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Association of Use of Anticoagulant and Antiplatelet Drugs in Covid-19 Infection and their Outcome in Relation to Duration of Hospital Stay and Mortality

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ABSTRACT

Venous and arterial thromboembolic complications affect around 16% of patients hospitalized with COVID-19 and approximately 49% of patients with COVID-19 in intensive care units (ICUs), with most patients being diagnosed with venous thromboembolism2. COVID-19 infection was more likely to have severe lymphopenia, elevated D-dimer, ferritin, LDH. So, to overcome complication because of thromboembolic event, use of anticoagulant and antiplatelets has increased. To assess use of anticoagulant and antiplatelet drugs in covid-19 infection. To analyze outcomes in relation to duration of hospital stay and mortality. This study was a retrospective observational study. Randomly selected 100 SARS-CoV-2 positive patients admitted to tertiary care hospital in January to June 2021 were taken as study population. Data had been collected and analyzed for association of covid-19 infection and use of anticoagulant and antiplatelet drugs used. Out 100 patients of covid-19, 52 were expired during treatment and 48 were cured. 52 patients who expired had more abnormal parameter like ferritin, LDH, CT score, SpO2 etc. These patients had less hospital stay with less days of anticoagulant and antiplatelets used as a treatment. Current study confirmed that if there is severe type of covid infection which spread to lungs and continuing to hypercoagulation is difficult to manage with drugs therapy like anticoagulants and antiplatelets.

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Key Words
Covid-19, anticoagulants, antiplatelets

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INTRODUCTION

The first case of COVID-19 found in Wuhan, China, in 2019. Since then, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been labelled as a global pandemic. Severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) has infected over 184 million people and caused over 3.9 million deaths worldwide according to the report by the WHO[1]. The Corona Virus Disease 2019 (COVID-19) pandemic is contributing to increased risk of intensive care unit (ICU) admissions, and increased mortality[1]. The incidence of thrombotic complications in patients with COVID-19 has been reported to be as high as 79%. Venous and arterial thromboembolic complications affect around 16% of patients hospitalized with COVID-19 and approximately 49% of patients with COVID-19 in intensive care units (ICUs), with most patients being diagnosed with venous thromboembolism[2]. COVID-19 infection was more likely to have severe lymphopenia, elevated D-dimer, ferritin, LDH. So, to overcome complication because of thromboembolic event, use of anticoagulant and antiplatelets has increased. Anticoagulant and antiplatelets like Enoxaparin, Heparin, Rivaroxaban, Aspirin, Clopidogrel, Warfarin were used to prevent complication.

Pathophysiology: Confirmed COVID-19 patients with symptoms and asymptomatic carriers are the primary source of new infections. In addition to the respiratory droplets and contact with contaminated surfaces, infection by the fecal-oral route has been guessed. When SARS-CoV-2 infects people, the viral spike (S) protein binds to the angiotensin-converting enzyme 2 (ACE2) receptor, which mediates the entry of SARS-CoV-2 into host cells surface such as nasal, bronchial epithelial cells, and pneumocytes. S protein undergoes further priming by type 2 transmembrane serine protease (TMPRSS2), a cellular protease particularly present in alveolar epithelial type II cells, which promotes viral uptake and coronavirus entry. To further explain the mechanism of viral entry into host cells, involves several stages.

Attachment: The S protein of SARS-CoV-2 binds to the ACE[2] receptor of the host cell. Priming: The S protein is then cleaved by a host protease enzyme called TMPRSS[2]. This cleavage allows the S protein to undergo a conformational change, exposing a fusion peptide that helps the fusion of the viral membrane with the host cell membrane.

Fusion: The viral membrane fuses with the host cell membrane, allowing the viral RNA to enter the host cell.

Replication: Once inside the host cell, the viral RNA is used as a template to produce more viral proteins and RNA.

Assembly and Release: The newly produced viral proteins and RNA accumulate into new viral particles, which are then released from the host cell to infect other cells.

Overall, the viral entry process starts with binding of the SARS CoV-2 S protein to the ACE[2] receptor on host cells plays a crucial role in the development of COVID-19. Understanding the molecular mechanisms underlying this process is crucial for developing effective strategies to prevent and treat COVID-19.

Infected individuals come with symptoms of fever, malaise, cough, and sputum production at the early stage. The host mounts an innate response that is mediated by cytokines and antiviral interferons and starts the adaptive immune response.

Patients that do not eradicate the virus at an early stage may lead to the clinical phase or later stage of the infection. It is estimated that 1/5th of the infected patients progresses to the involvement of the lower respiratory tract that involves infection to the alveolar epithelial type II cells, developing severe symptoms like acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), and pulmonary embolism.

