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Investigation of viral load in patients with Coronavirus disease-2019 with and without comorbidities

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ABSTRACT

Aims: Many fatal cases of Coronavirus disease-2019 (COVID-19) involved patients with comorbidities, in which a higher cellular viral copy was frequently reported. This study aimed to compare viral load (VL) among patients with COVID-19 with and without comorbidities.

Methods: This retrospective case-control study included COVID-19 patients with and without comorbidities who were hospitalized in two COVID-19 referral hospitals, Tanjungpura University Hospital and Doctor Soedarso General Hospital, in West Kalimantan, Indonesia. Demographic findings, clinical symptoms, comorbidities, and real-time polymerase chain reaction VL data were collected from medical records.

Results: This study included 136 patients (53% female and 47% male) divided equally into 68 patients with [median age interquartile range (IQR): 47 (40-58.5) years] and without comorbidities [median age (IQR): 25 (22-35.8) years]. A total of 48.5% of patients with comorbidities experienced severe COVID-19, whereas 61.8% of patients without comorbidities merely exhibited mild symptoms. The presence of comorbidities demonstrated a significant association with age and COVID-19 severity ($p<0.001$), with a trend of elevated VL among individuals with comorbidities ($p=0.023$, median: log10 1.86 vs 1.34 VL). Significant differences in VL were found between age groups ($p=0.019$) and COVID-19 severities ($p=0.001$), showing higher VL among older, moderately ill, and critically ill patients. Critical condition was experienced by COVID-19 patients with hypertension, cardiovascular disease, diabetes, and chronic obstructive pulmonary disease. Severe COVID-19 was observed in nearly all comorbid conditions, except in pregnant women and those with malignancies.

Conclusions: VL differed significantly between patients with and without comorbidities, age groups, and degrees of COVID-19 presentation. VL holds promise in monitoring disease progression in patients with COVID-19, particularly those with comorbidities.

Introduction

Coronavirus disease-2019 (COVID-19) was first reported in Indonesia on March 2nd, 2020. As of January 1st, 2021, 751.270 cases of COVID-19 were confirmed in Indonesia, with a mortality rate of 3.0% (1). Most COVID-19 fatal cases involved elderly patients and those with comorbidities. Mortality rates were reported to be higher in patients with comorbidities, such as cardiovascular disease (CVD) (10.5%), diabetes (7.3%),

chronic respiratory disease (6.3%), hypertension (6.0%), and malignancy (5.6%) (2).

As the gold standard for COVID-19 diagnosis, real-time polymerase chain reaction (RT-PCR) examination allowed the calculation of viral load (VL), a numerical description of the amount of virus copy in a fluid volume (3), which was associated with an increased risk of transmission and disease severity in other conditions (4). VL was directly linked to severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) viral binding ability on angiotensin-converting enzyme 2 (ACE2), a receptor for SARS-CoV-2 entry into the host; with VL having been suggested to be a useful marker for assessing COVID-19 severity and its prognosis (5). ACE2 expression was found to be elevated in COVID-19 patients with comorbidities, such as chronic obstructive pulmonary disease (COPD), human immunodeficiency virus (HIV) infection, type 2 diabetes mellitus, CVD, hypertension, liver diseases, and kidney diseases (6,7). Increased ACE2 levels allow more viruses to invade the cell, as observed in COVID-19 patients, in whom severely ill patients tend to have higher VL and longer viral shedding periods (8,9). Later on, increased VL was found to be associated with increased mortality rates among hospitalized patients (10), as survival analysis revealed a notable discrepancy in survival rates between individuals with high and low VL (4).

SARS-CoV-2 VL and its dynamics in different subsets of patients are still underexplored, and no study has compared VL among COVID-19 patients with and without comorbidities; though the presence of comorbidities, such as hypertension, coronary artery disease (CAD), congestive heart failure (CHF), COPD, and malignancy, was previously associated with poor prognosis in COVID-19 patients (11). This study aimed to compare VL in COVID-19 patients with and without comorbidities to observe the relationships between demographic status, clinical symptoms, comorbidities, and patients' VL; consequently, the potential application of VL as a quantitative determinant of disease progression in patients with COVID-19.

