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Managing Thrombotic Risk in Covid-19: A Comprehensive Review of Anticoagulant Therapies

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ABSTRACT
A higher risk of thrombotic events is closely linked to the aetiology of Coronavirus Disease-19 (COVID-19). Individuals admitted to the intensive care unit (ICU) due to respiratory failure linked with COVID-19 exhibit hypercoagulability, which is not discernible with conventional coagulation tests. Among the noteworthy findings are abnormally stiff clots, decreased fibrinolysis, and increased fibrinogen concentrations. It is necessary to do more research to clarify the pathophysiological basis of this hypercoagulable environment and assess the risk-benefit ratio of various anticoagulant dosages. This discussion also includes information about regional differences in COVID-19 incidence and anticoagulant usage in the treatment of the illness.

KEYWORDS: Covid-19, Thromboembolism, Prevalence, Anticoagulants, Inflammation, D-dimer

I. INTRODUCTION

Thromboembolism, ranking as the third most prevalent vascular disorder, represents a significant global health concern, manifesting at a rate of 1 to 2 occurrences per 1000 individuals annually. This condition encompasses two primary manifestations: deep vein thrombosis (DVT) and pulmonary embolism (PE). The worldwide annual incidence rates for DVT and PE stand at approximately 60-100 cases per 100,000 individuals and 23–107 cases per 100,000 individuals, respectively(Kefale et al., 2020). The research indicated that individuals with Severe Acute Respiratory Syndrome (SARS) commonly experienced coagulation abnormalities, including, thrombocytopenia, prolonged activated partial thromboplastin time (APTT), increased D-dimer levels, and some complications associated with the disseminated intravascular coagulation (DIC). The incidence rates for these complications were reported to be approximately 50–63%, 40–45%, 50%, and 2.5%, respectively(Jin et al., 2020). The histological finding of thrombotic microangiopathy in postmortem examinations of COVID-19 patients confirms clinical accounts of disproportionate frequencies of venous and arterial thromboembolism. Intravascular thrombosis can cause localized ischaemia, microhemorrhage, and inflammation in the lungs(Collett et al., 2021). D-dimer and fibrin degradation products were raised in nearly half of patients with laboratory-confirmed COVID-19 infection, with the elevation being more evident in severe cases. Elevated levels of D-dimer (>1g/mL) were significantly associated with in-hospital mortality in a multicenter retrospective cohort study conducted in China. Conversely, a retrospective analysis of 449 severe COVID-19 patients in Wuhan revealed that the administration of low molecular weight heparin was significantly correlated with improved 28-day overall survival among patients exhibiting markedly elevated D-dimer levels(Alonso-Fernández et al., 2020). The effectiveness of anticoagulants such as aspirin, heparin, warfarin, Enoxaparin, Streptokinase, Bivalirudin, Apixaben, Fondaparinux, and Argatroban is reviewed in this article.

COAGULATION DISORDER IN COVID-19

As the tally of confirmed severe COVID-19 cases continued to rise, subsequent investigations were brought to light that potential threat of thrombotic complications in individuals experiencing severe to critical manifestations of the disease. In severe cases of COVID-19, autopsy or imaging studies have increasingly revealed thrombo-embolism. The characteristics of thromboembolic consequences in mild to moderate instances are poorly understood. Pulmonary thromboembolism (PE) and venous thromboembolism (VTE) are two thrombotic consequences (VTE). The majority of studies have focused on PE, whereas venous clots, particularly sacral thrombosis, have received little attention. With an increase of venous, arterial, or microvascular related events, coagulopathy contributes to the severity of COVID-19

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infection(Chen et al., 2021). COVID-19 has been associated with over 10.1 million cases worldwide, resulting in more than 502,000 deaths. Infection with COVID-19 can lead to coagulopathy, which manifests in varying degrees, resembling disseminated intravascular coagulopathy (DIC) or sepsis-induced coagulopathy (SIC). Indicators of early clotting issues in COVID-19 are unusual prothrombin times. Also elevated are D-dimer, fibrinogen/fibrin breakdown products, platelet counts, and activated partial thromboplastin time.In severe COVID-19 cases, increased levels may be seen of certain inflammatory markers: ferritin, interleukin2, 7, 1, and 6; granulocyte colony stimulating factor; monocytechemoattractant protein 1; macrophage inflammatory protein 1-alpha; and tumor necrosis factor-alpha. This cytokine profile resembles that observed in secondary hemophagocytic lymphohistiocytosis(Kander, 2020). Thrombin serves as a pivotal player in hemostasis, primarily functioning to induce clot formation through the activation of platelets and the conversion of fibrinogen into fibrin. However, its influence extends beyond coagulation, encompassing diverse cellular effects and the potential to aggravate inflammatory responses via the activation of proteinase-activated receptors (PARs), notably PAR-1(Jose & Manuel, 2020).

Danying Liao and her colleagues have published a retrospective observational cohort study in The Lancet Haematology. The coagulation profiles of 380 COVID-19 patients hospitalized in Wuhan, China are analyzed. The study focuses on these profiles. The average age of the patients was 64 years, with a range from 53 to 73, and 174 of them, constituting 46 percent of the cohort, were women. Their findings suggest that the observed coagulopathy in these patients may be attributed to an underlying endotheliopathy. This endotheliopathy leads to the development of thrombotic microangiopathy and microcirculatory impairment. The hypothesized process aligns with observing endothelial demise and small vessel clot creation in post-mortem exams of COVID-19 victims. Furthermore, this pathological process may explain the occurrence of sudden cerebrovascular complications and myocardial ischemia seen in these patients. There have been increasing reports of such complications associated with COVID-19. The study indicates that patients displaying acute respiratory distress symptoms or declining lung health, yet without prior venous thromboembolism, ought to deliberate switching from preventative low molecular heparin or intermediate anticoagulation dosing to treatment-level anticoagulation. This adjustment in treatment may help mitigate the risk of further complications(Kander, 2020). COVID-19's coagulopathy (CoAC) substantially impacts mortality and morbidity. Especially in acute respiratory distress syndrome patients. Characteristics include high D-dimer and fibrinogen concentrations. CoAC may also present with altered prothrombin time, activated partial thromboplastin time, thrombocytosis, or mild thrombocytopenia. Clinical manifestations of CoAC have been extensively documented in clinical series, postmortem reports, and computed tomography angiography studies. In a prospective cohort study involving twenty COVID-19 ARDS patients, various coagulation and fibrinolysis markers were assessed. These included prothrombin fragment 1 + 2 (PF 1 + 2), a marker indicative of thrombin generation; plasmin–antiplasmin complex (PAP), reflecting plasmin generation; tissue plasminogen activator (tPA), an indicator of fibrinolysis activation; plasminogen activator inhibitor 2 (PAI- 2), associated with fibrinolysis inhibition; and fibrinopeptide A, a marker reflecting fibrin generation. They found 8survivors (40 percent) and 12 nonsurvivors (60 percent) in total. One patient (5%) had previously suffered a cerebrovascular event due to atrial fibrillation and was on straight oral anticoagulants. There were no cases of recognised thrombophilia recorded(Ranucci et al., 2020).

COAGULATION PARAMETERS AND COVID-19

1. Prothrombin time(PT)

Prothrombin Time (PT) exhibited frequent elevation in Disseminated Intravascular Coagulation (DIC), a condition encompassed within the diagnostic criteria outlined by the International Society on Thrombosis and Haemostasis (ISTH) for clear disseminated intravascularcoagulopathy identification. Conversely, within the context of COVID-19, the majority of patients manifest normal or near-normal PT levels, with only a marginal 5% demonstrating protracted PT. Fatal cases of COVID-19, however, present an average PT extension of 1.9 seconds in comparison to non-fatal instances. Moreover, approximately 48% of fatal cases showcase pronounced and progressive PT prolongation exceeding 6 seconds later in the disease progression. This progressive elongation of PT serves as a foreboding indicator and prognosticator of mortality risk(Hadid et al., 2021).

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2. Fibrinogen

In the context of COVID-19, a significant upsurge in fibrinogen levels is commonly observed among the majority of patients, registering a median level of 4.55 g/L. However, it is imperative to note that a progressive decline in fibrinogen concentration emerges as a pivotal predictor of mortality. Notably, an alarming 29% of fatal cases exhibit a consequential reduction in fibrinogen levels(Hadid et al., 2021).

3. Platelet count

Thrombocytopenia serves as a highly sensitive indicator for Disseminated Intravascular Coagulation (DIC), manifesting in approximately 97% of DIC cases. However, within the context of COVID-19, the platelet count frequently remains within normal parameters or experiences only a mild reduction, observed in 12-36% of patients, with a mere 5% exhibiting a platelet count below $100x10^9$/L. Severe thrombocytopenia demonstrates a correlation with disease progression, as evidenced by over 55% of fatal COVID-19 cases showcasing a platelet count below $100x10^9$/L. In a meta-analysis involving 1,779 COVID-19 patients, those with severe infection displayed a platelet count lowered by $31x10^9$/L compared to those with mild disease. Consequently, the exacerbation of thrombocytopenia often indicates clinical deterioration and likely onset of DIC, considered a pre-terminal occurrence in COVID-19. Moreover, the emergence of severe thrombocytopenia warrants an investigative evaluation for alternative etiologies.The occurrence of secondary infections is prevalent in 50% of critically ill COVID-19 patients, particularly those necessitating mechanical ventilation(Hadid et al., 2021).

4. Fibrin split products(FSP)

The Fibrin Split Product (FSP) assay represents a heterogeneous cohort offering a metric for fibrinolysis, exhibiting 100% sensitivity and 67% specificity in diagnosing Disseminated Intravascular Coagulation (DIC). Within the context of COVID-19, FSP levels tend to remain within normal ranges in individuals with mild or early stages of the disease. Conversely, in fatal cases, FSP levels exhibit a notable increase, with survivors showing concentrations around 4 µg/mL, in contrast to non-survivors who display levels at 7.6 µg/mL. Moreover, FSP serves as a prognostic marker, as its progressive elevation is inversely associated with survival rates(Hadid et al., 2021).

