Received: 26 August 2022 | Revised: 11 October 2022 | Accepted: 20 October 2022

DOI: 10.1111/cts.13445

ARTICLE

Relationship between blood glucose levels and length of hospital stay in patients with acute pancreatitis: An analysis of MIMIC-III database

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Abstract

We aimed to investigate the effect of blood glucose levels on length of stay (LOS) in patients hospitalized with acute pancreatitis (AP). We retrospectively collected clinical data of patients diagnosed with AP from the Medical Information Mart for Intensive Care III (MIMIC-III) database. Dose–response analysis curves of restricted cubic spline (RCS) function and multivariate logistic regression models were used to confirm the relationship between blood glucose levels and LOS. A total of 3656 patients with AP were included according to the inclusion and exclusion criteria. According to RCS, all patients were divided into three groups, namely the less than 68 mg/dl group, the 68-104 mg/dl group, and the >104 mg/dl group. RCS showed a significant nonlinear correlation between blood glucose levels and LOS ($p < 0.001$). Multivariate logistic regression revealed a 53% higher risk of LOS greater than or equal to 2 days (adjusted odds ratio [aOR] = 1.53, 95% confidence interval [CI] 1.24–1.89, $p < 0.001$), a 114% higher risk of LOS greater than or equal to 5 days (aOR = 2.14, 95% CI 1.86–2.47, $p < 0.001$), and a 130% higher risk of LOS greater than or equal to 7 days (aOR = 2.30, 95% CI 1.97–2.69, $p < 0.001$) in patients with glucose levels greater than 104 mg/dl than patients with glucose levels 68–104 mg/dl. The risk of LOS greater than or equal to 7 days was higher in patients with blood glucose less than 68 mg/dl than patients with glucose levels 68–104 mg/dl (aOR = 1.45, 95% CI 1.02–2.05, $p = 0.040$). In addition, we observed similar results in many subgroups. Our findings suggest that either hyperglycemia or hypoglycemia increase LOS in patients hospitalized with AP. For hospitalized patients with AP, blood glucose control in a reasonable range of 68–104 mg/dl is required.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Acute pancreatitis (AP) is a common emergency of the digestive system, and the number of hospitalizations due to AP is increasing every year, leading to an

Dongyan Wang, Jie Lu, and Pan Zhang contributed equally to this work.

increased global economic burden. Blood glucose levels can affect the length of stay (LOS) of hospitalized patients. The aim of this study was to investigate the effect of blood glucose levels on the LOS of patients hospitalized with AP.

WHAT QUESTION DID THIS STUDY ADDRESS?

Blood glucose levels can affect LOS in patients hospitalized with AP.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study demonstrates that blood glucose levels in inpatients with AP can affect LOS. High or low blood glucose can increase LOS in inpatients with AP. For inpatients with AP, blood glucose needs to be kept within reasonable limits.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Blood glucose levels can affect LOS in patients hospitalized with AP, and either too low or too high blood glucose levels can have adverse effects on patients hospitalized with AP. In hospitalized patients with AP, blood glucose needs to be controlled within a reasonable range of 68–104 mg/dl to minimize LOS and reduce the financial burden of hospitalization.

INTRODUCTION

Acute pancreatitis (AP) is an acute inflammation of the pancreas. It has multiple etiologies that self-activate pancreatic enzymes, with destruction of glandular alveolar cells as the main pathological feature, and is a common emergency of the digestive system.[1] It includes mild acute pancreatitis (MAP) and severe acute pancreatitis (SAP).[2] Studies have shown that the global incidence of AP is 33.74/100,000, and the mortality rate is 1.6/100,000.[3] MAP accounts for about 80% of AP, and its main causes are alcoholism and gallstones.[4] Severe pancreatitis can cause necrosis of pancreatic tissue, systemic inflammatory response syndrome (SIRS), and multiple organ dysfunction syndrome at an early stage, with a mortality rate of 30–47%.[5]

