

## The association between admission glucose levels and outcomes in adults admitted to a tertiary care hospital

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### ABSTRACT

**Background:** Hyperglycemia at the time of hospital admission has been associated with poor outcomes in several patient groups, but there is little information about this association in hospitalized patients with diverse diagnoses.

**Methods:** We identified all adult patients admitted between 10/1/2015 and 9/30/2016 who had glucose levels measured during the first 24 h after admission to the hospital. Clinical information included age, gender, glucose levels, diagnoses based on ICD 10 discharge coding, length of stay (LOS), and mortality. Patients were classified into quartiles based on glucose levels and into clinically relevant glucose categories.

**Results:** This study included 18,478 adult patients admitted to a tertiary care hospital. The median age was 53 years, the median LOS was 4 days, and the overall in-hospital mortality was 3.8%. The median admission glucose level was 117 mg/dL. Mortality increased in each glucose quartile; it was also highest in patients admitted with a glucose <55 mg/dL or with a glucose >200 mg/dL. The LOS was significantly shorter in patients in glucose quartiles 1 and 2.

**Conclusions:** Admission glucose levels were associated with in-hospital mortality and LOS in this cohort of hospitalized patients. Attention to glucose levels can help identify patients at risk for poor outcomes.

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### KEYWORDS

Glucose; admission; mortality; length of stay; COPD; sepsis

### 1. Introduction

All patients admitted to a hospital have some risk for morbidity and mortality independent of age and the admitting diagnosis. Hospitals clearly focus on mortality and have developed protocols to identify patients before any acute deterioration occurs. These protocols frequently have specific features relevant to suspected diagnoses, such as acute myocardial infarction, sepsis, and stroke, and require rapid testing and treatment. Some protocols, such as those for acute myocardial infarction, result in a reasonably secure diagnosis before treatment is initiated. Other protocols identify patients at increased risk for poor outcomes but do not provide a specific diagnosis. Patients with sepsis fall into the latter category. The 2016 consensus statement for sepsis and septic shock indicated that there was no gold standard for the identification of sepsis and that the goal of screening protocols was to identify patients with possible infection who would have worse outcomes [1–3]. Based on an extensive review of hospital data and outcomes, these new consensus statements introduced the qSOFA score for screening patients in emergency centers and on hospital floors. These authors reported that this score had a better predictive ability than the SIRS criteria. These various scores/criteria

identify patients who are at increased risk for poor outcomes. They do not necessarily identify patients with infection because other acute medical disorders, such as acute congestive heart failure and acute respiratory failure, can create abnormal scores. This uncertainty about the initial diagnosis does not necessarily represent a failure of any protocol if the main objective is to identify patients at risk for poor outcomes independent of the diagnosis.

Simple point of care laboratory tests has the potential to identify patients who are under metabolic distress secondary to infection and other acute disorders. Both elevated glucose levels and elevated lactate levels have been associated with poor outcomes in patients with sepsis and other acute disorders [4–6]. Both these metabolic parameters have complicated biochemical pathways, and it is possible that a classification system based on glucose or lactate levels can predict outcomes better than some more complex or detailed scoring system, such as SIRS or qSOFA. Our study goal was to determine whether or not elevated glucose levels at the time of admission helped predict outcomes in adult patients admitted to a tertiary care hospital. The outcomes analyzed included in-hospital mortality and length of stay.

## 2. Methods

This study used a retrospective design; the information technology division at University Medical Center in Lubbock, Texas, created an algorithm to identify all adult patients who have had glucose levels measured during the first 24 h of admission to the hospital. Inclusion criteria were all adult patients admitted to the University Medical Center between 10/1/2015 and 9/30/2016. Patients <18 years of age and >89 years of age were excluded. Demographic information included age and gender. Clinical information included vital signs (blood pressure and heart rate), body mass index, glucose levels within 24 h of admission, diagnoses, severity of illness and risk for mortality based on ICD 10 discharge coding and medical record department algorithms, length of stay, disposition, and mortality. University Medical Center is a 494-bed referral center in West Texas.

