Review Article

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COVID 19 vaccine in patients of hypercoagulable disorders: a clinical perspective

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Abstract: COVID 19 is an infectious disease caused by severe acute respiratory syndrome corona virus 2. Thromboembolism has been a characteristic manifestation in most of the severely ill COVID-19 patients. Thromboembolism in COVID 19 infection is attributed to injury to the vascular endothelial cell, hypercoagulability and blood stasis. The hypercoagulable state of blood and thrombophilic diseases leads to hypercoagulability. COVID 19 infected patients with pre-existing hypercoagulable disorders have higher risk of developing thrombosis and thromboembolism and such thrombotic episodes may prove to be severely morbid in these patients. As immune-prophylaxis COVID 19 vaccines are being administered to the public. The known side effects of the COVID 19 vaccine are mild to moderate and include fever, chills, nausea, vomiting, headache, fatigue, myalgia, malaise, pain and swelling at injection site and diarrhea. Thrombosis with thrombocytopenia has been noted as a rare side effect of COVID 19 vaccine. Such side effect of COVID 19 vaccine in patients of hypercoagulable disorder may prove to be fatal. The health care workers should be cautious and judicious in managing such patients. A detailed lab profile for coagulable state of blood should be carried out in all patients COVID 19 infected patients with pre-existing hypercoagulability diseases. The patients should also be health educated regarding side effects of vaccine especially with those indicating thrombosis and they should be warranted to receive immediate medical care in case of any side effects or complications. Paucity of literature gave us an impetus to review management profile in patients of hypercoagulable disorders.

Keywords: COVID 19 vaccine; hypercoagulability syndrome; hypercoagulable disorders; thrombocytopenia; thromboembolism; thrombosis.

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Introduction

COVID 19 pandemic has affected the physical and mental wellbeing among human population. COVID 19 disease which originated from Wuhan, China in the year 2019 is caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2). It spread globally and it was declared a pandemic on 11th March 2020 by the World Health Organization. This virulent infection has led to global health crisis with increasing morbidity and mortality worldwide. The most vulnerable population were those in geriatric age group or in individuals with existing co-morbidities such as hypertension, diabetes, cancer, coronary artery disease, chronic kidney diseases, chronic obstructive pulmonary disease (COPD), emphysema, chronic bronchitis, HIV infection, liver diseases, cystic fibrosis, obesity, metabolic syndrome, cerebrovascular disease, sickle cell disease, thalassemia, hypercoagulable disorders etc [1]. The common symptoms associated with COVID 19 infections includes dry cough, fever, muscle ache, shortness of breath, fatigue, headache, nausea, vomiting, diarrhea, loss of appetite and loss of smell and taste sensation. The common complications observed in COVID 19 patients are acute respiratory distress syndrome, heart failure, thromboembolism and multiple organ failure [2].

The thrombotic complications are significantly evident in severe COVID-19 infections. Thromboembolism has been a characteristic manifestation in most of the severely ill

COVID-19 patients. The receptor for SARS-CoV-2 is the Angiotensin I converting enzyme 2 (ACE-2) receptor. ACE2 receptors are present in the endothelium, lungs, heart, kidneys, ileum and intestines. The virus shows the host tropism activity by directly invading the endothelial cell and induces diffuse inflammation in these cells. Thromboembolism in COVID 19 infection is attributed to injury to the vascular endothelial cell, hypercoagulability and blood stasis [3]. The SARS-CoV-2 invades the alveoli and causes diffuse alveolar damage along with progressive capillary microthrombi involving pulmonary vasculature and this proves to be fatal in patients of COVID-19 leading to their death; primarily due to respiratory failure [4].

The patients of hypercoagulable disorders contracting COVID 19 infection may have higher risk of developing serious side effects pertaining to the thromboembolism episodes. In addition, hypercoagulability may contribute to a poor prognosis in these patients. Much have been discussed in literature regarding impact of COVID 19 infections in patients with other co-morbidities while there is paucity of literature regarding clinical manifestations and prognosis in patients of hypercoagulability syndrome having been infected with COVID 19. Therefore health workers and researchers should carefully monitor COVID-19 patients having existing hypercoagulability or thromboembolism disease.

