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Coagulopathy with COVID19 and Tyrosine Kinase Receptor Tie 2: Review Article

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ABSTRACT

Background: The newest coronavirus-caused SARS outbreak was first reported in December 2019 (COVID-19). The Director-General of the World Health Organization declared a global pandemic of COVID-19 three months after the first cases were identified. It is still not apparent how exactly COVID-19 causes coagulopathy, they may be similar to those which cause septic coagulopathy/disseminated intravascular coagulation (DIC) when bacteria are present. Endothelial cells have an abundance of the receptor Tyrosine Kinase Tie2. Additionally, it is expressed by a certain subpopulation of macrophages and has been shown to facilitate angiogenesis.

Objective: Review of coagulopathy with COVID19 and Tyrosine Kinase Receptor Tie2.

Methods: We scoured scholarly papers and databases including PubMed, Google Scholar, and Science Direct for information on COVID19 and Tyrosine Kinase Receptor. Between March 2016 and February 2023, however, only the latest or most comprehensive study was considered. The authors also assessed the usefulness of references taken from similar books. Documents written in languages other than English have been overlooked because of a lack of funding to translate them. Unpublished articles, oral talks, conference abstracts, and dissertations were all generally agreed upon not to constitute valid scientific investigation. **Conclusion:** Extreme cases of COVID-19 are characterized by microvascular thrombosis and accompanying endothelial dysfunction. Signaling through the Tie2 receptor helps keep the endothelial surface anticoagulant in a constitutive state. Angiopoietin-2 (Angpt-2) is a prothrombotic phenotypic switch induced by the Tie2 antagonist produced from endothelial cells during inflammation.

Keywords: Coagulopathy, COVID-19, Tyrosine kinase receptor.

INTRODUCTION

The newest coronavirus-caused SARS outbreak was first reported in December 2019 (COVID-19). Three months after the initial cases were reported, evidence suggested that COVID-19 patients frequently present with a coagulation issue, with the prevalence increasing in more severe instances [(1)].

Coagulopathy caused by COVID-19 warrants more study, so it's instructive to look back at what we know about coagulopathy caused by other RNA viruses involving Dengue fever virus (flavivirus) and Lassa virus (arenavirus), as well as Ebola virus (filovirus). In viral hemorrhagic fevers, vascular damage and coagulopathy are thought to be caused by unregulated virus replication and inflammatory reactions, with 30%-50% of Ebola infections showing hemorrhagic symptoms [(2)].

Contrarily, although coronavirus is a member of the family of enclosed, single-stranded RNA viruses, it does not result in hemorrhagic problems in humans. For example, while there was a relatively low incidence of bleeding associated with the coronavirus responsible for the 2002 outbreak of severe acute respiratory syndrome (SARS) (SARS-CoV-1), the virus was linked to thrombocytopenia in 55% of cases, thrombocytosis in 49% of cases, and a prolonged activated partial thromboplastin time (aPTT) in 63% of cases. Deep vein thrombosis occurred in 25% of individuals with SARS-CoV-1 infection, while pulmonary embolism occurred in 11% [(2)]. Like its sister clade SARS-CoV-1, the virus responsible for COVID-19, SARS-CoV-2, may cause thrombotic problems. According to Chinese specialists, ARDS and coagulation predominant-type coagulopathy can develop in really ill individuals [(1)].

In a study of individuals infected with COVID-19, **Tang *et al.*** [(2)] found that 71.4% of those who did not make it matched the criteria for disseminated intravascular coagulation, while only 0.6% of those who did make it did. In particular, pulmonary circulation and bronchoalveolar space coagulation and fibrinolysis disturbances are expected to play major roles in the aetiology of ARDS in COVID-19.

Variations in blood coagulation markers:

D-dimer values more than 0.5 mg/L were observed in about fort six percent of patients according to the analysis by **Guan *et al.*** [(3)] of 1099 patients. D-dimer levels were elevated in 43% of moderately and severely ill patients, but in 60% of intensive care unit (ICU) patients. D-dimer and FDP levels were also found to be significantly higher in non-survivors, as were PT and aPTT times upon admission.