Patients were classified into quartiles based on glucose levels. They were also classified into clinically relevant glucose range categories: <55mg/dL, 55–140 mg/dL, 140–200 mg/dL, and >200 mg/dL. Outcomes included the length of stay and in-hospital mortality. Unadjusted and adjusted hospital mortality rates and lengths of stay were calculated for each quartile for comparisons with the first quartile and for the clinically relevant categories of glucose levels. Prior to data collection, we planned to study patients with a discharge diagnosis of either COPD or sepsis based on our clinical interests and prior studies [7–9].

Descriptive analysis was provided by using either mean (standard deviation) or median (25<sup>th</sup>, 75<sup>th</sup> percentiles) as appropriate. Comparisons among groups were made using the Chi-square test. Pair-wise comparisons were made only when the overall testing was significant. Multiple testing adjustment was made using the Bonferroni method. All analyses were performed using the SAS (Windows version 9.3; SAS Institute, Cary, NC) and the R software (R Core Team; 2018; R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>). P values less than 0.05 were considered as statistically significant.

## 3. Results

This study included 18,478 adult patients admitted to the University Medical Center between 10/1/2015 2015, and 9/30/2016. The median age was 53 years (25<sup>th</sup> percentile-33 years; 75<sup>th</sup> percentile –67 years). Important medical diagnoses are listed in Table 1. The median length of stay (LOS) was 4 days (25<sup>th</sup> percentile-2 days; 75<sup>th</sup> percentile-6 days). The overall in-hospital mortality was 3.8%.

Mortality increased in each age quartile (Table 2). The mortality was highest in the first quartile for LOS, presumably reflecting critically ill patients who died after a short hospitalization (Table 2). After the first quartile, mortality rate increased with longer LOS. The median admission glucose level was 117 mg/dL (25<sup>th</sup> percentile-97 mg/dL; 75<sup>th</sup> percentile-155 mg/dL) (Figure 1). The mortality increased in each glucose quartile (Table 2); it varied in the clinically relevant categories and was highest in patients admitted with a glucose <55 mg/dL and patients admitted with glucose >200 mg/dL (Table 2). Table 3 provides a comparison of patients with initial glucose less than 55 mg/dL and patients with an initial glucose greater than 200 mg/dL. Patients with sepsis will more likely to have a glucose level <55 mg/dL.

The LOS was significantly shorter in patients in glucose quartiles 1 and 2 compared to quartiles 3 and 4 (Figure 2). This result did not change when patients with a LOS <1 day were excluded. The LOS for deceased patients was significantly shorter for patients in the highest glucose quartiles compared to patients in the lowest two glucose quartiles, indicating that elevated blood glucose levels were associated with mortality. Patients in the first and second glucose quartiles who survived hospitalization had significantly shorter average LOS than patients in the third and fourth glucose quartiles. Patients with glucose levels in the range of 55–140 mg/dL had shorter LOS than patients with glucose levels in the range of 140–200 mg/dL and >200 mg/dL. However, patients with glucose levels 140–200 mg/dL had longer LOS than patients with levels >200 mg/dL.

In patients discharged with the primary diagnosis of COPD, glucose levels were classified into four clinically relevant categories and into quartiles. The median LOS for patients with COPD was 4 days (25<sup>th</sup> percentile-3 days; 75<sup>th</sup> percentile-6days). The length of stay was analyzed in patients with COPD based on glucose quartiles, and there were no differences in LOS in the four quartiles. However, significant differences were found in LOS based on the clinically relevant categories, and all patients with COPD who had glucose levels >200 mg/dL had a shorter LOS than patients in the lower glucose categories. In addition, COPD patients who survived hospitalization had a shorter LOS if their admitting glucose was >200 mg/dL. There was no association between glucose category and LOS in COPD patients who died during hospitalization. The overall in-hospital mortality in patients with COPD was 2.5%. There was no difference in the mortality in patients with COPD when classified by either clinically relevant categories or quartiles.

