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The association of admission random blood glucose concentration and body-mass index with mortality in COVID-19 patients

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Abstract. – OBJECTIVE: This study aimed to investigate the association between hyperglycemia and body mass index (BMI), along with other associated comorbidities in hospitalized COVID-19 patients among the Indonesian population.

PATIENTS AND METHODS: This was a retrospective study conducted at Hasan Sadikin Hospital, Bandung between March 1, 2020, and August 30, 2020. Data were analyzed using the chi-square test for categorical data and unpaired *t*-test and Mann-Whitney alternative test for numerical data using SPSS version 24.0 (IBM SPSS Statistics for Windows, Version 24.0. IBM, Armonk, NY, USA) and GraphPad Prism version 7.0 for Windows.

RESULTS: A total of 142 hospitalized COVID-19 patients were documented between March and August 2020 at the Hasan Sadikin Hospital. Among the 142 patients, 116 (81.7%) survived, while 26 (18.3%) died. Sex, age, BMI, number of comorbidities, heart rate, respiratory rate, peripheral oxygen saturation, platelet count, random blood glucose (RBG), and length of stay (LOS) were significantly associated with mortality. Multivariate analyses demonstrated that admission RBG levels > 140 mg/dl were independently associated with an increased risk of mortality in COVID-19 patients (OR 4.3, 95% CI 1.1-17.5, $p = 0.043$), while BMI > 25 kg/m^2 was significantly associated with reduced mortality (OR, 0.22; 95% CI 0.05-0.88, $p = 0.033$).

CONCLUSIONS: Admission hyperglycemia, indicated by an increase in RBG levels >140 mg/dL, is independently associated with an increased risk of mortality in hospitalized COVID-19 patients, while obesity (BMI >25 kg/m2) might have protective properties against the risk of death.

Key Words:
Admission hyperglycemia, Random blood glucose, COVID-19, SARS-CoV-2, Body-mass index.

Introduction

The COVID-19 pandemic is affecting both our health and the socioeconomic aspects of life. Efforts to contain the global pandemic are far from over, as depicted by the increasing number of COVID-19 cases worldwide. Experts have suggested an alternative strategic approach using a forecasting model analyses that might help to provide insights into how to manage the growth of the outbreak[1].

Respiratory illness due to SARS-CoV-2 has broad clinical manifestations, from clinically asymptomatic to a more serious course of illness that leads to multi-organ failure, fatal thrombosis, and even death[2-5]. Patients aged 60 years or older, are at higher risk of contracting severe COVID-19 along with other comorbidities, such as diabetes mellitus (DM), hypertension, obesity, chronic kidney disease, cardiovascular disease, chronic heart failure, and chronic respiratory diseases[5-10].

Diabetic patients experience more severe COVID-19 and have a higher mortality rate compared to non-diabetic patients[11], causing great concern since the incidence of DM is predicted to increase significantly in the following decades. The relationship between DM and the occurrence of various infections is well known. Influenza and pneumonia often occur with increased se-

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verity in diabetic patients[12]. Moreover, DM and uncontrolled hyperglycemia have been reported as significant predictors of morbidity and mortality in previous viral pandemics[13,14]. Chronic inflammation in diabetic patients causes metabolic and vascular dysfunction, which may affect their immunological response to pathogens[15]. Furthermore, hyperglycemia and insulin resistance in DM increase the synthesis of advanced glycosylation end products (AGEs) and proinflammatory cytokines, which lead to increased infection risk and morbidity[16]. Moreover, diabetic patients are often found to have concurrent hypertension and obesity, which also serve as independent predictors of disease severity in COVID-19[17].

Hyperglycemia in diabetic and non-diabetic patients has been previously reported to be associated with increased mortality in COVID-19[18,19]. The association of uncontrolled blood glucose with poor prognosis in viral infection is probably due to the increase in the viral source of energy and the development of insulin resistance[20,21]. Furthermore, hyperglycemia causes an increase in inflammatory cytokines, leading to cytokine-storm syndromes and multi-organ failure in COVID-19[22].

However, the association between admission hyperglycemia and mortality in Indonesian hospitalized patients with COVID-19 is lacking. Therefore, this study aimed to investigate the association between hyperglycemia body mass index (BMI), and other associated comorbidities in hospitalized COVID-19 patients among the Indonesian population.

