High Stress Hyperglycemia Ratio Versus Absolute Hyperglycemia as a Predictor of Poor Outcome Among Patients With Type 2 Diabetes Mellitus and Moderate to Critical Covid-19 Infection Admitted at a Tertiary Hospital from 2020-21: A Retrospective Study

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ABSTRACT

Background Patients with diabetes are vulnerable and highly susceptible to contracting COVID-19. Stress hyperglycemia ratio (SHR) may provide prognostic information in hospitalized patients. It is debatable whether stress hyperglycemia directly leads to poor outcomes, or is simply a marker of increased stress and inflammation.

Objective This study investigates whether high SHR is associated with poor clinical outcomes among patients with type 2 diabetes mellitus (T2DM) and moderate to critical COVID-19 infection. Moreover, this study aims to compare high SHR versus absolute hyperglycemia as a predictor of poor outcomes.

Methodology A chart review was conducted on 146 COVID-19 patients with T2DM from March 2020 to December 2021. The area under the receiver operating curve was conducted to categorize SHR into low and high levels. The association of high SHR levels and absolute hyperglycemia with outcomes was analyzed using the regression analysis. Survival analysis was also utilized to allow differences in the time when in-hospital mortality occurred.

Result Patients with high SHR had a significantly higher proportion of mortality and invasive ventilation compared to those with low SHR. High SHR significantly increased the likelihood of invasive ventilation by 16.49 times and mortality hazards by 5.70 times compared to low SHR. Kaplan-Meier survival curves showed that those with high SHR had significantly lower survival rates than those with low SHR. In contrast, the survival estimates between

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Academic editor: Warren Bacorro

Submitted date: August 26, 2024

Accepted date: October 2, 2024

those with and without absolute hyperglycemia were not statistically significant.
Conclusion High SHR (>1.082) was associated with poorer outcomes, increased invasive mechanical ventilatory support and increased mortality.

Keywords Stress Hyperglycemia Ratio, Absolute Hyperglycemia, Type 2 Diabetes Mellitus, COVID-19, Poor outcome

INTRODUCTION

In 2019, the novel human coronavirus disease (COVID-19) was first identified in Wuhan, China.[1] Confirmed cases escalated worldwide and affected more than 600 million globally.[2] From January 2020 to October 2022, 3,996,818 confirmed cases in the Philippines, with 63,846 deaths was reported to the World Health Organization.[2] Prior studies[3,4] have identified special populations at a higher risk for developing severe disease and mortality from COVID-19. It has been suggested that COVID-19 might be involved in developing acute diabetes mellitus in certain patients by targeting angiotensin converting enzyme 2 (ACE2) receptors located in pancreatic islets resulting in pancreatic injury.[5] Type 2 diabetes mellitus (T2DM), therefore, is considered a risk factor for worse clinical outcomes in patients with COVID-19.[6]

Acute illness heightens the levels of counter-regulatory hormones such as catecholamine, growth hormone, cortisol and cytokines.[7] The release of these stress hormones results in increased hepatic glucose production and insulin resistance.[7] Stress hyperglycemia leads to both direct and indirect effects on inflammation and vascular injury resulting in increased hospital complications.[8] Previous analyses[9,10] reported the relationship of stress hyperglycemia with in-hospital or 30-day mortalities. Stress hyperglycemia ratio (SHR) may be used to predict unfavorable outcomes. It can be calculated by dividing the random serum glucose at admission with the estimated average glucose derived from HbA1c.[11]

In the CORONADO study, admission hyperglycemia, but not glycated hemoglobin (HbA1c), was associated with the primary composite outcome (death and tracheal intubation for mechanical ventilation within the first seven days after hospital admission).[12] Nevertheless, after adjustment for other biological parameters on admission, hyperglycemia in the CORONADO study was no longer significantly associated with severity of COVID-19. Roberts, et al. 2015 introduced SHR as a marker of critical illness in that hyperglycemia was associated with high morbidity and mortality among hospitalized patients. These conflicting results stress the need for more accurate glycemic measurement to reflect acute and chronic glycemic control in patients with diabetes.

