IJSCIA

International Journal of Scientific Advances
ISSN: 2708-7972
Volume: 4 | Issue: 2 | Mar – Apr 2023 Available Online: www.ijscia.com
DOI: 10.51542/ijscia.v4i2.16

Comorbid Diseases, Decreased PaO_2/FiO_2 Ratio, Increased Ferritin, Decreased Liver and Kidney Function as Risk Factors for Mortality in COVID-19 Patients

Yorike Elizabeth Latuheru, Ida Bagus Ngurah Rai, I Gede Ketut Sajinadiyasa, Ni Wayan Candrawati, Ida Ayu Jasminarti Dwi Kusumawardani, Ni Luh Putu Eka Arisanti, and I Gusti Ngurah Bagus Artana

Department of Pulmonology and Respiratory Medicine Faculty of Medicine Udayana University/Prof IGNG Ngoerah General Hospital, Denpasar, Indonesia, 80114

E-mail: elizabethyorike18@gmail.com; idabagus_ngurahrai@unud.ac.id; sajinadiyasa@unud.ac.id; niwayancandrawati@gmail.com; iajasminarti@unud.ac.id dr.eka.arisanti@gmail.com; ignb_artana@unud.ac.id

*Corresponding author details: I Gede Ketut Sajinadiyasa; sajinadiyasa@unud.ac.id

ABSTRACT

Background: Comorbid disease, a ratio of partial pressure of oxygen (PaO2) to a fraction of inspired oxygen (FiO2) (P/F ratio), ferritin serum, liver function, and kidney function correlate with mortality; hence, these factors are suggested as the prognostic markers in COVID -19. This study aims to analyze comorbid diseases, decreased PaO2/FiO2 ratio, increased ferritin, and decreased liver and kidney function as risk factors for mortality in COVID-19 patients. ***Methods:*** An analytic observational study with a match case-control design. Analysis was performed univariate, bivariate with the chi-squared test, and multivariate analysis using binary logistic regression analysis. ***Results:*** The subjects of the study were 220 people. The comorbid disease and the mortality of COVID-19 patients (p=0.038, OR=2.737, 95% CI 1.020 to 7.342), PaO2/FiO2 ratio to COVID-19 patient mortality (p=0.000, OR=43.1 95% CI 19.461 to 95.478), ferritin serum levels to COVID-19 patient mortality (p=0.000, OR=53.3, 95% CI 21.014 to 135.110), decreased liver function to COVID-19 patient mortality (p=0.000, OR=62.4 95% CI 25.323 to 153.567), decreased kidney function to COVID-19 patient mortality (p=0.000, OR=1389.7 95% CI 170.8 to 11307.2). The most dominant variable related to the death of COVID-19 patients is the decreased kidney function with an OR value of 722.447 (95% CI 33.356 to 15647.243). ***Conclusion:*** Risk factors of mortality of COVID-19 patients are comorbid disease, decrease in PaO2/FiO2 ratio, increase in ferritin, decrease in liver function, and decrease in kidney function. Of all these, the most dominant risk factor related to the highest mortality rate among COVID-19 patients is the decrease in kidney function.

Keywords: COVID-19; mortality; risk factors; comorbid disease; PaO2/FiO2 ratio; ferritin; liver function; renal function.

INTRODUCTION

COVID-19 infection causes disturbances in the lung organs that affect the respiratory tract, which causes pneumonia and acute respiratory failure.[1]Morbidity and death related to COVID-19 are due to complications primarily ARDS, which occurs in up to 15% of cases.[2,3]The ratio of partial pressure of oxygen (PaO_2) to a fraction of inspired oxygen (FiO_2) (P/F ratio), is currently used to assess the severity of respiratory failure in patients with ARDS and correlates with mortality.[2,4,5] The P/F ratio was recently proposed as a prognostic marker in COVID-19.[6]

In one study from China with twenty cases of COVID-19, it was found that individuals with severe disease often presented with elevated serum ferritin levels, with statistically significant differences between the severe and mild categories.

Whereas another study using records from a large New York City multi-hospital healthcare system showed poor performance of serum ferritin for mortality prediction.[7,8]

Liver damage has been reported as a common manifestation, with impaired liver function tests (LFTs) ranging from 14 to 75%. Previous studies have reported the prevalence of abnormal liver function parameters in patients with COVID-19, especially alanine aminotransferase (ALT) (12.9-41.6%) and aspartate aminotransferase (AST) (18.2-66.9%). Furthermore, several studies have reported abnormal liver function parameters to be associated with clinical outcomes of patients with COVID-19, including longer hospitalization, higher risk for severe COVID-19, and death.[9,10]

Kidneys are the main target organs of SARS-CoV-2, so damage to kidney function exacerbates damage to other organs. Older age, severe pneumonia, and pre-existing cardiovascular and kidney disease are potential risk factors for acute kidney failure in people with COVID-19.[11]Several studies have been conducted to prove that kidney disease has a relationship with the risk of death in patients infected with COVID-19. Factors associated with kidney disease, especially acute kidney failure were analyzed in hospitalized patients to identify the potential high risk of developing this disease so that intensive care can be given promptly to reduce mortality. One of the studies that have been carried out is a retrospective observational study with the result that reduced kidney function (OR 1.74; 95% CI: 1.35, 2.24) has a significantly higher risk of death in patients with COVID-19.[12]

In the current pandemic conditions, the focus of scientific efforts is to develop optimal therapeutic modalities to combat the virus, in addition to this, research is expected to predict disease progression, and to identify high-risk patients in the early stages of infection. This can optimize management objectives, and address the shortage of medical and material resources, especially evident amid this global emergency.[13,14] Based on this, the authors wanted to analyze a study of comorbid diseases, reduced PaO_2/FiO_2 ratios, increased ferritin levels, and decreased liver and kidney function as risk factors for mortality in COVID-19 patients to improve patient outcomes with COVID-19.