As the pandemic has caused global health and economic devastation; all the countries worldwide are trying to combat to the situation by dedicated health care approach towards management of the pandemic. COVID 19 vaccines are in forefront in further management of the pandemic with every country trying their best to get the population vaccinated against the -CoV-2. The known side effects of the COVID 19 vaccine are mild to moderate and include fever, chills, nausea, vomiting, headache, fatigue, myalgia, malaise, pain and swelling at injection site and diarrhea [5]. Moreover European Medicine agency (EMA's) safety committee and Pharmaco-vigilance Risk Assessment Committee (PRAC) has opined that unusual blood clots with low blood platelet count should be included as very rare side effects of Vaxzevria (formerly COVID-19 Vaccine AstraZeneca) [6]. The episodes of thrombosis and thrombocytopenia along with bleeding have been observed very rarely following vaccination with COVID-19 Vaccine AstraZeneca [7].

These facts gave us an impetus to review the literature regarding SARS CO-2 and thrombosis, hypercoagulable disorders (hypercoagulability Syndrome and hypercoagulable states), hypercoagulable disorders and COVID 19 infections; COVID 19 vaccine related side effects such as thrombosis, COVID 19 vaccines and risk of thrombosis and management perspective in patients of hypercoagulable disorders contracting COVID 19 infections.

SARS-CoV-2 and thrombosis

The patients with SARS-CoV-2 infections are known to have hypercoagulability [8]. The pulmonary thrombosis in patients of COVID-19 infection is found to be as high as 79% [8]. In studies conducted in intensive Care unit patients, the event of thrombosis was noted amongst range of 31–79% in COVID 19 patients [8, 9]. The enhanced pro-inflammatory and anti-fibrinolytic changes in circulation lead to severe thrombosis in critically ill COVID 19 patients. In cohort study conducted by Zhou et al., it was observed that 54 patients of COVID-19 infection who succumbed to the disease had profound lymphopenia, elevated D-dimer, lactate dehydrogenase, and IL-6 levels [10]. Elevated levels of D-Dimer are characteristic feature of COVID-19 infections complicated by coagulopathy. Tang et al. found that the increased levels of D-Dimer and fibrinogen degradation product had stronger association with poor outcomes in patients with COVID-19. The lung tissue autopsy report revealed higher numbers of ACE2-positive endothelial cells in the COVID-19 patients as compared to control [11]. The homeostasis in circulation is attributed to the structural and functional stability of the vascular endothelial cells. The injury to the vascular endothelial cells in pulmonary vasculature most likely leads to vasculopathy and thrombosis in COVID 19 infected patients and is mediated through the integral membrane protein, ACE2 receptor in the alveoli [12].

The coagulopathy in patients of COVID 19 infection is promulgated due to endotheliopathy. This is attributed to the vascular endothelial cell damage which causes increased release of von Willebrand Factor, activation of platelets, and hypercoagulability and this eventually results in prothrombotic changes in blood. This leads to venous, arterial, and microvascular thrombosis. Thrombosis may further progress to a state of disseminated intravascular coagulation (DIC) [13]. Pulmonary vasculature is more prone for thromboembolism and pulmonary vascular endothelialitis has been observed in patients of Covid-19 [14, 15]. The microvascular microthrombi trigger active tissue factor expression on the endothelial cells especially in that of the pulmonary vasculature [16].

A systematic review and meta-analysis revealed that there is higher risk of developing venous thromboembolism in patients of COVID 19. This meta-analysis included 66 research studies for quantitative analysis and total

28,173 patients were recruited in these studies. The mean age of these patients was 62.6 years and out of which 60 percent were males and 40 percent females and 20% among them were ICU-patients. The overall prevalence of venous thromboembolism was 14.1% (95% CI 11.6–16.9), 40.3% (95% CI 27.0–54.3) after ultrasound-screening and 9.5% (95% CI 7.5–11.7) without screening. Venous thromboembolism noted in 22.7% of patients of COVID-19 in the Intensive Care Unit. The study opines that risk of venous thromboembolism is also increased in non-ICU indoor patients [17].

