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A Review of Coagulopathy Disorders in COVID-19

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ABSTRACT

Countries all over the world have been affected by Coronavirus disease which started in small city of China as epidemic but soon was declared pandemic. In this review we outline major coagulopathy which is associated with COVID-19 and its clinical implication with what should be done in future. COVID-19 has resulted in huge mortality in the population of every country irrespective of developmental status. COVID-19 related coagulopathy has significant influence in patient's recovery. Surprisingly, this problem has been seen to occur despite prophylactic anticoagulant medication. According to recent findings, the most seriously unwell patients have coagulopathy and significant intravascular clot formation similar to Disseminated Intravascular Coagulation (DIC). Coagulation testing may so be considered. The clinical appearance of COVID-19 is important in distinguishing severe patients. Organ dysfunction is the primary effect of COVID-19 associated coagulopathy, whereas hemorrhagic event is less occurring. Massive increase of D-dimer and fibrin/FDP shows presence of coagulopathy. If we compare sepsis associated coagulopathy with COVID-19 coagulopathy disseminated intravascular coagulopathy, PT elevated are found in the latter. Antithrombin activity decreases and partial thromboplastin time is less common. COVID-19 has a low incidence of thrombocytopenia. However, the causes of coagulopathy are still unknown. It's thought that the deregulated immune system is to blame. Inflammatory cytokines coordinate immunological responses, lymphocyte cell death and endothelial injury and hypoxia are both involved.

Key words: COVID-19, DIC, D-dimer, coagulopathy

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INTRODUCTION

COVID-19 is caused by a RNA coronavirus which infects human cells primarily *via* binding to ACE-2, which is present on the cell surface cardiac myocytes, which are seen in greater numbers in the alveolar cells of the lungs. The virus which causes COVID-19 is single stranded RNA virus endothelial cells, vascular endothelial cells, and other cells. SARS-CoV-2 is passed with direct contact from the infected person. It is a communicable disease. A fragment of virus comes in the respiratory tract due to inhalation. Any surface infected with coronavirus has its infectivity till 72 hours if conditions are not changed [1,2].

The elevated level of D-dimer, a biomarker of fibrinolysis and a predictor of thrombosis, is a characteristic of COVID-19 associated coagulopathy. COVID-19 patients had a higher rate of arterial thrombosis [3]. Both pulmonary and non-pulmonary blood arteries are involved in COVID-19. Thrombosis, bleeding, edema, inflammation, and endothelial cell death are all signs of vascular involvement [4].

The severe acute respiratory coronavirus, which caused Severe Acute Respiratory Syndrome (SARS) in 2002, was linked to thrombocytopenia, thrombocytosis, and a prolonged APTT, but not to bleeding [5]. With SARS-CoV-1 infection, 20.5% of patients had DVT, and 11.4% had clinical indications of pulmonary embolism, according to the findings [6,7].

The COVID-19-causing virus, SARS-Coronavirus-2, is alike SARS-Coronavirus-1 that may have a comparable ability to cause thrombotic problems [8]. Patients can develop ARDS in extreme cases, according to Chinese doctors, with coagulation predominant type coagulopathy [9].

The presence of thrombocytopenia, extended PT, and increased D-dimer implies DIC, but its presentation differs from that of sepsis, in which low platelet count is significantly severe and elevated value of D-dimer does not extend at the levels seen in coronavirus disease subjects [10]. In COVID-19 related coagulopathy major influence on organ failure is due to the composite effect of low grade disseminated intravascular coagulation and pulmonary thrombotic microangiopathy [11]. Hematologic abnormalities in coagulation tests (increased value of D-dimer, extended Prothrombin Time, thrombocytopenia)

occur in 20% to 50% of COVID-19 hospitalized patients. Endothelial dysfunction causes respiratory depression and respiratory obstruction caused by thrombosis and micro vascular pathology respiratory depression and respiratory obstruction caused by thrombosis and micro vascular pathology due to elevated increase value of D dimer, FDA, thrombocytopenia, and increased CT [2,12-16].