Patients and Methods

This retrospective study was conducted on hospitalized COVID-19 patients at Hasan Sadikin Hospital, the National referral hospital for COVID-19 in West Java, between March 1, 2020 to August 30, 2020. Ethical approval was obtained from the Hospital Ethics Committee with the number LB.02.01/X.6.5/226/2020. Informed consent was obtained from all individuals included in this study. Hospitalized COVID-19 patients ≥ 18 years of age who were tested positive for reverse transcription polymerase chain reaction (RT-PCR) of SARS-CoV-2 were included in the study. Data were independently extracted by two authors from the medical records and validated by the treating physician. Age, sex, BMI, several clinical and laboratory parameters on admission, presence of comorbidities (DM, hypertension, and cardiovascular disease), length of stay (LOS), and final outcome were collected. Clinical and laboratory parameters collected on admission included vital signs, peripheral blood pressure, oxygen saturation, routine hematological examination, and random blood glucose (RBG). Data analysis was performed using the chi-square test (χ^2) for categorical data, while unpaired t-test and the alternative Mann-Whitney test were used for numerical data, followed by multivariate logistic regression analysis for mortality using SPSS version 24.0 (IBM, Armonk, NY, USA) and GraphPad Prism version 7.0 for Windows. Statistical significance was set at $p < 0.05$.

Results

A total of 142 hospitalized COVID-19 patients between March and August 2020 at Hasan Sadikin Hospital were documented. The baseline characteristics of the study samples are shown in Table I. Among 142 patients, 116 (81.7%) survived, while 26 (18.3%) died.

It was found that sex, age, BMI, presence of comorbidities, heart rate (HR), respiratory rate (RR), peripheral oxygen saturation, platelet count, RBG, and LOS were significantly associated with mortality (Table I). The mortality rate was higher in men than in women (80.8% *vs.* 50.9%), and the non-survivor group was older than the survivor group (57±13 *vs.* 45±14). The BMI in the non-survivor group was significantly lower than that in the survivor group (21.9 *vs.* 24.2%). The number of comorbidities in the non-survivor group was higher than that in the survivor group. HR, RR, and peripheral oxygen saturation were significantly associated with mortality. Based on routine hematological analysis on admission, only platelet count showed a significant association with mortality. The median platelet count in non-survivors was significantly lower than that in the survivor group ($177\times1000/mm^3$ *vs.* $279\times1000/mm^3$). Meanwhile, the RBG levels, serum urea, and creatinine on admission were higher in the non-survivor group than in the survivor group (Figure 1).

Majority of the patients in the non-survivor group had RBG levels > 140 mg/dl (54.2%), and only a small proportion had RBG ≤ 100 mg/dl (20.8%) and 101-140 mg/dl (25.0%) (Figure 2). Admission RBG levels > 140 mg/dl showed a significant association with increased risk of

Table I. Baseline characteristics of study samples.

Variables	Total (n = 142)	Survivor (n = 116)	Non-survivor (n = 26)	*p*-value
Gender, n (%)				
Male	80 (56.3)	59 (50.9)	21 (80.8)	0.005[a]*
Female	62 (43.7)	57 (49.1)	5 (19.2)	
Age (years)[§]	47 ± 15	45 ± 14	57 ± 13	< 0.001[b]*
BMI (kg/m^2)[φ]	23.5 (22.0-25.5)	24.2 (22.5-25.7)	21.9 (20.4-23.2)	< 0.001[c]*
Number of comorbidities[φ]	1 (0-2)	1 (0-2)	2 (1-3)	< 0.001[c]*
Hematology				
Hemoglobin (g/dL)[φ]	13.8 (12.7-14.7)	13.7 (12,1-14.6)	14.4 (13.4-15.5)	0.078[c]
Leukocytes (/mm^3)[φ]	7240 (5940-8970)	7245 (6050-8920)	7070 (5030-10020)	0.967[c]
Platelets (×1000/mm^3)[φ]	268 (200-336)	279 (224.8-340.5)	177 (135.5-298.5)	< 0.001[c]*
Hematocrit (%)[φ]	40.8 (37.7-43,3)	40.7 (37.7-42.8)	41,8 (37.7-44.4)	0.137[c]
Serum RBG[φ]	114 (97-137)	112 (97-129)	144 (105-213)	0.005[c]*
Serum Ureum[φ]	23,3 (18.0-35,9)	21.0 (17.1-29.0)	37.0 (24.5-62.2)	< 0.001[c]*
Serum Creatinine[φ]	0,88 (0.71-1.12)	0.87 (0.70-1.05)	0.93 (0.84-1.79)	0.012[c]*
Physical examination				
BP systole (mmHg)[φ]	120 (110-130)	120 (110-130)	120 (110-130)	0.300[c]
BP diastole (mmHg)[φ]	80 (70-82)	80 (70-83)	80 (70-80)	0.253[c]
Heart Rate[φ]	88 (80-96)	86 (80-94)	92 (84-107)	0.031[c]*
Respiratory Rate[φ]	20 (20-24)	20 (20-22)	26 (21-29)	< 0.001[c]*
Temperature[φ]	36.6 (36.4-36.8)	36.6 (36.4-36.8)	36.8 (36.3-37.2)	0.183[c]
Oxygen Saturation[φ]	98 (96-99)	98 (97-99)	93 (91-95)	< 0.001[c]*
Length of Stay (days)[φ]	11 (4-19)	13 (4-20)	6 (3-12)	0.005[c]*