It is important to note that laboratory findings in patients of COVID-19-associated coagulopathy includes prolonged prothrombin time, decreased platelet count, and enhanced D-dimer levels. Markedly raised D dimer levels and decreased plasminogen levels are associated with severe manifestation of COVID 19 infection. The decreased plasminogen levels are suggestive of consumption for fibrinolysis activation [18].

Hypercoagulable disorders

The enhanced tendency of blood to thrombose is referred as hypercoagulability and it reflects the hypercoagulable state of the blood. It refers to exaggerated coagulation state due to some pre-existing pathology. There is a balance between pro-coagulants and anti-coagulants in circulation under physiological conditions. The hyperactivity of the pro-coagulant factors or a deficiency in anti-coagulants may lead to formation of thrombus and eventually may lead to thromboembolism [19]. The hypercoagulable state of blood and thrombophilic diseases leads to hypercoagulability. The triad of hypercoagulability, vascular trauma and vascular stasis are described as the harbingers of vascular thrombosis [20]. Hypercoagulable disorders comprise the hypercoagulability syndrome and also other diseases associated with hypercoagulable state. Hypercoagulability syndrome is not a generalized disease process but a host of predisposing risk conditions which may lead to thrombosis depending on environmental injury and the type and efficacy of the predisposing risk factors [20, 21].

The mnemonic CALMSHAPES was proposed by Thomas to describe the causes of the hypercoagulable state and these causes includes: Protein C deficiency, Antiphospholipid syndrome, Factor V Leiden mutation, Malignancy, Protein S deficiency, Hyperhomocysteinemia, Antithrombin III deficiency, Prothrombin G2021A mutation, Factor Eight excess and Sticky Platelet syndrome [19]. The congenital and acquired diseases associated with hypercoagulable states are described in brief in Figure 1 [22].

Deficiency of Heparin cofactor II, Tissue factor pathway inhibitor, and thrombomodulin are the other causes of hypercoagulable disorders. The strength of the predictive values for thrombosis in various hypercoagulable disorders may define the nature of complications associated with thrombosis in these diseases [19, 20].

Hypercoagulable disorders and COVID 19 infections

With advent of COVID 19 infection there had been universal approach in managing and tackling various complications of the virus especially in patients with existing comorbidities. Searching the literature it was found that a hand few of experiences of managing COVID 19 patients with hypercoagulable disorders have been notified till date. The COVID 19 associated hypercoagulability in patients have seen to be having a severe course of disease and such patients have poor prognosis. The study conducted in patients of COVID-19 having preexisting digestive hypercoagulability disease revealed high risk of thromboembolism. Cirrhosis and Inflammatory bowel disease (IBD) are two major digestive hypercoagulability diseases and there is higher risk of developing thromboembolism in these conditions [23].

The advent of portal vein thrombosis (PVT) in cirrhosis proves to be fatal in these patients. The portal vein thrombosis has been found to be evident in patient of hypercoagulability Syndrome such as mutation of factor V Leiden, deficiency of antithrombin, protein C and S and prothrombin G20210A gene mutation. The portal veins vascular endothelial cells are injured on exposure to circulatory cytokines. This endotheliopathy leads to thrombotic changes. The hypercoagulability is found to be severer in COVID-19 patients with preexisting cirrhosis in comparison to non-cirrhosis COVID-19 patients [24].

A meta-analysis in inflammatory bowel disease patient revealed two fold increases in the risk of venous thromboembolism as compared to normal healthy individual [25]. Circulatory levels of cytokines are markedly increased in inflammatory bowel disease patient and moreover associated endothelial injury in these patient affect the coagulation and fibrinolysis pathways facilitating prothrombotic mechanism while obscuring fibrinolysis [26]. The altered coagulation activation or progression of vein thrombosis in COVID-19 patients with preexisting inflammatory bowel disease remains to be explored.