Methods

Study design and participants

This observational, retrospective, case-control design was conducted at Tanjungpura University Hospital and Doctor Soedarso General Hospital. Both settings are regional referral hospitals for COVID-19 patients in West Kalimantan, Indonesia. The study participants were the individuals who tested positive for COVID-19 between November 2020 and January 2021. The inclusion criteria were as follows: comprehensive written medical records detailing comorbidities, symptoms upon hospital admission, pertinent demographic information, and PCR analysis using identical examination kits. The exclusion criteria for the study were applied to COVID-19 patients lacking complete medical records for the specified parameters. Naso-oropharyngeal swabs were obtained from patients with suspected COVID-19, and then RNA extraction and ORF1ab (RdRp) gene amplification were performed using RT-PCR examination. Medical records of individuals with positive COVID-19 tests were compiled and analyzed.

The sample size was determined using the *OpenEpi* application (www.OpenEpi.com) using the *Sample Size: Mean Difference* formula, resulting in a minimum sample requirement of 65 cases and 65 control samples. During the study period, 262 patients tested positive for COVID-19. Among this group, 151 patients met the research criteria. Of these 151 patients 68 patients admitted with other comorbidities alongside COVID-19. Of the remaining 83 patients without comorbidities, 68 were randomly selected to be included in the "no comorbidity" group. The final analysis included 68 COVID-19 patients with comorbidities (case group) and 68 patients without comorbidities (control group).

Data collection

The study variables included demographic characteristics such as sex and age, pre-existing comorbidities, COVID-19 related symptoms upon admission along with their severity classification, and SARS-CoV-2 VL and corresponding cycle threshold (Ct) values. Patient age was categorized according to the Indonesian COVID-19 Task Force's classification (0-5, 6-18, 19-30, 31-45, 46-59, and ≥60 years old) as well as their comorbid conditions [hypertension, CVD, diabetes, COPD, chronic kidney disease (CKD), malignancy, cerebrovascular accident (CVA) or stroke, pregnancy, liver diseases, immunodeficiency, and other related conditions]. After dividing the participants into case and control groups, those with preexisting comorbidities were further stratified into subgroups based on the presence of either single or multiple comorbidities.

The severity of COVID-19 was categorized according to the China-China Centers for Disease Control and Prevention classification (12). Asymptomatic COVID-19 was defined as a positive COVID-19 nucleic acid test result without any clinical symptoms and normal chest imaging. In mild cases, the patient presented with symptoms of acute upper respiratory tract infection (fever, fatigue, myalgia, cough, sore throat, runny nose, sneezing) or digestive symptoms (nausea, vomiting, abdominal pain, diarrhea). In moderate cases, pneumonia manifested as frequent fever and cough, but there was no evident hypoxemia or detectable lesions on chest computed tomography. In severe cases, pneumonia patients presented with SpO_2 <92% (hypoxemia). During the critical phase, patients presented with acute respiratory distress syndrome (ARDS).

Ethics

This study was conducted in accordance with the principles of the 2013 revised Declaration of Helsinki. Research permit and ethical approval were obtained from the Ethics Committee of the Faculty of Medicine of Tanjungpura University (no: 2904/UN22.9/TA/2021; research permit no: 2931/UN22.20/TU/2021, date: 08.04.2021) and the Health Research Ethics Committee of Doctor Soedarso General Hospital (no: 03.04/RSDS/KEPK/2021; research permit: no: 070/2431/RSDS/PGB-b/2021, date: 08.04.2021).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 26.0 software (IBM Corp., Armonk, NY: USA). The variables analyzed include patients' demographic characteristics, comorbidity status, the severity of COVID-19 symptoms upon admission, and log10-transformed VL and their respective Ct values. Descriptive analyses of frequencies and proportions for categorical variables and medians and interquartile ranges for continuous variables were performed. The normality of the distribution of the numerical data was tested using the Kolmogorov-Smirnov test. Subsequently, the groups were compared using statistical methods appropriate for the data type. Categorical variables were analyzed using the Pearson Chi-square test or Fisher's exact test, whereas numerical data were assessed using the independent sample t-test or analysis of variance if normally distributed. Alternatively, non-normally distributed numerical data were analyzed using the Mann-Whitney U test or the Kruskal-Wallis test.

