

D-dimer relation with hypertension and non-hypertension in covid-19 patient

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Abstract

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by SARS-CoV-2. It mainly affects lungs, but it also affects other systems too including cardiovascular system. Apparently, comorbidity may exacerbate the COVID-19 symptoms. Hypertension is the most common comorbidities in COVID-19 patients. Some COVID-19 patients have increased their d-dimer level which is a test to detect coagulation. It is suspected that prolonged high blood pressure might cause inflammation in the endothel and release inflammatory markers. Thus, the blood viscosity might also increase. The purpose of this research is to understand the association between d-dimer with hypertension in patients with COVID-19 at Dr. Soetomo General Academic Hospital from March – June 2021. The study design of this research is retrospective cross-sectional model which use medical records of COVID-19 patients at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia in March 2021-June 2021. From 86 data which fulfil inclusion criteria will be tested using Chi-square. Most COVID-19 patients were aged between 30-60 years (68.6%). Based on sex distribution, the majority of patient was male (54.7%). There were no significant differences of d-dimer level based on hypertension ($p=0.890$), age ($p=0.494$), and sex (0.305). There was no correlation between d-dimer and hypertension comorbidity.

Keywords: D-Dimer; Comorbidity; COVID-19; Hypertension; SARS-CoV-2

1. Introduction

There are a lot of factors that affect the outcome of COVID-19 like age, lifestyle, and comorbidities. Data on 2020 from Indonesia showed that hypertension become the most common comorbidities in COVID-19 patients which is 52.1%. Besides, prevalence of hypertension in Indonesia is also high (84). Both conditions are associated with d-dimer level (6).

COVID-19 and hypertension may increase the risk of cardiovascular mortality because it damaged the endothel. Excessive inflammatory cytokine release in COVID-19 may lead to cytokine storm. This condition causes imbalance between the formation and breakdown of clots. On the other hand, hypertension puts stress on endothelial wall and causes damage. The damaged endothel attracts coagulant factors to form blood clots. After the wound healed, the clots were degraded. In the end, both conditions may increase d-dimer level (69).

The general purpose of this research is to know the association between d-dimer with hypertension in COVID-19 patients. Meanwhile the specific purpose is to know the prevalence of hypertension in COVID-19 patients and to know the prevalence of high d-dimer level among hypertensive COVID-19 patients. The reason why researcher choose hypertension because it is the most common comorbidities found in COVID-19 and the prevalence in Indonesia is still

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high. Other than that, research about d-dimer level in COVID-19 patients with hypertension is also still very limited so researchers would like to look further into this matter.

2. Material and methods

2.1. Study design

The study design of this research is retrospective cross-sectional model which use medical records of COVID-19 patients at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia in March to June 2021 to determine a relation between comorbid hypertension and d-dimer.

2.2. Population and sample

2.2.1. Population

COVID-19 patients that admitted to Dr. Soetomo General Academic Hospital, Surabaya, Indonesia in March to June 2021

2.2.2. Sample

All medical records of COVID-19 patients in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia in March to June 2021 and are in accordance with the inclusion and exclusion criteria. The minimal sample requirement is counted by formula below.

$$n = \frac{(Z\alpha)^2 PQ}{d^2}$$

n = minimum sample; $Z\alpha$ = alpha standard deviation; P = category proportion; Q = 1 - P ; d = precision

Based on the minimum sampling formula above, the minimum sample that needed is 80 subjects

2.3. Inclusion and exclusion criteria

2.3.1. Inclusion criteria

1. COVID-19 confirmed by PCR
2. D-dimer result that is from Dr. Soetomo General Academic Hospital
3. Data from period of March to June 2021

2.3.2. Exclusion criteria

1. Non-complete medical record

2.4. Variables

2.4.1. Dependent variable

The dependent variable in this study is d-dimer level in COVID-19 patients.

2.4.2. Independent variable

The independent variable in this study is hypertension can influence d-dimer level in COVID-19 patient.

