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D-dimer as Sensitive parameters in COVID-19 (Study of 200 patients)

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Abstract The 2019 Chinese flu pandemic has been traced back to a novel virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The 2019 coronavirus illness has been designated as COVID-19. Methods two hundred covid-19 cases were validated by RT PCR in a multi-center, prospective, observational and interventional research. At admission, all patients had their oxygen levels, inflammation marker D-Dimer, and chest HRCT taken. primary emphasis and subsequent dialogue. Age, gender, comorbidities, BIPAP/NIV use, and outcome were recorded, as was the presence or absence of lung fibrosis. Medical professionals can rule out DVT and PTE in some individuals with the help of CT pulmonary angiography and lower limb venous doppler. For statistical purposes, the Chi-square test is applied. **Results:** The severity score from the initial CT scan correlates highly with D-dimer concentration. [p<0.00001] The length of illness before admission is highly linked with D-Dimer levels.[p<0.00001] There is a strong association between elevated D-Dimer levels and the presence of co-morbid conditions. [p<0.00001] Saturation with oxygen has been found to significantly affect D-dimer concentrations.[p<0.00001] D-Dimer levels are highly associated with the requirement for BIPAP/NIV.[p<0.00001] The time of the necessity for BIPAP/NIV while hospitalized is highly associated with the D-Dimer concentration.[p<0.00001] When comparing normal and abnormal to entry point level, the D-Dimer titer is substantially linked with post-covid lung fibrosis, deep vein thrombosis, and pulmonary thromboembolism during hospitalization during follow-up.[p<0.00001]. conclusion D-Dimer has been shown to have a crucial role in forecasting the severity of illness and in assessing therapeutic response during hospitalization in covid-19 pneumonia, leading researchers to this conclusion. Aims: The consequences of Covid-19 pneumonia on the lung parenchyma, airways, and vasculature are different as this sickness is heterogeneous

Keywords: D-dimer, COVID-19, out-hospitalized patients, biomarker, pulmonary embolism, lung fibrosis, Covid-19 pneumonia.

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a novel member of group 2B β-coronavirus.1 The World Health Organization recorded 100 819 363 confirmed COVID-19 cases and 2 176 159 deaths worldwide as of January 29, 2021. Meanwhile, in Indonesia, since the first report of the case, there have been 1 051 795 confirmed COVID-19 cases and 29 518 deaths (case fatality rate: 2.8%) at the same date.2 The real-time reverse transcription-polymerase chain reaction (RT-PCR) test has become the gold standard for diagnosing COVID-19.3 However, several other laboratory markers, such as complete blood counts, hemostasis parameters, and inflammatory markers, are thought to be important, particularly as predictors of disease severity and prognosis.4 Increased D dimers are one of the most common laboratory results found in COVID-19 patients.5,6 However, in previous studies, the D-dimer cut-off point was found to vary. It is most widely recognized as greater than 2.00 mg/L,7-9 but one study found that a cut-off of 1.0 mg/L was adequate as a

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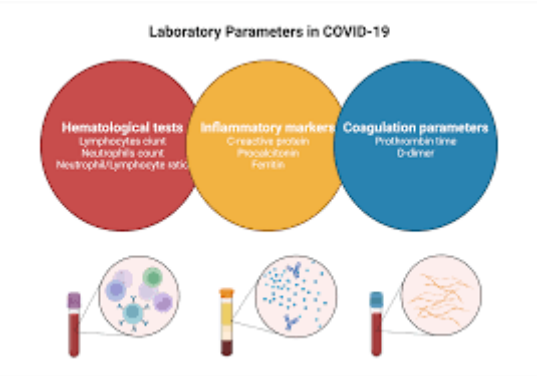
predictive biomarker.10 The International Society of Thrombosis and Haemostasis recommends using the D-dimer value of 3-4 times higher than the initial level upon hospital admission as the cut-off11 and carrying out treatment with close monitoring. 7 This phenomenon is thought to be caused by virus entry into vascular endothelial cells via
the angiotensin-converting enzyme 2 receptor, which disrupts the intercellular junction, basal membrane, complement pathway, cytokine formation, and fibrin deposition.12 Research on hemostasis laboratory parameters during admission or the assessment of COVID-19 patients is mandated to predict the management of coagulopathy. Early and precise predictor variables based on hemostasis laboratory results, especially D-dimer, are also critical for identifying the risk and survival of COVID-19 patients as D-dimer has been
strongly suggested as a marker of hypercoagulability due to its formation from fibrin formation and fibrinolysis.13,14 The objective of this research was to determine the relationship between D-dimer levels and the survival rate of COVID-19 patients.