Hence the patients of hypercoagulable disorders are having double the risk of developing thromboembolism if

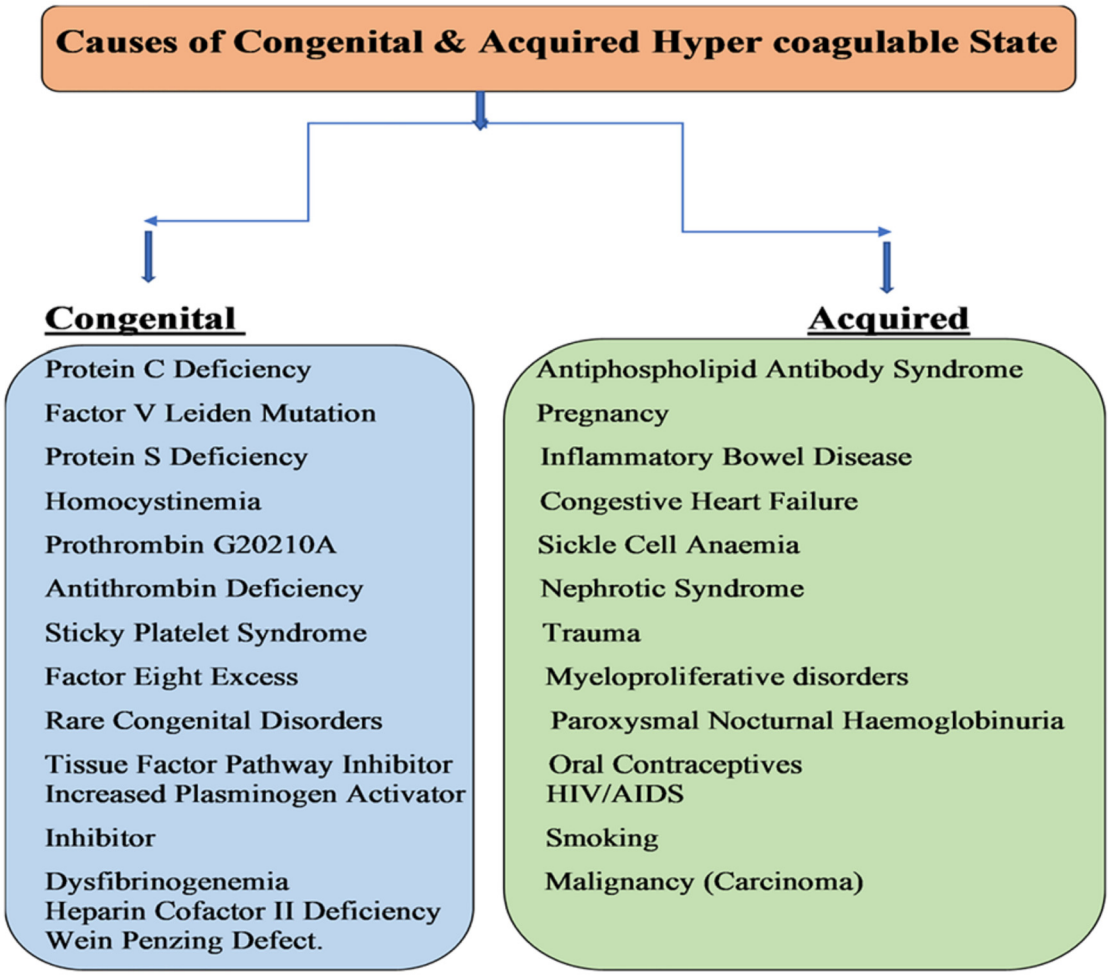

Figure 1: Causes of congenital & acquired hyper coagulable state.

infected with COVID 19. The manifestations of COVID 19 disease in these patients will be severe and they are likely to have poor prognosis. The COVID-19 patients with hypercoagulability or thromboembolism disease need to be carefully monitored and managed.