Results

Demographic characteristics and clinical presentation

A total of 136 patients were grouped according to their demographic findings: 47.1% were male (30 males with comorbidities and 34 without) and 52.9% were female (38 females with comorbidities and 34 without), with a median age of 47 (IQR, 40-58.5) and 25 (IQR, 22-35.8) years in those with and without comorbidities, respectively. Approximately half (48.5%) of the patients with comorbidities were admitted with severe COVID-19, whereas only two (2.9%) patients without comorbidities were admitted with severe COVID-19. The majority of those without comorbidities had either mild COVID-19 symptoms (61.8%) or were asymptomatic (30.9%). Among the comorbid groups, excluding those with severe COVID-19, approximately 29.4% of patients had mild COVID-19 symptoms and 11.8% were asymptomatic. Notably, there was a significantly higher proportion of moderately ill patients (22% vs 2.9%) and critically ill patients (11.8% vs 1.8%) in the comorbid group than in the non-comorbid group. Individuals with comorbidities were observed to be notably older than those without ($p<0.001$). A statistically significant relationship was identified between the presence of comorbidities and both patient age ($p<0.001$) and COVID-19 severity ($p<0.001$). The presence of comorbidities showed no correlation with patients' gender ($p=0.492$). Similarly, sex did not correlate with the severity of COVID-19 illness ($p=0.056$), although a higher proportion of male patients was observed among those with moderate to critical illness compared in both the case (86.7% vs 47.4%) and control (14.7% vs 0%) groups (Table 1).

Comparison of viral load distribution among patients with COVID-19

Patients' VL were categorized based on their log10-transformed values and the corresponding Ct ranges; though the normality test showed that the numerical data were not normally distributed ($p<0.001$), even after log transformation. Most of the participants (71.3%) exhibited low VL, as indicated by their higher Ct values (>30). A greater proportion of patients with comorbidities demonstrated high VL (Ct ≤25) compared with those without comorbidities (19.1% vs 7.4%). There was no statistically significant difference observed in the median VL [log10 1.9 (1.2-3.1) vs 1.3 (1.1-2.3); $p=0.230$] or Ct values [32.5 (35.1-27.6) vs 34.6 (36.1-30.9); $p=0.123$] between the groups (Table 1). The VL distribution varied significantly among individuals with and without comorbidities ($p=0.023$) (Figure 1C), across different age groups ($p=0.019$) (Figure 1B), and among different levels of COVID-19 severity ($p=0.001$) (Figure 1D). The median VL was highest among moderately ill patients and lowest among asymptomatic patients (Figure 1D). There was no significant difference in VL between male and female COVID-19 patients ($p=0.195$) (Figure 1A).

Distribution of comorbidities in patients with COVID-19

As previously defined, the participants' comorbidity status was categorized into three groups: no comorbidity, single comorbidities, and multiple comorbidities. Of the 68 patients with comorbidities, 63.2% had a single comorbidity and 36.8% had multiple comorbidities (Table 2). The majority of COVID-19 patients with comorbidities suffered from hypertension (42.6%), either as a single comorbidity or in conjunction with other comorbid conditions; followed by diabetes (23.8%), CVD (13.9%), pregnancy (9.9%), malignancy (4.0%), and CVA (3.0%). COPD and CKD were each identified in one patient, with both conditions occurring alongside other comorbidities, such as diabetes, hypertension, and CVD. HIV was observed in a patient with tuberculosis co-infection. Further analysis showed an association between patients' COVID-19 severity levels and comorbid conditions ($p<0.001$). COVID-19 patients with hypertension, CVD, diabetes, and COPD were found to experience critical conditions. Severe symptoms were observed in nearly all comorbid conditions, except in pregnant women and patients with malignancies. Asymptomatic COVID-19 was observed only in pregnant women (Figure 2).

