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Original Research

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ABSTRACT

Aim. The COVID-19 virus was first identified on December 31st of 2019. Since it was discovered, the virus has infected more than 700 million people worldwide. The delta variant was first discovered in October 2020 in India. The virus was found to be highly transmissible, with a 50-60% higher transmission rate compared to the previous variants. The variant was also found to be more difficult to treat and manage. The epidemiological data and the impact of this variant in Indonesia is still not fully understood. This study intends to investigate the factors that affected mortality in COVID-19 patients during the time of the delta variant in Rumah Sakit Universitas, Indonesia (RSUI).

Methods. This research utilizes a case-control design including 224 COVID-19 patients' medical records from June-August 2021. The factors analyzed are: age, gender, degree of severity, comorbidities, D-dimer, SGOT, and radiology findings.

Results. Logistic regression analysis revealed all the factors increased the odds ratio of mortality except for gender. CKD/AKI (p=0.01), liver injury (p=0.01), severe-critical degree (p=<0.01), and SGOT elevation (p=<0.01) significantly contributed to the final model. **Conclusion.** A significant relationship was found between mortality and age, degree of severity, comorbidities, D-dimer and SGOT elevation, and abnormal radiology findings. Additionally, these factors all contribute to increasing the odds ratio for mortality.

Keywords: COVID-19, Delta Variant, Mortality, Pandemic, D-Dimer

INTRODUCTION

The COVID-19 virus was first identified on December 31st of 2019 as a cluster of pneumonia cases in the province of Wuhan, China. The agent that caused this cluster of pneumonia was from the coronaviridae family and was later identified as SARS-CoV-2. On March 11, 2020, the WHO decided that COVID-19 cases had reached pandemic levels [1]. The pandemic which started in 2019 has spawned many variants, each of variants has caused a large number of deaths. Some of the variants that have occurred are: Alpha, Beta, Gamma, Delta, Epsilon, Eta, Iota, Kappa, N/A, Omicron, Zetta, Mu, and now there are also emerging sub-variants of the Omicron variant cases of which are also found in Indonesia, such as the Orthrus variant, and the Kraken variant has also been found in Indonesia [2]. The Delta variant of the SARS-CoV-2 virus was initially discovered in India in October 2020 and was the result of a spontaneous gene mutation. This variant is known to be highly contagious with a 50-60% higher transmission rate than other virus variants [3,4].

The number of cases caused by this virus continued to increase until mid-June 2021when this virus variant had become dominant among positive patients [5,6]. One of the variants with a high mortality rate and high hospitalization risk is the Delta variant, as shown by previous research, and these mutations were associated with higher transmissibility, higher mortality, and hospitalization rates [7-9]. Nowadays, in several countries, including the United States, the delta variant has the status of Variants Being Monitored (VBM), which is given to variants that have the potential to have a significant impact on existing medical conditions, more severe disease conditions, or variants with a marked increase in transmission, although it is now no longer detectable. However, as the name' being monitored' suggests, monitoring and evaluation as well as studies of this variant must still be carried out because the mutation of each mutation can carry the characteristics of the previous variant and it cannot be known if it will be more severe or milder [10].

Previous studies were conducted in China to examine the factors associated with the severity of the Delta variant. This study examines the factors of age, gender, comorbidities, and symptoms. After being tested, it was found that the factor that most affects the level of severity is age [11]. Other research that has been done before in Indonesia found that similar factors such as life expectancy, the presence of comorbidities, and socioeconomic characteristics. However, in that study, they did not look for factors that had the most influence on the death rate due to COVID-19. Therefore, in this study, the authors looked for the association of factors with deaths caused by the Delta variant [12,13].

This research was also carried out at RSUI, which is a referral hospital for COVID-19. Therefore, patient data collection was carried out optimally, including screening. If there are patients who have symptoms indicating COVID-19, then a SARS-CoV-2 OCR diagnostic examination is carried out so that patients undergoing treatment for COVID-19 infection have been previously confirmed as positive by an adequate gold standard examination. In addition,

as a COVID-19 referral hospital, the patient characteristics are diverse, such as age, gender, and with various comorbidities. Supporting examinations are also provided at RSUI for patients undergoing treatment, and data collection is carried out from these supporting results so that laboratory results and radiological examinations of patients infected with COVID-19 are also available [14].

