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Profile of Laboratory Test Value in Confirmed COVID-19 Patients with Comorbid

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ABSTRACT
Comorbid COVID-19 patients are a vulnerable group. This study aims to describe the characteristics of the laboratory values of COVID-19 patients with comorbidities. This type of research is descriptive observational. The population and sample in this study were patients with confirmed COVID19 at the Siloam Hospital Lippo Village as many as 94 patients. Laboratory values analyzed included Hemoglobin (Hb), Leukocytes (WBC), Platelets (PLT), D-dimer, Lactate dehydrogenase (LDH), C-reactive protein (CRP), and Procalcitonin (PCT). Respondent data and laboratory values were analyzed descriptively, in the form of a summary of data for each variable. Respondent data, mostly in the age range of 50-59 years (33%) and male (53.2%). The most common comorbidities were hypertension (29.8%), Diabetes Mellitus and Chronis Cardiac Disease (16%), Chronic Obstructive Pulmonary and Chronic Kidney Disease (8.5%), Autoimmune and Cancer (10.6%) .The results of laboratory values showed that the average values of D-dimer (2.1 μg/mL), Lactate Dehydrogenase (418.45 μL), C-Reactive Protein (39.69 mg/L) and Procalcitonine (1.59 ng/mL) was increased in all comorbidities. Meanwhile, the examination values of leukocytes, platelets and hemoglobin were in normal condition. The results of these laboratory tests can be used as prognostic predictors and risk of mortality in comorbid COVID-19 patients.
Keywords*: covid-19; comorbid; laboratory tests*

ABSTRAK
Pasien COVID-19 dengan komorbid merupakan kelompok yang rentan. Penelitian ini bertujuan untuk mendeskripsikan karakteristik nilai laboratorium pasien COVID-19 dengan komorbid. Jenis penelitian ini adalah deskriptif observasional. Populasi dan sampel dalam penelitian ini adalah pasien yang terkonfirmasi COVID-19 di RS. Siloam Lippo Village sebanyak 94 pasien. Nilai laboratorium yang dianalisa diantaranya Hemoglobin (Hb), Leukosit (WBC), Trombosit (PLT), D-dimer, Lactate dehydrogenase (LDH), C-reactive protein (CRP), dan Procalcitonin (PCT). Data responden dan nilai laboratorium dianalisa secara deskriptif, berupa rangkuman data masing-masing variabel. Data responden, sebagian besar ada pada rentang usia 50-59 tahun (33%) dan berjenis kelamin laki-laki (53,2%). Komorbid paling banyak berturut-turut adalah hipertensi (29,8%), Diabetes mellitus dan Penyakit Jantung Koroner (16%), Penyakit Paru Obstruktif Kronik dan Gagal Ginjal Kronik (8,5%) serta Kanker dengan Autoimun (10,6%). Hasil nilai laboratorium menunjukkan bahwa nilai rata-rata D-

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dimer (2,1 μg/mL), Lactate Dehydrogenase (418,45 μL), C-Reactive Protein (39,69 mg/L) dan Procalcitonine (1,59 ng/mL) meningkat pada semua komorbid. Sedangkan nilai pemeriksaan leukosit, trombosit dan hemoglobin berada dalam kondisi hasil yang normal. Hasil pemeriksaan laboratorium ini selanjutnya dapat digunakan sebagai prediktor prognostik dan risiko mortalitas pada pasien COVID-19 dengan komorbid.
Kata Kunci: covid-19; komorbid; hasil pemeriksaan laboratorium.

INTRODUCTION

Some patients infected with the SARS-CoV-2 virus have severe, potentially life-threatening respiratory symptoms. However, many infected individuals also experience no signs or symptoms, or only mild symptoms. A group of patients who have severe symptoms may experience multi-organ failure whose pathophysiology is due to disturbances in physiological pathways including hemostasis and fibrinolysis (Christensen *et al.*, 2020). Several studies have shown that abnormal laboratory values in hospitalized patients can predict a more severe outcome. Abnormal laboratory values play an important role in helping to classify and assess the patient's prognosis so that they can provide early therapy which is expected to achieve a better outcome. Early identification of patients who are at risk of falling into a critical condition is very important so that it can reduce the number of patients admitted to the intensive care unit (Christensen *et al.*, 2020). Laboratory abnormalities that occur in patients with COVID-19 are a decrease in albumin and lymphocyte count as well as an increase in C-Reactive Protein (CRP), Lactate Dehydrogenase (LDH), ESR, SGOT, SGPT and D-dimer (Lippi and Plebani, 2020).