Laboratory and imaging methods

Complete blood count, coagulation profile, renal and liver function, creatine kinase, electrolytes, myocardial enzymes, C-reactive protein, and procalcitonin were collected routinely on admission. D-dimer level is tested using immunoturbidimetric assay with reference range of 0–0.50 mg/L (Sysmex, CS5100).

Doppler ultrasound and CT pulmonary angiography were done for any patients with high clinical suspicion of pulmonary embolism/deep vein thrombosis (PE/ DVT). Chest CT scan was done for all inpatients.



Severity assessment

Clinically, severity of the COVID-19 patients was classified into mild, moderate, severe, and critically ill according to the Novel Coronavirus Pneumonia Diagnosis and Treatment Guideline (6th ed.) by the National Health Commission of China (Supplement table 1) [10]. Radiologically, the area of affected lungs consistent with viral pneumonia in each patient's first chest CT after admission was measured and classified into ≤ 30%, 31–50%, and ≥ 50% of total lung area. According to oxygenation index (OI) at admission,patients were grouped into 4 groups (group 1, OI ≥ 400 mmHg; group 2, OI 300–399 mmHg; group 3, OI 200–299 mmHg; group 4, OI < 200 mmHg). The scores of SOFA, qSOFA, ITSH for disseminated intravascular coagulation (DIC), CURB-65 for communityacquired pneumonia and Wells' rule [11], and the revised Geneva score [12] for assessing pulmonary embolism (PE) risk for each patient were documented.

High D-Dimer Levels May Be Predictive of a Poor Patient Outcome

The D-dimer levels of 169 COVID-19 patients on admission were ≤1.49 mg/L, and 118 patients had D-dimer levels greater than 1.49 mg/L, according to the cut-off value. There were 52 non-survivors, with 43 having D-dimer levels >1.49 mg/L and the rest having D-dimer levels of ≤1.49 mg/L. Male patients had a lower cut-off for D-dimer in comparison with female patients (>1.49 mg/L vs. >2.2 mg/L). Figure 2 shows the sex and comorbidities-adjusted survival curve between the patients with D-dimer levels of >1.49 mg/L and less than or equal to 1.49 mg/L. The unadjusted Kaplan–Meier plot is also provided in Supplementary Figure 1. The ROC curve for D-dimer's predictive role on patient death demonstrated 82.69% sensitivity and 68.09% specificity at the 1.49 mg/L cut-off. This graph's area under curve (AUC) was 0.786 ($P < .001$). Patients with D-dimer levels of >1.49 mg/L had a significantly higher risk of subsequent mortality ($P < .001$), as shown by the lower 30-day

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survival rate than patients with D-dimer levels of 1.49 mg/L, according to Kaplan-Meier curves and were analyzed using the Mantel– Haenszel log-rank test. The difference in average survival time between these groups is about 8 days (29 vs. 21 days). During hospitalization, there were 52 death occurrences, 43 of which were observed in patients with D-dimer levels of >1.49 mg/L on admission, while only 9 in those with lower D-dimer levels (HR = 8.72, 95% CI: 4.24-17.93, $P < .001$). After the multivariable analysis, only the D-dimer, sex, and coexisting disorders were found to be significant determinants for the risk of COVID-19 mortality.The adjusted HR value was provided in D-dimer showed the second-highest value of the C-index to predict in-hospital mortality in COVID-19 patients among regularly observed laboratory tests.

Main Points

Some demographic data including age and gender
were considered as the most essential factors in predicting patients' survival.

