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Incidence And Risk Factors Of Deep Venous Thrombosis In Lower Limbs Among COVID-19 Patients: A Systematic Review

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Abstract
The emergence of COVID-19 has been associated with a heightened risk of thrombotic events, notably deep venous thrombosis (DVT) in the lower limbs. This systematic review aims to elucidate the incidence and identify risk factors of lower limb DVT among COVID-19 patients. Comprehensive searches were conducted across PubMed, Scopus, Embase, and Web of Science databases for studies published between January 2020 and April 2025. Inclusion criteria encompassed studies reporting on the incidence and risk factors of lower limb DVT in adult COVID-19 patients. Data extraction and quality assessment were performed independently by two reviewers, adhering to PRISMA guidelines. The pooled analysis revealed a significant incidence of lower limb DVT among hospitalized COVID-19 patients, with higher rates observed in those admitted to intensive care units (ICUs). Identified risk factors included advanced age, male gender, obesity, prolonged immobilization, elevated D-dimer levels, and pre-existing comorbidities such as hypertension and diabetes mellitus. The hypercoagulable state induced by SARS-CoV-2 infection, characterized by endothelial dysfunction and inflammatory responses, underpins the pathogenesis of DVT in these patients. Prophylactic anticoagulation has been shown to mitigate the risk; however, optimal dosing strategies remain under investigation. The findings underscore the necessity for vigilant thrombotic risk assessment and management in COVID-19 patients, particularly those with identified risk factors. Further research is warranted to refine prophylactic protocols and improve patient outcomes.

Keywords: *COVID-19; Deep Venous Thrombosis; Lower Limbs; Incidence; Risk Factors; Systematic Review; Hypercoagulability; Anticoagulation.*

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I. Introduction

The emergence of the coronavirus disease 2019 (COVID-19) pandemic has unveiled a myriad of complications beyond respiratory manifestations, notably an increased incidence of thrombotic events such as deep vein thrombosis (DVT) in the lower limbs. Early observations from intensive care units indicated a heightened prevalence of thrombotic complications in COVID-19 patients, even among those receiving standard prophylactic anticoagulation (Klok et al., 2020).

DVT is a significant contributor to global morbidity and mortality, with pre-pandemic incidence rates estimated at 0.75–2.69 per 1,000 adults annually, escalating with age (Raskob et al., 2014). The pathogenesis of DVT traditionally involves Virchow's triad: venous stasis, endothelial injury, and hypercoagulability. In the context of COVID-19, these factors are exacerbated by the virus's systemic effects.

SARS-CoV-2 infection induces a distinct coagulopathy characterized by elevated D-dimer levels, fibrinogen consumption, and microvascular thrombosis, collectively termed COVID-19-associated coagulopathy (CAC) (Connors & Levy, 2020). This hypercoagulable state is driven by a complex interplay of inflammatory responses, including cytokine storms and complement activation, leading to endothelial dysfunction and subsequent thrombus formation.

Histopathological analyses have corroborated these findings, revealing extensive endothelialitis, platelet-fibrin microthrombi, and intussusceptive angiogenesis in the pulmonary vasculature of COVID-19 patients, surpassing the vascular alterations observed in influenza-induced acute respiratory distress syndrome (ARDS) (Ackermann et al., 2020). These vascular changes underscore the systemic nature of COVID-19 and its propensity to precipitate thrombotic events.

Epidemiological data indicate a substantial increase in DVT incidence among hospitalized COVID-19 patients. Klok et al. (2020) reported a 31% cumulative incidence of thrombotic complications in ICU patients, while Middeldorp et al. (2020) observed VTE rates nearing 26% at 21 days in similar settings, contrasting with a 9% incidence in general ward patients. These findings highlight the severity-dependent risk of thrombosis in COVID-19.

Biomarkers such as elevated D-dimer levels have been identified as independent predictors of thrombotic events and mortality in COVID-19 patients (Tang et al., 2020). These laboratory findings, combined with clinical risk factors like advanced age, male sex, obesity, and comorbidities, facilitate risk stratification and guide prophylactic strategies (Bilaloglu et al., 2020).

The mechanical aspects of critical illness, including prolonged immobilization and invasive ventilation, further contribute to venous stasis and thrombogenesis. Helms et al. (2020) reported life-threatening thrombotic complications in 42% of mechanically ventilated COVID-19 patients, emphasizing the need for vigilant thromboprophylaxis in this population.

Despite prophylactic anticoagulation, the high incidence of thrombotic events has prompted investigations into intensified anticoagulation regimens. Meta-analyses suggest that intermediate or therapeutic-dose anticoagulation may reduce thrombotic endpoints but at the cost of increased bleeding risk, necessitating individualized risk-based prophylaxis (Ortega-Paz et al., 2024; Spyropoulos et al., 2023).

Diagnostic challenges during pandemic surges, including limited access to Doppler ultrasound due to infection control measures, have led to variable DVT incidence estimates ranging from 6% to 46% across studies, reflecting methodological heterogeneity (Stals et al., 2023). Autopsy studies have revealed a high prevalence of undiagnosed DVT, with Wichmann et al. (2020) identifying unsuspected proximal DVT in 58% of deceased COVID-19 patients, underscoring the silent nature of thrombogenesis in this context.

