Factors associated with disease severity of COVID-19 in patients with type 2 diabetes mellitus

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Abstract. Diabetes mellitus causes a decline in immunological function, an increase in proinflammatory cytokines, and a prothrombotic state, thus providing risk factors for the severity of coronavirus disease 2019 (COVID-19) in patients with type 2 diabetes mellitus (T2DM). The aim of the present study was to analyze the risk factors associated with the severity of COVID-19 in patients with T2DM. A cross-sectional observational study was performed on 201 patients with T2DM from May 1 to August 31, 2020 and admitted to the isolation ward of Dr Soetomo General Hospital (Surabaya, Indonesia). The patients were divided into severe (108 cases; 53.7%) and non-severe (93 cases; 46.3%) groups, which were considered the dependent variables. Univariate and multivariate analysis was performed. The independent variables were age, sex, diabetes onset, chronic complications, presence of hypertension, randomized blood glucose, HbA1c, albumin, and neutrophil-lymphocyte ratio (NLR). A P-value <0.05 was considered to be statistically significant. The median age of the 201 subjects was 56 years, with 70.1% <60 years old, 52.7% male, 76.1% with diabetes onset <10 years, and 108 patients (53.7%) in severe condition. The results of the bivariate analysis revealed that diabetes onset >10 years (OR 2.5; P=0.011) was associated with severity of COVID-19 in patients with T2DM, however hypoalbumin (OR 1.93; P=0.054) was not associated with disease severity. Furthermore, multivariate analysis revealed that male sex (OR 2.07; P=0.042), age (≥60 years) (OR 2.92; P=0.008), HbA1c (≥8%) (OR 3.55; P=0.001), hypertension (OR 4.07; P=0.001), and an NLR ≥7.36 (OR 6.39; P=0.001) were associated with severe COVID-19. Collectively, it was revealed that increased NLR, hypertension, poor glycemic control, older age, and male sex were risk factors associated with the severity of COVID-19 among diabetic patients.

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Introduction

Coronavirus disease 2019 (COVID-19) continues to be a worldwide health problem, and the number of reported cases in Indonesia continues to increase. In Indonesia, an upsurge in COVID-19 cases was documented from May to August 2020. Due to a lack of consistent information and policies on COVID-19, various doubts concerning the risk factors associated with the mortality and severity of this disease, have arisen. COVID-19 has several clinical spectrums, ranging from asymptomatic infection to development of severe and critical illness. The asymptomatic stage is the first stage of infection where severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters the body infecting the host cell through angiotensin-converting enzyme 2 (ACE2) receptor. The diagnosis is made by analyzing the viral load using reverse transcription-quantitative polymerase chain reaction (RT-qPCR). It is well known that asymptomatic carriers can transmit SARS-CoV-2. Cases with mild to moderate infection exhibit cold-like symptoms, new loss of taste or smell, nausea or vomiting, and diarrhea. Severe and critical cases exhibit worsening of symptoms and require hospitalization or even invasive mechanical ventilation. Symptoms encountered in these stages include worsening dyspnea and refractory hypoxemia (1,2).

Furthermore, frequency of COVID-19 and preexisting comorbidities increase the risk of mortality. Hypertension is the most prevalent comorbidity among COVID-19 patients, followed by diabetes (3). Its prevalence varies by nation, ranging from 7 to 21% in China (4) to 36% in Italy (5). Type 2 diabetes mellitus (T2DM) increases the severity of COVID-19. A meta-analysis of 40 studies with 18,012 COVID-19 patients, associated T2DM to COVID-19 severity (RR, 2.45; P=0.001; I^2, 45%) (6). Hyperglycemia, reduced immune function, vascular problems, and concomitant diseases such

as hypertension, dyslipidemia, and cardiovascular disease increase the risk of infection and severity of COVID-19 in individuals with T2DM (7). Chronic hyperglycemia also increases proinflammatory and prothrombotic cytokines, aggravating the hypercoagulable condition in T2DM patients with COVID-19 infection, increasing the risk of bleeding (8). Patients with type 2 diabetes have therefore become a major concern during the COVID-19 pandemic.