Description: *p*-value was determined using aChi Square test, [b]Unpaired *t*-test, cMann-Whitney test, *Significant [§]Mean ± SD, [φ]Median (IQR). BMI: Body-Mass Index; RBG: Random Blood Glucose; BP: Blood Pressure.

mortality (OR 4.6, 95% CI 1.4-15.1, $p = 0.011$). On the contrary, higher BMI (> 25 kg/m^2) was significantly associated with a reduced risk of death (OR 0.2, 95% CI 0.1-0.7 $p = 0.012$), while hypertension and DM increased the risk of death (OR 3.1, 95% CI 1.3-7.8, $p = 0.011$, and OR 4.7, 95% CI 1.6-13.5, $p = 0.006$), respectively (Table II).

Multivariate analyses (Table III) demonstrated that admission RBG levels >140 mg/dl were independently associated with an increased risk of mortality in COVID-19 patients (OR 4.3, 95% CI 1.1-17.5, $p = 0.043$), while BMI > 25 kg/m^2

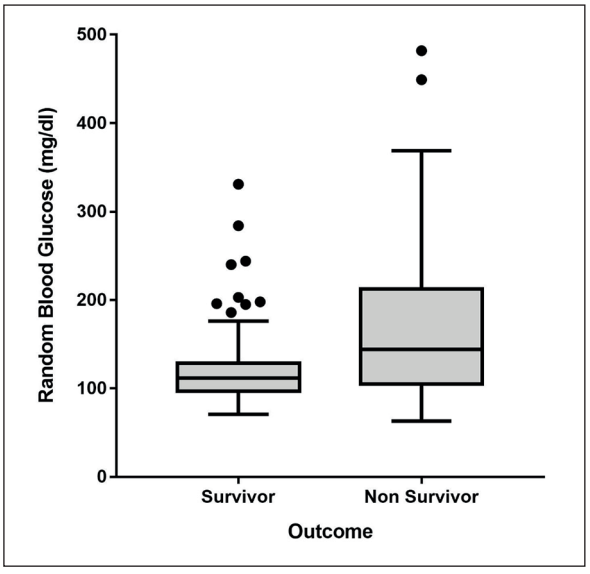

Figure 1. Boxplot comparison of the distribution of random blood glucose levels between subjects in the Survivor and Non-Survivor.

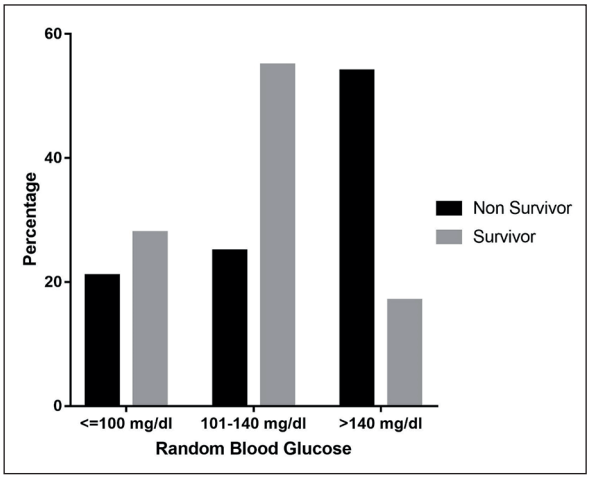

Figure 2. Bar chart comparison of percentage on random blood glucose levels between Survivor and Non-Survivor.

