listed and summarized.

Lodigiani (2020) categorized COVID-19 following endothelial dysfunction and coagulation activation. However, the study data did not substantiate thromboembolic complications in COVID-19 patients [17]. Lodigiani (2020) contributed by researching the consecutive symptomatic patients of COVID-19 in the University Hospital of Milan, Italy. The study was undertaken to determine the presence of ischemic stroke, venous thromboembolism, acute coronary syndrome, myocardial infarction, and disseminated intravascular coagulation. The study comprised 388 COVID-19 patients. It further revealed the potential of thromboprophylaxis in countering ICU admissions for COVID-19 [18]. The study findings reported arteriovenous thromboembolic events in COVID-19 patients within 24 hours of their hospital admission. The VTE (venous thromboembolism) imaging test results suggested an urgent need to improvise evidence-based strategies for the diagnostic assessment of VTE. The study findings support the necessity to examine the safety and efficacy of thromboprophylaxis in COVID-19 patients. The strategies followed in the university hospital were highlighted in this study. The study findings also questioned the meaningful use of diagnostic facilities and therapeutic management strategies in COVID-19 scenarios.

Table 1. Summarized Findings of the Selected Studies

No	References	Sample Size	Study design	Inclusion and exclusion criteria	Objectives	Findings
1	Lodigiani (2020)	388 patients	Retrospective cohort study	COVID-19 patients admitted in Milan hospital, Italy of median age (66 years) are included, in which 68% were men, 16% required ICU.	To investigate the risks of VTE and arterial and venous thromboembolism in Covid-19 patients in ICU	Arterial and venous thromboembolic events occurred in 8% of the patients, and VTE was confirmed in 16 patients.
2	Klok et al. (2020)	184 patients admitted to ICU	Cohort study	COVID-19 Patients admitted to the ICU of Dutch University.	To evaluate the deep-vein thrombosis incident, acute pulmonary embolism, myocardial infarction, ischemic stroke, or systemic arterial embolism in patients of COVID-19.	Pulmonary embolism was found to the most frequent thrombotic complication.
3	Middeldorp (2020)	75 patients admitted to ICU	Cohort study	Randomly selected COVID-19 patients in the ICU of Amsterdam University Medical Centers.	To evaluate the incidence of VTE in COVID-19 patients admitted in ICU.	Despite daily thrombosis prophylaxis, patients were diagnosed with VTE. However, the chances of VTE are found to be higher in ICU patients than in the wards.
4	Zerwes et al. (2020)	20 COVID-19 patients and 20 non-COVID-19 patients in ICU.	Prospective single-center study.	Patients admitted to ICU of the University Hospital Augsburg from 18th April 2020 to 30th April 2020.	To investigate the incidence of deep vein thrombosis (DVT) in COVID-19 patients present in ICU.	The rate of DVT was found to be too highly elevated in COVID-19 patients.
5	Maldonado et al. (2020)	A total of 7 studies was included.	Systematic review.	Studies were conducted from 1st January 2020 to 22nd April 2020.	To investigate the impact of antithrombotic therapy on patients with COVID-19 and thromboembolism.	Research is still required for evaluating whether thromboprophylaxis protocols can be used for treating COVID-19 patients or not.
6	Vivas et al. (2020)	A total of 14 studies was included.	Consensus study.	Studies were conducted on antithrombotic therapy for COVID-19 patients and other patients.	To investigate the effect of antithrombotic therapy through which thrombotic risks in COVID-19 patients can be minimized.	There is no proper evidence for the effectiveness of antithrombotic therapy for treating COVID-19 patients with thrombosis.
7	Godino et al. (2020)		Rationale and Evidence-based study.	Studies conducted on antithrombotic therapy and prevention.	To identify the effectiveness of antithrombotic therapy on COVID-19 patients.	There is no proper evidence available for antithrombotic therapy's effectiveness; however, preventive measures can reduce the risks.
8	Paar (2020)	PBMCs were taken from 7 randomly selected individuals.	In vitro study.	All of the selected volunteers are healthy.	To investigate the link between the inflammatory response and the coagulation pathway.	All the chemokines and cytokines' measures were remarkably more significant for serum compared to the heparinized plasma. Results also confirmed the link between the inflammatory response and the coagulation pathway.