The clinical phase of SARS-CoV-2 can be differentiated into three distinct phases:

Acute or pneumonia phase: The acute phase is characterized by pulmonary symptoms such as dyspnea, cough, and sputum production with imaging evidence of ground-glass opacity or consolidation in the lung. Diffuse alveolar damage, desquamation of pneumocytes, and hyaline membrane formation are seen during the development of ARDS in COVID-19.

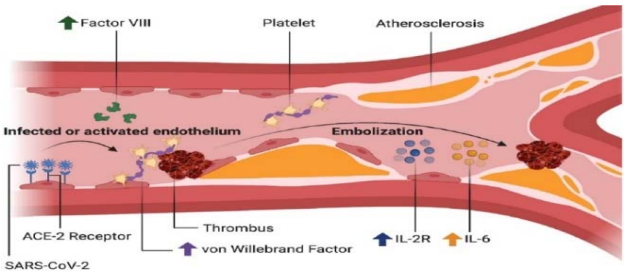
Viremia phase: The viremic phase starts when the virus enters the peripheral blood. The viremia and later host response contribute to multiple systemic inflammation and multiorgan failure. The inflammatory response during severe COVID-19 is mediated by a simultaneous increase in the multiple inflammatory cytokines such as IL-1a, IL-1b, IL-6, IL-8, IL-12, IL 17, TNF- a, interferons (IFN- b, IFN- l), MCP-1, and MIP-1.

Lethal phase: The lethal phase is manifested both locally and systemically. The inflammatory response in the form of cytokine storm and coagulation factors is significantly elevated in severe patients compared to non-severe patients. The inflammatory response triggers the expression of activated tissue factor on endothelial cells, macrophages, and neutrophils, enhancing activation of the coagulation cascade. For this reason, severe COVID-19 is not

restricted to the respiratory system but is a multisystem disease including the development of various cardiovascular manifestations with myocardial injury, arrhythmia, acute coronary syndrome, and venous thromboembolism. Based on all these features, anticoagulant therapy and immunomodulatory agents are necessary to attenuate the hyperinflammatory and prothrombotic states.

These patients may receive help from immune modulators such as steroids while antiviral agents have limited utility at this stage of the disease. Despite the obvious contribution of coagulation pathways in vascular disease, the use of anticoagulant therapy may be filled with the risk of increased bleeding. On the other hand, micro thrombi in capillaries and large vessels may already cause damage if administered too late[3].

Decreased platelet counts, prolongation of prothrombin time, activated partial thromboplastin time (aPTT), and elevated serum D- dimer and fibrinogen characterize the COVID-19 associated coagulopathy. The severe hypercoagulability seen in patients with COVID-19 has been accounted for critical cases of the disease. Therefore, anticoagulants and antiplatelets are important therapeutics for treating this potentially life-threatening condition. The specific aim of the current paper was to thoroughly review the pathophysiology of the COVID-19-induced hypercoagulable state and the clinical use of anticoagulants, including their pros and cons, in treating the infection with SARS-CoV-24.



Potential mechanisms of COVID-19 endotheliopathy and stroke.
COVID-19 infection leads to release of vWF and Factor VIII from activated endothelium, resulting in platelet aggregation and thrombus formation. A thrombus can occlude the vessel locally or embolize distally, leading to cerebral ischemia. Embolization is associated with elevations in IL-6 and sIL-2 receptor.

Aim and Objectives:

- To assess use of anticoagulant and antiplatelet drugs in covid-19 infection.
- To analyze outcomes in relation to duration of hospital stay and mortality.

MATERIALS AND METHODS

This study was a retrospective observational study. Study was conducted only after approval from the institutional ethics committee. Randomly selected 100 SARS-CoV-2 positive patients admitted to tertiary care hospital in January to June 2021 were taken as study population. Data had been collected for demographic parameter, anticoagulant and antiplatelet drugs used, associated lab parameter, comorbidities and clinical condition of patient, mortality and morbidity status during hospital stay and duration of hospital stay. Data was collected from files of patients in the medical record room. Data was analyzed for association of covid-19 infection and use of anticoagulant and antiplatelet drugs used.