Table II. The association of random blood glucose levels, BMI, hypertension, and DM on outcomes.

Variables	Total (n = 142)	Survivor (n = 116)	Non-survivor (n = 26)	*p*-value	OR (95% CI)
RBG levels	n = 133	n = 109	n = 24		
≤ 100	36 (27.1)	31 (28.4)	5 (20.8)		1 (reff)
101-140	66 (49.6)	60 (55.0)	6 (25.0)	0.488	0.6 (0.2-2.3)
> 140	31 (23.3)	18 (16.6)	13 (54.2)	0.011*	4.6 (1.4-15.1)
BMI	n = 132	n = 108	n = 24		
Underweight (< 18.5)	4 (3.0)	1 (0.9)	3 (12.5)	0.089	7.6 (0.7-79.0)
Normal (18.5-22.9)	53 (40.2)	38 (35.2)	15 (62.5)		1 (reff)
Overweight (23-24.9)	31 (23.5)	28 (25.9)	3 (12.5)	0.055	0.3 (0.1-1.0)
Obese (> 25)	44 (33.3)	41 (38.0)	3 (12.5)	0.012*	0.2 (0.1-0.7)
Hypertension	33 (23.2)	22 (19.0)	11 (42.3)	0.011*	3.1 (1.3-7.8)
DM	18 (12.7)	10 (8.6)	8 (30.8)	0.006*	4.7 (1.6-13.5)

Description: Analysis using the Chi Square test, *Significant. RBG: Random Blood Glucose; BMI: Body-Mass Index; DM: Diabetes Mellitus.

was significantly associated with reduced mortality (OR, 0.22; 95% CI 0.05-0.88, $p = 0.033$).

Discussion

The results of our study showed that admission RBG levels > 140 mg/dl were independently associated with an increased risk of mortality among hospitalized COVID-19 patients, which is in accordance with previous findings[23,24]. In agreement with previous reports, hypertension and DM were also associated with an increased risk of mortality in COVID-19[25-27]. On the contrary, this study showed controversial findings related to a reduced risk of death among patients with BMI >25 kg/m^2 as compared to non-obese patients.

The association between admission hyperglycemia and poor outcome in patients with COVID-19 suggests that hyperglycemia in the initial phase of illness may play a decisive role in disease severity. It is hypothesized that several factors may play a role in this phenomenon. First, hyperglycemia may be associated with increased binding of SARS-CoV-2 to human tissues through glycosylation of the angiotensin-converting enzyme 2 (ACE2) receptor, which is used as an entry point for this specific virus[28]. Increased cellular intrusion may lead to a higher viral load and disease severity of COVID-19. Second, hyperglycemia and poor prognosis may be associated with an increase in the viral source of energy and the development of insulin resistance[20,21]. Additionally, hyperglycemia causes an increase in inflammatory cytokines, leading to cytokine-storm syndromes and multi-organ failure in COVID-19[22]. ACE2 is also expressed in acinar and islet cells of the pancreas; thus, injur-

Table III. Multivariate analysis on the association of admission random blood glucose levels, BMI, and hypertension.

Variable	B	S.E.	*p*-value	Adjusted OR	95% Confidence Interval	
					Lower	Upper
RBG						
RBG 100			0.023			
RBG 101-140	-0.161	0.708	0.821	0.852	0.212	3.414
RBG > 140	1.454	0.718	0.043*	4.280	1.049	17.470
BMI						
BMI 18.5-22.9			0.067			
BMI < 18.5	0.698	1.274	0.584	2.010	0.165	24.424
BMI 23-24.9	-1.245	0.721	0.084	0.288	0.070	1.183
BMI > 25	-1.511	0.708	0.033*	0.221	0.055	0.885
Hypertension	0.656	0.582	0.259	1.927	0.616	6.028

Description: Analysis using logistic regression, *Significant. RBG: Random Blood Glucose; BMI: Body-Mass Index.

ing the islet cells may result in increased blood glucose levels and blood pressure[29,30], suggesting a more severe disease course of COVID-19.