In the United States, hospitalizations due to pancreatitis have increased by 20% in the last decade, with ~275,000 hospitalizations per year.[6] Complicating infections often exacerbate pancreatic necrosis, which is a major cause of late mortality.[7] Studies have shown that pancreatitis is associated with higher blood glucose levels and a history of diabetes, and that elevated fasting glucose and diabetes are risk factors that damage several organs, including pancreas.[8–10] In addition, a large prospective cohort study reported an 18% prevalence of diabetes in patients hospitalized for AP, and that diabetes increases the risk of developing AP.[11,12]

Recently, a number of studies have found that blood glucose levels affect the length of stay (LOS) of hospitalized patients.[13,14] However, the association between blood glucose levels and LOS in hospitalized patients with AP is not yet determined. Hence, in this study, we retrospectively analyzed the clinical data of patients hospitalized with AP to determine the relationship between blood glucose levels and LOS.

MATERIALS AND METHODS

Data sources

Clinical data of patients with AP included in this study were obtained from the US Medical Information Mart for Intensive Care III (MIMIC-III) database. The MIMIC-III database is a large, single-center, critical care public database developed by the Massachusetts Institute of Technology, and included greater than 40,000 inpatients admitted to Beth Israel Deaconess Medical Center (BIDMC) in the United States from 2001–2012.[15] The MIMIC-III database contains patient demographic characteristics, medical intervention records, records of basic physical signs, nursing records, imaging test results, discharge records, and many other medical data. After completing the web-based training course and the National Health Protection Human Research Institute (certification number: 44274909), we obtained permission to extract data from the MIMIC-III database. Because this study analyzed a public database, informed consent from patients and approval from the institutional review board were not required. In addition, we collected clinical data on 292 AP hospitalizations from January 2018 to December 2021 at Shanghai Pudong New Area Gongli Hospital and Shanghai Tenth People's Hospital.

Study population

A total of 4081 patients (age ≥ 18 years) and diagnosed with AP were retrieved based on the International Classification of Diseases, Ninth Revision (ICD-9, code 5770) and Tenth Revision (ICD-10, code K8500, K8502, K8510, K8511, K8512, K8520, K8521, K8522, K8530,

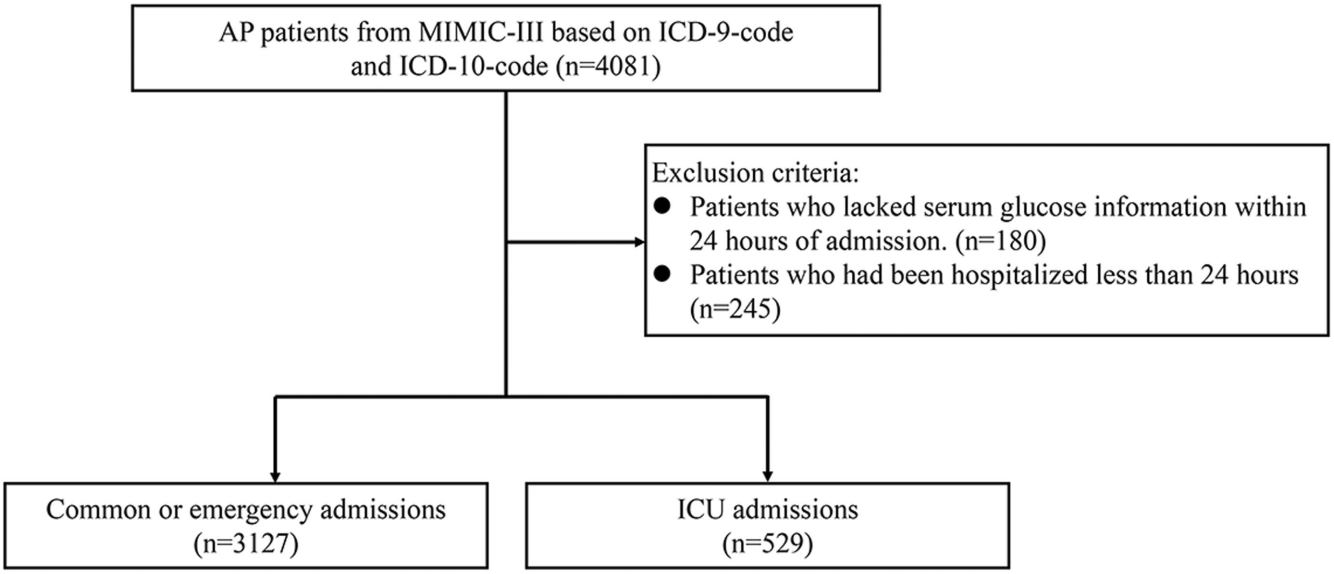

FIGURE 1 Flow chart for enrollment of patients and study design (created using Microsoft Office PowerPoint software). AP, acute pancreatitis; ICD, International Classification of Diseases; ICU, intensive care unit; MIMIC-III, Medical Information Mart for Intensive Care III.