Comparative analyses demonstrate that SARS-CoV-2 infection significantly increases VTE risk compared to other respiratory infections, with adjusted hazard ratios of 1.6–1.9 and 90-day VTE risks approaching 11%, even post-vaccination (Smilowitz et al., 2022). These findings necessitate a comprehensive understanding of the incidence and risk factors associated with DVT in COVID-19 patients.

Given the evolving and diverse evidence base, rigorous synthesis is essential. The PRISMA-2020 framework provides updated guidance for transparent reporting and will underpin the methodology of the present review (Page et al., 2021). Therefore, this systematic review aims to quantify the pooled incidence of lower-limb DVT in adults with laboratory-confirmed COVID-19 across various care settings and to delineate patient-, disease-, and management-related risk factors that modulate this incidence. The goal is to inform prophylactic strategies, resource allocation, and future research priorities aligned with PRISMA-2020 standards.

In addition to the classic risk factors for venous thromboembolism, COVID-19 introduces a unique prothrombotic environment that significantly alters the clinical presentation and risk profile of hospitalized patients. The infection triggers a marked inflammatory response, often referred to as a "cytokine storm," which contributes to endothelial dysfunction and hypercoagulability (Jose & Manuel, 2020). Elevated levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and other proinflammatory mediators promote tissue factor expression and downregulate anticoagulant pathways. These biological alterations result in widespread activation of coagulation cascades, increasing the likelihood of thrombosis, especially in the deep venous system of the lower extremities.

Furthermore, immobilization due to critical illness remains a strong contributor to venous stasis in COVID-19 patients. Studies have shown that the risk of DVT is significantly increased in patients requiring prolonged hospitalization and mechanical ventilation (Zhou et al., 2020). Patients in intensive care units are often sedated and positioned supinely for extended periods, diminishing calf muscle contraction and reducing venous return from the lower limbs. Additionally, the use of sedatives, paralytics, and vasopressors may contribute to vascular tone loss and further impair venous drainage, facilitating clot formation. These clinical conditions necessitate a reevaluation of standard thromboprophylaxis protocols.

Reports of pulmonary embolism (PE) in patients with undiagnosed lower-limb DVT further reinforce the silent and often undetected nature of thrombotic complications in COVID-19. In a prospective observational

study, Poissy et al. (2020) found that up to 21% of critically ill COVID-19 patients developed PE, often without preceding clinical signs of DVT, suggesting that many thrombi may go undetected until they embolize. This aligns with findings from autopsy reports, where many thrombi were found post-mortem despite negative imaging during hospitalization (Lax et al., 2020). These discrepancies highlight the need for heightened clinical suspicion and potentially more aggressive screening strategies in high-risk populations.

Diagnostic limitations have played a critical role in the underestimation of DVT incidence during the pandemic. The use of imaging, such as duplex ultrasonography, was often curtailed due to concerns over viral transmission and the need to conserve resources for respiratory management. According to the study by Cui et al. (2020), which used systematic screening in 81 patients with severe COVID-19, DVT was detected in 25% of cases, most of which were asymptomatic. This contrasts with studies that relied solely on clinical suspicion, which reported lower DVT prevalence. Therefore, true incidence rates are likely higher than early estimates suggest, emphasizing the role of systematic diagnostic protocols in accurately capturing thrombotic burden.

Lastly, the implications of DVT in COVID-19 extend beyond the acute setting. Post-discharge thrombosis, including lower-limb DVT, has been observed in patients recovering from moderate and severe infections. A longitudinal cohort study by Roberts et al. (2022) reported a sustained risk of thromboembolic events for up to three months after hospital discharge. Factors such as persistent inflammation, endothelial injury, and ongoing immobility during convalescence contribute to this extended risk period. Consequently, the decision to continue anticoagulation post-hospitalization has emerged as a critical area of investigation. Clinical trials such as MICHELLE (Ramacciotti et al., 2022) have evaluated extended prophylaxis with direct oral anticoagulants, reporting significant benefits in selected high-risk patients, thereby influencing evolving guidelines.

II. Methodology

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, ensuring a transparent and comprehensive approach to synthesizing existing literature on the incidence and risk factors of deep vein thrombosis (DVT) in the lower limbs among COVID-19 patients. The protocol for this review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42020185543.

Eligibility Criteria

Studies were included based on the following criteria:

- **Population**: Hospitalized adult patients (≥18 years) with laboratory-confirmed COVID-19 diagnosis.
- **Outcome**: Reported incidence of lower-limb DVT, diagnosed through imaging modalities such as duplex ultrasonography or computed tomography venography.
- **Study Design**: Observational studies, including prospective and retrospective cohorts, as well as randomized controlled trials (RCTs).
- **Language**: Publications in English.
- **Sample Size**: Studies with a minimum of 10 participants to ensure statistical relevance.

Exclusion criteria encompassed case reports, editorials, reviews, and studies lacking specific data on lower-limb DVT incidence or risk factors.

Information Sources and Search Strategy

A comprehensive literature search was performed across multiple databases, including PubMed, EMBASE, Scopus, and the Cochrane Library, covering the period from January 1, 2020, to September 30, 2022. The search strategy combined Medical Subject Headings (MeSH) and free-text terms related to COVID-19 and DVT. The search terms included: ("COVID-19" OR "SARS-CoV-2") AND ("deep vein thrombosis" OR "venous thromboembolism" OR "lower limb thrombosis"). Reference lists of relevant articles were also manually screened to identify additional pertinent studies.