- The proposed cut-off for D-dimer in predicting patient outcome was 1.49 mg/L
- The use of D-dimer as a predictive measurement of patient death has 82.69% sensitivity and 68.09% specificity.
- Higher D-dimer (>1.49 mg/L) was associated with a lower 30-day survival rate than the lower D-dimer groups (8 days difference).
- D-dimer was the second-best laboratory marker for the mortality prediction of coronavirus disease 2019 patients

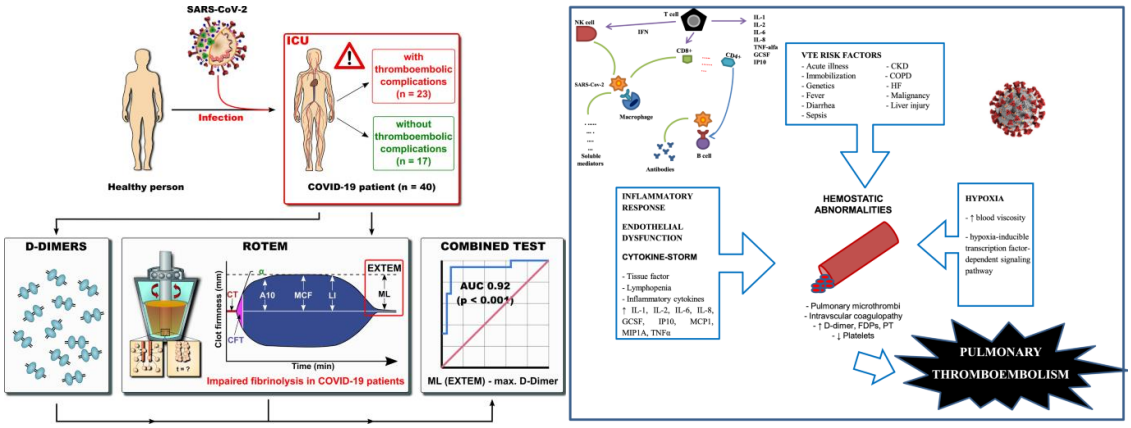

Fig. 2 A,B show infection with coved.19

Patients And Methods

A multi-center in diyala Baladruz General Hospital and Al.Khalis General Hospital , prospective, observational study was conducted between July 2020 and July 2021.

Included

Tow hundred instances of covid-19 pneumonia confirmed by RT PCR were analyzed to investigate the impact of D-Dimer in predicting disease severity, quantifying therapeutic response, and determining prognosis as post-covid fibrosis and DVT/PTE in patients admitted to the critical care unit. Following Institutional Review Board (IRB) authorization and patient signed informed consent, a total of 200 patients were enrolled in the investigation. Patients over the age of 18 who were hospitalized at study centers (regardless of severity or oxygen saturation) and who tested positive for Covid-19 by RT-PCR met the inclusion criteria.

Criteria for exclusion: Participants who were unable to offer informed permission, who had abnormal D-dimer values, or who rejected further follow-up were not included. All prospective research participants were screened using the following questions and procedures before enrollment: We retested all patients for Covid-19 if the first RT PCR result was negative, even if there was clear radiographic evidence of pneumonia. The severity of lung damage is assessed via high-resolution computed tomography (HRCT) of the chest.The third step is for the doctor to take note of the patient's vitals, including their pulse, respiration rate, blood pressure, and the presence or absence of any abnormal breathing sounds.

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Electrocardiogram, coagulation profile, blood sugar, liver function, and renal function
5. Assessing viral inflammatory markers (D-Dimer, C-Reactive Protein, and Interleukin-6) at the outset and at regular intervals during the illness course. Normal and abnormal ranges for parameters were determined by applying standards developed for use in pathology laboratories. The severity of the illness was determined by clinical criteria and the first D-dimer titer. Patients who had a negative D-Dimer test upon admission were retested on the day of discharge or if their health deteriorated while in the hospital. If a D-Dimer assay was abnormal upon admission, patients were seen every 72 hours to assess the severity, duration of disease, and titer level used to evaluate response to medical therapy. In rare cases if a D-dimer is abnormal or tachycardia persists, a CT pulmonary angiography may be warranted to rule for pulmonary embolism.

D-Dimer Levels and Their Meaning: Normal ranges typically fall between 70 and 470 mg/dL

Analyzing the Outcomes:

D-dimer levels as high as 470 ng/mL are regarded within normal range. Values exceeding 470 mg/dL are deemed positive. The concentration of D-dimer rose dramatically (by a factor of two). The D-Dimer count rose dramatically by 4.5 times its original value. Two- to four-fold changes in values throughout the follow-up are considered noteworthy. The statistical analysis was performed using the chi-squared test. Multiple significant 2 values for different degrees of freedom were included in the probability table. We considered a p-value to be statistically significant if it was less than 0.05 and highly significant if it was less than 0.001.

