Correlation Between D-Dimer and Interleukin-6 (IL-6) Values in Survival of Covid-19

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Abstract. Covid-19 survivors complain of persistent symptoms even though they have been declared cured. The main cause of these symptoms is increased cytokine activity, inflammation associated with Interleukin-6 (IL-6). The coagulation pathway is activated due to the immune response and thrombin activation also leads to procoagulant-anticoagulant imbalance, resulting various complications with increased D-dimer levels. D-Dimer and Interleukin-6 (IL-6) are clinical parameters often used as biomarkers to detect infection to determine whether Covid-19 survivors are experiencing health problems and are expected to provide more sensitive and accurate diagnosis results. The purpose of this study was to analyze the relationship between D-Dimer levels and Interleukin-6 (IL-6) in Covid-19 survivors. This is an analytic correlation study with a cross-sectional study design, using a retrospective approach from 102 historical data/medical records of Covid-19 survivors underwent D-Dimer and Interleukin-6 (IL-6) examinations at Laboratorium Klinik Pramita Surabaya from January 2022 until April 2023. This study analyzed by non-parametric Spearman test. The results showed there was a low positive correlation between D-Dimer and Interleukin-6 (IL-6) in groups 4-12 after recovering from Covid-19, $p = 0.020$ and $r = 0.325$. While in groups 12-24 after recovering from Covid -19 it was found there was no relationship between D-Dimer and Interleukin-6 (IL-6), $p= 0.312$ and $r= 0.144$. The conclusion of this study is D-Dimer and Interleukin-6 (IL-6) are biomarkers that are quite important for therapy and follow-up of Covid-19 survivors even though they have left the acute phase.

Keywords: Covid-19 survivors, D-Dimer, Interleukin-6 (IL-6)

1 Introduction

In November 2022, East Java Province recorded more than 629 thousand positive cases of Covid-19. Surabaya contributed 142 thousand cases with an accumulation of 3,057 death cases, 599 active cases, and 138,954 patients declared negative for Covid-19 based on Polymerase Chain Reaction (PCR) swab analysis and completed their isolation period. The group of patients who have passed this isolation and treatment period is referred to as Covid-19 survivors (Y. Kurniawan and MNIB Susilo, 2021). Covid-19 survivors complained of various symptoms up to 12 weeks or more

after being declared recovered, which is also known as long Covid-19 (T Greenlagh, 2020; E.Mahase, 2020).

A study stated that they experienced prolonged symptoms after being infected with Covid-19. Most of them had worse health conditions. Chronic fatigue, muscle pain, heart rhythm disturbances, headaches, sleep problems, and anxiety or depression issues were commonly experienced by Covid-19 survivors after 6 months of being declared negative or recovered from Covid-19 (N.J Lambert, 2020; C. Huang et al, 2021; C.F delas Penas et al, 2020)

Elevated levels of D-Dimer can persist for up to 2 months in patients who have been infected with Covid-19. This aligns with other research stating that long Covid-19 symptoms can last for 2-3 months (M.Garg et al, 2021). One indicator induced by hypercoagulable infection is an increase in D-Dimer, which can lead to various clinically relevant manifestations in the pathogenesis of 'long Covid' (L. Townsend et al, 2021; S.Mandal et al, 2021).

Inflammation associated with Interleukin-6 (IL-6) is believed to represent a potential main cause of these symptoms due to increased cytokine activity. During infection, the coagulation pathway is activated as part of the immune response, and thrombin activation also triggers other pathways leading to a procoagulant-anticoagulant imbalance, resulting in various complications with increased D-dimer levels [10]. Blood profiles from the early stages of infection indicate that cytokines are induced in pro-inflammatory lung macrophages in Covid-19, creating a feedback loop that can trigger long-term activation. Prolonged residual symptoms can disrupt the immune system (R.J Jose and A.Manuel, 2020)

A study found that D-Dimer levels increased in patients after SARS-CoV-2 infection for 6 months. In addition to D-dimer, inflammatory markers like Interleukin-6 (IL-6) also increased but slowly approached normal values after 3 months. This suggests that normalization of D-dimer values takes longer after Covid-19 infection. D-dimer values remained the same for up to 3 months but gradually decreased at the 6-month follow-up. Continuous monitoring of D-dimer values after recovery is crucial during anticoagulant therapy. Long Covid symptoms have a direct correlation with persistent D-dimer levels, indicating thromboinflammatory processes even after the acute phase (M.K Kalaivani and S. Dinakar, 2022).