5. D-Dimer

Quantitative measurement of D-dimer serves as a valuable instrument in both diagnosing and prognosticating the recurrence of venous thromboembolism (VTE). Additionally, it stands as a sensitive indicator in the early detection of disseminated intravascular coagulation (DIC), albeit with limited specificity. Notably, critically ill patients typically present with elevated D-dimer levels compared to those with less severe conditions, with an observed average level discrepancy of 2.4 mg/L v/s 0.5 mg/L, respectively. Moreover, there exists an inverse correlation between D-dimer levels and survival rates, as demonstrated by Tang et al., who revealed that over 85% of non-survivors of COVID-19 exhibited D-dimer levelsexceeding 3 mg/L(Hadid et al., 2021).

Mechanism of Coagulation

Macrophage activation syndrome results from overproduction of inflammatory cytokines and chemokines like TNF-α, IL-1, 6, and 8. This syndrome leads to the upregulation of tissue factor expression in endothelial cells, macrophages, and neutrophils within the lungs, consequently initiating and exacerbating pulmonary coagulopathy and microvascular thrombosis. In severe cases of COVID-19 infection, IL-6 emerges as a pivotal cytokine with substantially elevated levels. Studies have reported median IL-6 concentrations ranging from 121 to 218 pg/mL in COVID-19 patients requiring mechanical ventilation. Furthermore, preclinical models have demonstrated that SARS-CoV disrupts the delicate equilibrium between plasmin and the urokinase pathway, resulting in the accumulation of fibrin(Hadid et al., 2021).

The phenomenon known as cytokine storm precipitates a cascade of pathological events within the pulmonary system, resulting in diffuse alveolar damage and pulmonary edema. Viral infection and the subsequent release of pro-inflammatory cytokines trigger the activation or injury of endothelial cells lining blood vessels, thereby promoting the aggregation of platelets and monocytes along the vascular endothelium. Concurrently, this vascular insult prompts an upregulation of tissue factor (TF) expression, instigating the initiation of the extrinsic pathway of the coagulation cascade and ultimately culminating in the formation of thrombi.Additionally, thrombotic microangiopathy may ensue as a consequence of elevated levels of uncleaved large multimers of von Willebrand factor (VWF), attributable to diminished plasma levels of

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ADAMTS13. Compounding these effects, the viral infection of blood vessel endothelium results in the internalization of angiotensin-converting enzyme 2 (ACE2) and an increase in the shedding activity of ADAM17. This dual action leads to the downmodulation of ACE2 and the release of TNF-α and IL-6R, exacerbating the dysregulation of the renin-angiotensin system (RAS) and intensifying the inflammatory response.Furthermore, the exposure of phosphatidylserine (PtdSer) on the outer leaflet of cell membranes due to viral infection emerges as a pivotal mechanism underlying the activation of tissue factor (TF) and the extrinsic pathway of the coagulation cascade, amplifying the inflammatory cascade(Argañaraz et al., 2020).

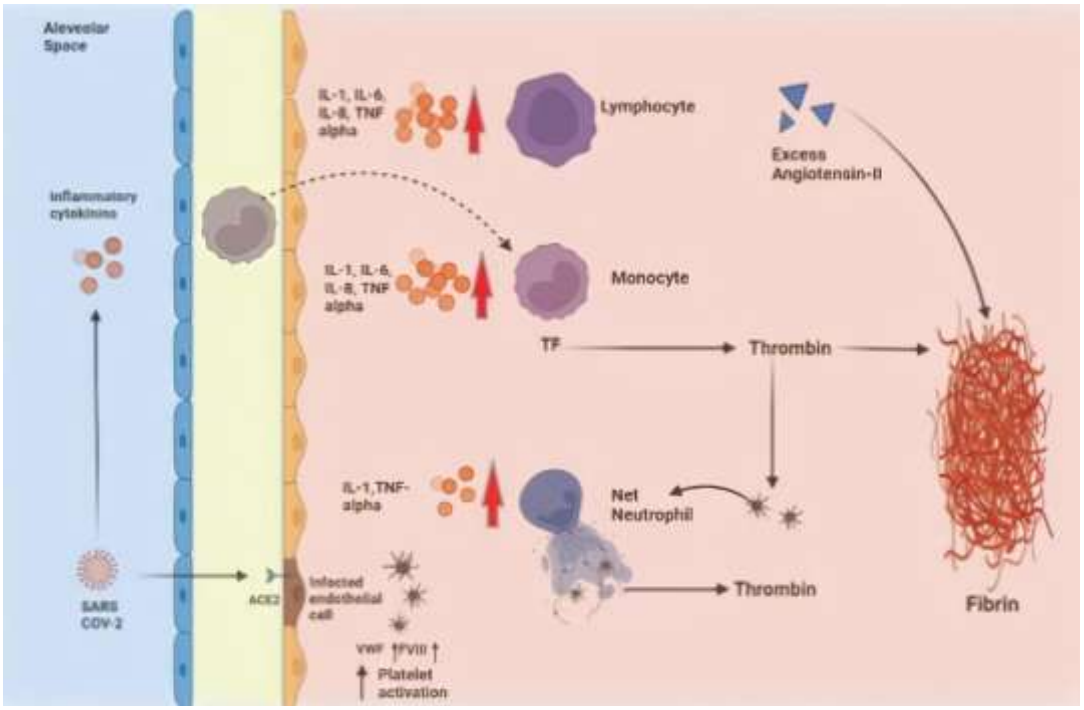

Figure 1 IllustrativediagramshowingCov-2 inducedcoagulationpathway

PREVALANCE

Utilizing the Centers for Disease Control and Prevention's (CDC) worldwide Covid-19 monitoring platform, statistical information pertaining to the documented instances of Covid-19 infections and the associated mortality rates were retrieved.

By gaining access to the global Covid-19 monitoring network of the Centers for Disease Control and Prevention (CDC), extensive data on confirmed cases of Covid-19 infections and associated death rates were retrieved. This platform provides a comprehensive statistical insight repository that facilitates well-informed study of the global pandemic's progression. Researchers and decision-makers may create focused measures to slow the virus's transmission and lessen its effects on public health systems by utilizing this abundance of data. These data-driven strategies are crucial for navigating the current pandemic's intricacies and protecting the world's population from its harmful impacts(Miller et al., 2020).

Chart 1: Presents the rankings of the top 10 countries based on their cumulative Covid-19 infection and fatality burden, both in absolute numbers and relative to their population size.

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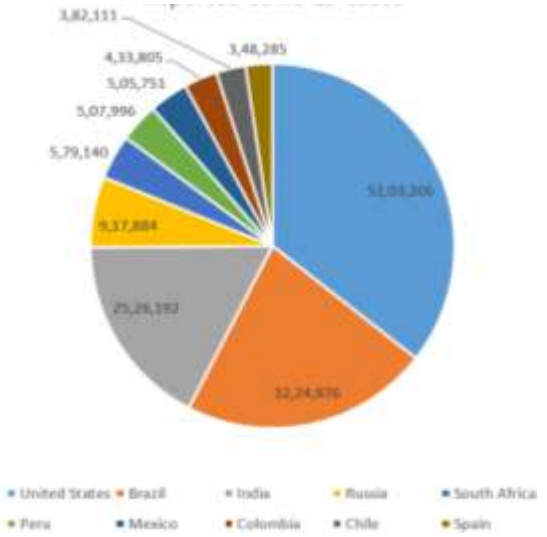
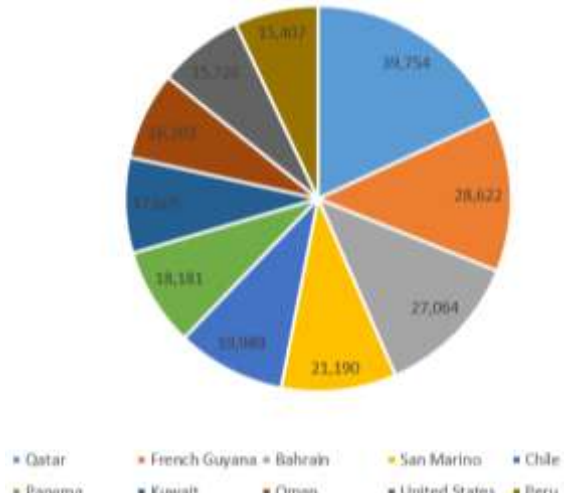
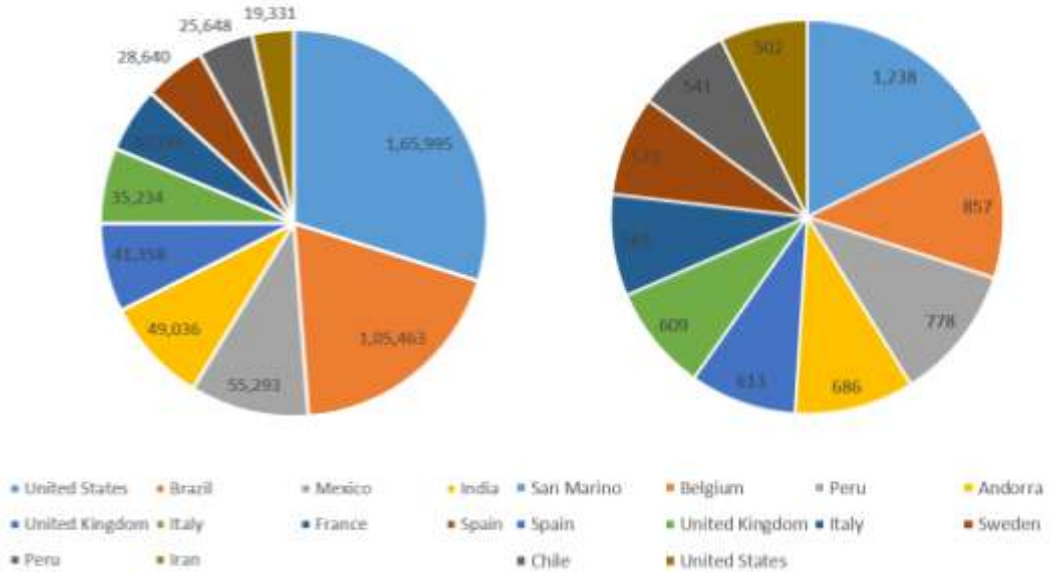


Reported Covid-19 Cases



Covid-19 Cases per Million

The data reveals the top 10 countries bearing the greatest burden of Covid-19 infections and fatalities. The United States leads with 5,203,206 confirmed cases, followed by Brazil with 3,224,876 cases and India with 2,526,192 cases. With differing numbers of instances, South Africa, Peru, Russia, Mexico, Chile, Colombia, and Spain complete the list. These statistics provide valuable insights into the worldwide dissemination and repercussions of the pandemic.



