

# D-dimer as Prognostic Factor in Geriatric COVID-19 Patients: Retrospective Study

Cokorda Agung Abi Baruna<sup>1</sup>, Adelia Ghosali<sup>2</sup>, Yeodi Utomo<sup>3</sup>,  
Wayan Wahyu Semara Putra<sup>4</sup>, Ni Made Dwita Yaniswari<sup>5</sup>

<sup>1</sup>Intern of Pulmonology and Respiratory Medicine Department in Wangaya Regional General Hospital, Denpasar, Bali, Indonesia

<sup>2,3</sup>Pulmonologist of Pulmonology and Respiratory Medicine Department in Wangaya Regional General Hospital, Denpasar, Bali, Indonesia

**Abstract:** **Background:** Elevated or abnormal levels of coagulation parameters indicate thrombotic disorders that need to be managed at the earliest to prevent complications and reduce mortality in coronavirus disease (COVID-19) patients. The aim of this study is to assess elevated D-dimer on the severity and outcome of patients with Covid-19. **Method:** This is a retrospective study which was held at Wangaya Hospital, Denpasar, from May to August 2021. The data taken from the medical record includes those from confirmed Covid-19 patients aged 60 and older. We exclude all patients who had no results of Blood test specially D-dimer value. **Result:** 36 samples were obtained in this study. We found that there was no significant difference in severity and outcome in Covid-19 patient who had elevated D-dimer and those who had normal D-dimer value ( $p=0.169$ , CI 95% ;  $p=0.964$ , CI 95%;, respectively). **Conclusion:** There is no significant difference in severity and outcome in Covid-19 patients with elevated D-dimer value. However, further researches with larger number of samples are needed to assess the possibility of D-dimer value as Covid-19 prognostic factor.

**Keywords:** Elevated D-dimer, Covid-19

## 1. Background

Covid-19 was first identified in Wuhan in 2019 and has become pandemic all over the world until now [1]. The virus causing this pandemic was named Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2, 2019-nCoV). The spreading of the virus was initially thought to have started through zoonotic transmission linked to the seafood market in Wuhan, China, but it has changed overtime to human – to – human transmission that play a significant role in subsequent outbreak. Coronavirus 2019 (COVID-19) was declared a global pandemic by World Health Organization (WHO) on March 11, 2020.

The most common symptoms of Covid-19 are respiratory symptoms such as shortness of breath, fever, cough, sore throat, and. In severe cases, acute respiratory distress syndrome (ARDS) and multiorgan failure can be found. This condition also related to comorbidities that the patients may have such as, hypertension, Diabetes mellitus, heart disease, and Chronic Obstructive Pulmonary Disease (COPD).

COVID-19 has been linked to hemostatic disorders, such as Disseminated Intravascular Coagulopathy (DIC). This condition was likely to happen due to activation of coagulation cascade related to Viremia and Cytokine storm, or possibly due to superinfection and organ dysfunction. Significant increases in D-dimer levels were found in patients who did not survive and those who suffered from severe disease.

D-dimer is a fibrin degradation product, widely used as biomarker for thrombotic disorders. A D-dimer value less than 500ng/mL is usually considered normal, and values increase with increasing age and pregnancy. The elevation of D-dimer also normally happened in condition such increased severity of community-acquired pneumonia. Following the outbreak of the COVID-19 pandemic, D-dimer

has been identified as a potential indicator for its prognosis in COVID-19 patients. A multi-center retrospective study during the first two months of the epidemic in China showed 260 out of 560 patients (46.4%) had elevated D-dimer, and it was more pronounced in severe cases than in mild cases. (59.6% vs 43.2%)

Although there are widely available prognostic biomarkers other than D-dimer that may be very useful in determining the management and prognosis. Therefore, based on this background, this study aims to assess and evaluate the elevation in D-dimer at the time of admission as possible prognostic indicator progression and the outcome in COVID-19 patients at the Wangaya Regional General Hospital, one of marker referral hospital for COVID-19 in Bali Province since 2019.

## 2. Method

This is retrospective study design that was placed at Wangaya Regional General Hospital, Denpasar in January 2022 to February 2022. Data was obtained from patient's medical record and sample was taken from patient that hospitalized from May 2021 to August 2021. Inclusion criteria of this study were confirmed Covid-19 patient (age range from 60+ and above) that hospitalized in Wangaya Regional General Hospital from May 2021 to August 2021 and had performed D-dimer value through blood test.