METHODS

The study design of this research is case-control, with secondary data from COVID-19 patients treated at Rumah Sakit Universitas Indonesia (RSUI) between June and July 2021 as the research subjects. The aim of this study is to calculate the mortality rate from the Delta variant and compare it to the other variants, and to identify the factors affecting mortality. This research was conducted from February to May 2023 at RSUI, where the data are stored. The patients that are included in this study are those admitted to Rumah Sakit Universitas Indonesia (RSUI) in the period of June-August 2021, and patients of all ages with confirmed COVID-19 infection in their medical records. Patients excluded from this study are those patients with confirmed COVID-19 infection with unknown outcome (deceased/alive), and patients that admitted outside the sampling period (1 June 2021 – 31 August 2021).

Statistical analysis was done in SPSS version 27, developed by IBM, SPSS Inc., Chicago. Univariate analysis was conducted to find the distribution and percentages of each variable. Data are presented in frequency tables, with cross tabulation between variables. A chi-square test of independence was also done to investigate the relationship between each variable and mortality. Variables that showed a significant relationship in the chi-square test of independence were entered into a multivariable logistic regression analysis. An equation which included these variables was formulated from the results.

RESULTS

A total of two hundred and twenty-four COVID-19 patients' medical records from Rumah Sakit Universitas Indonesia from June to August 2021 were extracted for this study. A control group of 105 surviving patients' medical records were collected and compared to the test group which included the medical records of 119 deceased patients. Samples were taken randomly using the consecutive method. The process by which the samples were collected is explained in Figure 1. The distribution between gender, age groups, as well as clinical findings are described in Table 1.

[Table 1 about here]

[Figure 1. The process of which the samples were collected about here]

A chi-square test of independence was performed to investigate the relationship between mortality and the patients' characteristics extracted from their medical records. Significant relationships were found between mortality and age, elevation in D dimer and SGOT, radiology results, and all comorbidities, except for asthma, COPD, and autoimmune disease. This is further explained in Table 2.

[Table 2 about here]

A multivariable logistic regression analysis was also performed by selecting variables that were significant in the chi-square test of independence, and by using a rule of thumb of a minimum of 10 subjects per case. This was done to see the impact of the variables on the likelihood of mortality. From this, we included the variables age, DM, hypertension, CHF, CAD/ACS, CKD/AKI, liver injury, degree of severity, laboratory examination, and radiology examination. We also decided to include the variable gender. Although not significant, we concluded that clinical significance outweighed the statistical significance of the variables. The full model containing all variables was statistically significant, $\chi 2(14)=151.08$, $p=<.001$. Overall, the model classified 85.7% of the cases correctly. Three variables that made a significant contribution to the model were liver injury, degree of severity, and SGOT elevation.

These are further explained in Table 3. A multivariable logistic regression equation was formulated from the results in Table 3 which included the variables mentioned above as predictors.

[Table 3 about here]

ln(*odds*) = -7.40 + 0.10 x *age group 45-60* + 0.40 x *age group >60* - 0.10 x *male* + 0.10 x *DM* + 0.26 x *HT* + 0.31 x *CHF* + 0.89 x *CKD/ACS* + 1.27 x *CKD/AKI* + 1.29 x *liver injury* + 1.25 x *D dimer elevation* + 1.56 x *SGOT elevation* + 1.62 x *opacity-infiltrate* + 1.64 x *consolidation*.

DISCUSSION

Our results showed that there was a significant relationship between mortality and multiple factors, such as: age, comorbidities which included DM, hypertension, CHF, CAD/ACS, CKD/AKI, and liver injury, degree of severity, elevation in D dimer and SGOT, and radiological findings. This is reflected by the significant results from the chi-square test of independence. Using a multivariable logistic regression, we were able to build a model using these factors as predictors. In the final model, we decided to include gender as a predictor, although it was not statistically significant, due to its clinical significance. The final model, which included all of these factors showed that they significantly better in predicting the odds when compared to the base model with no factors included. Overall, the model classified 85.7% of the cases correctly regarding mortality outcome. A multivariable logistic regression equation was also formulated to calculate the odds of mortality with the factors as predictors.

Looking at the variables independently, we observed that in the logistic regression model, all factors increased the odds ratio of mortality when present, except for gender. Although not contributing significantly to the model, this finding regarding gender differs from previous studies. In other studies, it was mentioned that women have a protective effect from different antibody responses and hormone regulation [15-17]. Though this was true in their case, other

factors might also contribute to the likelihood of death, such as smoking behavior and lifestyle, which in our case, could be the differing factor. Since these data are not relevant to this study, it was not looked into further. Another study also mentioned that women are more aware regarding general health issues than men. They are also more likely to adhere to infection prevention measures, which could explain the trend in mortality. These data were not available when only looking into medical records, so this then becomes one of the limitations of this study [18,19].