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It is not known which factors from the combination of laboratory results describe the severity of the risk of death in patients with these comorbidities. Several studies discuss the diagnostic and prognostic value of abnormal laboratory results in COVID-19 patients (Pourbagheri-Sigaroodi *et al.*, 2020). Another study reported on the effect of comorbid disease on the high risk of mortality in COVID-19 patients. Elderly COVID-19 patients with comorbid hypertension, diabetes, heart and lung disease, are more susceptible to infection and have a higher mortality rate than COVID-19 patients without comorbidities (Guan *et al.*, 2020). Most of the existing studies have focused on the clinical symptoms and radiological findings of COVID-19 patients (Fan *et al.*, 2020) as well as the clinical, biological and radiological characteristics of COVID-19 (J. Zhang *et al.*, 2020). Several prognostic factors have been evaluated such as lymphocyte count, lactate dehydrogenase, D-dimer, interleukin 6, procalcitonin, and CRP (Tan *et al.*, 2020). Other researchers discussed the description of the results of laboratory tests in patients with COVID-19 (Mardewi and Yustiani, 2021), but not in COVID-19 patients with comorbidities. It is still unclear what laboratory results can be used as a prognosis in COVID-19 patients, especially those with comorbidities. Data on the results of laboratory tests in COVID-19 patients with comorbidities are needed to help classify and assess the patient's prognosis so that they can provide early therapy which is expected to achieve a better outcome.

METHOD

This research is descriptive observational. The parameters to be analyzed are Hemoglobin (Hb), Leukocytes (WBC), Platelets (PLT), D-dimer, Lactate dehydrogenase (LDH), C-reactive protein (CRP), and Procalcitonin (PCT) in confirmed COVID-19 patients with comorbid factors. Samples were collected from COVID-19 patients at the Siloam Hospital Lippo Village with purposive sampling technique. The number of samples collected was 94 samples. Patient

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samples were examined using the Hematolyzer Sysmex KX-21 N, Hematolyzer Sysmex CS-2100 and Cobas 6000 Analyzer Series. The study was conducted in August-December 2021. Comorbid patients and laboratory results were analyzed descriptively. This research was conducted after obtaining approval from the Health Research Ethics Committee of STIK KESOSI Number: 03/I/8/LPPM_STIK KESOSI/2021.

RESULTS AND DISCUSSION

Table 1. Demographics and Clinical Characteristics

Characteristics	**Sample (N=94)**
Age (Year), n (%)	
20 – 29	4 (4.3)
30 – 39	16 (17.0)
40 – 49	17 (8.1)
50 – 59	31 (33.0)
60 – 69	15 (16.0)
70 – 79	11 (11.7)
Sex, n (%)	
Female	44 (46.8)
Male	36.8 (53.2)
Comorbidities, n (%)	
Hypertension (HP)	28 (29.8)
Diabetes Mellitus (DM)	15 (16)
Chronic Cardiac Disease (CH)	15 (16)
Chronic Obstructive Pulmonary (LO)	8 (8,5)
Chronic Kidney Disease (KD)	8 (8.5)
Cancer (CA)	10 (10.6)
Autoimmune (AU)	10 (10.6)
Parameters Laboratory (mean ± SD)	
Hemoglobin (Hb) (g/dL)	12.96 ± 1.88
Leukocyte (WBC) (10^3/µL)	7.93 ± 3.82
Platelet (PLT) (10^3/µL)	252.47 ± 103.54
D-dimer (µg/mL)	2.15 ± 2.38
Lactate Dehydrogenase (LDH) (µL)	418.45 ± 178.08
C-Reactive Protein (CRP) (mg/L)	39.69 ± 58.09
Procalcitonin (PCT) (ng/mL)	1.59 ± 1.83

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Most of the samples in this study were in the age range of 50 - 59 years (33.0%) and at least were in the age range of 20 - 29 years (4.3%) and gender was dominated by men (36.8%). It is known that men are 28% more at risk of infection than women. Comparable to the relationship between sex and mortality, which shows that men are 1.86% more at risk of dying than women (Susilo *et al.,* 2020). Men are known to have higher ACE2 expression, this is related to sex hormones that cause men to be more at risk for infection with SARS-CoV-2. ACE2 expression is encoded by a gene found on the X chromosome, women are heterozygous while men are homozygous, so it has the potential to increase ACE2 expressor. SARS-CoV-2 infection and several other clinical symptoms can be neutralized because women carry a heterozygous X allele called sexual dimorphism (Gemmati *et al.*, 2020). Meanwhile, women are more protected from exposure to COVID-19 because women have an X chromosome and sex hormones such as progesterone which play an important role in innate and adaptive immunity. Other studies suggest that men and women have the same risk of being infected with SARS-CoV-2. Men infected with SARS-CoV-2 are more at risk for worsening and even death. The number of deaths in men is 2,4 times that of women. Previous studies have suggested that this is related to the expression of ACE2 receptors. Elevated ACE2 receptor expression correlates with the presence of organ failure. Circulating ACE2 levels are higher in men than women and in patients with diabetes and cardiovascular disease (Shang *et al.*, 2020).

