Review Article

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TANAFFOS

D-dimer Levels in Predicting Severity of Infection and Outcome in Patients with COVID-19

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COVID-19 disease began to spread all around the world in December 2019 until now; and in the early stage it may be related to high D-dimer level that indicates coagulation pathways and thrombosis activation that can be affected by some underlying diseases including diabetes, stroke, cancer, and pregnancy and it also can be associated with Chronic obstructive pulmonary disease (COPD). The aim of this article was to analyze D-dimer levels in COVID-19 patients, as D-dimer level is one of the measures to detect the severity and outcomes of COVID-19. According to the results of this study, there is a higher level of D-dimer as well as concentrations of fibrinogen in the disease onset and it seems that the poor prognosis is linked to a 3 to 4-fold increase in D-dimer levels. It is also shown that 76% of the patients with ≥1 D-dimer measurement, had elevated D-dimer and were more likely to have critical illness than those with normal D-dimer. There was an increase in the rates of adverse outcomes with higher D-dimer of more than 2000 ng/mL and it is associated with the highest risk of death at 47%, thrombotic event at 37.8%, and critical illness at 66%. It also found that diabetes and COPD had the strongest association with death in COVID-19. So, it is necessary to measure the D-dimer levels and parameters of coagulation from the beginning as well as pay attention to comorbidities that can help control and management of COVID-19 disease.

Keywords: D-dimer; COVID-19; Diabetes; Cancer; Pregnancy; Stroke; Venous thromboembolism; Chronic obstructive pulmonary disease

INTRODUCTION

SARS-CoV-2 previously known as 2019-nCoV, is a newly identified β-coronavirus caused by COVID-19 virus (coronavirus disease-2019). Its clinical spectrum ranges from no or mild respiratory symptoms to severe acute respiratory disease (SARS) and Middle East respiratory syndrome (MERS). Typical COVID-19 symptoms include fever, cough, dyspnea, diarrhea, muscle aches, severe lymphopenia, prolonged coagulation profiles, heart disease, and sudden death (1).

D-dimer is one of the fibrin degradation products in blood coagulation and its levels are routinely measured in diagnosis of venous thrombosis. Any pathologic or non-pathologic process that enhances fibrin production or breakdown can also increase D-dimer plasma levels. Some of these processes include disseminated intravascular coagulation (DIC), arterial thrombosis, deep vein thrombosis (DVT), pulmonary embolism (PE), and cases such as pregnancy, inflammation, cancer, chronic liver disease, posttraumatic states, surgery, and vasculitis (2). D-dimer is the main degraded production of cross-linked fibrin by the plasmin that may degrade fibrin monomers during fibrinolysis and cross-linked fibrin polymers and likely fibrinogen during the systemic fibrinolysis after the

depletion of alpha2. All these particles are named fibrin degradation products (FDPs). It is known that D-dimer consists of two adjoining cross-linked fibrin 'D' domains (ends) that are released as an intact fragment and hence can called be D-dimer (3). First physicians in Wuhan, China reported that D-dimer can be increased in COVID-19 when the epidemic began. In a study on COVID-19 patients hospitalized in Wuhan during January 2020, an increase of D-dimer in many cases was observed and it was significantly greater in non-survivors (4).

Recent studies confirmed that most patients with COVID-19 had a mild infectious type of disease (5, 6). However, severe infection on admission time was associated with high mortality in some patients. Therefore, among subjects with COVID-19, it is important to discriminate accurately the high risk of severe infection and early guide to the proper use of different therapies. Elevated D-dimer as an abnormal coagulation function, has been reported to be more common in dead COVID-19 patients, with D-dimer levels greater than 1 μg/ml increasing the rate of in-hospital death (7, 8). However, the relation between D-dimer and COVID-19 severity is unclear. Therefore, this study intends to review the role of D-dimer levels in predicting the severity of infection and outcome of COVID-19 patients.

Value of D-dimer measurement

Although D-dimer is a production of cross-linked fibrin and is regarded as a sensitive biomarker for the evaluation of venous thromboembolism, it has low specificity. This is due to the fact that many other conditions associated with the continuous activity of the hemostatic system such as malignancy, pregnancy, trauma, heart disease, liver disease (reduced clearance), inflammation, sepsis resulting from hemodialysis, recent surgery or CPR increase D-dimer levels (9).

Different D-dimer units are reporting the two main kinds of D-dimer assays. First is the Fibrinogen Equivalent Unit (FEU) which reports the molecular weight of fibrinogen (340kDa) based on levels of D-dimer and the other D-Dimer Unit (DDU) reports it based on its molecular weight (195kDa), which is almost equal to half of the fibrinogen (10).

It should be noted that unit reporting is different based on the manufacturer, leading to 9 various presentations of results, such as mg/L, mg/mL, ng/dL, ng/L, ng/mL, mg/dL, μg/L, μg/mL and μg/dL. Low levels of D-dimer can be used to diagnose thrombotic vascular events such as DVT and PE. In other words, elevated D-dimer levels indicate the activity of the coagulation process, followed by fibrinolysis. The incidence of thrombotic events is one per one thousand adults and risk factors, such as infections and inflammatory diseases can contribute to it. before the coronavirus pandemic, increased D-dimer levels were reported in influenza as an infection that activates the coagulation system in the lung (11).

COVID-19 mortality is generally linked with hypercoagulability and higher venous thromboembolism (VTE) risk that in severe conditions leads to thrombo-inflammation (12). Thus, coagulation biomarkers may detect the severity and mortality rate, and be useful to determine patient triage, prognosis management, and therapeutic strategies.

Several studies have evaluated the correlation of higher D-dimer levels of up to 46.4% with severity as well as the adverse outcomes (13, 14); as a 20-fold increased mortality risk has been reported in patients with D-dimer of higher than 1000 ng/ml compared to the lower values (15). Therefore, in these patients, D-dimer should be considered as a potential VTE screening tool, and adjusting therapeutic anticoagulant doses based on D-dimer elevation compared to prophylactic doses is more beneficial for them (16). Thus, monitoring D-dimer levels in COVID-19 patients early after admission is necessary.

The most well-known use of the D-dimer test is in DVT and pulmonary embolism suspected patients. It is almost always increased in these patients, so a natural result is used commonly and widely to help in eliminating the diagnosis (7).

An increased level of D-dimer cannot be useful to diagnose DVT/PE due to its low specificity and association with many other conditions of thrombosis defined as abnormal increased blood coagulation and coagulopathy which can lead to higher D-dimer levels such as disseminated intravascular coagulation, aortic dissecting aneurysm, stroke, cancer, severe infection/sepsis, myocardial infarction, acute kidney injury and recently SARS-CoV-2 can be added to the list of such conditions (17).