The study by Klok et al. (2020) at the Dutch teaching hospital and the university hospital elaborated on potential causes of arteriovenous thromboembolism, including immobilization, hypoxia, excessive inflammation, and diffuse intravascular coagulation [19]. The patients considered for the study were admitted to the ICU and received thromboprophylaxis at standard doses. The study outcomes reported VTE in 27% of COVID-19 patients and 3.7% of COVID-19 patients with arterial thrombosis. However, 81% of COVID-19 patients experienced a pulmonary embolism. The study findings accordingly emphasized the requirement of pharmacological prophylaxis for managing COVID-19 complications in ICU.

The physicians should take extra precautions in managing COVID-19 cases in ICU and avoid administering anticoagulants in high dosages. However, the high risk of thromboembolism in COVID-19 patients in ICU still warrants anticoagulant prophylaxis. Middeldorp (2020)compared the risk of VTE in COVID-19 patients across inpatient wards and ICUs [20]. The author included 75 randomly selected COVID-19 patients admitted to the ICU. Approximately 8% of the patients were still in the hospital during the data collection for the study. However, 19% of them experienced death before study initiation. The included patients underwent a median follow-up over time, and 20% were diagnosed with VTE after seven days of study initiation. Despite the daily thrombosis prophylaxis, 13% of COVID-19 patients developed symptomatic VTE. The cumulative incidences of VTE were recorded as 16%, 33%, and 42% at 7, 14, and 21 days respectively. However, symptomatic VTE incidence was recorded as 10%, 21%, and 25%, respectively, following the subsequent week. The study findings affirmed the clinical correlation between COVID-19-related deaths and VTE. The study results also indicated a higher predisposition of COVID-19 patients for VTE in ICU versus the inpatient ward. These outcomes support the requirement of diagnostic assessment of COVID-19 patients for deep vein thrombosis (DVT) and pulmonary embolism (PE).

The episodes of thromboembolism potentially elevate the mortality risk of COVID-19 patients [21]. The research findings advocate the optimization of prophylactic and diagnostic measures for VTE prevention to elevate the survival of COVID-19 patients. Future studies must investigate the correlation between thromboembolism episodes and ICU admissions in COVID-19 scenarios.

Zerwes et al. (2020) evaluated the predisposition of ICU-admitted patients for thromboembolism [22]. The findings revealed 20 COVID-19 positive patients and 20 COVID-19 negative patients with thromboembolism in ICU. The authors analyzed the patient records retrieved in the context of demographic data, clinical outcomes, and laboratory results. The findings affirmed a 20% DVT development rate in COVID-19 positive patients versus 5% in COVID-19 negative patients [23]. The study outcomes revealed a high risk of DVT among COVID-19 positive patients than non-COVID-19 patients in the ICU setting.

The selected studies unequivocally revealed the high predisposition of ICU admitted COVID-19 patients for thromboembolism. The effective management of these patients via antithrombotic therapy is necessary to enhance their recovery and survival.

3.2. Antithrombotic Treatments in COVID-19 Patients

The rapid dissemination of COVID-19 infection across the globe is a serious concern for the scientific community and the health care sector. Comorbidities, including thrombosis, further add to the COVID-19-related fatal complications and adversities [24]. No therapy until date claims to remediate COVID-19 manifestations with 100% success. Prospective research studies need to explore viable solutions to prevent and treat thromboembolism episodes in COVID-19 patients. The systematic review by Maldonado et al. (2020) revealed thromboembolism among 25%-53% COVID-19 patients. The authors discussed the findings from three studies that focused on investigating the recovery patterns of COVID-19 patients with thromboembolism following their antithrombotic therapies [25].

The findings from the studies focusing on thromboembolism management (in COVID-19 scenarios) lack generalizability due to their inappropriate patient selection process, absence of reporting and modification for the patients' baseline characteristics, insufficient follow-up time, and minimal reporting of results [25]. These potential gaps necessitate prospective research to generate credible evidence to substantiate the use of antithrombotic therapies in COVID-19 scenarios [25].

Vivas et al. (2020) reported several incidences of thrombosis in COVID-19 patients. Few of the clinical studies emphasized the potential of COVID-19 to trigger inflammation, which is the leading cause of thromboembolism [26]. Our research summarized the studies' outcomes focusing on the clinical management of COVID-19 patients via antithrombotic therapy. However, the included studies' findings did not thoroughly support antithrombotic therapy's therapeutic efficacy in COVID-19 cases [26]. Contrarily, the findings by Godino et al. (2020) affirmed the therapeutic advantage of anticoagulant therapy for COVID-19 patients with coagulopathy in the setting of mechanical ventilation [27].