2.5. Data analysis

Data will be analyzed descriptively using statistics and correlation test with SPSS 25 using Chi-square. Level of significant is $p < 0.05$

3. Results and discussion

3.1. Number of COVID-19 patients with and without hypertension

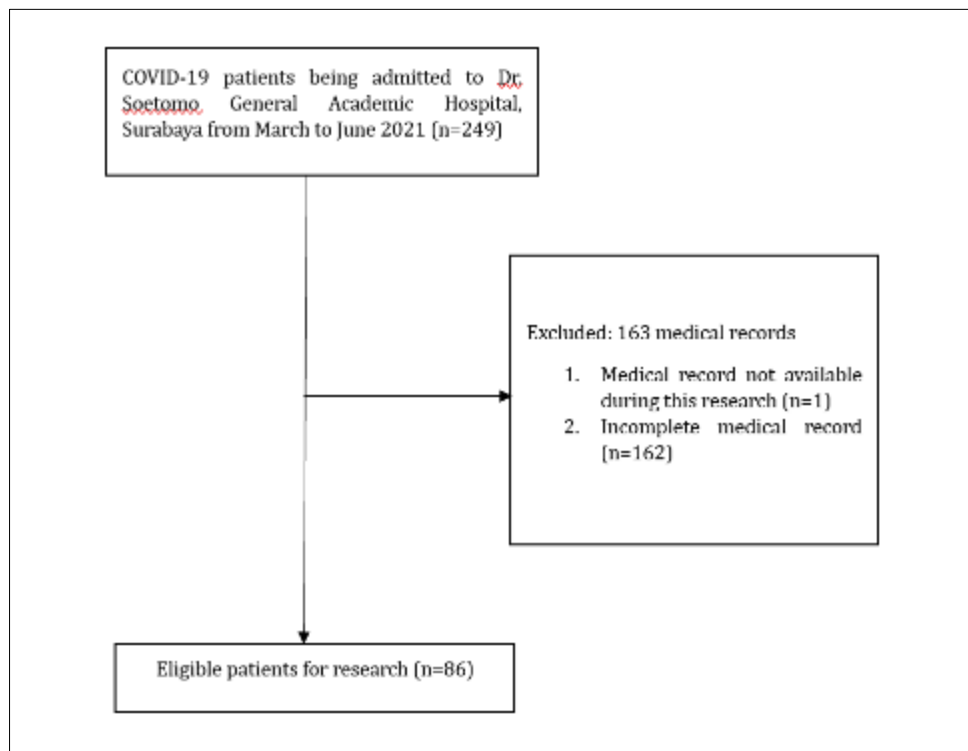


Figure 1 Number of COVID-19 patients with and without hypertension

3.2. General characteristic of patients

The data obtained showed the patient's age distribution ranged from 60 years. The most common age group were from 30 – 60 years old with 68.6%. Male patient (54.7%) with COVID-19 was more dominant than female patient (45.3%). COVID-19 patients without hypertension (65.1%) were more common than with hypertension (34.9%). The elevated d-dimer level (82.6%) was more dominant than normal d-dimer level (17.4%).

Table 1 General characteristic of patients

Characteristic		Frequency n (%)
Age	<30 years	7 (8.1)
	30-60 years	59 (68.6)
	>60 years	20 (23.3)
Sex	Female	39 (45.3)
	Male	47 (54.7)
Hypertension	No	56 (65.1)
	Yes	30 (34.9)
D-dimer level	Normal	15 (17.4)
	Elevated	71 (82.6)

From this research, most patients were aged between 30-60 years. This is in line with study from Indonesia that showed most of the COVID-19 patient were in productive age group which is 31 to 59 years (57.5%) (38). Since most workers were from productive age which means they get more exposure to environment, there is a high chance for transmission and increase cases among adults (11). Besides that, children experienced more respiratory infection which results in

immune cross protection from respiratory virus including other types of corona virus. Thus, children are less susceptible than adults to being contacted with the virus (27). In contrast, another report from CDC showed majority of patients came from 18-29 years age group (CDC, 2023). This report indicates that there is an age shift towards younger adults. However, the cause was not stated but it might be due to the school or college reopening.

