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Comorbidities Effects In COVID-19 Patients on Laboratory Inflammation Markers Test Results

Apriani[1*], Basuki Rachmad[1], Nuraddiyani Hidayah[2], Islakhun Ni'mah[1]

[1)] Program Study Medical Laboratory Technology, STIK KESOSI, Jakarta, Indonesia
[2)] Clinical Pathology Laboratory, Soeharto Heerdjan Hospital, Jakarta, Indonesia

apriani@stikeskesosi.ac.id

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Kata Kunci

Covid-19;
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Penanda Inflamasi;

Abstrak

Reaksi inflamasi memainkan peran penting dalam patofisiologi COVID-19. Kadar D-dimer, Procalcitonin (PCT) dan C-reaktif Protein (CRP) diketahui meningkat saat merespon reaksi inflamasi. Pasien komorbid COVID-19 sering dikaitkan dengan kondisi parah dan tidak bertahan hidup. Penelitian ini bertujuan untuk mengetahui pengaruh komorbiditas terhadap hasil pemeriksaan laboratorium penanda inflamasi. Penelitian dilakukan pada bulan Juni – Agustus 2022 di Rumah Sakit Siloam Lippo Village. Hasil laboratorium penanda inflamasi dan komorbid dianalisa secara deskriptif. Uji pengaruh parameter penanda nflamasi menggunakan uji regresi statistik (α=0,5%). Uji statistik menunjukkan tidak ada pengaruh yang signifikan terhadap komorbiditas pada hasil laboratorium penanda inflamasi D-dimer (P= 0,467) dan PCT (P= 0,834). Komorbiditas berpengaruh nyata terhadap hasil pemeriksaan CRP (P = 0,002). Dalam hal ini, semua pasien komorbid COVID-19 perlu diprioritaskan untuk menjalani pemeriksaan CRP untuk mengatasi penurunan saturasi oksigen yang cepat, trombosis vena dalam dan emboli paru serta kematian.

Keywords.

Covid-19;
Comorbidities;
Inflammatory marker;

Abstract

Inflammatory reactions play an important role in the pathophysiology of COVID-19. Levels of D-dimer, procalcitonin (PCT) and C-reactive Protein (CRP) are known to increase in response to an inflammatory reaction. Comorbid COVID-19 patients are often associated with severe conditions and do not survive. In handling COVID-19 patients with comorbidities, it is necessary to recommend specific laboratory examinations to make the actions given more effective and efficient and reduce costs and treatment time. This study aims to determine the effect of comorbid on the results of laboratory examination of inflammatory markers. The study was conducted in June – August 2022 at Siloam Lippo Village Hospital. Subjects and laboratory results were presented descriptively. Test the effect of comorbid and inflammatory marker parameters using a statistical regression test (α=0.5%). Statistical tests showed no significant effect on comorbidity on laboratory results of inflammatory markers D-dimer (P= 0.467) and PCT (P= 0.834). Comorbidities significantly affected CRP examination results (P = 0.002). In this case, it is necessary to prioritize all comorbid COVID-19 patients to have an early CRP examination to treat rapidly decreasing oxygen saturation, deep vein thrombosis and pulmonary embolism and death.

Introduction

In general, the results of laboratory tests in COVID-19 patients show abnormalities. COVID-19 infection can cause a series of inflammatory processes in its pathogenicity. C-reactive protein (CRP), D-dimer and Procalcitonin (PCT) are some of the inflammatory marker parameters considered in their use in this infection (1). As a non-specific marker of inflammation, CRP plays an essential role in monitoring bacterial infection, inflammation, neurodegeneration, tissue injury and recovery. CRP is considered a sensitive biomarker of infection, inflammation and tissue damage. During the acute inflammatory response, CRP levels will increase rapidly (2). In the field of immuno-serology related to COVID-19 cases, it was first carried out (3) that ferritin and CRP levels can be used as indicators of inflammation or COVID-19 infection where an increase in serum ferritin levels of 63% and CRP of 86% was found. Previously, it was also known that in addition to ferritin and CRP, other markers of inflammation in cases of severe infection increased levels of proinflammatory cytokines, namely TNF-, IL-1, IL-6 and IL-8 as well as procalcitonin (4). Patients with a significant increase in CRP should be given more attention and vigorous therapy (5).