Some of the factors contributing to the severity of COVID-19 in patients with T2DM have been previously reported, and include obesity, hypertension, cardiovascular disease, and dyslipidemia. Other factors include age, extended hyperglycemia, high ACE expression, hypoalbuminemia, and increased inflammation (8-10). Increased inflammatory indicators, including the neutrophil-lymphocyte ratio (NLR), have been revealed both in patients with T2DM and in infections such as COVID-19. However, there is no well-defined NLR cut-off value predicting the severity of COVID-19 in T2DM patients (11,12). According to Zhang *et al* (13), a reduction in $CD4^+$ lymphocytes and an increase in serum amyloid A, upon hospital admission, were independent risk factors for COVID-19 individuals with T2DM. In addition, having fasting blood glucose levels ≥7.0 mmol/λ (14) or >180 mg/dl (15) was demonstrated to be an independent risk factor for progression to critical disease among COVID-19 patients with T2DM. Individuals with HbA1c levels >9% were more prone to have severe COVID-19 symptoms (16,17). In fact, poor glycaemic management and a markedly higher immune inflammatory response in patients with T2DM were revealed to be associated with worse clinical outcomes among COVID-19 cases with T2DM (18).

The present study investigated the clinical characteristics of COVID-19 patients with T2DM at Dr Soetomo General Hospital (Surabaya, Indonesia). The characteristics associated with severity of COVID-19 in newly diagnosed COVID-19 patients with T2DM were also examined. The NLR cut-off value for severity of COVID-19 in individuals with T2DM was also identified.

Patients and methods

Research design and subjects. From May 1 to August 31, 2020, at Dr Soetomo General Hospital (Surabaya, Indonesia), a cross-sectional analytical observational study was performed using the medical records of patients with COVID-19 and T2DM. The COVID-19 variants circulating during the time of the study were alpha and beta, however, genetic analysis was not performed to determine the COVID-19 variant in each subject. The Research Ethics Committee of Dr Soetomo General Hospital authorized the present study (ref. no. 0182/LOE/301.4.2/XI/2020). All patients provided written informed consent prior to the data collection.

The research included all adult patients (≥18 years old) treated for COVID-19 (RT-qPCR, nasopharyngeal swab) and T2DM (ICD-10) at Dr Soetomo General Hospital. The participants had not been vaccinated at the time of the study. Moreover, it was compulsory for the medical records of patients to include all variables analyzed, such as diagnostic, clinical, and laboratory data, at the time of first hospital admission, and for COVID-19 symptoms to be <7 days. Those with type 1 diabetes mellitus, hemoglobin levels <10 g/dl, pregnant women or women on estrogen/progesterone hormone therapy were excluded, as were those with autoimmune disease, malignancy, or lung disease (asthma, COPD, or tuberculosis), diagnosed prior to COVID-19 infection.

Data collection methods and definitions of variables. The sampling method used in the present study was total sampling. Through patient medical records, the variables studied included age, sex, hypertension, chronic complications of diabetes, duration of diabetes, glycemic control (HbA1c), hyperglycemic conditions (random blood sugar), inflammatory markers (NLR) and hypoalbumin. These variables were analyzed in relation to the severity of COVID-19.

COVID-19 admissions were classified as either severe or non-severe based on their severity. According to WHO in 2020, severe cases were defined as those with indications of pneumonia (fever, cough, shortness of breath, and rapid breathing) plus any of the following symptoms including a free oxygen saturation level of ≤90% in room air, a respiratory rate of ≥30 breaths/min, and a PaO_2/FiO_2 ratio ≤300 mmHg. When PaO_2 data was not available, ARDS was indicated by an SpO_2/FiO_2 ratio of ≤315 (19). According to JNC 8 hypertension guidelines, hypertension was defined as having a systolic blood pressure of ≥140 mmHg and/or a diastolic blood pressure of ≥90 mmHg or being on antihypertensive medication (20). According to the American Diabetes Asociation, the chronic complications of T2DM were macrovascular and microvascular complications, which were coded as (ICD X) I25.9 (chronic ischemic heart disease); I73.9 (peripheral vascular disease); I60-I69 (cerebrovascular disease); E11.21 (diabetic nephropathy); E11.40 (diabetic neuropathy); and E11.31 (diabetic retinopathy) (21).