METHOD

This research is an analytic observational study with a match case-control design. This research started with 2 groups of research subjects according to the dependent variable category. The case group was COVID-19 patients who were discharged from the hospital dead, while the control group was COVID-19 patients who were discharged from the hospital alive.

The independent variables were then traced to each group at the time of first hospital admission with COVID-19. The research sample was COVID-19 patients who died or recovered and were treated in the isolation room at Prof. Hospital. Dr. IGNG Ngoerah Hospital for the period January 2021 to December 2021 which meets the inclusion criteria. The selection of case samples was carried out through random sampling until the number of samples was fulfilled while the selection of control samples was carried out by purposive sampling.

Inclusion criteria namely COVID-19 patients aged 18 years or older and patients confirmed positive for PCR SARS-CoV-2 who are being treated in the isolation room of Prof. Dr. IGNG Ngoerah Hospital who died/recovered while leaving the hospital. Exclusion criteria**:** 1) Incomplete medical records, 2) COVID-19 patients with blood disorders such as leukemia, blood clotting disorders, and iron deficiency anemia, 3) Patients with chronic liver disease and stage 4 and 5 kidney disorders. Univariate analysis was performed, then continued with bivariate analysis using the chi-squared test, and multivariate analysis using binary logistic regression analysis. Drawing conclusions based on the 95% confidence interval and the P value at the α limit of 0.05. The whole process of data analysis above uses the help of SPSS 25 statistical software.

RESULTS

This research was conducted from July 2022 to December 2022, using a sample of 220 subjects consisting of 110 subjects who were COVID-19 patients who died (cases) and 110 subjects who died (controls). The patient met the predefined inclusion and exclusion criteria. To reduce research bias, there are 2 controlled variables, namely age, and gender. The characteristics of the data are obtained in Table 1.

TABLE 1: Characteristics of the research sample.

characteristics	Case n(%) 110	control n(%) 110	p.s
Age			
< 60 years	65 (59.1)	63 (57.3)	0.785
≥60 years	45 (40.9)	47 (42.7)	
Gender			
Man	71 (64.5)	71 (64.5)	1,000
Woman	39 (35.5)	39 (35.5)	
Comorbid			
Cardiovascular disease	5 (4.5)	2 (1,8)	
Kidney illness	7 (6)	2 (1,8)	
DM	9 (8)	7 (6)	
HT	6 (5,5)	14 (13)	
COPD	3 (3)	1 (1)	
Strokes	3 (3)	0	0.172
Kidney disease, stroke	1 (1)	0	
DM, kidney disease	2 (1,8)	0	
DM, HT	4 (3,6)	5 (4.5)	
HT, Cardiovascular disease	2 (1,8)	1 (1)	
HT, kidney disease	2 (1,8)	0	
COPD, kidney disease	2 (1,8)	0	
DM, HT, kidney disease	2 (1,8)	0	
Comorbid disease			
No comorbid disease	62 (56.4)	78 (70.9)	0.038
1 comorbid disease	33 (30)	26 (23.6)	
>1 comorbid disease	15 (13,6)	6 (5,5)	

characteristics	Case n(%) 110	control n(%) 110	p.s
PaO_2/FiO_2 ratio			
Normal	11 (10)	91 (82.7)	0.000
Decrease	99 (90)	19 (17,3)	
Serum Ferritin level			
Normal	6 (5,5)	83 (75.5)	0.000
Increase	104 (94.5)	27 (24.5)	
Liver function			
Normal	7 (6,4)	89 (80.9)	0.000
Decrease	103 (93.6)	21 (19,1)	
Kidney function			
Normal	1 (0.9)	102 (92.7)	0.000
Decrease	109 (99.1)	8 (7,3)	

Comorbid disease variables were categorized into 3 categories, namely no comorbid disease, 1 comorbid disease, and more than 1 comorbid disease. The results of this analysis are listed in Table 2.

TABLE 2: Relationship between comorbid disease with COVID-19 Patient Mortality.

Variable		COVID-19 Mortality		p-value
		Die	Life	
Comorbid disease	More than 1 comorbid disease	15 (13.6%)	6 (5.5%)	0.038
	1 Comorbid Disease	33 (30%)	26 (23.6%)	
	There are no comorbid diseases	62 (56.4%)	78 (70.9%)	

From the chi-square analysis, the value of p=0.038so that it can be concluded that there is a statistically significant relationship between comorbid diseases and mortality in COVID-19 patients. Results of bivariate analysis between PaO_2/FiO_2 ratio with COVID-19 Patient Mortality are listed in Table 3.

TABLE 3: Relationship between PaO_2/FiO_2 ratio with COVID-19 Patient Mortality.

Variable		COVID-19 mortality		OR	CI 95%	p-value
		Die	Life			
Ratio PaO_2/FiO_2	Decrease	99 (90%)	19 (17.3%)	43,1	19,461-95,478	0.000
	Normal	11 (10%)	91 (82.7%)			

From the chi-square analysis, the value of p=0.000, it can be concluded that there is a statistically significant relationship between PaO2/FiO2 ratio with COVID-19 Patient Mortality. In the odds ratio analysis, the results show that decreased PaO_2/FiO_2 ratio has risk43,1 times greater for the result dies than a normal PaO_2/FiO_2 ratio (95% CI19,461-95,478).

