ORIGINAL ARTICLE

Trend Analysis of Clinical Characteristics of COVID-19 with Diabetes Based on Disease Severity

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ABSTRACT

Diabetes Mellitus (DM) increases the risk of COVID-19's severity and mortality than those without DM. The aim of this study was to determine the characteristics and trends by disease severity of DM patients with COVID-19. A cross-sectional study examining retrospective medical records was conducted in patients with diabetes mellitus who were confirmed to have COVID-19 by reverse transcription-quantitative polymerase chain reaction (RT-qPCR). All adult patients (age > 18 years) with DM and COVID-19 registered and treated at the Surabaya Hajj General Hospital from May 2021 to the end of December 2021 were included in this study. Trends in each subject's characteristics are displayed in a graph with a trendline based on the severity of COVID-19. The highest proportion of disease severity of DM patients with COVID-19 is mild and moderate cases (72.2%), with 27.8% severe and critical cases. The average aged of the subjects was 56.38 ± 9.60 years. The age group with the highest proportion was 50-59 (42.6%). There are slightly more female than male patients (50.4% vs. 49.6%). The tendency is that the disease's severity increases with BMI, increasing HbA1C level, low sodium level, high chloride level, and high CRP and D-dimer levels. The pattern of clinical and laboratory features of DM patients based on the severity of COVID-19 infection shows the tendency for the disease severity worsens with increasing BMI, HbA1C level, low sodium level, high chloride level, and high CRP and D- dimer levels.

Keywords: *COVID-19 severity, clinical characteristics, bmi, glycaemic control, diabetes*

INTRODUCTION

Diabetes mellitus (DM) is one of the most common comorbidities in patients infected with COVID-19 and significantly affects mortality.[1-3] DM increases 2.20-fold the risk of COVID-19's severity and increases mortality 2.52-fold compared with patients without DM.[4] In one study, COVID-19 patients with DM required a more extended hospital stay (14.4 days)than their counterparts (9.8 days).[5]

In DM patients, there is an increased expression of Angiotensin Converting Enzyme 2 (ACE-2) and furin receptors as well as immune system disturbance due to decreased T-cell function and increased interleukin-6 (IL-6) levels, leading to increased patient severity.[6,7] In addition, ACE-2 receptors are also found in various organs, such as on the surface of pancreatic beta cells, causing hyperglycemia, as well as in various other organs, so that multiple organ damage may develop (kidneys, liver, lungs, and other organs), which increases the severity of COVID-19 patients with DM. Moreover, the inability of the host to eliminate the virus due to DM and the dysfunction of the immune system will lead to a severe cytokine storm in COVID-19; hence the endothelial damage will increase.[7,8] All these eventually lead to organ hypoperfusion, tissue hypoxia, mitochondrial dysfunction, apoptosis, and necrosis, resulting insepsis, multiple organ dysfunction syndrome (MODS) to acute respiratory distress syndrome (ARDS)[3,9,10], and eventually increases the severity of COVID-19 patients.

The severity of COVID-19 infection in DM patients is influenced by hosts, pathogens, and the environment conditions. Host factors influencing glycemic control include older age[11], comorbid conditions (obesity)[3], electrolyte abnormalities, hypercoagulable states[12,13], and macrovascular and microvascular complications in DM.[2,4] HbA1c levels and blood glucose levels can assess the glycemic control of DM patients concerning disease severity, as they describe the glycemic state in the body.[14] Hyperglycemic states lead to immune system dysfunction and trigger oxidative stress and inflammatory processes that manifest as endothelial damage. Persistent endothelial damage leads to coagulation disorders causing both macrovascular and microvascular damage, a chronic complication of DM.[13,14] This study delves into the relationship between COVID-19 severity and DM, a critical comorbidity that hasn't been extensively studied, particularly in Indonesia. The study also investigates various clinical and laboratory factors to add to the growing research on the specific features affecting disease outcomes in this high-risk group.