The antithrombotic therapy probably assists the defensive mechanisms to counter the prothrombotic state of COVID-19 patients. The success rate of antithrombotic therapy/prophylaxis varies with the severity of COVID-19 infection and the affected patients' clinical history. Our research study collated diverse opinions and ideas to inform the antithrombotic management of COVID-19 cases. Furthermore, our findings substantiated the need for future studies to classify the endothelial thrombo-inflammatory condition progression in COVID-19 patients worsening symptomatology [27]. Prospective research studies with larger sample sizes need to investigate antiplatelet drugs' therapeutic benefits and antithrombotic treatment algorithms for COVID-19 patients [28].

Clinical studies reveal the attribution of antiviral activity of heparin and other antithrombotic agents in preventing thromboembolic events. Antithrombotic therapy further mitigates the episodes of microvascular thrombosis and disseminated intravascular coagulation. Future studies should accordingly investigate individualized antithrombotic algorithms to reduce the risk of thromboembolism and related cardiovascular complications in COVID-19 patients. COVID-19 patients with a clinical history of cardiovascular disorder experience a high risk for thromboembolism. Preventive measures should focus on improving the recovery and treatment outcomes of these patients in the ICU [29]. The COVID-19 infected diabetic, obese, and hypertensive patients further experience a high risk for cardiovascular disease and thromboembolism. Therapeutic management of these patients relies on prospective studies and systematic personalization of the currently approved treatment protocols.

In contrast to other viral diseases such as influenza, infection of extreme acute respiratory syndrome coronavirus-2 has been associated with a high mortality rate. The other forms of viral infections are primarily caused by other secondary severe diseases, such as acute respiratory distress syndrome (ARDS) [30]. By taking ARDS into account, it is found that ARDS is characterized by intense inflammation and excessive coagulation flow action, increasing the susceptibility to the occurrence of venous thromboembolism. In the study conducted by Paar (2020), it was found that the "Human Peripheral Mononuclear Blood Cells" (PBMCs) can be treated with heparinized plasma, autologous serum, and altered dosages of fibrin to investigate the relation between the impact and inflammation of the coagulation factors on their issue. Subsequently, the attentiveness of chemokines and proinflammatory cytokines with regard to PBMCs may also be assessed by immunosorbent interlinked enzyme assays. Analysis of the study showed that autologous serum could be used to substantially increase chemokine and cytokine secretion immediately after 24 hours of incubation [31]. Besides, in dose reliance, fibrin's addition enhanced the secretion of chemokine and cytokine by PBMCs. Subsequently, the idea that anticoagulation can be used as a promising method for treating COVID-19 has been illustrated in previous research studies, thus reducing the shared risk of thrombotic impairments and cytokine storms [31].

Table 2. GRADE Evidence Profile for the 8 Studies Included in the Systematic Review

Study	Limitation	Inconsistency	Indirectness	Imprecision	Quality of evidence
Lodigiani (2020)	Limited to hospital and did not include non-academic institutes	No serious inconsistency	No serious indirectness	No serious imprecision	⊕⊕⊕ Moderate
Klok et al. (2020)	Results were not suited for the administered dosage of ardeparin. The effect of the alterations in the local protocols is also not studied for thromboprophylaxis indication.	No serious inconsistency	No serious indirectness	No serious imprecision	⊕⊕⊕ Moderate
Middeldorp (2020)	small sample size, and during the data collection, 8% of the patients were still hospitalized.	No serious inconsistency	No serious indirectness	No serious imprecision	⊕⊕⊕ Moderate
Zerwes et al. (2020)	No serious limitation.	No serious inconsistency	No serious indirectness	No serious imprecision	⊕⊕⊕⊕ High
Maldonado et al. (2020)	The sequential process is used for study selection instead of the independent dual review procedure, quality assessment, and data abstraction for making a compacted timeline.	missing qualified studies	No serious indirectness	No serious imprecision	⊕⊕ Poor
Vivas et al. (2020)	Patients included in the study were only from China.	missing qualified studies	No serious indirectness	No serious imprecision	⊕⊕ Poor
Godino et al. (2020) c	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	⊕⊕⊕⊕ High
Paar (2020)	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	⊕⊕⊕⊕ High

While COVID-19 patients may assist in the anticoagulant-based treatment process, there is still no adequate evidence that this treatment will also reduce inflammatory reactions due to COVID-19 infection [32]. Therefore, more research is required to test oral anticoagulant therapy to minimize the chances of progressive bleeding in COVID-19 patients.