The results of the analysis of the relationship between serum ferritin levels with COVID-19 Patient Mortality are listed in Table 4.

TABLE 4: Relationship between serum Ferritin level with COVID-19 Patient Mortality.

Variable		COIVD-19 mortality		OR	CI 95%	p-value
		Die	Life			
Serum Ferritin level	Increase	104 (94.5%)	27 (24.5%)	53,3	21.014-135.110	0.000
	Normal	83 (75.5%)	83 (75.5%)			

From the chi-square analysis, the value of p=0.000 so can be concluded that there is a statistically significant relationship between serum ferritin level with the mortality of COVID-19 patients. In the odds ratio analysis, it was found that elevated serum ferritin levels had a 53.3 times greater risk of death than patients with normal serum ferritin levels (95% CI).21.014-135.110).

The relationship between decreased liver function and COVID-19 patient mortality is listed in Table 5.

TABLE 5: Relationship between Decreased Liver Function and Mortality of COVID-19 Patients.

Variable		COIVD-19 mortality		OR	CI 95%	p-value
		Die	Life			
Liver function	Decrease	103 (93.6%)	21 (19.1%)	62,4	25,323-153,567	0.000
	Normal	7 (6.4%)	89 (80.9%)			

From the chi-square analysis, the value of p=0.000so it can be concluded that there is a statistically significant relationship between a decreased liver function with mortality in COVID-19 patients. In the odds ratio analysis, the results showed that patients who experienced decreased liver function were at risk 62,4 times greater for the outcome of death when compared with patients with normal liver function (95% CI).25,323-153,567).

The relationship between decreased kidney function and COVID-19 patient mortality is listed in Table 6.

TABLE 6: Relationship between Decreased Kidney Function and Mortality of COVID-19 Patients.

Variable		COIVD-19 mortality		OR	CI 95%	p-value
		Die	Life			
Kidney Function	Decrease	109 (99.1%)	8 (7.3%)	1389,2	170.8-11307.2	0.000
	Normal	1 (0.9%)	102 (92.7%)			

From the chi-square analysis, the value of p=0.000so it can be concluded that there is a statistically significant relationship between decreased kidney function with COVID-19 patient mortality. In the odds ratio analysis, the results showed that patients who experienced decreased kidney function were at risk 1389,2 times greater for the outcome of death when compared with patients with normal renal function (95% CI).170.8-11307.2).

The multivariate analysis aims to assess or prove the strong relationship between each independent variable as a risk factor for mortality in COVID-19 patients. The analysis used is binary logistic regression analysis with the enter method. The results of the multivariate analysis are presented in Table 7.

TABLE 7: The results of multivariate analysis of binary logistic regression of comorbid disease variables, PaO_2/FiO_2 ratio, liver function and kidney function on the mortality of COVID-19 patients.

Variable	Exp (B)	CI 95%	p-value*
Comorbid Diseases	28,968	1,371-612,133	0.031
PaO2/FiO2 ratio	9,466	1.020-87.883	0.048
Ferritin levels	36,698	2,485-541,86	0.009
Liver function	39,385	2,617-592,831	0.008
Kidney Function	722,447	33,356-15647,243	0.000

Based on the results of multivariate analysis, it was found that comorbid diseases, PaO2/FiO2 Ratio, ferritin levels, liver function and kidney function, are predictors that are independently associated with mortality in COVID-19 patients.

The most dominant variable associated with death in COVID-19 patients is a decrease in kidney function with an OR value722,447(95% CI33,356-15647,243) means that patients with reduced kidney function have a risk of 722 times experiencing death compared to patients with normal kidney function.

DISCUSSION

In this study, we found age-old COVID-19 patients≥60 years old were 45 subjects in the case group and 47 subjects in the control group, with the sexes being mostly male compared to female. The older a person is, the more susceptible they are to be infected with COVID-19. Although the exact mechanism is not yet clear, several hypotheses have been proposed namely; First, elderly patients may experience age-related dysfunction with decreased production of T and B lymphocytes where these T lymphocytes and B lymphocytes are an important component of the adaptive immune response to emerging infections so that elderly patients are vulnerable to infections including COVID-19 infection.[15] Secondly, older people may have an increased risk of exposure to COVID-19, this is related to problems with access to health services, and fewer opportunities to receive breathing apparatus due to limited resources[16]; Thirdly, elderly people usually have comorbid conditions that are related to disease severity and mortality in COVID-19.[8] A previous study in China identified that COVID-19 mostly infects elderly people because their immune system has been reduced as a result of the aging process and most of the elderly have multi-morbidities that make them more susceptible to COVID-19 infection.[17]In Indonesia, the percentage of elderly patients with COVID-19 is 15%, however, the mortality rate for elderly people in Indonesia with COVID-19 is the highest compared to other age groups.[18]

Based on gender characteristics, it was found that in this study there were more males sex, namely, 71 people (64.5%) compared to women who died due to COVID-19 infection, this previous research was conducted at Prof. Dr IGNG Ngoerah Denpasar, there were more males, namely 63 people (70%) compared to 27 women (30%) in patients with a severe degree of COVID-19.[19]

A study in China also found that COVID-19 cases with a high fatality rate were more male in 653 samples (2.84%) compared to women who only accounted for 1.71% of cases.[20]