A number of recent studies in the world have suggested that D-dimer is higher in people with severe COVID-19 and it reached the highest level in people with more severe illness and non-survivors. Many COVID-19 studies over the past months focused on understanding the importance of high D-dimer levels and the COVID-19-induced coagulopathy that is supposed to be responsible for it. Much of COVID-19 research has been conducted in recent months to understand the importance of D-dimer elevation and its associated coagulation, which is thought to be responsible for this increase (18). In a study on consecutive COVID-19 positive patients older than 18 years, the D-dimer test was routinely done at admission and during admission, and the upper level of normal D-dimer assay was considered 0.23 µg/ml (230 ng/ml). The evaluated outcomes such as critical illness (death, discharge to hospice, mechanical ventilation, and intensive care), death during admission, acute kidney injury, and thrombotic events. There was an increase in the rates of adverse outcomes with higher D-dimer and levels of more than 2000 ng/mL are associated with the highest risk of death (47%), thrombotic event (37.8%), critical illness (66%) and acute kidney injury (58.3%) in the patients (4).

The diversity of studies about D-dimer and COVID-19 can be due to the different kits that are used by different laboratories for measurement and their accuracy and reliability that may be varied regarding the kit manufacturer (19). In addition, there are various units of reporting and this lack of standardization causes possible errors in the analysis and interpretation of D-dimer values in case of COVID-19.

The role of D-dimer in COVID-19

In COVID-19 disease, increased D-dimer levels are accompanied by a parallel rise in CRP, and in contrast to DIC which is classically associated with bacterial infections, there is a slight increase in the partial thromboplastin time (PTT) and prothrombin time (PT) in addition to a mild thrombocytopenia (Platelets ≈100 × 10^10/L) (20).

Several studies conducted in Wuhan; China suggested that COVID-19 patients with elevated D-dimer levels are at an increased risk of mortality. Although anticoagulant therapy for COVID-19 was not common when conducting these studies, lower levels of D-dimer were observed in patients receiving anticoagulants (18, 21).

However, there is still no agreement on how D-dimer levels can be used for patients' management and monitoring. According to the available COVID-19 experiences, D-dimer cut-off of more than 1 µg/mL may put the patients at higher risk of poor outcomes. Until now there is no agreement on how many times D-dimer should be measured in hospitalized patients or the way of results application concerning anticoagulation. D-dimer levels are directly associated with disease severity, the area of lung involvement shown in the CT images, and the level of oxygen index. No clear mechanisms could be identified in systemic inflammatory responses characterized by COVID-19 infection. In COVID-19 disease, the misalignment of the coagulation/ anticoagulation cascade leads to worsening of the complications of the pulmonary pathology (21, 22).

In influenza, pathogenicity occurs by increasing viral replication and diverting cellular immunity, including cellular and protein components. The pathological results of COVID-19 are diffuse alveolar damage (DAD) with cellular fibrinous exudation, the destruction of the squamous cell of the lung and the formation of hyaline membranes, pulmonary edema with hyaline membranes, infiltration of the single-nucleus inflammatory cells with

the presence of lymphocytes, similar to what happens in SARS and MERS. Increased D-dimer levels indicate increased fibrinolysis, an increase in COVID-19 infections, and extended anticoagulant therapy with reduced mortality, especially in mechanically ventilated patients (18-20). The new International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) guidelines emphasize the assessment of D-dimer levels in patients with COVID.

Studies conducted on SARS-CoV-2 infection have shown a strong association between the disease severity and its outcome in COVID-19 patients so that DIC can occur in very severe cases. In a study, increased D-dimer levels are considered a predictor of the development and exacerbation of respiratory distress from COVID-19, which may be due to pulmonary microembolism, especially in patients with severe COVID-19 infection. Studies performed in Wuhan, China, demonstrated that a D-dimer value of more than 2 µg/ml at the time of admission was related to an elevated chance of mortality (19, 20).

Evaluation of changes in D-dimer levels during COVID-19 infection and bacterial pneumonia, and comparative studies between COVID-19 and bacterial pneumonia have shown that both diseases can increase D-dimer levels, but this increase is much higher in COVID-19 infection. In COVID patients, the activity of the coagulation system increases with blood viscosity because of excessive sweating and high fever. Risk factors such as prolonged hospitalization, obesity, and aging can also increase the risk of thrombosis; therefore, with higher levels of D-dimer need for anticoagulant therapy is increased. D-dimer levels decrease with lower inflammation and patient recovery, while the D-dimer value remains high in some of these patients. This justifies the continued anticoagulant therapy in these patients to prevent venous thrombosis (23).

The association of D-dimer levels and disease severity has been examined in several studies and it was reported as 0.58 µg/ml in mild and 3.55 µg/ml in severe disease states (21, 22, 24-35).

In a case–control study on COVID-19 patients the results showed an increase of D-dimer levels in these patients (36). Another study conducted to evaluate COVID-19 and influenza patients demonstrated that D-dimer levels in the first group were higher than the second (37). Moreover, Yin et al. examined the patients with severe COVID-19 and pneumonia caused by other pathogens and concluded that D-dimer levels in non-COVID-19 pneumonia patients were higher than in COVID-19 patients (38).

The results of the mentioned studies showed that in non-severe conditions the mean value of D-dimers was significantly lower, and it is suggested that an increase in this parameter can effectively provide a contrary clinical picture in the disease progression. Elevated D-dimer up to more than 1 µg/ml may reflect disease progression and be applied as an independent risk factor for death in the patients. The higher levels of D-dimer can help clinicians effectively forejudge between patients with severe and non-severe diseases.

Regarding the fact that in severe COVID-19 patients, thrombosis can happen in various organs and association with following organ failure, D-dimer measurement is necessary for evaluating the patients with COVID-19 and its monitoring should be considered clinically as a critical approach in this infection.

3.1. D-dimer levels in children with COVID-19

The annual incidence of venous thrombosis is about 1/1000 in adults and 0.07– 0.14/10,000 in children and it occurs in 5.3/10,000 hospitalized children. The rate of VTE in children younger than 13 years with COVID-19 is 1.3% (39). In a cohort study on pediatric patients with COVID-19, 2% mortality was reported but no incidence of VTE has been found yet (40). There are inadequate data on the prognostic factors in pediatrics and D-dimer as a probable biomarker of severity and mortality has not been tested regularly. Although some recommendations have been published for the use of anticoagulation in symptomatic hospitalized adult patients by several hematological

societies, because of a few data on pediatric patients, such guidelines cannot be established for them (41-44).