The X chromosome and female sex hormones are said to play a major role in the innate (natural/nonspecific) immune response and the adaptive (specific) immune response in the pathogenesis of infectious diseases (Klein and Flanagan, 2016). Examples of components of innate immunity are phagocytic cells (monocytes, macrophages, neutrophils) which hereditary have a number of antimicrobial peptides and proteins capable of killing various pathogens. Adaptive immune response will increase after exposure to a pathogen. Lymphocytes (T cells and B cells) are basic components that play an important role in specific adaptive immune responses. Two important differences between the innate and adaptive immune responses are that the adaptive immune response is more specific for a particular pathogen/antigen and increases with each subsequent exposure to the same antigen.

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However, they cooperate at several stages (e.g., by releasing cytokine stimulus factors) to destroy the invading antigen. Sex chromosomes in humans are genomic structures that differentiate between males and females at the chromosomal level. The system of sex differentiation based on X and Y chromosomes applies to humans, in which women have two X chromosomes (XX) and men have one X chromosome and one Y chromosome (XY) (Schurz *et al.*, 2019). The two X chromosomes possessed by women strengthen the immune system, even though one of the X chromosomes may be inactive. The immune system is regulated by the X-coded gene on the chromosome, causing women to have higher CD4+ T cells, so they are less prone to inflammation and are less prone to viral infections. The production of inflammatory IL-6 in women after viral infection is lower than in men and this is related to the ability to survive in women. Women produce higher levels of antibodies and these antibodies last longer in the circulation than men (Conti and Younes, 2020). Other researchers say that men tend to be easily exposed to COVID-19 because most of their activities are outside the home for work or other activities (Hidayati, 2020).

From all comorbid data, hypertension is the most (29.8%), followed by Diabetes mellitus and Chronic Cardiac Disease (16%), Chronic Obstructive Pulmonary Disease and Chronic Kidney Disease (8.5%) and Comorbid Cancer and Autoimmune (10.6%). Case group analysis linking gender with the risk of COVID-19 infection. Indeed, there are no research results that confirm the definite link between hypertension and the severity of COVID-19 (Yang *et al.*, 2020). However, in general, the severity of COVID-19 will be easier for people with hypertension, which are generally associated with complications of other health problems and old age factors, making it difficult to separate the influence of each factor. Diabetes Mellitus is a disease of carbohydrate metabolism disorders caused by the failure of the pancreas gland to produce the hormone insulin. This condition causes high blood sugar levels and if it lasts chronically or for a long time it can cause a decrease in the function of white blood cells or leukocytes. As a result, the immune system will decrease so that individuals will be more susceptible to infection due to the entry of microorganisms including viruses (Smeltzer and Bare, 2017). This result is the same as other reports or studies, namely from (Karyono and Wicaksana, 2020)which states that Diabetes Mellitus is the second most common comorbid

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COVID-19 factor in Indonesia. Likewise, the results of a study in Malaysia, showed that the comorbid factor of COVID-19 was that almost 25% of treated cases had at least one comorbid chronic disease such as Diabetes Mellitus with a rate of 578 (9.8%) (Sim *et al.*, 2020). Coronary cardiac disease is a cardiovascular disease that also has a higher risk of experiencing more severe manifestations if infected with COVID-19 because it is thought to be associated with increased ACE2 expression in this group compared to patients without cardiovascular comorbidities (Gemmati *et al.*, 2020)