The exact mechanism of why there are more deaths from COVID-19 in males is still unknown, several hypotheses have been proposed to explain the gender gap, namely; The X chromosome encodes the receptor for angiotensin-converting enzyme 2 (ACE2), which is a mediator for the entry of SARS-CoV-2 into human cells.[21] Men and women have different immune responses to COVID-19 due to the presence of sex chromosomes (XY in males, XX in females), hormones (androgens, estrogens), and regulatory genes related to the immune system.[22]The X chromosome encodes the largest number of immunity-related genes in the human genome, because women carry two copies of the X chromosome, they may have greater resistance to viral pathogens, in addition, women have more estrogen receptors that protect the body and help the immune system, including T cells, B cells, macrophages, neutrophils, dendritic cells, and natural killer cells[23]Different socioeconomic behaviours and lifestyles such as smoking, alcohol consumption and personal hygiene may also play a role in gender differences in vulnerability to COVID-19 infection.[24]

In this study, the most common comorbid was hypertension in 20 samples (18.5%), and 21 (19.1%) samples had more than 1 comorbid. Statistically, there is a significant relationship between comorbid diseases and mortality in COVID-19 patients at Prof. Dr IGNG Ngoerah Hospital (p = 0.038). From the multivariate analysis, a history of comorbid illnesses was also consistently a predictor that was independently related to the mortality of COVID-19 patients. (p=0.031). This is to a study conducted by Khedr et al which stated that the number of comorbidities showed a significantly higher risk of becoming a more severe disease or even death compared to those who did not have comorbidities. In the sample with two comorbidities, OR 2.6 (95% CI. 1.4-4.7), whereas those with 3 or more comorbid OR 2,[25]Research at Prof. Dr IGNG Ngoerah Hospital in 2021 found that more severe COVID-19 patients had heart comorbidities (21% vs 6% ; p = 0.022) and kidney disease (17% vs 9% ; p = 0.037) compared to mild-moderate COVID-19.[19]

Other studies also state that hypertension, diabetes, and cardiovascular disease are the most common comorbidities.[26]Studies have shown that diabetes can activate CD4+ cell differentiation with Th1 and Th2 cells and cause Th17 and Treg cell dysfunction, which impairs the balance of pro-inflammatory and anti-inflammatory and induces inflammatory cytokines. IL-2, IL-6 and TNF concentrationsαsignificantly higher in the diabetic group than in the non-diabetic group, also with a higher mortality rate.[20]which may be due to decreased pulmonary function, excessive immune inflammation and aggressive glycosylation. Diabetic-induced aggressive glycosylation is thought to be related to immunoglobulin dysfunction and leads to susceptibility to COVID-19 and impaired viral clearance.[27]

Angiotensin II (Ang II), closely related to hypertension, is increased in patients with COVID-19 compared to healthy controls.[28]Ang II activates p44/42MAPK, p38MAPK, NF-κB and c-Jun pathway by increasing the expression of LOX-1 (such as ox-LDL receptor lectins), type 1 and type 2 Ang II receptors, which in turn increase the expression of proinflammatory genes, such as IL-6, IL-10 and TNF-α, and contribute to the severity of the cytokine storm.[29]

Research by Guan et al states that patients with comorbidities have a more severe degree of severity than patients without comorbidities. In addition, the more comorbidities a patient has, the more severe the degree of COVID-19 will be and this will lead to a high mortality rate.[30]

The mechanism of death is still being studied and of course, also depends on the type of comorbidity the patient has, but there have been several analyzes of the relationship between death and comorbidity, namely; the first, due to the invasion of SARS-CoV-2 into the central nervous system so that patients with severe degrees are more likely to develop neurological manifestations, especially acute cerebrovascular disease.[31] Second, the link between diabetes and COVID-19 may involve ACE2 and dipeptidyl peptidase-4, two human proteins that are important in the biological pathways of both diseases.[32] Third, cardiovascular disease increases the risk of in-hospital death in COVID-19, which may be mediated by ACE2-dependent myocardial infection or high inflammatory burden that can induce vascular inflammation, myocarditis, and cardiac arrhythmias so overall, comorbidity may be related to severity. and death of COVID-19 patients.[33,34]

Most of the samples that died in this study experienced a decrease in the ratio of PaO_2/FiO_2 by 99 samples (90%). This is to a study by the COVID-UPO Clinical Team and Sainaghi in Italy, which found a significantly lower P/F ratio in non-survivor patients compared to survivors (246 [184-300] vs 126 [100-202], p< 0.001).[35]

From the statistical analysis in this study, it was found that patients who experienced a decrease in the ratio of PaO_2/FiO_2 increased the risk of mortality by 43.1 times (95% CI 19.461-95.478; p <0.001). This is consistent with a study by Izcovich A, et al of 1887 patients showing an increase in mortality of 20.3% in patients with a low PaO_2/FiO_2 ratio (odd ratio 21.17, 95% CI 4.9-91.3).[36]An observational study by Feiner found that the PaO_2/FiO_2 variable < 300 was a predictor for COVID-19 patients who had a high risk of mortality (OR: 3.437, 95% CI 1.38-8.56).[37]

By using the PaO_2/FiO_2 ratio we can estimate the degree of hypoxemia in COVID-19 patients, and the lower the ratio means the more severe the patient's condition. The study conducted by Sartini et al showed that the lower the PaO_2/FiO_2 ratio, the higher the need for CPAP use, mechanical ventilation, the mortality rate (p <0.001) and duration of hospitalization (p <0.02).[38]Other studies have also stated that the PaO_2/FiO_2 ratio is correlated with mortality, so the PaO_2/FiO_2 ratio is proposed as a prognostic marker in Covid-19.[4,6]

