

Venous Thromboembolism in Covid-19 ICU Patients: A Narrative Review

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Authors' contributions

This work was carried out in collaboration among all authors. Author NEAA designed the study, managed the literature search, wrote the protocol, wrote the Introduction and performed part of the statistical analysis. Author AHAH wrote the discussion. Author HAOF wrote the methodology of the study. Author RKAG wrote the abstract and conclusion, performed grammar, spelling, punctuation and language editing. Author SGE performed the statistical analysis, wrote the result and performed the final revision of the study. All authors read and approved the final manuscript

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ABSTRACT

Aim: The purpose of this narrative review is to provide a summarized coverage of evidence-based researches reporting VTE in COVID-19 patients in the ICU. It aims to serve as a contribution to healthcare professionals in designing a comprehensive strategy in managing COVID-19 patients.

Background: SARS-CoV-2 (COVID-19) was declared a global pandemic by the WHO in March 2020, as cases continued to surge since January after its sudden outbreak in China. It commonly presents with respiratory symptoms along with a fever, however, comorbidities requiring ICU admission are documented. Several anecdotal reports of VTE amongst ICU patients have surfaced since the outbreak. There is a noticeably increased risk of what appears to be a COVID-19 induced hypercoagulable state despite prophylactic and therapeutic anticoagulation treatment, consequently emphasizing the importance of systemic screening of VTE amongst ICU patients. This calls for a high level of clinical suspicion and a low diagnostic threshold. Understanding the exact impact of VTE on COVID-19 ICU patients improves our ability to reach a timely diagnosis and initiating optimal management to potentially improve survival.

Methods: Google Scholar and Pub Med were used as sources for searching and obtaining the data, as they were critically appraised for the best evidence. The information collected was overviewed and summarized in this narrative review.

Results: After searching in the previously mentioned database, 21 articles were found, assessed, and then filtered to 11 articles in correlation with the review context. 8 full-text articles, 2 case reports, and 1 clinical investigation research were obtained overall. Even with the evidenced data, efficacy of prophylactic anticoagulants remains uncertain but is nonetheless, a practical preventive approach.

Conclusion: COVID-19 infection induces a hypercoagulable state that results in VTE amongst ICU patients. Early prophylactic and therapeutic therapy is deemed essential in the early phases. Further studies are required to develop a better understanding and hence more appropriate management.

Keywords: COVID-19; thromboembolism; ICU; patients; anticoagulants.

1. INTRODUCTION

An emergence of severe acute respiratory syndrome (CoV-SARS-2) originated from Wuhan, China in late December 2019 and was declared a worldwide pandemic by the WHO in 11th of March [1]. It has contributed to a relatively high mortality rate, at time of writing, estimated with at least 380,000 deaths and 6.4 million cases reported worldwide, according to John Hopkins University [2]. Unfortunately, there is no known cure or vaccine up to date and therefore only supportive treatment is being provided, whereas research efforts aimed at covering different aspects of COVID-19 are significantly expedited.

CoV-SARS-2, given the name COVID-19, is derived from the sub family Coronavirinae in the family Coronaviridae. It is a single-stranded +positive-sense ribonucleic acid (+ssRNA) virus, which formed of 5-cap structure and 3-poly-A tail, as well as structural and non-structural proteins. In reviewing protein structure of the virus, the non-structural proteins are mainly responsible for the replication process, while the structural ones

have different functions as follows: S protein (spike formation and host cell attachment), M protein (shape, membrane curvature and nucleocapsid binding), E protein (viral pathogenesis), N protein (viral replication) [3]. It causes respiratory symptoms as well as high-grade fever and headaches but may become complicated with other disorders and comorbidities that should be considered as predictive factors requiring intensive care unit (ICU) admission. An alarming issue was growing in Italy after they reported that 5% of the cases needed ICU, in addition to frequent reporting of pulmonary embolism (PE) and thrombosis related COVID-19 mortality [4]. Coagulopathy disorders soon became a burning issue in COVID-19 ICU patients owing to the fact that despite administration of prophylactic anticoagulation, an incidence of venous thromboembolism (VTE) was significantly rising as a secondary outcome to PE and DVT, thus requiring a higher anticoagulation target [4,5,6,8]. Moreover, high levels of D-dimer reflect a poor prognosis in COVID-19 ICU patients. Somehow, there is a relative risk of VTE in COVID-19 non-ICU patients as well [8].