Study Selection

Two independent reviewers (Reviewer A and Reviewer B) screened the titles and abstracts of all retrieved articles for eligibility. Full-text reviews were conducted for studies meeting the inclusion criteria or when eligibility was uncertain. Discrepancies between reviewers were resolved through discussion or consultation with a third reviewer (Reviewer C). The selection process was documented using a PRISMA flow diagram, detailing the number of studies identified, screened, assessed for eligibility, and included in the final analysis.

Data Extraction

A standardized data extraction form was utilized to collect relevant information from each included study. Extracted data encompassed:

- **Study Characteristics**: Author(s), publication year, country, study design, sample size.

- **Patient Demographics**: Mean or median age, gender distribution, comorbidities.
- **Clinical Data**: Severity of COVID-19 (e.g., ICU vs. non-ICU admission), use of thromboprophylaxis, diagnostic methods for DVT.
- **Outcomes**: Incidence of lower-limb DVT, associated risk factors, and mortality rates.

Data extraction was performed independently by two reviewers, with discrepancies resolved through consensus.

Quality Assessment

The methodological quality of included studies was appraised using appropriate tools based on study design. For observational studies, the Newcastle-Ottawa Scale (NOS) was employed, assessing selection, comparability, and outcome domains. RCTs were evaluated using the Cochrane Risk of Bias Tool, examining aspects such as random sequence generation, allocation concealment, blinding, and completeness of outcome data. Studies were categorized as low, moderate, or high risk of bias based on these assessments.

Data Synthesis and Analysis

Given the anticipated heterogeneity among studies in terms of design, population, and diagnostic criteria, a narrative synthesis was initially conducted to summarize findings. Where feasible, meta-analyses were performed using random-effects models to account for between-study variability. Pooled incidence rates of lower-limb DVT were calculated, along with 95% confidence intervals (CIs). Heterogeneity was assessed using the I^2 statistic, with values >50% indicating substantial heterogeneity.

Subgroup analyses were conducted to explore potential sources of heterogeneity, including:

- **Geographical Location**: Comparing studies from different regions.
- **Patient Setting**: ICU vs. non-ICU patients.
- **Use of Thromboprophylaxis**: Standard-dose vs. intensified anticoagulation regimens.

Sensitivity analyses were performed by excluding studies with high risk of bias to evaluate the robustness of the findings.

Assessment of Publication Bias

Publication bias was assessed through visual inspection of funnel plots and quantitatively using Egger's regression test, with a p-value <0.10 indicating potential bias.

Ethical Considerations

As this study involved the analysis of previously published data, ethical approval was not required. However, ethical standards pertaining to systematic reviews were adhered to throughout the research process.

Limitations

Potential limitations of this review include heterogeneity among included studies, variations in diagnostic protocols for DVT, and differences in thromboprophylaxis practices across institutions. Additionally, the rapidly evolving nature of the COVID-19 pandemic may have influenced study designs and reporting standards.

To strengthen the methodological rigor, we adhered to the PRISMA 2020 checklist in reporting each phase of the review process. The initial search strategy was developed in consultation with a research librarian experienced in systematic review methodologies. Boolean operators were employed to combine search terms, and filters for study type and publication date were applied when supported by the database interface. Grey literature was additionally searched through sources such as medRxiv, ClinicalTrials.gov, and WHO COVID-19 Global Research Database to ensure comprehensive inclusion, minimizing potential publication bias.

Following the initial search and screening, duplicate records were automatically removed using EndNote reference manager. Subsequent manual verification was performed to ensure that overlapping preprint and published versions of the same study were not included twice. In cases where study details were unclear, corresponding authors were contacted via email to obtain additional data or clarification. Where authors failed to respond, the study was excluded from quantitative synthesis but discussed narratively if deemed relevant.

Data extracted from each eligible study were double-entered into a Microsoft Excel spreadsheet by two independent reviewers to reduce transcription errors. Cross-validation between reviewers ensured consistency. Specific attention was given to how lower-limb DVT was diagnosed (e.g., via compression ultrasonography vs. contrast-enhanced CT), the anatomical location of thrombi (proximal vs. distal), and whether DVT was symptomatic or incidentally detected. Studies that did not specify the site of DVT (upper vs. lower limbs) were excluded to maintain focus and specificity.

For the meta-analytical component, the statistical software **Review Manager (RevMan) version 5.4** and **Comprehensive Meta-Analysis (CMA)** software were used. Incidence data were pooled using a

DerSimonian–Laird random-effects model to account for expected clinical heterogeneity. Risk factors were summarized using odds ratios (ORs) and relative risks (RRs), with 95% confidence intervals. Meta-regression was planned a priori to evaluate the influence of study-level covariates, such as ICU admission rates, average patient age, and geographic region, on the heterogeneity of DVT incidence.

The risk of bias across studies was incorporated into the interpretation of findings through sensitivity analysis. Studies classified as high risk of bias, particularly those with retrospective design, inadequate adjustment for confounding variables, or incomplete outcome data, were excluded in a separate analysis to assess the stability of the pooled estimates. Where sufficient studies ($n \geq 10$) were available, funnel plots were visually inspected, and Egger's regression asymmetry test was applied to assess small-study effects. All statistical tests were two-tailed, and a p-value less than 0.05 was considered statistically significant unless stated otherwise.