Only two published researches are investigating the association between COVID-19 and SHR. Recent studies demonstrating the relationship of SHR in diabetes patients with COVID-19 are emerging. In the methodology, they used tertiles of SHR and calculated points that divide ordered values of SHR into three parts. Other journals demonstrated SHR ≥1.14 as an indicator of poor outcomes.[13] In the current study by Aon, et al., SHR third tertile was significantly associated with worse outcomes and deaths in hospitalized COVID-19 patients with diabetes. However, further research is needed due to its limitation as a single-center study with an observational retrospective nature.

In the study conducted by Matias, et al., absolute hyperglycemia was defined as any blood glucose level greater than 140 mg/dL in the emergency department or within the first 24 hours after hospital admission. COVID-19 patients with high random blood sugar levels at admission were more susceptible to poor prognosis according to Lazarus, et al.'s research. However, due to paucity of studies and equivocal trends, they could not establish strong evidence on the independent prognostic value of admission random blood sugar.[14] Poor prognosis between patients with diabetes and chronic hyperglycemia has been well demonstrated.[11] High SHR has been associated with poor outcomes in patients with cerebrovascular stroke and myocardial infarction.[11,15] However, there is a scarcity of research utilizing SHR in COVID-19 patients with type 2 diabetes mellitus. Therefore, this study aims to investigate the association between high SHR and disease severity among type 2 diabetic patients with moderate to critical COVID-19 admitted at the University of Santo Tomas Hospital from 2020 to 2021. Furthermore, this study intends to compare

absolute hyperglycemia versus SHR as a predictor of poor outcome.

METHODOLOGY

This retrospective-cohort study involved patients admitted at the University of Santo Tomas Hospital from March 2020 to December 2021, diagnosed with type 2 diabetes mellitus, and had moderate to critical COVID-19 infection. The medical records of eligible participants within the above-mentioned timeframe were reviewed and relevant data was collected.

Patients who met the following criteria were included in the study: 1) age 18 years old and above, 2) previously diagnosed with T2DM or fulfilled American Diabetes Association (ADA) criteria for diabetes mellitus (DM) diagnosis, 3) positive reverse transcription-polymerase chain reaction (RT-PCR) for SARS-CoV-2 via nasopharyngeal and oropharyngeal swab, and 4) with capillary blood glucose (CBG) and glycosylated hemoglobin (HbA1c) results upon admission.

Patients who met the following criteria were excluded from the study: 1) pregnant, 2) patients with conditions affecting the HbA1c levels such as overt renal failure with a serum creatinine level higher than 2.0 mg/dL, receiving hemodialysis or peritoneal dialysis, kidney transplantation recipients and anemia defined as hemoglobin <10 g/dL[11] and 3) patients who died immediately after emergency department admission (<6 hours) and those with advance directives.

A total of 231 charts of patients with moderate to severe COVID-19 were reviewed using a combination of electronic medical records and manual chart review. Only 146 charts were included and met the criteria, while 85 were excluded, with 36 of those having no HbA1c record.

Pertinent demographic and clinical data were extracted from medical records and recorded in a data collection form, and patient data was assigned with numerical codes. Demographic data included age and sex, while clinical data included the anthropometric measurements, comorbidities and smoking history, COVID-19 severity, laboratory profile, stress hyperglycemia ratio, absolute hyperglycemia and clinical outcomes. The anthropometric measurements included height, weight and body mass index, while the COVID-19 severity was classified as moderate, severe and critical. COVID-19 disease severity was defined as follows: 1) moderate, if with clinical signs of non-severe pneumonia (eg, fever, cough, dyspnea, respiratory rate of 21 to 30 breaths/minute, peripheral capillary oxygen saturation [SpO_2] >92% on room air); 2) severe, if with clinical signs of severe pneumonia or severe acute respiratory infection as follows: fever, cough, dyspnea, RR>30 breaths/minute, severe respiratory distress or SpO_2 <92% on room air; and 3) critical, if patients manifested with acute respiratory distress syndrome, sepsis and septic shock.[16]