Inflammatory reactions play an essential role in the pathophysiology of COVID-19. Proinflammatory cytokines are elevated in the peripheral blood of patients, as well as increased inflammatory markers such as D-dimer and procalcitonin are predicted to increase in COVID-19 infection (6). D-dimer is a parameter that is also a reference in patient examination and is used to predict mortality in hospitalized patients. D-dimer is closely related to COVID-19 patients who do not survive (7). D-dimer levels in COVID-19 patients who died were higher than in those still alive (8). Another biomarker that is also routine as an indicator for the diagnosis of sepsis and is currently recommended in several countries is Procalcitonin (PCT). Serum PCT levels are elevated during sepsis. The meta-analysis by Uzzan et al. found that PCT was better than CRP in differentiating SIRS and sepsis (5,6). The study by Meynaar et al. concluded that PCT levels were better than other markers (such as CRP, lipopolysaccharide-binding protein (LBP, interleukin-6 (IL-6)) in differentiating SIRS and sepsis in critically ill patients.

In COVID-19 patients with comorbidities, the risk of death will be higher. Comorbidities describe the presence of other diseases than the primary disease (e.g. diabetes, hypertension, cancer, COPD, ischemic stroke and pulmonary TB). Of the 41 COVID-19 patients, 13 (32%) had underlying diseases, including cardiovascular disease, diabetes, hypertension and COPD (Chronic Obstructive Pulmonary Disease) (9). Of the 138 cases of COVID-19, 64 cases (46.4%) were found to have comorbidities (10). Patients who were admitted to the ICU (Intensive Care Unit) had higher comorbid illnesses (72.2%) than those who were not admitted to the ICU (37.3%). Several researchers reported on the effect of comorbid diseases on the high mortality risk in COVID-19 patients. Old-age COVID-19 patients with comorbid hypertension, diabetes, and heart and lung disease, are more susceptible to infection and have a higher mortality rate than COVID-19 patients without comorbidities (11).

Most existing studies have focused on the clinical symptoms and radiological findings of COVID-19 patients. Several studies have discussed the diagnostic and prognostic value of abnormal laboratory results in COVID-19 patients (12). Until now, no study has reported which comorbid disease is the most dominant in describing the severity to the risk of death in COVID-19 patients based on the results of laboratory tests. This research data is urgently needed to be used as a recommendation for effective and efficient laboratory tests, especially for inflammatory markers in detecting COVID-19 patients with comorbidities, so that it can reduce costs, treatment time, and mortality rates

Methods

This study is an observational analytic study with a prospective cross-sectional design. Research data were taken directly for laboratory values of inflammatory markers CRP, PCT and D-dimer in Siloam Hospital Lippo Village. Data was taken by purposive sampling technique. The inclusion criteria set were patients who were confirmed positive for SARS-CoV-2 by RT-PCR technique using a nasopharyngeal swab specimen and performing a complete examination of inflammatory markers (PCT, D-Dimer, and CRP). The study was conducted from June – August 2022. The D-dimer sample was analyzed using the Sysmex CS 1600. The CRP sample was analyzed using the Cobas C501, and the PCT sample was analyzed using the Cobas E501. Data analysis was performed by linear regression test (α = 0.05). The characteristics of the respondents and the results of laboratory examinations of inflammatory markers are presented in tabular form and then described. The health research ethics committee has approved this research of STIK KESOSI Number: 05/I/7/LPPM_STIKKESOSI/2022.

Results

The total respondent data in this study amounted to 191 samples. Based on the age range, the highest was in the age range of 50 – 59 years (31.9%), and the lowest was in the age range of 20 – 29 years (2.1%). The sex of most samples was male (55.8%), and the three highest comorbidities were Hypertension (31.9%), Diabetes Mellitus (DM) (26.2%) and Coronary Cardiac Disease (18.8%) (Table 1). The results of laboratory tests for COVID-19 inflammatory markers in all comorbidities showed an increase compared to normal values with an average value of CRP = 56.82 mg/L, PCT = 1.61 ng/mL, and D-dimer = 2.08 g/mL (Table 2). Based on the examination carried out on the inflammatory marker parameters (D-dimer, CRP, PCT) in each comorbid, it found that the CRP results in comorbid DM and Hypertension showed an increase compared to other comorbidities. PCT results in comorbid Chronic Kidney Disease (CKD) showed improvement compared to other comorbidities, and D-dimer results in comorbid Hypertension, Chronic Obstructive Pulmonary, and Chronic Kidney Disease showed improvement compared to other comorbidities (Figure 1).

