D-dimer and ferritin are the most important tests to diagnosis coronavirus

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ABSTRACT
The global pandemic of novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) .The incidence of liver injury after coronavirus disease 2019 (COVID-19) infection ranged from 15%-53%. The mechanism includes direct viral cytopathic effect, cytokinesis, and treatment drug-induced liver injury,due to the high number of infections with the emerging coronavirus, there is an urgent need to know the tests used to detect the virus, and one of the most important of these tests is the use of D-dimer as a coagulation marker and ferritin. D-dimer is considered as a diagnostic indicator for those infected with the Coronavirus, As well as determining the level of ferritin in the blood, as studies have shown that ferritin and D-dimer levels in the blood are highly related to Covid 19 disease occurrence. Only few researches have revealed predictive value of quantifying D-dimers and ferritin in the patients who have COVID-19. Affected patients have a blood clot because this virus infects small blood vessels, it is recommended to find an appropriate D-dimer and ferritin value that might aid in the diagnosis. In this review article, we highlight these examination and its relationship to the Corona virus. Thus, a diagnosis can be necessary as it helps in determining treatment.
Key Words: Corona virus; D-dimer (DD); ferritin, venous thromboembolism (VTE)

I. INTRODUCTION
Corona virus disease 2019 (COVID-19) is a newly developing infectious human coronavirus that originated in Wuhan, China, and has been quickly spreading throughout China and other nations since December 2019.[1,2] It can spread via the circulation or the endothelium of blood vessels, infecting all tissues.[3] The illness often appears as a respiratory syndrome, but it can also cause additional problems, COVID-19 disorder can lead to thrombosis and venous thrombosis, as well as cerebral infarction. A soluble fibrin degrade called D-dimer is one of the most important tests for spotting blood clots. The fibrinolytic system's orderly breakdown of clots results in the soluble fibrin degradation product known as D-dimer. Numerous works have shown that D-dimer is a helpful marker for the onset of fibrinolysis and coagulation. Thus, D-dimer has undergone substantial research and is now frequently utilized in VTE diagnosis. Additionally, D-dimer was investigated for calculating the ideal anticoagulation duration in VTE patients, monitoring and diagnosing disseminated intravascular coagulation, and identifying patients with a high risk of VTE.[4,5] In a research with 20 COVID-19 patients, those with severe and highly severe COVID-19 showed higher levels of serum ferritin, with the latter having serum ferritin that was significantly higher than the former (1006.16ng/ml) versus (291.13ng/ml). Twelve people who died from SARS-CoV-2 infection had high ferritin levels, according to autopsies .[6] the levels of Ferritin in peripheral blood of 69 patients who have got severe COVID-19 have been found to be greater than those of people with less severe COVID-19.[7] Serum ferritin levels were found to be highly related to COVID-19 severity as a consequence.[8] Last but not least, laboratory findings in COVID-19 patients revealed evidence of a cytokine storm with elevated inflammatory markers, such as ferritin that was related to serious and life-threatening disease.[9]
This review article discusses the role of D-dimer and ferritin its use in detecting the Corona virus.

COVID-19
Because of platelet activation, excessive inflammation, endothelial dysfunction, and stasis, COVID-19, viral respiratory disease that is caused by SARS-CoV2, could predispose individuals to

the thrombotic disease, in venous as well as arterial circulation. [10] Systemic microvascular thrombosis can occur in most deaths and has been corroborated through a patient autopsy.[11] Symptoms of this disease include fever, cough, dyspnea, watery diarrhea, myalgia, severe lymphopenia, long-term clotting patterns, heart disease, and sudden death. [12,13]

However, most of these COVID-19 cases first develop respiratory symptoms, followed by a stroke a few days later.[14,15] The most important event is the sympathetic activity increased by central stimulation, this activity increases the lung capillary leak.[3]