In Wuhan, D-dimer levels were tested in 79 infants with COVID-19 at the time of admission in a study and the COVID-19 children were divided into two groups of severe type and non-severe type. It was revealed that in the severe group, the D-dimer levels were higher as well as intravascular coagulation (43).

In an observational study on 36 students with COVID-19, D-dimer levels were increased in three children older than 5 years at the time of admission (43).

Regarding the studies, it has been demonstrated that higher D-dimer is associated with disease severity and longer hospitalization of children and prolonged PICU stay that suggest D-dimer serial measurements provide a prognostic value in the prediction of the need for critical care in COVID-19-infected children.

D-Dimer level and Diabetes

Diabetes is associated with a thrombosis-prone status. Obtained evidence shows that thrombosis activation may be due to hyperglycemia. Through these two different pathways, a pro-thrombotic status can be caused by hyperglycemia: non-enzymatic glycation and oxidative stress (45). Thrombin generation is increased by acute hyperglycemia, through oxidative stress (46), while the functionality of both heparin co-factor II and antithrombin III is reduced by non-enzymatic glycation (47). In conclusion, it shows that a pro-thrombotic status may be produced by hyperglycemia because of an imbalance between fibrinolysis, anti-coagulation, and pro-coagulation (45, 46, 48).

Mishra et al. have reported that in COVID-19 diabetic patients there is an increase of D-dimer compared to non-diabetic patients (49). Evidence showed that high blood glucose level correlated with poor prognosis in patients with COVID-19 disease.(47). Interestingly, increased levels of D-dimer have been found in people with hyperglycemia and COVID-19 (48). Additionally, it has been shown that hyperglycemia reduction is associated with a decreased level of D-dimer. It suggests that hyperglycemia might support thrombosis generation as a complication that is presented very often in COVID-19 (50).

In some studies, the mean D-dimer levels in two groups (without and with diabetic groups) were 0.8, and 1.68 (µg/ml), respectively (46, 51).

In another study performed on diabetic patients with COVID-19 (with no history of other underlying diseases), the levels of serum ferritin, D-dimer, and CRP could be significantly increased. This finding indicates that diabetic patients are more likely to be infected seriously (52). In addition, Yan et al reported that D-dimer levels in diabetic people were higher than in non-diabetics (53). Also, a study by Wang et al. on the COVID-19 patients with underlying diabetes showed that the difference was significant between the ICU and the non-ICU patients regarding the levels of D-dimer (54).

In conclusion, due to the impacts of thrombosis on the prognosis of COVID-19 patients, it is highly relevant to understand what increases the risk of thrombotic events. So, to achieve a better management of COVID-19 it can be useful to do specific studies to clarify the possible link of hyperglycemia and thrombosis.

Cancer

The data demonstrate that increase in D-dimer levels are related to systemic inflammation and endothelial cell dysfunction due to malignancy; therefor D-dimer levels higher than 1µg/ml FEU is seen in malignant patients with COVID-19 disease. It was interestingly similar in cancer patients with or without COVID-19 and low D-dimers. This evidence showed that during COVID-19 complement activation may be improved by coagulation and fibrinolysis activities, and pathways' cross-reaction of complement and coagulation (55). The results of a systematic review and meta-analysis to evaluate the cancer prevalence among the patients with COVID-19 and complications showed a higher risk of severe COVID-19 and mortality in the cancer patients as well as ICU admission and mechanical ventilation. A pilot analysis was

performed to find the differences between the patients with or without cancer regarding the coagulopathy and inflammatory (CRP) markers, which are increasingly considered as mechanisms of organ injuries in COVID-19 patients. It was reported that prothrombin time, CRP, and D-dimer were significantly higher in these patients, and in a single-arm analysis, it was shown that there were high serum IL-6 levels in cancer patients compared to reference values (55).

Yang et al. performed a study on cancer patients with COVID-19. They reported 19.2% lung cancer, 17.3% breast cancer, 15.4% rectal cancer, and 9.6% colon cancer, and the remaining 38.5% reported other types of cancer. The survey showed that 33 patients had mild cases of COVID-19 and 19 patients had severe conditions and the results demonstrated that the D-dimer level was 1.0 (0.6–2.3) and 2.8 (1.7–6.6) (μg/ml) in mild and critical patients at the time of admission, respectively (56).

Since endothelial cell damage and thrombosis are also symptoms of cancer thrombosis, it is not surprising that increased complement activation has been observed in cancer patients without COVID-19 but with high levels of D-dimers. Additionally, it would be increased significantly in COVID-19 and thromboinflammation combination. These findings are in accordance with the report of Bernard et al., on respiratory failure in non-cancer patients (57), which show complement activation is a general indicator of critical illness, but increases respiratory failure associated with COVID-19.

The cancer patients are at a higher risk for complications of COVID-19 due to significantly lower levels of platelet and higher prothrombin time, D-dimer and C-reactive protein, and also they of need particular preventive care approaches and aggressive supervision for early detection of the disease.

Pregnancy

Pregnant women are needed to be managed more carefully in such a pandemic, due to their physiological changes, susceptibility to infections, immunological and mechanical differences.

In a study comparing pregnant and non-pregnant COVID-19 infected women laboratory test results found significant higher levels of inflammatory markers including D-dimer, procalcitonin, C-reactive protein, neutrophil and white blood cell count. The mean of lymphocyte percentage in pregnant women was significantly lower (58).

One study was conducted on the D-dimer levels in pregnant COVID-19 women. A study was performed in Wuhan, by Qiancheng et al., on the same age pregnant and non-pregnant women with COVID-19. The findings revealed that the D-dimer level was significantly elevated in pregnant women in comparison with the non-pregnant women on admission (59).

However, for the first time in the study of Uzel et al it showed that in PCR (+) pregnant women there were a lower D-dimer levels and fever compared to whom with PCR (-) and it may be due to the inclusion of suspected COVID-19 patients. In fact, fever is a symptom that raises the suspicion of COVID-19 infection. However, it is not clear why D-dimer was lower in pregnant women with PCR (+). It can be related to an undetectable infection with similar symptoms to COVID-19 among the pregnant women with negative PCR. The situation can be explained more with further studies in a similar population (60).

Concerningly, in recent reports elevated D-dimer levels were considered as an indicator of poor prognosis in non-pregnant women. Huang et al. pointed to the higher levels of D-dimers in patients requiring ICU admission with median D-dimer of 2.4 mg/L in comparison with those who did not (0.5 mg/L) (3). Tang et al. compared the D-dimer level in non-survivors vs. survivors and reported the higher D-dimers in non-survivors as 2.12 ug/mL (range 0.8-5.3 ug/mL) vs. 0.6 ug/mL (0.4-1.3 ug/mL) in survivors (7). Given the typical increase of D-dimer during gestation (5), it is not obvious what threshold of D-dimer would indicate unfavorable prognosis in pregnancy. It is suggested that those with significant raise of D-dimer

levels (more than 3-4 fold of normal range) should be hospitalized even without any other important symptoms. (61).