Table 1. Demographic characteristics and viral load in patients with and without comorbidities

Characteristics	Total (n=136)	With comorbidities (n=68)		Without comorbidities (n=68)		p value*
Gender, Female, n (%)	72 (52.9)	38 (52.8)		34 (47.2)		0.492
Age, median (IQR)		47 (40-58.5)		25 (22-35.8)		**<0.001**
0-5, n (%)	4 (2.9)	-		4 (100)		
6-18, n (%)	6 (4.4)	-		6 (100)		
19-30, n (%)	41 (30.1)	8 (19.5)		33 (80.5)		
31-45, n (%)	41 (30.1)	22 (53.7)		19 (46.3)		
46-59, n (%)	28 (20.6)	22 (78.6)		6 (21.4)		
≥60, n (%)	16 (11.8)	16 (100)		-		
Disease severity, n (%)		**Male**	**Female**	**Male**	**Female**	
Asymptomatic	29 (18.4)	4 (13.8)	4 (13.8)	9 (31)	12 (41.8)	
Mild	62 (45.6)	4 (6.5)	16 (25.8)	20 (32.6)	22 (35.5)	
Moderate	17 (12.5)	10 (58.8)	5 (29.4)	2 (11.8)	-	0.056
Severe	25 (18.4)	12 (48)	11 (44)	2 (8)	-	
Critical	7 (5.1)	4 (57.1)	2 (28.6)	1 (14.3)	-	
Cycle threshold, n (%)						
>30	97 (71.3)	44 (45.4)		53 (54.6)		
25-30	21 (15.4)	11 (52.4)		10 (47.6)		0.129
≤25	18 (13.2)	13 (72.2)		5 (27.8)		
Median (IQR)		32.45 (35.1-27.6)		34.58 (36.1-30.9)		0.123
Viral Load, Log10, median (IQR)		1.86 (1.20-3.12)		1.34 (1.09-2.28)		0.230

IQR: Interquartile range

The VL distribution across different comorbid conditions is depicted in Figure 3A, which shows that patients with CVD, hypertension, diabetes, and COPD had the highest median VL [log10 values of 2.13 (1.66-2.03), 1.98 (1.31-3.14), 1.86 (1.24-3.51), and 1.84, respectively]. However, no significant differences were observed in the VL distribution (p=0.457) or median (p=0.632) among the comorbid conditions (Figure 3A). VL distribution according to the degree of comorbidity is displayed in Figure 3B. Patients with multiple comorbidities exhibited a notably higher median VL compared with those with single comorbidity or no comorbidity [log10 values of 1.88 (1.24-2.65), 1.72 (1.11-3.16), and 1.34 (1.09-2.28), respectively], although this finding did not reach statistical significance (p=0.232). There was a marginally significant difference in VL between patients without comorbidities and those with either single or multiple comorbidities (p=0.072).

Discussion

Comorbidity status and characteristics of patients with COVID-19

Advanced age is associated with an increased risk of developing COVID-19. Apart from being an independent risk factor for COVID-19, older age was also associated with comorbidities (13), as evidenced in this study, which showed COVID-19 patients with comorbidities were significantly older than those without comorbidities. Most COVID-19 patients without comorbidities were younger, ranging from 19 to 30 years of age, whereas patients with comorbidities ranged from 31 to 59 years of age. A prior study from the United Kingdom indicated that individuals aged 40-64 years face the highest risk of COVID-19 infection, followed by those aged 65-74 years and individuals aged 75 years and older (14). As of July 2021, data from the Indonesian Government COVID-19 Task Force showed that the highest positivity rate for COVID-19 was in those aged between 31 and 45 years, with the mortality rate being dominated by patients aged 60 years and above (50%) (1).

Not only age but also comorbidity status was associated with disease severity. Nearly half of the patients with comorbidities suffered severe COVID-19 in this study, whereas the majority of patients without comorbidities had mild disease or were asymptomatic. Comorbidities, such as hypertension and CVD, have been reported to increase the risk of COVID-19 infection, resulting in severe clinical presentation (15), particularly among elderly individuals. A meta-analysis also reported that the presence of one or a combination of comorbidities significantly increased the severity of COVID-19 (16).