The purpose of this research is to investigate the relationship between D-Dimer levels and Interleukin-6 (IL-6) in Covid-19 survivors.

2 Result

Characteristics of Respondents This research was conducted with a total of 102 historical/medical record data of Covid-19 survivors who underwent D-Dimer and Interleukin-6 (IL-6) examinations during the period from January 2022 to April 2023.

Table 1. Characteristics of respondents

Respondent Characteristics	n	%
Gender (n=102)		
1. Male	50	49.9
2. Female	52	50.1
Age Group (years)		
1. < 25 - 44	25	24.5
2. 45 - 64	40	39.2
3. 65 ->74	37	36.3
Comorbidity History		
1. Dyslipidemia	12	11.8
2. Liver function disorder	4	3.9
3. Kidney function disorder	5	4.9
4. Diabetes	10	9.8
5. Pneumonia	3	2.9
6. None/not recorded	68	66.7

Based on Table 1, the characteristics of the 102 Covid-19 survivor patients, it was found that there were 50 males (49.9%) and 52 females (50.1%). The highest number of respondents based on age was in the 45-64 age group at 39.2%, while the lowest was in the <25-44 age group at 24.5%. Regarding comorbidity history, patients with dyslipidemia accounted for 11.8%, liver function disorders 3.9%, kidney function disorders 4.9%, diabetes 9.8%, pneumonia 2.9%, and the majority of Covid-19 survivors had no or no recorded comorbidity history, with the highest percentage being 66.7% (68 individuals).

Table 2. D-Dimer and IL-6 Values of Covid-19 Survivor Patients with Inclusion Criteria 4-12 Weeks After Testing Negative for Covid-19

Variable	D-Dimer	IL-6
Total (N)	51	51
Mean	612.6	9.9
Standard Deviation	327.4	16.5
Maximum	1383	90.4
Minimum	124	<1.5

Based on Table 2, the D-Dimer and Interleukin-6 (IL-6) values of Covid-19 survivors with inclusion criteria 4-12 weeks after testing negative for Covid-19 have a total of N or data count of 51. Out of the 51 data samples, the mean value for D-Dimer is 612.6, and for Interleukin-6 (IL-6), it is 9.9.

The standard deviation for D-Dimer is 327.4, and for Interleukin-6 (IL-6), it is 16.5. The maximum value for D-Dimer is 1383, and for Interleukin-6 (IL-6), it is 90.4. The minimum value for D-Dimer is 124, and for Interleukin-6 (IL-6), it is <1.5.

Table 3. D-Dimer and IL-6 Values of Covid-19 Survivor Patients with Inclusion Criteria 12-24 Weeks After Testing Negative for Covid-19

Variable	D-Dimer	IL-6
Total (N)	51	51
Mean	384,8	4,2
Standard Deviation	176,6	4,0
Maximum	798	20,0
Minimum	110	< 1,5

Based on Table 3, the D-Dimer and Interleukin-6 (IL-6) values of Covid-19 survivors with inclusion criteria 12-24 weeks after testing negative for Covid-19 have a total of N or data count of 51. Out of the 51 data samples, the mean value for D-Dimer is 384.8, and for Interleukin-6 (IL-6), it is 4.2.

The standard deviation for D-Dimer is 176.6, and for Interleukin-6 (IL-6), it is 4.0. The maximum value for D-Dimer is 798, and for Interleukin-6 (IL-6), it is 20.0. The minimum value for D-Dimer is 110, and for Interleukin-6 (IL-6), it is <1.5.

Percentage of D-Dimer and Interleukin-6 (IL-6) values in Covid-19 survivor patients is not provided in the given text.