The duration of T2DM was defined as the period from when the patient was first diagnosed with diabetes mellitus to the time of assessment, with a cutoff of >10 years indicating a severe disease in T2DM patients with COVID-19. Glycemic control using HbA1c with an ≥8% cutoff indicated severe COVID-19 in patients (22). HbA1c was measured during hospitalization with DCA Vantage equipment and the reagent kit (supplied by Siemens Healthineers Indonesia; manufactured by Siemens Healthcare Diagnostic Manufacturing Ltd.), Siemens DCA HbA1c (supplied by Siemens Healthineers Indonesia; manufactured by Siemens Healthcare Diagnostic Manufacturing Ltd.), which uses the immunoagglutination technique. Hyperglycemia, according to the Indonesian Society of Endocrinology, in 2019, was defined as a random blood sugar level of >200 mg/dl that was measured at the time of admission (23).

The NLR is a measure of inflammation that is determined by dividing total neutrophils by total lymphocytes (12). A complete blood count was used to acquire NLR data. Hypoalbumin was defined as serum albumin of <3.5 g/dl, as measured by the Siemens Dimension EXL instrument (supplied by Siemens Healthineers Indonesia; manufactured by Siemens Healthcare Diagnostic Manufacturing Ltd.) at Dr Soetomo General Hospital.

Statistical analysis. For categorical data types (nominal and ordinal), descriptive data included frequency and

Table I. Severity of COVID-19 among research subjects.

Patients	n (%)
Severe COVID-19	108 (53.7%)
Non-severe COVID-19	93 (46.3%)

COVID-19, coronavirus disease 2019.

percentage, whereas for continuous data types the mean ± SD or median (IQR) were used (interval and ratio). The Chi Square test was used for bivariate analysis of variables associated with extreme severity of COVID-19 in the present research. By combining all variables with P-value of <0.25 in the bivariate analysis, a multivariate logistic regression analysis was used to determine the dominating factor of severe COVID-19. The findings were expressed as an odds ratio (OR), with a P-value <0.05 considered to indicate a statistically significant difference, and the 95% confidence interval (CI) was calculated. The cut-off value, sensitivity, and specificity of NLR were determined using a receiver operating characteristic (ROC) curve. Statistical Package for the Social Sciences (SPSS) version 25.0 was used to examine all data (IBM Corp.).

Results

An overview of the characteristics of the study participants at the time of their admittance to hospital. The research subjects were classified as severe and non-severe cases of COVID-19 according to their medical records. From the 201 study subjects included in the present study, 108 patients (53.7%) were defined as severe and 93 patients (46.3%) as non-severe COVID-19 (Table I). The general characteristics of COVID-19 patients with T2DM who were treated at Dr Soetomo General Hospital, included an average age of 55.69±9.47 years with the majority being <60 years old (70.1%), and males (52.7%). In addition, 67.7% were non-referral patients. Furthermore, for the majority of patients, diabetes onset was <10 years (76.1%) (Table II).

T2DM patients treated in an isolation room at Dr Soetomo General Hospital had an average of 4.3±1.92 days from onset of symptoms until admission to the hospital. The most prevalent clinical symptoms noted in the medical records of the patients were dry cough (79.6%), shortness of breath (69.2%), and fever (66.7%), with 114 individuals having concomitant hypertension (56.7%) (Table III).

The median hemoglobin, hematocrit, leukocytes, platelets, serum creatinine, sodium, potassium, chloride, and procalcitonin levels of the study participants were all in the normal range. In addition, the median neutrophil, SGOT, baseline blood sugar, HbA1c, and CRP levels were significantly higher than the normal values. Lymphocytes, BUN, and albumin median values were all below the normal range, with a median NLR of 7.96. The majority of the study participants had albumin levels of <3.5 g/dl (71.6%), blood sugar levels of ≥200 mg/dl (62.2%), and HbA1c levels ≥8% (61.7%). The chest X-rays revealed that the majority of the

Table II. General characteristics of research subjects with COVID-19 at admission to hospital.

Variables	Total (%), total N=201 patients
Age, years (mean ± SD) (min-max)	55.69±9.47 (27-81)
<60	141 (70.1%)
≥60	60 (29.9%)
Sex	
Male	106 (52.7%)
Female	95 (47.3%)
Admitted to hospital	
Without referral	136 (67.7%)
With referral	65 (32.3%)
Diabetes mellitus onset	
<10 years	153 (76.1%)
≥10 years	48 (23.9%)

COVID-19, coronavirus disease 2019.