The LOS in patients with a discharge diagnosis of sepsis was also analyzed using clinically relevant glucose

**Table 1.** Primary diagnosis.

Category	Gender		Mortality		
	Female	Male	Alive	Expired	Total
All patients	10,224 (55.3%)	8,254 (44.7%)	17,775 (96.2%)	703 (3.8%)	18,478
Sepsis (A41.01, A41.51, A41.9)	644 (49.6%)	655 (50.4%)	1139 (87.7%)	160 (12.3%)	1,299
Pneumonia (J18.9)	149 (50.3%)	147 (49.7%)	291 (98.3%)	5 (1.7%)	296
COPD (J44.1)	135 (48.4%)	144 (51.6%)	272 (97.5%)	7 (2.5%)	279
Acute kidney failure (N17.9)	124 (43.8%)	159 (56.2%)	274 (96.8%)	9 (3.2%)	283
Urinary tract infection (N39.0)	96 (67.1%)	47 (32.9%)	140 (97.9%)	3 (2.1%)	143
Other diseases of digestive system (K92.0, K92.1, K92.2)	112 (36.5%)	195 (63.5%)	291 (94.8%)	16 (5.2%)	307
Ischemic heart diseases (I20-I25)	136 (34.9%)	254 (65.1%)	382 (97.9%)	8 (2.1%)	390
Acute heart failure (I50.23, I50.33, I50.43, I50.9)	120 (37.7%)	198 (62.3%)	298 (93.7%)	20 (6.3%)	318
Pancreatitis (K85.1, K85.9)	110 (55.8%)	87 (44.2%)	194 (98.5%)	3 (1.5%)	197
Acute respiratory failure (J96.00, J96.01, J96.21, J96.22)	119 (51.5%)	112 (48.5%)	195 (84.4%)	36 (15.6%)	231

Information in parentheses represents ICD-10 codes.

**Table 2.** Mortality outcomes.

Age, years	Alive at discharge	Death at discharge**
<b>Mortality in age quartiles</b>		
<33	4411 (99.0)*	43 (1.0)
33 ~ 53	4459 (97.7)	104 (2.3)
53 ~ 67	4574 (95.1)	236 (4.9)
≥67	4331 (93.1)	320 (6.9)
LOS, days	Alive at discharge	Death at discharge**
<b>Mortality in LOS quartiles</b>		
<2	1510 (90.3)	163 (9.7)
2 ~ 4	7102 (98.2)	129 (1.8)
4 ~ 6	3647 (97.5)	92 (2.5)
≥6	5516 (94.5)	319 (5.5)
Glucose level, mg/dL	Alive at discharge	Death at discharge**
<b>Mortality in glucose quartiles</b>		
<97 (Q1)	3725 (97.1)	112 (2.9)
97 ~ 117 (Q2)	3986 (96.7)	134 (3.3)
117 ~ 155 (Q3)	3798 (95.6)	173 (4.4)
≥155 (Q4)	3722 (93.3)	267 (6.7)
Glucose level, mg/dL	Alive at discharge	Death at discharge**
<b>Mortality based on glucose category</b>		
<55	78 (85.7)	13 (14.3)
55–140	10,392 (96.8)	348 (3.2)
140–200	2577 (94.1)	161 (5.9)
>200	2184 (93.0)	164 (7.0)

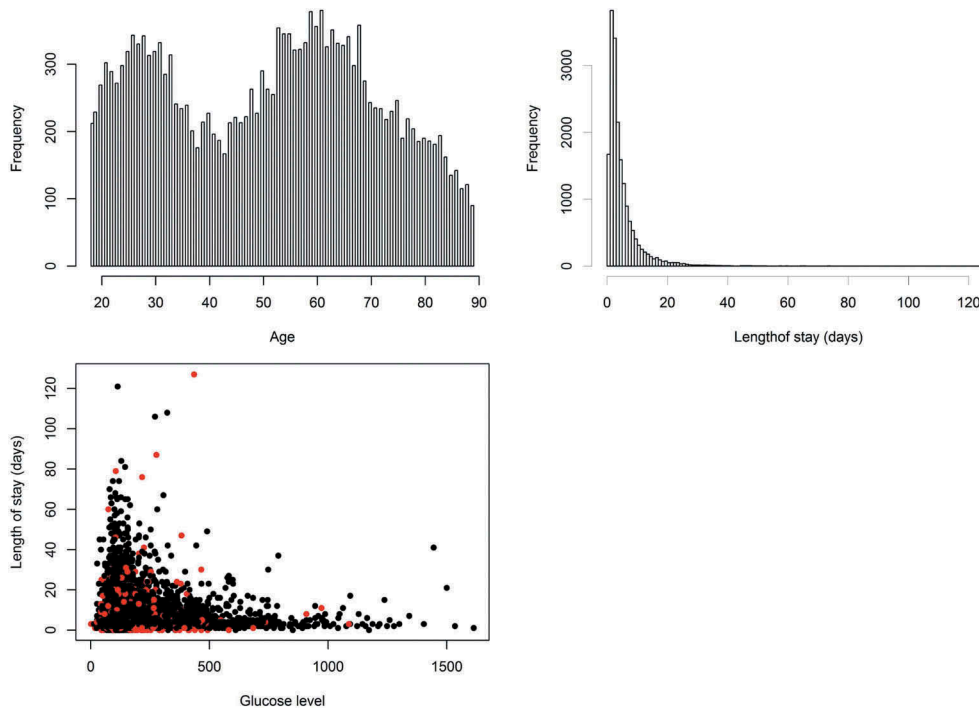
\* All values in the columns represent the number and percentage.