Coronavirus and liver failure
From modest pains and aches to serious illness and death, SARS-CoV-2 symptoms are diverse, although COVID-19 typically results in pneumonia, epidemiological and clinical research have revealed that COVID-19 can also produce a variety of other clinical symptoms. [12,16] The majority of bodily organs are significantly altered by SARS-CoV-2 infection, according to studies of whole-body autopsies in COVID-19 patients. [17] In COVID-19 patients, signs of gastrointestinal and hepatic involvement have gradually become apparent.[18] Hepatic injury occurs in 14.8% to 53.8% of COVID-19 patients; in patients with severe COVID-19, the rate of liver injury can reach 58-78%. The most common sign of liver injury in COVID-19 is an increase in ALT/AST levels, which is followed by a modest increase in bilirubin levels.[19,20] There are several potential processes that could lead to hepatic injury, including: hepatocytes and the biliary epithelium are damaged directly by SARS-CoV-2 and indirectly by an excess of cytokines and/or drug-induced hepatotoxicity. Yet, the precise reason for liver injury is still unknown.[21] A significant increase in ferritin was observed in those with moderate and severe COVID-19.[13] The liver serves as the body's main repository for iron, which is deposited as intricate protein molecules called ferritin or hemosiderin.[22] In physiological conditions, iron participates in a number of enzymatic reactions and oxygen transport.[23] At the same time, excessive iron causes oxidative tissue damage by producing free radicals and oxidizing molecules.[24] Therefore, too much iron might lead to cell damage and liver toxicity.[25]

D-dimer Formation
Plasma fibrinogen is converted by thrombin to fibrin monomers in Figure 1. After that, thrombin stays connected to fibrin and turns on factor XIII, which is circulated while tied to fibrinogen. As fibrin polymerizes and continues to do so after turning into an insoluble gel, factor XIIIa is created. The successive actions of FXIIIa, thrombin, and plasmin result in D-dimer antigen formation.
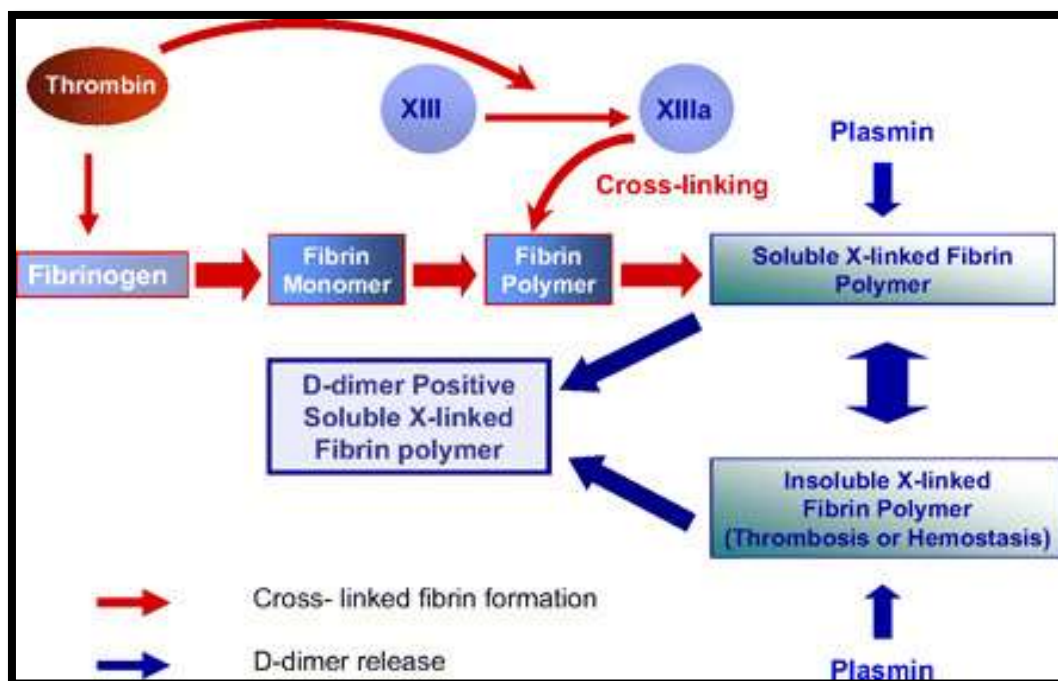

Figure 1: D-dimer formationdynamics

Prior to and following fibrin gels, plasmin releases D-dimer antigen from the polymers of the fibrin. D-dimer antigen, as it has been identified through commercially available assays, could therefore either result from plasmin cleavage of fibrin clot or be produced from soluble fibrin polymers prior to their uptake in the clot. Adapted from [36].