ARDS is a severe complication with a poor prognosis, and Coagulation issues were linked to ARDS development **by Wu *et al.*** [(1)]. These findings suggest that COVID-19 raises the risk of coagulopathy in seriously ill patients. D-dimer and PT levels are useful for patient triage and management. As part of its guidelines for the care of coagulopathy in COVID-19, the International Society on Thrombosis and Haemostasis (ISTH) recommended routine testing and monitoring of hemostatic markers in all cases.

Although thrombocytopenia is the most sensitive indicator of sepsis-induced coagulopathy/DIC, it is unusual in COVID-19. In their study of SARS-Cov-1 patients, **Iba *et al.*** [(4)] found that 44.8% of those affected by the condition had thrombocytopenia.

Those with COVID-19 and a low platelet count are more likely to experience serious complications and

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even death. Similar to thrombocytopenia, patients with extremely high platelet counts and lymphopenia are said to spend more time in the hospital. The difference between thrombocytosis and thrombocytopenia may be thought of as being a matter of degree. Although not yet proved in SARS-CoV-2 infection, it is believed that direct infection of hematopoietic cells or activation of an autoimmune response against blood cells is the mechanism of thrombocytopenia. It has also been hypothesized that the thrombocytopenia is caused, at least in part, by the existence of persistent consumptive coagulopathy as a result of chronic inflammation [(5)].

However, the processes underlying the paradoxical rise in platelet count during a coronavirus infection remain unknown. Proinflammatory cytokines are suspected to have a role. Despite the thrombocytopenia, some studies have revealed elevated levels of thrombopoietin in SARS-CoV-1 infection, which may lead to enhanced platelet formation [(2)].

COVID-19 coagulopathy clinical manifestations:

In contrast to SARS-CoV-1, patients with COVID-19 rarely bleed even when diagnosed with DIC. Thrombocytopenia, delayed aPTT, and increased D-dimer have all been documented in multiple studies of SARS-CoV-1 patients. Patients with acute respiratory failure experienced no pulmonary emboli or other thrombotic events such as hemorrhage [(6)].

In contrast, thromboembolism in SARS-CoV-2 infected individuals has garnered a lot of research and interest. **Cui *et al.*** [(7)] looked for thrombosis in asymptomatic ICU patients using ultrasound and found 25% (20/81) had it. It has been observed that between 20% and 30% of COVID-19 intensive care unit patients would develop thrombosis or severe thromboembolic consequences.

However, among septic ICU patients who were not COVID-19 and who were administered heparin or enoxaparin for VTE prevention, the incidence was 12.5%. When dealing with severely ill patients who suddenly experience oxygen desaturation and shock, it is imperative to evaluate the risk of pulmonary thromboembolism [(8)].

COVID-19 activation of coagulation mechanisms:

Although the exact processes by which COVID-19 causes coagulopathy are not yet known, they may be similar to those which cause septic coagulopathy/DIC when bacteria are present. Coagulation abnormalities are typically brought on by an overabundance of proinflammatory cytokines, damage to the vascular endothelial cells, activation of cell death mechanisms, and an overall rise in damage-associated molecular patterns are all hallmarks of a severe infection. Higher levels of fibrin-related biomarkers, in addition to delayed PT and aPTT, are typically detected in COVID-19, in comparison with bacterial sepsis-induced coagulopathy/DIC [(9)].