This study showed no statistically significant association between comorbidity status and patients' sex. Nevertheless,

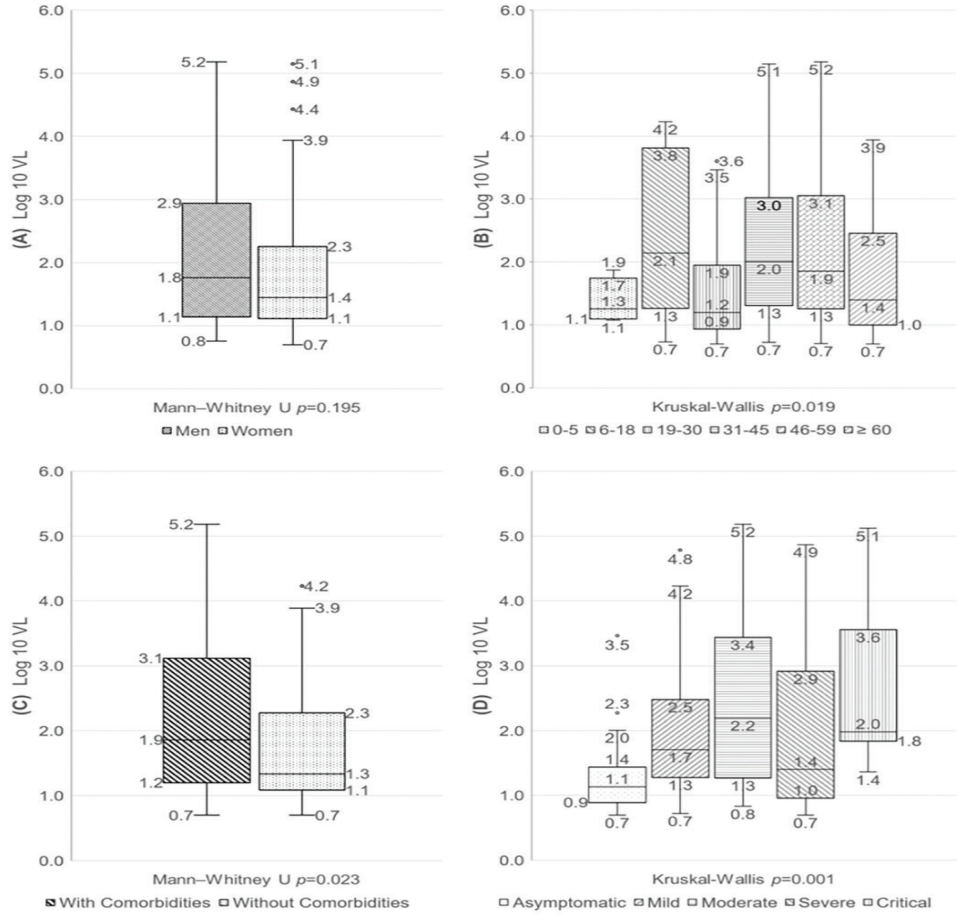

Figure 1. Distribution of log10 VL values in subsets of patients with COVID-19 according to (A) sex, (B) age range, (C) comorbidity status, and (D) disease severity

COVID-19: Coronavirus disease-2019, VL: Viral load

Table 2. Viral load distribution by comorbidity characteristics

Variables	**Total (n=136)**	**With comorbidities**	**Without comorbidities**	
Degree of comorbidity, n (%)		**Log10 VL, median (IQR)**	**Log10 VL, median (IQR)**	
Single	43 (31.6)	1.72 (1.11-3.16)	-	
Multiple	25 (18.4)	1.88 (1.24-2.65)	-	
Without	68 (50)	-	1.34 (1.09-2.28)	
Comorbidities, n (%)	**Total (n=101)**	**As single comorbidity**	**Among multiple comorbidities**	**Log10 VL, median (IQR)**
Hypertension	43 (42.6)	20 (46.5)	23 (53.5)	1.98 (1.31-3.14)
Cardiovascular disease	14 (13.9)	3 (21.4)	11 (78.6)	2.13 (1.66-2.03)
Diabetes	24 (23.8)	8 (33.3)	16 (66.7)	1.86 (1.24-3.51)
Chronic obstructive pulmonary disease	1 (1.0)	-	1 (100)	1.84
Chronic kidney disease	1 (1.0)	-	1 (100)	1.14
Malignancy	4 (4.0)	3 (75)	1 (25)	1.37 (1.05-2.02)
Cerebrovascular accident	3 (3.0)	1 (33.3)	2 (66.7)	1.26
Pregnancy	10 (9.9)	7 (70)	3 (30)	1.35 (1.05-2.01)
Immunological disorders	1 (1.0)	1 (100)	-	1.11