K8531, K8580, K8581, K8590, and K8591). We used the following exclusion criteria: (1) patients who lacked serum glucose information with 24 h of admission ($n = 180$), and (2) patients who had been hospitalized for less than 24 h ($n = 245$). Finally, 3656 individuals who met the criteria were selected (Figure 1).

Data extraction

We obtained three types of information from the database. Demographic information: age, gender, ethnicity, marital status, and insurance status. Comorbidity information: chronic heart failure (CHF), hypertension, chronic obstructive pulmonary disease (COPD), diabetes mellitus, renal failure, liver disease, coronary artery disease (CAD), hyperlipidemia, admitted to the intensive care unit (ICU), Charlson comorbidity index (CCI), sequential organ failure assessment score, SIRS score, and simplified acute physiology score II (SAPSII) score. Laboratory tests: white blood cell (WBC) count, albumin, total bilirubin (TBil), lipase, amylase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine, and glucose. In addition, we obtained information on LOS in the hospital and hospital deaths.

Statistical analysis

Continuous variables were presented as median and interquartile range, whereas categorical variables were expressed as n (%). For categorical variables, p values were analyzed by chi-square test. For continuous variables, the Kruskal-Wallis test was used in a non-normal model. LOS was considered as a dichotomous variable (≤2 days or >2 days, ≤5 days or >5 days, and ≤7 days or >7 days).

The restricted cubic spline (RCS) function allows a more intuitive description of the dose–response relationship between continuous variables and outcomes.[16] Dose–response analysis curves using the RCS function were used to confirm the relationship between blood glucose levels and LOS greater than or equal to 2 days, LOS greater than or equal to 5 days, and LOS greater than or equal to 7 days. The relationship between blood glucose levels and LOS greater than 2 days, LOS greater than 5 days, and LOS greater than 7 days were assessed using univariate and multivariate logistic regression methods, and adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were calculated. In multivariate logistic regression analysis, three models were constructed, namely model A, model B, and model C. Model A included five variables in the demographic information. Model B added 13 variables in the comorbidity information to model A. Model C added nine variables, excluding glucose, LOS, and hospital mortality, in the laboratory test information to model B. In addition, we performed the same analysis for subgroups with a proportion greater than 50% to determine the relationship between different blood glucose levels and LOS in the subgroups. Statistical analyses were performed using SPSS software (version 24.0) and Rstudio software (version 1.4.1106). Probability values of $p < 0.05$ were considered as statistically significant.

RESULTS

A total of 3656 patients were included in the study according to the inclusion and exclusion criteria. In all patients, after adjusting for five variables in the demographic information, 12 variables in the comorbidity information, and nine variables, excluding glucose, LOS, and hospital mortality, in the laboratory test information, the dose–response curve of the RCS showed a significant nonlinear correlation between blood glucose levels and LOS greater than or equal to 2 days, LOS greater than or equal to 5 days, and LOS greater than or equal to 7 days (all $p < 0.001$; Figure 2).

Based on the dose–response curve of the RCS, we calculated the blood glucose concentrations corresponding to 68 mg/dl and 104 mg/dl at odds ratio (OR) = 1. Based on the blood glucose levels, we divided all patients into three groups as follows, the less than 68 mg/dl group, the 68–104 mg/dl group, and the greater than 104 mg/dl group. The demographic and clinicopathological characteristics of all patients are shown in Table 1. We found a difference among the three groups in variables of age, gender, race, CHF, hypertension, diabetes mellitus, renal failure, liver disease, CAD, hyperlipidemia, ICU stay, SIRS score, WBC, Tbil, lipase, AST, BUN, creatinine, LOS, and hospital mortality. The 68–104 mg/dl group had the lowest rates of age greater than or equal to 60 years (42.8%), Medicare (30.9%), comorbid CHF (4.7%), comorbid COPD (0.5%), comorbid diabetes (7.5%), comorbid CAD (10.0%), ICU admissions (8.3%), and lowest levels of CCI (3.0 [1.0,