Table III. Clinical profile of research subjects with COVID-19 at admission to hospital.

Variables	Total (%), total N=201 patients
From the onset of symptoms to the time of admission, mean ± SD (min-max)	4.3±1.92 (1-7) days
Clinical symptoms	
Dry cough	160 (79.6%)
Short of breath	139 (69.2%)
Fever	134 (66.7%)
Sore throat	80 (39.8%)
Decreased appetite	76 (37.8%)
Tired easily	48 (23.9%)
Cough with phlegm	22 (10.9%)
Diarrhea	21 (10.4%)
Loss of consciousness	17 (8.5%)
Runny nose	17 (6%)
Anosmia	9 (4.5%)
Muscle aches	8 (4%)
Hypertension	
Yes	114 (56.7%)
No	87 (43.3%)
Chronic complications	
Yes	42 (20.9%)
No	159 (79.1%)
Vital Signs (median, range)	
Systolic blood pressure (mmHg)	140 (77-209)
Diastolic blood pressure (mmHg)	82 (50-116)
Pulse (x/min)	98 (69-132)
Respiratory rate (x/min)	2 (18-40)
SpO_2 (%)	92 (60-100)

COVID-19, coronavirus disease 2019.

Table IV. Additional findings of research subjects with COVID-19 admitted to hospital.

Parameters	Median	Min-max	Frequency, n (%)	Normal
Laboratory findings				
Hemoglobin (g/dl)	13.5	10-17.4		11-15
Hematocrit (%)	39.5	30.1-53.4		33-47
Leukocytes ($x10^9$/l)	8.91	3.69-49.6		4-10
Neutrophils ($x10^9$/l)	7.71	1.95-45.38		2-7
Lymphocytes ($x10^9$/l)	0.98	0.22-3.85		1-4
Platelets ($x10^9$/l)	257	26.7-881		150-450
BUN (mg/dl)	19	7-141		20-67
Creatinine (mg/dl)	1.1	0.4-8.76		0.4-1.2
eGFR	73	7-141		60
SGOT	54	14-779		20-50
SGPT	46	10-338		25-70
CRP (mg/l)	10.7	0.1-76		<10
Sodium	136	107-163		135-145
Potassium	4.1	2.6-6.6		3.5-5.5
Chloride	98	68-134		96-126
Procalcitonin (ng/ml)	0.2	0.1-100		<0.5
NLR	7.96	1.48-62.81		
Albumin (g/dl)	3.16	2.14-3.93		3.5-5.4
<3.5			144 (71.6%)	
≥3.5			57 (28.4%)	
Blood sugar (mg/dl)	242	61-989		<200
<200			76 (37.8%)	
≥200			125 (62.2%)	
HbA1c (%)	8.8	6-16.5		<7
<8%			77 (38.3%)	
≥8%			124 (61.7%)	
Radiology findings (lung chest X-ray)				
No abnormalities			11 (5.5%)	
Bilateral lung disorders			172 (85.57%)	
Unilateral lung disorders			18 (8.93%)	

COVID-19, coronavirus disease 2019; NLR, neutrophil-lymphocyte ratio.

abnormalities were bilateral pulmonary disorders (85.57%) (Table IV).

The ROC analysis (Fig. 1) revealed an AUC of 0.833 (P<0.0001) and the NLR cut-off value was 7.36 to evaluate the severity of COVID-19 in patients with T2DM. The NLR value was 79.6% sensitive and 74.24% specific in determining the severity of COVID-19 individuals with T2DM using this cut-off value.

Bivariate analysis of factors associated with the severity of COVID-19 at admission of study subjects to hospital. The results of a bivariate chi-square study of factors linked with the severity of COVID-19 in patients with T2DM are presented in Table V. Age (P=0.002), sex (P=0.015), onset of diabetes mellitus (P=0.011), presence of hypertension (P<0.001), NLR (P<0.001), and HbA1c (P=0.002) were found to be associated with the severity of COVID-19. These factors were further assessed using multivariate analysis.

