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Diabetes Mellitus and the Following Risk Factors Associated with an Increased Risk of COVID-19 Severity and Mortality in Adult Patients

Komang Septian Trisna Jaya[1], I Made Siswadi Semadi[2]

[1, 2]Department of Internal Medicine, Bali Jimbaran Hospital, Jimbaran, Bali, Indonesia
Corresponding author Email: *septiantrisnajaya[at]gmail.com*

Abstract: ***Diabetes mellitus is one of the most common comorbidities in patients with COVID-19 and is associated with poor outcomes. This study aimed to investigate the association of diabetes mellitus with other risk factors in the severity and mortality of COVID-19 patients.Method: This retrospective study identified adult patients with COVID-19 admitted to Bali Jimbaran Hospital (Indonesia) from July 02, 2020, to May 04, 2021. The risk of severity and mortality were compared between COVID-19 patients with diabetes and without any comorbidities who were of the same sex and age. The other risk factors were explored in subgroup of patients with diabetes using logistic regression analysis.Results:The diabetes group had a significantly increased risk of COVID-19 severity (p <0.001) and mortality (p =0.026). The logistic regression analysis showed that significantly increase COVID-19 patients' severity and mortality in diabetic patients with hypertension and D-dimer ≥1000 ng/mL (p < 0.05). Conclusions: Risk of COVID-19 severity and mortality generally increases in diabetes patients. Presence of hypertension or D-dimer ≥1000 ng/mL were independent risk factor for both severity and mortality in COVID-19 patients with diabetes. Diabetes mellitus patients presenting with other risk factors must be take an extra attention to prevent a poor outcome.***

Keywords: diabetes mellitus, risk factors, morbidity, mortality, COVID-19

1. Introduction

The novel coronavirus disease (COVID-19) caused by SARS coronavirus 2 (SARS-CoV-2), was initially identified as a mysterious pneumonia in Wuhan, China in December 2019. This disease has emerged as an infectious disease that is spreading rapidly and is developing into the global crisis has been declared as a global pandemic by the World Health Organization (WHO) on March 11, 2020.[1] Until early May 2021, the incidence of this disease has reached 155 million confirmed cases with 3 million deaths worldwide. In Indonesia, there have been nearly 1.7 million confirmed cases of COVID-19, with the death rate reaching 46 thousand people.[2]To determine if a person has infected by SARS-CoV-2, a polymerase chain reaction (PCR) assays of nasopharyngeal swab examination is needed.[3]

In Indonesia, the classification of COVID-19 based on the severity of cases is divided into asymptomatic, mild, moderate, severe, and critical. Mild COVID-19 cases were defined in patients with symptoms without any evidence of viral pneumonia or without hypoxia. Those symptoms include fever, cough, fatigue, anorexia, shortness of breath, myalgia, and other non-specific symptoms. Patients with clinical signs of pneumonia (fever, cough, shortness of breath, rapid breathing) but no signs of severe pneumonia including SpO2 ≥ 93% in room air were categorized as moderate symptoms. Meanwhile, severe symptoms occurred in patients with clinical signs of pneumonia plus one of the respiratory rates > 30/minutes, severe respiratory distress, or SpO2 <93% in room air. COVID-19 patients with symptoms of acute respiratory distress syndrome (ARDS) accompanied by sepsis and septic shock were defined as critical symptoms.[3]