categories and glucose quartiles for classification. The median LOS was 6 days (25<sup>th</sup> percentile-4 days; 75<sup>th</sup> percentile-11 days). There was no difference in LOS when patients with sepsis were classified by glucose quartiles. There was no significant difference in LOS in the clinically relevant categories of all patients with sepsis or of patients with sepsis who died. In patients who survived hospitalization the LOS was shorter in patients with glucose values in the range of 55–140 mg/dL than in patients with glucose values >200 mg/dL (p = 0.047). The overall in-hospital mortality in sepsis was 12.3%. There was no difference in mortality in the groups based on a clinically relevant classification of glucose or glucose quartiles.

This study population included 122 patients with a discharge diagnosis of type 1 diabetes and 97 patients with a discharge diagnosis of type 2 diabetes. The median admission glucose levels were 484 mg/dL (386, 601 md/dL) for type I diabetic patients and 297 mg/dL (193,576 mg/dL) for type 2 diabetic patients (P < 0.001). The median LOS was 3 days (2,3days) for type I diabetic patients and 4 days (2, 7 days) for type 2 diabetic patients (P < 0.001). There was no difference in the LOS in patients with type 2 diabetes and all other patients (p = 0.07). One patient with type 2 diabetes died during hospitalization.

#### 4. Discussion

This study included more than 18,000 adults admitted to a tertiary care hospital in West Texas. The median admission glucose level was 117 mg/dL. The median length of stay was 4 days, and the overall in-hospital mortality rate was 3.8%. Mortality increased in each glucose quartile. In addition, mortality was higher in patients who had an admission glucose level <55 mg/dL or >200 mg/dL. Patients with glucose levels in the lower two quartiles had shorter lengths of stay. Patients who survived hospitalization for sepsis had a shorter length of stay if their glucose levels were in the 55–140 mg/dL range compared to patients whose glucose levels were >200 mg/dL. However, patients with COPD had a shorter length of stay if their admission glucose levels were >200 mg/dL. Consequently, this study indicates that admission glucose levels in all adults admitted to this tertiary care hospital are associated with both mortality and length of stay, but there was no association between glucose levels and mortality in prespecified patients with either COPD or sepsis.



**Figure 1.** Provides the frequency distribution of age at admission (A), the frequency distribution of various lengths of stay (B), and the association between glucose levels and length of stay (C). The red symbols represent patients who expired during hospitalization.

These results provide important information to clinicians at the time of patient admission and raise interesting questions about clinical factors associated with outcomes in hospitalized patients.

### 5. Studies with undifferentiated patients

Kutz et al. studied the outcomes of 7,132 adult patients admitted to emergency departments in Switzerland, France, and the USA[10]. In this study, severe hyperglycemia was defined as glucose levels greater than 200 mg/dL. Patients without diabetes and with severe hyperglycemia had an adjusted odds ratio for 30-day mortality of 1.9 (95% confidence interval [CI] 1.1–3.3). These patients also had an increased risk of admission to intensive care units. Patients with diabetes did not have an increased risk for mortality but did have an increased risk for intensive care unit admission. Yoshinaga et al. analyzed the relationship between glucose levels in patients in an emergency room as a predictor of in-hospital mortality[11]. This study included 57,443 consecutive patients >18 of the years of age who were brought to the emergency room by ambulance over an 8-year period. The lowest inpatient mortality occurred in patients with plasma glucose levels between 90 mg/dL and 106 mg/dL. Mortality is increased in patients with plasma glucose levels less than 5 mmol/L and greater than 9 mmol/L. These authors suggested that patients with hypoglycemia

who were not taking glucose-lowering medications should receive an extra assessment. Bruno et al. analyzed the association between glucose values measured on admission and hospital mortality[12]. This study included data from 96,405 patients. Patients who have died during hospitalization were matched with control subjects who had similar characteristics, including gender, age, marital status, education, type of admission, and type of treatment. The lowest risk for inpatient mortality was found in patients with a mean glucose level of 89 mg/dL (range 78–101 mg/dL). The odds ratio for death increased when the admission glucose was in a higher range (100–200 mg/dL) or in a lower range (60–80 mg/dL).

