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Original Research Article

Hyperglycaemia in predicting severe COVID-19 at Tabanan general hospital, Bali

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ABSTRACT

Background: Hyperglycaemia has been shown to be associated with disease progression and poor prognosis in Corona virus disease 2019 (COVID-19) patients. This study aims to find the effect of hyperglycaemia on disease severity and investigate whether high blood glucose levels on admission can predict severity of COVID-19 infection
Methods: in this cross-sectional study, a total of 286 COVID-19 patients in Tabanan general hospital, Bali were retrospectively analysed. Data were obtained from medical records from January 1 to December 31, 2021. Hyperglycaemia was defined as random blood glucose (RBG) >140 mg/dl. The severity of COVID-19 was determined according to the 4th edition of the Indonesian COVID-19 management guidelines. Clinical and biochemical characteristics of COVID-19 patients with or without diabetes were compared. Receiver operating characteristic (ROC) analysis was used to identify optimal admission plasma glucose levels to predict COVID-19 severity.
Results: 47.2% of subjects had hyperglycaemia at admission, 67.5% experienced severe COVID-19, of which 68.4% died. Admission RBG values were positively correlated with leukocyte and NLR values. In ROC analysis, admission RBG >145 mg/dl can predict severe COVID-19 with sensitivity of 56% and specificity of 76% (AUC 0.663, p<0.01).
Conclusions: Hyperglycaemia is an independent predictor of severe COVID-19 and impose a significantly higher mortality rate compared to normoglycemic patients regardless of diabetic status. Early measurement of plasma glucose levels upon admission can help identify patients who are likely to experience a worse clinical course.

Keywords: Hyperglycaemia, COVID-19, Severity, Diabetes mellitus

INTRODUCTION

Corona virus disease 2019 (COVID-19) is highly contagious infection caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) which mainly attacks respiratory tract and lungs causing pneumonia.[1] Condition can progress to acute respiratory distress and into septic shock that requires intensive care and causes high rates of morbidity and mortality. Based on data from WHO, as of August 16, 2023, there are more than 500 million cases of COVID-19 globally with >6 million deaths. Meanwhile Indonesia, confirmed cases of COVID-19 amounted to 6,813,095 cases with 161,916 deaths.[2]

Comorbidities including hypertension, malignancy, cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD) and diabetes mellitus (DM) were found to have a major impact on the course of COVID-19 disease.[3,4] COVID-19 patients with comorbidities are at high risk of death and diabetes is one of the most common comorbidities in COVID-19 patients.[5] DM and hyperglycaemia with or without a previously known history of DM receive special attention due to their associated with poor COVID-19 outcomes. Previous research showed that 7.4-19% of COVID-19 patients had DM, and the proportion of patients with DM was higher (16.2-26.9%) among patients with severe COVID-19.[6,7] COVID-19 patients with DM and/or uncontrolled hyperglycaemia (Plasma blood sugar >10 mmol/L=180 mg/dL) had longer duration of stay (LOS) (5.7 vs. 4.3 days) and significantly higher mortality rates

(28.8 vs. 6.2%) than patients without DM or hyperglycaemia.[8]

Hyperglycaemia has been shown to be associated with adverse outcomes in COVID-19 patients.[9] Several observational studies have provided clinical evidence that uncontrolled hyperglycaemia can lead to longer LOS and significantly higher mortality in COVID-19 patients. Poor glycaemic control in COVID-19 patients without DM also contributes to the high risk of mortality. Prior to the onset of COVID-19, hyperglycaemia deleterious effects already proven to exist among patients with pneumococcal pneumonia, where the 30-day mortality among patients with admission RBG levels ≥10 mmol/L (i.e., ≥180 mg/dL) had a 3.4 times higher risk than patients with admission RBG levels <7 mmol/L (i.e., <126 mg/dL). There was also a strong association between disease severity and high RBG levels among patients without DM.[10]

Dysregulation of glucose metabolism is thought to underlie the process of hyperglycaemia in COVID-19 infection. Numerous studies have reported that in addition to the respiratory tract, SARS-CoV-2 also infects other organs including pancreatic endocrine cells that express angiotensin-converting enzyme 2 (ACE2) which is the receptor for this virus, thus directly affecting insulin production and glucose metabolism. SARS-CoV-2 infection is also known to stimulate the widespread release of cytokines, causing hyperinflammatory syndrome and triggering inflammatory cytokine storms. This cytokine storm is often associated with dysregulation in glucose metabolism and manifests as DM and/or hyperglycaemia, leading to metabolic disorders.[11,12]