Diabetes mellitus (DM) is a chronic metabolic disease which affects around 422 million people worldwide.[4,5] In Indonesia itself, the prevalence of diabetes mellitus patients reaches 10.7 million population.[6]With the high prevalence of diabetes, it is important to understand the specific aspects of COVID-19 infection in diabetic patient. Diabetes mellitus is one of the most common comorbidities other than hypertension and cardiovascular disease in patients with COVID-19 and is associated with poor outcomes including the need for care in an intensive care unit (ICU) and death.[7,8] Patients with diabetes with multiple comorbidities should take extra precaution for the prevention of possible infection risk due to COVID-19.[8]It has been well established that hypertension, cardiovascular disease, cerebrovascular disease and chronic renal disease coexist with diabetes, leading to a higher risk of morbidity and mortality for COVID-19.[9] Diabetes mellitus appears to be a major, age-independent risk factor for severity of COVID-19.[10] There was reported a significantly higher percentage of critical cases in patients with diabetes and COVID-19.[11]Some meta-analyses have assessed the severity of COVID-19 in patients with comorbidities including diabetes. In a meta-analysis from Chinese, including 1527 patients, 9.7% of all COVID-19 cases had diabetes, and it increased the risk of developing severe disease or requiring ICU by two-fold.[6]

There are many other things that can be independent factors for the increased risk of mortality in COVID-19 patients apart from diabetes mellitus. Male patients, advanced ages especially age ≥ 65 years, patients with underlying disease such as hypertension, cerebrovascular disease, renal disease were the predictors for mortality and could assist clinicians in early identification of poor prognosis among COVID-19 patients.[12,13,14] Patients presenting with severe-critical symptoms at admission and requiring ICU care are also independent predictors of high mortality risk, regardless of

whether the patient has comorbidities or not. Not only that, the risk of mortality among obese patients with COVID-19 was 118% higher compared to non-obese patients, and mortality among COVID-19 patients with the history of smoking was 81% higher compared to the patients without history of smoking.[14]

Blood glucose monitoring poses a special challenge as it necessitates frequent visits to patient's bedside, especially if the patient is critically ill and receiving intravenous insulin. However, attempts could be made to minimize exposure.[15] HbA1c testing can well represent average blood glucose levels within 2–3 months before testing and is not influenced by factors such as acute infection, stress, or recent medications that could alter glucose metabolism, like corticosteroids. Therefore, HbA1c is a reasonable diagnostic parameter for the quick identification of the background glucose metabolic state in severe and critical patients with COVID-19.[16] In the management of diabetes mellitus patients with either oral anti-diabetes drugs or insulin, the expected target HbA1c level is <7% (NGSP).[17] HbA1c testing at admission can provide important information for patient assessment and help identify those who have not been diagnosed but are at great risk.By testing the HbA1c level at admission, we can reduce the omission diagnostic rate of diabetes and prevented the overdiagnosis of diabetes because of stress-induced hyperglycaemia, since HbA1c is relatively unaffected by the stress of acute illness.[16,17] Some studies have shown a significant association between admission HbA1c and disease progression or mortality in COVID-19 patients. Liu Z. et al showed 1% increase in HbA1c was significantly associated with disease progression and mortality in COVID-19 patients.[18] Two recent U.K. studies reported that diabetes was independently associated with a higher risk of morbidity and mortality of COVID-19 patients which increased with higher HbA1c. Compared with people without diabetes, one study reported that patient with diabetes with HbA1c >7.5% had a higher chance of in-hospital death than those with HbA1c <7.5%. These data suggest that diabetes control preinfectional has a role to play in COVID-19 outcomes.[19] The higher levels of HbA1c in severe patients indicated that poor glycaemic control in DM patients could lead to a severe COVID-19, which also suggested that hyperglycaemia may play a vital role in poor outcomes of DM patients with COVID-19.[6]

Guo et al. compared the haematological and biochemical profile of total 174 patients of COVID-19, of which 37 had diabetes compared to 137 without diabetes. Interestingly, both the haematological and biochemical parameters that are generally characterized as a marker of severe COVID-19, were significantly higher in patients with diabetes, compared to without diabetes. Significant decrease in lymphocyte, red blood cells (RBC), level of haemoglobin and a marked increase in neutrophils, and D-dimer was observed in patients with diabetes, compared to the without diabetes. Moreover, when the patients with diabetes were compared to patients without diabetes and without other comorbidities, even then, the biochemical and haematological markers of severe COVID-19 were significantly higher in patients with diabetes. These changes clearly point to a poor prognosis and suggests an excessive inflammatory response or cytokine storm, and increase hypercoagulability in patients with diabetes, compared to the groups without diabetes.[13]

At present, the rapid worldwide spread of COVID-19 requires continual improvement of knowledge about diabetes mellitus with COVID-19 infection. This study aimed to investigate association of diabetes mellitus accompanied or not by another risk factorswith the severity and the risk of deathin COVID-19 patients, which may be instructive for clinical practice.