For a better understanding of VTE occurrence, PE and DVT were the particular events of concern in COVID-19 ICU patients [9]. How COVID-19 affects homeostasis is still questionable, but it is apparent it brings about a persistent hyper-coagulopathy state that may lead to disseminated intravascular coagulation (DIC). Diagnosing VTE in COVID-19 ICU patients according to their coagulation profile was not found to be solid enough [10]. Reporting of an increasing risk of arterial thrombosis in COVID-19 ICU patients is an alarming conjecture [9].

Talking about the high rate of mortality rate reports related to VTE in COVID-19 ICU patients has been challenging in the United States of America, with 70% of it being related to African Americans. Moreover, all documented death cases had at least 1 co-morbidity. Whether it was hypertension, diabetes mellitus or immune suppressed patients, they were all classified as high-risk patients [9].

To correlate with the suggestive coagulation complication related to COVID-19 ICU patients with an evidence basis, an advanced level of autopsy in confirmed or suspected post-mortem cases was applied in the USA. Despite facing challenges, the Center of Disease Control (CDC) and Occupational Safety and Health Administration (OSHA) has finally approved post-mortem autopsy under certain guidelines and strict safety measures [10].

Clinical suspicion of VTE in COVID-19 ICU patients has become crystal clear following many cases being reported by relying on D-dimer levels and radiological imaging, including chest CT scan, as strong pillars. Subsequently, there was a huge paradox in 2 case reports questioning the diagnosis of PE by CT as one study showed that CT pulmonary angiography (CTPA) is better than non-contrast chest CT [11], while the other revealed that CTPA is unable to catch PE in the early stages [12]. Furthermore, performing a Complete Doppler Ultrasound (CDU) took place as a standard work-up in COVID-19 ICU patients [13]. Using single-photon emission computed tomography (SPECT) CT perfusion could help in identification of perfusion abnormalities in early stages [14].

The objective of this study is to summarize and collate available evidence based researches of VTE in COVID-19 ICU patients as a narrative review, in order to help healthcare professionals

design a well-structured strategy in managing COVID-19 ICU patients.

2. METHODOLOGY

On the 1st of June 2020, the review title was established, scope and aim were determined. Then, the research data bases (Pub Med and Google Scholar) were screened for "Venous Thromboembolism among COVID-19 ICU Patients". Additionally, the selection of published research literature was performed by looking for the following key words: COVID-19, ICU, Venous thromboembolism, and anticoagulants. About the inclusion criteria: this review involved any published (full text) articles that were written in English and all clinical study designs, including case series, that were published within a timeframe between April to May 2020. In addition, any articles were deployed before April 2020, and those with no significance or duplicated information were excluded. Eventually, reference lists of reviewed articles were searched to find more relevant articles. Assessments of the selected endorsed papers were undertaken precisely by all authors equally. On light of that, the most pertinent information was summarized into different sections by each author independently, as well as revising and formatting the final version of the text. Two reviewers cooperated to finalize the screening of the titles and abstracts. All authors independently completed full-text screening for identified articles and participated in the steps of manuscript preparation, writing and final revision. The PICO method was used to initialize the review question in a standardized form (Table 1).

Concerning the review question, it was formulated using the PICO method, as shown below:

P: COVID-19 confirmed patients.

I: Venous thromboembolism.

C: ICU COVID-19 patients with no thrombosis.

O: Outcome of patients with venous thromboembolism.

Lastly, presentation of the data was designed in a narrative review form.

