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Characteristic profiles of patients with diabetes mellitus and COVID-19 during the second epidemic wave in East Java, Indonesia: a retrospective study

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ABSTRACT

Background: The transmissibility and severity of coronavirus disease 2019 (COVID-19) are higher in the delta variant (B.1.617.2) infection responsible for Indonesia's second epidemic wave. This study aimed to establish an epidemiological profile of COVID-19 in patients with diabetes mellitus, a comorbid that has been widely suggested for its association with increased severity and mortality.

Methods: This study employed a retrospective observation on medical records from May to December 2021. Patients (n=115) aged >18 presented with COVID-19 and diabetes mellitus were enrolled. The SARS-CoV-2 infection was confirmed by a pharyngeal swab sample's reverse transcription-quantitative polymerase chain reaction (RT-qPCR). The diabetic condition was determined by previous medical records and persistent level of random blood sugar (RBS) of >200 mg/dL. Demographic, clinical characteristics, COVID-19 symptoms, radiological findings, and hematological and coagulopathy markers were collected from the medical records. The data were presented as frequency (%) assigned based on severity levels: mild, moderate, severe, and critical COVID-19.

Results: A group of patients aged 50—59 years had higher prevalence of severe COVID-19 (n=14; 28.6%) than the other groups. Severe cases were relatively more common in a group with body mass index (BMI) ranged from 30—<35 kg/m^2 (n=13; 27.1%). Notably higher number of severe cases was recorded in patients having <3.5 mg/dL albumin (n=11 out of 50), >200 mg/dL RBS (n=22 out of 93), and ≥1 µg/mL D-dimer (n=18 out of 73). Critical COVID-19 cases were found in those with C-reactive protein levels of <5 mg/L (n=6; 6.8%) and procalcitonin levels of ≥0.05 ng/mL (n=6; 7.1%). Patients who had stage 1 and 3 chronic kidney disease (CKD) were found to develop critical COVID-19 with a frequency of 5.9% (n=2) and 10.5% (n=4), respectively.

Conclusion: The severity of COVID-19 in diabetic patients is indicatively associated with the age, BMI, hematological and coagulopathy markers, and CKD. Active monitoring of these parameters in diabetic COVID-19 patients is encouraged.

Keywords: blood glucose, chronic disease, comorbidity, pneumonia, SARS-CoV-2.
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INTRODUCTION

Up to this date, coronavirus disease 2019 (COVID-19), a respiratory disease caused by a severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), remains as a major public health challenge. Since this virus is a positive-sense single-stranded RNA virus, its rapid mutation has been expected and proven to keep emerging.[1,2] This fact underlies the challenge in treating this disease, especially with limited FDA-approved drugs and effective vaccines.[3-5] The second wave in Indonesia is thought to be resulted from the spread of Delta variant (B.1.617.2), which was also experienced by the countries nearby.[6,7] This epidemic wave dampened many health facilities in the country, affecting vulnerable populations such as pregnant women.[8]

The emergence of delta variants has triggered attention from public health practitioners, owing to its higher transmissibility and ability to evade antibodies.[1] According to a published report by Centers for Disease Control and Prevention (CDC), the in-hospital mortality rate during the delta-predominating phase reached 15.1%.[8,9] During the epidemic wave, despite the Indonesian vaccine coverage that had successfully reached 5.5%, there were still 919 COVID-19-associated deaths reported daily.[6] Even after being vaccinated, the individuals are not completely immune from SARS-CoV-2 infection, and those with hypertension remained likely to be hospitalized.[10] Studies in understanding factors contributing to the severity and mortality of this disease is of urgent matter. Notably, the research should focus on people at risk, including those suffering from diabetes mellitus.