Evaluation and findings:

130 men and 70 women, 600 above the age of 50, and 400 under the age of 50 were among the 200 people whose cases of pneumonia were confirmed by covid-19 RT PCR as being caused by this virus.In cases with covid-19 pneumonia, D-dimer levels are significantly correlated with CT entry severity score.[p<0.00001] .In cases of covid-19 virus pneumonia, a greater D-Dimer level is associated with a longer duration of illness. [p<0.00001] (Table 2).Variables such as age, sex, diabetes mellitus, ischemic heart disease, high blood pressure, chronic obstructive pulmonary disease, and obesity have been demonstrated to have a substantial influence on D-Dimer and COIVD-19 pneumonia. [p<0.00001].D-Dimer concentration is highly linked with oxygen saturation in cases with covid1-19 pneumonia. [p<0.00001].

Statistical analysis

The demographics of the study population were described using descriptive analysis; this included sex, age, the incidence of hypertension, stroke, and cardiovascular disease in connection to anemia and renal function. Data was tabulated according to variables of interest and provided as frequencies, percentages, means, and standard deviations. We considered statistically significant a p-value less than 0.05. The correlation between the categorical variables was analyzed using chi-square statistics. After being double-checked by hand, the data were coded, entered, and sent to IBM SPSS version 22.0 for analysis.

Results

Table 1. Duration of illness (Doi) at entry point during hospitalization and D-Dimer level in covid-19 pneumonia cases (n=200)

Duration of illness	Normal D-Dimer (n=64)	Abnormal D-Dimer (n=136)	Analysis
<7 days (n=34)	6	62	Chi test value
8-15 days (n=46)	32	60	185.65 p<0.00001
>15 days (n=20)	26	14	
Total	**64**	**136**	**200**

Table 2. Other variables and D-Dimer level in Covid-19 Pneumonia cases (n=200)

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COVID-19 RT PCR positive (n=100)	Normal D-Dimer (n=64)	Abnormal D-Dimer (n=136)	Chi test value and P value
Age >50 years	**28**	**92**	**$\chi 2=51.75$**
Age <50 years	**36**	**44**	**p<0.00001**
Male gender	**38**	**92**	**$\chi 2=6.6$**
Female gender	**26**	**44**	**p< 0.010**
Diabetes mellitus	**30**	**90**	**$\chi 2=33.74$**
Without diabetes	**34**	**46**	**p< 0.00001**
Hypertension	**32**	**10**	**$\chi 2=238.56$**
Without Hypertension	**32**	**126**	**p< 0.00001**
COPD	**10**	**10**	**$\chi 2=97.44$**
Without COPD	**44**		**p< 0.00001**
IHD	**22**	**126**	**$\chi 2=60.74$**
Without IHD	**42**	**10**	**p< 0.00001**
obesity	**4**	**118**	**$\chi 2=33.29$**
Without obesity	**60**	**18**	**p< 0.00001**

Table 3 Test characteristics of D-dimer for predicting in-hospital mortality with the optimal sensitivity and specificity scores

Cutoff point for D-dimer (mg/L)	**2.13**
Area under curve	0.85
Subjects with D-dimer > 2.14 mg/L (%)	77 (31.2%)
95% CI	0.77–0.92
Specificity (%)	71.2
Sensitivity (%)	88.8
Likelihood ratio	3.07

Table 4 .Oxygen saturation at entry point and D-Dimer level in Covid-19 pneumonia cases (n=100)

Oxygen saturation	Normal D-Dimer (n=64)	Abnormal D-Dimer (n=136)	Analysis Chi test value
>90% (n=21)	**21**	**20**	60.37 p<0.00001
75-90% (n=49)	**30**	**68**	
<75% (n=30)	**13**	**48**	

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Total	**64**	**136**

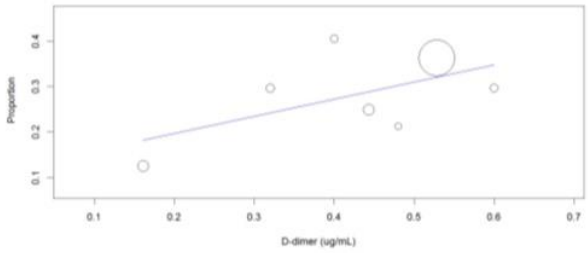

Figure 3. A scatter plot demonstrating the association of plasma D-dimer and severity