Tumor necrosis factor-alpha, interleukin-1beta, and monocyte chemoattractant protein-1 are only a few of the proinflammatory cytokines and chemokines mentioned in Cancer Virus Infectious Disease-19. The increased production of inflammatory cytokines and chemokines, which attract immune cells to diseased organs, has both protective and harmful effects on the host. Bacterial infections use the same method, although the lymphatic response is less evident in those cases than it is in viral infections [(2)]. Lymphopenia is a hallmark of SARS-CoV-1 infection, and it has been suggested that an uptick significant lymphoid depletion occurs in the lymph nodes when lymphocytes undergo apoptosis due to TNF-related apoptosis-inducing ligand. After being stimulated by the immune system, monocytes/macrophages and vascular endothelial cells increase their expression of tissue factors. Surface protein tissue factor is essential for triggering blood clotting. Ebola virus infection causes a much more severe coagulopathy than SARS coronavirus infection, which causes thrombocytopenia, fibrin deposition, high FDPs, and normal PT and aPTT. Tissue ischemia and organ failure are linked to the formation of microvascular thrombi in association with consumptive coagulopathy [(9)].

In contrast to the rare liver and vascular damage seen in COVID-19, hemorrhagic signs are typical of an Ebola infection. Coagulopathy has both thrombosis and bleeding as symptoms, however the prevalent one varies from virus to virus (figure 1) [(2)].

Modifications to Fibrinolysis:

Coagulation problems in COVID-19 are characterised by an increase in D-dimer and fibrinogen degradation product (FDP) rather than a prolongation of the prothrombin time (PT) and thrombocytopenia. D-dimer testing resulted in the highest DIC parameter score in the deceased. This finding provides further evidence that subsequent hyperfibrinolysis following coagulation activation is a key contributor to the coagulopathy associated with COVID-19. However, there is limited data in COVID-19 for assessing fibrinolysis [(10)]. Using knockout mice, researchers have analysed the role of urokinase in SARS-CoV-1 infection and discovered that this pathway plays a role in controlling mortality. Higher levels of urokinase-derived peptides from plasminogen were seen in individuals with fatal SARS-CoV-1 infection compared to those with milder disease [(2)].

The nucleocapsid (N) protein of SARS-CoV-1, on the other hand, has been shown in an in vitro research to promote the production of plasminogen activator inhibitor-1, a finding that may be relevant to lung fibrosis [(11)].

Patients with Dengue hemorrhagic fever had slightly increased levels of thrombin activatable fibrinolysis inhibitor, plasminogen activator inhibitor-1, and t-PA. However, it is not yet known whether COVID-19 stimulates or represses fibrinolysis, nor what mechanism causes an unbalanced rise in D-dimers [(9)].