IQR: Interquartile range

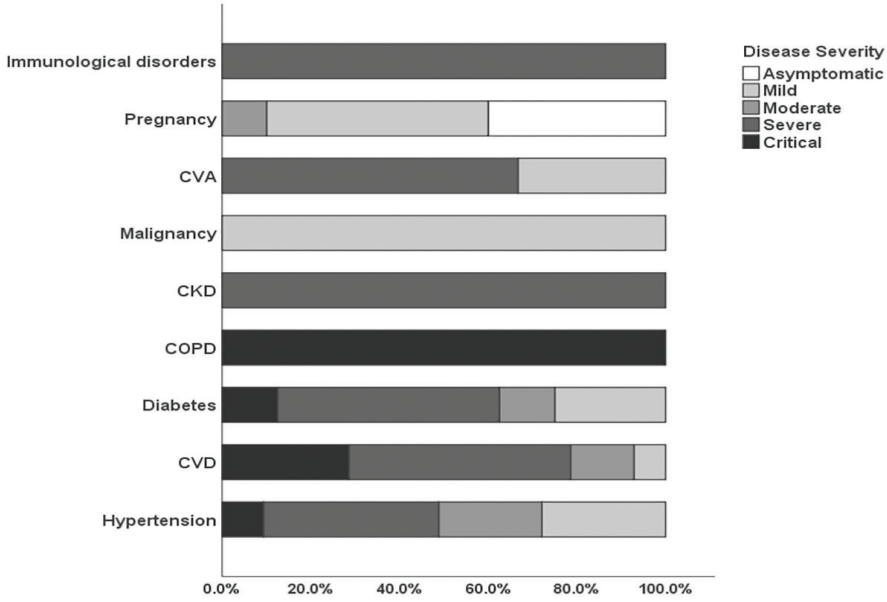

Figure 2. Distribution of COVID-19 severity according to patients' comorbidity type showed an association between various comorbidities and stages COVID-19 presentation (p<0.001)

CVA: Cerebrovascular accident, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, CVD: Cardiovascular disease