Reported Fatal Covid-19 cases

Fatal Covid-19 cases per Million

The provided dataset elucidates the rankings of the top 10 nations concerning the cumulative burden of Covid-19 infections and fatalities, both in absolute terms and normalized to their respective population magnitudes. At the forefront of reported fatal Covid-19 cases stands the United States, registering 165,995 fatalities, succeeded by Brazil with 105,463, and Mexico with 55,293. India closely follows with 49,036 fatalities. Subsequently, the United Kingdom, Italy, France, Spain, Peru, and Iran occupy the subsequent positions in descending order of reported fatalities. This dataset highlights the gravity of the pandemic's impact globally, offering

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insights into the distribution of infection and fatality burdens concerning the population sizes of these nations.

This systematic review encompasses analysis of data from 19 distinct studies, incorporating a collective cohort of 2,520 COVID-19 patients who required hospitalization. Thirteen studies retrospectively analyzed cohorts. In 2020, research thoroughly emphasized various demographic characteristics. Notably, in France, the adjusted sample sizes ranged from 2,618 to 38,813 hospitalized patients. The distribution of research efforts concerning patient care settings revealed eight studies focused solely on patients in the intensive care unit (ICU), eight studies encompassing both ICU and non-ICU patients, and two studies specifically targeting non-ICU patients. The research by Tsaplin et al. reported on thromboembolism prevalence in hospitalized COVID-19 patients. However, the participants were unnamed. Overall data showed thromboembolism prevalence ranging from 2.9% to 85.4%. In ICUs specifically, it spanned 16.8% to 85.4%. Geographically, the research was exclusively conducted within Europe and Asia. Specifically, eight studies originated from France, two from China, two from the Netherlands, and one each from Italy, Russia, the United Kingdom, and Spain(Kefale et al., 2020).

Table 1 presents a thorough summary of the salient features from the integrated research on COVID-19 patients experiencing thromboembolic events is provided in Table 1. It provides a thorough summary of all relevant variables, such as treatment methods, outcomes, test results, clinical presentation, demographics, and comorbidities. It clarifies the complex nature of thromboembolic events in the context of COVID-19 by combining data from several research, enabling a clearer comprehension of the risk factors, diagnostic techniques, and treatment treatments that are linked to them. This thorough study helps to improve clinical care and directs future studies in this important field.

Authors	Design Of Study	Country of Study	Sample Size	Admission (Ward/Class)	Prevalence of TE, N(in%)
Tsaplin et al.	RC	Russia	168	Not Clear	11(6.5)
Demelo-Rodriguez et al.	PC	Spain	156	Non-ICU	23(14.7)
Lodigiani,et al.	RC	Italy	388	ICU and Non-ICU	28(7.7)
Zhang et al.	CS	China	143	ICU and Non-ICU	66(46.1)
Xu et al.	RC	China	138	ICU and Non-ICU	4(2.9)
Artifoni et al.	RC	France	71	Non-ICU	23(32.5)
Middeldorp et al.	RC	Netherlands	198	ICU and Non-ICU	33(17)
Nahum et al.	PC	France	34	ICU	27(79)
Chen et al.	RC	China	88	ICU	40(46)
Llitjos et al.	RC	France	26	ICU	18(69)
Helms et al.	PC	France	150	ICU	64(42.7)

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Cui et al.	RC	China	81	ICU	20(25)
Klok et al.	PC	Netherlands	184	ICU	31(16.8)
Whyte et al.	RC	United Kingdom	214	ICU and Non-ICU	80(37)
Grillet et al.	RC	France	100	ICU and Non-ICU	23(23)
Leonard-Lorant, et al.	RC	France	106	ICU and Non-ICU	32(30)
Ren et al.	CS	China	48	ICU	41(85.4)
Bompard et al.	RC	France	135	ICU and Non-ICU	32(23.7)
Fraisse et al.	RC	France	92	ICU	37(40)

Note: ICU: Intensive CareUnit, CS:Cross sectional, TE: Thromboembolism, N:Number, PC:ProspectiveCohort, RC: Retrospective Cohort

Through analysis of the data in Table 2, it can be concluded that hospitalized COVID-19 patients have an overall prevalence of thrombotic events of 33%. It is discernible that the propensity for thromboembolism is contingent upon the particularities of the research framework and the site of admission. Notably, admission to the intensive care unit (ICU) correlates with an escalated susceptibility to thromboembolic occurrences.

In pursuit of quantifying the prevalence of acquired thrombophilia, a comprehensive investigation engaged a cohort comprising 89 patients. The characteristics of the populace are delineated in Table 3, elucidating the demographic attributes therein.

Table 2 Covid-19patientscharacteristics

Covid-19patientscharacteristics(n=89)	
Age	68(63-71)
Sex:Male	68.5
CRPmg/L	105(85-103)
Fibrinogeng/l	6.45(5.96-6.75)
D-dimerng/ml	1799(1441-2352)
Activated partial thromboplastin time (sec)	29.7(29.3-30.1)
Prothrombin Time (%)	83(81-85)
Severeform	31/89(35%)
DVTorPE	14/89(15.7%)
Death	10/89(11%)

Note: CRP: C-reactive protein, DVT: Deep vein thrombosis, PE: pulmonary embolism

None of the patients had prior encounters with thrombotic episodes. Covid-19 infection manifested severely in 31 cases, leading to critical care interventions and/or respiratory support. C-reactive protein (CRP) levels surged to a peak of 105 mg/l. The median fibrinogen level stood at 6.45 [5.96-6.75] g/l, while the median concentration of D-dimer measured 1799 [1441-2352] ng/ml. Nine patients developed deep vein thrombosis symptoms without pulmonary embolisms. Another seven suffered pulmonary embolisms with symptoms. All events occurred during hospitalization. The overall mortality rate was 11%, with no instances of arterial thrombosis observed in this cohort. The comprehensive coagulation profile was analyzed for the entire patient cohort, distinguishing between severe and non-severe cases. Although prothrombin time (PT)

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and activated partial thromboplastin time (aPTT) exhibited no significant disparities, D-dimer concentrations were notably higher in severe cases compared to non-severe ones ($p<0.001$). However, the fibrinogen levels between these groups did not demonstrate a substantial difference ($p=0.1$). A minimal occurrence of protein C (PC) or antithrombin (AT) deficiencies was identified, with median values of 58% (54-62) and 64% (61-69), respectively. In terms of protein S (PS) insufficiency, 20% of patients exhibited a major deficit, with a median PS value of 31% (24-45). There was no discernible variance in the prevalence of PS insufficiency between non-severe and severe patients (22% v/s 19%). Additionally, the average values of PS deficit were comparable between severe and non-severe cases, measuring 32% (24-42) and 31% (25-45), respectively.

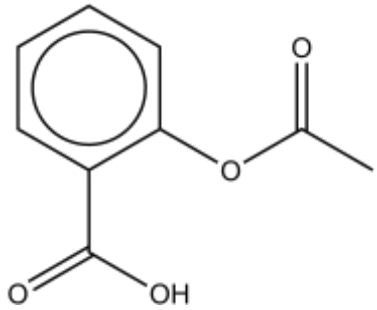
The prevalence of antiphospholipid antibodies (aPL) was found to be notably high, with a striking 71.9% of patients exhibiting positivity for at least one type of aPL test. Remarkably, there was no discernible distinction in prevalence between the two groups studied. Among the positive tests, lupus anticoagulant (LA) was the most prevalent, detected in 66.3% of patients, with a median positivity titer of 1.36 [1.33-1.41]. Furthermore, 6.7% of patients had 2-glycoprotein I antibodies. Specifically, four cases had IgG alone, one had IgM alone, and another had both IgG and IgM. The median positive titer was 44.7.Furthermore, anti-cardiolipin antibodies (aCL) were present in seven instances (7.9%), with IgG subtype in five cases and IgM subtype in two cases, exhibiting a median positivity titer of 36.3 (23-260). Notably, two patients (2.2%) were found to be triple positive (LA + 2GPI), while three patients (3.4%) exhibited double positivity (LA + 2GPI). Importantly, all of these findings were validated through a confirmatory second assay.

