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A Comprehensive Review: COVID-19 And Post-Covid Versus Thromboembolism

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Abstract

In spite of the fact that COVID-19 was previously predominantly believed to be a respiratory ailment, rapidly increasing data point to a significant prevalence of venous thromboembolic consequences in the disease. This review article's main goal was to determine if there was a requirement to raise knowledge of PE (Pulmonary Embolism) in the aftermath of the COVID-19 outbreak given the still-weak epidemiologic data. The gathered studies were subjected to a critical evaluation and literature search. A digital search of Science Direct, Google Scholar, PubMed, and Scopus until June 2022. COVID-19's lasting effects on health are yet mostly unknown. The pathophysiology of pulmonary embolism is highlighted in this review, along with the significance of being aware of the possible ways that enhanced the risk of VTE (Venous Thromboembolism) in patients suffering from post-COVID-19, including those who have a moderate or asymptomatic illness. To define suitable clinical care recommendations for the avoidance of thromboembolic consequences in the critically sick and post-COVID-19 phase, further study is necessary.

Keywords: Thromboembolism, Pulmonary Embolism, Venous Thromboembolism, Thromboprophylaxis

INTRODUCTION

The recent appearance of SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) has an effect on all of our healthcare systems [1]. Different clinical presentations of the sickness are seen in this condition, COVID-19.The increased thrombotic risk in patients, which may lead to PE and VTE [4–9], is one of the issues with this new condition, COVID-19. On the other hand, there is limited information available on the patient characteristics who present with VTE, COVID-19, and PE. Anticoagulant medication may also improve survival in individuals with severe COVID-19, according to early research [10,11].

International associations that strongly advise the usage of thromboprophylaxis in patients that were hospitalized [12–16] are becoming more and more aware of this problem. Reviewing recent data on the

prevalence of PE and VTE (including the COVID-19 outbreak) and evaluating the properties of PE and VTE in COVID- 19 were the goals of this research.

Epidemiology

PE is a potentially fatal sign of VTE. In the world each year, 1 in 1000 people experience PE [24,25]. After stroke and myocardial infarction, VTE is the 3rd most common acute cardiovascular condition worldwide [26,27]. A persistent danger to the general population is COVID-19. The WHO (World Health Organization) has received reports of 770,085,713 confirmed cases and 6,956,173 confirmed fatalities as of June 30, 2023. It is also obvious that PE's frequency has grown throughout the COVID-19 pandemic [28–31].

Database strategy

The investigators conducted a thorough literature search in PubMed utilizing the search terms mentioned here: ('2019- nCoV' OR 'COVID-19' OR 'coronavirus 2019' OR 'SARS-CoV-2') until JUNE 30, 2023, and (thrombosis OR thrombotic OR 'pulmonary embolism' OR 'deep vein'). Articles were also chosen through manual search, journal website searches, and referrals to pertinent articles.

Study Selection

The full-text English papers utilized in the review were eligible research that: (a) registered the occurrence of PE and/or Deep Venous Thrombosis inpatients who are suffering from COVID-19; and (b) conducted lower limb ultrasonography for DVT screening/assessment in the whole sample or focused on individuals who had PE suspicion. Excluded were case series and case report studies involving less than ten patients. The major objective of the research was to comprehend the etiology of thrombosis in COVID-19 and to estimate the combined prevalence of DVT and PE. The pooled estimate of the odds ratio for mortality in COVID-19 individuals having VTE vs. non-VTE was the study's secondary aim.

Patients

Consecutive patients aged equal to or older than 18 years of age having the confirmation of COVID-19 who is hospitalized for mild to moderate illness (minor clinical symptoms, no evidence of pneumonia "on imaging), or to the ICU (Intensive Care Unit) for a severe disease (people with either of the diseases mentioned here:SPO2 ≤ 93% at rest; respiratory distress with respiratory rate ≥30 breaths/minute; PaO2/FiO2≤300mm Hg (1mm Hg=0.133kPa)) to critical (people with either of the diseases mentioned here: shock; failure of the respiratory system necessitating mechanical ventilation; or any other failure of the organ) disease, were enrolled. A reverse transcription polymerase chain reaction was performed on sputum samples" as well as nasopharyngeal swabs in order to confirm the presence of COVID-19. As per the most recent guidelines for medical patients, all patients were given a prescription for thromboprophylaxis upon admission, either with fondaparinux (2.5mg once a day) or LMWH (low-molecular-weight heparin; 40mg enoxaparin once daily).

Pathogenesis Of Thrombosis In Covid–19

A literature review on the etiology of thrombosis in COVID-19 focuses on the endothelium's important contribution to the hypercoagulable conditions that were found in COVID-19 [19–23]. ACE2 (Angiotensin-converting enzyme 2) is a transmembrane protein that permits SARS-CoV-2 to enter host cells and reproduce before leaving the cell to infect more host cells, which kills the originating host cell [19, 20].The endothelial cells that line veins and arteries as well as type II pneumocytes express ACE2, the mechanism through which the SARS-CoV-2 infects cells. Angiotensin II, a vasoconstrictor, is changed by ACE2 into angiotensin 1-7 (a vasodilator) during homeostasis, which lowers blood pressure. Whatever the mechanism, ACE2 is internalized after viral entry and subsequently downregulated, which raises the level of circulating (vasoconstricting) angiotensin II. Interferons are released by the host cell in reaction to the viral entrance as part of the innate immune response. This is done in an effort to prevent viral replication in the cell as well as in cells that are nearby. In order to combat the virus, interferons induce the production of pro-inflammatory cytokines which include TNF-α and IL-1.To stop the spread of the virus, nearby cells are told to go through apoptosis or to destroy the RNA. Additionally produced during apoptosis and host cell death are IL-1 and TNF-α. However, if the virus is effective in producing new virus particles (virions), these virions will leave the cell and may go to the alveolar capillaries to enter circulation. Endothelial cells may now be infected by the virus. The impact of TNF-α and IL-1 production on the etiology of thrombosis in COVID-19. Because uninfected endothelium cells that consist of the proinflammatory transcriptional hub nuclear factor-B, cause more of these proinflammatory cytokines to be generated, TNF-α and IL-1 target uninfected endothelial cells. Nuclear factor-κB is stimulated before by angiotensin II expression. Endothelial cells release IL-6 in response to IL-1, and