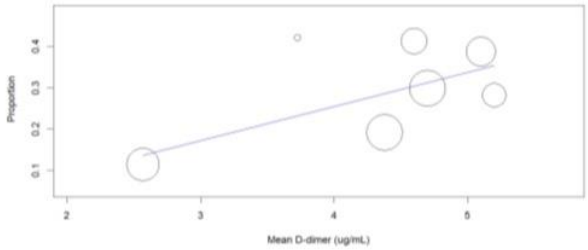

Figure 4. A scatter plot demonstrating the association of plasma D-dimer and mortality

Discussion

When a blood clot breaks down, a protein fragment called a D-dimer is produced. Untreated thrombotic events, such as deep vein thrombosis (DVT), pulmonary embolism (PE), or disseminated intravascular coagulation (DIC), are associated with D-dimer levels above the normal range.

Patients with COVID-19 who have elevated D-dimer levels tend to have more severe illness and a worse prognosis. The exact mechanisms by which the virus stimulates blood clot generation are unclear, but they are thought to contribute to the increased risk of thrombotic events. Measuring D-dimer levels in the clinic can assist doctors pinpoint COVID-19 carriers who are at an increased risk of thromboembolic complications. Patients at high risk of death or intensive care unit admission from COVID-19 can be pinpointed with the use of one of many prognostic scoring systems. The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) Clinical Characterization Protocol, which accounts for the presence of D-dimer, is one such method. D-dimer levels are generally high during pregnancy, but they can also be raised following cancer therapy, surgery, trauma, or liver sickness. As a result, D-dimer results need to be understood in the wider picture of the patient's health.

Because it is a result of fibrinolytic breakdown of fibrin and because elevated levels suggest the existence of a hypercoagulable condition and secondary fibrinolysis, D-dimer is a useful biomarker for the diagnosis of thrombotic diseases. Patients with COVID-19 have been shown to be hypercoagulable(10), and whereas 71 percent of those who passed away from the virus met the DIC requirement, just 0.6 percent of those who made it through the ordeal did so(5, 6).In addition, 25% of patients with severe COVID-19 experienced venous thromboembolism (VTE), and 30% of COVID-19 patients were identified with pulmonary embolism(6,11).

D-dimer levels were found to be abnormal in 84 individuals (36.6%) out of a total of 231. Patients under home monitoring as well as outpatients with mild symptoms were included in this study, giving it a high p-value. Using real-time reverse transcription-polymerase chain reaction (PCR), patients in this research varied in age from 14 to 75 years old, with a mean of 44.5 years.

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Numerous investigations on severely and extremely severely ill COVID-19 hospitalized patients were undertaken, and many of these patients died. It has been observed that fatal outcomes from COVID-19 are accompanied with cytokine storm syndrome, and that ferritin level was substantial in COVID-19 home observation patients(12). There appears to be a high mortality rate associated with coagulopathy and overt disseminated intravascular coagulation. In a research including 191 patients, an elevated D-dimer level was the strongest independent predictor of mortality among the coagulation markers. Among the 183 cases studied, 21 of the non-survivors had significantly longer prothrombin and activated partial thromboplastin durations than the survivors (5), and high levels of D-dimer were discovered in 91 of the fatalities (8). Numerous studies, including those by Han et al. (13), Wu et al. (14), Zhang et al. (15), and Gao et al. (16), have found that D-dimer levels are elevated in severe cases compared to mild ones.

Conclusion

1. In December 2019, a cluster of illnesses linked to the 2019 Corona virus (COVID-19) were identified in China.
2.After its rapid global spread, the World Health Organization (WHO) officially classified COVID-19 as a pandemic.
3.D-dimer levels are strongly correlated with disease severity in individuals with COVID-19, as shown in this study.
4.Increased thrombotic event rates have been linked to novel coronavirus infections, which in turn induce inflammatory and coagulation responses.
5.D-dimer testing is not yet part of the standard procedure for diagnosing COVID-19 in the laboratory.
6.Patients with COVID-19 may be stratified by disease severity with the use of laboratory tests for D-dimer and proinflammatory cytokines.
• This might, in turn, be beneficial in sufficient and more effective management of such persons.

RECOMMENDATIONS

The test indicates the existence of clots in the body when COVID gets significant. The lungs are unable to function properly due to the prevalence of blood clots in the human body, particularly in the pulmonary system. Due to clotting, blood flow is restricted. The body responds to this by attempting to dissolve the clots. Up to eight hours after its creation, D dimer can still be detected until it is eliminated by the kidneys.

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