None of the patients exhibited awareness of an underlying antiphospholipid syndrome (APS) or presented with symptomatic manifestations attributable to an undiagnosed APS. The presence of antiphospholipid antibodies (aPL) did not yield a statistically significant impact on the initial activated partial thromboplastin time (aPTT) readings ($p=0.55$). In our cohort, aPL were detected in 71 percent (22/31) of severe cases and 72.4 percent (42/58) of less severe cases (p=NS), with severity classification based on the requirement for intensive care hospitalization and/or mechanical ventilation due to Covid-19 infection. They further investigated the presence of primary antiphospholipid syndrome (PS) insufficiency or positivity for aPL, alongside other proposed criteria for assessing the severity of Covid-19 infection. Patients displaying PS insufficiency or positivity for aPL did not exhibit elevated concentrations of D-dimer, fibrinogen, or C-reactive protein (CRP). Furthermore, no correlation existed between positive thrombophilia test results and deep vein thrombosis, pulmonary embolism incidence, or in-hospital mortality in patients without anticoagulant adjustment. This observation held true even when examining patients who were positive for two or three types of aPL. Ultimately, no correlation was established between any of these coagulation abnormalities and mortality rates(Ferrari et al., 2020).

TREATMENT

Many potential medications have been chosen and tested for their anticoagulant activity in order to treat and prevent thromboembolism induced by SARS Cov-2.

1. Aspirin



The antithrombotic impacts of aspirin have been thoroughly researched over time. Aspirin permanently hinders cyclooxygenase (COX), thus lowering platelet tally.Aspirin irreversibly binds to serine 530 on cyclooxygenase (COX)-1. Typical doses of 75-81 mg daily are enough. This reduces platelet thromboxane A2. As a result, aspirin provides antithrombotic benefits.The COX-1 and COX-2 enzymes are inhibited at intermediate dosages (650 mg to 4 g/day), which has analgesic, anti-inflammatory, and antipyretic properties.Studies have demonstrated the antiviral qualities of aspirin, which include the augmentation of type I interferon production and the suppression of prostaglandin E2 (PGE2) synthesis in macrophages, despite the fact that it is not frequently included in SARS-CoV-2 therapy regimens. In lung injury models, aspirin has been shown to reduce neutrophil and platelet aggregation, and platelets are also involved in the

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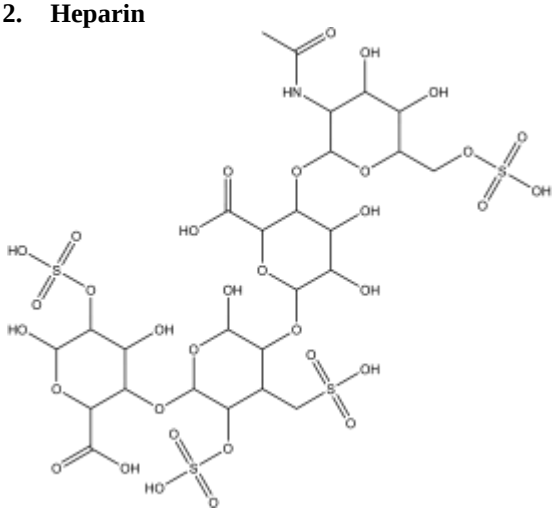
innate immune response. There is ongoing research on the potential links between NSAIDs and respiratory and cardiovascular side effects, leading to caution against routine NSAID use for managing COVID-19 symptoms. Aspirin administration to pediatric or adolescent patients is contraindicated due to the risk of Reye's syndrome. Evidence on the association between COVID-19, SARS, or MERS infections and mortality in both adults and children remains of very low certainty. The impact of NSAIDs on the risk of stroke and myocardial infarction in individuals with acute respiratory infections is also undetermined. Research suggests minimal differences between Ibuprofen and acetaminophen regarding their effects on mortality, hospitalization, renal failure, and gastrointestinal bleeding in pediatric patients with fever. Aspirin exhibits multifaceted effects, including anticoagulant and anti-inflammatory properties, and inhibition of platelet aggregation, which may help mitigate lung damage in COVID-19 patients. However, caution is advised, especially in patients with disseminated intravascular coagulation (DIC) or other venous thromboembolic events associated with severe COVID-19, as aspirin could exacerbate bleeding tendencies, particularly in individuals with severe thrombocytopenia(Mohamed-Hussein et al., 2020).

When complete clinical data were available in 1994, RT-PCR analysis verified that the patients under investigation had the SARS-CoV-2 amplicon. Among the cohort, there were 1709 individuals who had not been exposed to aspirin, while 285 had been. To discern whether the effects observed were specific to aspirin or more broadly related to no steroidal anti-inflammatory drugs (NSAIDs), the study included 1445 patients who had not received NSAID therapy and 465 who had. The trial yielded intriguing results, indicating that low-dose aspirin treatment did not confer protection against mortality or thrombotic events in COVID-19 patients. Several factors may contribute to this outcome, including the dosage administered, the potential insensitivity of COVID-19 to aspirin's mechanism of platelet inhibition, or alterations in platelet phenotype induced by the virus. Research by Manne et al. provided evidence of disrupted platelet function and altered phenotype in COVID-19 patients. Additionally, prior work by Cameron et al. demonstrated a distinct platelet profile in individuals with chronic vascular disease and diabetes, suggesting that sick platelets may exhibit diminished responses to aspirin and clopidogrel(Sahai et al., 2021).

2. Heparin



Heparin is a complex mixture consisting of long, linear chains of highly sulfated heparan sulfate (HS) glycosaminoglycans derived from the intestines of swine. These chains confer heparin with a remarkable negative charge density, making it one of the most negatively charged biomolecules known. This high level of sulfation distinguishes heparin from other glycosaminoglycans and contributes to its diverse biological activities and clinical applications. The electric charge of heparin enables it to form strong and selective interactions with a diverse array of proteins. One of its most notable effects is its ability to prevent blood clotting, achieved through its interaction with the serine protease inhibitor antithrombin-III (AT3). This interaction requires the presence of a specific pentasaccharide sequence within longer heparan sulfate (HS) chains, which facilitates binding to AT3 and thus confers its anticoagulant properties. In addition to its interaction with AT3, heparin is known to engage with hundreds of other biologically relevant proteins. This broad spectrum of interactions has led to the discovery of numerous potential off-target effects of heparin, the clinical consequences of which remain uncertain. Overall, the complex network of heparin-protein interactions highlights its versatility and potential for diverse biological effects. A retrospective analysis conducted in Wuhan, China, examined 449 COVID-19 patients and investigated the potential use of heparin as an anticoagulant in managing the disease. The study was groundbreaking in its exploration of heparin's role in COVID-19 treatment. It was observed that prophylactic doses of heparin are not typically administered to medical patients in Wuhan due to the low incidence of venous thromboembolism (VTE) in the population.

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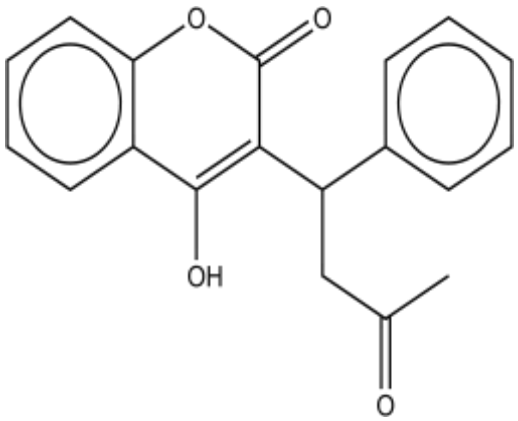
Out of the 449 patients studied, 350 did not receive any form of heparin therapy, while 99 were administered low-dose prophylactic heparin. Notably, patients who received prophylactic heparin and showed elevated levels of d-dimer or sepsis-induced coagulopathy scores experienced a 20% decrease in mortality compared to those who did not receive such treatment.

Moreover, intravenous Tissue Plasminogen Activator (tPA), a potent thrombolytic agent, has shown effectiveness in improving oxygenation levels in COVID-19-related acute respiratory distress syndrome. Heparin sulphate is theorized to interact with the spike protein of SARS-CoV-2 as an adhesion molecular co-receptor, possibly serving as the initial point of interaction between the virus and the ACE2 receptor. This interaction exhibits a higher affinity compared to other coronaviruses like SARS-CoV and MERS-CoV. Despite ongoing research efforts, pharmaceutical interventions for COVID-19 remain limited. While heparin shows promise in managing the coagulopathy associated with the disease, the use of therapeutic anticoagulation before thrombosis occurs in COVID-19 is still not well-studied.

Additionally, it's important to recognize that heparin has non-anticoagulant properties that could be beneficial in COVID-19 patient care. However, a comprehensive understanding of the efficacy and safety of pre-thrombotic anticoagulation with heparin in the context of COVID-19 requires further rigorous scientific investigation(Hippensteel et al., 2020). The correlation between obesity and increased susceptibility to severe COVID-19 has gained widespread acknowledgment within the medical community. Obese individuals constitute a substantial portion of COVID-19 patients requiring hospitalization.

This phenomenon can be attributed, in part, to the association between high body weight and diminished levels of anti-factor Xa, a key component involved in coagulation pathways. In light of this, implementing a tailored dosing regimen utilizing low molecular weight heparin (LMWH) guided by anti-factor Xa levels could serve as a strategic intervention to mitigate the risk of thromboprophylaxis failure in obese patients(Kow & Hasan, 2020).

3. Warfarin



A systematic algorithm has been proposed for the management of outpatient warfarin therapy, outlined to enhance the discussion that follows. Table 3 illustrates a comparative analysis of various anticoagulant strategies.