Multivariate analysis of parameters associated with severity of COVID-19 at admission of study participants to hospital. As revealed in Table VI, the logistic regression coefficient for the NLR ≥7.36 factor was 1.85, with an OR or exp (B) value of 6.39. For the occurrence of hypertension, the logistic regression coefficient was 1.4, with an OR or exp (B) value of 4.07. The logistic regression coefficient for HbA1c ≥8% was 1.27 with an OR or exp (B) value of 3.55. For the factor with regard to age ≥60 years, the logistic regression coefficient was 1.07, with an OR or exp (B) value of 2.92. For the male sex factor, the logistic regression coefficient was 0.73, with an OR or exp (B) value of 2.07.

Discussion

In the present study, multivariate analysis revealed that the presence of an NLR ≥7.36, hypertension, an HbA1c ≥8%, age ≥60 years, and male sex were significantly associated

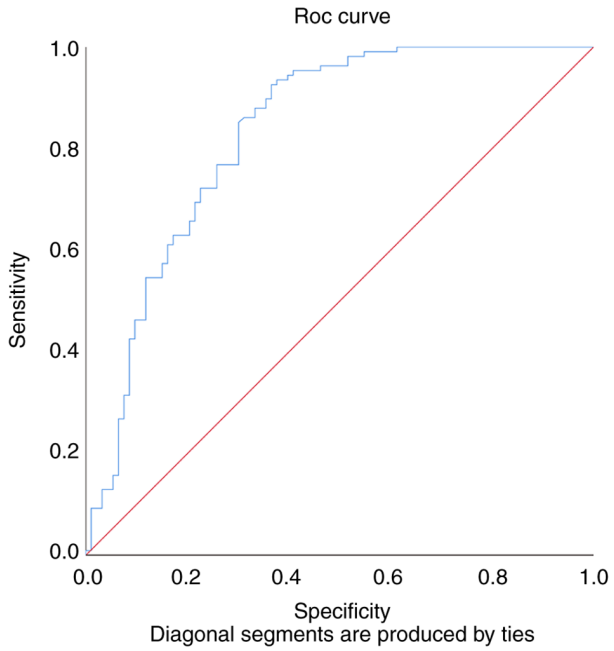

Figure 1. Analysis of the NLR cut-off value using a ROC curve. A ROC curve was used to determine the NLR cut-off value of the severity of COVID-19 patients with type 2 diabetes mellitus, which was 7.36. NLR, neutrophil-lymphocyte ratio; ROC, receiver operating characteristic.

with severe COVID-19 in patients with type 2 diabetes. Consequently, these factors may aid clinicians in identifying the severity of COVID-19 infection more rapidly and provide more aggressive treatment, as well as become a target for prevention, particularly in the management of hypertension and glycemic control, in order to reduce the severity of disease in COVID-19-infected T2DM patients. In a previous study it was revealed that there was a slightly increased antibiotic usage in the diabetic group, but there was no significant difference in treatment provided to non-diabetic COVID-19 infections and the non-diabetic control group (24).

Furthermore, it was identified that age (≥60 years) was associated with severity of COVID-19 in patients with T2DM. In addition, the research subjects had a mean age of 55.69±9.47 with a median of 56 years and an age range of 27-81 years, similar to the findings of previous studies conducted in China in which the median age of COVID-19 patients with T2DM was 54-58 years (25,26). A meta-analysis of 3,027 COVID-19 patients in China revealed that age (>65 years) was a risk factor for severe COVID-19 development (OR 6.06; P=0.00001) (27). Another meta-analysis of studies conducted in China, France, Germany, Singapore, and the USA found that age (≥60 years) was likewise associated with severe COVID-19 (OR 3; 95% CI: 1.4-6) (26). Du *et al* (28), also revealed a significant association between older age and the degree of severity in COVID-19 patients (OR 2.62; I^2=0%; n=2). In patients with T2DM, COVID-19 is more severe as they get older. This is due to a number of factors, including the fact that people >60 years of age are more likely to have diabetes for a long period of time, resulting in complications; diabetes in the elderly is closely associated with various other comorbidities such as cardiovascular disease, hypertension, and obesity; and, in addition, there are defects in the function of T and B cells, as well as overproduction of proinflammatory cytokines (29-33). In the present study, the severity of COVID-19 was not compared between diabetic and non-diabetic groups, however, a study conducted by Zhang *et al* (24) revealed that patients with diabetes and secondary hyperglycemia were of greater risk (2.5 fold) of more severe COVID-19 infections compared to non-diabetic patients.