The high rate of DM and/or hyperglycaemia among COVID-19 patients increase the need of special attention to glycaemic control in this population. Moreover, it remains unclear whether COVID-19 patients presenting with hyperglycaemia upon hospital admission, but are unaware of their previous DM status, have a higher risk of severe COVID-19 than those with known history of DM. Therefore, in this study we aimed to further analyse the impact of hyperglycaemia towards disease severity among COVID-19 patients with and without DM treated at Tabanan general hospital. We aim to facilitate a better understanding of the effects of hyperglycaemia on disease severity and investigate whether blood glucose levels on admission and DM status can predict severity and mortality in COVID-19 patients.

METHODS

This study is a cross-sectional study which retrospectively analysed patients diagnosed with COVID-19 from January 1, 2021 to December 31, 2021 at Tabanan general hospital, Bali. All patients aged 18 years and above with a confirmed diagnosis of COVID-19 confirmed by the real-time reverse transcriptase polymerase chain reaction (RT-PCR) method were included in the study. Patients with history of malignancy, history of immune deficiency, pregnancy, two consecutive negative COVID-19 real-time RT PCR, incomplete medical records, and patients with no RBG data at admission were excluded.

Demographic data, comorbid history, laboratory results, severity and mortality of COVID-19 patients were obtained from electronic medical records. The severity of COVID-19 was determined by reviewing the course of the disease during treatment and was defined according to the 4th edition of the Indonesian COVID-19 Management Guidelines published on January 2022. Moderate COVID-19 was defined as patients with signs of pneumonia including fever, cough, dyspnoea, and/or tachypnoea with oxygen saturation (SpO_2) ≥93% in room air. Meanwhile, severe COVID-19 was defined as patients with signs of pneumonia with at least one of the following signs: respiratory rate >30x/min, severe respiratory distress, or SpO_2<93% in room air. Hyperglycaemia in this study was defined as RBG >140 mg/dl.

A total of 286 COVID-19 patients were included in this study. Statistical analysis was performed using SPSS software. Continuous data is presented as the mean ± standard deviation or as the median (interquartile range). Categorical data are reported as a percentage or n (%). Percentage values were compared among different groups with chi-square tests or Fisher's exact tests as indicated. Two groups of non-normally distributed continuous data were compared using the Mann-Whitney U-test and with the T test for the normally distributed data. The correlation between plasma glucose levels and levels of inflammatory markers was assessed with the Spearman correlation. The relationship between plasma glucose levels at admission and severity of COVID-19 was further assessed by multinomial logistic regression analysis. ROC analysis was then performed to identify optimal admission plasma glucose levels to predict COVID-19 severity.

RESULTS

Of the 286 patients confirmed with COVID-19 at Tabanan general hospital in 2021, 57.7% were male with a median age of 59 years. Hypertension was the highest comorbidity followed by DM. As many as 67.5% of patients experienced severe COVID-19, of which 68.4% died. Hyperglycaemia at the time of admission was found in as many as 135 patients.

Compared to moderate COVID-19 patients, severe COVID-19 patients tend to be older, more prevalent in men, have higher leukocyte count and NLR values (Leukocytes 10 vs 7.2×103 uL, p<0.01; NLR 8.84 vs 3.87 p<0.01), higher hyperglycaemia incidence (56.6% vs 28% p<0.01), and higher mortality at the end of treatment (68.4%, p<0.01) (Table 1).

In the multivariate analysis, RBG levels at admission, age, heart rate, NLR and history of hypertension were

significantly related to the severity of the COVID-19 after adjusting for other variables (Table 2).

According to Table 3, patients with a history of DM had higher incidence of severe COVID-19. DM patients who were hyperglycaemic at admission were found to have significantly higher incidence of severe infections than DM patients who were normoglycemic at admission. Severe infections also occur more prevalently in patients with no history of DM who hyperglycaemic ($p<0.01$).

Hyperglycaemic patients with or without a history of DM were also found to have significantly worse outcomes with a greater proportion of mortality compared to normoglycemic patients (Table 3).

In the correlation test (Table 4), RBG values on admission were found to be positively correlated with leukocyte and NLR values.