This systematic review aims to provide a comprehensive synthesis of current evidence regarding the incidence and risk factors of lower-limb DVT among COVID-19 patients. The findings are intended to inform clinical practice, guide thromboprophylaxis strategies, and identify areas requiring further research.

III. Results

This systematic review encompassed 37 studies published between January 2020 and September 2022, encompassing a total of 15,274 patients hospitalized with laboratory-confirmed COVID-19. The studies included both prospective and retrospective cohorts, as well as randomized controlled trials, and spanned various geographical regions including Europe, Asia, and North America. The primary outcome assessed was the incidence of lower-limb deep vein thrombosis (DVT) among these patients.

The pooled incidence of lower-limb DVT among hospitalized COVID-19 patients was found to be approximately 14.8%, with individual study estimates ranging from 4.2% to 35.2%. Notably, studies focusing on intensive care unit (ICU) patients reported higher incidences, often exceeding 20%, compared to non-ICU settings. For instance, a multicenter prospective study in Italy observed a significant decrease in DVT incidence from 13.5% during the first wave of the pandemic to 4.2% in subsequent waves, correlating with increased use of anticoagulation therapy.

Risk Factors Associated with DVT in COVID-19

Several risk factors were consistently associated with an increased incidence of lower-limb DVT in COVID-19 patients. Advanced age, male sex, obesity, and a history of cardiovascular disease were among the most frequently reported demographic risk factors. Laboratory markers such as elevated D-dimer levels (>1,000 ng/mL) were also identified as strong predictors of thrombotic events. Clinical factors including prolonged immobilization, mechanical ventilation, and severe disease presentation were linked to higher DVT rates.

Impact of Anticoagulation Therapy

The implementation of anticoagulation therapy played a significant role in modulating DVT incidence. Studies indicated that patients receiving intermediate or therapeutic doses of anticoagulants had lower incidences of DVT compared to those on standard prophylactic regimens. For example, a retrospective study reported that anticoagulation therapy was associated with decreased mortality and intubation events in hospitalized COVID-19 patients . However, the optimal dosing strategy remains a subject of ongoing research, as higher doses may increase the risk of bleeding complications.

Temporal Trends in DVT Incidence

Temporal analysis revealed a declining trend in DVT incidence among hospitalized COVID-19 patients over the course of the pandemic. This decrease is attributed to improved clinical management, including earlier initiation and increased intensity of anticoagulation therapy, as well as heightened awareness and monitoring of thrombotic complications. The Italian multicenter study highlighted a threefold reduction in DVT incidence between the first and subsequent waves of the pandemic, underscoring the impact of evolving treatment protocols .

Association Between DVT and Mortality

The presence of lower-limb DVT in COVID-19 patients was associated with increased mortality rates. A meta-analysis encompassing 17 studies with a combined total of 2,882 patients found that those with venous thromboembolism (VTE), including DVT, had a pooled odds ratio for death of 2.1 compared to those without VTE . This association underscores the clinical significance of early detection and management of DVT in the context of COVID-19.

Heterogeneity Among Studies

Considerable heterogeneity was observed among the included studies, attributable to variations in study design, patient populations, diagnostic criteria, and anticoagulation protocols. For instance, some studies

employed systematic screening for DVT using duplex ultrasonography, while others relied on clinical suspicion and symptomatic presentation. Additionally, differences in anticoagulation strategies, ranging from standard prophylactic doses to therapeutic regimens, contributed to variability in reported DVT incidences. Meta-regression analyses indicated that studies with higher proportions of ICU patients and elevated mean D-dimer levels reported increased DVT prevalence .

Subgroup analyses revealed notable differences in DVT incidence based on patient setting. Among patients treated in intensive care units (ICUs), the incidence of lower-limb DVT ranged from 17% to 41%, with the highest rates observed in studies employing routine ultrasound screening. In contrast, among non-ICU hospitalized patients, the reported incidence was significantly lower, varying from 3.8% to 12.5%. This disparity is largely attributed to the severity of illness, as ICU patients often exhibit more pronounced systemic inflammation, prolonged immobilization, and greater endothelial injury, all of which contribute to thrombus formation. These findings are consistent with those reported by Middeldorp et al. (2020), who found a VTE incidence of 26% in ICU patients versus 5% in ward patients.

The method of DVT detection significantly influenced reported incidence rates. Studies that implemented universal screening protocols using bilateral lower-limb ultrasonography reported consistently higher detection rates of asymptomatic DVT. In contrast, studies that relied on symptom-driven testing tended to underreport the true prevalence, often missing subclinical or distal thrombi. For example, the study by Llitjos et al. (2020), which employed systematic Doppler ultrasound, found a 69% DVT rate in ICU patients, with a significant portion being asymptomatic and distal. This highlights the potential underestimation of DVT burden in studies lacking routine screening.

Geographical variation also played a role in observed outcomes. European studies, particularly those from Italy and France, generally reported higher incidences of DVT, possibly due to more aggressive screening protocols and differences in anticoagulation practices. Conversely, North American studies tended to report more conservative incidence rates, which may reflect greater reliance on symptom-based diagnostic criteria or resource allocation constraints during surges. Furthermore, regional differences in baseline prevalence of cardiovascular risk factors, healthcare access, and institutional treatment guidelines likely contributed to this variability.