On the other hand, result have showed majority of the patient were male. This data was in line with research from China (34). The possible reason why male has higher number compared to female because when they get infected with corona virus, they start to produce higher number of pro inflammatory cytokine. In addition, the T cell response in female is more vigorous while male had lower proportion of activated T cell. Thus, lead to faster virus clearance (95).

3.3. Bivariate relationship between variables

3.3.1. Relationship between d-dimer and hypertension

There were only 30 patients with hypertension in this research from a total of 86 patients. Of these 30 patients, 25 of them had elevated d-dimer level and the remaining 5 had normal d-dimer level. The other 56 patients had no comorbidities. Of 56 patients, 46 of them had elevated d-dimer and 10 of them had normal d-dimer (Table 2). The chi-square measurement showed that the level of d-dimer was not significantly associated with hypertension ($p=0.890$).

Table 2 Relationship between d-dimer and hypertension

		d-dimer level		Total
		Elevated	Normal	
Hypertension	No	46	10	56
	Yes	25	5	30
Total		71	15	86

In this research, d-dimer level is categorized as normal ($<500 \mu\text{g/L}$) and elevated ($>500 \mu\text{g/L}$). From this research 71 out of 86 patients had elevated d-dimer. 46 patients with elevated d-dimer were found in patients with no known comorbidity. This is in line with a clinical case report study which showed that patients without any comorbidity have increasing d-dimer even though it's not rise significantly (63). Unfortunately, this report did not state the possible cause of that. In contrast, research from Iraq showed that there was significant correlation between d-dimer and chronic illness such as diabetes mellitus and hypertension (5).

Adding to that, there are several possibilities that could explain the association between d-dimer and hypertension. A high d-dimer level indicates an increase in thrombotic events which lean more towards the procoagulant state. On the other hand, endothel function is impaired in hypertensive patients. Prolonged high blood pressure puts stress on vascular wall and activates NADPH oxidase which acts as a main producer for free radicals. The dominance of free radicals causes DNA, protein, and lipid damage in blood vessels. Over time, this condition will turn into chronic inflammation which marked b cytokine release such as IL-6, TNF- α , and TNF- β . This inflammatory cytokine activates the synthesis of fibrinogen which leads to procoagulant state. The procoagulant state led to an increase in blood viscosity which can be measured from the increase of d-dimer (70). Thus, hypertension might increase d-dimer level because it increases blood viscosity as explained above.

However, statistical analysis showed that there was no correlation between d-dimer and hypertension. First, researchers only taken d-dimer results that was from Dr. Soetomo General Academic Hospital which leads to smaller sample size. Second, comorbid hypertension was collected from past medical records and classified into two which is yes and no. So, researcher did not obtain the data from blood pressure measurement due to the lack of it. Thus, there was a possibility of undetected hypertensive patients.

3.3.2. Relationship between d-dimer and sex

The result showed comparison between d-dimer level and sex. D-dimer level is divided into two groups, elevated and normal. There were 31 females with elevated d- dimer and 8 females with normal d-dimer. In the other hand, there were 40 males with elevated d-dimer and 7 males with normal d-dimer (Table 3). The chi-square measurement showed that the level of d-dimer was not significantly associated with sex ($p=0.494$).

Table 3 Relationship between d-dimer and sex

		d-dimer level		Total
		Elevated	Normal	
Sex	female	31	8	39
	male	40	7	47
Total		71	15	86

Majority of the patient that had elevated d-dimer were male. This is in line with a study from Italy which showed that most of male patient had elevated d-dimer compared to female patient (37). It is supported by other study in Iraq which showed that 43.7% of males and 38.79% of females have elevated d- dimer. It may be due to weaker immunology response in male (2). A lot of study showed that female has more innate and adaptive immune response compared to males which lead to faster clearance of virus. In turn, it led to more cytokine release in men which marked by increase CRP, IL-6, IL-8, IL-18, and d-dimer. Besides that, recent study from USA showed men that hospitalized due to COVID-19 had greater risk on developing thrombosis which put them at risk to more d-dimer formation (57; 110).