COVID 19 vaccines and risk of thrombosis

Thrombosis with thrombocytopenia was noted with Vaxzevria (formerly COVID-19 Vaccine AstraZeneca) vaccine. The European Medical Agency on investigation and reviewing the reported cases found that very rare types of thrombosis associated with thrombocytopenia were noted in few cases. This thrombosis was observed in unusual locations such as cerebral venous sinus thrombosis and splanchnic vein thrombosis apart from arterial thrombosis and this occurred in females under 60 years of age. The time for occurrence of this event was within two weeks after receiving their first dose of COVID-19 Vaccine AstraZeneca. The reporting of such incidence after the second dose is limited. It was opined that the vaccine may trigger an immunological response leading to occurrence of atypical heparin-induced-thrombocytopenia like disorder [6, 7]. European Medicine agency (EMA's) safety committee and Pharmaco-vigilance Risk Assessment Committee (PRAC) have recommended that unusual blood clots with decreased blood platelet count are to be included as highly rare side effects of Vaxzevria (formerly COVID-19 Vaccine AstraZeneca) [7]. As patients with hypercoagulability syndrome has twice the risk of developing thrombosis, therefore rare side effects of COVID 19 Vaccine (Vaxzevria) such as thrombosis with thrombocytopenia in these patients may prove to be fatal.

Hence health care workers should be extra cautious while administering COVID 19 vaccine in patient of pre-existing hypercoagulable disorders.

Management perspective in COVID 19 infected patients with preexisting hypercoaguability syndrome or those having hypercoagulable states

The health care workers should ensure that the patients of hypercoagulability syndrome those having hypercoagulable state are carefully monitored after COVID 19 vaccinations. These patients should be instructed to report if they develop any signs and symptoms such as chest pain, breathlessness, continuous abdominal pain and swelling of legs to immediately report to hospital as these changes are suggestive of thrombosis [6, 7]. They may also seek immediate medical care if they develop any other symptoms such as persistent headaches and blurred vision or petechiae at site of vaccination. We recommend health education of the public so that they are aware of the side effects of COVID 19 vaccine and the same has been depicted in Figure 2.

The health care workers should enquire regarding the family history of any blood coagulation disorder and past history of any blood clot at younger age, miscarriages or stroke. As thromboembolism with thrombocytopenia is a noted side effect of COVID 19 vaccine, test for prothrombin time, activated partial thromboplastin time, platelet count, platelet aggregation test and clotting time need to be conducted post vaccination in any individual having past history of thrombosis and thromboembolism. The lab investigations to be conducted in patient with pre-existing hypercoagulable states are detailed in Figure 3 [27].

Moreover the health care workers should be vigilant about the abnormal coagulation activation and venous thromboembolism in patients of pre-existing hypercoagulability disease [7, 28]. The decrease in oxygen arterial pressure in critical ill COVID 19 patients promulgates the