In the logistic regression model, older age groups had a higher odds ratio compared to the younger ones. This finding was in line with the findings of previous studies. The relationship between age and COVID-19 infection has been thoroughly studied. The trend is that the elderly population has a higher risk of contracting COVID-19 and developing a more severe illness. Differences in immune responses are thought to be the underlying cause of this trend [20,21]. Looking at our sample, the proportions are higher in older age groups. The number of patients with comorbidities was also higher, which is often seen in older age groups. In a study conducted in the United States by Adjei et al. (2022), mortality was highest in the elderly group aged >65 years with a disability or with three or more preexisting conditions. The odds ratio for mortality in our study was highest in the age group of >60 years when compared to younger groups. After all factors were tested, we could interpret that the odds of mortality for patients aged >60 with COVID-19 during the Delta period was 1.5 times the odds of patients aged <45 [22].

Vaccination status could also play a role in this case. It is known that vaccination reduced the risk of developing severe illness in adults with COVID-19 [23,24]. In Indonesia, the elderly were eligible for vaccination only 2 months before the sampling period of this study [25]. This could mean that during that period the scope of vaccination for the elderly was still relatively low. Initially, our study planned to include vaccination history as one of the factors. However,

when screening the medical records, the information regarding vaccination history was rarely recorded, or it could be that many of the patients have not yet been vaccinated. Thus, we decided to omit the variable from our study [25].

Our study showed that all comorbidities were responsible for increasing the odds ratio for mortality in the final model. This was in line with previous studies which reported that mortality was mostly found in populations of older age with preexisting conditions [22]. A recent study in Indonesia also reported that hypertension, diabetes mellitus, and cardiovascular diseases were among the top three comorbidities found in patients with COVID-19 in 2020. This was also true in our study, as hypertension and diabetes mellitus were two of the most prevalent comorbidities found in COVID-19 patients in RSUI during the sampling period [26].

For kidney disease, we found that its presence increased the odds ratio of mortality. In our model, the variable CKD/AKI as a predictor significantly contributed to the model. Previous studies also reported similar results in this matter. In a meta-analysis published in 2020, it was observed that CKD was associated with increased risk of severe COVID-19 infection [27]. A prospective cohort study by Cheng et al. (2020), also reported that COVID-19 patients with elevated serum creatinine at admission presented a higher prevalence of intensive care admission and risk of in-hospital death compared to those with normal serum creatinine at baseline. Kidney involvement in COVID-19 patients with a history of kidney disease was thought to be caused by the exertion of the cytopathic effect and virus-induced cytokines, which in turn led to worsening of kidney function [28].

It is known that patients with a higher degree of severity have a poor prognosis which can lead to death. In our study, we obtained an odds ratio of 22.39, which means that patients with severe to critical severity had 22.39 times higher odds of mortality than those with mild to moderate degrees, after controlling all factors.

Patients infected with COVID-19 can experience various clinical manifestations of symptoms that can show different degrees of severity of COVID-19 infection. The variety of manifestations can range from no symptoms at all to a critical degree. However, in this study, which was conducted in a hospital so that the data in the study were taken from patients who were hospitalized and the indications for hospitalization were symptomatic, the degrees of severity included in this study are mild illness, moderate illness, severe illness, and critical illness. Patients who had a mild degree of illness demonstrated clinical manifestations such as fever, cough, sore throat, fatigue, anorexia, myalgia, malaise, headache, loss of smell (anosmia), and gastro-intestinal symptoms such as nausea, vomiting and diarrhea. To ensure that a patient is classified as mildly ill, they must not experience symptoms of shortness of breath or dyspnea on exertion, and when radiological imaging is performed no abnormal features of the lungs should be found [29,30].

Clinical manifestations in patients infected with COVID-19 categorized as moderate are those with or without symptoms defined as a mild degree, but with symptoms that lead to pneumonia as indicated by the presence of fever, cough and shortness of breath, followed by a measurement of SpO2 saturation ≥94% on room water. Meanwhile, in moderate-grade pediatric patients, it is indicated by complaining of coughing or difficulty breathing, with rapid breathing and/or the presence of chest wall indrawing [30].