The laboratory profile included admission capillary blood sugar, HbA1c, hemoglobin level, serum creatinine level and admission inflammatory markers (hs-CRP, LDH, serum ferritin, D-dimer). Stress hyperglycemia ratio was calculated as admission blood glucose divided by estimated average glucose derived from glycosylated hemoglobin. Glycosylated hemoglobin (HbA1c) was used to estimate average blood glucose using the equation, estimated average glucose = (1.59 x HbA1c) – 2.59.[13] A low SHR was defined as <1.082, and a high SHR as ≥1.082. This cut-off of the SHR was determined after conducting binary logistic regression and post-estimation procedures (area under the receiver characteristic curve) to determine the predictive ability of SHR levels. In contrast, absolute hyperglycemia at hospital admission was defined as any blood glucose level greater than 140 mg/dL within the first 24-hour after hospital admission.[17]

The endpoints or outcomes were clinical outcomes of hypoxemia, need for invasive mechanical ventilation, need for ICU admission and in-hospital mortality. Hypoxemia was defined as SpO_2 <92% upon admission, while invasive mechanical ventilation was positive pressure delivered to the patient's lungs via an endotracheal tube or tracheostomy tube. The need for ICU admission was defined as having spent at least two hours in any ICU, while in-hospital mortality was defined as death that occurs during hospitalization.

Ethical Consideration

The Declaration of Helsinki, Good Clinical Practice, and the National Ethical Guidelines for Health and Health Related Research 2017 carried out this

study. The UST Hospital Research Ethics Committee approved this study (REC-2022-11-151-TF).

Statistical Analysis

Mean and standard deviation were used to describe quantitative continuous variables, while the median and interquartile range (IQR) was used to summarize ordinal variables. The distribution of categorical variables was described as frequencies and proportions.

Demographic and clinical characteristics and clinical outcomes were compared according to SHR levels (low vs. high). The comparison was performed using the independent samples *t*-test when the outcome was a normally distributed, quantitative variable. Meanwhile, the Mann-Whitney U test was used when the outcome had a skewed distribution. On the other hand, the comparison was done using the chi-square test when the outcome variable was categorical. If the sample size requirement of the chi-square test was not met, Fisher's exact test was used instead.

The cut-off for the SHR levels was determined using estimates from a binary logistic regression model with in-hospital mortality as the outcome, SHR as a covariate, and COVID-19 severity and myocardial infarction as factors. The predictive ability of the model was assessed and predicted values were used to identify the maximum Youden's Index. This index was then used to determine the optimal cut-off score, dichotomizing the SHR scores into low and high categories.

Furthermore, binary logistic regression was used to determine associations between SHR levels and absolute hyperglycemia (CBG >140 mg/dL) with clinical outcomes, specifically invasive ventilation and ICU admission.

Survival analysis was also employed to account for time to in-hospital mortality. Kaplan-Meier survival curves were constructed to depict survival rates according to SHR levels and absolute hyperglycemia status. Moreover, Cox proportional hazards regression was used to determine the associations of SHR levels and absolute hyperglycemia status with time to in-hospital mortality.

The assumptions of statistical tests performed were assessed, including checking the normality assumption using the Shapiro-Wilk test. Missing data were imputed using variable mean imputation; however, variables with more than 10% missing data were excluded from the analysis.

A *p*-value ≤0.05 was considered statistically significant for all tests performed. All analyses were conducted using STATA MP – Parallel Edition Statistical Software, Version 18.

RESULT

A total of 146 patient records were reviewed during data collection with no missing values in all the extracted data. The mean age of patients included in this study was 58.75 years, with the majority of patients being male (see Table 1). Most of the patients were obese, had hypertension and experienced moderate COVID-19 infection. The data reveals that most patients were administered antiviral medications, steroids, insulin, oral hypoglycemic agents and antihypertensive medications.

Using an adjusted logistic regression model with in-hospital mortality as the outcome and SHR as a covariate, the optimal cut-off value for SHR was determined to be 1.082. This cut-off score yielded an Area under the Receiver Operating Characteristic Curve (AUC-ROC) of 70.10%, a sensitivity of 81.30% and a specificity of 57.70% (see Table 3). With this cut-off score, 46.58% of the participants were classified as having high SHR and 53.42% had low SHR.