In COVID-19, inflammation and edema in the alveoli are the main causes of hypoxemia in the early stages of the disease, so the P/F ratio is quite related to the severity of decreased diffusion which is characterized by hypoxemia and a decrease in the PaO_2/FiO_2 ratio. In the development of COVID-19 disease (consolidation phase), intrapulmonary shunt occurs and causes early arterial hypoxaemia which is mainly caused by ventilation/perfusion imbalance and persistent pulmonary blood flow to unventilated alveoli, and there can be a relative failure of pulmonary vasoconstriction. This can develop into a state of ARDS, where ARDS is an acute condition characterized by hypoxemic respiratory failure and the presence of bilateral pulmonary infiltrates on radiological examination.[39]

A total of 131 samples experienced increased levels of ferritin, and as many as 104 samples (94.5%) of these samples experienced death. Deng et al (2021) stated that the amount of ferritin was significantly higher in the critical group compared to the moderate and severe groups. Notably, the high ferritin group was associated with a higher incidence of death, with an adjusted odds ratio of 104.97 [95% confidence interval (CI) 2.63–4185.89; p = 0.013].[40]In this study, samples with increased ferritin levels had a 53.3 times greater risk of death compared to samples with normal ferritin levels (95% CI 21.014-135.110; p = 0.000.

Active ferritin production can occur during inflammatory disease. Macrophages, which produce cytokines and are responsible for most of the immune cells in the lung parenchyma, may be responsible for serum ferritin secretion. In addition, ferritin synthesis can be induced by several inflammatory stimuli including cytokines, such as IL-6. High concentrations of IL-6 in COVID-19 patients have been correlated with disease severity. A complex feedback mechanism between ferritin and cytokines in the control of pro-inflammatory and anti-inflammatory mediators may exist because cytokines can induce the expression of ferritin, but ferritin can induce the expression of pro- and anti-inflammatory cytokines as well.[7,41,42] Ahmed et al (2021) found that out of 336 patients who tested positive for COVID-19 during the duration of the study, there was a statistically significant difference in ferritin found in the two categories based on severity and mortality. Binary logistic regression showed ferritin to be an independent predictor of all-cause mortality supplemented by an AUC of 0.69 on ROC analysis.[43]

Laboratory findings in patients with severe COVID-19 show data consistent with a cytokine storm that involves elevated inflammatory markers, including ferritin and has been associated with a critical and life-threatening illness.[42,44,45] So it was concluded that serum ferritin concentration is a promising predictor of death in COVID-19 cases.

Most of the COVID-19 patients who died as many as 103 samples (93.6%) had decreased liver function. From the statistical analysis, it was found that the risk of death increased by 62.4 times in samples with decreased liver function (95% CI, 25.323-153.567). This is to previous research data which states that patients with severe COVID-19 have a higher rate of liver dysfunction. In a study by Xu W, et al, an increase in AST was observed in eight (62%) of 13 patients in the intensive care unit (ICU) compared to seven (25%) of 28 patients who did not require ICU treatment.[9] Moreover, in a large cohort including 1099 patients from 552 hospitals in 31 provinces or municipalities, patients with more severe diseases had abnormal hepatic aminotransferase levels than patients with the non-severe disease.[46,47]

Liver damage in patients with coronavirus infection may be directly caused by a viral infection of the liver cells. In addition, immune-mediated inflammation, such as cytokine storms and pneumonia-associated hypoxia, might also contribute to liver injury or even progress to liver failure in critically ill patients with COVID-19.[45] Xu et al (2021) found that patients with severe COVID-19 had significantly higher liver function parameters from baseline to 30 days after admission to the hospital than patients with non-severe symptoms. COX analysis revealed that ALT > 2 ULN (HR=7.0, p=0.011), AST > 2 ULN (HR=34.7, p <0.001), and TBIL > 2 ULN (HR=54.6, p <0.001) were associated with higher mortality.[9]

COVID-19 cases that died, 109 samples (99.1%) experienced decreased kidney function. From the results of the analysis, patients with decreased kidney function have a risk of death 722 times higher than patients with normal kidney function. These results are similar to previous studies by Gabarre, et al where only 16 patients who survived had a history of comorbid kidney disorders, but in the non-surviving group, there were 109 patients with decreased kidney function. And from the results of their research, a significant association was found between the incidence of AKI and increased mortality.[28]

The incidence of decreased kidney function in Covid-19 patients is quite high, especially in critical cases, so AKI has been recognized as a common complication in Covid-19 patients. Besides causing AKI, SARS-Cov-2 infection can also affect various pre-existing chronic kidney diseases (CKD), including hemodialysis (HD) patients and kidney transplants as well as various conditions related to CKD including hypertension.[48,49] The independent predictors of AKI in Covid-19 patients are old age, diabetes, hypertension, cardiovascular disease, use of mechanical ventilation, high levels of interleukin-6, and use of vasopressor drugs.[50,51]

In infection with the Covid-19 virus, there are specific and non-specific mechanisms that cause AKI and will ultimately increase the risk of death. Specific mechanisms such as viral infection directly cause injury to the kidney through its receptor (ACE2), unbalanced activation of the Renin-angiotensin-aldosterone system (RAAS) which causes glomerular dysfunction, inflammation, fibrosis and vasoconstriction as well as an increased in pro-inflammatory cytokines elicited by a viral infection and microvascular thrombosis. While non-specific mechanisms include patients with AKI tend to be elderly patients and have more comorbid factors such as hypertension or DM, these factors cause kidney function to be easily impaired. In addition, other non-specific factors are patients with acute respiratory failure, nephrotoxic drugs, fluid restriction and unstable hemodynamics. Covid-19 patients with AKI have a high incidence of acute thrombotic events, especially venous thrombosis and pulmonary embolism. This event is a risk factor for death.[28]