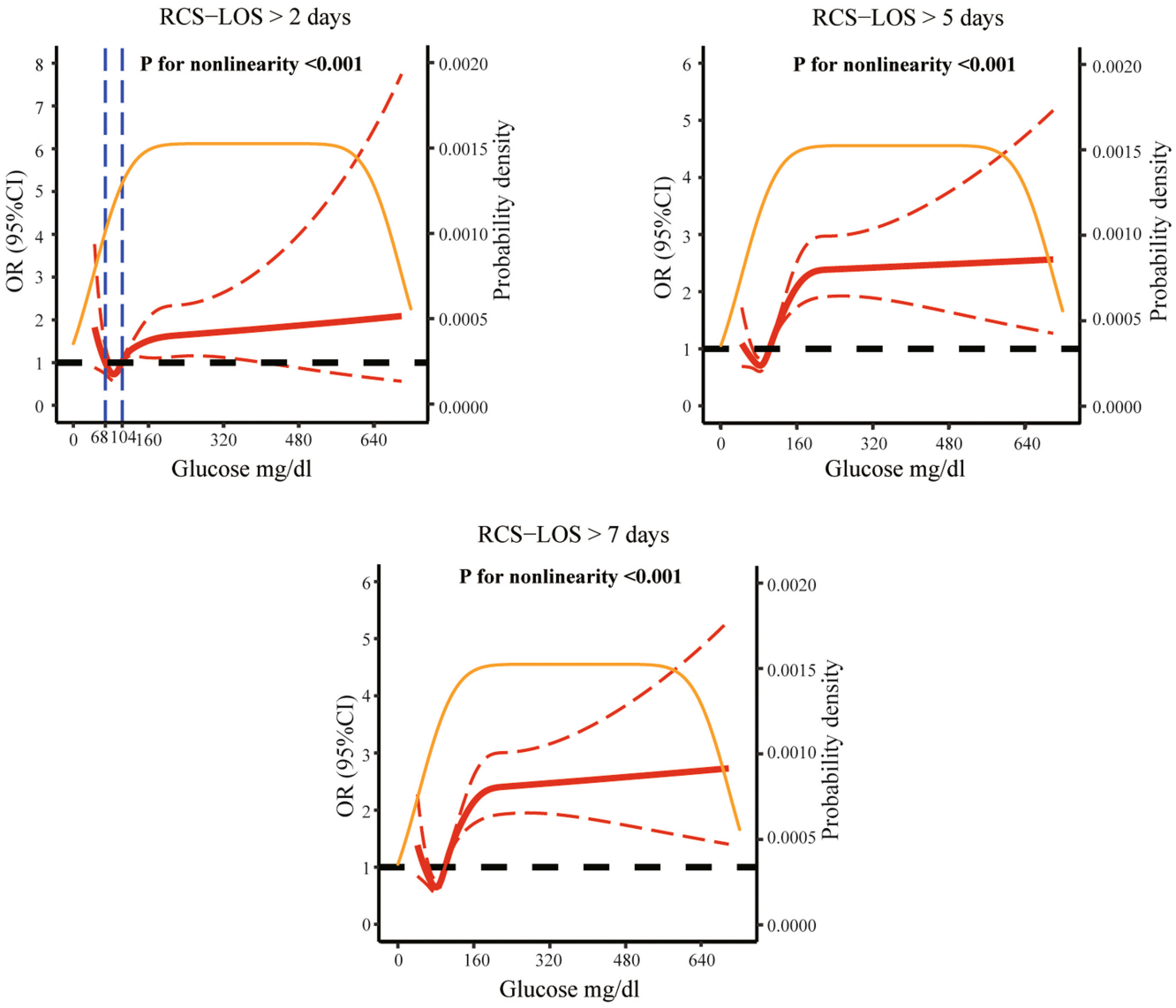

FIGURE 2 Relative risk of a hospital LOS of greater than 2, greater than 5 days, and greater than or equal to 7 days according to blood glucose in the MIMIC-III database (created using RStudio software version 1.4.1106). CI, confidence interval; LOS, length of stay; OR, odds ratio; RCS, restricted cubic spline.