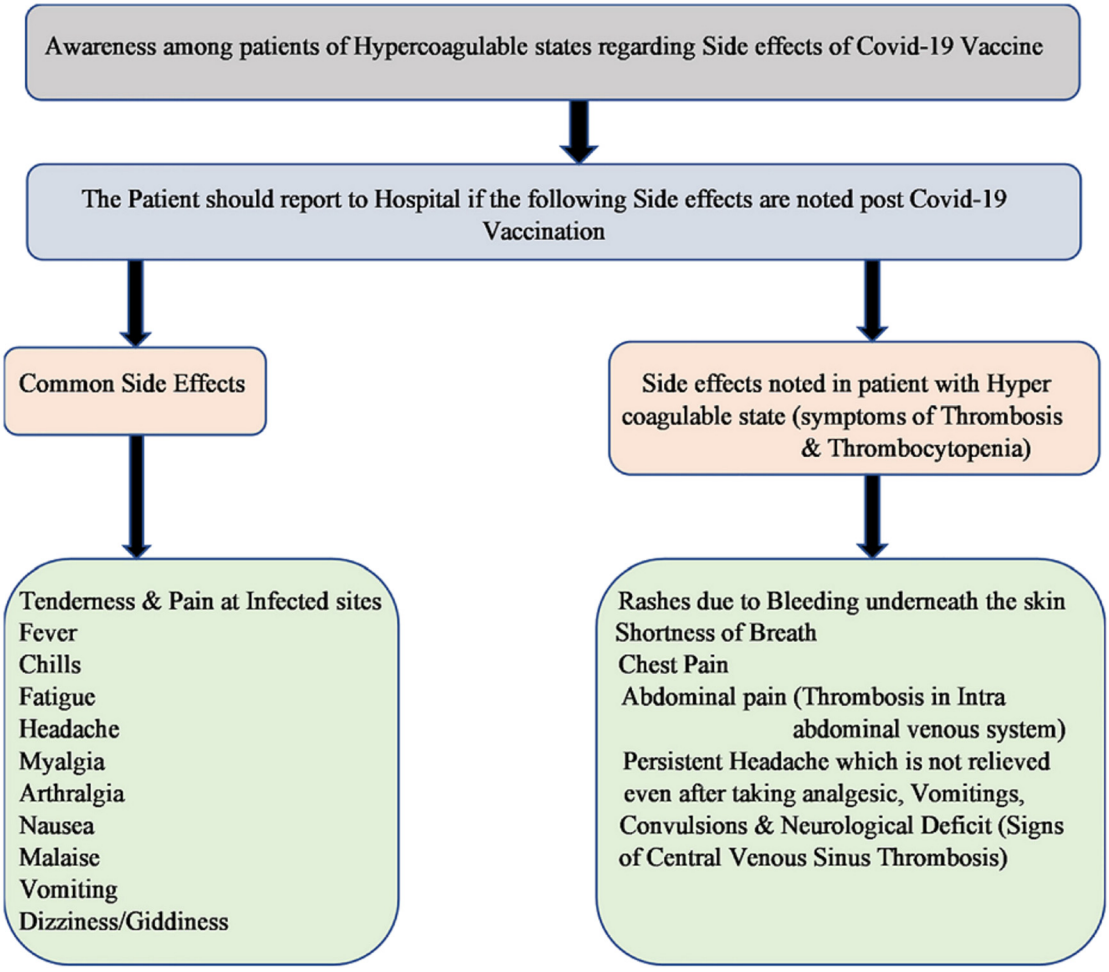

Figure 2: Schematic side-effects flowchart.