Objective: These review article summaries the coagulation disorder's pathophysiology and clinical implication associated with COVID-19.

LITERATURE REVIEW

Pathophysiology

SARS-CoV-2 pathogenesis: Angiotensin Converting Enzyme-2 (ACE-2) has been proposed as the key molecular surface element utilized by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) to enter human cells [17]. In experimental research, the loss or increase of function of this protein (ACE-2) has been demonstrated to influence endothelial cell-protective barriers. ACE-2 has been found in several researches to have anti-inflammatory and antioxidant properties [18]. Given that the COVID-19 virus disrupts these cell surface antigens as the major barrier, cells rich in these antigens, such as pneumocytes and endothelial cells, may contribute in the viral infection's pathology [19].

SARS-CoV-2 infection reduces ACE-2 and thus increases Angiotensin II (AT-II), according to studies [20]. Furthermore, AT-II is known to be linked to hypertension, and recent research has linked AT-II to the pathogenesis of thrombus formation in the arterioles. In fact, chronic AT-II infusion has been shown to increase platelet-endothelial cell adhesion and thrombogenesis within the arterial system in animal models. Coagulation cascade is activated due to amplification of expression of tissue factor which is linked with increased AT-II [21].

Altered coagulation biomarkers

Patients with more serious coronavirus disease infection had elevated value of D-dimer and FDP as well as a prolonged Prothrombin Time (PT) and Activated Partial Thromboplastin Time, according to studies (APTT) [4]. Patients with increased value of D-dimer levels show prognosis high mortality [19]. D dimer values become high if disease severity increases [22].

Another potential sign that can vary in COVID-19 patients is platelet count [4]. Thrombocytopenia is not common among COVID-19 patients, in contrast to sepsis induced coagulopathy [4].

Low platelet count, on the other hand, has been identified as a sign of illness severity [23]. Thrombocytosis has been associated to a more serious COVID-19 infection in some studies, and individuals with high platelet counts have been observed to have longer hospital stays [24].

In addition, individuals with SARS-CoV-2 coagulopathy complications had increased serum levels of Von Willebrand Factors (VWF) [17]. The existence of antiphospholipid antibodies in some COVID-19 individuals is another unresolved laboratory marker. About 45% of COVID-19 patients exhibited lupus anticoagulant antibodies in their serum, according to a study of 56 individuals. Although acute infections may cause the development of these antibodies to be temporary, the clinical importance of this connection has yet to be determined [25,26].

Inflammatory cytokines and COVID-19 infection

Recent research looking at the values of hemostatic factor like inflammatory cytokines in coronavirus disease patients found that severe cases had higher levels of circulatory interleukin-6, interleukin-10, tumor necrosis factor, and interleukin-2 receptor than less severe cases [28]. Rapid increases in circulating values of these key proinflammatory factors have been associated with cytokine release syndrome, a clinical illness characterised by high body temperature, headaches, low BP, night sweats, and various organ dysfunction, as well as a bad prognosis. It is worth noting, however, that this syndrome is not limited to COVID-19 infection [27].

Multiple researches have looked into the function of interleukin 6 in coronavieus disease-related problems. IL-6 is involved in several of inflammatory processes, like coagulation factor synthesis, platelet formation, and vascular permeability [17]. These factors could also have major participation in coronavirus-related coagulopathy. In light of these functions, some research has focused on this cytokine's receptor as a capable treatment option for coronavirus disease, with promising results [29,30].

COVID-19 infection has been linked to higher degree of hemostatic factors such mainly Tumor Necrosis Factor, IL-1, and Monocyte Chemoattractant Protein-1, which are similar to IL-6 [27].

These elements attract additional immune cells to sick tissues and create an environment in which other factors can be expressed. Tissue factor expression on monocytes/macrophages and vascular endothelial cells is stimulated by immunological activation [20].