TABLE 1 Participants' baseline characteristics

Characteristics	All patients no. (%)	Glucose level (mg/dl)			*p* value
		Glucose <68 no. (%)	Glucose: 68–104 no. (%)	Glucose >104 no. (%)	
Total patients	3656	169 (4.6)	1711 (46.8)	1776 (48.6)	
Demographics					
Age, years	58.5 (46.0, 71.7)	57.6 (43.9, 74.5)	56.8 (43.2, 70.3)	60.6 (48.5, 72.3)	<0.001
Age categorized, years					
<60	1936 (53.0)	95 (56.2)	979 (57.2)	862 (48.5)	<0.001
≥60	1720 (47.0)	74 (43.8)	732 (42.8)	914 (51.5)	
Gender					
Male	1851 (50.6)	60 (35.5)	762 (44.5)	1029 (57.9)	<0.001
Female	1805 (49.4)	109 (64.5)	949 (55.5)	747 (42.1)	
Ethnicity					
White	2535 (69.3)	108 (63.9)	1207 (70.5)	1220 (68.7)	0.001
Black	428 (11.7)	34 (20.1)	208 (12.2)	186 (10.5)	
Other	693 (19.0)	27 (16.0)	296 (17.3)	370 (20.8)	
Marital status					
Married	1677 (45.9)	68 (40.2)	780 (45.6)	829 (46.7)	0.262
Non-married	1979 (54.1)	101 (59.8)	931 (54.4)	947 (53.3)	
Insurance					
Medicare	1207 (33.0)	64 (37.9)	528 (30.9)	615 (34.6)	0.073
Medicaid	384 (10.5)	20 (11.8)	180 (10.5)	184 (10.4)	
Other	2065 (56.5)	85 (50.3)	1003 (58.6)	977 (55.0)	
Comorbidities					
CHF					
No	3435 (94.0)	157 (92.9)	1631 (95.3)	1647 (92.7)	0.005
Yes	221 (6.0)	12 (7.1)	80 (4.7)	129 (7.3)	
Hypertension					
No	2601 (71.1)	132 (78.1)	1303 (76.2)	1166 (65.7)	<0.001
Yes	1055 (28.9)	37 (21.9)	408 (23.8)	610 (34.3)	
COPD					
No	3634 (99.4)	167 (98.8)	1702 (99.5)	1765 (99.4)	0.569
Yes	22 (0.6)	2 (1.2)	9 (0.5)	11 (0.6)	
Diabetes mellitus					
No	3040 (83.2)	150 (88.8)	1582 (92.5)	1308 (73.6)	<0.001
Yes	616 (16.8)	19 (11.2)	129 (7.5)	468 (26.4)	
Renal failure					
No	3540 (96.8)	166 (98.2)	1675 (97.9)	1699 (95.7)	<0.001
Yes	116 (3.2)	3 (1.8)	36 (2.1)	77 (4.3)	
Liver disease					
No	3540 (96.8)	166 (98.2)	1675 (97.9)	1699 (95.7)	<0.001
Yes	116 (3.2)	3 (1.8)	36 (2.1)	77 (4.3)	
CAD					
No	3170 (86.7)	142 (84.0)	1540 (90.0)	1488 (83.8)	<0.001
Yes	486 (13.3)	27 (16.0)	171 (10.0)	288 (16.2)	

TABLE 1 (Continued)