Finally, it should be noted that in pregnant patients there is a hypercoagulable state coinciding with increased levels of D-dimer that make it important to not use D-dimer to assign the severity of COVID-19 infection among them (62).

Stroke

Research into the mechanisms by which SARS-CoV-2 causes ischemic stroke has become an interesting research topic. SARS-CoV-2 has been shown to lead to systemic hypercoagulation which leads to increased levels of fibrinogen and D-dimer, as the trigger of ischemic stroke (63). As a result, some researchers have hypothesized that COVID-19 causes ischemic stroke by causing excessive coagulation in patients, but the mechanisms by which COVID-19 increases coagulation are unclear and it is important for the targeted treatment of COVID-19-induced ischemic stroke (64).

In the early stages of COVID-19 some of Acute ischemic stroke (AIS) cases have been reported by Fara et al. (65). Mao et al. concluded that 18.7% of patients with COVID-19 are in need of ICU admission due to treatment of severe neurological symptoms, and AIS has been reported in 5.7% of them with severe COVID-19 (64). Beyrouti et al. found that AIS might happen 8-24 days after the early symptoms of COVID-19 and the laboratory tests revealed the significant increase of C-reactive protein, D-dimer levels, lactate dehydrogenase and fibrinogen (66). Li et al. reported the presence of SARS-CoV-2 in patients' cerebrospinal fluid, indicating that the virus could penetrate the barrier of blood-brain and damage tissue (67).

A study was conducted on 3,556 hospitalized COVID-19 patients; 32 received a diagnosis of ischemic stroke after performing a radiological test, as compared with 46 non-COVID patients with ischemic stroke. In COVID-19 patients the mean of D-dimer level was 3,913 µg/ml at the closest time to diagnosis of stroke, whereas 0.526 µg/ml was reported in group without COVID-19 infection. Furthermore, during treatment, the D-dimer level in the COVID-19 patients was elevated by more than 10 µg/ml. However, no increase in the D-dimer level was observed during treatment of the patients without COVID-19 (68).

The AIS pathogenesis includes artery-to-artery embolization, hypoperfusion, thrombosis and also COVID-19. Patients with secondary AIS and COVID-19 at admission were shown to have an increased National Institutes of Stroke Scale score, high D-dimer levels, and a poor prognosis compared to non-COVID-19 stroke patients, indicating blood coagulation plays a key role in COVID-19 secondary AIS(68). The secondary AIS cases in young COVID-19 patients of increased D-dimer and fibrinogen were studied and some of them had no stroke risk factors, indicating that COVID-19 causes AIS through the increase of blood clotting (69). However, the exact mechanisms by which COVID-19 causes excessive coagulation in patients still remain unclear.

Venous thromboembolism (VTE)

DVT and PE are considered as the keys to manifesting VTE, and they may be fatal (70-72). Some studies show an elevated risk of DVT and PE in patients with COVID-19 (8, 21, 73, 74).

Zhang et al. conducted a retrospective study on 143 COVID-19 patients in Wuhan, China. The patients were divided into DVT and non-DVT groups. The results showed that in the elderly, the prevalence of DVT was higher than the younger patients. Furthermore, the D-dimer levels in COVID-19 and DVT patients were significantly higher than those without DVT during hospitalization (75). It is important to know DVT was related to poor prognosis and elevated mortality. Additionally, 88.5% of DVT patients and 47.1% of non-DVT cases showed D-dimer levels higher than 1 (µg/ml) (76). Another study performed on the hospitalized patients found that the D-dimer levels were elevated in COVID-19 patients with DVT as compared with non-DVT cases.

Furthermore, Demelo-Rodríguez et al. found that D-dimer with 1.57 µg/ ml cutoff point and showed a sensitivity and specificity of 95.7% and 29.3% respectively. Such criteria can be used to diagnose the asymptomatic DVT (73). Evaluation of the prevalence of VTE in the patients admitted to the ICU due to the COVID-19 was done by Cui et al. According to the results of a study D-dimer with cutoff point of 1.5 (µg/mL) showed a sensitivity of 85% and a specificity of 88.5% for prediction of VTE. In this study, D-dimer levels in patients with PE were higher than those in people without PE and were more potential to have an aggressive type. COVID-19 patients were treated in severe cases of low-weight molecular heparin (LMWH) or unfractionated Heparin (UFH) (77).

In a study on diagnostic value of D-dimer, the three levels of D-dimer have been identified that classified the patients into three groups of low-probability (<1000 ng/mL), intermediate-probability (1000–7500 ng/mL), and high-probability (>7500 ng/mL). With a 16% of VTE prevalence, the post-test possibilities of VTE at each level were 3%, 18%, and 43%, respectively. In critically ill COVID-19 patients D-dimer levels were evaluated using intermediate-dose thromboprophylaxis and showed that D-dimers level less than 2000 ng/mL had a 100% negative predictive value for VTE and more than 8000 ng/mL had a significantly elevated likelihood ratio, suggesting that cut-off points of 2000 ng/mL and 8000 ng/mL seems to be useful to identify patients with low and high chance of developing VTE (9). The same cut-off points have been identified that may be useful for detection of the patients with different possibilities of developing VTE. Regarding the lowest D-dimer level of less than 1000 ng/mL, we are still identifying some VTE patients. The clinicians should be cautious about the only use of low D-dimer to VTE in these patients. (78, 79).

In a retrospective cohort study on consecutive non-ICU hospitalized patients with COVID-19 and adequate thromboprophylaxis, undergone systematic low limb venous duplex ultrasonography, the results showed that D-dimers were significantly higher at the baseline in DVT patients. For asymptomatic DVT, the negative predictive value of 1000 ng/ml baseline D-dimer level was screened using complete compression doppler ultrasound (73, 80). So, in COVID-19 patients, higher cut-off levels of D-dimer may be necessary for DVT diagnose. In fact, autopsy studies have reported the occurrence of diffuse microthrombosis that is not detectable by routine ultrasound or radiological methods, but instead is expressed by multiorgan dysfunction (81). Therefore, not only the high values of D-dimer in patients with COVID19 disease, does not necessarily indicate the DVT diagnosis, but also a significant increase in D-dimer values of COVID-19 patients' needs further investigation in order to prevent the possible DVT.