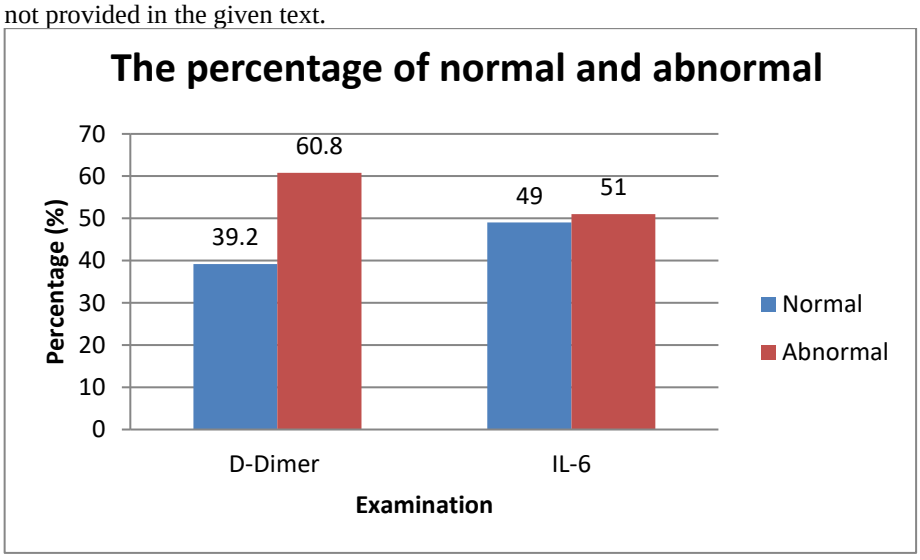

Fig. 1. Percentage of D-Dimer and IL-6 Values in Covid-19 Survivor Patients with Inclusion Criteria 4-12 Weeks After Testing Negative for Covid-19

Based on Figure 1, in Covid-19 survivors with inclusion criteria of 4-12 weeks, those with abnormal D-Dimer levels are 31 individuals (60.8%), while abnormal Interleukin-6 (IL-6) levels are found in 26 individuals (51.0%). Those with normal D-Dimer levels are 20 individuals (39.2%), and normal Interleukin-6 (IL-6) levels are found in 25 individuals (49.0%).

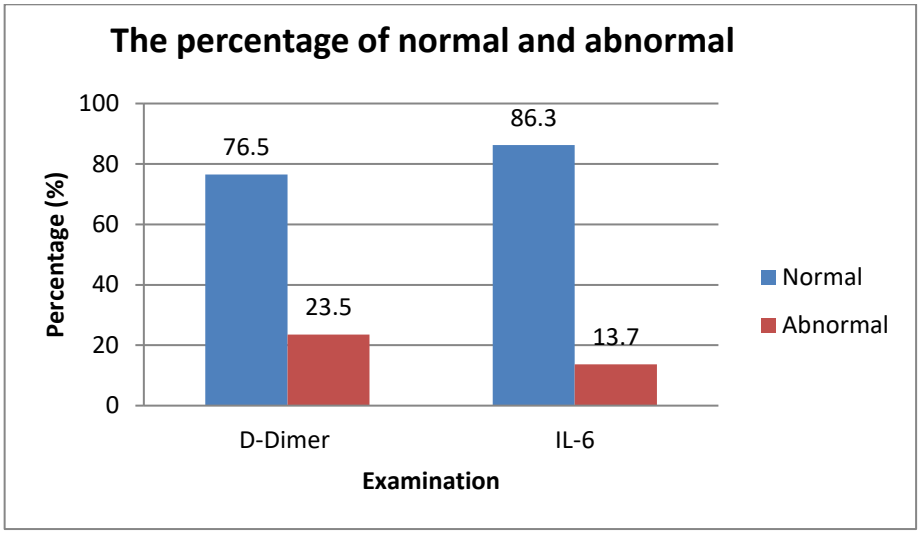

Fig. 2. Percentage of D-Dimer and IL-6 Values in Covid-19 Survivor Patients with Inclusion Criteria 12-24 Weeks After Testing Negative for Covid-19

Based on Figure 2, in Covid-19 survivors with inclusion criteria of 12-24 weeks, those with abnormal D-Dimer levels are 12 individuals (23.5%), while abnormal Interleukin-6 (IL-6) levels are found in 7 individuals (13.7%). Those with normal D-Dimer levels are 39 individuals (76.5%), and normal Interleukin-6 (IL-6) levels are found in 44 individuals (86.3%).