Diabetes mellitus comorbidity is thought to contribute to the worsening progression of pathogen infections.[11] Prevalence of diabetic patients infected by the delta variant was reported to be 18.4% among French population.[12] In a previous report, individuals with diabetes mellitus were found to be more susceptible against viral infections.[13] Interestingly, incidence of type 2 diabetes mellitus increased among patients with COVID-19, hinting the risk of blood glucose dysregulation by the SARS-CoV-2 infection.[14] However, the higher prevalence of infection among diabetic populations could be derived from the overlapping between diabetes and factors contributing to health disparities such as poverty, racism, improper sanitation, and high-risk jobs.[13] In regards with the case in Indonesia, there have been several epidemiological studies performed, but they were not thorough and specific for diabetic population.[15] Thus, this study aimed to close the gap of epidemiological studies on COVID-19 and diabetes mellitus.

METHODS

Study design

This was a retrospective study aiming to observe the characteristics of diabetic patients with respect to the severity of COVID-19. A total of 115 patients having laboratory-confirmed SARS-CoV-2 infection and diabetes mellitus, admitted to the Haji Surabaya General Hospital, were recruited. Medical records dated from May 2021 to December 2021 were used for the investigation. Since this study was based on medical records, no signed informed consent was required.

Subject enrolment

Due to the limited number of patients admitted to the hospital, we decided to employ total sampling, where all patients meeting the inclusion criteria were enrolled. Patients aged above 18 years, diagnosed with diabetes mellitus, and admitted to the hospital with COVID-19 were recruited. The COVID-19 status was confirmed by the reverse transcription-quantitative polymerase chain reaction (RT-qPCR) using a pharyngeal swab with a cycle threshold (Ct) cut-off of 40. A diabetic patient was defined as an individual having random blood sugar (RBS)>200 mg/dL on admission and the level persisted until discharged from the hospital. No specific exclusion criteria were adopted, but medical records with incomplete characteristics data were excluded.

Data retrieval

From the medical records, we collected the patient's characteristics including age, sex (male or female), body mass index (BMI), and smoking habits ('yes' or 'no'). Clinical characteristics observed in this study included systolic and diastolic blood pressures, pulse, respiration rate, temperature, and oxygen saturation. The BMI was measured by dividing the patient's body weight by the square of the body length, where the obtained value was expressed as kg/m^2. Herein, we employed the WHO criteria in classifying the BMI into underweight (<18.5 kg/m^2), normal (18.5—<25 kg/m^2), overweight (25—<30 kg/m^2), class 1 obesity (30—<35 kg/m^2), class 2 obesity (30—<40 kg/m^2), and class 3 obesity (≥ 40 kg/m^2).

The clinical characteristics were recorded during the initial admission. Previous disease histories such as hypertension, hypertensive heart disease, coronary heart disease, and hemodialysis were extracted as well from the medical records. The presence of COVID-19 symptoms (dyspnea, cough, fever, nausea, weakness, appetite loss, throat pain, headache, abdominal pain, reduced consciousness, diarrhea, sputum, myalgia, and anosmia) was also acquired. Findings based on the chest X-ray images were included in this report, where pneumonia and bronchitis were observed. Moreover, we also collected laboratory findings including serum levels of hemoglobin, albumin, natrium, potassium, chloride, RBS, HbA1c, D-dimer, procalcitonin, C-reactive protein, and creatinine. Chronic kidney disease (CKD) was classified based on the estimated glomerular filtration rate (eGFR) derived from the calculation using serum creatinine level, based on the suggestion from a previous study.[16] Patients were categorized for having stage 1 CKD, if the eGFR reached ≥90 mL/min; stage 2 — 60 to 89 mL/min; stage 3 — 30 to 59 mL/min; stage 4 —15 to 29 mL/min; and stage 5 — < 15 mL/min.

COVID-19 severity criteria

Herein, the COVID-19 severity was divided into four criteria, namely mild, moderate, severe, and critical. Patients were considered to have mild COVID-19 if viral pneumonia and hypoxia were not found. Patients with mild COVID-19 had symptoms such as fever, cough, shortness of breath, myalgia, anosmia, ageusia, head pain, throat pain, nose congestion, nausea, and diarrhea. As for patients considered to have moderate COVID-19, they presented with clinical features of pneumonia (fever, cough, dyspnea, and rapid breathing) but the signs for severe pneumonia were not observable with saturated oxygen >90%. COVID-19 patients presented with a respiratory rate of >30 times/min, heavy respiratory distress, or saturated oxygen <90%, in addition to the foregoing clinical signs of pneumonia, were assigned for having severe COVID-19. Patients categorized as having critical COVID-19 were those presented with acute respiratory distress syndrome (ARDS), sepsis, and septic shock.