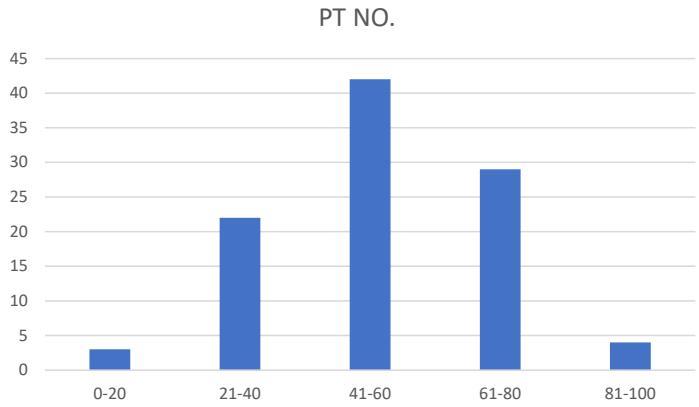
RESULTS AND DISCUSSIONS

Out of 100 randomly selected patient, 61 were male patients and 39 were female patients. Maximum covid positive patients were found in age group 41-60. In this age group, 42 patients were covid positive. In age group 61-80, there were 29 patients, while in age group 21-40, there were 22. In age group 81-100 and 1-20, patients were 4 and 3, respectively.

Out of 100 patients, 52 were expired during treatment. These patients showed more abnormal lab parameter and clinical status than those cured. On an average mortality is associated with less days of hospitalisation compared to cured patients despite use of anticoagulants and antiplatelets. 48 patients were cured with treatment of covid. From table 1, it is cleared that expired patients had a greater number of comorbidities than cured patients.

On average, mortality is associated with less days of use of anticoagulant and antiplatelets. In 52 expired patients, 40(76.92%) were having comorbidities. In 48 cured patients, only 22(45.83%) patients were having comorbidities. From this data, patients who expired during covid treatment have more comorbid conditions.

100 patients were treated with anticoagulant and antiplatelets like Inj. Clexane, Inj. Heparin, Inj. Enoxaparin, Tab. Rivaroxaban, Tab. Dabigatron, Tab. Aspirin, Tab. Clopidogrel, Tab. Stiloz. Average 1.29 anticoagulant and antiplatelets were used in 100 patients while average 1.47 same were used in cured patients and 1.11 anticoagulant and antiplatelets were used in patients expired. This would suggest that if anticoagulant started early in disease course, it would be helpful in covid-19 infection in preventing lives of patients. But in progressed diseased condition use of anticoagulant and antiplatelets were not much helpful. Also, in progressed diseased condition used of Inj Clexane and Inj Heparin were increased much more compared to in cured patients. This is because, in complex diseases, most of the other anticoagulants and anti-platelets are contraindicated because of systemic involvement.



Graph 1: Age group wise distribution of patients

From table 3, D-dimer is slightly less in expired patient compared to cured patients. In expired patients mean D-dimer was 2.59+1.99 while in cured patients it is 2.71+2.6. But ferritin, LDH, and CT score were tremendously increased in expired patients compared to cured patients. This suggest coagulopathy and infectivity was more in expired patients. Coagulopathy is ultimate pathology in covid infection and may continue as a reason for death. Severely ill patients have difficulty in breathing that is why they were showing less SpO2 i.e., in expired patients it is shown as 79.38% while in cured patients it is 94.24%.

According to Honarmandpour *et al*.[5], demographic characteristics of the evaluated patients in their study were as follows. Total number of evaluated COVID-19 patients were 347 including 13 (4.1%) patients in the range of 15-30, 64 (20.2%) in the range of 31-45, 93 (29.3%) in the range of 46-60, 92 (29.0%) in the range of 61-75, 53 (16.7%) in the range of 76-90, and 2 (0.6%) patients in the range of >90. Whereas in this study Out of 100 randomly selected patient, 61 were male patients and 39 were female patients. Maximum covid positive patients were found in age group 41-60. In this age group 42 patients were covid positive. In age group 61-80, there were 29 patients, while in age group 21-40, patients were 22. In age group 81-100 and 1-20, patients' number were 4 and 3, respectively. Data suggested from both studies that maximum covid positive patients were from 41-60 age group. This age group populations looked very vulnerable for covid-19 infection.

According to F. Khamis *et al*.[6], In total, 1002 patients with COVID-19 infection with an overall and intensive care unit (ICU) mortalities were of 26% (n = 257) and 42% (n = 199/473), respectively while in this study Out of 100 patients, 52 were expired during treatment. These patients showed more abnormal lab parameter and clinical status than those cured.

As per Miesbach and Makris *et. al*[7], Increase in D-dimer, ferritin, LDH and low SpO2 may show the presence of thrombosis and pulmonary embolisms in critically ill COVID-19 patients. Therefore, there is a need to prevent thrombotic events and organ damage. In this study also expired patients have higher level of LDH, ferritin, and CT score compared to cured patients' suggestive high infectivity and coagulopathy in covid infection. To prevent thrombotic events and cytokines storms early use of anticoagulant and antiplatelets suggested in covid-19 infection. The incidence of thrombosis in critically ill patients is high and thrombotic events or death may occur despite use of LMWH. That is why severely ill patients with comorbidities have more probability of mortality and less duration of hospital stay despite anticoagulant and antiplatelet therapy.