There were no significant differences in demographic and clinical characteristics based on SHR levels, except for the average levels of CBG and lactate dehydrogenase (see Table 1). Individuals with high SHR displayed significantly higher levels of CBG (13.36 ± 4.78 vs. 8.44 ± 2.91, $p = 0.001$) and lactate dehydrogenase (415.61 ± 248.44 vs. 349.39 ± 148.36, $p = 0.049$) in comparison to those with low SHR.

Table 2 displays the clinical outcomes of participants categorized according to their stress hyperglycemia ratio levels. Analyses revealed that only 10.96% were admitted to the ICU, 23.97% experienced hypoxemia and 13.70% needed invasive ventilation. Results showed that 89.04% of participants survived, while 10.96% expired. Patients with high SHR had significantly higher rates of invasive ventilation (22.06% vs. 6.41%, $p = 0.006$) and in-hospital mortality (19.12% vs. 3.85%, $p = 0.003$) than those with low SHR.

Table 1 Demographic and Clinical Characteristics

	Stress Hyperglycemia Ratio (SHR) Levels (N = 146)			*p*-value (Two-Tailed)
	Low SHR (n = 78)	**High SHR (n = 68)**	**Total (N = 146)**	
Age (Years; $\bar{x}$, SD)	58.60 (14.26)	58.93 (14.84)	58.75 (14.48)	0.893
Sex (*f*, %)				0.512
Male	44 (56.41%)	42 (61.76%)	86 (58.90%)	
Female	34 (43.59%)	26 (38.24%)	60 (41.10%)	
Weight (Kilograms; $\bar{x}$, SD)	70.53 (15.11)	71.84 (17.25)	71.14 (16.10)	0.625
Height (Meters; $\bar{x}$, SD)	1.63 (0.06)	1.64 (0.08)	1.63 (0.07)	0.607
Body Mass Index (kg/m^2; $\bar{x}$, SD)	26.39 (5.32)	26.72 (5.65)	26.55 (5.46)	0.713
Body Mass Index Category (*f*, %)				0.218
Underweight	4 (5.13%)	4 (5.88%)	8 (5.48%)	
Normal	16 (20.51%)	10 (14.71%)	26 (17.81%)	
Overweight	10 (12.82%)	11 (16.18%)	21 (14.38%)	
Obese 1	38 (48.72%)	25 (36.76%)	63 (43.15%)	
Obese 2	10 (12.82%)	18 (26.47%)	28 (19.18%)	
Comorbidities (*f*, %)				
Hypertension	62 (79.49%)	47 (69.12%)	109 (74.66%)	0.151
Cerebrovascular Accident	5 (6.41%)	4 (5.88%)	9 (6.16%)	1.000
Myocardial Infarction	5 (6.41%)	4 (5.88%)	9 (6.16%)	1.000
Smoking History (*f*, %)	5 (6.41%)	5 (7.35%)	10 (6.85%)	1.000
Pack-Years (Md, IQR)	4 (0.10 – 10)	66 (28 – 68)	19 (2.68 – 67)	0.101
COVID-19 Severity (*f*, %)				0.290
Moderate	49 (62.82%)	34 (50.00%)	83 (56.85%)	
Severe	22 (28.21%)	25 (36.76%)	47 (32.19%)	
Critical	7 (8.97%)	9 (13.24%)	16 (10.96%)	
Vital Signs				
Systolic Blood Pressure (mmHg; $\bar{x}$, SD)	129.72 (17.94)	129.24 (18.71)	129.50 (18.24)	0.874
Diastolic Blood Pressure (mmHg; $\bar{x}$, SD)	77.85 (8.57)	76.95 (8.45)	77.43 (8.50)	0.521
Heart Rate (bpm; Md, IQR)	92 (81 – 102)	92.50 (82 – 103)	92 (82 – 103)	0.378
Respiratory Rate (cpm; Md, IQR)	22 (20 – 24)	22.50 (20.50 – 24)	22 (20 – 24)	0.316
Temperature (Celsius; $\bar{x}$, SD)	36.88 (0.74)	36.61 (1.41)	36.75 (1.10)	0.149
Oxygen Saturation (%; Md, IQR)	96 (92 – 98)	95 (89.50 – 98)	96 (92 – 98)	0.270
Laboratory Test Results				
Capillary Blood Glucose (mmol/L; $\bar{x}$, SD)	8.44 (2.91)	13.36 (4.78)	10.73 (4.60)	0.001*
HbA1c (%; $\bar{x}$, SD)	8.19 (2.06)	7.67 (1.69)	7.95 (1.91)	0.104
Estimated Blood Glucose (eAG; mmol/L; $\bar{x}$, SD)	10.43 (3.27)	9.61 (2.69)	10.05 (3.03)	0.104
Hemoglobin (mg/dL; $\bar{x}$, SD)	137.35 (15.10)	138.18 (16.53)	137.72 (15.73)	0.760
Creatinine (mg/dL; $\bar{x}$, SD)	0.94 (0.37)	0.95 (0.34)	0.94 (0.35)	0.845
D-Dimer (mg/dL; $\bar{x}$, SD)	7.07 (32.41)	2.32 (4.14)	4.86 (23.91)	0.233
Lactate Dehydrogenase (U/L; $\bar{x}$, SD)	349.39 (148.36)	415.61 (248.44)	380.23 (203.24)	0.049 *