Characteristics	All patients no. (%)	Glucose level (mg/dl) Glucose <68 no. (%)	Glucose: 68–104 no. (%)	Glucose >104 no. (%)	*p* value
Hyperlipidemia					
No	2672 (73.1)	132 (78.1)	1327 (77.6)	1213 (68.3)	<0.001
Yes	984 (26.9)	37 (21.9)	384 (22.4)	563 (31.7)	
Admitted to the ICU					
No	3127 (85.5)	154 (91.1)	1569 (91.7)	1404 (79.1)	<0.001
Yes	529 (14.5)	15 (8.9)	142 (8.3)	372 (20.9)	
CCI	4.0 (2.0, 6.0)	4.0 (1.0, 6.0)	3.0 (1.0, 5.0)	4.0 (2.0, 6.0)	<0.001
SOFA score	1.0 (0.0, 3.0)	2.0 (0.0, 4.0)	1.0 (0.0, 3.0)	1.0 (0.0, 3.0)	0.908
SIRS score	3.0 (2.5, 4.0)	3.0 (2.0, 3.0)	3.0 (2.0, 3.0)	3.0 (3.0, 4.0)	0.017
SAPSII score	38.0 (28.0, 49.0)	44.0 (31.0, 50.0)	38.0 (28.0, 46.0)	38.0 (28.0, 51.0)	0.305
Laboratory examination					
WBC, 10^9/L	8.8 (6.2, 12.5)	7.2 (5.6, 10.0)	7.7 (5.8, 10.8)	10.1 (6.9, 14.6)	<0.001
Albumin, g/L	3.4 (2.9, 3.8)	3.4 (2.8, 3.6)	3.4 (3.0, 3.8)	3.4 (2.9, 3.8)	0.317
TBil, mmol/L	0.9 (0.5, 2.1)	0.9 (0.5, 2.0)	0.8 (0.5, 1.9)	0.9 (0.5, 2.2)	0.011
Lipase, IU/L	183.0 (61.0, 710.5)	165.0 (64.5, 503.8)	169.0 (60.0, 622.5)	208.0 (63.0, 796.0)	0.024
Amylase, IU/L	145.0 (66.0, 404.0)	162.5 (79.8, 324.0)	149.5 (69.0, 403.3)	141.0 (61.0, 408.0)	0.460
AST, U/L	57.0 (25.0, 142.0)	76.0 (29.0, 148.5)	53.0 (24.0, 137.0)	58.0 (27.0, 148.0)	0.011
ALT, U/L	54.0 (22.0, 178.0)	57.5 (22.3, 197.8)	54.0 (20.0, 176.8)	54.0 (23.0, 177.3)	0.460
BUN, mmol/L	13.0 (9.0, 20.0)	11.0 (8.0, 19.0)	11.0 (8.0, 17.0)	15.0 (10.0, 24.0)	<0.001
Creatinine, mg/dl	0.8 (0.6, 1.1)	0.7 (0.6, 1.0)	0.8 (0.6, 1.0)	0.9 (0.7, 1.3)	<0.001
Glucose, mg/dl	103.0 (87.0, 134.0)	62.0 (57.0, 66.0)	89.0 (81.0, 96.0)	136.0 (116.0, 171.0)	<0.001
LOS, days	4.8 (2.9, 8.8)	4.0 (2.9, 8.1)	3.9 (2.6, 6.8)	5.8 (3.4, 11.0)	<0.001
Hospital mortality, *n* (%)	123 (3.4)	5 (3.0)	30 (1.8)	88 (5.0)	<0.001

Note: Continuous variables were presented as the median and interquartile range (IQR) and categorical variables were expressed as *n* (%). For categorical variables, *p* values were analyzed by χ^2 test. For continuous variables, the Kruskal-Wallis test was used in the non-normal model.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; CCI, Charlson Comorbidity Index; ICU, intensive care unit; LOS, length of stay; SAPS, simplified acute physiology score; SIRS, systemic inflammatory response system; SOFA, sequential organ failure assessment; TBil, total bilirubin; WBC, white blood cell count.

5.0]), SAPSII score (38.0 [28.0, 46.0]), TBil (0.8 [0.5, 1.9] mmol/L), AST (53.0 [24.0, 137.0] U/L), ALT (54.0 [20.0, 176.8] U/L), BUN (11.0 [8.0, 17.0] mmol/L), LOS (3.9 [2.6, 6.8] days), and hospital mortality (1.8%).