SARS-affinity CoV's for Angiotensin Converting Enzyme-2 (ACE-2), which is expressed on alveolar epithelial type II cells and other extra pulmonary organs, including endothelial cells, may be one route of micro vascular thrombosis. COVID-19 mediated micro vascular damage, thrombosis, and ultimately multisystem organ failure may be caused by endothelial cell activation [31,32].

COVID-19-associated coagulopathy compared to other causes of coagulopathy

It's important to distinguish COVID-19 related coagulopathies from bacterial induced DIC and other thrombotic micro angiopathies. Pro-inflammatory cytokines and other host defence mechanisms are presented in the pathophysiology of DIC caused by bacteria and coagulopathy, as mentioned previously for COVID-19. When compared to non-sepsis induced DIC, a

key distinction of sepsis-induced DIC is the less increase value of D-dimer with increasing disease seriousness [33,34].

To put it another way, sepsis-induced DIC is linked to clot formation and fibrinolysis suppression. Because of an increase in the production of plasminogen activator inhibitor-1, fibrinolysis is slowed, also known as fibrinolysis shutdown [35]. Furthermore, COVID-19 infection is characterised by elevated VWF levels in the blood, and may present with clinical symptoms comparable to Thrombotic Thrombocytopenic Purpura (TTP) [5].

COVID-19 associated coagulopathy occurs despite anticoagulant administration

In patients receiving VTE prophylaxis and suffering from influenza pneumonia, pulmonary emboli and arterial thrombotic events have been observed [5]. Despite the fact that the exact process of this is unknown, one study's finding has proposed that influenza A/H_1N_1 infection is believed to be linked with Hypercoagulability and endothelial dysfunction are linked [36]

Cases related to Thrombotic incidents have been documented in COVID-19 subjects those were previously healthy receiving an anticoagulant prophylactic dosage agent. According to French report when we compare thromembolic event in COVID 19 ARDS with non-COVID-19 ARDS it shows more occurrence [37]. Another study from the Netherlands found that thrombotic events occur at a rate of 31% in Intensive Care Units (ICU) COVID-19 patients who have undergone at least one treatment at the very least, routine thromboprophylaxis doses [38]. The event arose as a result of the under dosing of anticoagulant agents and invalidity of data such incidents demonstrates the need of venous thromboembolism prevention. Categorization and consideration of risk of an anticoagulant prophylactic dose that is appropriate while caring for people infected with this disease [1]

Clinical features in coagulopathy

COVID-19 related thrombotic events have been reported in the range of 16 to 31% of people with severe SARS-CoV-2 infection [39-41]. Venous thromboembolic events are also more common than arterial thromboembolic events, according to recent study [5].

Cui, et al. conducted ultrasonography to check for thrombosis in asymptomatic ICU patients and discovered that 25% (20/81) had it [42]. In 20% to 30% of COVID-19 ICU patients, thrombosis and severe thromboembolic consequences have been documented [40,43]. In 12.5% of subjects heparin or enoxaparin is used as prophylaxis in venous thromboembolism in non-COVID-19 septic ICU subjects [44]. Patients who encounter an unanticipated drop in oxygenation and shock have a risk of thromboembolism at pulmonary site and these include patient who have very serious COVID-19 infection [19].

Cell death and organ damage

The lung epithelial cell, lymphocyte, vascular endothelial cell are the major targets of the severe acute respiratory syndrome coronavirus and these findings may explain why serious coronavirus is represented by respiratory depression, shock, and coagulopathy [45,46].

Interstitial fluid collection with major infiltration of white blood cells especially neutrophill and enhanced vascular permeability are pathological features of bacterial sepsis associated ARDS [19]. In sepsis associated ARDS, studies have shown that alveoli with infiltration of neutrophil resulting in thrombus development in the lung all add up to injury to alveoli causing fluid collection, as well as enhanced vascular damage [47].