Chronic obstructive pulmonary disease (COPD)

Regarding COVID-19 which can infect older individuals with comorbidities more easily, it is also expected to be more common in these patients. However, data on COPD prevalence among them is highly restricted and inconsistent and it has been stated to be 2–3% at the onset of pandemic, in China (82, 83), but later publications reported a higher rate between 8–16% (83, 84).

During this pandemic, most studies demonstrated the relation between COPD with worse outcomes. In a meta-analysis, it has been reported that in COPD patients compared to the general population it is more possible to have severe disease and higher risk of mortality (85).

There may be several reasons why COVID-19 course is worse in COPD patients. First, COPD patients are usually older and have more co-morbidities that may increase the severity of COVID-19 (86, 87). It should be noted that respiratory failure and hypoxemia are more common in COPD patients as well as the most significant cause of death in this group of patients (88). However, there is a few data on prognosis of COVID-19 patients with COPD.

Although data confirmed that approximately 5% of SARS-CoV-2 patients were diagnosed with COPD, but there are some symptomatic, radiological, laboratory and demographic differences between COPD and non-COPD

COVID-19 infected patients. The studies showed no statistical difference in total survival rates between COVID-19 patients with or without COPD, although there were some poor prognostic features in COPD patients with COVID-19. Hypoxemia and presence of pneumonia were reported as the significant predictors of mortality as well as the high age among them (89).

High blood level of D-dimer and low lymphocyte count were the laboratory parameters that are significantly associated with COVID-19 mortality and lymphopenia at the admission time which has been related to poor outcomes in these patients. In a cohort study a higher rate of COVID-19 positivity was found in the COPD patients with an absolute lower lymphocyte count (90). In the Turkish National Guideline for COVID-19, D-dimer cut-off of more than 1000 µg/L has been considered as a poor prognostic criteria (90). D-dimer levels may be increased in both situations of COPD and COVID-19 due to association of these chronic diseases with inflammatory processes which is illustrated by a hypercoagulable state.

In some studies, the significant association of COPD with the higher risk of adverse effects in the COVID-19 patients has been reported (91). Zhao et al. reported a 4.4-fold elevated risk of severe COVID-19 and also poor outcomes in the patients with COPD (85). Because patients with COPD have poor prognosis due to pathological changes such as emphysema and chronic airway inflammation, low lung function, abnormal lung structures, and immune system, infection with SARS-CoV2 may lead to a poor prognosis (92).

A higher mortality rate has been reported in COPD patients with COVID-19 (13.2% vs. 7%); therefore COPD is a mortality risk factor in the severe cases of COVID-19(93). It has been approved that old age is a risk factor for COVID-19 death (94). Graziani et al. revealed that COPD and COVID-19 patients with mean age of 75 years have significantly higher risk of death than non-COPD patients with the mean age of 66 (95). So, it is suggested to hospitalize and monitor the COVID-19 patients older than 50 years, considering the high risk of severe disease and outcomes such as mortality. So, in order to prevent the COVID-19 poor prognosis in the elders there is need of careful observation and early intervention (96).

Finally, it can be said that COPD not only is one of the most common COVID-19 patients' comorbidities; but it can also worsen the prognosis in these patients. Although there are some poor prognostic features in COPD patients with COVID-19, but overall no significant difference was seen in survival rates of COVID-19 patients with or without COPD. The high serum D-dimer level, hypoxemia, old age, presence of pneumonia and low lymphocyte count are among the important predictors of mortality in hospitalized COVID-19 patients.

Outcomes

According to earlier studies, there is a significant connection between the increased rates of D-dimer and mortality (4, 7, 10-15).

Some papers investigated the association od D-dimer levels and survival rate. The relative results reported that patients with D-dimer levels of 0.79 (µg/ml) survived and patients with D-dimer levels of 3.78 (µg/ml) died (4, 7, 9-15). As it shown in Table 2, the mean D-dimer level in patients with mild and severe disease was registered as 0.58 (µg/ml) and 3.55 (µg/ml), respectively. There is a strong association between the incidence of the disease and mortality with underlying disease (96). Comorbidities such as diabetes mellitus, malignancy, coronary artery disease, bronchial asthma, hypertension, and COPD were seen in most of the patients (79.5%). Diabetes mellitus has been reported as the most frequent comorbidity (65.1%); the total of 89.0% death happened in the patients with underlying disease, among them 70% patients were diabetics. In median D-dimer levels a significant difference has been observed between diabetic and nondiabetic patients (97). In the first group the median D-dimer level was reported to be 1.68 µg/ml. Recently, it has reported that there is a relation between diabetes and elevated levels of D-dimer in moderately ill COVID 19 patients (49). Mukona and Zvinavashe have focused that diabetic people

are at a higher risk of COVID-19 infection and would be infected more severely (98).

Besides the association of D-dimer levels and adverse clinical outcomes (Table 1), the studies have also tried to evaluate the relationship between D-dimer level of admission time and the final outcome in COVID-19 patients including death or survival which is shown in table 2.

Table 1. Prediction of the outcome regarding the D-dimer level (46, 97)

Stage of Disease	D-dimer level (µg/ml)
Hospital admission with COVID	≥1.44
Prediction of mortality during hospital stay	≥2.01
Admission time mortality	≥1.5
Survivor	0.94
Non survivors	6.34

Table 2. D-dimer level in different underlying diseases (44, 46, 56, 68, 73)

Patient group	Cut off value of D-dimer (µg/ml) in the two stage of disease	
	Severe	Non severe
Children	1.19	0.88
Cancer	2.08	1.0
Stroke	10	3.91
VTE	1.57	1.1
Diabetes	2.01	1.68

Abnormalities in D-dimer levels in COVID-19 patients indicated the higher risk of critical illness and death. In a meta-analysis an increased D-dimer level in severe versus non-severe infected patients was noted. A group of 4 studies reported the D-dimer level in the critically ill and dead patients as ≥500 versus <500 ng/mL with a 2-fold higher risk of critical illness and 4-fold of death. In one study, Zhou et al. found the association of an 18-fold higher risk of mortality with the baseline D-dimer of more than 1000 ng/mL (8). However, there is still much uncertainty around this association due to the small sample size and wide CIs in the provided studies (99, 100).

CONCLUSION

In patients with COVID-19, coagulopathy is an important complication that is closely related to the clinical outcome and D-dimer level is one of the measures which is used to detect thrombosis. Some studies have reported that in the early stages of COVID-19, a 3 to 4-fold rise in D-dimer levels and fibrinogen concentrations can be linked to poor prognosis. It should be noted that underlying diseases such as stroke, cancer, diabetes, and pregnancy may cause an elevation of D-dimer levels in patients with COVID-19. According to the results of this study, D-dimer is a reliable and convenient coagulation parameter to predict mortality. It is also reported that a D-dimer value ≥ 2.01 µg/ml can be effectively contributing to predicting in-hospital mortality, but it is necessary to pay attention that on admission the value of D-dimer is not an effective predictor. Finally, it is concluded that early measurement of the coagulation parameters and D-dimer at the disease onset can be effective in controlling and management of COVID-19.