3. RESULTS

After searching in the previously mentioned data base, 21 articles were found and assessed in

Table 1. Summary of retrieved evidence of COVID-19 patients admitted to the ICU in 2020

Reference	Lodigiani, et al, 2020 [3]	Artifoni, et al 2020 [5]	Pavoni, et al, 2020. [7]	Helms, et al,2020 [8]	LLITJOS, et al, 2020 [13]	Klok et al, 2020 [15]	Cui et al, 2020.[16]	Maatman, et al , 2020[17]	Rodríguez, et al , 2020 [18]	Middeldorp, et al,2020 [19]
Study	Retrospective	Retrospective	Single-center, retrospective, observational	A multicenter prospective	Retrospective	Observational	Retrospective	Observational	Prospective	Single-center cohort study
No. of patients admitted to ICU	61	13	11.6 + or – 4	150	26	184	81	109	156	38%
Population Studied	Median age 61; 80% male	Median age 64; 60.6% male	Mean age 61; 60 % male	Median age 68; 63% male	Median age 68; 77 % male	Mean age 64; 76% male	Mean age 59..9; 46% male	Median age 61; 57 % male	Mean age 68.1; 65.4 % male	Mean age 61; 66% males
Anticoagulant or Thrombo-prophylaxis	Low-molecular weight Heparin	Enoxaparin	Low molecular weight heparin	Anticoagulants	- Prophylactic Anticoagulation - Therapeutic Anticoagulation	Nadroparin	None	Subcutaneous heparin enoxaparin	Enoxaparin or bempiparin	Nadroparin
Comorbidity /Cardiovascular risk factors	-History of thrombosis - Hypertension - Diabetes - Dyslipidemia -Renal dysfunction - Smoking -Cancer	-Hypertension -Diabetes -Cancer	- Hypertension - Diabetes -Cardiovascular disease - COPD	-Cardiovascular diseases -Cerebrovascular diseases -Chronic renal diseases -Chronic liver diseases– mmunosuppre-ssive diseases -Respiratory diseases - Diabetes	-Previous VTE -Hypertension - Smoking	- Active cancer - Renal replacement therapy	- Hypertension - Diabetes - Smoking - Coronary heart Disease	-Hyperten-sion - Diabetes- Hyperlipide-mia - Chronic kidney disease - Smoking -Congestive heart failure	-Thrombo-philia - Cancer	- Cancer
VTE (%)	6.6%	22.5 %	20%	11.7%	69%	27%	25%	28%	19.2%	47%
Common sites ofThrombosis	PE (±DVT)	- DVT 21.1% - PE 10%	-15% DVT -5% PE	11.7 % PE	DVT	PE		DVT	- 14.7% proximal DVT - 4.5% bilateral distal DVT	- 15% PE - 32% DVT
Mortality	-	1	10 % and 12.5% respectively	8.7 %	12%	13%	10%	26%	Not mentioned	19%

Coagulation Markers	Elevated D-dimer	Elevated D-dimer	- Elevated D-dimer at T0, lowered at T10 and aPTT normal at T0, decreased at T10. Fibrinogen greatly increased at T0 decreased at T10	Elevated D-dimer	Prolonged APTT & PT	-Prolonged APTT -Elevated D-dimer	-Elevated D-dimer -Higher fibrinogen	- Elevated D-dimer and fibrinogen. - Normal apt, pt, platelets and antithrombin	Elevated D-dimer and high fibrinogen
					1.5 µg/mL was used as the D-dimer cut-off value to predicting VTE, the sensitivity was 85.0%, the specificity was 88.5%, and the negative predictive value (NPV) was 94.7%.		Patients diagnosed with thrombotic complications were at higher risk of all-cause death, for a HR of 5.4 (95%CI 2.4–12).		

correlation with the review context, which were filtered to be 11; 8 full text articles, 2 case reports, and 1 clinical investigation research. 10 were excluded from our search due to duplicated information in addition to not including ICU patients in their study.

Results of all searched papers are presented in the following Table 1.

4. DISCUSSION

Critically ill patients diagnosed with COVID-19 are at a high risk of VTE due to the combined specific risk factors of the virus together with the general ICU risk factors of VTE, such as sedation, immobilization, vasopressors or central venous catheter. This Review is focused on the Incidence and risk factors of VTE including DVT and PE.