Table 1 Demographic and Clinical Characteristics

	Stress Hyperglycemia Ratio (SHR) Levels (N = 146)			*p*-value (Two-Tailed)
	Low SHR (n = 78)	**High SHR (n = 68)**	**Total (N = 146)**	
Ferritin (ng/mL; $\bar{x}$, SD)	1,594.33 (1,925.79)	1,955.29 (2,378.07)	1,762.45 (2,148.30)	0.313
C-Reactive Protein (mg/L; $\bar{x}$, SD)	135.65 (235.20)	135.65 (235.20)	130.13 (186.00)	0.739
Medications (*f*, %)				
Antiviral	71 (91.03%)	58 (85.29%)	129 (88.36%)	0.311
Steroids	60 (76.92%)	54 (79.41%)	114 (78.08%)	0.717
Insulin	44 (56.41%)	49 (72.06%)	93 (63.70%)	0.051
Oral Hypoglycemic Agents	59 (75.64%)	54 (79.41%)	113 (77.40%)	0.587
Antihypertensive Medications	55 (70.51%)	40 (58.82%)	95 (65.07%)	0.139
Diet (*f*, %)				0.082
Conventional	70 (89.74%)	54 (79.41%)	124 (84.93%)	
Enteral Feeding	8 (10.26%)	14 (20.59%)	22 (15.07%)	

Note: (f, %) frequency and percentage

Table 2 Clinical Outcomes

	Stress Hyperglycemia Ratio (SHR) Levels (N = 146)			*p*-value (Two-Tailed)
	Low SHR (n = 78)	**High SHR (n = 68)**	**Total (N = 146)**	
Intensive Care Unit (ICU) Admission (*f*, %)	7 (8.97%)	9 (13.24%)	16 (10.96%)	0.411
Hypoxemia (SpO_2 <92%; *f*, %)	15 (19.23%)	20 (29.41%)	35 (23.97%)	0.151
Invasive Ventilation (f, %)	5 (6.41%)	15 (22.06%)	20 (13.70%)	0.006 *
In-Hospital Mortality (*f*, %)				0.003 *
Survived	75 (96.15%)	55 (80.88%)	130 (89.04%)	
Expired	3 (3.85%)	13 (19.12%)	16 (10.96%)	

Note: (f, %) frequency and percentage

Table 3 Post-Regression Estimation of the Predictive Capacity [Accuracy, Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), and Likelihood Ratios (LR)] of Stress Hyperglycemia Ratio (SHR) in Predicting In-Hospital Mortality Among the Participants (N = 146)