As per Kichloo *et al*.,[8] thrombotic complications of the novel coronavirus (COVID-19) are a concerning aspect of the disease, due to the high incidence of critically ill patients showed poor clinical outcomes. COVID-19 predisposes patients to a hypercoagulable state. Pathogenesis involves a host immune response contributing to vascular endothelial cell injury, inflammation, activation of the coagulation cascade via tissue factor expression, and shutdown of fibrinolysis. Treatments targeting these pathways may need to be considered to improve clinical outcomes and decrease overall mortality due to thrombotic complications. But this treatment is helpful only when it is started in viremia phase. Once patient landed in cytokine storm and hypercoagulable state, then there is less or negligible benefit of treatment with antiplatelets and anticoagulants. This is the reason patients who were expired have less hospital stay though using antiplatelets and anticoagulants compared to those patients who were cured.

According to Connors and Levy *et al*.[9], the concept of using full-dose anticoagulation in COVID-19 patients for preventing microvascular thrombosis

Table 1: About Average no. of days patients stays in hospital and anticoagulant and antiplatelets used and no. Of patients with comorbidities

Day/ patient	Average Days stays in hospital	Average days of anticoagulant and antiplatelets used	No. of patients with comorbidities (%)
Total (100)	8.09	7.79	62 (62%)
Expired (52)	6.15	6.11	40 (76.92%)
Cured (48)	10.18	9.60	22 (45.83%)

Table 2: Utilization of anticoagulant and antiplatelets during covid infection

Anticoagulant and Antiplatelets	100 Patients	Cured Patients	Expired Patients
INJ Clexane	79	40	39
INJ Heparin	15	1	14
INJ Enoxaparin	3	3	0
TAB Rivoroxaban	5	5	0
TAB Dabigatron	6	5	1
TAB Aspirin	18	15	3
TAB Clopidogrel	2	2	0
TAB Stiloz	1	0	1
Total	129	71	58
Average	1.29	1.47	1.11

Table 3: Analysis of Laboratory Parameters in Distinct Groups

Parameter/Patients	D-dimer(Mean+ SD)	Ferritin(Mean+ SD)	LDH(Mean+ SD)	CT score(Mean+ SD)	SpO2(Mean)
Total (100)	2.66+1.80	950.4+ 1106.9	1197.54+ 857.08	15.1+ 4.80	85.56%
Expired (52)	2.59+1.99	1052.96+ 824.21	1469.14+ 957.04	15.92+ 5.10	79.38%
Cured (48)	2.71+ 2.6	851.4+ 1332.96	722.25+ 273.96	14.46+ 4.61	94.24%

during severe infection has been considered. Infection can result in the development of ARDS, in which fibrin-platelet rich microthrombi form in the pulmonary microcirculation and parenchyma, seen in postmortem of lung infected with COVID-19, a syndrome consistent with thrombotic DIC microvascular thrombosis. However, prior studies using anticoagulants in the setting of DIC have found no decrease in mortality. The same is seen in a current study showing that if covid infection is of severe grade involving lung profoundly, then there is no use of anticoagulant and anti-platelet therapy.

According to Aalinezhad M. study[10], study showed that patients with hypoxia had a significantly higher CT severity score. It is shown that covid infection with comorbidities like diabetes mellitus, hypertension, COPD, were significantly associated with decreased oxygen saturation. This finding is consistent with present study.

According to Lopes, Renato D[11], randomized data on the use of therapeutic anti coagulation with heparin in patients hospitalised with COVID-19 have shown divergent results. Critically ill patients admitted to intensive care units did not benefit from therapeutic or intermediate doses of anticoagulation compared with prophylactic doses. Same observed in current study also. In this study it was found that there were increased used of Inj Clexane and Inj Heparin in critically ill patients as these patients were contraindicated to most of the anticoagulants and antiplatelets because of systemic involvement of diseased condition.

CONCLUSION

Current study confirmed that if there is severe type of covid infection which spread to lungs and continuing to hypercoagulation is difficult to manage with drugs therapy like anticoagulants and antiplatelets. Patient who had succumb to death during treatment showed deranged coagulation parameter with increased CT score, associated hypoxia and less hospital stay and less days of used of anticoagulants and antiplatelets. Current study does not show promising evidence with the use of therapeutic anticoagulation in high-risk individuals. Further studies are needed to analyse the risks and benefits of anticoagulation in critically ill patient. But use of anticoagulants and antiplatelets in initial stages of covid-19 infection may be beneficial.

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