Although pathological data for COVID-19 are still scarce, Luo et al described visible vasculature damage, thickened wall, and vascular lumen getting and thrombus development, in addition to ARDS symptoms [48].

Evaluation of thromboembolic events

The ISTH has issued guidelines on investigation and treatment of COVID-19 related coagulopathy. All hospitalized coronavirus patients should be investigated for values of D-dimer, PT, and platelet counts daily, as well as for values of serum fibrinogen level (if possible). These test results have predictive significance and can help clinicians make better clinical decisions in the future. If these signs worsen, more intensive critical care support or the administration of investigational medicines and blood product support may be considered [13]. Stepping down treatment may be contemplated if indicators of coagulation have stabilized [5].

The Working Party on Hemostasis suggested routine monitoring of PT, D-dimer, Fibrinogen, Platelet Count, Lactate Dehydrogenase (LDH), Creatinine, and Alanine Aminotransferase (ALT) in hospitalized COVID-19 patients [49].

Monitoring anti-XA activity might be considered if there is an indication, such as renal impairment. It did not propose antithrombin monitoring unless disseminated intravascular coagulopathy, coagulopathy due to sepsis, or heparin resistance were present. HIT should also be evaluated in cases of increases in thrombocyte count or evidence of heparin resistance [49].

Management

When haemostatic factors rise, low-molecular-weight heparin may be the best option, while substantial data is still lacking [19]. A study differentiated twenty-eight day mortality in stratified subjects given low molecular weight heparin versus those not treated with heparin, and found that mortality was at lesser side in subjects with D-dimer value >3.0 g/ml or coagulopathy due to sepsis defined by ISTH criteria [12,50]. Low molecular weight heparin has the potential to enhance the outcome not only by preventing VTE but also by suppressing micro thrombosis [19].

Lin et al. also suggested using LMWH for patients who had a value of D-dimer quadruple than the typical upper limit [51].

Aside from heparins, nafamostatmesylate, a synthetic serine protease inhibitor with anticoagulant properties including FVIIa inhibition, has been described as a powerful Ebola virus inhibitor and MERS-CoV infection. CathepsinB is an inhibitor which is be used to inhibit proteolytic process of glycoproteins present on surface. Nafamostatmesylate reduced SARS -coronavirus-2 disease in both *in vitro* and *in vivo* investigation [52,53].

Patients with coronavirus disease infection, according to Thachil, may require a larger dose of Low molecular weight heparin, such as an enhanced preventive dose of low molecular weight heparin in patients with a high BMI, considerably high value of D-dimers, or increased demand of ventilation (oxygen requirements), or ARDS [54].

All hospitalized COVID-19 patients with no contraindications should receive thrombophylactic medication, according to the Working Party on Haemostasis (Swiss Society of Haematology) [49]. Patients with a creatinine clearance of>30 mL/min should be given low molecular weight Heparin, but if they are overweight (weighing >100 kg), there should be increase in dose. Those with a creatinine clearance of <30 mL/min, on the other hand, should get UFH (subcutaneous 2-3 times/day or intravenous), with the dose being increased in overweight patients (>100 kg) [49]. In patients with a high value of D-dimer, inflammation, organ failure, intermediate or therapeutic doses of LMWH or UFH are also suggested. In subjects receiving extracorporeal membrane oxygenation, doses of Unfractionated heparin should be investigated (ECMO). However, due to a lack of evidence, they did not have any recommendations for treating individuals with direct oral anticoagulants.

Thrombotic events still occur in certain patients despite preventive medication, according to Barret et al response on the ISTH interim recommendations [55]. They recommended that COVID-19 patients who are hospitalized and do not have a considerable risk of bleeding start anticoagulation treatment with UFH right away. Antithrombin supplementation was also mentioned as a possible solution.