In severe and critical illness, most patients have to receive intensive care. Patients who are classified as having the severe illness are those who have severe symptoms, especially severe shortness of breath as indicated by an increase in respiratory rate, with a respiratory rate measurement of >30 breaths/min, or lung abnormalities on imaging such as extensive infiltrates that can reach more than 50% of the lungs. Another symptom of the severe degree of COVID-19 infection is a decrease in peripheral saturation with SpO2 <93% of room air [30,31].

The most severe degree of COVID-19 infection is the critical degree, where the patient has a very high probability of developing acute respiratory distress syndrome (ARDS), which is one of the causes of death in COVID-19 infection. In this condition, most patients already need life support equipment, including mechanical ventilation. Very severe infections of this degree also increase the incidence of sepsis, up to virus-induced distributive (septic) shock. In conditions of critical degree infection there can also be an excessive inflammatory response, or what is also known as a cytokine storm, which is also the cause of death from COVID-19 infection [30,31].

In patients with the severe to critical degree of the disease, less oxygen can be received by the body which can lead to hypoxemic conditions. Hypoxemia itself is a condition where there is a decrease in the partial pressure of oxygen in the arteries. In the presence of a hypoxemic condition, if it is left untreated and deteriorates, the patient will fall into a hypoxic condition. In previous studies, it was found that hypoxemia was responsible for death in patients with severe COVID-19. Ischemic or hypoxic events also occur in ICU patients and are responsible for the death of COVID-19 patients receiving treatment in the ICU [31,32].

Some patients with COVID-19 infection experience the elevation of D-dimer values. It is known that patients with D-dimer elevation have a higher probability of mortality. In our study, we obtained an odds ratio of 3.48, which means that patients with D-dimer elevation have 3.48 times higher odds of mortality than those with normal D-dimer levels after controlling all factors, although the difference is not significant. From the Chi square analysis, D-dimer elevation and mortality related significantly with a p value of $p<0.001$.

D-dimer is a soluble fibrin degradation product which is the result of the systematic degradation of a vascular thrombus previously through a fibrinolytic mechanism in the blood clotting system. The function of D-dimer is as a marker of coagulation activation, so the value of D-dimer can also be a biological marker in conditions of hemostatic disorders, and as an

indicator of intravascular thrombosis. From previous studies, it was found that patients infected with COVID-19 with severe symptoms had higher D-dimer levels than patients with mild clinical manifestations, where this condition was due to the greater risk of developing thrombosis in patients with increased D--dimer values. In addition, increased D-dimer is an indirect manifestation of an inflammatory reaction that can lead to septic conditions because inflammatory cytokines can cause coagulation dysfunction and fibrinolysis in the alveoli [33-35].

Clinically, the results of this study showed that of the 119 patients who died, there were 115 patients who had increased D-dimer and 4 patients who had D-dimer values within normal limits. On the basis of previous research, increased D-dimer is also a significant marker in several clinical conditions such as pulmonary embolism, deep vein thrombosis (DVT), and disseminated intravascular coagulation (DIC). These three clinical conditions also have a prognosis of mortality in individuals who experience them. So, aside from COVID-19 infection, there is still the possibility that the patients in this study already had a high baseline D-dimer prior to COVID-19 infection because they had underlying clinical conditions [36].

In our study, increased SGOT was significantly associated with mortality. From the chi-square analysis a significant relationship was found with a p value $p = 0.00$. With multivariate analysis, an odds ratio of 4.74 was obtained with a significance of $p = 0.003$. This odds ratio means that patients with increased SGOT have 4.74 times higher odds of mortality than those with normal SGOT, after controlling all factors.

In previous research it was found that an increase in aminotransferase levels could predict death in COVID-19 infection in severe cases, and this study also produced output to optimize SGOT measurements because it can be useful as an identification of the risk of death in patients infected with COVID-19. Apart from increasing levels of aminotransferase, the risk of death can also occur in patients with a history of liver injury. We found that liver injury increased

the odds of mortality in our model and significantly contributed to our model. Liver injury significantly contributed to the mortality in patients with COVID–19 with an increased OR of 3.64 This result was in line with the results of a recent meta-analysis published in 2020. It was reported that the pooled ORs of 40 studies which included 908,032 participants were 2.44 and 2.35 for increased severity of COVID-19 infection and death, respectively, when compared to patients without chronic liver disease [37-39].

Radiological findings are often used as one of the factors to classify degrees of severity in COVID-19 patients. In our case, as a predictor, findings of abnormality in chest x-ray increased the odds of mortality in the model. Our chi-square test of independence of the results showed that there was a significant relationship between chest x-ray and mortality.