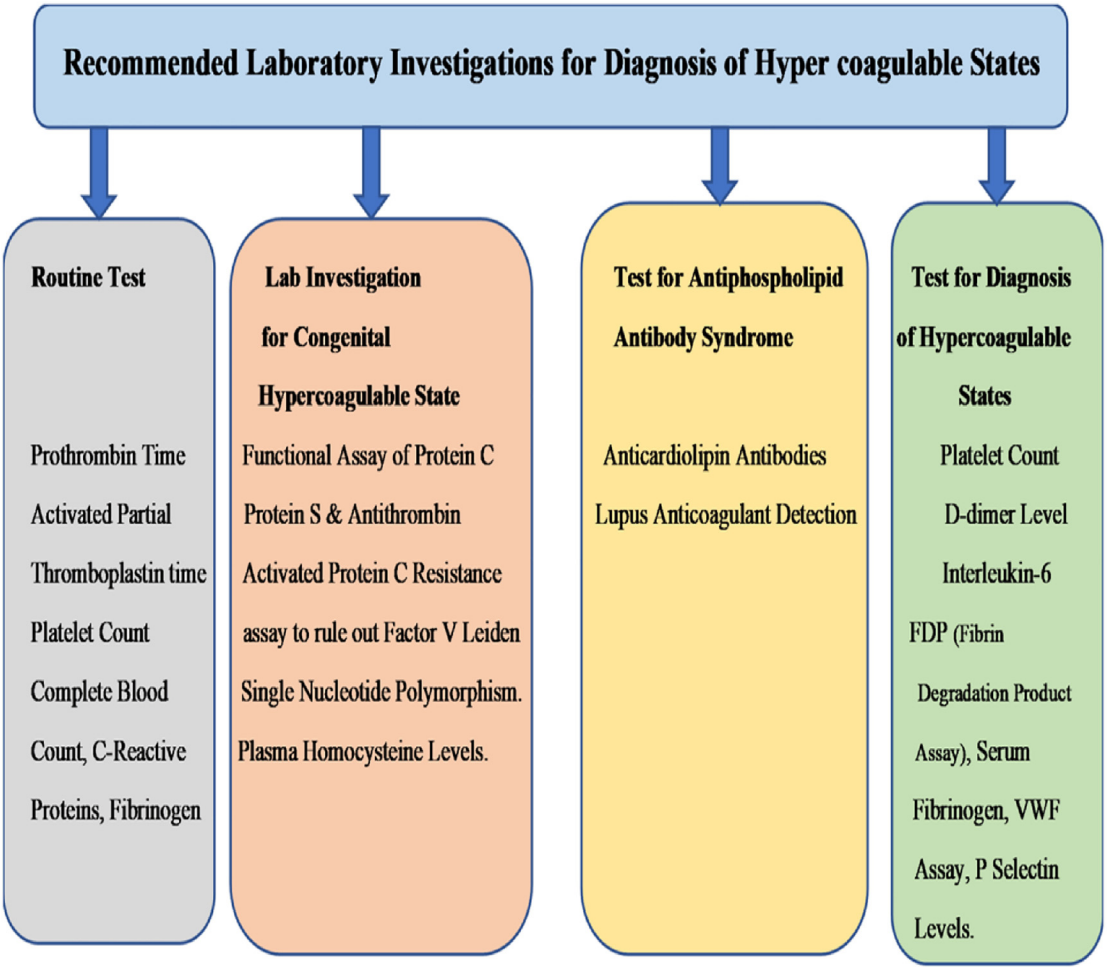

Figure 3: Recommended laboratory investigations.

development of thrombosis and ischemic syndrome. The cause of concern is regarding employing suitable anti-coagulation therapy in COVID-19 patients with preexisting hypercoagulable disorders.

A retrospective research analysis was carried out in the hospital of Tongji (Wuhan, China) and it was reported that there were less mortality in severe COVID-19 patients who were administered unfractionated heparin or low-molecular weight heparin as anti-coagulant. These patients had Sepsis-induced coagulopathy (SIC) score of ≥4 and significantly enhanced D-dimer levels (more than 6 times the upper limit of reference range). The International Society on Thrombosis and Haemostasis (ISTH) and the American Society of Hematology (ASH) has recommended use of low-molecular-weight heparin as anticoagulant for the thrombosis in COVID 19 patients but the best effective dosage is yet to be defined and needs further exploration. Fewer studies have pointed out increased incidence of deep vein thrombosis in up to 40% of the patients with low-molecular-weight heparin [29]. Many more research studies are warranted so that a standard regime and protocol can be formed for administering anticoagulant therapy in patients with severe COVID-19 especially in those having hypercoagulability disorders. The algorithm to assess thrombogenesis in patients with COVID-19, as well as therapeutic protocol needs to be defined.

Conclusions

COVID 19 infection associated hypercoagulable state has been link with higher risk of thrombosis and thromboembolism leading to severe manifestation of the disease and poor prognosis. COVID 19 infected patients with pre-existing hypercoagulable disorders have higher risk of developing thrombosis and thromboembolism and such thrombotic episodes may prove to be severely morbid in

these patients. Though thrombosis with thrombocytopenia has been noted as a rare side effect of COVID 19 vaccine Vaxzevria (formerly COVID-19 Vaccine AstraZeneca); the health care workers should be cautious and judicious in managing such patients. A detailed lab profile for coagulable state of blood should be carried out in all patients COVID 19 infected patients with pre-existing hypercoagulable disorders. The patients should also be health educated regarding side effects of vaccine especially with those indicating thrombosis and they should be warranted to receive immediate medical care in case of any side effects or complications. Very few studies have been conducted towards exploring clinical manifestations, interventional protocol and management of patients of COVID 19 with pre-existing hypercoagulable disorders hence the prospective researchers should further conduct a meticulous follow up of these patients so that rational management protocol can be recommended.

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