Table 3 Comparative analysis of various anticoagulant strategies

Situation	Warfarin	DOACs	LMWH/fonaparinux
A recommendation for long-term outpatient therapy	Antiphospholipid syndrome, cardioembolic ischemic stroke, VTE (DVT, PE), prosthetic heart valve, and atrial fibrillation	VTE (DVT, PE), cardioembolic ischemic stroke, AF	VTE(DVT,PE)
Dosing	Oral dosage once daily	Oral dosage: one time or two times a day	One or two subcutaneous injections per day
Monitoringtherapy	Regular INR monitoring is necessary, which means that most patients must visit a clinic on a regular basis or, for qualified applicants, self-test.	Regular CBC and kidney function monitoring	Regular evaluation of renal function, CBC, and antiXa levels (when applicable)

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Effect of comorbid conditions	Renal function has little effect on pharmacokinetics, thus patients who are exceedingly fat need not be concerned about dose.	Pharmacokinetics are impacted by renal function; dosage should be carefully considered in patients with excessive obesity; and cancer patients lack clinical experience.	Pharmacokinetics are impacted by renal function; dosage in severely obese patients is uncertain.
Other concerns	A month's supply is manageable despite numerous DDIs, food and drug interactions, and herb interactions.	Few DDIs, insufficient clinical expertise with patients who are nursing, and a tolerable one-month supply	LMWH: Porcine-derived heparin may cause thrombocytopenia when administered to persons who practice Islam; One-month supply is challenging to manage. Fondaparinux: insufficient clinical background in individuals who are nursing

Note: A systematic approach to the management of warfarin in outpatient settings is given. DOAC (direct oral anticoagulant), INR (international normalized ratio), and LMWH (low-molecular-weight heparin).

(a) Consider the current risk of bleeding and whether the prescription for warfarin is appropriate.

(b) Consider the presence of DOACs in the drug list, situations where their usage might not be ideal, any possible risks, and monetary constraints.

(C) This applies exclusively to patients with venous thrombosis. Considerations include cost, suitability for injection, kidney health, and personal preference. The feasibility of self-administration and/or self-monitoring of INR should also be considered, as well as the need for training prior to initiation. Other things to think about are access to surrounding healthcare services and financial implications.

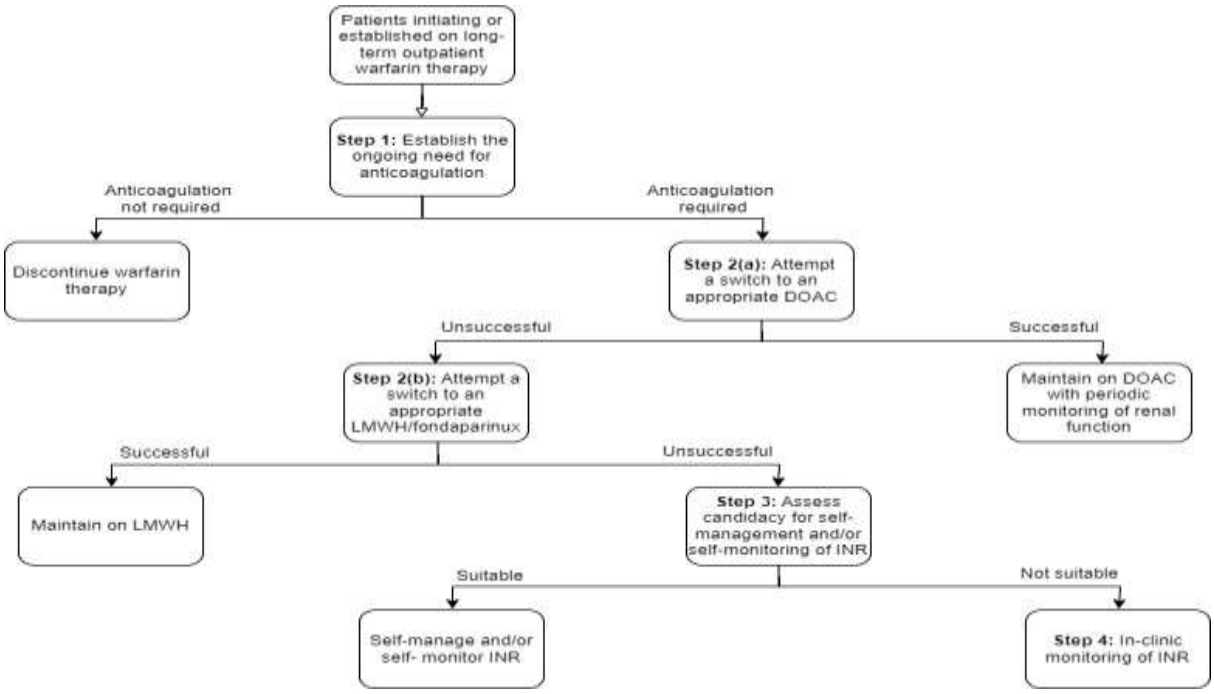

Figure 2 Atrial fibrillation (AF), lowmolecular-weight heparin (LMWH), direct oral anticoagulants (DOACs), INR (international normalized ratio), DVT (deep vein thrombosis), drug-drug interactions (DDIs), VTE (venous thromboembolism) and PE (pulmonary embolism)

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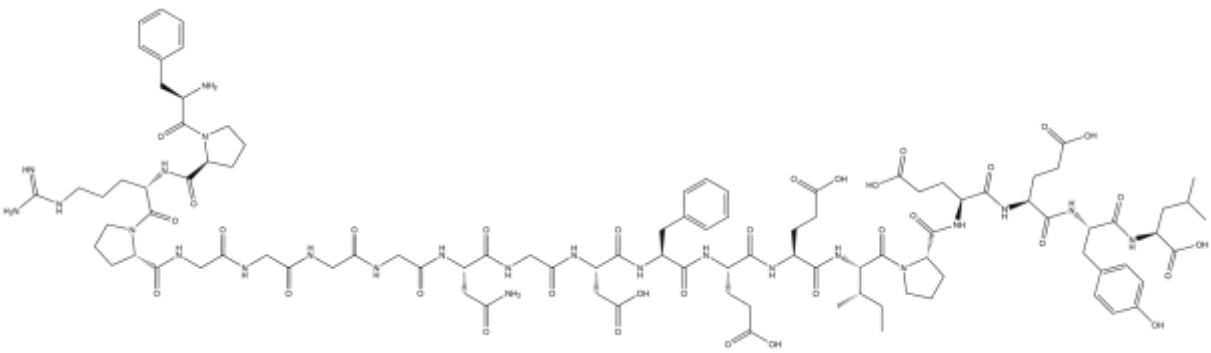
Warfarin initiation typically occurs within a hospital setting, after which patients are discharged with instructions for follow-up care by their primary care physician. Regardless of the initial context, clinicians must diligently evaluate the rationale for continuing warfarin therapy as an outpatient. This assessment process is essential for ensuring appropriate management and monitoring of the patient's condition. Those individuals who have undergone a three to six month warfarin treatment regime and possess recorded evidence of conditions such as deep vein thrombosis (DVT) or pulmonary embolism (PE) may be considered for termination of drug use. For individuals experiencing a provoked incident of venous thromboembolism (VTE) due to transient risk factors, such as surgery or immobilization, and assuming the risk factor is no longer present, the decision to extend anticoagulation therapy beyond the typical 3-6 month duration is not typically automatic. Particularly, this applies to individuals who are prone to subsegmental or unintended pulmonary embolisms (PE), isolated distal deep vein clots (DVT), or those who have a higher likelihood of bleeding. The decision to prolong anticoagulation therapy in such cases requires careful consideration of the potential benefits weighed against the risks, taking into account individual patient factors and preferences, as well as emerging evidence from clinical studies. Patients who rely on warfarin for secondary prophylaxis of venous thromboembolism indefinitely should undergo periodic reassessment of their bleeding risk. Grasping the fact that the benefits of taking warfarin medication to avert repeat venous thromboembolism could be overshadowed by a marked or excessively high danger of bleeding is essential. Thus, clinicians must carefully weigh the potential risks and benefits of continued warfarin use in such patients, considering alternative therapeutic options if necessary. The utilization of warfarin medication may no longer be deemed necessary due to certain circumstances; however, it may be prudent to resume anticoagulation once the bleeding risk diminishes to a reasonable level. This recommendation stems from the heightened risk of atrial fibrillation recurrence within the initial month following the restoration of sinus rhythm, as well as the potential for transient post-cardioversion atrial stunning during the immediate peri-cardioversion phase. Consequently, it is advised to maintain warfarin therapy for a duration of up to four weeks subsequent to the re-establishment of sinus rhythm.

For patients with sufficient reasons to carry on using warfarin medication, it might be prudent to evaluate transitioning them to direct oral anticoagulants (DOACs). These could include medications like dabigatran, rivaroxaban, apixaban, and edoxaban. Anticoagulation with each of the DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) has led to similar or lower rates of both ischemic stroke and major bleeding compared with adjusted-dose warfarin (INR 2.0–3.0) in patients with nonvalvular atrial fibrillation in large randomized trials. The majority of these clinical studies were structured as noninferiority trials, aiming to compare Direct Oral Anticoagulants (DOACs) with conventional anticoagulation therapy, typically consisting of initial heparin administration followed by oral warfarin. The findings consistently demonstrated comparable levels of safety and efficacy between the two treatment modalities(Kow et al., 2020).

4. Bivalirudin



COVID-19 induces profound hypoxemia refractory to conventional mechanical ventilation, compelling the imperative escalation towards extracorporeal membrane oxygenation (ECMO) in

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meticulously chosen individuals. Bivalirudin is a direct thrombin inhibitor that produces transitory inhibition of thrombin to prevent fibrinogen from being cleaved to its active state. Moreover, their ability to directly capture and restrain both adhered fibrin and thrombin that freely circulates might hold advantages during treatments involving extracorporeal membrane oxygenation (ECMO). Bivalirudin, a medication granted approval by the U.S. Food and Drug Administration, is greenlit for use in adult individuals undergoing percutaneous coronary intervention (PCI). This approval extends for a concise duration, up to four hours following the surgical procedure. This medicine is double-acting, semi-synthetic and serves as a thrombin prohibitor whose function is to temporarily halt the action of thrombin.Bivalirudin, thanks to its metabolic process that's largely independent of organ performance, boasts a brief half-life approximately 25 minutes in individuals possessing typical kidney effectiveness. When opposed to heparin, other stated advantages of this medication class include the capacity to suppress both circulation and clot-bound thrombin, as well as the lack of correlation with HIT(Seelhammer et al., 2021). A woman, 65 years in age with a prior medical record of high blood pressure and elevated cholesterol levels, was hospitalized due to low-oxygen and high-carbon-dioxide levels in her bloodstream. This significant health deterioration was confirmed by a PCR test to be an outcome of an authentic COVID-19 infection. She was sent to the authors' facility so that ECMO treatment might be investigated. Key clinical events are enumerated in the following figure.