Table 1. Respondent characteristics

Characteristics	Sample (N=191)
Age (years), n (%)	
20 - 29	4 (2.1)
30 - 39	26 (13.6)
40 - 49	33 (17.3)
50 - 59	61 (31.9)
60 - 69	44 (23.0)
70 - 79	23 (12.0)
sex, n (%)	
Female, n (%)	84 (43,97%)
Male, n (%)	107 (56,02%)
Comorbidities, n (%)	
Hypertension	61 (31.9)
Diabetes mellitus (DM)	50 (26.2)
Coronary Cardiac Disease	36 (18.8)
Chronic Kidney Disease	12 (6.3)
Cancer	10 (5.2)
Autoimmune	11 (5.8)
Thyroid	3 (1.6)
Chronic Obstructive Pulmonary	8 (4.2)

Table 2. Inflammatory marker laboratory results

Inflammation markers	Mean	Normal (n/N)	SD	Min-Max	95%CI
C-reactive protein (0 – 6 mg/L)	56,82	42/191	73,29	1,0 – 316,0	46,37 – 67,29
Procalcitonin (<0,5 ng/mL)	1,61	40/191	3,58	0,03 – 33,19	1,10 – 2,13
D-Dimer (0 – 0,3 μg/mL)	2,08	3/191	4,82	0,19 – 59,00	1,39 – 2,77

Source: Siloam Lippo Village Hospital

To assess the effect of comorbidity on inflammatory marker parameters, using linear regression statistical test (SPSS ver24) (α = 0.05). The results of the regression test showed that there was no effect on all comorbidities on the values of inflammatory markers D-dimer (P = 0.467, r = 0.053) and PCT (P = 0.834, r = 0.015). However, all comorbidities significantly affected the value of the inflammatory marker CRP (P = 0.002, r = 0.224) (Table 3).

Table 3. Effect of comorbid on inflammatory marker laboratory parameters

Inflammatory markers			
	r	**P**	**CI 95%**
C-reactive protein (mg/L)	0.224	0.002	62.46 – 98.31
Procalcitonin (PCT) (ng/mL)	0.015	0.834	0.798 - 2.599
D-Dimer (ug/mL)	0.053	0.467	1.243 – 3.663

Source: Siloam Lippo Village Hospital

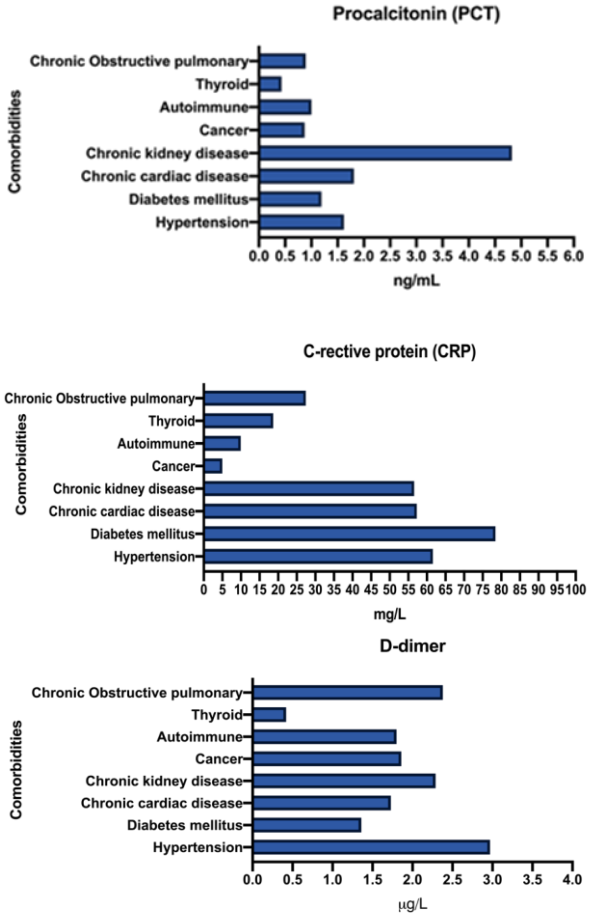

Figure 1. Mean values of D-dimer, CRP and PCT in comorbidities

Mean values of D-dimer in comorbidities; Hypertension and Chronic Obstructive Pulmonary have highest levels of D-dimer than other comorbid. Mean values of CRP in comorbidities; Diabetes mellitus and Hypertension have highest levels of CRP than other comorbid. Mean values of PCT in comorbidities; Chronic Kidney Disease have highest levels of PCT than other comorbid