Predictive Capacity of Stress Hyperglycemia Ratio (SHR)	In-Hospital Mortality	
	Point Estimate	**95% CI**
Cut-Off Score	1.082	
Accuracy (95% CI)	70.10%	58.70% to 80.20%
Sensitivity (95% CI)	81.30%	54.40% to 96.00%
Specificity (95% CI)	57.70%	48.70% to 66.30%
Positive Predictive Value (95% CI)	19.10%	10.60% to 30.50%
Negative Predictive Value (95% CI)	96.20%	89.20% to 99.20%
Positive Likelihood Ratio (95% CI)	1.92	1.41 to 2.62
Negative Likelihood Ratio (95% CI)	0.33	0.12 to 0.91

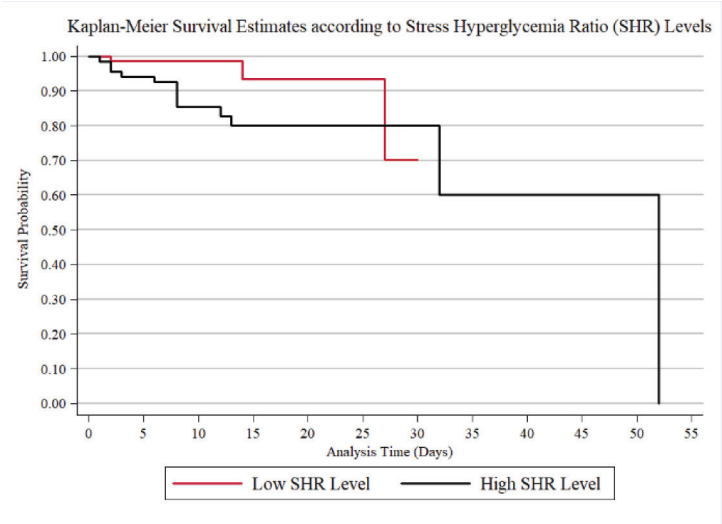

Figure 1 Kaplan-Meier Survival Curves According to Stress Hyperglycemia Ratio (SHR) Level (Left Image) and Absolute Hyperglycemia Status (Right Image)

The overall median survival time of patients was 52 days (95% CI: 32, 72) (see Figure 1). The Kaplan-Meier survival estimate curves indicated significantly lower survival rates for subjects with high SHR than those with low SHR (median survival time: 27 days vs. 52 days, $p = 0.031$). Patients with low SHR have a 100% probability of survival, while those with high SHR have 80% probability of surviving. There was no significant difference in survival rates between those with and without absolute hyperglycemia ($p = 0.482$).

High SHR levels significantly predicted invasive ventilation and in-hospital mortality, but not ICU admission and hypoxemia status (see Tables 4 and 5). The adjusted regression models showed that high SHR levels increased the odds of invasive ventilation by 16.49 times (aOR=16.49, $p = 0.028$) and increased hazards of in-hospital mortality by 5.70 times (aHR=5.70, $p = 0.041$). Absolute hyperglycemia was not significantly associated with ICU admission, hypoxemia, invasive ventilation or in-hospital mortality ($p>0.05$).

DISCUSSION

The outcomes of this research have provided insight into the association between high SHR and poor clinical outcomes among patients with type 2 diabetes mellitus and moderate to critical COVID-19 infection. In this study, patients with high SHR had significantly higher rates of invasive ventilation and expired compared to those with low SHR. A high SHR (≥1.082) during admission is a more reliable indicator of in-hospital mortality and the need for invasive ventilation compared to absolute hyperglycemia. The findings are consistent with existing literature on the effect of high SHR on severity outcomes.