Comorbid Chronic Obstructive Pulmonary and Chronic Kidney Failure in this study were listed at the last order with a small number. According to the pathology of COVID-19 disease, the corona virus first infects the respiratory tract, so if there is interference in the respiratory tract, then the possibility of more severe COVID-19 symptoms is very possible (Karyono and Wicaksana, 2020). Kidney failure patients who experience COVID-19, can experience worse or more severe symptoms and tend to increase the risk of mortality, especially if they are in moderate to severe conditions when they enter the hospital (Henry and Lippi, 2020). This finding was also obtained in the study by Williamson et al, where individuals with Stage 4-5 Chronic Renal Failure had an increased risk of death by 2.52 (2.33 - 2.72) times. The process of the COVID-19 disease course generally involves the release of inflammatory cytokines and the formation of antigen-antibody complexes that will affect cell membrane permeability. However, in patients with Chronic Kidney Failure, the glomerular filtration process has worsened, so that systemic inflammation due to COVID-19 can worsen kidney function. In addition, due to the presence of ACE2 receptors in the urogenital system, the COVID-19 virus can also easily stimulate the inflammatory process in the kidneys which will worsen the patient's condition (Williamson *et al.*, 2020).

Based on the analysis of laboratory tests, it is known that the average value increased in all comorbidities in the D-dimer test (2.1 g/ml), Lactate Dehydrogenase (LDH) (418.45 L), C-Reactive Protein (CRP) (39.69 mg/L) and Procalcitonin (PCT) (1.59 mg). /ml) (Table 1). The results of this analysis are in line with the findings (Mardani *et al.*, 2020) which stated that several laboratory parameters, namely ALT, CRP, NEU, LDH and Urea increased. The LDH value is also known to increase

significantly (Chen *et al.*, 2020). The values of CRP and D-dimer are also known to increase, but the PCT is in normal values (Mardewi and Yustiani, 2021). D-dimer, CRP and PCT values of COVID-19 patients are known to be elevated in severe patients (J. jin Zhang et al., 2020). All comorbid COVID-19 patients show an increase in CRP values in the early phase of infection (Fachri *et al.*, 2022).

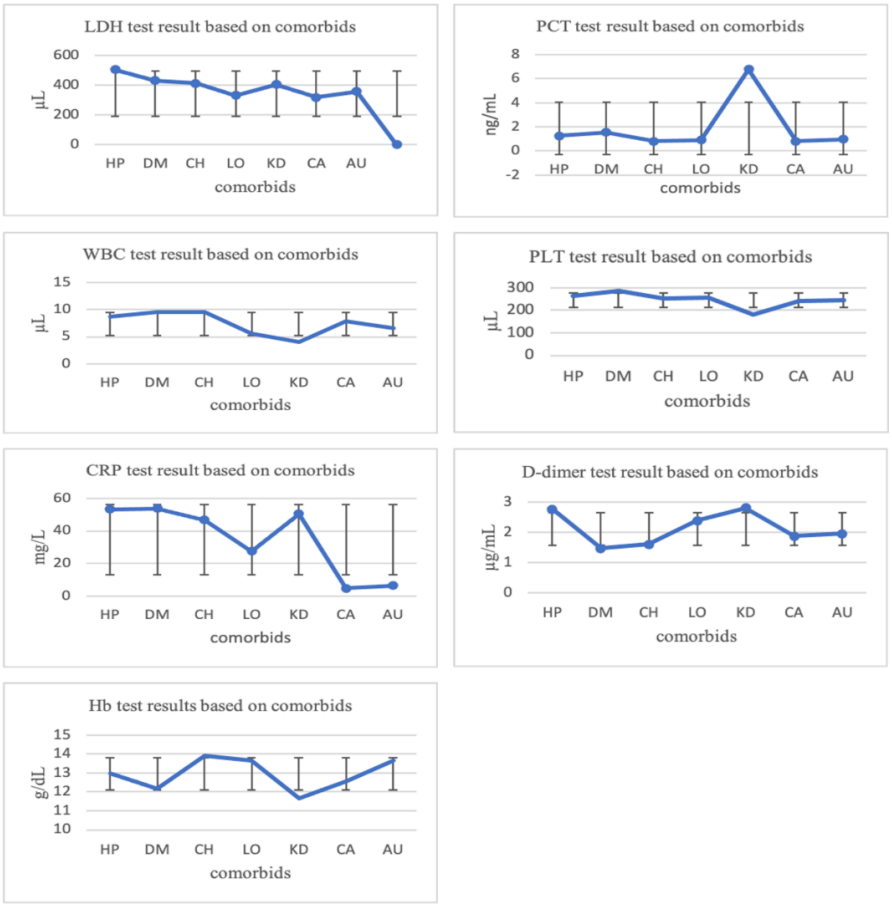

Figure 1. Laboratory Test Results Based on Comorbid

Picture shows the results of several laboratory parameters; Hb (Hemoglobin), WBC (White blood cell), PLT (Platelet), LDH (Lactate Dehydrogenase), CRP (C-reactive protein), PCT (Procalcitonin) with comorbid factors, HP (Hypertension), DM (Diabetes Mellitus), CH (Chronics Cardiac Disease), LO (Chronics Obstructive Pulmonary Disease), KD (Chronic Kidney Disease), CA (Cancer), AU (Autoimmune).