In addition, in ROC analysis, RBG values were found to significantly predict the severity of COVID-19 infection (AUC 0.663, $p<0.01$) (Figure 1) where RBG levels above 145 mg/dl at admission can predict the severity of COVID-19 with sensitivity of 56% and the specificity of 76% (Table 5).

Table 1: Characteristics of COVID-19 patients based on severity.

Variables	Total, (n=286) (%)	Moderate COVID-19, (n=93) (%)	Severe COVID-19, (n=193) (%)	P value
Age, (In year)	59 (51-68)	53.2±14.2	61.1±13.7	0.000
Gender				
Male	165 (57.7)	52 (55.9)	113 (58.5)	0.673
Female	121 (42.3)	41 (44.1)	80 (41.5)	
LOS, day	9 (5-13)	11 (8-13)	7 (3-11)	0.000
Comorbidities				
DM	75 (26.2)	17 (18.3)	58 (30)	0.034
Hypertension	144 (50.3)	29 (31.2)	115 (59.6)	0.000
Heart disease	49 (17.1)	13 (14)	36 (18.7)	0.326
Respiratory disease	14 (4.9)	5 (5.4)	9 (4.7)	0.793
Liver disease	2 (0.7)	0 (0)	2 (1)	0.455
Kidney disease	42 (14.7)	8 (8.6)	34 (17.6)	0.044
Neurological disease	22 (7.7)	8 (8.6)	14 (7.3)	0.689
Vital signs				
Systolic blood pressure, mmHg	118 (110-138)	110 (110-130)	120 (110-141.5)	0.044
Diastolic blood pressure, mmHg	71 (70-80)	70 (70-80)	73 (65-80)	0.910
Heart rate, x/menit	89 (80-101)	84 (80-94)	91 (82.5-103)	0.000
Respiratory rate, x/menit	24 (20-30)	20 (20-22)	26 (22.5-32.5)	0.000
Temperature, Celcius	36.5 (36-36.8)	36.6 (36.2-36.9)	36.5 (36-36.8)	0.064
SpO_2, %	89 (83.8-95)	96 (95-98)	87 (78-89)	0.000
Laboratories result				
Hb, mg/dL	13.4 (11.8-14.7)	13.3 (11.7-15)	13.5 (11.9-14.7)	0.714
Hct, %	40 (35.4-43.9)	39.6 (34.7-44.1)	40.2 (35.6-43.9)	0.624
Thrombocyte, 10^3 uL	190 (147-248)	187 (151.5-235.5)	193 (144.5-252.5)	0.734
Leukocyte, 10^3 uL	9 (6.5-12.5)	7.2 (5.5-10.1)	10 (7.3-14.2)	0.000
Diff count (%)				
Basophils,	0.2 (0.1-0.6)	0.5 (0.2-0.85)	0.2 (0.1-0.4)	0.000
Eosinophils,	0.1 (0-0.5)	0.4 (0.1-1.25)	0.1 (0-0.3)	0.000
Neutrophils,	80.8 (71.9-88.5)	72.8 (61.6-79)	84.9 (76.7-90.2)	0.000
Lymphocytes,	12.2 (6.7-20)	20.9±11.2	9.9 (5.2-15.4)	0.000
Monocytes,	5.9 (3.7-8.1)	7.7±2.9	4.9 (2.95-6.9)	0.000
NLR	6.6 (3.8-13.2)	3.87 (2.2-6.7)	8.84 (5.1-17.7)	0.000
BUN	18 (12-34)	15 (10-19.5)	23 (14-37)	0.000
Serum creatinine	1.1 (0.9-1.8)	1.07 (0.8-1.4)	1.2 (0.9-1.9)	0.017
SGOT	43 (26-68.5)	31 (24-44)	50 (30-88)	0.000
SGPT	29 (18-48.3)	28 (17-44)	31 (18-54)	0.053
Blood sugar levels	136 (110-208.8)	119 (105-144)	154 (115.5-231)	0.000
Normoglycaemia	151 (52.8)	67 (72)	84 (43.5)	0.000
hyperglycaemia	135 (47.2)	26 (28)	109 (56.6)	
Mortality	134 (46.9)	2 (2.2)	132 (68.4)	0.000

Table 2: Multivariate analysis.