Multivariate analysis was performed to assess the effect of other confounding variables on the independent variables studied. Based on the analysis results (Table 7), it appears that comorbid disease, PaO_2/FiO_2 ratio, ferritin, liver function and kidney function are predictors that are independently associated with mortality in COVID-19 patients. When further analysis was carried out using comorbid diseases hypertension, DM and COPD found a significant association with death in COVID-19 (p= 0.031). Subjects with comorbid hypertension, DM and COPD have a probability of experiencing mortality of 28,968 times when compared to subjects without comorbid diseases, range the probability in the population ranges from 11,371-612,133. Guan, et al (2020) found that comorbid COPD, DM and hypertension had a significant relationship with the mortality of COVID-19 patients with hazard ratios of 2.681, 1.586 and 1.575 respectively (p-value 0.002, respectively). 0.037 and 0.022).[30]

Subjects with a decreased ratio of PaO_2/FiO_2 have the possibility of experiencing mortality9.466 times when compared to subjects with a normal PaO_2/FiO_2 ratio, with range probabilities in the population range between1.020-87.883with p-values0.048. Subjects with increased serum ferritin levels have the possibility of experiencing mortality as much as 36.698 times when compared to subjects with normal serum ferritin levels, the range of

probabilities in the population ranges from 2.485-541.86 with a p-value of 0.009. Subjects with decreased liver function have the possibility of experiencing mortality39,385times when compared to subjects with normal liver function, the range of probabilities in the population ranges from,617-592,831with a p-value of 0.008 while decreased kidney function has the possibility of experiencing mortality722,447times when compared to subjects with normal kidney function, the range of probabilities in the population ranges from33,356-15647,243with a p-value of 0.000. From the results of this multivariate analysis, it was found that the ratio of comorbid diseases, serum ferritin, PaO_2/FiO_2, liver function and kidney function were predictors that were independently related to the mortality of COVID-19 patients.

From this study, decreased kidney function is the most influential risk factor for mortality in COVID-19 patients. This is consistent with the multivariate analysis in the study of Chan L, et al that increased mortality is associated with the severity of the decline in kidney function (0R=6.62, 95% CI, 3.13-14.1, p-value <0.001). In patients with impaired renal function, electrolyte imbalance, metabolic acidosis, and hypervolemia can occur which contribute to the worsening of the patient's clinical condition. In addition, in patients with severe COVID-19 infection, where there is respiratory failure and impaired heart function, kidney injury is also getting worse which can increase mortality.[52]

This research has advantages namely; First, this study is the first study in Bali to examine comorbid diseases, reduced PaO_2/FiO_2 ratios, increased ferritin, decreased liver function and kidney function as risk factors for mortality in COVID-19 patients, so it is hoped that this can become the basis for further research on other risk factors that may be involved. increase mortality; Second, this study has controlled for 2 confounding factors, namely age and gender using randomization and matching techniques so that it can control research bias the weakness of this study are that there is no initial data on the kidney function of patients being treated so it cannot be determined whether the increase in kidney function in these patients due to progressive or comorbid patients.

CONCLUSION

The comorbid disease, decreased PaO2/FiO2 Ratio, elevated serum ferritin levels, decreased liver function and decreased kidney function is a risk factor for mortality in COVID-19 patients.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest related to the publication of this research article.

FUNDING

This research did not receive funding from the government or other private sectors

ETHICS IN RESEARCH

This research has received approval from the research ethics committee of the Prof. Dr IGNG Ngoerah Hospital/ University of Udayana with No. 2807/UN 14.2.2VII.14/LT/2022

REFERENCES

[1] Stawicki S, Jeanmonod R, Miller A, Paladino L, Gaieski D, Yaffee A, et al. The 2019-2020 novel coronavirus (severe acute respiratory syndrome coronavirus 2) pandemic: A joint american college of academic international medicine-world academic council of emergency medicine multidisciplinary COVID-19 working group consensus paper. J Glob Infect Dis 2020;12:47–93. https://doi.org/10.4103/jgid.jgid_86_20.

[2] Grasselli G, Tonetti T, Protti A, Langer T, Girardis M, Bellani G, et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. Lancet Respir Med 2020;8:1201–8. https://doi.org/10.1016/S2213-2600(20)30370-2.

[3] Li L quan, Huang T, Wang Y qing, Wang Z ping, Liang Y, Huang T bi, et al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol 2020;92:577–83. https://doi.org/10.1002/jmv.25757.

[4] Sakr Y, François B, Solé-Violan J, Kotfis K, Jaschinski U, Estella A, et al. Temporal changes in the epidemiology, management, and outcome from acute respiratory distress syndrome in European intensive care units: a comparison of two large cohorts. Crit Care 2021;25:87. https://doi.org/10.1186/s13054-020-03455-8.

[5] Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: The Berlin definition. Jama 2012;307:2526–33. https://doi.org/10.1001/jama.2012.5669.

[6] Cortinovis M, Perico N, Remuzzi G. Long-term follow-up of recovered patients with COVID-19. Lancet 2021;397:173–5. https://doi.org/10.1016/S0140-6736(21)00039-8.

[7] Carubbi F, Salvati L, Alunno A, Maggi F, Borghi E, Mariani R, et al. Ferritin is associated with the severity of lung involvement but not with worse prognosis in patients with COVID-19: data from two Italian COVID-19 units. Sci Rep 2021;11:1–11. https://doi.org/10.1038/s41598-021-83831-8.