REFERENCES

1. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. ***Nature*** 2020;579(7798):270-3.
2. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. ***Lancet*** 2020;395(10223):507-13.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. ***Lancet*** 2020;395(10223):497-506.
4. Berger JS, Kunichoff D, Adhikari S, Ahuja T, Amoroso N, Aphinyanaphongs Y, et al. Prevalence and Outcomes of D-Dimer Elevation in Hospitalized Patients With COVID-19. ***Arterioscler Thromb Vasc Biol*** 2020;40(10):2539-47.
5. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. ***N Engl J Med*** 2020;382(18):1708-20.
6. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. ***Clin Infect Dis*** 2020;71(15):762-8.
7. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients

with novel coronavirus pneumonia. ***J Thromb Haemost*** 2020;18(4):844-47.

8. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. ***Lancet*** 2020;395(10229):1054-62.
9. Zhan H, Chen H, Liu C, Cheng L, Yan S, Li H, et al. Diagnostic Value of D-Dimer in COVID-19: A Meta-Analysis and Meta-Regression. ***Clin Appl Thromb Hemost*** 2021;27:10760296211010976.
10. Fruchter O, Yigla M, Kramer MR. D-dimer as a prognostic biomarker for mortality in chronic obstructive pulmonary disease exacerbation. ***Am J Med Sci*** 2015;349(1):29-35.
11. Snijders D, Schoorl M, Schoorl M, Bartels PC, van der Werf TS, Boersma WG. D-dimer levels in assessing severity and clinical outcome in patients with community-acquired pneumonia. A secondary analysis of a randomised clinical trial. ***Eur J Intern Med*** 2012;23(5):436-41.
12. Guo L, Wei D, Zhang X, Wu Y, Li Q, Zhou M, et al. Clinical Features Predicting Mortality Risk in Patients With Viral Pneumonia: The MuLBSTA Score. ***Front Microbiol*** 2019;10:2752.
13. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. ***J Am Coll Cardiol*** 2020;75(23):2950-2973.
14. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, Tobin KA, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. ***BMJ*** 2020;369:m1966.
15. Ghosheh GO, Alamad B, Yang KW, Syed F, Hayat N, Iqbal I, et al. Clinical prediction system of complications among patients with COVID-19: A development and validation retrospective multicentre study during first wave of the pandemic. ***Intell Based Med*** 2022;6:100065.
16. Fan BE, Chong VCL, Chan SSW, Lim GH, Lim KGE, Tan GB, et al. Hematologic parameters in patients with COVID-19 infection. ***Am J Hematol*** 2020;95(6):E131-E134.
17. Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association? ***Eur Heart J*** 2020;41(19):1858.
18. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. ***JAMA*** 2020;323(11):1061-9.
19. Zou Y, Guo H, Zhang Y, Zhang Z, Liu Y, Wang J, et al. Analysis of coagulation parameters in patients with COVID-19 in Shanghai, China. ***Biosci Trends*** 2020;14(4):285-9.
20. Lv Z, Cheng S, Le J, Huang J, Feng L, Zhang B, et al. Clinical characteristics and co-infections of 354 hospitalized patients with COVID-19 in Wuhan, China: a retrospective cohort study. ***Microbes Infect*** 2020;22(4-5):195-99.
21. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. ***Allergy*** 2020;75(7):1730-41.
22. He R, Lu Z, Zhang L, Fan T, Xiong R, Shen X, et al. The clinical course and its correlated immune status in COVID-19 pneumonia. ***J Clin Virol*** 2020;127:104361.
23. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. ***J Clin Invest*** 2020;130(5):2620-9.
24. Zhang G, Hu C, Luo L, Fang F, Chen Y, Li J, et al. Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. ***J Clin Virol*** 2020;127:104364.
25. Wan S, Xiang Y, Fang W, Zheng Y, Li B, Hu Y, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. ***J Med Virol*** 2020;92(7):797-806.
26. Fu J, Kong J, Wang W, Wu M, Yao L, Wang Z, et al. The clinical implication of dynamic neutrophil to lymphocyte ratio and D-dimer in COVID-19: A retrospective study in Suzhou China. ***Thromb Res*** 2020;192:3-8.
27. Liu Y, Liao W, Wan L, Xiang T, Zhang W. Correlation Between Relative Nasopharyngeal Virus RNA Load and Lymphocyte Count Disease Severity in Patients with COVID-19. ***Viral Immunol*** 2021;34(5):330-335.
28. Gao Y, Li T, Han M, Li X, Wu D, Xu Y, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. ***J Med Virol*** 2020;92(7):791-796.