Variables	Exp (B)	95% CI	P value
Age (In years)	1.039	1.016-1.062	0.001
SBP	0.992	0.978-1.007	0.321
Heart rate	1.037	1.015-1.059	0.001
Leukocytes	0.975	0.911-1.044	0.470
NLR	1.067	1.016-1.122	0.010
RBG	1.009	1.002-1.015	0.009
HT	0.330	0.164-0.664	0.002
DM	1.708	0.699-4.172	0.240
Hyperglycaemia	1.032	0.418-2.548	0.946

SBP-systolic blood pressure, NLR-neutrophil-lymphocyte ratio, RBG-random blood glucose, HT-hypertension, DM-diabetes mellitus.

Table 3: Characteristics of COVID-19 patients based on DM comorbidity and admission glycaemic status.

Variables	Non-DM, (n=211)	Non-DM, (n=211)		DM, (n=75)	DM, (n=75)	
		Normo-glycemia, (n=142)	Hyper-glycaemia, (n=69)		Normo-glycemia, (n=9)	Hyper-glycaemia, (n=66)
Age, (Years)	58.1±15.2	56.2±16.1	61.9±12.4^{++}	59.7±11.4	58.8±9.6	59.8±11.7
Gender						
Male	121 (57.3)	84 (59.2)	37 (53.6)	44 (58.7)	6 (66.7)	38 (57.6)
Female	90 (42.7)	58 (40.8)	32 (46.4)	31 (41.3)	3 (33.3)	28 (42.2)
LOS, day	9 (5-13)	9.5 (6-13)	7 (2-12)	8.4±5.2	11±6.9	8.1±4.9
Laboratories result						
Hb, mg/dL	13.4 (11.7-14.8)	13.4 (11.7-14.7)	13.6 (11.6-14.9)	13.4 (11.9-14.5)	12.4 (10.2-14.9)	13.4 (11.9-14.4)
Hct, %	40.2 (35-44)	40.1 (34.9-43.9)	40.2 (35.3-44.2)	39.6 (35.5-43.2)	37.4 (29.9-44.9)	39.9 (35.8-42.9)
Thrombocyte, 10^3 uL	193 (147-248)	189 (141.8-237)	207 (153-276)	184 (145-247)	187 (147-269.5)	182.5 (144.8-235)
Leukocyte, 10^3uL	9.1 (6.4-12.5)	8.7 (6.1-11.5)	10.1 (6.8-14.2)$^{+}$	8.7 (7.1-13.4)	10 (7.5-19.9)	8.6 (7.1-12.9)
Diff count (%)						
Basophils	0.2 (0.1-0.6)	0.3 (0.1-0.6)	0.2 (0.05-0.3)$^{+}$	0.3 (0.1-0.6)	0.6 (0.2-0.95)	0.2 (0.1-0.5)
Eosinophils	0.1 (0-0.6)	0.2 (0-0.6)	0 (0-0.25) $^{++}$	0.1 (0-0.4)	0.8 (0.15-2.1)	0.1 (0-0.4)**
Neutrophils	80.7 (70.3-89.2)	78.4 (66.4-87.1)	85.9 (75.6-90.8)$^{++}$	81.8 (72.8-87.1)	77.5 (65.1-88.1)	82.4 (72.9-87.2)
Lymphocytes	12.5 (6.6-21.7)	13.85 (8-23.5)	8.2 (4.5-15.5)$^{++}$	12 (7.5-17.1)	11.4 (6.2-23.1)	12.1 (7.3-17)
Monocytes	5.8 (3.6-8.2)	6.2 (3.9-8.8)	4.9 (3.4-6.6)$^{+}$	6.1 (3.9-7.5)	7.7 (4.3-9.4)	5.9 (3.9-7.4)
NLR	6.61 (3.34-13.2)	5.6 (2.8-10.6)	10.2 (5.3-19)$^{++}$	6.9 (4.2-11.4)	6.5 (3.1-15.6)	6.9 (4.4-11.9)
BUN	17 (12-34)	16 (12-27.5)	25 (13-47.5)$^{+}$	23 (14-36)	17 (11.5-37.5)	23 (15-34.5)
Serum creatinine	1.11 (0.9-1.6)	1.1 (0.9-1.6)	1.2 (0.9-2.0)	1.2 (0.9-1.9)	1.1 (0.6-1.8)	1.2 (0.9-1.9)
Random blood sugar	122 (105-55)	110.5 (97.8-122)	176 (155-214)$^{++}$	255 (200-348)^^	118 (109-131.5)	268.5 (220.5-382)**
COVID-19 severity						
Moderate	76 (36)	63 (44.4)	13 (18.8)	17 (22.7)	4 (44.4)	13 (19.7)
Severe	135 (64)	79 (55.6)	56 (81.2)$^{++}$	58 (77.3)^	5 (55.6)	53 (80.3)*
Mortality	92 (43.6)	48 (33.8)	44 (63.8)$^{++}$	42 (56)	2 (22.2)	40 (60.6)*