4.1 Incidence of VTE in COVID-19 Patients Admitted to ICU

The overall incidence of VENOUS THROMBOEMBOLISM among COVID-19 patients admitted to ICU varied between 6.6% and 69%, with mean age of 59 – 68 years and a mortality rate between 10% and 26%. Furthermore in a subgroup analysis, PE is reported in six out of 10 COVID-19 studies with incidence of 5 – 15% .3 – 30% risk of pulmonary embolism after different surgical procedures [20], while DVT it is reported in seven out of ten studies as 15 – 30% of the reported VTE cases.

PE is one of the most frequently underdiagnosed illnesses detected during autopsies. Autopsy studies done in other diseases detected PE in 7 to 27 % of critically ill patients; of these, only one-third were clinically suspected [21,22]. This is more than the 18.7% reported clinically in other studies [23]. Regarding the autopsy of COVID-19 patients, almost one-third of the deaths were attributed to massive PE as reported in the study done by Charuhas Deshpande [24].

DVT is considered a major cause of morbidity and mortality worldwide. DVT was reported in 33% of general ICU patients [23]. Moreover, it was found as a possible cause of death in one-fourth of the COVID-19 cases in the autopsy study done by Charuhas Deshpande [24]. Furthermore, DVT was repeatedly reported in the previous SARS-COV infection, as recorded in the retrospective analysis done in 2003 by Raymond

et al. where it was noticed in 2.5% of the patients [25].

4.2 Risk of VTE in COVID-19 Patients Admitted to the ICU

Many risk factors are mentioned in the literature that increase the likelihood of developing VTE in general patients such as cancer, obesity, oral contraceptives and many others [26]. In this review, hypertension and diabetes mellitus were the most commonly reported risk factors in these studies, followed by cancer and renal impairment, with most of the cases being reported in old aged males. Interestingly, these clinical pictures were also common in previous MERS patients who required ICU admission [16]. Therefore, regular measurements of blood pressure and blood glucose for COVID-19 patients in the ICU would be a cost effective method in preventing VTE. In other patient groups, the most prominent risk factors for developing VTE in critically ill patients were obesity, previous trauma, and surgery [27].

4.3 Hypercoagulability Testing in COVID-19 Patients Admitted to ICU

Many studies were done to identify a rapid and sensitive test for VTE. D-dimer has been the focus of many of these studies as it is sensitive for VTE with a high negative predictive value [28]. It is considered as a good predictor for VTE in COVID-19 patients [16]. Furthermore, it has been suggested as a severity indicator in many previous studies [29,30]. In this work, elevated D-dimer was used as a marker in 9 out of 10 papers. Moreover, coagulation profile was markedly elevated in all the papers; hence the use of these tests along with D-dimer will help in confirming the diagnosis. These parameters were markedly high in the previous SARS-CoV-1 pandemic as noticed in the study done by Lee et al., who described a cohort of 156 SARS-CoV-1 infected patients with prolonged activated partial-thromboplastin time (42.8%) and elevated D-dimer [31].

There are several limitations in our review as we did not include all available papers in our work. Additionally, statistical analysis was not done for the included papers.

In this review, ten papers were reviewed regarding ICU COVID-19 patients. Here we conclude that in any critical COVID-19 patient

admitted to the ICU with the reported risk factors, all prevention methods should be implemented to prevent the occurrence of VTE.

5. CONCLUSION

Findings undoubtedly confirm alarming reports of VTE in COVID-19 patients in the ICU. D-dimer levels are a valuable index for identifying high-risk groups in addition to serving as a monitoring tool for therapy. Thorough evaluation to promptly detect and manage the coagulopathy early is crucial.

Based on the available evidence, we recommend prophylactic anticoagulation therapy in severe COVID-19 patients. Moreover, conducting more researches on the topic as well as post mortem autopsies will be beneficial to establishing an effective approach for prevention and management.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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This work is dedicated to our families who were in the frontline in our success, to our friends who always provide support and lastly, to all doctors who gave their lives for saving patients' lives during COVID-19 pandemic, may your souls rest in peace.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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