2. Methods

Study design and population

This retrospective study aimed to investigate the impact of diabetes mellitus on the severity and mortality of COVID-19. We screened all adult patients with confirmed diagnosis of COVID-19 who were admitted to the Bali Jimbaran Hospital at Jimbaran, Bali, from July 02, 2020, to May 04, 2021.We took data from all COVID-19 patients who had diabetes mellitus accompanied or not by another comorbid, then with adjustments the sex and age, we took the same amount of data on COVID-19 patients who did not have any comorbidities as a comparations group. All the patients were followed up to their discharge or in-hospital death.

Definition of COVID-19, disease severity and diabetes

The diagnosis of COVID-19 confirmed patient according to the Indonesian COVID-19 management guideline, that is the patient who was tested positively for SARS-CoV-2 using quantitative polymerase chain reaction (PCR) assays of nasopharyngeal samples. Disease severity classification and treatment protocol were also based on this guideline. In this study severity classification was divided into two classifications that are mild-moderate and severe-critical. Diabetes mellitus (DM) was determined based on self-reported diabetes history. If patients denied having a history of diabetes and their HbA1c levels at admission were ≥ 6.5% (NGSP), they were established to have diabetes.

Data abstraction

Using a standardised data collection form, the demographic data of age and gender, clinical manifestation and another comorbid, laboratory findings, and outcome data of patients with COVID-19 were extracted from electronic and non-electronic medical records. All data were collected as of May 4, 2021 and were independently checked by two physicians. The laboratory findings included first in-hospital HbA1c levels and D-dimer.The severity of COVID-19 patient calculated based onclinical manifestation at admission.

Statistical analysis

All statistical analysis were performed using SPSS Statistics. All data were made into categorical variables are presented as numbers and percentages. Comparisons between groups were analysed using the Chi-Square or Fisher's exact test. The prevalence risk (PR) and 95% confidence intervals (Cis) also presented. The severity of COVID-19 and mortality during hospitalisation were analysed and compared between patients with diabetes mellitusvs without comorbid, patients with diabetes only vs without comorbid, and patients with diabetes accompanied by another comorbid vs without

comorbid.The other risk factor associated with the severity of COVID-19 and mortality rate were performed in a subgroup of patients with diabetes mellitus using demographic data, laboratory findings, and another comorbid. The other risk factors were also evaluated with logistic regression analysis. A two-sided *p* value < 0.05 for each statistical test used was considered statistically significant.

3. Results

Characteristics of sample

There are 622 confirmed COVID-19 cases admitted to our hospital during the study period. Of these patients, there were 69COVID-19 patients with diabetes mellitus. Among them, 42 (60.9%) patients were male, while 27 (39.1%) were female. At the first, we divided the patient's age into 5 group ranges, which ispatient groups aged 30-39, ages 40-49, ages50-59 ages 60-69 and ages 70-80. There were 22 (31.9%) patients having age ≥60 years old, while 47 (68.1%) other patients had age <60 years old. Based on these, we selected another 42 male and 23 female patients who were confirmed COVID-19 but did not have any comorbid and had the same sex and age range with the COVID-19 patients with diabetes. So that, the total of subjects became 138 with the prevalence of COVID-19 patients with diabetes mellitus and without any comorbid being the same.