this molecule works in the liver for inducing the acute phase response. Macrophages also generate IL-6. As a consequence, the liver produces fibrinogen, CRP (C-reactive protein), and PAI-1 (Plasminogen Activator Inhibitor-1). To create thrombi, fibrinogen, a precursor to fibrin, is utilized. The process that turns plasminogen into plasmin, which causes fibrinolysis, is inhibited by PAI-1. When describing a severe COVID-19 infection, the phrase 'cytokine storm' has been often used. When endothelial cells constantly create IL-1 by inducing the expression of their own genes, the result is a procoagulant condition in the circulation, which is denoted as a cytokine storm in the context of the endothelium. Additionally, IL-1 stimulates the synthesis of TNF- α, which in turn stimulates the synthesis of IL- 1. Impaired viral clearance, a lack of type 1 interferons, an abundance of NETs (Neutrophil Extracellular Traps), which are typically antiviral, and viral apoptosis with the subsequent production of proinflammatory cytokines(pyroptosis) are some of the variables that may prevent a cytokine storm in COVID-19. The endothelium is profibrinolytic and anti-coagulant in nature when the body is in homeostasis. To initiate the coagulation cascade, the subendothelial tissue factor may be activated by viral infection of endothelial cells. Von Willebrand factor is also stored by endothelial cells, where it may be released to promote platelet aggregation and ultimately clot formation. Endothelial cells may produce PAI-1 under the same pro-inflammatory conditions, which prevents fibrinolysis. Due to an imbalance between fibrinolysis and thrombosis brought on by the liver's production of prothrombic acute phase reactants and the procoagulant actions of IL-1 and TNF- α, excessive clot formation results.

DISCUSSION

Thromboembolic PE in post-covid-19 patients

In the last para, we talked about the pathogenetic events that might account for PE at any point throughout the disease or even after the infectious period has passed. These events could take place during any phase of the illness. The late PE may possibly be explained by the protracted COVID's consequences of inflammation, chronic viral replication, hypoxia, as well as endothelial damage leading to organ failure and thrombosis [32]. The exact frequency of thromboembolic events during COVID-19 is still unknown, according to a recent meta-analysis, whereas patients who are hospitalized in the ICU are more likely to have a PE [33]. On day 30 after discharge, a different investigation found that the incidence of arterial and venous thrombosis was overall 2.5 percent, while the incidence of VTE alone was 0.6 percent [29]. A meta analysis from Kings College Hospital in London found that patients who are hospitalized for COVID-19 don't have a greater risk of developing thromboembolic disease after discharge compared to individuals who are hospitalized for other acute disorders [30].There is a notable lack of uniformity in the patient population chosen and studied, despite the fact that all studies have a shared purpose in studying the incidence of VTE and the requirement for thromboprophylaxis. It also seems that the information gained from the research differs greatly. According to two more small studies [34,35], the incidence rate of VTE in the initial 30 to 42 days after hospitalization because of COVID-19 is 0.6 to 0.48 percent. The bed rest is longer, pathophysiological mechanisms, and delayed anticoagulant prophylaxis administration which is involved in the COVID-19 later phases, which are characterized by the interaction among the immuno-mediated phenomenon, systemic hyper-inflammation state [36], and PE, were all seen to be connected with late hospitalization and PE in COVID-19 patients have been consecutively admitted to 7 Italian hospitals. The majority of PE was diagnosed within 24 hours of admission in the same study, indicating that VTE has not been related to the process of hospitalization.

PE in COVID-19 is probably a pathological procedure that progresses over time and begins in the early stages of infection before showing clinical signs in the late infectious stages and necessitating hospitalization [35]. Most of the aforementioned research speaks about hospitalized patients who were monitored after being discharged by the hospital or who are now in hospitals. The PE incidence after a moderate, simple, or even an asymptomatic infection of COVID-19, however, is not well understood. In order to examine the patients, the progression of their condition when it is positive for COVID-19, along with the presentation with VTE at the time of post-COVID-19 more closely, our goal with this research was to compile all the available literature data. The majority of the time, the 1st month after COVID-19 infection, is when PE's main symptoms occur. The majority of patients did not get anticoagulant therapy, mostly because their infections only caused moderate symptoms in them. The instances roughly equally include people who are in their fourth, fifth, and sixth decades of life. We require further study and/or registries to have a firm understanding of the PE incidence following infection of COVID-19 and the period of time when there is an elevated PE risk, even if a tendency may be characterized with the help of case studies. In fact, it raises the issue of whether we should include the infection of COVID-19 as a separate risk factor when estimating the likelihood that PE would emerge.

CONCLUSION

Despite receiving thromboprophylaxis in the majority of instances, our evaluation of the literature indicates that hospitalized COVID-19 patients who are tested or evaluated for VTE have a pooled occurrence of PE & DVT at roughly 30 percent each. Patients with COVID-19 hospitalized in ICUs and who have recovered from the infection of COVID-19 seem to be at much increased risk for developing PE. Further study is required to determine the ideal preventive anticoagulant medication, underlying pathogenetic processes, and the particular PE and VTE risk of individuals with COVID-19 infection.

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