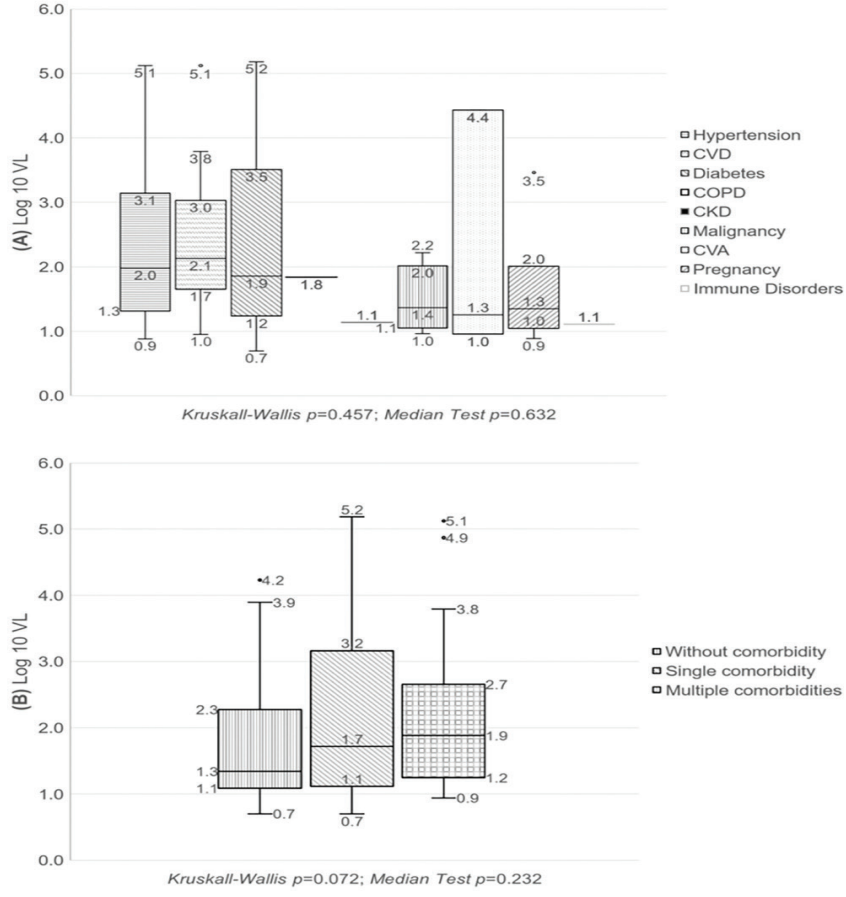

Figure 3. Distribution of log10 VL values in COVID-19 patients with comorbidities according to their (A) comorbidity type/condition and (B) comorbidity classification (single or multiple)

CVD: Cardiovascular disease, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, CVA: Cerebrovascular accident, VL: Viral load, COVID-19: Coronavirus disease-2019

male patients constituted significantly higher proportions of patients with moderate to critical illness compared with female patients, regardless of comorbidity status, consistent with findings reported in a systematic review and meta-analysis examining sex differences in COVID-19 (17). This finding could be attributed to higher immune responses to viral infections in women due to sex hormones, leading to cytokine and chemokine production (18). After viral exposure, antigen expression, recognition, and initiation of adaptive immune responses were reported to be higher in women than in men (19).

Viral load in patients with COVID-19

Significant differences in VL distribution were observed among patients with and without comorbidities, across different age groups, and at different COVID-19 severity levels. Patients with comorbidities tend to have higher VLs than patients without comorbidities, which could be attributed to the increased expression of ACE2 receptors in several comorbid conditions, such as hypertension, CVD, diabetes, kidney disease, COPD, and HIV (6,7). Elevated ACE2 receptor levels in these patients might manifest as a higher VL and a higher rate of cell damage (20). Further VL increase in comorbid individuals can contribute to hyper-inflammation, alveolar apoptosis, and ultimately ARDS and multi-organ failure (21).

The distribution of VL varied significantly across different age groups, which contrasted with a previous study that described VL in patients with COVID-19 as comparable across age groups and suggested that age is not a strong predictor of disease outcome (22). Older age was previously associated with higher VL peaks in nasopharyngeal samples, which was associated with a weaker immune system and a higher prevalence of comorbidities in elderly patients (23). Comparisons of VL between adult and pediatric patients may also be influenced by external factors, such as lower swab volumes due to smaller pediatric swab sizes and the frequently missed symptoms of mild COVID-19 in children (24). A study examining infectiousness during SARS-CoV-2 infection indicated that differences in VL were minor and insufficient to affect SARS-CoV-2 transmission dynamics significantly. Children were found to have slightly lower VL than adults, but the difference was not clinically significant (25).

All symptomatic patients had higher VL than asymptomatic patients, which was in line with a study on the relationship between VL and secondary transmission in COVID-19 (26). Higher VL was observed in mild COVID-19 rather than severe COVID-19 because it reflected the onset of infection (27). This observation was consistent with the progression of VL among patients in this study: VL levels began relatively lower in asymptomatic patients, increased in patients with mild symptoms, reached a peak in those with moderate symptoms, decreased in patients with severe COVID-19, and showed a slight increase in critically ill patients. This finding is consistent with a study investigating viral dynamics in mild and severe COVID-19 cases, showing lower VL levels in mild cases and stable or increasing VL levels in severe COVID-19 cases (5). Another study that investigated whether higher SARS-CoV-2 VL was associated with death also reported that baseline VL in patients with moderate COVID-19 was significantly higher than those with mild or severe COVID-19 (10).