The preventive dose of LMWH may be beneficial in mild to moderate hospitalized COVID-19 patients, according to Barret et al. However, because severe COVID-19 individuals may develop hypercoagulability and DIC-related organ failure, they advocated the British Society for Hematology's DIC management with UHF [55]. Furthermore, COVID-19 individuals were shown to have greater fibrinogen levels and decreased antithrombin levels. Prophylactic doses of low molecular weight heparin and unfractionated heparin may be less effective in serious COVID-19 individuals because elevated serum fibrinogen levels impair the efficiency of prophylactic medication in avoiding thrombosis [56]. Fibrinogen levels >900 mg/dl increase blood viscosity with low shear, causing thrombosis; hence, intensive anticoagulation therapy may prevent multi-organ failure and ARDS. [55]. Furthermore, because coronavirus disease patients have a high rate of pulmonary embolism, Barret et al. suggested that UFH might be a better option because these patients required Tissue Plasminogen Activator (TPA), and treating patients with TPA after receiving LMWH may increase the risk of unstoppable bleeding. Furthermore, COVID-19 individuals are more likely to develop renal failure, making UFH a preferable option for these patients.

In coronavirus disease patients when thromboembolic incidents are considered Potential drug-drug interactions, especially in individuals with inherited bleeding disorders should also be seen [5].

Another thing to keep in mind when starting anticoagulant therapy for these patients is to keep in mind the possibility of inherited bleeding disorders [5]. As previously mentioned, the severity of the infection can impact coagulation indicators. In patients with COVID-19, for example, lupus anticoagulant may transiently become positive, resulting in APTT prolongation [5].

In patients with comorbidities that enhance the likelihood of coagulopathy episodes, extended post-discharge thromboprophylaxis has also been recommended [56].

DISCUSSION

COVID-19 infections are distinguished by a wide range of phonotypic manifestations that affect the majority of major organs and organ systems [56]. COVID-19-associated coagulopathy is an acquired sickness that has developed and demonstrated to be prevalent, complex, involving the venous, arterial, and microcirculatory systems, and unique from other viral infections.

When the major anticoagulation guidelines are examined, they all agree on the importance of administering thromboprophylaxis to patients hospitalised for COVID-19 [11].

Some guidelines recommend increasing the dosage in patients admitted to the ICU or who have extra risk factors. Preliminary findings indicate a benefit in terms of mortality and organ function from the use of heparin with anticoagulant dose in patients with moderately severe disease who are not hospitalised in ICU, leading to the adaption of the NICE guidelines in their most recent edition [10]. Indeed, the use of anticoagulant heparin dosages has been studied by three large worldwide clinical studies, ACTIV-4 (NCT04505774), REMAP-CAP (NCT02735707), and ATTACC (NCT04372589), which have standardised their methods for faster findings. The major goal was to achieve a combination of hospital mortality and organ support-free days in patients in hospital (moderate COVID-19) or in ICU at 21 days (severe COVID-19). According to preliminary examination of these findings, therapeutically dosed heparin would not improve outcome or death in critically sick patients, and could even be hazardous.

In contrast, in patients with mild COVID-19, treatment anticoagulation appears to lessen the need for organ support in both high and low D-dimer patients. The difference between critically ill and non-critically unwell patients could be explained by the fact that the inflammatory and coagulation changes in the patient with severe COVID-19 are too deep and ingrained to be restored [4].

CONCLUSION

In the COVID-19 era, thromboembolism has been suggested as a possible cause of higher mortality. COVID-19 induced coagulopathy may be a separate entity involving numerous mechanisms, including inflammation, endothelial cell activation, and an imbalance of pro and anti-coagulant proteins, though this is still theoretical. Studies should be conducted to see why there is coagulopathy in those patients also in which anticoagulant therapy was already given. Proper management guidelines should be laid down to how to treat these types of cases. The national and international agencies should extend their support to club different studies and come to a standardized management guideline of treat people with COVID-19 related coagulopathy.

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