Platelet (PLT) and C-Reactive Protein (CRP) values in comorbid Diabetes mellitus (DM) were higher than other comorbidities. These results are in line with research that there is a significant relationship between D-dimer and CRP levels with diabetes, CRP and D-dimer are used as predictors of mortality in COVID-19 patients with diabetes (Miri *et al.*, 2021). Platelet values in diabetes mellitus which

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were higher than other comorbidities in this study were still in the normal range, the same as those obtained in the results of the study (Mardewi and Yustiani, 2021). However, in general, platelet values are decreased in COVID-19 patients (Guan *et al.*, 2020) and are associated with increased D-dimer values. Elevated D-dimer is associated with thrombocytopenia conditions (Terpos *et al.*, 2020). While the value of Lactate Dehydrogenase (LDH) is known to be higher in hypertension comorbid than other comorbidities. LDH values are positively correlated with carotid artery intima-media thickness, which is considered a predictor of atherosclerotic disease (Cai *et al.*, 2021). Hypertension can occur due to chronic atherosclerosis (Suhatri *et al.*, 2014). Meanwhile, D-dimer and procalcitonin (PCT) were higher in comorbid Chronic Kidney Disease. PCT levels in COVID-19 patients indicate the presence of bacterial coinfection that can increase disease severity and the likelihood of sepsis and cytokine storm. Measurement of serum PCT levels is useful as a marker of severe systemic inflammation, infection and sepsis (Becker, Snider and Nylen, 2008). PCT levels correlate with acute renal failure conditions (Wang, He and Kang, 2021). COVID-19 patients with severe symptoms have significant laboratory abnormalities including lymphocytopenia, leukopenia, neutrophilia, prolongation of prothrombin time, elevated levels of CRP (C-Reactive Protein), D-dimer, Albumin, LDH (Lactate Dehydrogenase) and PCT (Procalcitonin) (Liu *et al.*, 2020).

Table 2. Overview of laboratory test results of several comorbidities

Parameters	HP	DM	CH	LO	KD	CA	AU
Hb 13,2 – 17,3 g/dl	↔	↔	↔	↔	↓	↔	↔
WBC 3,8 – 10,6$^{10\wedge3}$/µL	↔	↔	↔	↔	↔	↔	↔
PLT 150 – 440$^{10\wedge3}$/µL	↔	↔	↔	↔	↔	↔	↔
LDH 135 – 215 µL	↑	↑	↑	↑	↑	↑	↑
CRP 0,0 – 6.0 mg/L	↑	↑	↑	↑	↑	↔	↑
PCT <0,5 ng/mL)	↑	↑	↑	↑	↑	↑	↑
D-dimer 0,0 – 0,3 µg/mL	↑	↑	↑	↑	↑	↑	↑

Tables shows overview laboratory test result in several comorbidities; ↔ normal; ↓ decreased; ↑ increased

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In this study, for examination of hemoglobin, platelets and leukocytes, the average results were still within normal limits (↔). Meanwhile, the results of the LDH, PCT, D-dimer, and CRP tests for all comorbidities showed increased results (↑). Hemoglobin in COVID-19 patients is within normal limits in cases with severe symptoms, as well as leukocytes and platelets (Nabila, Puspitasari and Erwinayanti, 2020). Hemoglobin levels in COVID-19 patients are known to have no effect on cases of mild, moderate, or severe symptoms (Ding *et al.*, 2020). The leukocyte values in COVID-19 patients who were admitted to the ICU or not admitted to the ICU had normal leukocyte levels. Leukocyte levels were also found to be normal in the condition of patients with mild, moderate, severe and critical conditions (H. Zhang *et al.*, 2020). This increase in laboratory values can be used as a predictor or biomarker in assessing the outcome of comorbid COVID-19 patients.

CONCLUSION

The most COVID-19 patients in this study had comorbid hypertension. The results of the examination of LDH, PCT, D-dimer, and CRP for all comorbidities showed improved results. These results can then be used as predictors or biomarkers in assessing the outcome of comorbid COVID-19 patients. but it is necessary to study further among the parameters of the laboratory results, which parameters are more influential to be used as biomarkers in assessing the prognosis of COVID-19 patients with comorbidities.

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