Comorbidities in patients with COVID-19

Previous reports have indicated positive correlations between VL and conditions such as malignancies and diseases other than hypertension (27). Patients with CAD, CHF, cerebrovascular disease, hypertension, COPD, CKD, and active malignancy have been consistently noted to be at increased risk of high VL (11). The present study found that comorbidity status was associated with COVID-19 severity. Upon admission, critically ill presentations of ARDS were observed among patients with comorbidities such as hypertension, CVD, diabetes, and COPD. Severe COVID-19 was also noted across nearly all comorbid conditions, except in pregnant women and those with malignancies, who predominantly exhibited mild symptoms. Hypertension, diabetes, and CVD such as CHF and CAD dominated the comorbid conditions in this study, all of which have been reported to increase the risk of severe COVID-19 infection, poor prognosis, and increased mortality (28,29). Among patients with COVID-19 and CVD, increased ACE2 expression in pericytes and cardiomyocytes predisposes them to a higher risk of severe cardiac complications (30).

Comorbidities with lower prevalence in this study included pregnancy, malignancies such as osteosarcoma and colorectal cancer, and ischemic and hemorrhagic CVA. Pregnant women face an elevated risk of COVID-19 infection and related mortality due to physiological changes associated with pregnancy, such as increased oxygen demand, reduced lung capacity, and increased susceptibility to thromboembolic events (31). Patients with malignancy were also at greater risk of SARS-CoV-2 infection due to immunosuppressive therapy and repeated hospital visits, resulting in worse clinical outcomes than those without malignancy (32). COVID-19 patients with pre-existing cerebrovascular disease also exhibited worse outcomes (33). Dysregulation of ACE2 resulting from SARS-CoV-2 binding reduces perfusion in ischemic areas and contributes to increased infarct volume in patients with ischemic stroke (34). Similar dysfunctions also play a role in cerebrovascular endothelial disorders, which contribute to the pathogenesis of intracerebral hemorrhage in patients with COVID-19 (34).

COPD and CKD were each identified in one patient, with both conditions previously reported to be associated with a twofold increased risk of severe COVID-19 and death (35). ACE2 receptor expression was reported to increase in COPD, contributing to lung structural damage, weakened immunity,

and excessive mucus production (7). CKD was reported to be an independent risk factor for the development of acute kidney injury in COVID-19 patients (13). SARS-CoV-2 infection could impact the disease progression of patients with HIV and HIV-tuberculosis coinfection, particularly in individuals with suboptimal treatment adherence. Previous reports have highlighted untreated *Mycobacterium tuberculosis* as an independent risk factor associated with poorer prognosis in COVID-19 patients co-infected with tuberculosis (36). However, the prognosis was reportedly better for patients on anti-retroviral therapy (37).

Swab samples were collected upon admission rather than prospectively based on infection onset or symptoms. As a result, patients at different disease stages displayed highly varied VL results in this study. Additionally, the range of comorbidities studied during the study period was relatively limited to a select few conditions. Consequently, data on the impact of comorbidities with smaller sample sizes on VL outcomes are limited.

Conclusion

The VL in patients with COVID-19 exhibited significant variability based on comorbidity status, age, and clinical presentation severity. VL is a tool for monitoring disease progression in patients with COVID-19, particularly those with comorbidities. However, additional studies are required to validate the utility of this approach in clinical practice.

Ethics

Ethics Committee Approval: Research permit and ethical approval were obtained from the Ethics Committee of the Faculty of Medicine of Tanjungpura University (no: 2904/UN22.9/TA/2021; research permit no: 2931/UN22.20/TU/2021, date: 08.04.2021) and the Health Research Ethics Committee of Doctor Soedarso General Hospital (no: 03.04/RSDS/KEPK/2021; research permit: no: 070/2431/RSDS/PGB-b/2021, date: 08.04.2021).

Informed Consent: Retrospective case-control study.

Footnotes

Authorship Contributions

Concept: C.J., A.A., M.M., Design: C.J., A.A., M.M., Data Collection or Processing: C.J., A.A., M.M., Analysis or Interpretation: C.J., A.A., M.M., Literature Search: C.J., Writing: C.J., A.A., M.M.

Conflict of Interest: No conflict of interest was declared by the authors.

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