Comparisons between COVID-19 patients with diabetes mellitus and without any comorbidities

We present the data of comparisons between COVID-19 patients with diabetes and without any comorbidities in **Table. 1.** From total of69 COVID-19 patients with diabetes, 35 (71.4%) patients came to the hospital with severe-critical symptoms.This is higher than the prevalence of COVID-19 patients without any comorbidities who came to the hospital with the same symptoms, which is only 14 (28.6%) patients. The comparative test in the two groups showed a result of *p* = 0.000,PR (95%CI) = 4.0 (1.9-8.5), which showed that overall patients withdiabetes mellitusincreased 4 times therisk of COVID-19 severity than in patients without any comorbidities. A significant risk of severity is also 2.9 times higher in diabetic patients who are accompanied by other comorbid (64.9% vs 35.1%, *p* = 0.017, PR (95%CI) = 2.9 (1.2-7.0)) as well as in patients who only had diabetes as a comorbid are 18 times more likely to experienced severe-critical symptoms (91.7% vs 8.3%, *p* = 0.001, PR (95%CI) = 18 (2.1-156)) than in the patients without any comorbidities. Meanwhile, the risk of in-hospital deathis increased 3.2 times in overall diabetic patients (71.4% vs 28.6%, *p* = 0.026, PR (95%CI) = 3.2 (1.1-9.5)), and risk of mortality in diabetic patients accompanied by another comorbid 4.2-fold increased (76.5% vs 23.5%, *p* = 0.015, PR (95%CI) = 4.2 (1.2-14)) compared with patients without any comorbidities. We found no significant difference between patients with diabetes only and patients without any comorbidities in the increased risk of mortality.

Table 1: Comparisons between COVID-19 patients with DM and without any comorbidities

Variables	Total (%)	Severity		*p* value; PR (95% CI)	Mortality		*p* value; PR (95% CI)
		Severe-Critical (%)	Mild-Moderate (%)		Death (%)	Survive (%)	
DM vs No Comorbid							
Diabetes	69 (50)	35 (71.4)	34 (38.2)	0.000; 4.0 (1.9-8.5)	14 (71.4)	55 (46.2)	0.026; 3.2 (1.1-9.6)
No Comorbid	69 (50)	14 (28.6)	55 (61.8)		5 (28.6)	64 (53.8)	
Only DM vs No Comorbid							
Diabetes Only	26 (50)	11 (91.7)	15 (37.5)	0.001; 18 (2.1-156)	1 (50.0)	25 (50.0)	1.000; 1.0 (0.06-17)
No Comorbid	26 (50)	1 (8.3)	25 (62.5)		1 (50.0)	25 (50.0)	
DM with another comorbid vs No Comorbid							
Diabetes with others	43 (50)	24 (64.9)	19 (38.8)	0.017; 2.9 (1.2-7.0)	13 (76.5)	30 (43.5)	0.015; 4.2 (1.2-14)
No Comorbid	43 (50)	13 (35.1)	30 (61.2)		4 (23.5)	39 (56.5)	

The following risk factors associated with severity and mortality of COVID-19 patients with diabetes mellitus.

To further investigate the following risk factors associated with an increased risk of severity and mortality in COVID-19 patients with diabetes, logistic regression was performed. Using univariable analysis by fisher and chi square test (**Table.2.**), it was found that the risk of COVID-19 severity was significantly increased in diabetic patient who accompanied by hypertension (*p* = 0.011; PR (95%CI) = 3.5 (1.3-9.5)) than those without hypertension. Increased of HbA1c levels ≥ 7% and D-dimer≥ 1000at admission also showed a significant increase in the risk of COVID 19 severity, with *p* = 0.025 and *p* = 0.024, respectively. Moreover, all of patients with HbA1c levels ≥ 7% (n = 24, 100%) present with severe-critical symptoms in this study. In the other hand, increased risk of mortality significantly increased in diabetic patients who accompanied by hypertension (*p* = 0.010; PR (95%CI) = 5.5 (1.4-22)), cardiovascular disease (*p* = 0.038; PR (95%CI) = 4.0 (1.1-14)), neurological disease (*p* = 0.013; PR (95%CI) = 10 (1.7-65)), and D-dimer levels ≥ 1000 at admission (*p* = 0.001; PR (95%CI) = 10 (2.1-54).