Data analysis

Dichotomous data (yes or no) were scored as 1 or 0, respectively, and presented as frequency (%). Continuous data were presented as Mean ± standard deviation (SD). All descriptive statistical data were calculated by using Microsoft Excel (Way Redmond, WA, USA).

RESULTS

Characteristics of the patients

Characteristics of patients enrolled in this study have been presented in table 1. A total of 115 patients diagnosed with both diabetes mellitus and COVID-19 had the average age of 56.38±9.6 years old. The numbers of male (n=57; 49.6%) and female (58; 50.4%) were nearly balanced. Most of these patients were having class 1 obesity (n=48; 41.7%) and overweight (n=48; 41.7%) status. The average systolic blood pressure was slightly above the normal range (134.50±28.75), with diastolic blood pressure almost exceeding the normal range (79.38±16.64). These numbers are somewhat in line with the high percentage of patients having hypertension (n=60; 52.2%). The averaged oxygen saturation was 88.08±17.74 (%).

Severity and symptoms of COVID-19

Of the 115 patients enrolled in this present study, 70.4% of which were diagnosed with moderate COVID-19 while the 22.4% others – severe COVID-19 (Table 2). Top five commonly reported COVID-19 symptoms were dyspnea, cough, fever, nausea, weakness, and loss of appetite with frequencies of 82.6%, 76.5%, 63.5%, 53.9%, 40%, and 35.7%, respectively. Other symptoms such as throat pain (10.4%), headache (8.7%), abdominal pain (8.7%), reduced consciousness (6.1%), diarrhea (5.2%), and sputum (8.7%) were also reported. Almost all patients (98.26%) presented with pneumonia based on the chest X-ray finding (Table 2).

Table 1. Characteristics of diabetic patients with COVID-19 (n=115).

Characteristics	n (%)
Age, Mean±SD (years old)	56.38±9.6
Sex	
Male	57 (49.6)
Female	58 (50.4)
BMI	
Underweight	0 (0)
Normal	26 (22.6)
Overweight	35 (30.5)
Class 1 Obesity	48 (41.7)
Class 2 Obesity	6 (5.2)
Smoking	1 (0.9)
Clinical characteristics	
Systolic blood pressure, Mean±SD (mmHg)	134.50±28.75
Diastolic blood pressure, Mean±SD (mmHg)	79.38±16.64
Pulse (bpm)	98.94±21.83
Respiration rate (bpm)	25.91±6.27
Temperature (°C)	36.68±0.77
Oxygen saturation (%)	88.08±17.74
Previous medical record	
Hypertension	60 (52.2)
Hypertensive heart disease	28 (24.3)
Coronary heart disease	18 (15.7)
Hemodialysis	1 (0.9)

Table 2. Clinical features of COVID-19 experienced by the patients (n=115).

Clinical features	n (%)
Severity	
Mild	2 (1.7)
Moderate	81 (70.4)
Severe	26 (22.4)
Critical	6 (5.2)
Clinical symptoms	
Dyspnea	95 (82.6)
Cough	88 (76.5)
Fever	73 (63.5)
Nausea	62 (53.9)
Weakness	46 (40)
Appetite loss	41 (35.7)
Throat pain	12 (10.4)
Headache	10 (8.7)
Abdominal pain	10 (8.7)
Reduced consciousness	7 (6.1)
Diarrhea	6 (5.2)
Sputum	10 (8.7)
Myalgia	1 (0.9)
Anosmia	1 (0.9)
Radiological findings	
Pneumonia	113 (98.26)
Bronchitis	1 (0.9)
Normal	1 (0.9)

The distribution of the number of patients with respect to the COVID-19 severity and characteristics

The numbers of patients, grouped based on the COVID-19 severity and their characteristics, are presented in Table 3. Most patients aged 50—59 and 69—69 years (n=49 and 35, respectively), and both groups have relatively higher moderate case. The prevalence of severe COVID-19 was higher in 50—59 years old group, as compared with other age groups. Similarly, in terms of sex, both male and female were predominating the moderate case. Relatively higher numbers of moderate COVID-19 cases were also found in patients with all BMI categories. However, number of severe cases was more pronounced in class 2 obesity group (n=13; 27.1%).