Data Analysis

Based on the normality test results, it was found that the relationship assessment between variables with non-normal data distribution, thus, the non-parametric statistical test, Spearman correlation, was used. The significance level (α) used was 0.05**.** Statistically significant differences occur when $p<0.05$. The data processing results are as follows:

Table 4. Correlation Test Results for D-Dimer and IL-6 Values in Covid-19 Survivor Patients with Inclusion Criteria 4-12 Weeks After Testing Negative for Covid-19

Variable	P-value (Sig p<0.05)	r Value

D-Dimer IL-6	0.02	0.325

Based on Table 4, a correlation test was conducted, and the analysis results indicate a significance value of 0.020 ($p<0.05$). This suggests that there is a relationship between D-Dimer and Interleukin-6 (IL-6) values in Covid-19 survivor patients with inclusion criteria of 4-12 weeks after testing negative for Covid-19. The r value in this study is 0.325, indicating a low positive correlation between D-Dimer and Interleukin-6 (IL-6).

Table 5. Correlation Test Results for D-Dimer and IL-6 Values in Covid-19 Survivor Patients with Inclusion Criteria 12-24 Weeks After Testing Negative for Covid-19

Variable	P-value (Sig $p<0.05$)	r Value
D-Dimer IL-6	0.312	0.325

Based on Table 5, a correlation test was conducted, and the analysis results indicate a significance value of 0.312 ($p>0.05$). This indicates that there is no relationship between D-Dimer and Interleukin-6 (IL-6) values in Covid-19 survivor patients with inclusion criteria of 12-24 weeks after testing negative for Covid-19.

3 Discussion

Coronavirus Disease 2019 (COVID-19) is a disease caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) virus (YR.Guo et al, 2020). SARS-CoV-2 is an RNA virus composed of four structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N) (J.Cui, F.Li and Z.L.Shi, 2019). The spike protein plays a crucial role in helping the virus attach to host cells. The virus enters the host cell through the Angiotensin Converting Enzyme 2 (ACE2) receptor present on the cell membrane (R.Lu et al, 2020; P.Zhou et al, 2020).

Research data show that there were 50 male individuals (49.9%) and 52 female individuals (50.1%) with a predominance in the age group between 45-64 years, accounting for 39.2%, and the age group between 55->75 years, accounting for 36.3%, accompanied by several comorbidities. Other studies have explained that the clinical presentation appears to correlate with older age due to age-related changes in the immune system, which can be compounded by nutritional deficits, evolving into systemic inflammation, especially affecting the immune system. Lungs, heart, kidney function, and coagulation system, the second stage of hyperinflammation is marked by the massive production of pleiotropic cytokines (e.g., IL-6) by macrophages and circulating immune cells (G.Canedo-Marroquin et al, 2020). A study has shown that neurological symptoms in long Covid-19 are significantly correlated with hypercoagulable conditions, and elevated D-Dimer levels can be a predictor for this condition (D.K Mirawati et al, 2022).

D-Dimer is a degradation product of cross-linked fibrin, generated from plasmin activity (H.Asakura and H.Ogawa, 2021). The coagulation cascade representing secondary hemostasis leads to the formation of thrombin, where fibrinogen acts to produce

fibrin. Factor XIII acts to cross-link and stabilize fibrin to help form a stable thrombus. Plasmin acts to break down fibrin into fibrin degradation products (FDPs), which predominantly contain D fragments (G.Lippi et al, 2014). The process continues by forming fragment X, which is subsequently cleaved into fragments Y, D, and E. Two D fragments and one E fragment then strongly bind to form D-Dimer, making it the smallest fragment resulting from fibrin breakdown (I. Umar and R.W Sujud, 2020).

Interleukin-6 (IL-6) belongs to one of the proinflammatory cytokine groups produced by various cell types, including activated macrophages, T cells, endothelial cells, and smooth muscle cells. Thus, it can serve as an indicator to assess the level of inflammation experienced by the endothelial cells of blood vessels, stimulating the immune response during infection. In addition, Interleukin-6 (IL-6) also influences various cellular actions, including effects on platelets, endothelium, metabolic factors, and coagulation (P.Oky et al, 2014).