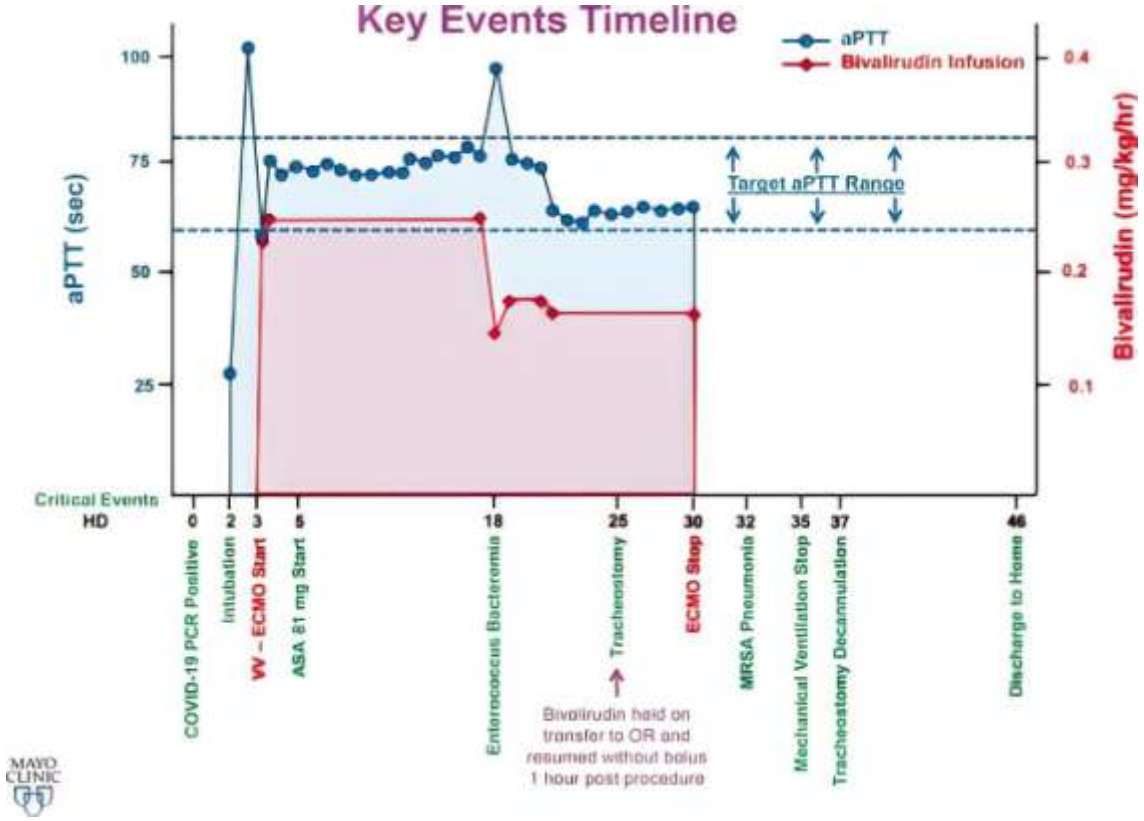

Figure 3 Timeline of important events. The y-axis overlays the values of the activated partial thromboplastin time (scaled on the left margin in seconds) and the dose of bivalirudin (scaled on the right margin in mg/kg/h). The x-axis shows noteworthy events by hospital day. The dotted line represents the goal range activated partial thromboplastin time, which is 60 to 80 seconds. Active partial thromboplastin time, or aPTT; The terms aspirin, coronavirus illness 2019, hospital day, polymerase chain reaction, MRSA (methicillin-resistant Staphylococcus aureus), OR (operating room), and VV-EMCO (venovenous extracorporeal membrane oxygenation) are used in this sentence(Seelhammer et al., 2021).

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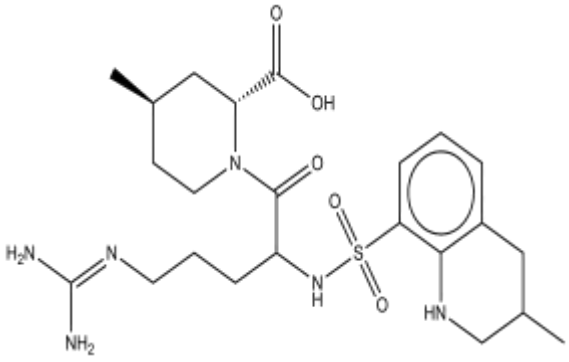
Bivalirudin, due to its ability to directly bind to and inhibit both circulating and fibrin-bound thrombin, along with its predominantly organ-independent clearance, is employed in the setting of extracorporeal membrane oxygenation (ECMO). Bivalirudin was successfully administered continuously as part of a treatment plan for a COVID-19 positive patient who had severe hypoxemic and hypercarbic respiratory failure and required veno-venous ECMO (VV-ECMO). It was shown that therapeutic anticoagulation was achieved quickly, that pharmacokinetics were stable, and that dose titration was quite simple. Throughout her 27-day ECMO stay, she did not require any circuit procedures, such as oxygenator exchange or thrombus excision. Bivalirudin may be a viable choice for sustaining systemic anticoagulation during ECMO in the COVID-19 era, with the ability to attenuate the prothrombotic character of the underlying pathophysiologic state(Seelhammer et al., 2021).

5. Argatroban



The synthetic small molecule and peptidomimetic argatroban inhibits thrombin, an essential enzyme involved in blood coagulation. At about 39 nanomolar (nM), its Ki value indicates that it has strong activity. Argatroban, in contrast to heparins, works by directly blocking thrombin, both free and linked to clots, without the need for antithrombin to be present. Parenterally given, this reversible inhibitor exhibits competitive inhibition against thrombin with good specificity. This actively stops blood-clotting components V, VIII, and XIII from getting triggered by thrombin, thus inhibiting the formation of fibrin, a protein that aids blood clots. To further decrease the development of clots, it also suppresses the activity of protein C, an anticoagulant protein, and inhibits platelet aggregation. The year 2000 saw the US Food and Drug Administration (FDA) granting approval to argatroban. Its use was recognized for both the treatment and prevention of thrombosis, a condition occurring among patients suffering from heparin-induced thrombocytopenia (HIT). Moreover, it is used as an anticoagulant for persons who have HIT or are at risk of getting it following percutaneous coronary intervention (PCI)(Aliter & Al-Horani, 2021).

In our investigation, ten patients with COVID-19 were included; despite taking preventive doses of low molecular weight heparin (LMWH), ninety percent of them presented with confirmed thrombosis upon admission. These patients exhibited heparin resistance attributed to low levels of antithrombin (AT), necessitating alternative anticoagulation therapy with argatroban, which proved successful. The median age of the cohort was 44.5 years, ranging from 22 to 61, with the majority (90%) being male. Every room—eight of which were on ECMO—had a mechanical ventilation system. All patients were started on UFH according to institutional procedure, with a weight-adjusted IV bolus followed by a 12units/kg/hour initial infusion rate (representing concern aboutincreased bleeding risk in critically unwell patients) adjusted to maintain a heparin level of 0.3-0.7anti-Xa units/mL. (Arachchillage, Kamani et al. 2017). Argatroban infusion was initiated at a rate of 0.3 grams per kilogram per minute and titrated upward gradually until the activated partial thromboplastin time (APTT) reached the target range of 47-78 seconds. Subsequent monitoring revealed no additional thrombotic events, including renal replacement therapy or extracorporeal membrane oxygenation (ECMO) circuit thrombosis, or ECMO cannula thrombosis. As patients recovered from COVID-19, their antithrombin (AT) levels either improved or remained low until their demise (Arachchillage et al., 2020).

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Table 4 Overall characteristic of ten patients

Characteristic	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
Age(in years)	36	38	48	54	22	61	54	43	45	44
Sex(male/Female)	M	M	M	M	M	M	M	M	F	M
Past history of thrombosis	N	N	N	Y	N	N	N	N	N	N
Thrombotic incident during our unit's presentation	PE	PE	PE	Absence of sickle cell trait in acute thrombosis	Subacute thrombus in the right iliac vein, PE, and right MCA infarct	PE	PE	PE	PE on both sides and ischemic basilar stroke	Microvascular disorders of the lungs and intestinal ischaemia
On VV-ECMO	Y	Y	Y	Y	N	N	Y	Y	Y	Y
On renal replacement therapy	N	Y	Y	Y	Y	Y	Y	Y	N	Y
AT level on admission(IU/dL)	28	26	43	20	19	49	44	32	43	39
Maximum UFH dosage administered before switching to argatroban (units/kg/hr)	17	16	21	12.5	20	23	18	20	15	15
Bleeding issue when on argatroban, including brain CT showing signs of ICH	None	None	None	Clinically significant mild hemorrhage due to hemorrhoids	haemorrhagictransformation of MCAinfarct	bleeding from the rectal artery that has to be plugged	None	None	None	None
Progression or new thrombosis whilst on argatroban	N	N	N	N	N	N	N	N	N	N

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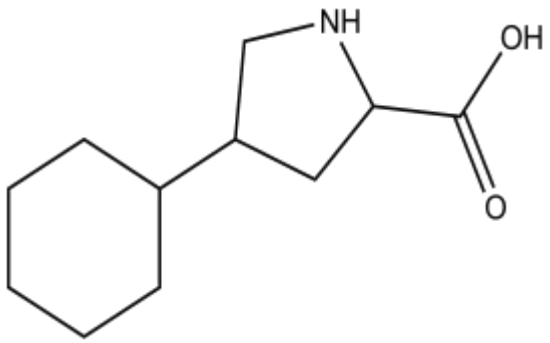
Thrombosis inECMOorRRT circuit whilstonArgatroban	N	N	N	N	N	N	N	N	N	N
Clinicaloutcome	Living	Living	Living	Living	Deceased	Deceased	Living	Living	Deceased	Deceased
Cause of death	NA	NA	NA	NA	The hemorrhagic transformation of MCA injury and MOF	MOF and Rectal Artery Bleeding	NA	NA	MOF	Bowel preformation and MOF - on
AT level at death or discharge (IU/dL)	106	76	107	75	47	56	81	86	64	105

Note:Antithrombin (AT), Veno-extracorporeal membrane oxygenation (VV-ECMO), pulmonary embolism (PE), multiorgan failure (MOF), middle cerebral artery (MCA), and renal replacement therapy (RRT) are some such terms. P stands for patient numbers, N stands for NO, Y stands for YES.(Arachchillage et al., 2020).