According to serum parameters (hemoglobin, albumin, natrium, potassium, chloride, RBS, HbA1c, D-dimer, CRP, and procalcitonin), all groups were predominated by the moderate cases. Meanwhile, prevalence of severe COVID-19 was notably higher in patients with <3.5 mg/dL albumin (n=11 out of 50), >200 mg/dL RBS (n=22 out of 93), and ≥1 µg/mL D-dimer (n=18 out of 73). None of patients with CRP level of <5 mg/L developed severe or critical COVID-19; while the cases of severe or critical COVID-19 were present in those with CRP level of ≥5 mg/L (22.7% and 6.8%, respectively). Similarly, patients with <0.05 ng/mL procalcitonin did not develop severe or critical COVID-19; while 22.4% and 7.1% of those with ≥0.05 ng/mL procalcitonin developed severe and critical COVID-19, respectively. Moderate cases of COVID-19 predominated patients with stage 1—5 CKD; and those with stage 1 and 3 CKD developed critical COVID-19.

Table 3. Patient frequency distribution based on the COVID-19 severity.

Characteristics	COVID-19 severity			
	Mild n (%)	Moderate n (%)	Severe n (%)	Critical n (%)
Age (years old)				
<40 (n=5)	0 (0.0%)	3 (60.0%)	1 (20.0%)	1 (20.0%)
40—49 (n=18)	0 (0.0%)	12 (66.7%)	6 (33.3%)	0 (0.0%)
50—59 (n=49)	1 (2.0%)	32 (65.3%)	14 (28.6%)	2 (4.1%)
60—69 (n=35)	1 (2.9%)	26 (74.3%)	5 (14.3%)	3 (8.6%)
<70 (n=8)	0 (0.0%)	8 (100.0%)	0 (0.0%)	0 (0.0%)
Sex				
Male (n=57)	0 (0.0%)	43 (75.4%)	12 (21.1%)	2 (3.5%)
Female (n=58)	2 (3.4%)	38 (65.5%)	14 (24.1%)	4 (6.9%)
BMI (kg/m^2)				
Normal (n=26)	0 (0.0%)	20 (76.9%)	6 (23.1%)	0 (0.0%)
Overweight (n=35)	0 (0.0%)	27 (77.1%)	6 (17.1%)	2 (5.7%)
Class 1 Obesity (n=48)	2 (4.2%)	29 (60.4%)	13 (27.1%)	4 (8.3%)
Class 2Obesity (n=6)	0 (0.0%)	5 (83.3%)	1 (16.7%)	0 (0.0%)
Hemoglobin (g/dL)				
<10 (n=8)	0 (0.0%)	7 (87.5%)	1 (12.5%)	0 (0.0%)
≥10 (n=106)	2 (1.9%)	74 (69.8%)	24 (22.6%)	6 (5.6%)
Albumin (mg/dL)				
<3.5 (n=50)	0 (0.0%)	37 (74.0%)	11 (22.0%)	2 (4.0%)
≥3.5 (n=45)	2 (4.4%)	31(68.9%)	9 (20.0%)	3 (6.7%)
Natrium (mmol/L)				
<136 (n=79)	1 (1.3%)	52 (65.8%)	21 (26.6%)	5 (6.3%)
136—145 (n=33)	1 (3.0%)	27 (81.8%)	4 (12.1%)	1 (3.0%)
>145 (n=2)	0 (0.0%)	2 (100.0%)	0 (0.0%)	0 (0.0%)
Potassium (mmol/L)				
<3.5 (n=6)	0 (0.0%)	4 (66.7%)	2 (33.3%)	0 (0.0%)
3.5—5.0 (n=92)	2 (2.2%)	65 (70.7%)	20 (21.7%)	5 (5.4%)
>5.0 (n=15)	0 (0.0%)	11 (73.3%)	3 (20.0%)	1 (6.7%)
Chloride (mmol/L)				
<96 (n=57)	0 (0.0%)	40 (70.2%)	14 (24.6%)	3 (5.3%)
96—106 (n=49)	2 (4.1%)	34 (69.4%)	10 (20.4%)	3 (6.1%)
>206 (n=7)	0 (0.0%)	7 (100.0%)	0 (0.0%)	0 (0.0%)
RBS (mg/dL)				
<70 (n=1)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)
70—200 (n=20)	0 (0.0%)	17 (85.0%)	2 (10.0%)	1 (5.0%)
>200 (n=93)	2 (2.2%)	64 (68.8%)	22 (23.7%)	5 (5.4%)
HbA1c (%)				
≤7 (n=1)	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)
>7 (n=39)	2 (5.1%)	26 (68.8%)	9 (23.1%)	2 (5.1%)
D-Dimer (µg/mL)				
<1 (n=22)	0 (0.0%)	18 (81.8%)	3 (13.6%)	1 (4.5%)
≥1 (n=73)	2 (2.7%)	49 (67.1%)	18 (24.7%)	4 (5.5%)
Procalcitonin (ng/mL)				
<0.05 (n=6)	1 (16.7%)	5 (83.3%)	0 (0.0%)	0 (0.0%)
≥0.05 (n=85)	1 (1.2%)	59(69.4%)	19 (22.4%)	6 (7.1%)
CRP (mg/L)				
<5 (n=5)	0 (0.0%)	5 (100.0%)	0 (0.0%)	0 (0.0%)
≥5 (n=88)	2 (2.3%)	60 (68.2%)	20 (22.7%)	6 (6.8%)
CKD				
Stage 1 (n=34)	1 (2.9%)	23 (67.6%)	8 (23.5%)	2 (5.9%)
Stage 2 (n=30)	0 (0.0%)	24 (80.0%)	6 (20.0%)	0 (0.0%)