In the present study, male sex was also revealed to be associated with the severity of COVID-19 in patients with T2DM. This finding was in line with other research which linked male sex with severity of COVID-19 in individuals with T2DM (13,22,34). Men are at a higher risk of severe COVID-19 due to lifestyle factors such as smoking addiction, which is more prevalent in men than in women, and the presence of estrogen, an immune-regulating gene encoded by the X chromosome that is present in women and plays a protective role in SARS by not only activating the immune response but also suppressing SARS-CoV replication, allowing estrogen to regulate ACE2 expression (35,36). Additionally, in an animal model, it was revealed that males have higher ACE2 receptor activity due to increased enzyme velocity (37).

In the present study, most participants (79.1%) had no chronic complications (both macrovascular and microvascular) as revealed by their medical records, while in a study conducted by Zhang *et al* (24) it was identified that at the time of admission to hospital, 57.7% of COVID-19 patients with T2DM had chronic diabetic complications. Chronic complications were noted in only 20.9% of the patients in the present study, most likely due to the facts that diabetes mellitus onset for the majority was <10 years and most patients were aged <60 years. The longer a patient has T2DM, the more vascular complications there are, particularly cardiovascular complications (38). A study performed in Israel on 5,869 COVID-19 individuals with T2DM revealed that for the majority of patients T2DM onset was >10 years (22). According to the 2019 statistics from the International Diabetes Federation (IDF), Indonesia ranks fifth in terms of patients with predicted undiagnosed diabetes. It has been reported that as many as 50% of individuals with T2DM in the population do not know that they have T2DM (remain undiagnosed) (39).

Moreover, in the present study the majority of subjects had HbA1c levels of ≥8% and random blood glucose levels of ≥200 mg/dl upon admission to hospital. Research performed in China on a COVID-19 population with T2DM revealed a median HbA1c of 8.7% and a median blood glucose level of 147.74 mg/dl, respectively (13). According to the CORONADO trial, the mean HbA1c in COVID-19 patients with T2DM was 8.1±1.9%, and the median baseline blood sugar level was 165.77 (IQR 122.52-227.39) mg/dl (40). Various studies have revealed that the HbA1c and random blood glucose (RBG) levels of diabetes mellitus patients infected with COVID-19 are still higher than the Indonesian Society of Endocrinology and ADA objectives of <7% and <200, respectively (21,23).

In the present study, diabetes onset of ≥10 years was associated with severe COVID-19 in patients with T2DM admitted to hospital. In comparison with onset of ≤5 years and 6-10 years, diabetes onset of >10 years was significantly associated (P<0.001) with severity of COVID-19 at first hospital admission (22). Vascular endothelial damage is more common in patients with long-term T2DM (26). Varga *et al* (41), also

Table V. Bivariate analysis of factors associated with severity of COVID-19 in study subjects admitted to hospital.

Characteristics	Severe [n (%)]	Non-severe [n (%)]	P-value	OR	95% CI	
					Lower limit	Upper limit
Age, years						
≥60	43 (21.4%)	17 (8.5%)	0.002	2.96	1.54	5.68
<60	65 (32.3%)	76 (37.8%)				
Sex						
Male	66 (32.8%)	40 (19.9%)	0.015	2.08	1.18	3.66
Female	42 (20.9%)	53 (26.4%)				
Diabetes mellitus onset						
≥10 years	34 (16.9%)	14 (7%)	0.011	2.5	1.3	5.2
<10 years	74 (36.8%)	79 (39.3%)				
Hypertension						
Yes	78 (38.8%)	36 (17.9%)	<0.001	4.12	2.28	7.45
No	30 (14.9%)	57 (28.4%)				
Chronic complications						
Yes	26 (12.9%)	16 (8%)	0.307	1.53	0.76	3.06
No	82 (40.8%)	77 (38.3%)				
NLR						
≥7.36	79 (39.3%)	28 (13.9%)	<0.001	6.32	3.4	11.69
<7.36	29 (14.4%)	65 (32.2%)				
Albumin (g/dl)						
<3.5	84 (41.8%)	60 (29.9%)	0.054	1.93	1.03	3.58
≥3.5	24 (11.9%)	33 (16.4%)				
Blood sugar (mg/dl)						
≥200	71 (35.3%)	54 (26.9%)	0.33	1.39	0.78	2.46
<200	37 (18.4%)	39 (19.4%)				
HbA1c (%)						
≥8%	78 (38.8%)	47 (23.4%)	0.002	2.67	1.48	4.77
<8%	30 (14.9%)	46 (22.9%)				

COVID-19, coronavirus disease 2019; NLR, neutrophil-lymphocyte ratio; OR, odds-ratio.

demonstrated that SARS CoV-2 can infect endothelial cells directly, indicating that in patients with endothelial disorders, such as T2DM, the severity of COVID-19 is exacerbated, thereby increasing susceptibility to infection and thereby increasing the severity of patients infected with SARS CoV-2.