METHODOLOGY

Study Design and Research Subject

This study is part of a larger research project that has been previously published.[15] The previous study established the epidemiological profile of COVID-19 in DM patients with various comorbidities associated with increased severity and death. Meanwhile, in this study, we examine the trends in clinical characteristics in DM patients with COVID-19 based on theseverity of the disease. A cross-sectional study examining retrospective medical records was conducted in patients with diabetes mellitus who were confirmed to have COVID-19 by reversetranscription- quantitative polymerase chain reaction (RT-qPCR). All adult patients (age > 18 years) with DM and COVID-19 registered and treated at the Surabaya Hajj General Hospital from May 2021 to the end of December 2021 were included in this study. A diabetic patient isdefined as an individual who has random blood sugar (RBS) >200 mg/dL on admission, and this level persists until discharge from the hospital. The Institutional Ethics Commission has approved all research procedures with the number 073/30/ KOM.ETIK/2021.

Variables

The severity of COVID-19 in this study was divided into four criteria, mild, moderate, severe, and critical, referring to the classification of the Decree of the Minister of

Health of the Republic of Indonesia (HK.01.07/MENKES/4641/2021) and World Health Organization (WHO).[16]

Patient demographic characteristics such as age and gender were collected. Clinicalcharacteristics related to the severity of COVID-19 refer to previous studies, including Body Mass Index (BMI [kg/m^2]), hemoglobin levels (g/dL), albumin (mg/dL), random blood glucose (g/dL), HbA1c (%), electrolyte levels (potassium, sodium, chloride), renal profile (e-GFR), and several clinical biomarkers for inflammation and infection such as procalcitonin (%), creatinine reactive protein (CRP [mg/L]) and D-dimers (µg/dL).

WHO Asia Pacific criteria[17] are used in classifying BMI into underweight (<18.5 kg/m^2), normal (18.5 - <25 kg/m^2), overweight (25 - <30 kg/m^2), obesity class 1 (30 - < 35 kg/m^2), class 2 obesity (30 - <40 kg/m^2), and class 3 obesity (≥40kg/m^2).

RESULT

A hundred and fifteen DM patients in whom COVID-19 was confirmed between May 2021 and December 2021 were included in this study. The distribution of severity in DM patients infected with COVID-19 at Surabaya Haji Hospital found 2 (1.7%) cases of mild COVID-19, moderate degree, the highest number of cases of 81 (70.4%) cases, 26 (22.6%) severe cases, and 6 (5.2%) critical cases.

The age characteristics of the patients in this study averaged 56.38 ± 9.60 years. The youngest affected person was 36 years old, and the oldest was 83 years old. The age group with the highest proportion was 50-59 (42.6%). There are slightly more female than male patients (50.4% vs. 49.6%). The mean BMI of patients in this study was 25.20 ± 2.81 kg/m2, with 41.7% belonging to the BMI category of class 1 obesity, followed by 30.5% overweight (Table 1).