Whitcomb et al. evaluated the admission glucose levels in 2,713 patients admitted to intensive care units at the University of Maryland Medical Center between 1996 and 1998[13]. The adjusted odds ratio for death in patients with severe hyperglycemia defined as glucose level greater than 200 mg/dL was 1.76 (95%CI 1.23–2.53) in patients without diabetes. Higher mortality rates occurred in patients admitted to the cardiothoracic, cardiac, and neurosurgical intensive care units but not to medical or surgical intensive care units. There was not an increase in mortality in patients with diabetes admitted with severe hyperglycemia. Sung and colleagues prospectively collected data on 1,003 consecutive trauma patients admitted to an intensive care unit over 2 years[14]. Twenty-five percent of these patients had severe hyperglycemia defined by glucose levels >200 mg/dl. These

**Table 3.** Comparison of patients with low versus high glucose levels.

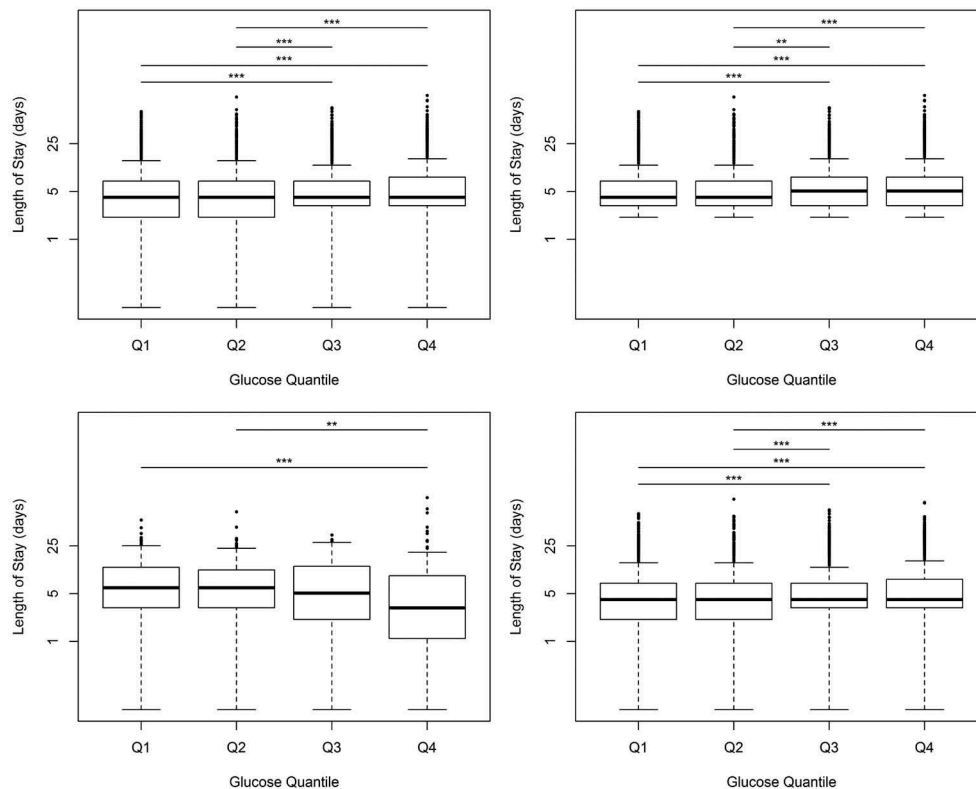
Category	Glucose level		P value
	<55 mg/dL N = 91	≥200 mg/dL N = 2348	
Age, years			0.218
<33	7	213	
33 ~ 53	23	696	
53 ~ 67	31	889	
≥67	30	550	
Gender			0.863
Male	51	1281	
Female	40	1067	
<b>Sepsis</b> (A41.01, A41.51, A41.9)			<b>0.002</b>
Yes	22	319	
No	16	643	
Pneumonia (J18.9)			0.666
Yes	2	39	
No	36	923	
COPD (J44.1)			0.623
Yes	0	29	
No	38	933	
Acute kidney failure (N17.9)			1.000
Yes	2	51	
No	36	911	
Urinary tract infection (N59.0)			0.620
Yes	0	25	
No	38	937	
Other diseases of digestive system (K92.0, K92.1, K92.2)			0.656
Yes	2	37	
No	36	925	
Ischemic heart diseases (I20-I25)			1.000
Yes	2	60	
No	36	902	
Acute heart failure (I50.23, I50.33, I50.43, I50.9)			0.076
Yes	5	56	
No	33	906	
Pancreatitis (K85.1, K85.9)			1.000
Yes	1	35	
No	37	927	
Acute respiratory failure (J96.00, J96.01, J96.21, J96.22)			0.253
Yes	0	48	
No	38	914	