Discussion

1. Respondent Characteristics

The age range of the most comorbid respondents at Siloam Lippo Village Hospital is 50-59 years. According to WHO (2016), this age is classified as advanced. Elderly COVID-19 patients are more at risk of increased mortality, 76.6% (13). Kim et al. said that age > 65 years was the highest risk of

death from COVID-19 (14). The study of (15) stated that as many as 6-29% of COVID patients aged 85 would require intensive care. Why are older people susceptible to COVID-19? This is because the immune system tends to weaken with age, making it more difficult to fight off infections. Lung tissue becomes less elastic over time, making respiratory diseases like COVID-19 a particular concern for the elderly. Inflammation in the elderly can be more intense, causing organ damage. The homeostatic function will decrease with age which positions the elderly in unfavourable conditions to fight aggressive infections, such as COVID-19 (16).

The male gender in patients with COVID-19 in this study was found to be more than female. Regarding gender, men are 28% more at risk of infection than women. This is directly proportional to the relationship between sex and mortality, which illustrates that men are 1.86% more at risk of dying than women (4). This is influenced by the presence of ACE2 expression. In men, higher ACE2 expression is associated with sex hormones, thus giving men a higher potential for infection with SARS-CoV-2. A gene encodes ACE2 expression on the X chromosome, males are homozygous, and females are heterozygous. Because the male is homozygous, it will be able to provide an opportunity to increase the ACE2 expression. SARS-CoV-2 infection and some other clinical symptoms can be neutralized in women who carry the heterozygous X allele or also known as sexual dimorphism (17).

Most COVID-19 patients with comorbidities identified in this study were COVID-19 patients with a comorbid history of Hypertension (33.3%) and Diabetes mellitus (27.3%). It is known from previous studies that COVID-19 patients with comorbidities have a higher mortality rate than patients without comorbidities (18). This is supported by research which shows that 88% of deaths in SARS-CoV-2 positive patients are caused by a history of comorbidities (19). The most common comorbidities found in COVID-19 patients are diabetes mellitus, hypertension, and obesity. The results of the most comorbid identification in this study are in line with the study in Wuhan, China which had 41 patients hospitalized, 73% (30/41) were men with an average age of 49 years, 66% (27/41) of these patients had been exposed to the Huanan market, 32% (13/41) had underlying diseases such as diabetes 20% (8/41), hypertension 15% (6/41), and cardiovascular 15% (6/41) (9). In hypertensive patients suffering from COVID-19, there is an increase in ACE-2 expression, which causes a high susceptibility to SARS-CoV-2 infection, especially treatment with angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEi) (20). ACE-2 receptors are expressed by endothelial cells, so the dysfunction of vascular endothelial cells that often occurs in hypertensive patients can increase the expression of ACE-2 receptors. Thus, vascular endothelial dysfunction in COVID-19 patients with hypertension increases the severity of the infection and up to the risk of death (20).

Diabetes mellitus was the second most common comorbid in this study. Conditions of high blood sugar levels can increase viral replication and suppress the antiviral immune response (21). Impaired T-cell function and elevated levels of interleukin-6 (IL-6) also play an essential role in increasing the severity of COVID-19 in diabetics. In addition, in diabetic conditions, there is also an increase in furin, a type 1 membrane protease, which plays a role in the entry of SARS-CoV-2 into cells and facilitates viral replication (22).

2. Comorbid relationship with Inflammatory marker parameters

Inflammatory marker parameters such as D-dimer and CRP have been identified as potential markers for critical patient conditions. Many facts state that critically ill patients have a hyperinflammatory character consisting of increased CRP, procalcitonin, D-dimer and hyperferritinemia. This fact points to the possible important role of cytokine storms in the pathophysiology of COVID-19 (23). In this study, all values of the inflammatory marker parameters showed an average increase from their normal values. Elevated CRP indicates excessive inflammation in host immune cells (24). Before the COVID-19 pandemic, up to 90% of the occurrence of elevated CRP was associated with an infectious etiology, most often from bacterial pathogens (25). Although CRP is better known as a strong marker of bacterial infection, because of its potential to detect tissue damage, CRP is considered to be able to see the severity of COVID-19 inflicted on the body. CRP is also known to increase in COVID-19 patients with complications of shock, ARDS, kidney damage, and heart damage (26). This is in line with the results in this study which showed that the CRP values for all comorbid were above the normal range (0-6 mg/dL), except for malignancy/cancer comorbidities whose CRP values were in the normal range. Likewise, the results of statistical tests on the effect of comorbid and inflammatory markers of CRP in this study showed a significant effect. This indicates that the CRP value can be used as an independent predictor for the severity of COVID-19 with severe symptoms.