4. Discussion

The COVID-19 disease was caused by the *severe acute respiratory syndrome coronavirus-2* and eventually contributed to the worldwide pandemic. No preoper treatment has been established and research for the COVID-19 vaccine is ngoing. Age, HTN and obesity have been identified as risk factors for severe infection. Organ failure, especially in the lungs, pneumonia and death may result from infection [33]. This research is a systematic review that includes these papers focused on evaluating the chances of thromboembolism in patients with COVID-19 and antithrombotic therapy on the removal of the chances of thromboembolism in patients with COVID-19. Studies included in this analysis have shown that, compared to non-COVID-19 patients, the chances of thromboembolism in COVID-19 patients are remarkably high, especially if these patients are admitted to the ICU [34]. Inflammation was mainly responsible for the elevated risks of thromboembolism. Consequently, COVID-19 severity increased the risk of thromboembolism.

This must be handled as a top priority to tackle such an issue, and antithrombotic therapy must minimize inflammation. Studies have also shown insufficient evidence to determine antithrombotic therapy's efficacy in treating COVID-19 patients with thromboembolism. Some studies have shown evidence that it would be effective in antithrombotic therapy [35]. This must be handled as a top priority to tackle such an issue, and antithrombotic therapy must minimize inflammation. Studies have shown insufficient evidence to determine antithrombotic therapy's efficacy in treating COVID-19 patients with thromboembolism [36]. Some studies have shown that there is evidence that it would be effective in antithrombotic therapy. In COVID-19 patients admitted to a hospital, thromboembolism risks are higher than in patients who are self-isolated at home. Due to the use of drips and heavy medications, hospitalized patients are more vulnerable to inflammation, so their condition is more serious [37]. The information provided in this analysis is focused solely on previous study results. This analysis will help to attract the researchers' attention to working on the issues found. Since the research is time-limited and time-relevant, as these problems are tremendously highlighted in current studies, there are high chances that new knowledge will be available soon.

This study's limitations include a small number of tests due to limited data on the selected subject, but this analysis has contributed to highlighting the main blame facing patients with COVID-19 and the need to remove it to increase the chances of survival for patients with COVID-19. The best effort was made to select the most relevant studies based on the inclusion and exclusion criteria. The standard table is intended to illustrate the critical points of the research explained by the study standard. Furthermore, as there are few studies available on this topic, further studies will be performed and released at the end of this study's search date.

Once previous studies have been reviewed, it is recommended that all COVID-19 patients, whether in the ward or the ICU, undergo risk stratification by considering all of them at high risk of developing a thrombosis disease. It is, therefore, necessary that all of them receive prophylaxis [38]. To prevent thrombosis in COVID-19 patients by various VTE prophylaxis interventions, proper clinical guidance must be provided to health care professionals. It is necessary to internationally recognize all the doses given to them, i.e., WHO interim guidance

[39]. It is also recommended that extended VTE prophylaxis should be considered after the discharge of the patients. To determine how effective antithrombotic therapy is, it is proposed that different types of COVID-19 patients with various degrees of severity should undergo clinical investigations [40].

5. Conclusion

For a thorough evaluation of thromboembolism and COVID-19 patients' chances and the effect of antithrombotic therapy on reducing the chances of thromboembolism in COVID-19 patients, a total of 8 studies were chosen. The risks of thromboembolism are high in COVID-19 patients admitted to the ICU or have a history of cardiovascular disease. Therefore, the incidence of thromboembolism has been shown to rise with the severity of the illness. There is, however, no proof available that thromboembolism would occur in any COVID-19 patient. Also, only a limited amount of evidence suggests that COVID-19 patients with thromboembolism can be successfully treated with antithrombotic therapy. Therefore, it has been recommended that more research should be carried out to determine an effective procedure for treating such patients, and adequate recommendations should be given to health care professionals to avoid complications such as inflammation and bleeding that will make the condition worse.

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