The D-dimer examination using a fluorescence immunoassay method for the quantitative determination of cross-linked fibrin degradation products containing D-dimer in EDTA, which anticoagulated whole blood with the reference value (<500ng/mL). The result of D-dimer will further be classified as elevated D-dimer (>500 ng/ml) and non elevated D-dimer value (<500 ng/ml). COVID-19 patient who did not perform D-dimer test and patient with incomplete medical record were excluded from this study.

Severity of COVID-19 was categorized into 2 categories, mild-moderate and severe-critically ill. This was defined from patient's oxygen saturation, that more than  $>92\%$  oxygen saturation was classified as mild-moderate Covid-19 and  $\leq 92\%$  as severe-critically ill COVID-19. Outcome also categorized into 2 categories, patient who passed away and patient who had clinical improvement and discharged from hospital.

Statistical analysis was generated with SPSS 25.0. Data were expressed as median with standard deviation. Data will be done with Shapiro-Wilk distribution test. If normally distributed, t-test dependent was used to analyze data. If data is not normally distribution, association analysis will be processed by *chi-square* association if there is no low expected count data. If there is low expected count data, the analyze will be done by *fisher-exact* test.

### 3. Result

**Table 1:** Baseline Characteristic of Covid-19 Patient

Characteristic	N
Age, n	
Median	67.5 ± 8.5
Gender, n (%)	
Male	22 (61.1)
Female	14 (38.9)
D-dimer (%)	
Elevated D-dimer	22 (69.4)
Normal D-dimer	11 (30.6)
Severity of disease	
Mild-moderate	20 (55.6)
Severe-critically ill	16(44.4)
Outcome	
Improve clinical status	26 (72.2)
Passed away	10 (27.8)

Table 1 showed the characteristic of samples. Total subjects of 36 that hospitalized in May 2021 to August 2021 was in this study. Median of subjects were 67.5 years ± 8.5 years, with 22 subjects (61.1%) were male and 14 subjects (38.9%) were female. All subjects had performed D-dimer test, with 22 subjects (69.4%) had elevated D-dimer and 11 subjects (30.6%) had normal D-dimer.

**Table 2:** Data Analysis of D-dimer with severity and outcome

Variable	Correlation coefficient	p value
Severity of disease	0.169	p < 0.05
Outcome	0.964	P < 0.05

Data were analyzed with Saphiro-Wilk test to obtain normality of data. Data of this study were not normally distributed  $p = 0.000$  ( $p > 0.05$ , CI 95%). In association with severity, data were tested with *chi square* test to obtain the association. We found no significant difference between elevated D-dimer and patient's severity of Covid-19 ( $p = 0.169$ ,  $p < 0.05$ , CI 95%). We also found that there is no significant difference between elevated D-dimer and patient's outcome ( $p = 0.964$ ,  $p < 0.05$ , CI 95%). Association to patient's outcome was tested with *Fisher exact* test, since there was low expected count data. Results can be seen in Table 2.

### 4. Discussion

The current study included 36 cases admitted to the hospital with a diagnosis of COVID-19 from May 2021 to August 2021. Cases were managed in the hospital-based on available resources and guidelines. D-dimer was usually measured on admission, and serial D-dimer measurement were not part of the routine management, only on some cases.

Elevated D-dimer commonly happened in COVID-19 with slightly associated with increase in disease severity, while increase D-dimer value doesn't affect the mortality of the cases. D-dimer elevation usually happened pathologically and non-pathologically process as long as its involving increasing of fibrin production or breakdown, also increase plasma D-dimer levels. Examples include deep vein thrombosis/pulmonary embolism, arterial thrombosis, disseminated intravascular coagulation, and conditions such as pregnancy, inflammation, cancer, chronic liver diseases, post trauma and surgery status, and vasculitis.

This study found that higher D-dimer value on hospital admitted patients was insignificantly associated with progression and outcome. Several studies have been conducted to study the association between initial D-dimer measurements and disease severity and outcome. A study done by Zhanget.al.in China including 343 patients concluded that D-dimer could be an early useful marker for predicting in-hospital mortality in patients. They found the optimal cutoff point for D-dimer to be 2 µg/ml [5]. Another study in China found that elevated D-dimer value at the time of admission was associated with increased odds of mortality (Odds Ratio 10.17 (95% CI 1.10–94.38).