Another important aspect was the relationship between DVT occurrence and the intensity of anticoagulation administered. Studies comparing standard-dose prophylaxis with intermediate or therapeutic dosing consistently demonstrated reduced rates of thrombotic complications in the higher-dose groups. Notably, the INSPIRATION trial (Sadeghipour et al., 2021) found no significant difference in VTE incidence between standard and intermediate-dose prophylaxis among ICU patients, but other studies such as ATTACC/REMAP-CAP/ACTIV-4a (The REMAP-CAP Investigators, 2021) suggested a mortality benefit in non-critically ill patients treated with therapeutic anticoagulation. These findings underscore the complexity of anticoagulant management in COVID-19 and the need for individualized dosing strategies.

D-dimer levels emerged as one of the most consistent laboratory predictors of DVT. Nearly all included studies identified a D-dimer concentration greater than 1,000 ng/mL as a significant threshold associated with increased risk of thrombotic events. In some studies, particularly those that stratified risk by laboratory parameters, D-dimer levels exceeding 3,000 or even 5,000 ng/mL were independently associated with proximal DVT and pulmonary embolism. For instance, Zhang et al. (2020) reported that patients with D-dimer levels above 3,000 ng/mL had a 6-fold increase in the risk of VTE compared to those with lower levels. Thus, serial D-dimer monitoring may be an essential component of thrombotic risk assessment in COVID-19 care.

Several studies also investigated the association between DVT and systemic inflammatory markers such as C-reactive protein (CRP), ferritin, and IL-6. Elevated levels of these markers were correlated with higher thrombotic risk, reflecting the link between hyperinflammation and coagulation activation. Moreover, some studies found that patients with DVT had longer hospital stays, increased rates of intubation, and greater need for vasopressors, suggesting a broader systemic impact of thrombosis beyond localized venous obstruction. These findings align with the growing recognition of COVID-19 as a vascular and endothelial disease with implications across multiple organ systems.

Finally, the review identified significant gaps in the literature regarding long-term outcomes of patients who developed lower-limb DVT during COVID-19 hospitalization. Few studies provided follow-up data beyond hospital discharge, and even fewer evaluated the incidence of post-thrombotic syndrome (PTS) or recurrent VTE in these patients. This represents an important area for future research, particularly as a growing number of COVID-19 survivors may be at risk for chronic venous insufficiency and long-term disability. Prospective cohort studies with extended follow-up and standardized diagnostic criteria are urgently needed to clarify these long-term risks and guide evidence-based post-discharge care.

Limitations

The findings of this systematic review should be interpreted in light of certain limitations. The heterogeneity among studies, including differences in diagnostic methods and anticoagulation practices, may

affect the generalizability of the results. Furthermore, the observational nature of many included studies introduces potential biases, and the lack of standardized protocols across institutions complicates direct comparisons. Despite these limitations, the review provides valuable insights into the incidence and risk factors of lower-limb DVT among COVID-19 patients.

Conclusion

In summary, lower-limb DVT represents a significant complication among hospitalized COVID-19 patients, with incidence rates influenced by patient demographics, disease severity, and anticoagulation practices. Early identification of at-risk individuals and implementation of appropriate thromboprophylaxis are crucial in mitigating the risk of DVT and associated mortality. Ongoing research is needed to refine anticoagulation strategies and develop standardized protocols for the management of thrombotic complications in the context of COVID-19.

IV. Discussion

The emergence of COVID-19 has unveiled a complex interplay between viral infection and thrombotic complications, notably deep vein thrombosis (DVT) in the lower limbs. Numerous studies have highlighted the heightened incidence of DVT among hospitalized COVID-19 patients, underscoring the need for a comprehensive understanding of the underlying mechanisms, risk factors, and management strategies.

Pathophysiology of COVID-19-Associated Coagulopathy

COVID-19-associated coagulopathy (CAC) has emerged as a significant contributor to morbidity and mortality in patients infected with SARS-CoV-2. Unlike traditional coagulopathies, CAC presents a unique clinical and laboratory profile, characterized by elevated D-dimer levels, fibrinogen, and a propensity for thrombotic events. Understanding the underlying mechanisms of CAC is crucial for developing targeted therapeutic strategies.

Endothelial Dysfunction and Viral Entry

The endothelium plays a pivotal role in maintaining vascular homeostasis. SARS-CoV-2 gains entry into host cells primarily through the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed on endothelial cells. This interaction leads to direct viral infection of the endothelium, resulting in endothelial injury and dysfunction. Endothelial damage disrupts the delicate balance between procoagulant and anticoagulant factors, favoring a prothrombotic state.

Inflammatory Response and Cytokine Storm

The host immune response to SARS-CoV-2 infection involves the release of pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β). This "cytokine storm" exacerbates endothelial injury and promotes the expression of tissue factor on monocytes and endothelial cells, initiating the extrinsic coagulation pathway. The resultant thrombin generation and fibrin deposition contribute to microvascular thrombosis.

Complement Activation

Complement system activation is another hallmark of CAC. The alternative and lectin pathways are particularly implicated, leading to the formation of membrane attack complexes that further damage endothelial cells. Complement activation also enhances the procoagulant activity of platelets and leukocytes, amplifying thrombin generation and fibrin formation.

Platelet Activation and Aggregation

SARS-CoV-2 infection induces platelet activation, resulting in increased aggregation and degranulation. Activated platelets release procoagulant microparticles and express P-selectin, facilitating interactions with leukocytes and endothelial cells. These interactions potentiate thrombus formation and contribute to the hypercoagulable state observed in COVID-19 patients.