Characteristics	COVID-19 severity			
	Mild n (%)	Moderate n (%)	Severe n (%)	Critical n (%)
Stage 3 (n=38)	0 (0.0%)	25 (65.8%)	9 (23.7%)	4(10.5%)
Stage 4 (n=9)	1 (11.1%)	6 (66.7%)	2 (22.2%)	0 (0.0%)
Stage 5 (n=1)	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)

BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein; RBS, random blood glucose

DISCUSSION

A study from East Java, Indonesia, revealed that diabetes mellitus is correlated strongly with mortality rate caused by SARS-CoV-2 infection.[16,17] A retrospective study revealed that diabetes mellitus, chronic kidney disease, and coronary heart disease are associated factors of COVID-19 mortality.[18] Herein, the patients were predominated by those with uncontrolled blood glucose (RBS and HbA1c of >200 mg/dL and >7 %, respectively); as the consequence, they were more prevalent in each severity level. In a previous study, HbA1c level on admission was revealed to possess no correlation with the severity, but higher blood glucose level was found in patients with severe COVID-19 as compared to those with moderate COVID-19.[19] SARS-CoV-2 infection has been witnessed in vitro to cause apoptosis on ACE2-expressing pancreatic β cells.[20] It is suggested that the COVID-19 patients with diabetes mellitus would develop poor glycaemic profile, affecting innate immune response and elevating pro-inflammatory cytokine release.[21] Moreover, the use of a certain type of antivirals or corticosteroid therapy may yield the worsening of glycaemic control in diabetic patients.[21,22] Other than that, HbA1c has been found as an important marker for the mental state of diabetic patients. Previously, among elderly population, the level of HbA1c was significantly associated with depression during the COVID-19 period.[23] Another study also revealed the correlation between hyperglycemia and anxiety related to COVID-19, in which this correlation is dependent on the diabetes mellitus onset.[24] Taken altogether, these findings hint for active glycaemic monitoring on diabetic COVID-19 patients.