Information in parentheses represents ICD-10 codes. Compared to those without sepsis, patients with sepsis are more likely to be associated with lower glucose level (lower than 55 mg/dL), with an odds ratio of 2.77 (95% CI 1.44–5.35).

patients with severe hyperglycemia had an increased risk of infection, longer hospital lengths of stay, and higher mortality after adjustment for age and the injury severity score. These five studies demonstrate that admission levels of glucose have important associations with outcomes in patients presenting to emergency departments, in patients admitted to intensive care units, and in patients admitted with trauma. The mortality rates in our patients admitted to a tertiary care hospital increased in each glucose quartile. These mortality rates were not explained by a discharge diagnosis of either type 1 diabetes or type 2 diabetes.

## 6. Studies in specific patient groups

Hyperglycemia does not have a consistent association with poor outcomes in well-defined patient groups. For example, Lipton reported that patients admitted to the intensive cardiac care unit had a longer length of stay and increased mortality if they were in the upper tertile of admission glucose levels[15]. In addition, these investigators noted that hypoglycemia was associated with an increased mortality rate and that an increase in the average glucose level during the ICU stay was associated with increased mortality. Karetnikova et al. studied 529 patients admitted with an ST-segment elevation myocardial infarction[16]. They found a linear association between the blood glucose level and in-hospital mortality in nondiabetic patients. Kasirye et al. studied 209 patients admitted to the hospital with an acute exacerbation of COPD[17]. They did not find any correlation between hyperglycemia and adverse outcomes, including increased length of stay, 30-day readmission rates, and 90-day all-cause mortality. Our study included 279 patients with a discharge diagnosis of COPD. There is no association between the admission glucose quartile or glucose category and mortality. However, patients with an admission glucose levels greater than 200 mg/dL had decreased lengths of stay. There is no obvious explanation for this result, and it could reflect prehospitalization corticosteroid treatment which eventually shortened the hospital course but did not prevent hospitalization. Van Vught did an extensive study of the relationship between the admission glucose levels and outcomes in critically ill patients with sepsis[18]. This study included 987 patients, including 201 patients with severe hyperglycemia defined by glucose levels greater than 200 mg/dL. Multivariable regression analysis demonstrated that patients with severe hyperglycemia had an increased risk of mortality by day 30. This occurred in patients both with diabetes and without diabetes. This association between severe hyperglycemia and mortality persisted in patients after adjustment for lactic levels in patients with diabetes but not in patients without diabetes. Our study included 1299 patients with a discharge diagnosis of sepsis. There was no association between the admission glucose level and mortality in these patients. However, patients who were admitted with glucose levels in the 55–140 mg/dL range had a shorter length of stay than patients admitted with a glucose level >200 mg/dL. This result could reflect increased stress and more severe disease in patients with higher glucose levels compared to patients with more moderate glucose levels.



**Figure 2.** Provides semi-log plots of the length of stay versus glucose quartile. The boxes represent the median and the 25th and 75th percentiles. The bars represent the upper adjacent and lower adjacent, respectively. The upper adjacent equals to the largest value below the 75th percentile+1.5\*(75th percentile-25th percentile); and the lower adjacent equals to the smallest value above the 25th percentile-1.5\*(75th percentile-25th percentile). The dots represent outliers. \*\*\*represents P values less than 0.001 for comparisons indicated by the dark lines.