Table 1. Subject Characteristics

Characteristics	Frequency	%	Characteristics	Frequency	%
Age (Years) [x±SD; Min-Max]	56.38±9.60	36-83	**HbA1C (%) [x±SD; Min-Max]**	10.85±1.99	6.40-15.40
<40	5	4,3	≤7	1	2.5
40-49	18	15,7	>7	39	97.5
50-59	49	42,6	**Natrium (mmol/L) [x±SD; Min-Max]**	132.56±6.34	108-151
60-69	35	30,4	<136	79	69.2
≥70	8	7	136-145	33	29
Sex			>145	2	1.8
Male	57	49.6	**Kalium (mmol/L) [x±SD; Min-Max]**	4.86±5.75	2.5-6.5
Female	58	50.4	<3.5	6	5.3
BMI (kg/m2) [x±SD; Min-Max]	25.20±2.81	19.5-34.31	3.5-5.0	92	81.4
Normal	26	22.6	>5.0	15	13.3
Overweight	35	30.5	**Chloride (mmol/L) [x±SD; Min-Max]**	93.10±16.69	64-110
Obese Class 1	48	41.7	<96	57	50.4
Obese Class 2	6	5.2	96-106	49	43.4
Hb (g/dL) [x±SD; Min-Max]	13.45±2.36	4.10-18.50	>206	7	6.2
<10	8	7	**Procalcitonin (%) [x±SD; Min-Max]**	0.58±1.36	0.02-9.87
≥10	106	93	<0,05	6	11.5
Albumin (mg/dL) [x±SD; Min-Max]	3.43±0.44	2.4-4.3	≥0,05	85	88.5
<3,5	50	52.6	**CRP (mg/L) [x±SD; Min-Max]**	131.70±195.00	1.1-1,338.0
≥3,5	45	47,4	<5	5	5.4
RBG (g/dL) [x±SD; Min-Max]	302.18±139.12	53-830	≥5	88	94.6
<70	1	0.9	**D-dimer (µg/dL) [x±SD; Min-Max]**	3.99±7.16	0.40±63.00
70-200	20	17.5	<1	22	23.2
>200	93	81.6	≥1	73	76.8
			e-GFR(mL/min) [x±SD; Min-Max]	76.81±44.95	6.45-261.81

Most patients had a Hb level (g/dL) ≥10 (93%) and an albumin level < 3.5 mg/dL (52.6%). The glycaemic control of the DM patients in this study was poor, with a proportion of 81.6% RBG > 200 mg/dL and 97.5% HbA1C values > 7%. The electrolyte level results showed that most patients had sodium levels < 136 mmol/L (69.2%), potassium levels 3.5-5.0 mmol/L (81.4%), and chloride levels < 96 mmol/L (50.4%). Most patients had elevated levels for

inflammatory markers: Procalcitonin ≥ 0.05% at 88.5%, CRP ≥ 5 mg/L at 94.6%, and D- dimer ≥1 µg/dL at 76.8%. The mean e-GFR of patients was 76.81±44.95 mL/min (Table 1). Trends in clinical characteristics of DM patients based on COVID-19 severity.

Based on age, the trend analysis showed a tendency for the severity of the disease to decrease with increasing age (Fig. 1A.). This shows that the older age group in this study is not always linear with higher COVID-19 severity. The BMI trend found that the higher the BMI, the higher the severity of the disease (Figure. 1B).

Analysis of the blood glucose levels shows that the severity of the disease tends to decrease with higher random blood glucose levels (Figure. 2A). In contrast, the graph shows the disease worsening with increasing HbA1C levels (Fig. 2B.). Based on the hemoglobin level of the patients, the severity of the disease tends to increase with higher Hb levels (Figure. 2C). Analysis of the albumin level revealed a trend pattern indicating an increase in severity the higher the albumin level (Figure. 2D).

Electrolyte level testing involves the analysis of sodium, potassium, and chloride. Analysis of the trend pattern of sodium electrolyte levels revealed a trend pattern that showed an increase in severity as the sodium level increased. When the potassium electrolytes were examined, there was no clear trend pattern of potassium values at different severity levels. In addition, when the chloride level was examined, a trend pattern showed an increase in severity with increasing chloride levels. In this study, the assessment of chronic kidney disease stages was calculated based on glomerular filtration rate (e-GFR), as shown in the graph below, which shows a pattern of increasing disease severity in patients with decreasing e-GFR (Fig. 4A-D). Examination of inflammatory markers showed a trend toward decreasing severity with increasing procalcitonin levels. In contrast, CRP and D-dimer levels analysis showed that disease severity tended to worsen with increasing both markers levels (Figure. 5A-C).