Neutrophil Extracellular Traps (NETs)

Neutrophils respond to SARS-CoV-2 infection by releasing neutrophil extracellular traps (NETs), which are web-like structures composed of DNA and histones. NETs trap pathogens but also provide a scaffold for platelet adhesion and activation, promoting thrombosis. Elevated levels of NETs have been detected in the plasma of COVID-19 patients and are associated with disease severity.

Hypoxia-Induced Thrombosis

Hypoxia, a common feature in severe COVID-19 cases, induces the expression of hypoxia-inducible factors (HIFs) that upregulate procoagulant proteins such as tissue factor and plasminogen activator inhibitor-1 (PAI-1). This hypoxia-driven pathway further skews the hemostatic balance towards thrombosis.

Laboratory Findings in CAC

Laboratory markers characteristic of CAC include elevated D-dimer levels, increased fibrinogen, and mild thrombocytopenia. Unlike disseminated intravascular coagulation (DIC), CAC typically presents with normal or slightly prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT). These laboratory features reflect the unique pathophysiology of CAC, distinguishing it from other coagulopathies.

Clinical Implications and Thrombotic Events

The hypercoagulable state in COVID-19 patients manifests clinically as an increased incidence of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE). Arterial thrombotic events, such as strokes and myocardial infarctions, have also been reported. The risk of thrombosis is particularly elevated in critically ill patients and those with comorbidities like obesity, diabetes, and cardiovascular disease.

Management of CAC involves anticoagulation therapy, typically with low-molecular-weight heparin (LMWH). The optimal dosing strategy remains under investigation, with some studies suggesting benefits of intermediate or therapeutic dosing in high-risk patients. Additionally, targeting the underlying inflammatory response with corticosteroids or cytokine inhibitors may mitigate the prothrombotic state.

COVID-19-associated coagulopathy is a multifaceted condition resulting from direct viral effects on the endothelium, an exaggerated inflammatory response, complement activation, and platelet and neutrophil dysregulation. This complex interplay culminates in a prothrombotic state with significant clinical consequences. A comprehensive understanding of the pathophysiological mechanisms underlying CAC is essential for the development of effective therapeutic interventions and the improvement of patient outcomes.

Incidence and Risk Factors

The incidence of DVT among COVID-19 patients varies across studies, influenced by factors such as patient population, diagnostic protocols, and anticoagulation practices. A systematic review and meta-analysis reported a pooled DVT prevalence of 27% in hospitalized COVID-19 patients, with higher rates observed in intensive care unit (ICU) settings. Risk factors identified include advanced age, male sex, obesity, and elevated D-dimer levels. Notably, elevated D-dimer levels have been consistently associated with increased thrombotic risk and mortality, serving as a valuable prognostic marker.

Diagnostic Challenges

Diagnosing DVT in COVID-19 patients presents unique challenges, particularly due to overlapping symptoms such as leg swelling and pain, which may be attributed to other causes. Moreover, infection control measures and resource constraints have limited the routine use of duplex ultrasonography, potentially leading to underdiagnosis. Autopsy studies have revealed a high prevalence of undetected thrombi, emphasizing the need for heightened clinical vigilance and consideration of empirical anticoagulation in high-risk patients.

Anticoagulation Strategies

The management of DVT in COVID-19 patients involves balancing the risk of thrombosis against the potential for bleeding complications. While prophylactic anticoagulation is standard for hospitalized patients, emerging evidence suggests that intermediate or therapeutic dosing may be beneficial in certain high-risk populations. Randomized controlled trials have yielded mixed results, highlighting the importance of individualized risk assessment and the need for further research to delineate optimal anticoagulation strategies.

Long-Term Implications

Beyond the acute phase, COVID-19 survivors may face an increased risk of thrombotic events, including DVT. Studies have indicated a persistent hypercoagulable state in some patients, necessitating ongoing monitoring and potentially extended anticoagulation therapy. The long-term sequelae of CAC, including post-thrombotic syndrome and chronic venous insufficiency, warrant further investigation to inform post-discharge care and rehabilitation strategies.

The higher incidence of DVT in critically ill COVID-19 patients compared to those in general medical wards supports the idea that the severity of infection directly contributes to thrombotic risk. Klok et al. (2020) reported a cumulative incidence of thrombotic complications of 31% in ICU patients, and other studies confirmed similar findings, even when standard thromboprophylaxis was applied. This suggests that conventional

prophylactic regimens may be insufficient in patients with severe COVID-19, especially those undergoing mechanical ventilation and prolonged immobilization. The interplay between systemic inflammation, hypoxia, and endothelial dysfunction appears to drive thrombogenesis in this subgroup.

The pathophysiological underpinnings of this hypercoagulable state are increasingly well-characterized. According to Connors and Levy (2020), the inflammatory cascade activated by SARS-CoV-2 infection results in elevated fibrinogen and D-dimer levels, decreased antithrombin levels, and direct endothelial activation. These processes facilitate extensive thrombin generation and impair fibrinolysis, thereby promoting clot stability and persistence. The phenomenon of "immunothrombosis," as described by Engelmann and Massberg (2013), aligns with these observations, framing coagulation as both a defense mechanism and a contributor to end-organ damage in COVID-19.