In addition, in the present study, hypertension was associated with the severity of COVID-19 in patients with T2DM. These findings are consistent with a study by Hayek *et al* (22), which revealed that hypertension was significantly more prevalent in the severely ill COVID-19 group than in the non-severely ill COVID-19 group (85.5 vs. 68.7%; P<0.001). By contrast, research by Zhang *et al* (42), revealed no significant correlation between concomitant hypertension and severity of COVID-19. Conversely, hypertension was the comorbidity most commonly associated with an increased risk of severity in individuals with COVID-19 (27,28,43-55). Immune system disruption in patients with T2DM and hypertension increases the risk of infection with COVID-19 (46). Hypertension is hypothesized to exacerbate the inflammatory process associated with COVID-19 infection in patients with T2DM, which is characterized by higher levels of inflammatory markers such as TNF-α and IL-6 in patients with severe COVID-19 (47). Additionally, individuals with T2DM whose conditions are exacerbated by hypertension have a weakened immune system ($TCD8^+$ cell malfunction) and are under chronic stress (27,45,48). It has been revealed that the structure of blood vessels of individuals who have diabetes and hypertension, for an extended period of time, undergoes damage, rendering these individuals more susceptible to complications if infected with COVID-19 (27). Additionally, hypertension may result in a reduction in ACE2 expression, resulting in an increase in angiotensin 2 and a decrease in angiotensin 1-7 levels, as well as renin-angiotensin system dysfunction, affecting fluid-electrolyte balance and, of course, blood pressure (8,30).

In the present study, an NLR ≥7.36 was associated with severe COVID-19 in patients with T2DM admitted to hospital. This finding is in line with a study by Liu *et al* (34), which

Table VI. Estimation results of the severity risk logistics model for COVID-19 patients with type 2 diabetes mellitus.

Factors	B (coefficient)	P-value	OR	95% CI	
				Lower limit	Upper limit
Diabetes mellitus onset 10 years	0.002	0.996	1.01	0.41	2.47
Albumin <3.5 g/dl	0.66	0.094	1.93	0.9	4.16
Male sex	0.73	0.042[a]	2.07	1.03	4.17
Age ≥60 years old	1.07	0.008[a]	2.92	1.32	6.5
HbA1c ≥8%	1.27	0.001[a]	3.55	1.68	7.52
Hypertension	1.4	<0.001[a]	4.07	2.01	8.26
NLR ≥7.36	1.85	<0.001[a]	6.39	3.14	12.99

[a]P<0.05, indicating statistical significance. COVID-19, coronavirus disease 2019; NLR, neutrophil-lymphocyte ratio; OR, odds-ratio.

revealed that the higher the NLR, the greater the severity of COVID-19. It is possible that the chronic inflammation associated with T2DM, as well as with COVID-19 infection, may increase NLR (42,49). Because both neutrophils and lymphocytes are involved in the immune response, virus-induced inflammation increases NLR. Neutrophils are the first and most abundant cell population to reach the site of infection, and their number is increased due to inflammatory factors, whereas lymphopenia occurs due to immune system suppression of cellular immunity. A secondary immune response may occur 4-7 days following the first symptoms of COVID-19, thus worsening the condition of the patient, consistent with the findings in the present the study which revealed that the median time for hospital admission since the first symptoms was 4 days (44,50).