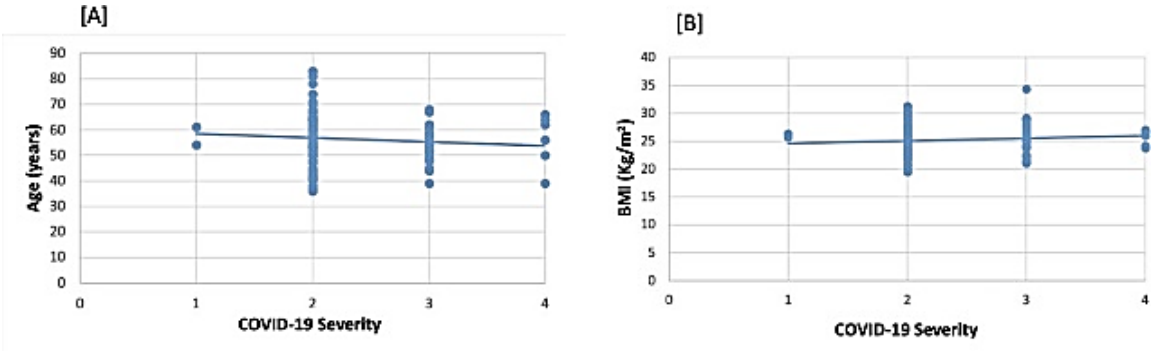

Figure 1. Trend in Age (years) and BMI (kg/m2) by COVID-19 Severity

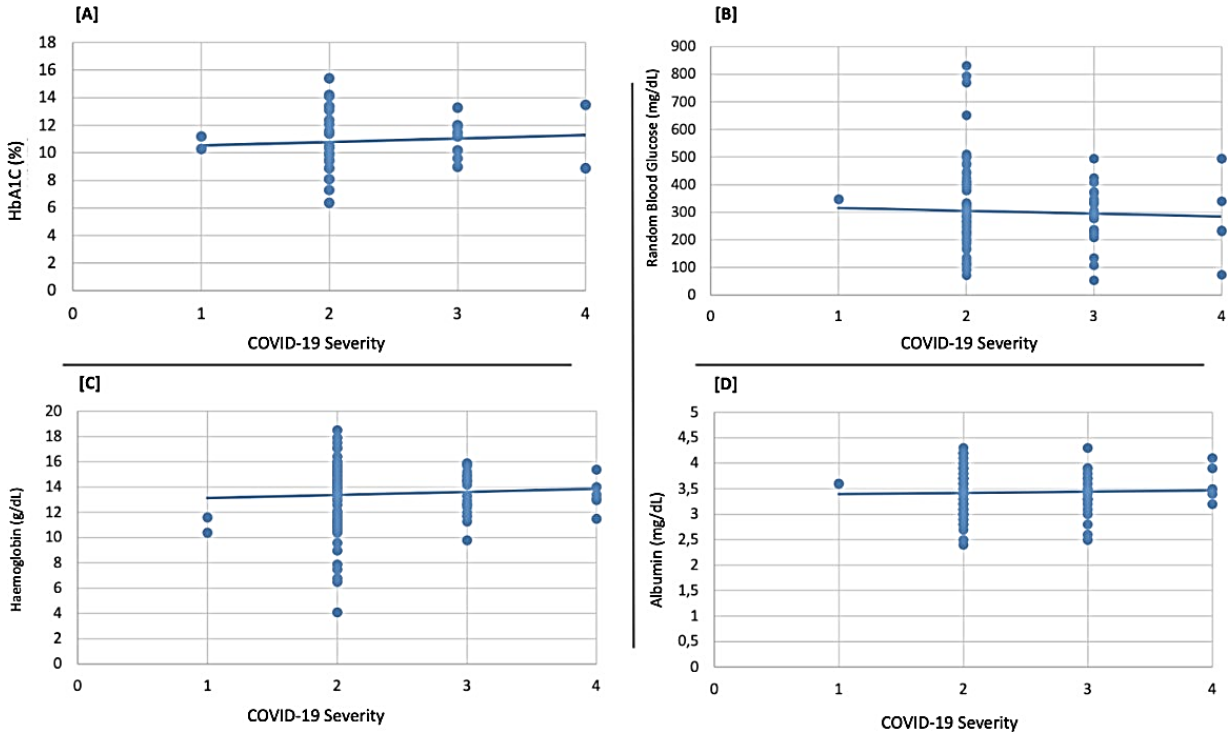

Figure 2. Trend in HbA1C (%), RBG (g/dL), Hemoglobin (g/dL) and Albumin (mg/dL) by COVID-19 Severity

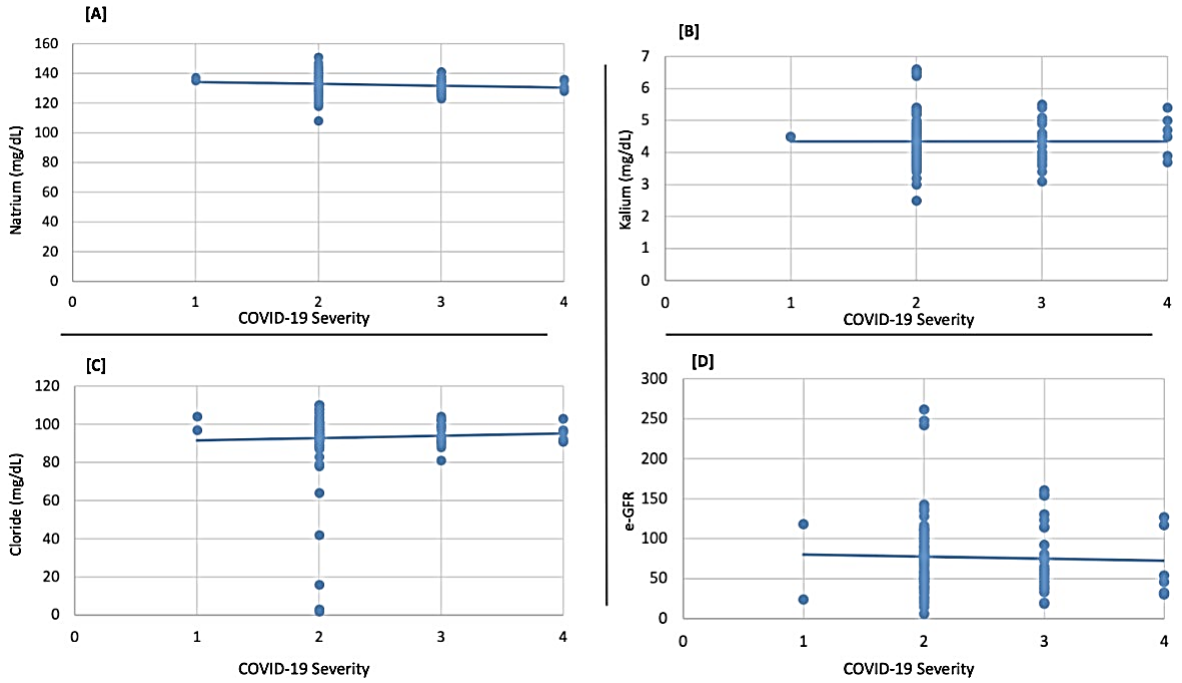

Figure 3. Trend in Natrium, Potassium, Chloride (mmol/L) and e-GFR (mL/minute) by COVID-19 Severity