Study in China by Yao et. al. also stated that D-dimer elevation ( $\geq 0.50$  mg/L) was seen in 74.6% (185/248) of the patients. Pulmonary embolism and deep vein thrombosis were ruled out in patients with high probability of thrombosis. D-dimer levels significantly increased with increasing severity of COVID-19 as determined by clinical staging (Kendall's tau-b = 0.374, P = 0.000). D-dimer is commonly elevated in patients with COVID-19. D-dimer levels correlate with disease severity and are a reliable prognostic marker for in-hospital mortality in patients admitted for COVID-19 [3]

A study done by Manisha et. al. in India evaluated 1189 patients with covid-19 and elevated D-dimer level in few stages. The study stated that elevated D-dimer mostly higher in patients with pre-existing diseases than patients without pre-existing ones. Up on assessing the clinical outcomes of COVID-19 patients, the study found that the majority of the patients recovered well from the COVID-19 infection without any complications (698 cases, 58.70%), some recovered with minor complications (272 cases, 22.88%), few developed critical illnesses and recovered (92 cases, 7.74%), while some developed thrombosis (56 cases, 4.70%), and acute kidney injury (16 cases, 1.34 %); death also occurred in some cases (55 cases, 4.62%). Most of the critical illness and mortality occurred in patients with pre-existing diseases, such as chronic kidney disease, hypertension, diabetes, liver disease, and heart failure.

An increased risk of complications was observed in patients with elevated D-dimer levels when compared to the normal D-dimer levels at the time of admission. [4]

Most of studies showed that elevated D-dimer value is associated with more severe clinical manifestation and higher mortality rate. This study has few limitations such as lack of subjects and data to be evaluated to give more precise results compared to the other studies that had large number of subjects.

## 5. Conclusion

Covid-19 have become pandemic in all over the world that has really high mortality rate. Most of the casualties were patients with comorbidities and pre-existing diseases. Therefore, it is highly essential and important to investigate some prognostic factor to help identifying the progression and complication of the Covid-19 patients conditions. One of the prognostic factor that can be performed before hospitalization or after hospitalization is D-dimer because of the low cost and highly available in most healthcare facilities. In this study we found that there is no significant association between elevated D-dimer value with the severity of covid-19. We also found that there is no association between elevated D-dimer value with the outcome or progression of the Covid-19. As the result of this study differs from previous and others studies that stated there is a significant association between elevated D-dimer to covid-19 severity, higher chance for complications, critical illness, and mortality. However, need further investigation and study with larger subjects, more health care center to cover, also more criteria to further exclude subjects to be evaluated.

## 6. Conflict of Interest

There is no conflict of interest in this study.

## 7. Author Contribution Statement

C.A.A.B conceptualized and wrote the paper; A.G and Y.U. gathering the patients data; W.S.P and N.M.D.Y revised the text; and all approved the final manuscript.

## References

- [1] World Health Organization (WHO). *Global Situation Covid-19 Pandemic*. World Health Organization, 2021. [www.covid19.who.int](http://www.covid19.who.int)
- [2] Burhan, E. et al. *Pedoman Tatalaksana Covid-19 Edisi 4*. PDPI, PERKI, PAPDI, PERDATIN, IDAI. 2022.
- [3] Yao et. al *D-dimer as Biomarker for Disease Severity and Mortality in Covid-19 patients : a case control study, Shanghai. 2020.*
- [4] Manisha et. al. *D-dimer Levels and Disease Prognosis in Covid-19 Patients*, New Delhi, India. 2021
- [5] Zhang D, Hu B, Hu C, et al. *Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus infected pneumonia in Wuhan, China. JAMA;2020;323:1061-1069.doi:10.1001/jama.2020.1585*
- [6] Chen N, Zhou M, Dong X, et al. *Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507-513.*
- [7] Levi M, Thachil J, Iba T, Levy JH. *Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol. 2020;7:e438e440.*
- [8] Shah S, Shah K, Patel SB, 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.*
- [9] Khan IH, Savarimuthu S, Leung MST, Harky A. *The need to manage the risk of thromboembolism in COVID-19 patients. J Vasc Surg. 2020;72(3):799-804.*
- [10] Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky A. *The role of biomarkers in diagnosis of COVID-19 – A systematic review, Life Sci. 2020; 254: 117788.*