In contrast, study from Saudi Arabia that used 148 patients that compared d-dimer based on COVID-19 severity, age, and gender, showed that gender has no role in d- dimer level. However, this finding has limitations because the sample that was being used was small. The association might be visible if the sample size is increased (5). In conclusion, the association of d-dimer in COVID-19 and age are variable between literature.

However, statistical analysis showed that there was no correlation between d-dimer and gender. There are several factors that caused this result. First, d-dimer was not always measured in every COVID-19 patient. Therefore, patients without d-dimer results will be excluded from the inclusion criteria. Second, even though there was a d-dimer results, not all data from were from March-June which also excluded from inclusion criteria.

3.3.3. Relationship between d-dimer and age

The results showed a comparison between d-dimer level and age. Age is divided into two, 19 years to 60 years and > 60 years because it does not comply with chi-square rules. Therefore, Fisher's exact test was used. Most patients who had elevated d-dimer were from group of 19 years to 60 years old which consist of 57 patients and the remaining 10 had normal d-dimer level. Meanwhile, age > 60 years old consist of 14 patients with elevated d-dimer and 5 patients with normal d-dimer. In short, from both age groups, there were 71 patients with elevated d-dimer and 15 patients with normal d-dimer (Table 4). The Fisher exact test measurement showed that the level of d-dimer was not significantly associated with age ($p=0.305$).

Table 4 Relationship between d-dimer and age

		d-dimer level		Total
		Elevated	Normal	
Age	19-60 years	57	10	67
	>60 years	14	5	19
Total		71	15	86

Elevated d-dimer is mostly found in age 19-60 years. In contrast, other study showed that elevated d-dimer mostly found in elderly (> 65 years) which is 89.2% (92). Adding to that, study from Indonesia showed that d-dimer elevation is in accordance with increasing age. As people get older, the body undergoes an aging process which decreases cell and organ function. Later, the body cannot give proper immune response when there is a pathogen entering the body. Thus, it makes them more susceptible to many diseases (67).

The association between aging and the immune system is complex. Cellular senescence might be the reason behind this. Cellular senescence is the state where a cell has reached the maximum limit of proliferative life span. It means the cell lost its ability to proliferate. Senescent cells are accumulating throughout life. When it is affecting immune cells, both

innate and adaptive immunity undergo some changes which increase disease susceptibility in elderly. Senescence in innate immunity is indicated by reduction in antigen processing which leads to weaker response to stimuli. Meanwhile, senescence in adaptive immunity is marked by decrease diversity function of B cell and T cell. It can lead to uncontrolled infection, reduction in B cell memory, and increase tumorigenesis. In conclusion, the changes in innate and adaptive immunity lead to imbalance immune cell which in turn, increase inflammatory responses, susceptibility to infections, and increase autoantibody production (60; 18). As mentioned before, inflammatory responses increased fibrinogen synthesis cause more thrombotic events which are marked by increased d-dimer level.

However, statistical analysis showed that there was no correlation between d-dimer and age. As mentioned before, this was because d-dimer was not always measured in COVID-19 patient. Moreover, even though d-dimer result is available, the period is not March-June 2021 which cannot be included on inclusion criteria.

4. Conclusion

This study concluded that there were no differences in d-dimer level between hypertensive and non-hypertensive patients which means there was no correlation between d-dimer and hypertension. Moreover, the prevalence of hypertension in COVID-19 patients is 34.9% and prevalence of high d-dimer level in COVID-19 patients with hypertension is 82.6%. The result of this research may contribute to the development of knowledge especially in association between hypertension and d-dimer in COVID-19 patients.

Compliance with ethical standards

Disclosure of Conflict of Interest

The authors report no conflicts of interest.

Statement of ethical approval

The study was approved by the health research ethics committee (No. 0561/KEPK/1/2023) on 2 January 2023.

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