On radiological examination using chest x-ray, the results that can be described are normal lung images or abnormal images, which are interpreted with findings such as infiltrates, consolidation, and the appearance of masses. However, in cases of COVID-19 infection, the findings that were most often found in previous research were consolidation, opacity and nodules. Other studies also found that the appearance of lung consolidation had a significant relationship with patients who were positive for RT-PCR COVID-19, and from this study the increased risk of having a consolidated lung appearance was defined in patients infected with COVID-19 [40-41].

We found that there was no significant relationship between COPD or asthma, and mortality. This finding contradicted previous systematic review and a meta-analysis which investigated the effect of pre-existing asthma and COPD on COVID-19. Yuka (2022) suggested that having COPD significantly increased the likelihood of mortality in COVID-19 patients. We believe that our finding of no relationship was more likely due to the very small number of cases found with pre-existing asthma and COPD. As seen in the chi-square table, there were further than 10 cases of both asthma and COPD. In contrast, in the review and meta-

analysis previously mentioned, hundreds and thousands of asthma and COPD cases were included, respectively [42].

Comparing Delta to the previous variants, one study investigated factors affecting death rate and intensive care admission. Vassalo et al (2020) suggested that maximum oxygen flow and degree of severity were significantly related to death and intensive care admission. Our study also found that the degree of severity was significantly related to mortality, and when this was included in the logistic regression model, it was found to contribute significantly to it [43].

We identified that there were many limitations to our study. Firstly, our study was only able to find correlations and not causation between the factors and mortality. Additionally, there might have been bias during the assessment and writing of the medical report by the health care providers throughout the treatment of these patients. As mentioned previously, there was a variable that we decided to omit due to data availability. These matters cannot be assessed due to the retrospective nature of our study. Secondly, our study also did not take into consideration treatments given during the length of hospitalization. These might influence our main outcome given the variation of patients included in our study. We consider this to be another question left to be answered in another study. However, we still believe that our study could provide insights regarding the factors affecting COVID-19 outcome since this was not the first time we were faced by this type of pandemic, since it is known that the pathogen causing this disease had its roots in the same SARS-CoV that was identified back in 2003 [44].

CONCLUSION

In summary, we found that there was a relationship between mortality and age, comorbidities including DM, hypertension, ACS/CAD, CHF, CKD/AKI and liver injury, degree of severity, D-dimer and SGOT elevation, and radiological findings. The mortality rate was found to be higher in males, the elderly aged >60, those with comorbidities, moderate-

severe disease, elevated D dimer and SGOT, and abnormal radiology findings. From a multivariable logistic regression analysis, we were able to formulate a model showing that all these factors increase the odds of mortality when present. However, the nature of this study only allowed us to find correlations between mortality and these factors and not the causations.

Recommendation

Future studies using other study designs, such as a prospective cohort, might be able to investigate further the causal relationship between the factors and mortality, although we realize that this type of study requires a lengthy amount of time and significant funding. This is why we opted for a study type that was more feasible. Additionally, survival analysis may also be done in the future when looking into COVID-19 patients with the factors mentioned in this study.

What is already known on this topic: The Delta variant was found to be highly transmissible, with a 50 – 60% higher transmission rate compared to the previous variants. The variant was also found to be more difficult to treat and manage. Research in China found that the factor that most affected the level of severity is age.

What this study adds: There was significant relationship between mortality and age, degree of severity, comorbidities, D-dimer and SGOT elevation, and abnormal radiology findings. Additionally, these factors all contributed to increasing the odds ratio for mortality.

Author's contributions: Acquisition, analysis and interpretation of data: RH, NH, SA, and NSB; Drafting the article: RH, NH, SA, NSB, ACI, SV, RAP, CPA, AL, SSZ, HRPA, NW, APM, and GCF; Revising it critically for important intellectual content: RH, NH, SA, and NSB; Approved final version of the manuscript: RH, NH, SA, and NSB. All authors have

critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Ethics approval and consent to participate

This research has received ethical approval **(registration number: S006/KETLIT/RSUI/II/2022)** from the Research Ethics Committee of the University of Indonesia Hospital - University of Indonesia. Participants were informed about the study verbally and in written form and all provided written consent. All methods were carried out in accordance with relevant guidelines and regulations in the declaration of Helsinki.

Declaration of Conflicting Interests

The authors declare that they have no competing interests.

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Data availability statement

Data in this study are available from corresponding author upon reasonable request

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