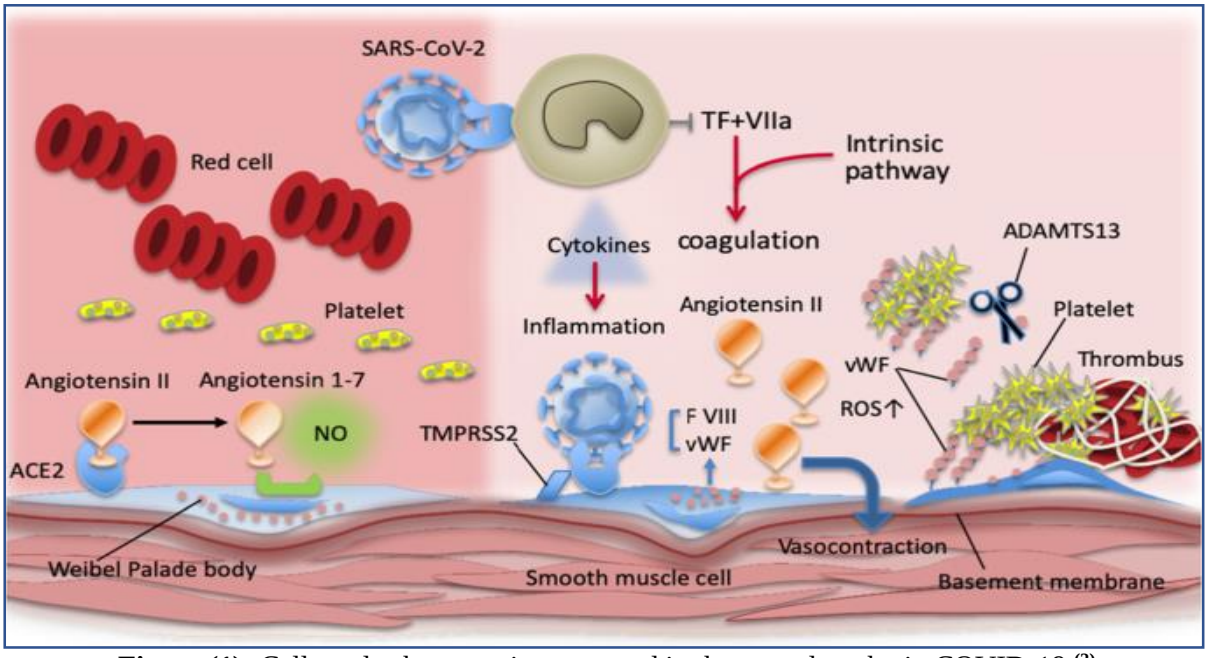

Figure (1): Cells and substances incorporated in the coagulopathy in COVID-19 [(2)]

Damage related to endothelium:

Hemorrhagic fevers produced by arenaviruses, particularly the Lassa virus, can worsen bleeding caused by shock. Both clinical and experimental findings point to a function for the vascular system in Lassa hemorrhagic fever, specifically the vascular endothelium. Multiple in vitro investigations demonstrated that the Lassa virus disrupts endothelial cell function and rapidly replicates in endothelial cells [(12)].

Mild thrombocytopenia, decreased platelet function, and shock are connected with the hemorrhagic episode in Lassa fever, all of which result from endothelial injury. Fibrin deposition induction is uncommon in Lassa fever compared to other hemorrhagic fevers like Ebola and Marburg. This finding suggests that the pathogenesis of Lassa fever is unique among hemorrhagic fevers [(11)].

Pneumocytes and endothelial cells express a high quantity of angiotensin-converting enzyme, which the coronavirus uses to infect these cells. After contracting SARS-CoV-1, many evaluations noted a rise in endothelial cell-specific autoantibodies. Pathogenesis of COVID-19 should also entail endothelial cell infection with CoV-2 and subsequent endothelial damage [(9)].

The endothelium glycocalyx is a major player in the pathophysiology of virus-induced coagulopathy. The flavivirus family, which includes the virus responsible for dengue disease, is known to increase vascular permeability by disrupting the glycocalyx [(12)].

The Dengue virus has been demonstrated to cause endothelial cells to release the glycocalyx degradation factor heparanase and to control immune cells' production of matrix metalloproteinase, according to research by **Chen *et al.*** [(12)]**,** it's possible that COVID-19 uses similar tactics, but it's not known for sure.

Death of cells and organ malfunction:

Infectious agents responsible for viral hemorrhagic fevers are particularly dangerous. They set off a cascade of organ failure known as a "cytokine storm." The Ebola virus is particularly dangerous because it can spread to various body systems. The Ebola virus not only compromises the immune system, but also infects and kills cells in key organs including the liver, spleen, and kidneys that regulate coagulation, fluid and chemical equilibrium, and immunological reactivity [(2)].

Like other coronaviruses, the Ebola virus can harm a person's respiratory and circulatory systems. The Ebola virus causes dysregulation of the innate immune system by, for example, downregulating the Type-I interferon response, disrupting the network of cytokines and chemokines, and causing dendritic cell and natural killer cell failure [(9)].

Both humoral and cell-mediated immunological arms of the adaptive immune system are known to be suppressed. Lymphocyte apoptosis induction in monkey models and humans is a major result. Massive depletion of CD4 and CD8 T-lymphocytes was documented in the deceased patients. Cytometry revealed that only 9.2% and 6% of mononuclear cells were CD4 and CD8 lymphocytes in Ebola virus deaths, but that these percentages were over 40% and 20% in healthy people and survivors, respectively [(2)].