D-dimer test

The fibrin D-dimer (DD) test, one of the most significant tests for diagnosing suspected venous thromboembolism (VTE), is now commonly used to rule out this condition.[26] D-dimer, which reflects the activation of fibrinolysis and coagulation, is produced by the production and lysis of reticulated fibrin.[27] It has been claimed that COVID-19 was linked to hemostatic problems, and that these dead people had D-dimer levels that were noticeably increased.[28] could be useful in predicting hospital mortality in covid19 patients.[29] In addition to pulmonary embolism (PE), D-dimer concentrations rise in a wide range of other diseases and illnesses, such as cancer, inflammation, trauma, pregnancy, and sepsis. [30] In various clinical contexts, imaging is avoided by using the D-dimer exclusion test.[26] Actually, in patients who have a moderate or low clinical risk of PE in an outpatient setting, D-dimer has negative predictive value for ruling out PE. [31] The high D-dimer level could be detected in some of the physiological states such as the pregnancy and pathological conditions, which include inflammation, cancer, and surgeries. [32] D-dimer kit sensitivity varies from one manufacturer to the next.[33]

Although some works have examined predictive value of D-dimer testing in PE patients who are hospitalized, there are no researches tackling this topic in COVID-19 patients. Its efficiency in hospitalized patients who have suspected thromboembolism is uncertain.[34] COVID-19 was found in many works to predispose people to thrombosis in both veins and arteries. As a result, it's of an even higher convenience to find an adequate D-dimer value which might be helpful in the case of requesting imaging studies, like CTPA, in COVID pandemic context, where patients with serious illnesses have respiratory symptoms.[35] Thus, people with COVID-19 had an increased chance of developing DVT, VTE, and perhaps PE.[35,29] A recent Chinese study using Padua model discovered that 40% of hospitalized COVID-19 patients had a high VTE risk. Information on the use of thromboprophylaxis or VTE occurrences was not included in the research.[20] In physiological settings like pregnancy

and pathological states like inflammation, cancer, and surgery, D-dimer level is elevated.[32] Depending on the manufacturer, D-dimer kits have varying degrees of sensitivity.[33] There has been growing evidence that D-dimer antigen testing can be useful to physicians in a variety of contexts.[36]

Clinicians need to be aware of performance properties of particular D-dimer test being used at their institution since D-dimer analyte isn't a simple structure with consistent composition.[37] It is possible to rule out a patient with DVT and negative D-dimer test.[38] D-dimer levels are commonly high in people with SARS-CoV-2 infections, and critically ill patients had significantly higher levels, which could be used as a marker for in-hospital mortality, the quantity of D-dimer in the body is technically evaluated with the use of a monoclonal antibody and different commercial kits that are available on the market.[39] However, underlying illnesses such as cancer, diabetes, pregnancy, and stroke, might result in levels of D-dimer to rise in patients who have COVID-19. Evaluating of D-dimer amount and coagulation parameters from onset of COVID-19 illness could be helpful in regulating and managing the condition.[40] The majority of studies linking the levels of D-dimer to COVID-19 results have had their findings falsified because of sample size restrictions or questionable methodology. The most frequent hemostatic issues with COVID-19 are mild thrombocytopenia and increased levels of D-dimer.[41,42] Guan and colleagues examined 1099 individuals from more than 550 hospitals in China who had Covid-19 that had been confirmed in the lab.[43] And found that non survivors had much higher D-dimer levels than survivors (median, 2.12g/mL vs. 0.61 g/mL. [28] discovered abnormal results of coagulation, including noticeably elevated D-dimer, in fatalities with Covid-19.[44]