Remarkably, we found conflicting evidence with the results of our study regarding the reduced risk of death in COVID-19 patients with BMI > 25 kg/m^2 than in those with BMI < 25 kg/m^2. Previous meta-analyses reported that obesity is associated with an increased risk of poor outcome[8,9]. Interestingly, most of the included studies used BMI > 30 kg/m^2 as a cut-off value to define obesity, even in studies originating from the Asian region. The definition of overweight and obesity in the Asian population is generally defined as BMI ≥ 23 kg/m^2 and ≥ 25.0 kg/m^2, respectively[31]. The median BMI of our population was 23.5 (22.0-25.5) kg/m^2, with only four patients having a BMI > 30 kg/m^2. Therefore, these factors must be considered when interpreting the results of this study.

Furthermore, the optimal BMI cut-off value for healthy well-being is controversial, particularly in terms of ethnicity, specific illness, and the elderly population[31]. Pes et al[32] showed that being moderately overweight (BMI 27.5-29.9 kg/m^2) among elderly populations >60 years old was associated with lower risk of comorbidities compared with a BMI in the range of 25.0-27.4 kg/m^2. Moreover, a study[33] among human immunodeficiency virus (HIV)-infected adults showed that 12-month immune reconstitution on antiretroviral therapy was highest among patients with a BMI of 25-30 kg/m^2, suggesting the presence of an ideal BMI cut-off value for optimal immune recovery[33]. Both studies suggest that relatively increased BMI or "overweight" may be beneficial for specific populations.

The impact of obesity on immune responses to infection is a matter of interest and may be related to the biological properties of insulin[34,35]. Hyperinsulinemia is frequently found in obesity, which is a condition that is sometimes referred to as "hyperinsulinemic hyperglycemia." The phenomenon of the relatively high incidence of hyperglycemia, as shown in our study, may hypothetically signify qualitative failure of insulin at the cellular level along with the possibility of parallel failure of insulin secretion due to COVID-19 associated islet cell injury. While the role of excess insulin or hyperinsulinemia in the immune system is still unclear, normal physiological insulin promotes T-cell and monocyte activation[34]. After resting T cells are activated by polyclonal stimulators, insulin can modulate its further activation and function[36]; thus, it is considered that insulin plays a crucial role in the immune system. Whether the high insulin levels in the state of "relatively" increased BMI (or overweight) might have protective properties in reducing the risk of death in COVID-19 remains unclear. Furthermore, using insulin as hyperglycemic management in DM to achieve optimal blood glucose control might be superior in the context of biological plausibility, but this is not supported by existing evidence.

Implementing a specific dietary plan and approach in COVID-19 has been suggested to exert beneficial metabolic and immune effects[37]. Immune cells from innate and adaptive defenses require nutrients, such as glucose, amino acids, and fatty acids, to meet energy requirements[38]. Energy requirements and nutritional preferences depend on the cell type and cellular activity. For example, when T-cells are activated, they become highly proliferative and secretory, and hence require an abundant energy source that rapidly produces large amounts of ATP[39]. In contrast, macrophages and neutrophils are generally considered to be non-proliferative and therefore have different metabolic profiles and nutritional requirements[38,40]. Although glucose and fatty acids are important energy sources for body defense and immune function, increased levels of this nutrient, as in obese people, can impact immune cell activity. A dietary approach following the Dietary World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) recommendations is suggested to modulate the cytokine storm in COVID-19, especially through the NLRP3 inflammasome pathway and AMPK-mediated cytokine[37].

A major limitation of this study was related to the retrospective nature of the study design; thus, any causality cannot be suggested and the strength of the association was limited. Furthermore, our study sample was relatively small with a limited number of outcomes, as depicted by very wide confidence intervals, which consequently causes a risk of overfitting the regression model. An attempt to reduce the risk of an overfitted model was made by restricting the number of variables in the multivariate analysis. Despite all the limitations, this study has reported the real-world data of patients with COVID-19 in Indonesia. We have strengthened the evidence of the utmost necessity to implement strict glycemic control among hospitalized patients with COVID-19.

Conclusions

Admission hyperglycemia, as depicted by an increase in RBG levels > 140 mg/dL, is independently associated with an increased risk of mortality in hospitalized COVID-19 patients, while BMI > 25 kg/m^2 might have protective properties against the risk of death. Further research is needed regarding infection in obese Asian populations. In addition, the role of insulin in the immunomodulatory system needs further investigation, especially during the COVID-19 pandemic.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Data Availability

The data used to support the findings of this study are included within the article. The corresponding author may be contacted for additional data.

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