Table 2: The following risk factors associated with severity and mortality of COVID-19 patients with DM

Variables	Total (%)	Severity		*p* value; PR (95% CI)	Mortality		*p* value; PR (95% CI)
		Severe-Critical (%)	Mild-Moderate (%)		Death (%)	Survive (%)	
Characteristics							
Sex							
Male	42 (60.9)	22 (62.9)	20 (58.8)	0.731; 1.2 (0.4-3.1)	9 (64.3)	33 (60.0)	0.769; 1.2 (0.3-4.0)
Female	27 (39.1)	13 (37.1)	14 (41.2)		5 (35.7)	22 (40.0)	

Age							
≥60 years old	22 (31.9)	10 (28.6)	12 (35.3)	0.549; 0.7 (0.3-2.0)	6 (42.9)	16 (29.1)	0.349; 1.8 (0.5-6.1)
<60 years old	47 (68.1)	25 (71.4)	22 (64.7)		8 (57.1)	39 (70.9)	
Laboratory Findings							
HbA1c (NGSP)							
≥ 7%	46 (88.5)	24 (100)	22 (78.6)	0.025; -	6 (85.7)	40 (88.9)	1.000; 0.75 (0.1-7.5)
< 7%	6 (11.5)	0(0.0)	6 (21.4)		1 (14.3)	5 (11.1)	
D-dimer (ng/mL)							
≥ 1000	25 (46.3)	18 (60.0)	7 (29.2)	0.024; 3.6 (1.2-11)	11 (84.6)	14 (34.1)	0.001; 10 (2.1-54)
< 1000	29 (53.7)	12 (40.0)	17 (70.8)		2 (15.4)	27 (65.9)	
Other Comorbid							
Hypertension							
Yes	33 (47.8)	22 (62.9)	11 (32.4)	0.011; 3.5 (1.3-9.5)	11 (78.6)	22 (40.0)	0.010; 5.5 (1.4-22)
No	36 (52.2)	13 (37.1)	23 (67.6)		3 (21.4)	33 (60.0)	
Cardiovascular Disease							
Yes	18 (26.1)	12 (34.3)	6 (17.6)	0.116; 2.4 (0.8-7.5)	7 (50.0)	11 (20.0)	0.038; 4.0 (1.1-14)
No	51 (73.9)	23 (65.7)	28 (82.4)		7 (50.0)	44 (80.0)	
Neurological Disease							
Yes	6 (8.7)	3 (8.6)	3 (8.8)	1.000; 1.0 (0.2-5.1)	4 (28.6)	2 (3.6)	0.013; 10 (1.7-65)
No	63 (91.3)	32 (91.4)	31 (91.2)		10 (71.4)	53 (96.4)	
Kidney Disease							
Yes	4 (5.8)	2 (5.7)	2 (5.9)	1.000; 1.0 (0.1-7.3)	2 (14.3)	2 (3.6)	0.181; 4.4 (0.5-34)
No	65 (94.2)	33 (94.3)	32 (94.1)		12 (85.7)	53 (96.4)	

Subsequently, we used hypertension, cardiovascular disease, HbA1c and D-dimer levels as variables for multivariable logistic regression analysis for risk of severity in COVID-19 patients with diabetes mellitus. While we used hypertension, cardiovascular disease, neurological disease, kidney disease and D-dimer levels as variables for multivariable logistic regression for the risk in-hospital death in COVID-19 patients with diabetes.