29. Liu J, Li S, Liu J, Liang B, Wang X, Wang H, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. ***EBioMedicine*** 2020;55:102763.
30. Zhou Y, Zhang Z, Tian J, Xiong S. Risk factors associated with disease progression in a cohort of patients infected with the 2019 novel coronavirus. ***Ann Palliat Med*** 2020;9(2):428-436.
31. Zheng C, Wang J, Guo H, Lu Z, Ma Y, Zhu Y, et al. Risk-adapted Treatment Strategy For COVID-19 Patients. ***Int J Infect Dis*** 2020;94:74-77.
32. Sun Y, Dong Y, Wang L, Xie H, Li B, Chang C, et al. Characteristics and prognostic factors of disease severity in patients with COVID-19: The Beijing experience. ***J Autoimmun*** 2020;112:102473.
33. Wang F, Hou H, Luo Y, Tang G, Wu S, Huang M, et al. The laboratory tests and host immunity of COVID-19 patients with different severity of illness. ***JCI Insight*** 2020;5(10):e137799.
34. Liu X, Li Z, Liu S, Sun J, Chen Z, Jiang M, et al. Potential therapeutic effects of dipyridamole in the severely ill patients with COVID-19. ***Acta Pharm Sin B*** 2020;10(7):1205-1215.
35. Han H, Yang L, Liu R, Liu F, Wu KL, Li J, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. ***Clin Chem Lab Med*** 2020;58(7):1116-1120.
36. Spiezia L, Boscolo A, Poletto F, Cerruti L, Tiberio I, Campello E, et al. COVID-19-Related Severe Hypercoagulability in Patients Admitted to Intensive Care Unit for Acute Respiratory Failure. ***Thromb Haemost*** 2020;120(6):998-1000.
37. Luo Y, Yuan X, Xue Y, Mao L, Lin Q, Tang G, et al. Using a diagnostic model based on routine laboratory tests to distinguish patients infected with SARS-CoV-2 from those infected with influenza virus. ***Int J Infect Dis*** 2020;95:436-40.
38. Yin S, Huang M, Li D, Tang N. Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. ***J Thromb Thrombolysis*** 2021;51(4):1107-10.
39. Cushman M. Epidemiology and risk factors for venous thrombosis. ***Semin Hematol*** 2007;44(2):62-9.
40. Celkan T, Dikme G. Thrombosis in children: Which test to whom, when and how much necessary? ***Turk Pediatri Ars*** 2018;53(1):1-9.
41. Goldenberg NA, Sochet A, Albisetti M, Biss T, Bonduel M, Jaffray J, et al. Consensus-based clinical recommendations and research priorities for anticoagulant thromboprophylaxis in children hospitalized for COVID-19-related illness. ***J Thromb Haemost*** 2020;18(11):3099-105.
42. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. ***N Engl J Med*** 2020;383(4):334-46.
43. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. ***Lancet Infect Dis*** 2020;20(6):689-96.
44. Saleh NY, Aboelghar HM, Salem SS, Ibrahem RA, Khalil FO, Abdelgawad AS, et al. The severity and atypical presentations of COVID-19 infection in pediatrics. ***BMC Pediatr*** 2021;21(1):144.
45. Thakur P, Kumar A, Kumar A. Targeting oxidative stress through antioxidants in diabetes mellitus. ***J Drug Target*** 2018;26(9):766-76.
46. Soni M, Gopalakrishnan R, Vaishya R, Prabu P. D-dimer level is a useful predictor for mortality in patients with COVID-19: Analysis of 483 cases. ***Diabetes Metab Syndr*** 2020;14(6):2245-9.
47. Ceriello A. Diabetes, D-dimer and COVID-19: The possible role of glucose control. ***Diabetes Metab Syndr*** 2020;14(6):1987.
48. Sardu C, D'Onofrio N, Balestrieri ML, Barbieri M, Rizzo MR, Messina V, et al. Outcomes in Patients With Hyperglycemia Affected by COVID-19: Can We Do More on Glycemic Control? ***Diabetes Care*** 2020;43(7):1408-15.
49. Mishra Y, Pathak BK, Mohakuda SS, Tilak TVSVGK, Sen S, P H, et al. Relation of D-dimer levels of COVID-19 patients with diabetes mellitus. ***Diabetes Metab Syndr*** 2020;14(6):1927-1930.
50. Zhu L, She ZG, Cheng X, Qin JJ, Zhang XJ, Cai J, et al. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. ***Cell Metab*** 2020;31(6):1068-77.e3.
51. Zhang Y, Li H, Zhang J, Cao Y, Zhao X, Yu N, et al. The clinical characteristics and outcomes of patients with diabetes and secondary hyperglycaemia with coronavirus disease 2019:

A single-centre, retrospective, observational study in Wuhan. ***Diabetes Obes Metab*** 2020;22(8):1443-54.

52. Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. ***Diabetes Metab Res Rev*** 2020;36(7):e3319.
53. Yan Y, Yang Y, Wang F, Ren H, Zhang S, Shi X, et al. Clinical characteristics and outcomes of patients with severe covid-19 with diabetes. ***BMJ Open Diabetes Res Care*** 2020;8(1):e001343.
54. Wang F, Yang Y, Dong K, Yan Y, Zhang S, Ren H, et al. Clinical characteristics of 28 patients with diabetes and covid-19 in wuhan, china. ***Endocr Pract*** 2020;26(6):668-74.
55. ElGohary GM, Hashmi S, Styczynski J, Kharfan-Dabaja MA, Alblooshi RM, de la Cámara R, et al. The Risk and Prognosis of COVID-19 Infection in Cancer Patients: A Systematic Review and Meta-Analysis. ***Hematol Oncol Stem Cell Ther*** 2022;15(2):45-53.
56. Yang F, Shi S, Zhu J, Shi J, Dai K, Chen X. Clinical characteristics and outcomes of cancer patients with COVID-19. ***J Med Virol*** 2020;92(10):2067-3.
57. Bernard A, Cottenet J, Bonniaud P, Piroth L, Arveux P, Tubert-Bitter P, et al. Comparison of Cancer Patients to Non-Cancer Patients among COVID-19 Inpatients at a National Level. ***Cancers (Basel)*** 2021;13(6):1436.
58. Wang Z, Wang Z, Xiong G. Clinical characteristics and laboratory results of pregnant women with COVID-19 in Wuhan, China. ***Int J Gynaecol Obstet*** 2020;150(3):312-7.
59. Qiancheng X, Jian S, Lingling P, Lei H, Xiaogan J, Weihua L, et al. Coronavirus disease 2019 in pregnancy. ***Int J Infect Dis*** 2020;95:376-83.
60. Uzel K, Lakhno I. PCR positivity and D-dimer levels in pregnant women with COVID-19. ***Clinical and Experimental Obstetrics & Gynecology*** 2020;47(5):638-44.
61. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. ***J Thromb Haemost*** 2020;18(5):1023-6.
62. Kadir RA, Kobayashi T, Iba T, Erez O, Thachil J, Kazi S, et al. COVID-19 coagulopathy in pregnancy: Critical review, preliminary recommendations, and ISTH registry-Communication from the ISTH SSC for Women's Health. ***J Thromb Haemost*** 2020;18(11):3086-98.
63. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. ***J Thromb Haemost*** 2020;18(6):1324-9.
64. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. ***JAMA Neurol*** 2020;77(6):683-90.
65. Fara MG, Stein LK, Skliut M, Morgello S, Fifi JT, Dhamoon MS. Macrothrombosis and stroke in patients with mild Covid-19 infection. ***J Thromb Haemost*** 2020;18(8):2031-3.
66. Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY, et al. Characteristics of ischaemic stroke associated with COVID-19. ***J Neurol Neurosurg Psychiatry*** 2020;91(8):889-91.
67. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. ***J Med Virol*** 2020;92(6):552-5.
68. Yaghi S, Ishida K, Torres J, Mac Grory B, Raz E, Humbert K, et al. SARS-CoV-2 and Stroke in a New York Healthcare System. ***Stroke*** 2020;51(7):2002-11.
69. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. ***N Engl J Med*** 2020;382(20):e60.
70. Moser KM, Fedullo PF, LitteJohn JK, Crawford R. Frequent asymptomatic pulmonary embolism in patients with deep venous thrombosis. ***JAMA*** 1994;271(3):223-5.
71. Kearon C. Natural history of venous thromboembolism. ***Circulation***. 2003;107(23 Suppl 1):I22-30.
72. Dalen JE. Pulmonary embolism: what have we learned since Virchow? Natural history, pathophysiology, and diagnosis. ***Chest*** 2002;122(4):1440-56.
73. Demelo-Rodríguez P, Cervilla-Muñoz E, Ordieres-Ortega L, Parra-Virto A, Toledano-Macías M, Toledo-Samaniego N, et al. Incidence of asymptomatic deep vein thrombosis in patients with COVID-19 pneumonia and elevated D-dimer levels. ***Thromb Res*** 2020;192:23-6.
74. Léonard-Lorant I, Delabranche X, Séverac F, Helms J, Pauzet C, Collange O, et al. Acute Pulmonary Embolism in Patients

with COVID-19 at CT Angiography and Relationship to d-Dimer Levels. ***Radiology*** 2020;296(3):E189-E191.