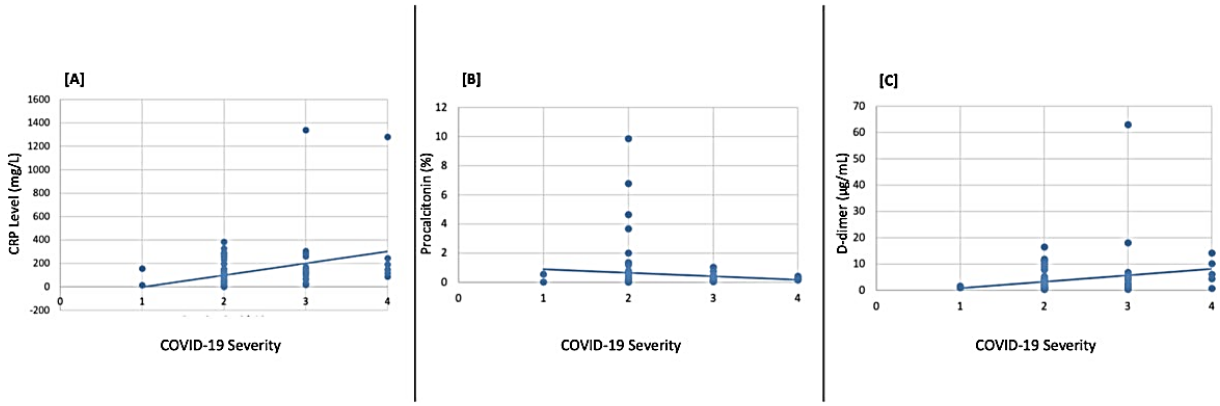

Figure 4. Trend in CRP (mg/L), Procalcitonin (%), and D-dimer (µg/mL) by COVID-19 Severity

DISCUSSION

From the analysis results, it was found that the trend of disease severity was sloping withage but increased with higher BMI. A study with the same research subject, COVID-19 patientswith type 2 DM, by Zhang et al. (2020) obtained different results that the older the age, the degree of severity would increase (p=0.012), with the median age in the severe group being 72 years.[18] Another study also reported that Older age was independently associated with a higherrisk of death (≥80 vs <40 years: odds ratio [OR], 11.15, p<0.05).[19] A meta-analysis in China involving 3027 COVID-19 patients also showed that age >65 was a risk factor for disease progression to severe (OR 6.06, 95% CI: 3.98-9.22, p<0.00001).[18] This could be due to the variation in the age of the patients who visited the hospital, where most of the patients who came to the Hajj Hospital were in the 50-59 year age group.

A study in New York using 504 samples stated that overweight and obesity in COVID-19 patients increased the risk of severity and mortality compared to patients with normal nutritional status. Obesity increases the risk of complications in the age group of 45-64 years.[20]Meta-analytic studies state that obesity in COVID-19 patients increases severity and mortality.[21] The mechanism that causes them is that obesity reduces the expansion of the diaphragm, which reduces. the total lung capacity. Obesity increases levels of proinflammatory IL-6, leading to a cytokine storm.[22] The hormone leptin also increases. Increased leptin causesleptin resistance, and the maturation of B cells decreases, resulting in decreased immune response.[23] Adipose tissue increases in obese patients, which aligns with the increase in ACE-2 receptors so that the virus can quickly enter the body.[24,25] ACE-2 receptors are expressed in the gastrointestinal, lung, liver, and kidney pathways. Obese patients are associated with comorbidities such as DM, hypertension, and heart disease.[26,27]

The trend analysis also illustrated the sloping disease severity trend along with higher random blood sugar levels. On the other hand, the disease's severity worsens as the HbA1C level increases. These results contrast a study by Kandinata et al., where RBG levels were independently related to the severity, and HbA1C was not significantly related. The study explained the primacy of RBG risk factors concerning the severity of COVID-19 in DM patients; RBG modulates the inflammatory response and exacerbates cytokine storm, endothelial damage, and glucotoxicity, which causes interstitial lung damage and increases the risk of ARDS and death.[28] The different results may be affected by the different RBG variations,and the significance analysis used. This study examined only trends without analysis and control for possible confounding variables.