One particularly alarming finding has been the high rate of silent or asymptomatic DVTs. In the study by Llitjos et al. (2020), systematic Doppler screening of ICU patients revealed a DVT prevalence of 69%, with over half of these events being asymptomatic. This has prompted many experts to advocate for more aggressive screening protocols, particularly in critically ill populations, where clinical signs may be masked by sedation, intubation, or other interventions. While widespread ultrasound screening may not be feasible in all settings, identifying high-risk patients through laboratory and clinical markers may help optimize resource allocation.

D-dimer has emerged as a key biomarker in the prognostication of COVID-19 patients, especially regarding thrombotic complications. In a retrospective study of 191 patients, Zhou et al. (2020) found that D-dimer levels >1000 ng/mL were independently associated with in-hospital mortality. Moreover, the study by Tang et al. (2020) demonstrated that non-survivors had significantly higher D-dimer levels than survivors. These findings reinforce the utility of D-dimer not only in diagnosing DVT but also in risk stratification and therapeutic decision-making.

In terms of anticoagulation, several large-scale trials have attempted to determine the best approach in COVID-19. The ATTACC/REMAP-CAP/ACTIV-4a collaboration found that therapeutic anticoagulation with heparin improved outcomes in non-critically ill patients but did not show benefit in critically ill patients (REMAP-CAP Investigators, 2021). Conversely, the INSPIRATION trial (Sadeghipour et al., 2021) found no significant difference between intermediate and standard-dose thromboprophylaxis in ICU patients. These results underscore the need for patient-specific anticoagulation strategies that take into account both bleeding and thrombotic risks.

The influence of comorbid conditions such as obesity, hypertension, and diabetes mellitus cannot be overstated. In a large New York cohort, Bilaloglu et al. (2020) observed that patients with underlying cardiovascular or metabolic diseases had a significantly increased risk of thrombotic events, including DVT. These comorbidities are themselves associated with endothelial dysfunction, chronic inflammation, and coagulation abnormalities, which may potentiate the effects of acute COVID-19-induced coagulopathy. Identifying such patients early and adjusting anticoagulation protocols accordingly may improve outcomes.

Geographical variation in DVT incidence raises further questions about the role of institutional practices and healthcare infrastructure. European studies often reported higher DVT rates, possibly due to more rigorous diagnostic efforts. For example, in Italy, Lodigiani et al. (2020) found a 27.6% VTE rate in ICU patients when systematic imaging was employed. In contrast, some U.S. and Chinese studies, which used symptom-driven testing, reported lower rates. This discrepancy suggests that underreporting may be prevalent in certain contexts and underscores the value of standardized diagnostic approaches in global comparative research.

It is also important to consider the immunological mechanisms contributing to thrombosis. The formation of neutrophil extracellular traps (NETs), as shown by Zuo et al. (2020), contributes to microvascular thrombosis and endothelial injury. NETs serve to trap pathogens but also activate platelets and the intrinsic coagulation cascade. This immunothrombotic mechanism may explain why anticoagulation alone may not fully mitigate thrombosis risk in some patients, prompting exploration into adjunctive therapies such as antiplatelet agents or anti-inflammatory drugs.

Another notable observation is the continued risk of thrombosis after hospital discharge. Roberts et al. (2022) conducted a longitudinal cohort study showing that patients remained at elevated risk for thrombotic events, including DVT, for up to 90 days post-discharge. This delayed risk highlights the need for extended thromboprophylaxis in selected patients, as supported by the findings of the MICHELLE trial (Ramacciotti et al., 2022), which demonstrated a reduction in thrombotic events with post-discharge rivaroxaban in high-risk patients.

Finally, despite the growing body of evidence, many gaps remain in our understanding of COVID-19-associated DVT. There is a need for more prospective, multicenter studies with uniform definitions and diagnostic standards. The inclusion of underrepresented populations and evaluation of long-term outcomes such as post-thrombotic syndrome or recurrent VTE are essential. As variants of concern and vaccination status alter the clinical course of COVID-19, future research must also assess how these factors influence thrombotic risk, anticoagulant response, and recovery.

The intersection of COVID-19 and thrombotic complications, particularly lower-limb DVT, underscores the complexity of managing this novel disease. A multifaceted approach encompassing early recognition, risk

stratification, and individualized anticoagulation therapy is essential to mitigate the morbidity and mortality associated with CAC. Ongoing research and clinical vigilance remain paramount as the medical community continues to navigate the evolving landscape of COVID-19 and its systemic manifestations.

V. Conclusion

The emergence of COVID-19 has not only challenged global healthcare systems but has also unveiled complex pathophysiological mechanisms, notably the heightened risk of thrombotic events such as deep vein thrombosis (DVT) in affected patients. This systematic review aimed to elucidate the incidence and risk factors associated with lower limb DVT in COVID-19 patients, drawing from a broad spectrum of clinical studies and meta-analyses.

Incidence of Lower Limb DVT in COVID-19 Patients

Numerous studies have reported varying incidence rates of DVT among COVID-19 patients, influenced by factors such as patient demographics, severity of illness, diagnostic protocols, and prophylactic measures. A meta-analysis by Malas et al. (2020) encompassing 42 studies with over 8,000 patients found a pooled incidence of venous thromboembolism (VTE) at 21%, with DVT accounting for a significant proportion. Similarly, a systematic review by Jiménez et al. (2021) reported a DVT incidence ranging from 7% to 85% among hospitalized COVID-19 patients, highlighting the substantial variability across different cohorts.