Measurement of HbA1c can be used to evaluate glucose-lowering therapy for diabetes. Additionally, HbA1c is not acutely affected by critical illness. [18] According to the study conducted by the Lee, et al., group using HbA1c to estimate background glycemia and calculate relative hyperglycemia, it showed significant association with mortality. It was found that relative hyperglycemia, as defined by SHR, had a higher correlation with mortality than absolute glycemia, even after correcting for the risk of death score.[19]

Stress hyperglycemia, a marker of critical illness, can cause adverse effects due to oxidative stress and endothelial dysfunction.[20] COVID-19 patients with new hyperglycemia have poorer outcomes than patients with pre-existing diabetes since background hyperglycemia protects against harmful effects of stress hyperglycemia due to the down-regulation of glucose transporters.[21] SHR represents true stress hyperglycemia because, in patients with diabetes, absolute hyperglycemia may be a marker of long-term poor control rather than true stress hyperglycemia. [22] Our study demonstrated a significant association of high SHR, but not absolute hyperglycemia with mortality and the need for invasive ventilation. Comparable to this outcome, analysis by Ramon, et al. and Aon, et al., showed similar results that a higher SHR was significantly associated with worse

Table 4 Crude and Adjusted Binary Logistic Regression Analyses of the Associations of Stress Hyperglycemia Ratio (SHR) and Absolute Hyperglycemia with Clinical Outcomes (ICU Admission, Hypoxemia Status)Among the Participants (N = 146)

Predictors	Clinical Outcome: ICU Admission				Clinical Outcome: Hypoxemia (SpO_2 <92%)				Clinical Outcome: Invasive Ventilation			
	Crude OR (cOR)	*p*-value (Two-Tailed)	Adj. OR[a] (aOR)	*p*-value (Two-Tailed)	Crude OR (cOR)	*p*-value (Two-Tailed)	Adj. OR[a] (aOR)	*p*-value (Two-Tailed)	Crude OR (cOR)	*p*-value (Two-Tailed)	Adj. OR[a] (aOR)	*p*-value (Two-Tailed)
SHR Level (High SHR)	1.55	0.414	3.59	0.195	1.75	0.153	1.50	0.377	4.13 [†]	0.009	16.49 [*]	0.028
Absolute Hyperglycemia Status (CBG >140 mg/dL)	1.25	0.837	0.12	0.312	2.64	0.368	0.54	0.589	1.64	0.647	0.25	0.597

[a] Note: The odds ratios (aOR) were adjusted for confounding effects of the following variables: COVID-19 severity, comorbidities of cerebrovascular disease and myocardial infarction, creatinine, D-dimer and LDH.
[b] Note: The odds ratios (aOR) were adjusted for confounding effects of the following variables: COVID-19 severity, smoking status and C-reactive protein.
[c] Note: The odds ratios (aOR) were adjusted for tconfounding effects of the following variables: Age, COVID-19 severity, comorbidity of myocardial infarction, creatinine and LDH.
[*] Significant at 0.05

outcomes and mortality correlated to admission glucose.[13,23] There is no standardized cut-off for SHR, the cut-off score of 1.140 was used in the previous study by Aon, et al. In this study, we opted to use a cut-off score of 1.082 with a higher accuracy in predicting in-hospital mortality. This cut-off score acquired an accuracy of 70%, sensitivity of 81% and specificity of 57%.

High SHR is not associated with hypoxemia SpO_2 of <92% and ICU admission, but there is an increasing tendency in high SHR participants. The plausible explanation is that stress hyperglycemia could be related to worsening hypoxemia in the longer course.

Diabetes mellitus (DM) is an established condition for worse clinical outcomes in patients with coronavirus disease 2019 (COVID-19).[24] Several studies have described the direct and indirect effects of COVID-19 on patients with diabetes. In the pathophysiology of DM and COVID-19, heightened hyperglycemia gives rise to inflammation, endothelial dysfunction and thrombosis via generation of oxidative stress leading to further dysregulation of glucose metabolism and hypercoagulability.[25] Individuals predisposed to vasculopathy and impaired immunity with severe infection may intensify thrombotic and ischemic complications associated with multiorgan failure and increased mortality rates.[26] The demographic and clinical profiles in this study showed that the majority were males with a mean age of 58-59 years old, obese and with hypertension. Researchers have identified several risk factors for the development of severe COVID-19. Comorbidities and decreased efficiency of the immune system are related to normal aging. Male sex is also a risk factor for severe disease due to the effect of health behaviors, sex hormone-mediated immune responses and differential expression of ACE2 between sexes. In obesity, aside from developing comorbidities such as hypertension, cardiovascular disease and diabetes, increased circulating cytokine levels may be contributory.[4,27]