$^{+}$p<0.05 vs normoglycaemic non-DM group, $^{++}$ p<0.01 vs normoglycaemic non-DM group; ^p<0.05 vs non-DM group; ^^p<0.01 vs non-DM group; *p<0.05 vs normoclycaemic DM group; **p<0.01 vs normoclycaemic DM group.

Table 4: Correlation of admission blood glucose with inflammatory parameters.

Variables	WBC		NLR	
	R	P value	R	P value
Blood glucose	0.136	0.021	0.206	0.00

Table 5: RBG values in predicting severe COVID-19.

RBG (mg/dL)	Sensitivity (%)	Specificity (%)
135.5	61	72
136.5	59	72

Continued.

RBG (mg/dL)	Sensitivity (%)	Specificity (%)
138.0	58	72
140.0	56	72
142.0	56	73
143.5	56	74
145.0	56	76
146.5	55	76
147.5	54	77
148.5	53	77

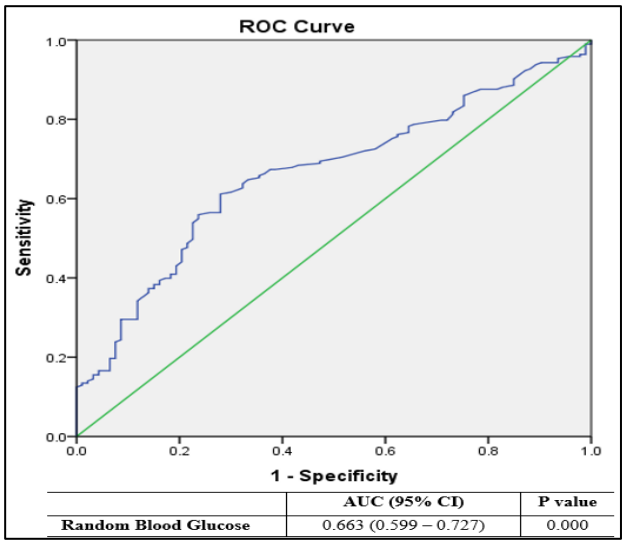

Figure 1: ROC analysis of RBG values and severe COVID-19.

DISCUSSION

The COVID-19 pandemic, which escalated sharply in 2020, has posed a threat to public health around the world, exhausted a lot of medical resources resulting in major economic problems. Special attention to the clinical characteristics of COVID-19 patients that can lead to poor outcomes is important, and among these characteristics, patients with hyperglycaemia have been widely associated as one of the conditions that increase the risk of disease severity and poor prognosis of COVID-19 patients.

In this study, 47.2% of patients were hyperglycaemic at admission and severe COVID-19 infection was found to be higher in hyperglycaemic patients without a history of DM ($p<0.01$). The results of this study are similar with the one by Wang, et. al who found COVID-19 patients with hyperglycaemia without a history of DM are more likely to experience severe or critical infections (severe: 38.46% vs 23.46%-30.70%; critical 7.69% vs 0.61%-3.96%).[15] The risk of severe/critical COVID-19 disease was higher in the hyperglycaemic group than in the euglycemic group (OR=2.08, 95% CI, 1.45-2.99, I2=77.9%, $p<0.001$).[16]

Our study also found hyperglycaemic patients with or without a history of DM had significantly higher mortality rates compared to normoglycemia patients. These results are in line with several studies including a meta-analysis by Yang et al that included more than 6386 patients with COVID-19 where compared to COVID-19 patients in the control group, patients who were hyperglycaemic at the time of admission had an increased risk of death and severe/critical degree of infection.[16-18] This suggests that hyperglycaemia at admission may be an important predictive indicator for determining COVID-19 outcomes.