A D-dimer level of no less than 1 g/mL at admission has been linked to in-hospital mortality, according to a retrospective analysis of 191 Covid-19 patients. The analysis also revealed that the levels of D-dimer at admission have been higher in the patients who needed critical care assistance than in the ones who didn't (median, 0.5 g/mL).[13] Those hemostatic changes suggest to a coagulopathy which might predispose to thrombotic events, while the cause is unknown. They also point to an increased risk of death that goes along with them.[45] D-dimer levels could rise in a range of conditions, such as cancer, sepsis, pregnancy, and surgical recovery. This decreases the specificity of the test.[46] A normal D-dimer was demonstrated to rule out VTE in the case when utilized in conjunction with a low pretest

likelihood for VTE because of its high level of sensitivity (80-100 %) and NPV of as high as 100%.[47] The International Society of Thrombosis and Haemostasis lately released guidance on the management and recognition of the coagulopathy in Covid-19, which "arbitrarily defined markedly raised D-dimers on admission as three-four folds increase," Yet, these prior studies did not provide a well-evaluated D-dimer threshold.[48] The presence of an increased D-dimer in a patient with Covid-19 indicated a hypercoagulable condition. This condition could be caused by a variety of causes, starting with the fact that viral infections are typically combined with a strong pro-inflammatory response and insufficient anti-inflammatory management.[49]

It might lead to endothelial cell dysfunction, which would lead to an excessive production of thrombin, Second, severe Covid-19 hypoxia could induce thrombosis by the increase of blood viscosity and triggering a signaling cascade that is dependent on hypoxia-inducible

transcription factors.[50,28] Third, patients who were hospitalized, especially those who were taking Covid-19, were more possible to be older, have underlying illnesses, be confined to bed for an extended period of time, and be receiving invasive therapy—all of which are risk factors for hypercoagulation or thrombosis.[51,52] The dissection of a serious patient with Covid-19's lung organ demonstrated pulmonary small artery obstruction and microthrombosis as evidence.[44] Fourth, certain people could develop sepsis-induced coagulopathy or even disseminated intra-vascular coagulation. [28,53] D-dimer levels that are elevated have historically been associated with unfavorable results. D-lack dimer's lack of selectivity was previously thought to be a drawback.[27] Indicating that D-dimer can be a helpful early marker for better Covid-19 patient management, D-dimer levels higher than 2.0μg/mL (a fourfold spike) on admission might accurately predict in-hospital mortality in patients who have Covid19, [44] as can be seen in table 1.

Table 1: Reports on COVID19 and D-dimer distribution by area.[40]

Country	Articles (N)
China	54
Italy	6
America	3
France	4
Spain	2
Ireland	1
U.k	1
Total	72

Ferritin

The diagnosis of anemia brought on by iron deficiency is made easier with the help of ferritin, an iron-storing protein whose serum level reflects the normal levels of iron. As a gauge of viral replication, the amount of ferritin in the blood rises throughout viral infections. Elevated levels of ferritin have been observed in severe COVID-19 patients as a result of the cytokine storm and sHLH.[54,55] cytokine storm in COVID-19 results in the fast production of several inflammatory cytokines, including TNF-, IL-6, IL-12, IL-1, and IFN-, stimulating the hepatocytes, Kupffer cells, and macrophages to secrete ferritin.[56,57] Inflammatory cytokines like IL-6, TNF-, IL-8, and IL-12 are released in large amounts during disease progression, possibly causing systemic organ failure and ARDS. This immune response is dysfunctional and uncontrolled and takes place in immuno-pathogenic mechanism of COVID-19, comparable to the one seen in severe influenza.[58] According to data, blood levels of IL-6, ferritin,

lactate dehydrogenase, and d-dimer increase as the illness worsens, indicating a higher risk of death.[54,59,6] In order to comprehend the disease's pathogenesis and determine how these markers contribute to the COVID-19 process, earlier research examined various laboratory markers.[60] According to recent studies, COVID-19 patients also have lower hemoglobin levels and higher ferritin levels. In research conducted in the US, ferritin levels were shown to be pathologically high in 5700 patients who were hospitalized for having COVID-19.[61] Anemia brought on by hyper-ferritinemia is a potent predictor of mortality, in spite of the underlying illnesses. Elevated ferritin levels in COVID-19 might indicate the start of inflammatory reaction may be related to viral spread in the body, which would impair the metabolism of iron. [62,63] In this regard, iron is a crucial micro-nutrient for human cells as well as the pathogens; as a result, pathogen's ability to use iron could be restricted by the immune system's natural response when an infection occurs. Yet, this

technique can also cause anemia, reducing the delivery of oxygen to the tissues and causing multiple organ failure. [63,64] which is why, we think it's crucial to look into how iron metabolism and COVID-19 progression are related. Our study aims to determine whether ferritin levels could predict COVID-19 severity.