In this present study, we found that severe COVID-19 cases were relatively higher in 50-59 years old group, as compared with others. Further, higher prevalence of severe and critical COVID-19 was found among patients with class 1 obesity. Previously, age and comorbidities (*i.e.* hypertension and cardiac events) were reported as the determining factor for COVID-19-associated deaths.[25] Patients with diabetes mellitus and COVID-19 are mostly aged above 50 years as found in a couple of studies.[26,27] A retrospective study from Paris revealed that the patient with delta variant infection had a median age of 62 years old, where 36.3% and 12.5% of them were having hypertension and overweight, respectively.[12] Moreover, the previous study also suggested that being ≥60 years old was strongly correlated with higher mortality.[17] However, in another report from USA, the number of in-hospital patients who died from delta variant infection was significantly higher in <50 years old group.[28] In the aforementioned study, several characteristics such as age, race, gender, BMI, and chronic diseases (including diabetes and CKD) were associated with higher hospitalization risk.[28]

Herein, we found the stage 1 and 3 CKDs are confounding with critical COVID-19. SARS-CoV-2 infection in diabetic patients possibly contributes to the development of CKD through two ways. First, the SARS-CoV-2 infection causes the worsening of dysglycaemia leading to the increased workload of a proximal tubule in reabsorbing glucose molecules which underlies the diabetic kidney disease.[21,29] Second, as the virus attaches to and causes angiotensin-converting enzyme 2 degradation, the SARS-CoV-2 infection disrupts the renin-angiotensin system which eventually causes renal damage and dysfunction.[30] In 2020, a group of researchers found that median eGFR was significantly lower in type 2 diabetes mellitus patients who developed severe COVID-19 than in those who did not develop severe COVID-19.[27]

In this present study, severe or critical COVID-19 cases were mostly found in individuals having ≥1 µg/mL D-dimer, ≥0.05 ng/mL procalcitonin, and ≥5 mg/L CRP levels. A previous study reported that diabetic COVID-19 patients are likely to develop hypercoagulable prothrombotic state as they found the significantly increased level of the foregoing coagulopathy parameters as compared with non-diabetic COVID-19 patients. In a meta-analysis, CRP, procalcitonin, as well as D-dimer are suggested as biomarkers for severe COVID-19, in which the authors correlate their findings with the hemostatic system dysfunction as the result of the infection.[31] These findings are also corroborated by another meta-analysis, where procalcitonin, CRP, hemoglobin, and D-dimer have been suggested as the predictors for the progression of severe COVID-19.[32]

In addition, this present study suggested that fever, cough, and dyspnea as common COVID-19 symptoms with almost all patients developed pneumonia. In line with a previous study, fever was the most common symptom (53.7%), followed by cough (51%) and breathing difficulties (49.8%).[12] These parameters could be used to predict the antibodies titer in the convalescent plasma. Previously, convalescent plasma from donors having cough, fever, dyspnea, and pneumonia was found to significantly having higher SARS-CoV-2 neutralizing antibodies titers as compared to those who were asymptomatic.[33]

This study provides significant information pertaining the prevalence of COVID-19 with respect to its severity and characteristics of the diabetic patients. Unfortunately, this study is limited to report the outcome and factors affecting the outcome. We were also unable to statistically draw the correlation between the severity and the patients' characteristics. The results reported herein

might be biased from the limited number of samples.

CONCLUSIONS

Moderate COVID-19 is the most prevalent case among diabetic patients regardless their demographic and clinical characteristics. Severe or critical COVID-19 cases were present in patients with age of 50—59 years old, class 1 obesity, uncontrolled blood glucose, D-dimer level above 1 µg/mL, procalcitonin level above 0.05 ng/mL, and CRP level equal or above 5 mg/L. Future studies employing robust statistical calculation along with higher patient enrollment are necessary to provide comprehensive epidemiological data on diabetes mellitus and COVID-19.

ETHICAL APPROVAL

The Ethical Committee had approved the ethical clearance for Health Research – East Java Provincial Haji Surabaya General Hospital (No. 073/30/KOM.ETIK/2021).

COMPETING INTERESTS

The authors declare no competing interest.

GRANT INFORMATION

None.

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