[8] Deng F, Zhang L, Lyu L, Lu Z, Gao D, Ma X, et al. Increased levels of ferritin on admission predicts intensive care unit mortality in patients with COVID-19. Med Clínica (English Ed 2020;156:324–31. https://doi.org/https://doi.org/10.1016/j.medcli.2020.11.03.

[9] Xu W, Huang C, Fei L, Li Q, Chen L. Dynamic changes in liver function tests and their correlation with illness severity and mortality in patients with covid-19: A retrospective cohort study. Clin Interv Aging 2021;16:675–85. https://doi.org/10.2147/CIA.S303629.

[10] Yang H, Jin B, Mao Y. Liver injury in COVID-19: What do we know now? Hepatobiliary Pancreat Dis Int 2020;19:407–8. https://doi.org/10.1016/j.hbpd.2020.07.009.

[11] Xiao G, Hu H, Wu F, Sha T, Zeng Z, Huang Q, et al. Acute kidney injury in patients hospitalized with COVID-19 in Wuhan, China: a single-center retrospective observational study. Nan Fang Yi Ke Da Xue Xue Bao 2021;41:157–63. https://doi.org/10.12122/j.issn.1673-4254.2021.02.01.

[12] Bennett KE, Mullooly M, O'Loughlin M, Fitzgerald M, O'Donnell J, O'Connor L, et al. Underlying conditions and risk of hospitalisation, ICU admission and mortality among those with COVID-19 in Ireland: A national surveillance study. Lancet Reg Heal - Eur 2021;5:100097. https://doi.org/10.1016/j.lanepe.2021.100097.

[13] Pan F, Yang L, Li Y, Liang B, Li L, Ye T, et al. Factors associated with death outcome in patients with severe coronavirus disease-19 (Covid-19): A case-control study. Int J Med Sci 2020;17:1281–92. https://doi.org/10.7150/ijms.46614.

[14] Vafadar Moradi E, Teimouri A, Rezaee R, Morovatdar N, Foroughian M, Layegh P, et al. Increased age, neutrophil-to-lymphocyte ratio (NLR) and white blood cells count are associated with higher COVID-19 mortality. Am J Emerg Med 2021;40:11–4. https://doi.org/10.1016/j.ajem.2020.12.003.

[15] Zhou Z, Zhang M, Wang Y, Zheng F, Huang Y, Huang K, et al. Clinical characteristics of older and younger patients infected with SARS-CoV-2. Aging (Albany NY) 2020;12:11296–305. https://doi.org/10.18632/aging.103535.

[16] Lloyd-Sherlock P, Ebrahim S, Geffen L, McKee M. Bearing the brunt of covid-19: Older people in low and middle income countries. BMJ 2020;368:1–2. https://doi.org/10.1136/bmj.m1052.

[17] Niu S, Tian S, Lou J, Kang X, Zhang L, Lian H, et al. Clinical characteristics of older patients infected with COVID-19: A descriptive study. Arch Gerontol Geriatr 2020;89:104058. https://doi.org/10.1016/j.archger.2020.104058.

[18] Haryanto B, Nurlambang T. Coronavirus (COVID-19) Outbreaks, Environment and Human Behaviour. 2021. https://doi.org/10.1007/978-3-030-68120-3.

[19] Pambudi, I.G.P.B, Suryana, I.K., Rai, I.B.N., Kusumawardani, I.A.J.D., Candrawati, N.W., Sajinadiyasa IGK. High Neutrophil to Lymphocyte Ratio, C-reactive Protein, Procalcitonin and D-dimer and Risk Faktors for Severe COVID-19. Medico-Legal Updat 2022;22:41–6.

[20] Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in coronavirus disease 2019 patients: A systematic review and meta-analysis. Int J Infect Dis 2020;94:91–5. https://doi.org/10.1016/j.ijid.2020.03.017.

[21] Cao Y, Li L, Feng Z, Wan S, Huang P, Sun X, et al. Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. Cell Discov 2020;6:4–7. https://doi.org/10.1038/s41421-020-0147-1.

[22] Walter LA, McGregor AJ. Sex- And gender-specific observations and implications for COVID-19. West J Emerg Med 2020;21:507–9. https://doi.org/10.5811/westjem.2020.4.47536.

[23] Jaillon S, Berthenet K, Garlanda C. Sexual Dimorphism in Innate Immunity. Clin Rev Allergy Immunol 2019;56:308–21. https://doi.org/10.1007/s12016-017-8648-x.

[24] Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 2021;397:220–32. https://doi.org/10.1016/S0140-6736(20)32656-8.

[25] Khedr EM, Daef E, Mohamed-Hussein A, Mostafa EF, Zein M, Hassany SM, et al. Impact of comorbidities on COVID-19 outcome. MedRxiv Prepr Serv Heal Sci 2020. https://doi.org/10.1101/2020.11.28.20240267.

[26] Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 2020;369. https://doi.org/10.1136/BMJ.M1966.

[27] Liu Y, Yan LM, Wan L, Xiang TX, Le A, Liu JM, et al. Viral dynamics in mild and severe cases of COVID-19. Lancet Infect Dis 2020;20:656–7. https://doi.org/10.1016/S1473-3099(20)30232-2.

[28] Gabarre P, Dumas G, Dupont T, Darmon M, Azoulay E, Zafrani L. Acute kidney injury in critically ill patients with COVID-19. Intensive Care Med 2020;46:1339–48. https://doi.org/10.1007/s00134-020-06153-9.