Participants with high SHR had higher lactate dehydrogenase compared to those with low SHR. Lactate dehydrogenase (LDH), a key enzyme in the glycolytic pathway and a cytoplasmic enzyme found in most organs, has been linked to inflammation response and cell damage.[28] Various research has suggested that serum LDH was elevated in severe COVID-19 patients.[29,30] A study by Zou, et al., consistently showed that patients infected by SARS-

Table 5 Crude and Adjusted Cox Proportional Hazards Regression Analyses on the Association of Stress Hyperglycemia Ratio (SHR) and Absolute Hyperglycemia on In-Hospital Mortality Status Among the Participants (N = 146)

Predictors	In-Hospital Mortality Status (Expired)			
	Crude Hazard Ratio (cHR)	*p*-value (Two-Tailed)	Adjusted Hazard Ratio[a] (aHR)	*p*-value (Two-Tailed)
Stress Hyperglycemia Ratio (SHR) Level (High SHR Level)	3.70 *	0.046	5.70 *	0.041
Absolute Hyperglycemia Status (CBG >140 mg/dL)	1.87	0.997	1.53	0.999

[a] Note: The hazards ratios (aHR) were adjusted for confounding effects of the following variables: Sex; COVID-19 severity; comorbidities of hypertension, cerebrovascular disease and myocardial infarction; hemoglobin; LDH, ferritin; and, use of steroids.
* Significant at 0.05

CoV-2 with high levels of LDH on admission are more likely to develop Acute Respiratory Distress Syndrome (ARDS). Higher LDH levels have been found in COVID-19 patients than in patients with SARS-CoV-2-negative confirmed pneumonia.[28] To gain a better understanding of the relationship between SHR and LDH levels, further investigation is warranted.

The study's reliance on retrospective and observational clinical records limits its scope. Despite its limitations, our study reinforces that high SHR correlates with poor clinical outcomes in patients with COVID-19 regarding invasive ventilation and in-hospital mortality. In addition, the sample size may be insufficient since post-hoc power analysis indicated low power in select analytics (regression analysis for absolute hyperglycemia); thus, results must be analyzed with caution.

Tenforde, et al. found that COVID-19 vaccination was associated with 90% reduction in risk for severe COVID-19 outcomes, including invasive mechanical ventilation and in-hospital death across all variant periods. In this paper, we did not study the vaccination status in relation to outcome. Therefore, future research investigating the association of SHR in non-diabetic patients and vaccination status is recommended.

CONCLUSION

In conclusion, our results showed that high SHR was associated with poor outcomes, increased likelihood of invasive ventilation and increased mortality hazards. The results demonstrated that high SHR could be a better prognostic marker than absolute hyperglycemia. The introduction of SHR in clinical practice will help identify patients with T2DM and COVID-19 at risk of developing worse outcomes. By using SHR, patient-centered comprehensive intervention and monitoring could be improved. High SHR might be a potential treatment target for intensifying glycemic treatment and monitoring.

Acknowledgements

I would like to express my gratitude for the unwavering support of my family, Virginia, Arsenio, Genicar and Arlene. This paper would not have been possible without the invaluable assistance of my co-authors, statistician and valuable ideas contributed by other consultants from the University of Santo Tomas Hospital's section of Endocrinology, Diabetes and Metabolism.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Credit Author Statement (based on Author Form)

MKB: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition **EC:** Conceptualization, Methodology, Validation, Formal analysis, Writing – review and editing, Visualization, Supervision **EM:** Conceptualization, Methodology, Validation, Formal analysis, Writing – review and editing, Visualization, Supervision **JPMB:** Conceptualization, Methodology, Validation, Formal analysis, Writing – review and editing, Visualization, Supervision

Authors Disclosure

The authors declared no conflict of interest.

Funding Source

None.

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