Argatroban's diverse pharmacological activities, which include antithrombotic, anti-inflammatory, and antiviral qualities, make it a promising treatment drug for COVID-19 and its related comorbidities. Numerous studies carried out in diverse experimental models, including cellular research, animal trials, and human subject clinical examinations, have validated these qualities. Because of its pharmacological profile, argatroban may be able to reduce aberrant coagulation, reduce excessive inflammatory reactions, and prevent the virus from replicating, especially in patients with severe instances of COVID-19 who are critically sick(Aliter & Al-Horani, 2021).

6. Streptokinase



The thrombolytic activity of streptokinase was checked on 2 patients, the two patients benefitedfrom thrombolysis because it helped them enhance their respiratory function and chest imaging.UnfortunatelyOne patient died as a result of septic respiratory problems. Rescue thrombolysis wasperformed in both cases on a compassionate basis following an interdisciplinary debate. Thistechnique, however, should not be performed on a regular basis unless it is part of a clinicalinvestigation. In both instances, instances of bleeding were observed, which were effectively managed either by halting the infusion or by administering tranexamic acid. Consequently, they posit that thrombolysis may present a viable option for COVID-19 patients who have experienced treatment failure with anti-inflammatory and anticoagulant medications, and who exhibit pulmonary micro or macrothrombosis. However, the efficacy of thrombolysis in COVID-19 patients

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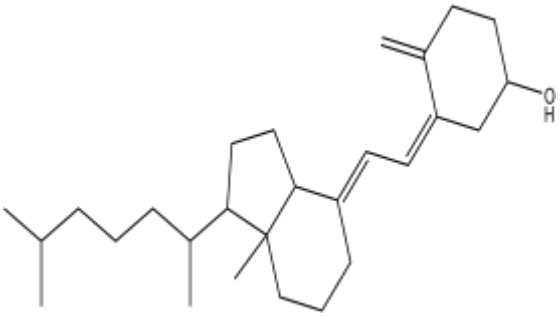
should be substantiated through randomized clinical trials(Caballero López et al., 2021).

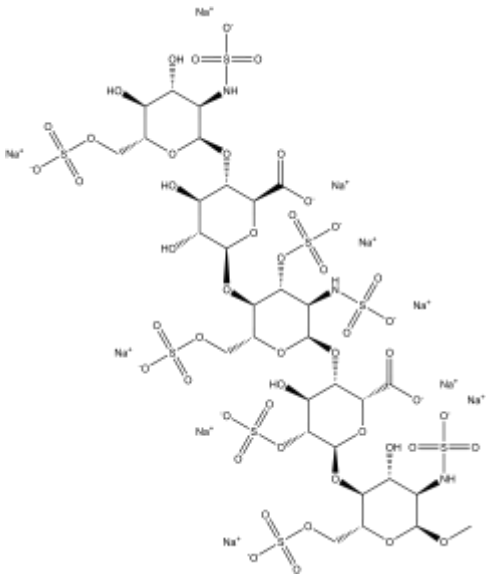
7. Vitamin-D



Our bodies contain two different types of vitamin D, a vital steroid hormone: vitamin D2 and vitamin D3. Initially, both variants experience a metabolic process, transforming into 25 hydroxyvitamin D [25(OH)D]. Subsequently, this form gets morphed into the bioactive version, known as 1,25-dihydroxyvitamin D [1,25(OH)2D]. Research has indicated that vitamin D3 is superior than vitamin D2 in terms of raising blood 25(OH)D concentrations. Following their attachment to vitamin D binding protein (VBP), the active forms of vitamin D are delivered to certain organs where they function as endogenous ligands for vitamin D receptors (VDR). VDR is broadly distributed in many different organs and is a member of the nuclear hormone receptor family. It plays a crucial role in regulating the expression of numerous genes involved in cellular processes such as proliferation, differentiation, apoptosis, and angiogenesis(Sengupta et al., 2021).

According to Connors et al., a personalized evaluation of bleeding risk should be the foundation for determining the appropriate anticoagulant medication dosage for COVID-19 patients. Anticoagulant treatment may have the ability to reduce hemorrhagic consequences by carefully evaluating each patient's risk factors. As part of this risk reduction approach, vitamin D supplementation and a reduced anticoagulant dosage may be used. Research has suggested that vitamin D can help lessen bleeding problems brought on by anticoagulant medication. Hejazi et al.'s research showed that vitamin D supplementation could enable patients with thromboembolism to take less dosages of warfarin, a popular anticoagulant. Furthermore, there were less negative responses associated with this supplementation. Therefore, a preventative dosage of anticoagulant medication combined with vitamin D supplementation shows potential as a treatment for coagulopathy due to COVID-19. The impact of Vitamin D supplements on decreasing the harshness and death rate of COVID-19 due to clotting complications needs more examination in clinical studies. A randomized, double-blind, placebo-controlled study would be the best way to find out how vitamin D supplementation affects COVID-19 results. In the context of COVID-19, such research would offer insightful information on the possible function of vitamin D in controlling thrombotic problems and enhancing patient outcomes(Sengupta et al., 2021).

8. Fondaparinux



VTE prophylaxis was given to 100 consecutive COVID-19 patients admitted to internal medicine units of five Italian hospitals between February 15, 2020, and March 15, 2020, in accordance with international norms. According to local laws, either fondaparinux 2.5 mg daily or enoxaparin 4.000 units/d were administered; moreover, 6.000 units/d of enoxaparin were reserved for patients whose Padua prediction score indicated they were at high risk of VTE. The hospital ethics committee authorized the trial, and each patient provided written consent to take part. The principal safety end objectives have been established by the International Society of Hemostasis and Thrombosis (ISTH) as major bleeding (MB) and clinically relevant non-MB (CRNMB). The main goal for effectiveness was to pinpoint the combination of deep vein thrombosis (DVT) and pulmonary embolism (PE). Both were

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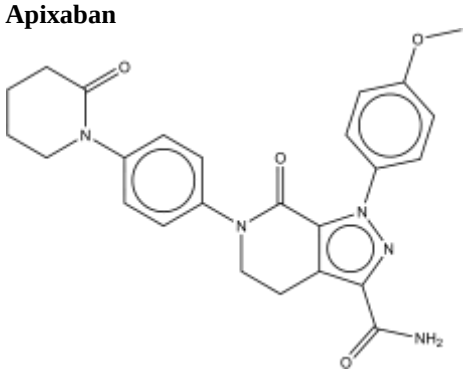
identified using color Doppler duplex sonography and computed tomography pulmonary angiography, correspondingly. Additionally, the secondary aim for efficiency encompassed within-hospital death rates and acute respiratory distress syndrome (ARDS), as outlined by the Berlin crite-ria.During their hospitalization, a noteworthy percentage of patients (38%) were administered fondaparinux. This indicates that the medication's use is gradually rising in Italy's internal medicine departments to deter venous thromboembolism (VTE). Our observational study revealed a comparatively high cumulative incidence of VTE episodes (11%) when heparin-based pharmacological prophylaxis was administered. This percentage, however, was less than that reported in earlier studies carried out in Europe (37%) and China (25%) and only included patients with severe COVID-19 who were referred to critical care units. The idea that fondaparinux 2.5 mg/d is a safe and effective treatment choice for COVID-19 patients admitted to internal medicine units is supported by preliminary studies. However, more large-scale prospective studies with a sizable patient cohort are necessary to confirm and corroborate our field observations(Russo et al., 2020).

9. Apixaban



They delved into the effects of apixaban in treating clotting issues, focusing on confirmed or suspected cases of venous thromboembolism (VTE) or atrial fibrillation (AFib). The study revolved around 21 critically ill individuals battling severe respiratory complications brought on by COVID-19, all of them under intensive care in the ICU. It's significant to note that out of twenty-one patients, eighteen, which is 85.7%, had been taking blood thinning drugs. They were prescribed either enoxaparin or unfractionated heparin (UFH) in the day prior to shifting to apixaban. This subgroup included 11 patients who were undergoing full-dose of therapeutic anticoagulation(Wenzler et al., 2020).