[29] Del Valle DM, Kim-Schulze S, Huang H-H, Beckmann ND, Nirenberg S, Wang B, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. Nat Med 2020;26:1636–43. https://doi.org/10.1038/s41591-020-1051-9.

[30] Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708–20. https://doi.org/10.1056/nejmoa2002032.

[31] Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol 2020;77:683–90. https://doi.org/10.1001/jamaneurol.2020.1127.

[32] Bornstein SR, Rubino F, Khunti K, Mingrone G, Hopkins D, Birkenfeld AL, et al. Practical recommendations for the management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol 2020;8:546–50. https://doi.org/10.1016/S2213-8587(20)30152-2.

[33] Alemzadeh-Ansari M. Coronavirus disease 2019 (COVID-19) and cardiovascular events. Res Cardiovasc Med 2020;9:1. https://doi.org/10.4103/rcm.rcm_9_20.

[34] Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential Effects of Coronaviruses on the Cardiovascular System: A Review. JAMA Cardiol 2020;5:831–40. https://doi.org/10.1001/jamacardio.2020.1286.

[35] Klain A, Indolfi C, Dinardo G, Decimo F, Miraglia Del Giudice M. Covid-19 and spirometry in this age. Ital J Pediatr 2022;48:4–9. https://doi.org/10.1186/s13052-022-01199-5.

[36] Izcovich A, Ragusa MA, Tortosa F, Marzio MAL, Agnoletti C, Bengolea A, et al. Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. PLoS One 2020;15:1–30. https://doi.org/10.1371/journal.pone.0241955.

[37] Feiner JR, Weiskopf RB. Evaluating Pulmonary Function: An Assessment of Pao2/Fio2. Crit Care Med 2017;45:e40–8. https://doi.org/10.1097/CCM.0000000000002017.

[38] Sartini S, Massobrio L, Cutuli O, Campodonico P, Bernini C, Sartini M, et al. Role of sato2, PaO2/FiO2 ratio and pao2 to predict adverse outcome in covid-19: A retrospective, cohort study. Int J Environ Res Public Health 2021;18. https://doi.org/10.3390/ijerph182111534.

[39] bendjelid karim, Giraud R. Treating hypoxemic patients with SARS-COV-2 pneumonia: Back to applied physiology. Anaesth Crit Care Pain Med 2020. https://doi.org/10.1016/j.accpm.2020.04.003.

[40] Deng F, Zhang L, Lyu L, Lu Z, Gao D, Ma X, et al. Increased levels of ferritin on admission predicts intensive care unit mortality in patients with COVID-19. Med Clin (Barc) 2021;156:324–31. https://doi.org/10.1016/j.medcli.2020.11.030.

[41] Cheng L, Li H, Li L, Liu C, Yan S, Chen H, et al. Ferritin in the coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. J Clin Lab Anal 2020;34:1–18. https://doi.org/10.1002/jcla.23618.

[42] Rosário C, Zandman-Goddard G, Meyron-Holtz EG, D'Cruz DP, Shoenfeld Y. The Hyperferritinemic Syndrome: Macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome. BMC Med 2013;11. https://doi.org/10.1186/1741-7015-11-185.

[43] Ahmed S, Ansar Ahmed Z, Siddiqui I, Haroon Rashid N, Mansoor M, Jafri L. Evaluation of serum ferritin for prediction of severity and mortality in COVID-19- A cross sectional study. Ann Med Surg 2021;63:102163. https://doi.org/10.1016/j.amsu.2021.02.009.

[44] Kernan KF, Carcillo JA. Hyperferritinemia and inflammation. Int Immunol 2017;29:401–9. https://doi.org/10.1093/intimm/dxx031.

[45] Ponti G, Maccaferri M, Ruini C, Tomasi A, Ozben T. Biomarkers associated with COVID-19 disease progression. Crit Rev Clin Lab Sci 2020;0:389–99. https://doi.org/10.1080/10408363.2020.1770685.

[46] Cabibbo G, Rizzo GEM, Stornello C, Craxì A. SARS-CoV-2 infection in patients with a normal or abnormal liver. J Viral Hepat 2021;28:4–11. https://doi.org/10.1111/jvh.13440.

[47] Cai Q, Huang D, Yu H, Zhu Z, Xia Z, Su Y, et al. COVID-19: Abnormal liver function tests. J Hepatol 2020;73:566–74. https://doi.org/10.1016/j.jhep.2020.04.006.

[48] Nadim MK, Forni LG, Mehta RL, Connor MJ, Liu KD, Ostermann M, et al. COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. Nat Rev Nephrol 2020;16:747–64. https://doi.org/10.1038/s41581-020-00356-5.

[49] Paul Palevsky. COVID-19: Issues related to acute kidney injury, glomerular disease, and hypertension. UpToDate 2021:1–27.

[50] Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int 2020;98:209–18. https://doi.org/10.1016/j.kint.2020.05.006.

[51] Xia P, Wen Y, Duan Y, Su H, Cao W, Xiao M, et al. Clinicopathological Features and Outcomes of Acute Kidney Injury in Critically Ill COVID-19 with Prolonged Disease Course: A Retrospective Cohort. J Am Soc Nephrol 2020;31:2205–21. https://doi.org/10.1681/ASN.2020040426.

[52] Lotfi B, Farshid S, Dadashzadeh N, Valizadeh R, Rahimi MM. Is coronavirus disease 2019 (COVID-19) associated with renal involvement? A review of century infection. Jundishapur J Microbiol 2020;13:1–6. https://doi.org/10.5812/jjm.102899.