75. Zhang L, Feng X, Zhang D, Jiang C, Mei H, Wang J, et al. Deep Vein Thrombosis in Hospitalized Patients With COVID-19 in Wuhan, China: Prevalence, Risk Factors, and Outcome. ***Circulation*** 2020;142(2):114-28.
76. Rostami M, Mansouritorghabeh H. D-dimer level in COVID-19 infection: a systematic review. ***Expert Rev Hematol*** 2020;13(11):1265-75.
77. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. ***J Thromb Haemost*** 2020;18(6):1421-4.
78. Choi JJ, Wehmeyer GT, Li HA, Alshak MN, Nahid M, Rajan M, et al. D-dimer cut-off points and risk of venous thromboembolism in adult hospitalized patients with COVID-19. ***Thromb Res*** 2020;196:318-21.
79. Conte G, Cei M, Evangelista I, Colombo A, Vitale J, Mazzone A, et al. The Meaning of D-Dimer value in Covid-19. ***Clin Appl Thromb Hemost*** 2021;27:10760296211017668.
80. Artifoni M, Danic G, Gautier G, Gicquel P, Boutoille D, Raffi F, et al. Systematic assessment of venous thromboembolism in COVID-19 patients receiving thromboprophylaxis: incidence and role of D-dimer as predictive factors. ***J Thromb Thrombolysis*** 2020;50(1):211-6.
81. Nicolai L, Leunig A, Brambs S, Kaiser R, Weinberger T, Weigand M, et al. Immunothrombotic Dysregulation in COVID-19 Pneumonia Is Associated With Respiratory Failure and Coagulopathy. ***Circulation*** 2020;142(12):1176-89.
82. van Es J, Beenen LF, Douma RA, den Exter PL, Mos IC, Kaasjager HA, et al. A simple decision rule including D-dimer to reduce the need for computed tomography scanning in patients with suspected pulmonary embolism. ***J Thromb Haemost*** 2015;13(8):1428-35.
83. Dronkers CEA, van der Hulle T, Le Gal G, Kyrle PA, Huisman MV, Cannegieter SC, et al. Towards a tailored diagnostic standard for future diagnostic studies in pulmonary embolism: communication from the SSC of the ISTH. ***J Thromb Haemost*** 2017;15(5):1040-3.
84. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. ***Lancet*** 2020;395(10234):1417-1418.
85. Zhao Q, Meng M, Kumar R, Wu Y, Huang J, Lian N, et al. The impact of COPD and smoking history on the severity of COVID-19: A systemic review and meta-analysis. ***J Med Virol*** 2020;92(10):1915-21.
86. Leeflang MM, Moons KG, Reitsma JB, Zwinderman AH. Bias in sensitivity and specificity caused by data-driven selection of optimal cutoff values: mechanisms, magnitude, and solutions. ***Clin Chem*** 2008;54(4):729-37.
87. Korevaar DA, Gopalakrishna G, Cohen JF, Bossuyt PM. Targeted test evaluation: a framework for designing diagnostic accuracy studies with clear study hypotheses. ***Diagn Progn Res*** 2019;3:22.
88. Wynants L, Van Calster B, Collins GS, Riley RD, Heinze G, Schuit E, et al. Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal. ***BMJ*** 2020;369:m1328.
89. Collins GS, van Smeden M, Riley RD. COVID-19 prediction models should adhere to methodological and reporting standards. ***Eur Respir J*** 2020;56(3):2002643.
90. Attaway A, Hatipoğlu U. Management of patients with COPD during the COVID-19 pandemic. ***Cleve Clin J Med*** 2020.
91. Xiao WW, Xu J, Shi L, Wang YD, Yang HY. Is chronic obstructive pulmonary disease an independent predictor for adverse outcomes in coronavirus disease 2019 patients? ***Eur Rev Med Pharmacol Sci*** 2020;24(21):11421-7.
92. Wu F, Zhou Y, Wang Z, Xie M, Shi Z, Tang Z, et al. Clinical characteristics of COVID-19 infection in chronic obstructive pulmonary disease: a multicenter, retrospective, observational study. ***J Thorac Dis*** 2020;12(5):1811-23.
93. He Y, Xie M, Zhao J, Liu X. Clinical Characteristics and Outcomes of Patients with Severe COVID-19 and Chronic Obstructive Pulmonary Disease (COPD). ***Med Sci Monit*** 2020;26:e927212.
94. Kang SJ, Jung SI. Age-Related Morbidity and Mortality among Patients with COVID-19. ***Infect Chemother*** 2020;52(2):154-164.

95. Graziani D, Soriano JB, Del Rio-Bermudez C, Morena D, Díaz T, Castillo M, et al. Characteristics and Prognosis of COVID-19 in Patients with COPD. ***J Clin Med*** 2020;9(10):3259.
96. Turan O, Mirici A. Chronic obstructive pulmonary disease and COVID-19. ***Eurasian Journal of Pulmonology*** 2020;22:56.
97. Poudel A, Poudel Y, Adhikari A, Aryal BB, Dangol D, Bajracharya T, et al. D-dimer as a biomarker for assessment of COVID-19 prognosis: D-dimer levels on admission and its role in predicting disease outcome in hospitalized patients with COVID-19. ***PLoS One*** 2021;16(8):e0256744.
98. Mukona DM, Zvinavashe M. Self- management of diabetes mellitus during the Covid-19 pandemic: Recommendations for a resource limited setting. ***Diabetes Metab Syndr*** 2020;14(6):1575-8.
99. Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. ***J Intensive Care*** 2020;8:49.
100. Shah S, Shah K, Patel SB, Patel FS, Osman M, Velagapudi P, et al. Elevated D-Dimer Levels Are Associated With Increased Risk of Mortality in Coronavirus Disease 2019: A Systematic Review and Meta-Analysis. ***Cardiol Rev*** 2020;28(6):295-302.