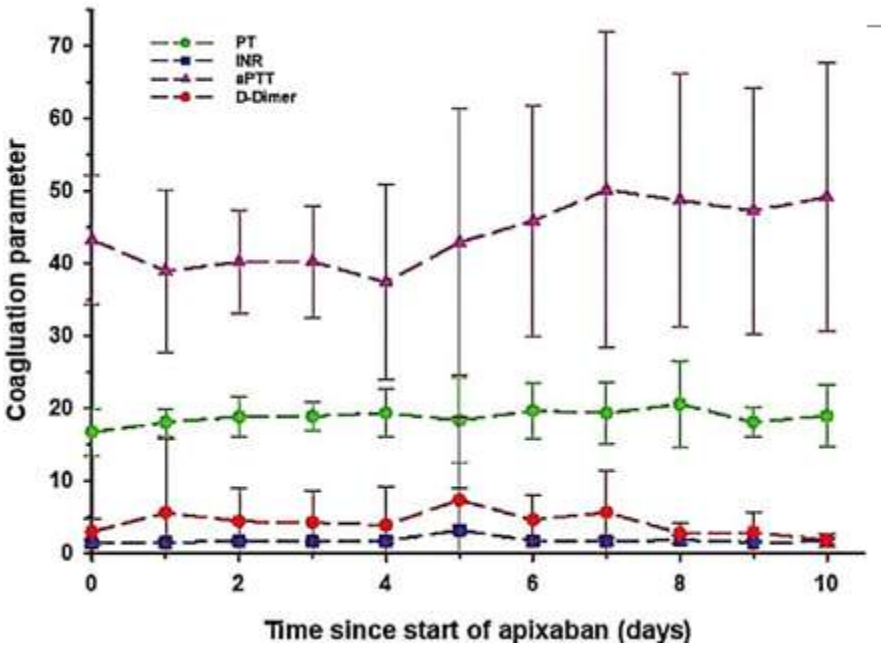


Figure 3 Some coagulation markers measured in COVID-19 ICU patients throughout a 10-day period starting with the start of apixaban. Standard deviations are represented by error bars next to mean values. COVID-19, a new coronavirus illness of 2019; ICU, intensive care unit; aPTT, activated partial thromboplastin time; INR, international normalized ratio; PT, prothrombin-time (Wenzler et al., 2020).

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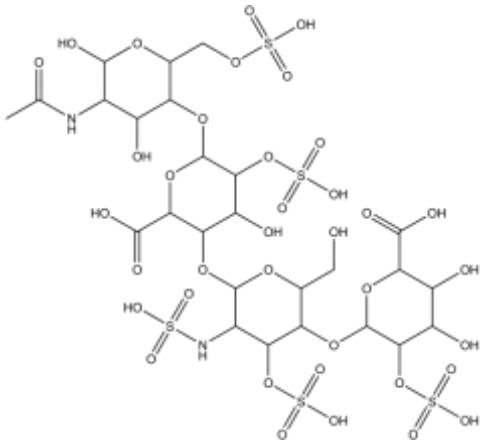
Intriguingly, a dozen minus one patients who were administered apixaban for a heart ailment called atrial fibrillation (AFib) or suspected or confirmed blood-clotting disorder, Venous Thromboembolism (VTE), had initially been prescribed therapeutic volumes of enoxaparin or non-fractionated heparin. This was done within the span of a day before the medication was switched to Apixaban. This switch post-COVID-19 diagnosis approximately occurred after 9 days, with the apixaban treatment being retained for an average duration of 14 days. Bar the platelet count, all other measured blood coagulation factors were observed to rise beyond the normal levels with the initiation of the apixaban intervention. The elevated elements encompassed prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), and D-dimer concentrations.These four measures continued to be abnormal but consistent during the course of the study's 10-day observation period. Crucially, none of the patients developed thrombotic events, significant bleeding, or bleeding that required stopping apixaban during the research period, despite the severity of the disease and the level of renal impairment seen in this patient population. With two exceptions, the majority of patients were released from the hospital and the intensive care unit (ICU) after median hospital stays of 22 [9.5–35] and 25 [20–35] days, respectively. Throughout the 10-day trial period, apixaban showed promise in this group of high-risk patients. These results lend encouragement to additional study focused at optimizing anticoagulant strategies for critically sick COVID-19 patients. (Wenzler et al., 2020)

10. Enoxaparin



Weight-adapted parameters are conspicuously absent in overweight and obese persons. For preventing blood clots in COVID-19 patients in the Intensive Care Unit, many European health guidelines recommend administering an intermediate dosage of low-molecular-weight heparin (specifically enoxaparin 40 mg two times a day or enoxaparin 0.5 mg/kg twice daily). This suggested dosage differs from the typically recommended dosage (enoxaparin 40 mg once daily).Conversely, the guidance panel comprising of the American College of Chest Physicians and the American Society of Hematology recommend retaining the preventive anticoagulation dosage (enoxaparin at 30 mg, twice per day) for patients in intensive care. This recommendation stems from concerns about elevated risk of significant bleedings when dosages are increased to intermediate or therapeutic levels. Increased volume of distribution and clearance of enoxaparin have been linked to lower drug exposure in ICU COVID-19 patients, according to pharmacokinetic studies. Consequently, administering enoxaparin at a dosage of 40 mg once daily may not suffice to achieve thromboprophylactic anti-Xa levels. This study suggests that a minimum daily dosage of 60 mg is advisable for thromboprophylaxis in ICU COVID-19 patients(Billett et al., 2020).

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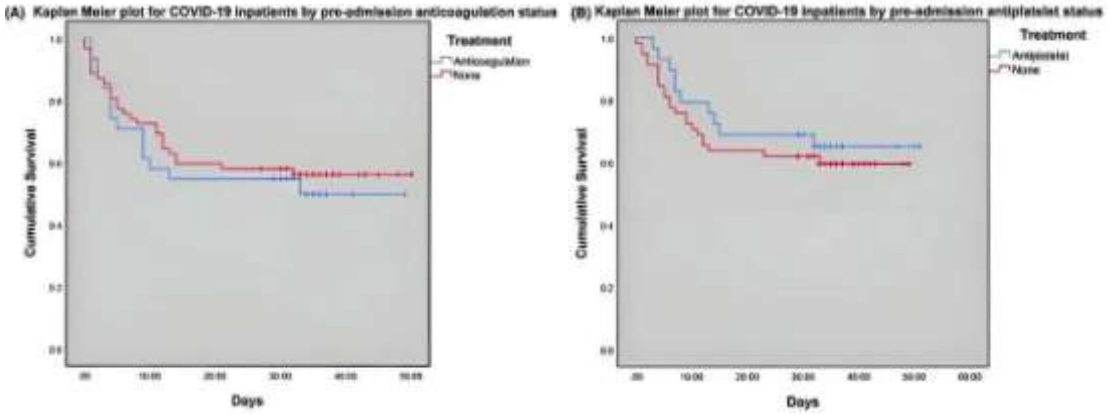
Enoxaparin treatment and unfractionated heparin (UFH) at any dosage were not linked to a lower death rate, according to further research. The similar pattern continued with D-dimer levels > 10 µg/mL; prevention and treatment with apixaban and enoxaparin were all linked to lower mortality(Billett et al., 2020).

II. DISCUSSION



A) A Kaplan-Meier plot comparing COVID-19 inpatients receiving anticoagulation prior to admission to those not receiving it.

B) Kaplan-Meier plot comparing COVID-19 inpatients receiving antiplatelets prior to admission to those not receiving them.

The study provides a thorough investigation of the possible therapy approaches utilizing anticoagulant medicines as well as the increased risk of thrombotic events linked to Coronavirus Disease-19 (COVID-19). This work clarifies the hypercoagulable condition seen in severe COVID-19 patients, highlighting the need of comprehending the pathophysiology underpinnings and evaluating the relative risks and benefits of different anticoagulant doses. In mild to severe cases of COVID-19, the frequency of thromboembolic effects is discussed. The influence on mortality and morbidity, as well as the correlation with changed coagulation parameters and inflammatory markers, are highlighted.

Additionally, the study examines the effectiveness of anticoagulants, including warfarin, aspirin, heparin, Enoxaparin, bivalirudin, aptaparinux, fondaparinux, and argatroban, in controlling thrombotic risk in COVID-19 patients. It also offers insights into the pharmacological characteristics of these medications and their possible advantages in the treatment and prevention of thromboembolism.

The thorough study explores the coagulation condition associated with COVID-19, covering the typical coagulation measures like D-dimer levels, fibrinogen, platelet count, and prothrombin time. The study focuses on the mechanism of COVID-19 coagulation, clarifying how thrombin, cytokine storm, and inflammatory cytokines and chemokines contribute to coagulopathy and thrombotic microangiopathy. In addition, the study sheds light on the prevalence of COVID-19 by presenting statistical data on recorded cases of the virus and the corresponding death rates across different nations.The study provides important insights into the worldwide spread and consequences of the pandemic by ranking the top 10 nations according to their cumulative COVID-19 infection and death load, both in absolute numbers and proportionately to their population size.

The study also includes an examination of data from 19 other trials, which together include a cohort of 2,520 COVID-19 patients who needed to be hospitalized. It provides a thorough summary of the essential characteristics taken from the included research, focusing on the incidence of thromboembolism in COVID-19 patients. In addition, the study discusses possible drugs such aspirin, heparin, warfarin, Enoxaparin, streptokinase, bivalirudin, apixaban, fondaparinux, and argatroban in order to manage thrombotic risk in COVID-19 patients.It highlights the necessity of additional thorough scientific research to fully comprehend the safety and effectiveness of heparin-based pre-thrombotic anticoagulation in the context of COVID-19, as well as the possible contribution of vitamin D supplementation to the

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management of thrombotic issues and improvement of patient outcomes.(Sivaloganathan et al., 2020)

III. CONCLUSION

Serious thrombotic events are linked to SARS Cov-2 infection. In Covid, a number of candidates with anticoagulant qualities are tested; heparin, apixaban, and low molecular weight heparin (LMWH) have encouraging outcomes. Because of their rapid reversibility and shorter half-lives than oral anticoagulants, LMWH or unfractionated heparin (UH) are recommended. Compared to anticoagulants, antiplatelet medicines had fewer adverse effects and a lower risk of severe bleeding when used to treat coagulopathy linked to COVID-19. Consequently, more research on the use of antiplatelet medications in coagulopathy associated to COVID is required.

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