These results point to apoptotic processes as a major contributor to Ebola hemorrhagic fever. Increased T-lymphocyte apoptosis has been described in SARS and MERS, two other coronavirus infections. Lymphopenia is a common symptom of these infections, and lymphocyte counts have been shown to be helpful in gauging the severity of the disease and determining prognoses [(14)].

Because the SARS-CoV-2 primarily infects lung epithelial cells, lymphocytes, and vascular endothelial cells, ARDS, shock, and coagulopathy characterize the clinical presentation of severe COVID-19. Histological features of bacterial sepsis-associated acute respiratory distress syndrome (ARDS) include alveolar and interstitial edoema, significant neutrophil infiltration, and increased vascular permeability [(14)].

Alveolar injury, interstitial emphysema, and enhanced vascular damage have all been linked to neutrophil infiltration into alveoli, neutrophil extracellular traps, and thrombus formation in the lung microvasculature in sepsis-associated ARDS. However, pathological data are still inadequate, despite Luo's observation that wall thickening, narrowing of the arterial lumen, and the development of microthrombus followed the ARDS symptoms in COVID-19 [(15)].

Tyrosine Kinase Receptor Tie2 in COVID19:

Endothelial cells have an abundance of the receptor tyrosine kinase Tie2. Also, it is expressed by subpopulation of macrophage, playing a role in promotion of angiogenesis [(16)]. In septic DIC, Tie2 signaling disruption via Angiopiotin-1 (Angpt-2), which is a paralog of Angpt-1 occurs leading to endothelial changes promoting microvascular thrombus formation. Proteolytic cleavage and release of the ectodomain from the full-length, cell-surface receptor results in soluble Tie2 in Covid19 patients [(17)].

Endothelial dysfunction and microvascular thrombosis are both characteristic of severe COVID-19. The endothelium surface is anticoagulant by nature, and the Tie2 receptor plays a role in maintaining this trait. Angiopoietin-2 (Angpt-2) is secreted from endothelial cells and acts as a Tie2 antagonist, inhibiting Tie2 and inducing a prothrombotic phenotypic change during inflammation (Figure 2) [(18)].