As aforementioned, in the present study, an HbA1c value of ≥8% was associated with the severity of COVID-19 in patients with T2DM admitted to hospital. A recent study revealed that an HbA1c of 8% was a risk factor for severe COVID-19 with intubation or death after 7 days of therapy (OR 2.26; P<0.05) (51). In patients with T2DM, an HbA1c >9% was revealed to be an independent predictor of multiple organ damage (OR 2.98; P=0.043) (17). Additionally, diabetic patients with poor glycemic control (HbA1c >8%) exhibited significantly reduced lung function as a result of chronic low-grade inflammation and microangiopathy of pulmonary vascular tissue, impairing lung connective tissue metabolism and causing basement membrane and alveolar epithelium thickening (52,53). As a result, it was determined that COVID-19 in T2DM patients results in a deterioration of the glycemic profile, which further weakens the innate immune response and increases proinflammatory cytokines, whereupon a vicious cycle is created (54,55).

In the present study, albumin levels of ≤3.5 g/dl did not indicate a significant correlation with severe COVID-19 in patients with T2DM admitted to hospital. However, a study by Zhang *et al* (13) revealed that in severe COVID-19 patients with T2DM, a lower median albumin level (3.13 vs. 3.85 g/dl; P<0.001) was observed compared with non-severe COVID-19 patients with T2DM. A previous study, involving various research centers in China and 482 COVID-19 patients revealed that hypoalbumin was a risk factor for severe COVID-19 (OR: 2,121; 95% CI: 1,258-3,577; P=0.005) (56). A high albumin value upon admission to hospital, is a strong predictor of a better prognosis in patients with COVID-19 (10). The majority of patients in the present study had albumin levels below normal, with a median of 3.5 g/dl. Albumin has physiological features such as anti-inflammatory, antioxidant, anticoagulant, and antiplatelet action, as well as colloid osmotic activity (10,56). Hypoalbuminemia may arise in COVID-19 patients with T2DM as a result of inflammation-mediated capillary leakage, reduced albumin production in hepatocytes, or as a result of chronic consequences of diabetes or direct kidney injury. Hypoalbumin increases the occurrence of acute respiratory failure from ARDS due to plasma leakage causing changes in osmotic pressure and decreased ability to combat oxidative stress (10,56).

The present study has some limitations that may have an impact on the findings. First, this is a centralized research performed at one of the main referral hospitals of East Java (Indonesia). Therefore, non-severe patients may be underrepresented since they self-isolate at home or visit local government-prepared health facilities such as field hospitals. Second, this research used a cross sectional design and secondary data from medical records, such as medication history, D-dimer and BMI were excluded. Third, this study was performed from May to August 2020, excluding the delta variant period. Fourth, comparison of the severity of the disease between diabetic and non-diabetic groups was not performed.

The present study may be useful in providing insights into the severity of COVID-19 and comorbities, particularly T2DM. Several studies found a correlation between severity of COVID-19 and increased inflammatory responses (34,42,45,48,49), while other studies determined that glycemic control was associated with patient outcome (24,51-53), and certain others found that there is a correlation between hypertension, diabetes and COVID-19 infection (22,27,28,43-45). The aforementioned are independent studies, and while they support each other and the findings of the present study, to the best of our knowledge, research comparing a combination of several factors has yet to be performed. The present research contributes to the future development of preventative measures by managing various parameters (NLR, albumin level, blood sugar level and hypertension), resulting in a reduction in the number of severe COVID-19 patients with T2DM as well as other comorbidities.

In the present study, it can be concluded that variables including age, sex, diabetes onset, hypertension, NLR, albumin, and HbA1c are associated with severity of COVID-19. Patients with T2DM who were infected by COVID-19 were more likely to have severe symptoms if they had an NLR ≥7.36, hypertension, an HbA1c of ≥8%, were aged ≥60 years, and were of the male sex. These characteristics may assist clinicians in diagnosing, controlling, and avoiding morbidity and mortality of COVID-19 patients with T2DM. In addition, studies using a multicenter design and a larger sample size are required. Further research which involves more of the SARS CoV-2 virus variant is also warranted.

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Availability of data and materials

The datasets used during the present study are available from the corresponding author upon reasonable request.

Authors' contributions

All authors (HN, SAS, UH, AP, CC and NS) conceived and designed the study, acquired and analyzed the data as well as drafted the manuscript and revised it, and confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethical approval and consent to participate

The present study was approved (ref. no. 0182/LOE/301.4.2/XI/2020) by the Research Ethics Committee of Dr Soetomo General Hospital (Surabaya, Indonesia). All patients provided written informed consent prior to the data collection.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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