Table 3: Univariable and multivariable analysis for the risk of severity and mortality in COVID-19 patients with diabetes

Variables	Univariable Analysis		Multivariable Analysis	
	p value	OR (95%CI)	*p* value	OR (95% CI)
Risk of severity				
HbA1c (NGSP) ≥ 7%	0.025	-	-	-
D-dimer ≥ 1000 ng/mL	0.024	3.6(1.2-11)	0.015	24 (1.8-324)
Hypertension	0.011	3.5 (1.3-9.5)	0.004	15 (2.3-98)
Cardiovascular Disease	0.116	2.4 (0.8-7.5)	0.780	0.7 (0.1-5.6)
Risk of mortality				
D-dimer ≥ 1000	0.001	10 (2.1-54)	0.037	4.3 (1.0-17)
Hypertension	0.010	5.5 (1.4-22)	0.042	3.4 (1.0-11)
Neurological Disease	0.013	10 (1.7-65)	0.181	0.2 (1.2-81)
Cardiovascular Disease	0.038	4.0 (1.1-14)	0.202	2.6 (0.6-11)
Kidney Disease	0.181	4.4 (0.5-34)	0.999	0.000

The result of logistic regression presented in the **Table. 3.** The risk factors that affect the severity of COVID-19 patients with diabetes are hypertension (OR 15, 95%CI 2.3-9.8) andD-dimerlevels ≥ 1000 ng/ mL (OR 24, 95% CI 1.8-324). HbA1c levels cannot be analysed in multivariable test because in fact, in this study an increase of HbA1c levels ≥7 was found in all patients who presented with a severe-critical symptom. Hypertension (OR 3.4, 95% CI 1.0-11) and D-dimer levels ≥1000 ng/ mL (OR 4.3, 95% CI 1.0-17) was also increasing risk of mortality in COVID-19 patients with diabetes mellitus based on multivariable logistic regression analysis. Although the result of multivariable analysis was not consistent with those of univariable analysis for neurological and cardiovascular disease, we cannot rule out the risk of death in diabetic patients who are accompanied by heart disease and neurological disorders.However, it is certain and indicated from these results that hypertension and an increase ofD-dimer levels ≥1000 ng/ mL were a risk factors that affect the severity and mortality of COVID-19 patients with diabetes mellitus.

4. Discussion

Potential mechanisms underlying the increased risk of COVID-19 severityin diabetes mellitus

Individuals with diabetes are more susceptible to a broad range of infections. In addition, several infections may result in less well-controlled diabetes.[1] Some literature has reviewed several pathophysiology that may be associated between COVID-19 and diabetes mellitus. COVID-19 is a viral infection characterized by storms of inflammatory responses and higher levels of circulatory cytokines. Also, DM is associated with chronic low-grade inflammation in the body, and patients with diabetes have higher circulatory levels of cytokines. Due to the presence chronic inflammation in DM, it could be a potentiator of inflammatory responses and increase the likelihood of inflammation storms in COVID-19 patients.[20] Patients with COVID-19 also exhibit elevation of inflammatory markers, such as D-dimer and ferritin which might contribute to an increased risk of microvascular and macrovascular complications originatingfrom low-grade vascular inflammation in patients with underlying diabetes mellitus.[7,20]

SARS-CoV2, which is responsible for the recent pandemic of COVID-19, has close interactions with RAAS activity which may be another underlying mechanism for the detrimental effects of diabetes on the prognosis of COVID-19.SARS-CoV2 enters host pneumocytes via binding with

spike (S) protein of ACE2 receptors.[21,22] On the other hands, patients with diabetes were reported to have a higher expression concentration of ACE2 and its level is significantly raised in those taking angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) to prevent or treat diabetes-induced vascular disorders.[4,20]Thus, it could be hypothesized that patients with DM are more likely prone to more severe degrees of COVID-19 at least partly due to their altered RAAS functions which may facilitate virus entry into the cells.[10]Over a decade ago, SARS-CoV was detected in pancreas, in addition to lung, suggesting pancreas is the target of coronavirus attack. Noteworthy, pathological changes in pancreas, mainly focal enlargement of the pancreas or dilatation of the pancreatic duct, were observed in patients with severe COVID-19, indicating SARS-CoV-2 may cause pancreatic injury. However, ACE2 expression is not limited to the lung. It has been found in pancreas islets, which highlights the need for vigilance in consideration of whether SARS-CoV-2 infection may contribute to the exacerbation or development of diabetes.[22]

The following comorbid associated withrisk of severity in COVID-19 patientswith diabetes mellitus.