In addition, in this study we found that RBG levels at admission can significantly predict the severity of COVID-19 infection (AUC 0.663, $p<0.01$) where RBG levels above 145 mg/dl at admission can predict the severity of COVID-19 with sensitivity of 56% and specificity of 76%. Blood glucose levels were also found to be an important prognostic predictor of disease progression and mortality of COVID-19 patients, Wang et.al found that patients with elevated blood glucose levels >6.1 mmol/L (>110 mg/dl) had a 58% higher risk of disease progression and a 3.22-fold higher risk of death.[17] In addition, high fasting blood glucose >110 mg/dl at admission was also found to be an independent predictor of worsening SARS-CoV-2 infection, regardless of DM history.[19] This suggests that intensive monitoring and control of blood glucose are essential for all COVID-19 patients. These results are also in line with previous studies that found hyperglycaemia contributed to the development of acute respiratory distress syndrome in COVID-19 patients.[20-23]

Patients with severe COVID-19 infection in this study tended to be older. These results are similar to studies showing a significantly higher risk of severe COVID-19 ($p<0.05$) in middle-aged adults and older adults compared to young adults.[13] This can be due to differences in innate, adaptive and heterologous immunity, as well as differences in endothelial function and clotting in old age. Elderly patients can have poor, uncoordinated T cell responses with an additional scarcity of naïve T cells.[14]

Hyperglycaemia with or without a history of DM has long been associated with adverse outcomes in COVID-19 patients and the two conditions are said to affect one another.[24] High levels of proinflammatory cytokines accompanied by weakening of innate immune defences are said to contribute to the onset of hyperinflammatory conditions in COVID-19 patients with hyperglycaemia. Hyperglycaemia causes a spike in IL6 levels that play a role in the emergence of cytokinetic storms. IL-6 is the main proinflammatory cytokine produced by macrophages and T-helper 2 (Th2) cells. IL-6 has been shown to be

significantly associated with COVID-19 severity because it can damage DNA and lipids by increasing oxidative stress.[12] In addition, IL-6 can inhibit T-cell proliferation and B-cell differentiation to induce immune dysfunction.[25] Abnormalities of inflammatory cytokines and the immune system due to hyperglycaemia are the reason why this population are more at risk of worsening and even death.

Patients with hyperglycaemia also had the highest rates of inflammatory parameter abnormalities and complications and there was a 5-fold increased risk of ICU admission during hospitalization in patients with high blood sugar whether or not they had a previous history of DM (HR=5.38, 3.46-8.35, p<0.001).[15] Similar results were found in this study where GDS levels at admission were positively correlated with leukocyte and NLR values (WBC: r=0.136, p=0.021; NLR: r=0.206, p=0.000). NLR has been shown to be an indicator that can be used to determine disease severity in COVID-19. A Cochrane Meta-analysis of twenty Chinese studies determined that NLR is an independent prognostic marker for distinguishing severe vs. non-severe COVID-19 disease.[26] This is thought to be due to hyperglycaemia in severe COVID-19 patients who have been shown to reduce the proportion of immune cells, including CD4+, CD8+, and macrophage T cells. COVID-19 patients with hyperglycaemia tend to have lower lymphocyte counts than COVID-19 patients with normoglycemia. Thus, the severity of COVID-19 infection is also thought to occur due to a decrease in the function of innate immune defence which decreases the proportion of immune cells.

Limitations

First, very few COVID-19 patients were measured for HbA1c at admission; Therefore, the patient's average glucose control over the previous 3 months is unknown. COVID-19 patients with uncontrolled glucose levels at admission cannot be specifically diagnosed as prediabetes, diabetes or new-onset diabetes due to COVID-19. Second, our study only analysed blood glucose values at one point in time during hospitalization and may not fully reflect variations in patients' glycaemic levels. Third, this study is a retrospective study, which can only provide analytical results to show the association between admission GDS levels, previous DM comorbid status and COVID-19 severity. Further interventional studies are therefore needed to definitively determine the causal role for admission GDS levels and/or awareness of an individual's prior glycaemic status to the severity of COVID-19 infection.

CONCLUSION

This study showed that 47.2% of COVID-19 patients at Tabanan general hospital had hyperglycaemia. More patients in the DM group developed hyperglycaemia during COVID-19 infection. Early measurement of plasma glucose levels upon admission can help identify patients who are likely to experience a worse clinical course. Hyperglycaemia is positively correlated with increased inflammatory parameters and is an independent predictor of severe COVID-19 where RBG levels >145 mg/dl at admission can predict the occurrence of severe COVID-19 infection with sensitivity of 56% and specificity of 76%. Hyperglycaemic patients with or without a history of DM also has a significantly higher mortality rate compared to normoglycemic patients.

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