Based on the patient's blood hemoglobin level, it is shown that the severity of the disease tends to increase along with high hemoglobin levels. In several studies, hemoglobin level is associated with the severity of COVID-19 cases. Nonetheless, most studies associate

low Hb levels (<10 g/dL) with disease severity and risk of death.[13,29-31] The study conducted by Sayad et al. yielded slightly different results.[32] His study found an increase in Hb in patients who did not survive, although it was not statistically significant. Similar results were also shown in a study by Sarcia et al., where some patients who did not survive showed elevated Hb levels. The underlying mechanism is unclear, but it is associated with hypercoagulability and polycythemia vera in some COVID-19 patients, which can cause systemic thrombosis.[29]

The results showed an increase in severity with lower sodium levels for electrolyte levels. Nevertheless, the pattern trend is different with potassium levels, and there is no clear pattern of trends at various degrees of severity. Meanwhile, the higher the chloride level, the more likely, the higher disease severity found in the patients. Research reveals that abnormal sodium levels are a risk factor for poor prognosis in COVID-19 patients. In many viral diseases, electrolyte imbalance, especially hypokalaemia, has significant clinical implications in patientmanagement and contributes to the pathogenesis of COVID-19.[33,34] Type 2 DM causeselectrolyte balance disturbances such as hyponatremia and hyperkalemia. Patients with type 2DM tend to experience more frequent hyperkalemia due to redistribution into the intravascular fluid, whereas COVID-19 causes hypokalaemia due to increased excretion of K^+ in the urine. Researchers found that chloride levels in critical patients were higher when comparing the number of patients with hypochloraemia and normal chloride. Electrolyte imbalance in COVID-19 patients with Type 2 DM comorbidities can potentially increase the risk of death or more severe COVID-19 disease.[33,35]

Based on the e-GFR, this study found a tendency for the disease to worsen in patients with decreasing e-GFR. A study conducted by Zhang et al. (2020) on the subject of COVID- 19 patients with DM found that the severely ill group had a lower median eGFR than those who were less severe (81 vs. 89, p<0.001).[18] Meanwhile, in another study also conducted by Zhang et al. (2020), it was found that there was no difference in e-GFR values at admission and severity in COVID-19 patients with DM. The examination and analysis of inflammatory markers found that the severity pattern tends to worsen with increasing CRP and D-dimerlevels.[36] However, a trend of severity sloping with increasing procalcitonin levels is obtained. Research in COVID-19 patients with type 2 DM found that CRP and procalcitonin were significantly higher in severe cases than in less severe cases (CRP 51.8 vs. 8.7, p<0.001 and procalcitonin 0.19 vs. 0.05, p = 0.012).[36]

Different trends in procalcitonin levels in this study could be due to different examination time points in patients. The results of previous studies showed that the average serum procalcitonin levels were more than four times higher in critically ill patients and more than eight times higher in critically ill patients than in moderately ill patients. However, procalcitonin levels slowly decrease in patients who go home and showimprovement.[37] The study suggests that healthcare providers should consider personalized care for COVID-19 patients with diabetes. Factors like BMI, HbA1C levels, and electrolyte imbalances appear to correlate with disease severity, which may help in risk stratification. The findings emphasize the significance of glycemic control for diabetic COVID-19 patients, managing electrolyte imbalances, and monitoring elevated CRP and D-dimer that may help in early risk assessment and targeted interventions.

This study, however, has several limitations. First, the study is limited to a single center; thus, the sample size may not fulfill all variations in DM patients. A multi-center approach must be considered. Second, the nature of the cross-sectional study utilizing retrospective medical records could not show the temporal effect of clinical characteristics by COVID-19 severity.

CONCLUSION

The pattern of clinical and laboratory features of DM patient based on the severity of COVID-19 infection treated at Haji Surabaya General Hospital shows the tendency that the severity of the disease increases with increasing BMI, HbA1C level, low sodium level, high chloride level, and high CRP and D-dimer levels.

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