In this study, we found that the prevalence of COVID-19 patients with diabetes mellitus presented with severe-critical caseswas 71.4%, a way more than theof patients without any comorbidities. This difference is statistically significant (p = 0.000, PR = 4.0), which showed that the presence of diabetes mellitus had a 4-fold increased risk of developing severe-critical symptoms compared with patients without any comorbidities.Significant results were consistent whether the patient was accompanied by other comorbid or not. Patients with diabetes with multiple comorbidities should take extra precaution to prevent the possibilityof an increased risk of severity due to COVID-19 cases.[8]In our study, hypertension is one of the following risk factors which leads to an increased risk of COVID-19 severity in diabetic patients. The presence of hypertension in diabetic patients had a 3.5-fold increased risk of developing severe-critical case compared with diabetic patients without hypertension.A dysfunctional of CD8+ T cell observed in patients with hypertension in general, leading to inability of fight against viral infection and contribute to over productive of cytokines as same as in diabetes mellitus. The mechanism of SARS-CoV-2 infection causeRAAS dysfunction as previously explained in diabetic patients, also affecting electrolyte and fluid balance which influence blood pressure.[23]This can be hypothesized to be the cause of COVID-19 patients with diabetes accompanied by hypertension are more likely prone to more severe degrees of COVID-19. Although we did not find the same significant results in other comorbid such as cardiovascular disease, neurological disease, and kidney disease. The other study was showed significant differences in comorbidities for diabetic COVID-19 patients versus non-diabetic patients,including hypertension, cardiovascular disease, and chronic renal disease. It has been well established that hypertension, cardiovascular disease, cerebrovascular disease, and chronic renal disease coexist with diabetes, leading to a higher risk of morbidityand mortality for COVID-19.[9]

The following comorbid associated with risk of mortality in COVID-19 patients with diabetes mellitus

Our study does not only provide significant results on the association of diabetes mellitus with the severity of COVID-19, but wealso found significant difference in the mortality risk between COVID-19 patients with diabetes mellitus and patients without any comorbidities (p = 0.026).COVID-19 patients with diabetes mellitus were 3.2 times more likely to experience in-hospital death (PR = 3.2) compared to the patients without any comorbidities. The result is more significant in the COVID-19 patients with diabetes accompanied by another comorbid (p = 0.015, PR = 4.2). But on the other hand, we found no significant difference in the comparison of the prevalence of death cases in patients with diabetes only and patients without any comorbidities. This could be an indication that the risk of death in COVID-19 patients with diabetes is increased in the presence of other risk factors. But further studies with larger samples are still needed to verify our results.

As we mentioned before, the following comorbid such as hypertension, cardiovascular disease, cerebrovascular disease, and chronic renal disease coexist with diabetes, leading to a higher risk of morbidity and mortality for COVID-19 patients.[9]In our study showed that existence of hypertension, cardiovascular disease, neurological disease had a 5.5-fold, 4-fold, 10-fold, respectively, increased risk of death in COVID-19 patients with diabetes.So that diabetes patients who are accompanied by these diseases need more attention to prevent a poor prognosis. Male gender has been widely referred to as the independent risk factor of mortality in COVID-19 patients. While in this study, we found no significant difference in the increased risk of mortality in COVID-19 patients with diabetes who were male or female, older or younger.