The values of D-dimer and Interleukin-6 (IL-6) in survivors with inclusion criteria of 4-12 weeks after being declared negative for Covid-19 show an average D-Dimer value of 612.6 and Interleukin-6 (IL-6) of 9.9. The maximum D-Dimer value indicates 1383, while Interleukin-6 (IL-6) is at 90.4. However, in Figure 1, it is found that the percentage of abnormal D-dimer levels is 60.8%, and for Interleukin-6 (IL-6), it is 51.0%. These results indicate that D-Dimer and Interleukin-6 (IL-6) values in patients recovering from Covid-19 within 4-12 weeks still show a significant increase.

Persistent systemic vascular inflammation and dysfunction caused by thrombosis are key factors driving various long-term complications of Covid and often occur during the recovery phase of Covid-19 patients and are not related to the acute phase that is currently underway (H.Forgaty et al, 2021). Increased Interleukin-6 (IL-6) also has adverse effects, such as raising body temperature, and in chronic increases, Interleukin-6 (IL-6) can cause tissue damage characterized by inflammation and increased leukocyte production (IK.Wardika and IGPH Sikesa, 2021). Serum Interleukin-6 (IL-6) levels can increase with age due to stimulation of Interleukin-6 (IL-6) production related to increased levels of free radicals. Vascular endothelial damage can be caused by long-term viral infections and inflammatory responses. This initiates the coagulation process and microthrombosis, which can lead to various systemic functional disorders and residual clinical symptoms (P.Ambrosino et al, 2021; M.J Peluso et al, 2021; J.Garcia-Abellan et al, 2022).

The values of D-dimer and Interleukin-6 (IL-6) in survivors with inclusion criteria of 12-24 weeks after being declared negative for Covid-19 show an average D-Dimer value of 384.8 and Interleukin-6 (IL-6) of 4.2. The maximum D-Dimer value indicates 798, while Interleukin-6 (IL-6) is at 20.0. Figure 2 indicates that the percentage of abnormal D-dimer levels is 23.5%, while for Interleukin-6 (IL-6), it is 13.7%. These results suggest that, in patients recovering from Covid within 12-24 weeks, the D-Dimer and Interleukin-6 (IL-6) values are on average within the normal range. In this data analysis, D-Dimer and Interleukin-6 (IL-6) levels in survivors after 3 months of recovery are approaching normal ranges, although some survivors still have abnormal D-Dimer and Interleukin-6 (IL-6) levels. Previous research studies have shown the normalization of inflammatory markers, including Interleukin-6 (IL-6), despite the persistence of elevated D-Dimer levels.

The analysis results indicate a correlation between D-dimer values and Interleukin-6 (IL-6) in Covid-19 survivor patients 4-12 weeks after being declared negative for Covid-19. The mechanism behind the increase in D-dimer levels is due to the activation of an inflammatory storm and the release of proinflammatory cytokines, including Interleukin-6 (IL-6), which induces endothelial dysfunction mechanisms, leading to microvascular system damage and increased activation of the coagulation system. Therefore, targeting the Interleukin-6 (IL-6) pathway can aid in the treatment and prevention of long Covid. Long Covid symptoms are directly correlated with persistently elevated D-dimer levels, indicating a thromboinflammatory process even after the acute phase has subsided.

However, the analysis results show that there is no correlation between D-dimer values and Interleukin-6 (IL-6) in Covid-19 survivor patients 12-24 weeks after being declared negative for Covid-19. From the research results above, the D-Dimer and Interleukin-6 (IL-6) levels approach the normal range, although some survivors still have abnormal levels. This indicates that it could be due to a reduction in the coagulopathy process caused by the induction of proinflammatory cytokines, namely Interleukin-6 (IL-6), which can lead to vasoconstriction, resulting in increased fibrin and D-Dimer deposition (L.Ortega-Paz et al, 2021).

4 Conclusion

There is a relationship indicating a low positive correlation in the group of survivors 4-12 weeks post-recovery. However, in the group of survivors 12-24 weeks post-recovery, the results show no significant relationship between D-Dimer levels and Interleukin-6 (IL-6).

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