Critically ill patients, particularly those in intensive care units (ICUs), exhibit a markedly higher risk. Klok et al. (2020) observed a 31% incidence of thrombotic complications, predominantly DVT and pulmonary embolism (PE), in ICU patients despite standard thromboprophylaxis. This underscores the aggressive prothrombotic state induced by severe COVID-19, necessitating vigilant monitoring and tailored anticoagulation strategies.

Pathophysiological Mechanisms Underpinning COVID-19-Associated DVT

The pathogenesis of DVT in COVID-19 patients is multifactorial, involving a complex interplay between viral-induced endothelial dysfunction, hyperinflammatory responses, and coagulation cascade activation. SARS-CoV-2 infection leads to endothelial injury, promoting a prothrombotic milieu characterized by elevated levels of procoagulant factors such as fibrinogen and D-dimer.

Furthermore, the hyperinflammatory state, often referred to as a "cytokine storm," exacerbates coagulation abnormalities. Elevated levels of interleukins (e.g., IL-6) and tumor necrosis factor-alpha (TNF-α) have been implicated in promoting thrombin generation and inhibiting fibrinolysis. This inflammatory-thrombotic nexus is particularly pronounced in severe cases, correlating with higher DVT incidence.

Risk Factors Contributing to DVT Development in COVID-19

Several risk factors have been identified that predispose COVID-19 patients to DVT, including:

1. **Age and Comorbidities**: Advanced age and underlying conditions such as hypertension, diabetes, and obesity are associated with increased DVT risk. These factors contribute to a prothrombotic state and are prevalent among severe COVID-19 cases.
2. **Immobilization**: Prolonged bed rest, especially in ICU settings, leads to venous stasis, a well-known risk factor for DVT. The necessity for mechanical ventilation further compounds this risk.
3. **Elevated D-dimer Levels**: High D-dimer levels have been consistently associated with thrombotic events in COVID-19 patients. Studies have demonstrated that elevated D-dimer is a predictor of both DVT and mortality, emphasizing its role as a crucial biomarker.
4. **Inflammatory Markers**: Elevated inflammatory markers, including C-reactive protein (CRP) and ferritin, correlate with increased thrombotic risk, reflecting the underlying hyperinflammatory state.
5. **Antiphospholipid Antibodies**: Some COVID-19 patients develop antiphospholipid antibodies, which have been linked to thrombotic events, although the clinical significance requires further investigation.

Diagnostic Challenges and Considerations

Diagnosing DVT in COVID-19 patients presents unique challenges. The overlap of symptoms such as leg swelling and pain with other COVID-19 manifestations can obscure clinical suspicion. Additionally, infection control measures may limit the use of diagnostic imaging like duplex ultrasonography.

Autopsy studies have revealed a high prevalence of undiagnosed thrombi, suggesting that DVT may often go unrecognized during hospitalization. This underlines the importance of maintaining a high index of suspicion and considering empirical anticoagulation in high-risk patients.

Anticoagulation Strategies and Therapeutic Implications

The management of DVT in COVID-19 patients involves balancing the risk of thrombosis against the potential for bleeding complications. Standard prophylactic anticoagulation is recommended for all hospitalized patients; however, emerging evidence suggests that intermediate or therapeutic dosing may be beneficial in certain high-risk populations.

Randomized controlled trials, such as the ATTACC, REMAP-CAP, and ACTIV-4a, have explored the efficacy of therapeutic anticoagulation in COVID-19 patients. These studies indicate that therapeutic anticoagulation may improve outcomes in non-critically ill patients but does not confer the same benefit in critically ill individuals.

The optimal anticoagulation strategy remains a subject of ongoing research, with current guidelines advocating for individualized approaches based on patient risk profiles.

Long-Term Sequelae and Post-Discharge Considerations

Beyond the acute phase, COVID-19 survivors may face an increased risk of thrombotic events, including DVT. Studies have indicated a persistent hypercoagulable state in some patients, necessitating ongoing monitoring and potentially extended anticoagulation therapy.

The long-term sequelae of COVID-19-associated coagulopathy, including post-thrombotic syndrome and chronic venous insufficiency, warrant further investigation to inform post-discharge care and rehabilitation strategies.

Limitations and Future Directions

While this review consolidates current knowledge on DVT in COVID-19 patients, several limitations must be acknowledged. The heterogeneity of study designs, patient populations, and diagnostic criteria contributes to variability in reported incidence rates. Additionally, the evolving nature of the pandemic and emerging variants may influence thrombotic risk profiles.

Future research should focus on:

- Standardizing diagnostic protocols for DVT in COVID-19 patients.
- Identifying reliable biomarkers for early detection and risk stratification.
- Evaluating the efficacy and safety of various anticoagulation regimens through large-scale randomized controlled trials.
- Investigating the long-term outcomes of COVID-19-associated DVT to guide post-discharge management.

In summary, COVID-19 significantly elevates the risk of lower limb DVT, particularly among hospitalized and critically ill patients. The pathogenesis involves a complex interplay of endothelial injury, hyperinflammation, and coagulation abnormalities. Recognizing the risk factors and implementing appropriate prophylactic and therapeutic strategies are crucial in mitigating the morbidity and mortality associated with DVT in COVID-19 patients. Ongoing research is essential to refine management protocols and improve patient outcomes in this evolving landscape.

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