The effect of increasing HbA1c and D-dimer on morbidity and mortality of COVID-19 patients with diabetes mellitus

In our study, from total of 24 diabetic patients who experienced severe-critical COVID-19 symptoms, all of them had HbA1c levels more than 7%. We only had 6 COVID-19 patients with diabetes who had HbA1c levels less than 7%, and all of them had mild-moderate symptoms during admission. Thus, we found a significant difference between diabetes patients with HbA1c ≥7% compared to the patients with HbA1c <7% in the severity of COVID-19 (p = 0.025). However, in the risk of mortality, we found no significant difference between diabetes patients with HbA1c ≥7% and patients with HbA1c levels <7%. Although patients with HbA1c of 6.5% or more were more likely to develop acute respiratory distress syndrome leading to the high risk of morbidity and mortality than patients with HbA1c less than 6.5%, the risk remained higher in multiple models adjusting for age, sex, comorbidities, and laboratory results.[24] It is noteworthy that in this study we included all COVID-19 patients with diabetes who had an HbA1c lab result, regardless of other comorbid and other lab results that occur in each diabetes patient, which might affect the outcomes of interest. HbA1c reflects the average blood glucose concentration over the past 2–3 months. Therefore, the effect of short-term viral infection on HbA1c levels may not be prominent for increasing risk of mortality.[22]

Nevertheless, additional research with large sample size is needed to verify our results.

Patients with COVID-19 also exhibit elevation of inflammatory markers, such as D-dimer, which might contribute to an increased risk of microvascular and macrovascular complications in patients with underlying diabetes mellitus.[20]Elevated serum D-dimer levels >1 g/L may indicate higher risk of death in infected patients. An elevated level of D-dimer signifies a hypercoagulable state in patients with COVID-19. An exceptionally high percentage of aberrant coagulation cases was noticed in severe and critical COVID-19 patients. D-dimer levels keep increasing steadily in severely ill patients starting from the initial viraemia phase.[24]The result of our study showed that a serum D-dimer levels ≥1000 ng/mL significantly increases the risk of disease severity 3.6-fold (p = 0.024), and a 10-fold increase (p = 0.001) in the risk of mortality in COVID-19 patients with diabetes.Consistently significant results were obtained in either univariable or multivariable analysis. These findings suggest that diabetic patients with COVID-19 are more likely to show abnormal blood coagulation function in clinical practice. During the inflammatory storm, blood coagulation was abnormal. In the early stage, this is the result of inflammation-activating plasmin. Subsequently, hypoxia-induced molecules can activate thrombin directly, with progressive inflammation, and the activation of monocyte macrophages also secretes a few tissue factors, activating the exogenous coagulation pathway, which leads to an overall hypercoagulable state.[9, 24]

5. Conclusion

In conclusion, the risk of COVID-19 severity and mortality generally increases in diabetes patients. Presence of hypertension or D-dimer ≥1000 ng/mL were independent risk factor for both severity and mortality in COVID-19 patients with diabetes. Moreover, HbA1c level≥7% in diabetic patients have a higher risk of developing severe-critical symptoms, while the presence of cardiovascular and neurological disease increases risk of mortality. Diabetes mellitus patients presenting with other risk factors must be take an extra attention to prevent a poor outcome.

6. Future Scope

Our study has some limitations. First, it was single-centre study with limited number of patients. We enrolled COVID-19 patients with diabetes mellitus as many as we could and excluded non-diabetic patients who had other comorbidities. So that, we do not present comparative data between patients with diabetes and patients with other comorbid. Second, not all patients had their HbA1c level tested during the hospitalization, even though in diabetic patients. At the very beginning of the pandemic, some medical staff had not realized the potential benefits of evaluating HbA1c in patients with COVID-19. Thus, the prevalence of diabetes in our COVID-19 population may even be higher than what we reported in this study. Third, we only included D-dimer in the risk factor analysis, also not all patients had their D-dimer tested. We did not analyse other inflammatory biomarkers, such as serum C-reactive protein (CRP), IL-6, or ferritin, due to the limited amount of data. Involving multicentre or more patients may better investigate the clinical features of DM patients with COVID-19 and confirm the risk factors of severe disease.

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