Coronavirus and Ferritin

The levels of serum ferritin have been higher in people with severe and very severe COVID-19, with the latter having considerably high levels (1006.16ng/ml vs. 291.13ng/ml) compared to the former, another research discovered that patients who have COVID-19 had high ferritin levels upon admission to hospital and throughout their hospital stay, following day 16 of hospitalization, the median serum ferritin levels in such patients exceeded the upper limit of detection, suggesting that ferritin levels continuously increased. [6] Additionally, Chen etal. Had examined the clinical data of 99 individuals, 63 of whom had levels of serum ferritin that have been considerably above the normal range.[16] Additionally, elevated levels of ferritin have been discovered in autopsies of 12 patients who had died from SARS-CoV-2 infection.[7] Peripheral blood samples from 69 patients with severe COVID-19 disease showed higher levels of ferritin when compared to those of patients with less severe disease. COVID-19 severity has thus been found highly correlated with serum ferritin levels.[8] In addition, test data from patients with severe COVID-19 revealed high inflammatory markers, particularly ferritin, which was linked to serious and life-threatening disease.[9] The role of ferritin throughout inflammation brought on by Covid-19 infection is depicted in Figure 2. [62,65,66]
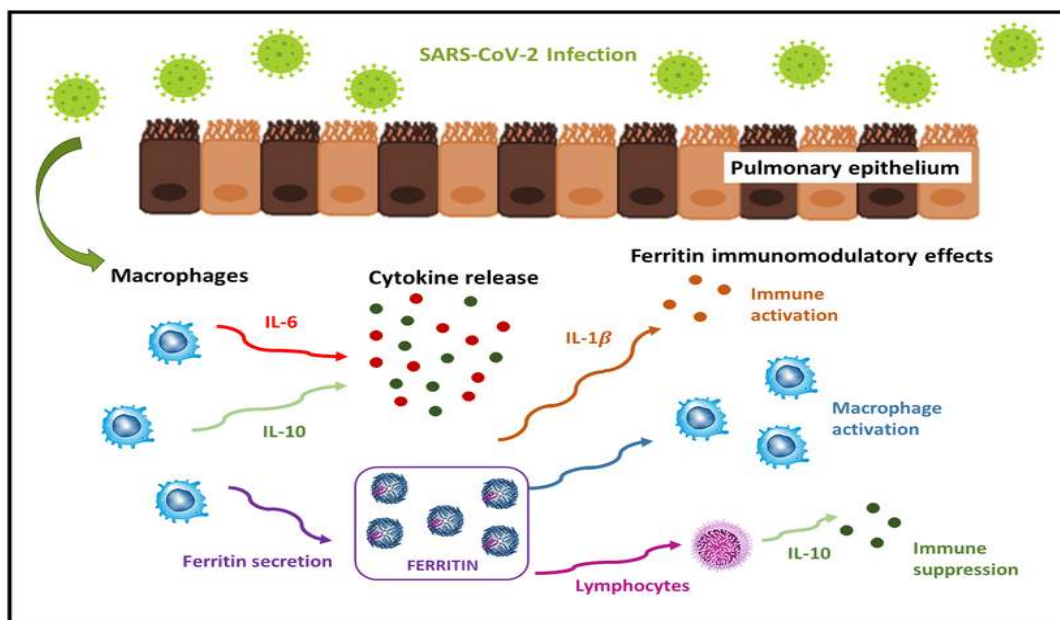

Fig. 2: Role of ferritin in inflammation brought on by Covid-19. Hyperferritinemia might result from active ferritin production by cytokines and macrophages. Numerous anti-inflammatory (IL-10) and pro-inflammatory (IL-1) cytokines could be produced as a result. Illustration based on.[62,65,66]

II. CONCLUSION

The current study concludes the elevated levels of D-Dimer and ferritin is the important biomarkers to estimate the severity of coronavirus ,patients with coronavirus suspected of having DVT. The conducting such tests helps in early diagnosis and treatment of the Corona virus, yet with the help of radiographic imaging. The infection in Covid-19 caused a considerable rise in ferritin and D-dimer levels and was linked to the severity and progression of the illness, demonstrating the necessity of using such tests for the early diagnosis to this virus and the diagnosis of certain serious cases.

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