## 7. Pathophysiology

High glucose levels represent an acute stress response to the underlying medical problem(s) resulting in hospitalization[19]. These levels could also reflect comorbidity, such as diabetes, recent nutrition, and adverse drug effects. The clinical importance of hyperglycemia probably depends on the medical condition and the level of acute stress. Moderate levels of hyperglycemia represent an adaptive stress response and may have physiologic benefit [20,21]. In patients with abnormal vascular beds secondary to inflammation and with hypoperfusion secondary to blood low pressures or reduced cardiac output, glucose uptake into cells depends on the diffusion gradient. This is particularly true in the central nervous system and in the immune system. Consequently, higher levels of glucose may support cellular metabolism and energy production. More toxic levels or prolonged increases in glucose represent a maladaptive response and have the potential for adverse clinical outcomes. Acute hyperglycemia has multiple direct effects on innate immunity[22]. High levels of glucose can increase the production of reactive oxygen species which cause diffuse cellular injury. In addition, hyperglycemia increases urine output in patients with normal renal function which results in volume contraction and

electrolyte loss. Finally, hyperglycemia may increase formation of the glycated proteins which may interfere with protein function and membrane function. In some diseases, such as sepsis, a high glucose level is a biochemical marker for stress and does not contribute to poor outcomes because the underlying disorder is the dominant driver affecting outcomes. In some diseases, such as an acute exacerbation of COPD, a high glucose level may alert the clinician to important comorbidity and may alter management plans, but the prognosis is good, and high glucose levels do not impact outcomes.

Hypoglycemia also has an important effect on the risk of mortality in hospitalized patients. In some patients, this represents an adverse effect associated with medications used to manage diabetes. Tsujimoto et al. analyzed the outcomes in patients who presented with severe hypoglycemia, defined by clinical symptoms could which could not be managed by the patient without medical assistance[23]. This study included 163 patients without diabetes and 367 patients with diabetes. The initial blood sugar the blood glucose in patients without diabetes was  $42.9 \pm 23.2$  mg/dL. The variables associated with death in these patients included blood glucose level less than 40 mg/dL, age, advanced liver disease, cancer, and coexisting sepsis. The most frequent causes of death in patients without

diabetes were infection, liver disease, and cancer. The patients in our study who had glucose levels below 55 mg/dL were more likely to have sepsis. This could reflect pre-existing chronic disease or the acute effect of sepsis.

## 8. Measurement strategies

Our study analyzed the association between a single measurement of glucose on admission to the hospital and outcomes. However, most hospital patients have multiple glucose measurements with routine laboratory testing. This creates the opportunity to analyze the effect of glucose patterns on hospital outcomes. Some studies have evaluated the effect of the mean glucose level throughout hospitalization. Other studies have looked at the variability or swings in glucose levels during hospitalization[4]. Finally, several studies have demonstrated that both high and low glucose levels potentially have adverse effects on outcomes. In our patient population, only 91 patients had glucose levels below 55 mg/dL on admission. However, this had a significant association with mortality.

## 9. Limitations

This study reports information from a large number of hospitalized patients, but it has several limitations. First, the diagnostic classification was based on hospital discharge coding and was not independently verified through chart review. Second, we did not determine a comorbidity index for these patients or record the location of initial inpatient care. Third, we did not analyze the causes of mortality in these patients or identify complications possibly related to hyperglycemia. Fourth, we did not analyze glucose levels throughout the hospitalization. Fifth, we did not review the treatment protocol is used in patients with hyperglycemia.

## 10. Conclusions

Admission glucose levels were associated with mortality and length of stay in this large cohort of hospitalized patients. This laboratory test is easily available during the admission process. Attention to the glucose levels, especially high levels, can help clinicians focus on the underlying level of stress related to the admitting diagnosis, on important comorbidities which may or may not be known prior to admission, and on glucose management strategies when the levels are high and remain high. In some situations, the complexity of the primary diagnosis dominates management decisions and high glucose levels are overlooked. In general, glucose levels are greater than 200 mg/dL or less than 55 mg/dL warrant more attention and more frequent follow-up. This information provides the clinician with a simple

indicator which has the potential to predict poor outcomes.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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