The mean value of CRP for all comorbidities in this study was 56.82 mg/L. Liu et al. proposed a cut-off value of 41.8 mg/L to predict severe COVID. Meanwhile, Koozie et al. stated that the cut-off value for increasing serum CRP was 1000 mg/L (2), and Ryoo et al. set it at 140 mg/L (1). Based on these facts, it is necessary to determine the CRP level as the optimal cut-off value for prognostic COVID-19. The period for measuring serum CRP is critical. CRP will reach its peak 72 hours after initial infection

(1,27). However, factors affecting CRP levels include age, gender, smoking status, weight, lipid levels, blood pressure, and liver injury (27).

The same is true for CRP laboratory parameters. The D-dimer laboratory parameter also plays a role in assessing disease severity and risk of death in Covid-19 patients due to the increased risk of developing pulmonary embolism (28,29). As a marker of inflammation, D-dimer will work to activate coagulation and thrombin formation. High D-dimer levels are often associated with impaired liver function. COVID-19 can trigger thrombotic microangiopathy and microcirculation disorders due to endothelial cell injury. This can be exacerbated by hepatic dysfunction since most coagulation factors, anticoagulants, and fibrinolytic proteins are synthesized in the liver. The value of D-dimer in comorbid hypertension, kidney disease and obstructive pulmonary in this study obtained the highest value of other comorbidities. This is in line with the results of a study (30) which reported that a significant increase in D-dimer in patients with chronic kidney disease stages 3 and 4 was associated with abnormal coagulation and bleeding disorders. Meanwhile, severe pulmonary inflammation will cause activation and damage to pulmonary blood vessels and can trigger pulmonary thrombosis early in the course of the disease (31). Although there was a significant increase in the value of D-dimer in all comorbidities, statistically, it showed that comorbidity did not affect the value of the D-dimer inflammatory marker. The measured value of D-dimer in this study showed an increase of 6 times (average 0 – 0.3 g/mL). Although not showing a significant effect on all comorbidities, COVID-19 patients with significantly elevated D-dimer (cut-off 2.0 g/mL, 4-fold increase) on admission to the hospital still require close monitoring. Therefore, the identification and management of coagulopathy in COVID-19 patients at the time of hospital admission should be considered even if there are no severe symptoms because the increase in D-dimer determines the severity of the disease.

PCT laboratory parameters are often used as biomarkers of sepsis. The value of PCT levels in comorbid chronic renal failure is higher than in other comorbidities in this study. Meanwhile, thyroid comorbidities had relatively normal PCT levels. The high PCT detected in chronic kidney disease is due to organ failure due to sepsis (1). However, of all comorbidities, it did not show a significant effect on the PCT value. However, it is theoretically suggested that PCT is a component of the inflammatory response specific to systemic bacterial infections. The average in this study all increased. Increased PCT in COVID-19 patients may indicate the presence of bacterial coinfection that increases disease severity and the likelihood of sepsis, and the occurrence of cytokine storms (5).

Based on the test of the effect between comorbidities and laboratory results of inflammatory marker parameters from this study, it can recommend to prioritize the examination of CRP inflammatory markers in comorbid COVID-19 patients. Furthermore, clinicians can provide adequate medical measures, especially optimal oxygen therapy, because CRP levels can pathophysiologically cause decreased oxygen saturation, deep vein thrombosis, pulmonary embolism, and death. IL-6 and CRP levels correlate with the development of respiratory failure (32). On the other hand, CRP as a biomarker is considered an acute phase inflammatory response that is easy and inexpensive to measure compared to other inflammatory markers. CRP is also used as a prognostic marker for inflammation (33) and to monitor the development and improvement of COVID-19 patients (34).

Conclusion

Statistical tests showed no significant effect on comorbidity on inflammatory markers D-dimer and PCT laboratory results. Comorbidities significantly affected CRP examination results. In this case, it is necessary to prioritize all comorbid COVID-19 patients to have an early CRP examination to treat rapidly decreasing oxygen saturation, deep vein thrombosis, pulmonary embolism, and death.

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