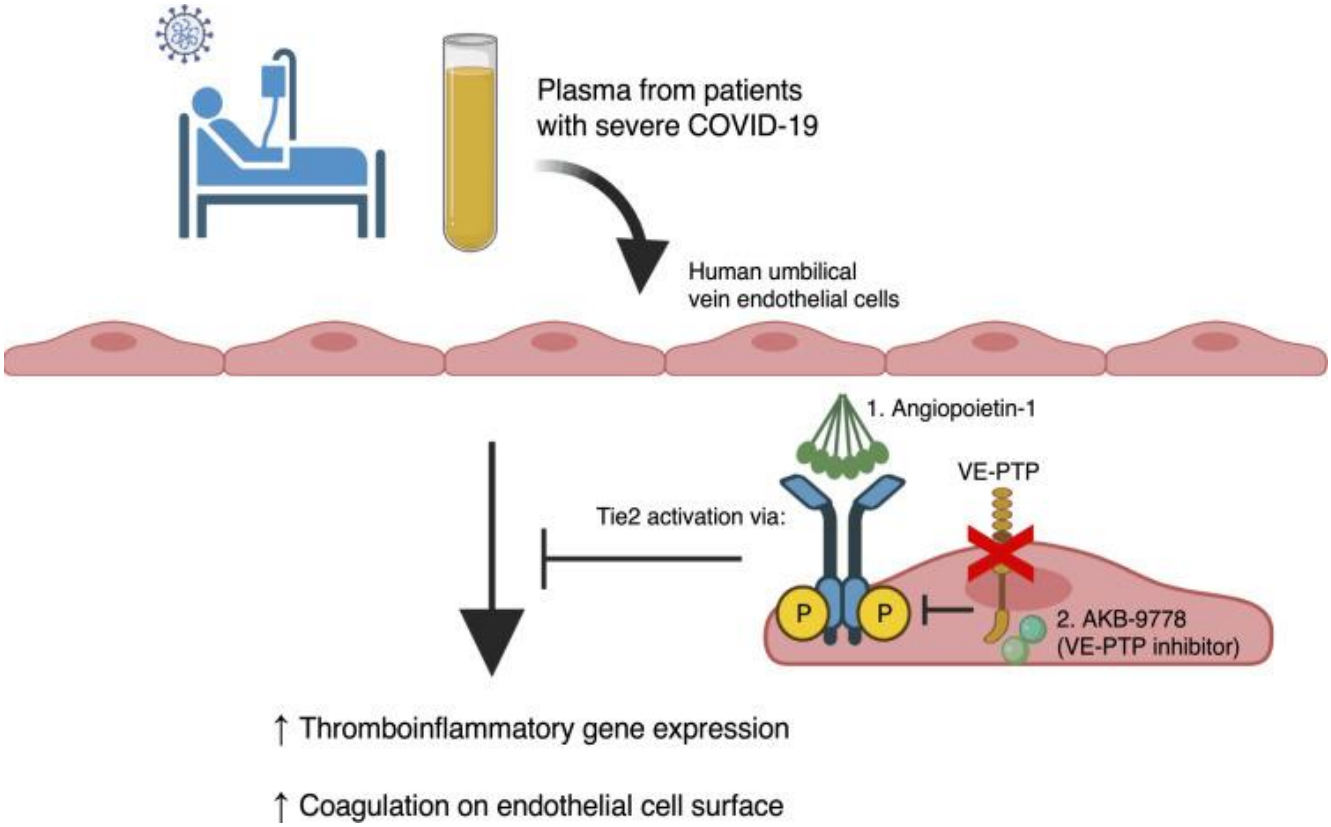

Figure (2): Role of Tie2 in endothelium [(18)].

Previous studies have shown that COVID-19 has elevated levels of Ang-2 and VEGF-A. The current study extends these findings to soluble Tie2 and soluble VEC. It was shown that sTie2 was substantially higher and sVEC was significantly lower. The former may result through pssive degradation of the receptor or from an active secretion pathway [(19)].

Treatment of COVID19 patients associated with coagulopathy:

The endothelium's principal role is to act as a barrier to prevent leakage through blood vessels and as an antithrombotic surface to improve blood flow. Continuous secretion of Angpt1 from perivascular cells and platelets keeps Tie2 engaged throughout the healthy adult vasculature, where it plays a crucial role in the process [(20)]. By inhibiting inflammatory NF-B, which in turn increases production of anticoagulant genes and decreases expression of tissue factors, the receptor tyrosine kinase Tie2 promotes vascular quiescence. Endothelial cells exposed to plasma from COVID-19 carriers were found to be protected from thromboinflammatory changes by using either direct Tie2 agonism with Angpt-1 or VE-PTP antagonism with AKB-9778. However, these two strategies of activating Tie2 are distinct. Genes encoding Angpt-2, endothelium adhesion indicators, tissue factor, complement C3, and complement factor B are all NF-kappaB target genes that are downregulated. In non-COVID infectious illnesses, including as Gram-negative sepsis, anthrax, and malaria, activation of Tie2 has been demonstrated to reduce proinflammatory endothelium characteristics [(21)].

Preventing hypercoagulation is crucial, and prior research has demonstrated that maintaining Tie2 signalling is sufficient to re-establish pathological thrombosis during systemic inflammation. Tie2 activation can only be indirectly assessed by measuring soluble Tie2 as well as circulating Angpt-2. More research is needed to confirm whether or not COVID-19 causes decreased Tie2 activation in endothelial cells [(22)].

CONCLUSION

Extreme cases of COVID-19 are characterized by microvascular thrombosis and accompanying endothelial dysfunction. Signaling through the Tie2 receptor helps keep the endothelial surface anticoagulant in a constitutive state. Angiopoietin-2 (Angpt-2) is a prothrombotic phenotypic switch induced by the Tie2 antagonist produced from endothelial cells during inflammation.

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