Subsequently, logistic regression analysis was used to assess the relationship between blood glucose levels and LOS greater than or equal to 2 days, LOS greater than or equal to 5 days, and LOS greater than or equal to 7 days (Table 2). Univariate analysis showed an increased risk of LOS greater than or equal to 2 days, LOS greater than or equal to 5 days, and LOS greater than or equal to 7 days in glucose in the less than 68 mg/dl and glucose in the greater than 104 mg/dl groups compared with glucose in the 68–104 mg/dl group (glucose >104 mg/dl group: significant in LOS > 2 days, LOS > 5 days, and LOS > 7 days; glucose <68 mg/dl group: significant in LOS > 7 days). In multivariate logistic regressions for models A and B, there was an increased risk of LOS greater than or equal to 7 days (model A: aOR = 1.51, 95% CI 1.07–2.13, $p = 0.020$; and model B: aOR = 1.46, 95% CI 1.03–2.07, $p = 0.032$) in the glucose less than 68 mg/dl group compared to the glucose 68–104 mg/dl group; and an increased risk of LOS greater than or equal to 2 days (model A: aOR = 1.55, 95% CI 1.27–1.90, $p < 0.001$; and model B: aOR = 1.55, 95% CI 1.26–1.90, $p < 0.001$), LOS greater than or equal to 5 days (model A: aOR = 2.12, 95% CI 1.85–2.43, $p < 0.020$; and model B: aOR = 2.10, 95% CI 1.83–2.41, $p < 0.001$), and LOS greater than or equal to 7 days (model A: aOR = 2.25, 95% CI 1.94–2.62, $p < 0.001$; and model B: aOR = 2.24, 95% CI 1.93–2.60, $p < 0.001$) in the glucose greater than 104 mg/dl group compared to the glucose 68–104 mg/dl group (Table 2). Multivariate logistic regression of model

TABLE 2 Relative risk of having a hospital LOS of >2, >5 or >7 days was calculated according to glucose level in different groups

		Univariate analysis		Model A		Model B		Model C	
Characteristic	***N***	**OR (95% CI)**	***p* value**	**aOR (95% CI)**	***p* value**	**aOR (95% CI)**	***p* value**	**aOR (95% CI)**	***p* value**
LOS > 2 days									
Glucose, mg/dl			**<0.001**		**<0.001**		**<0.001**		**<0.001**
Glucose 68 to 104	1711	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Glucose <68	169	1.54 (0.93–2.55)	0.096	1.54 (0.93–2.55)	0.096	1.50 (0.91–2.50)	0.115	1.47 (0.89–2.45)	0.136
Glucose >104	1776	**1.59 (1.30–1.94)**	**<0.001**	**1.55 (1.27–1.90)**	**<0.001**	**1.55 (1.26–1.90)**	**<0.001**	**1.53 (1.24–1.89)**	**<0.001**
LOS > 5 days									
Glucose, mg/dl			**<0.001**		**<0.001**		**<0.001**		**<0.001**
Glucose 68 to 104	1711	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Glucose <68	169	1.25 (0.90–1.72)	0.179	1.25 (0.91–1.73)	0.169	1.22 (0.88–1.68)	0.226	1.20 (0.87–1.66)	0.272
Glucose >104	1776	**2.17 (1.90–2.49)**	**<0.001**	**2.12 (1.85–2.43)**	**<0.001**	**2.10 (1.83–2.41)**	**<0.001**	**2.14 (1.86–2.47)**	**<0.001**
LOS > 7 days									
Glucose, mg/dl			**<0.001**		**<0.001**		**<0.001**		**<0.001**
Glucose 68 to 104	1711	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Glucose <68	169	**1.49 (1.06–2.11)**	**0.024**	**1.51 (1.07–2.13)**	**0.020**	**1.46 (1.03–2.07)**	**0.032**	**1.45 (1.02–2.05)**	**0.040**
Glucose >104	1776	**2.32 (2.01–2.69)**	**<0.001**	**2.25 (1.94–2.62)**	**<0.001**	**2.24 (1.93–2.60)**	**<0.001**	**2.30 (1.97–2.69)**	**<0.001**

Note: Adjusted covariates: model A: five variables in the demographic information; model B: model A plus 13 variables in the comorbidity information; model C: model B plus nine variables excluding glucose, LOS, and hospital mortality in the laboratory test information.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; LOS, length of stay; OR, odds ratio.

The *p* values <0.05 are shown in bold.

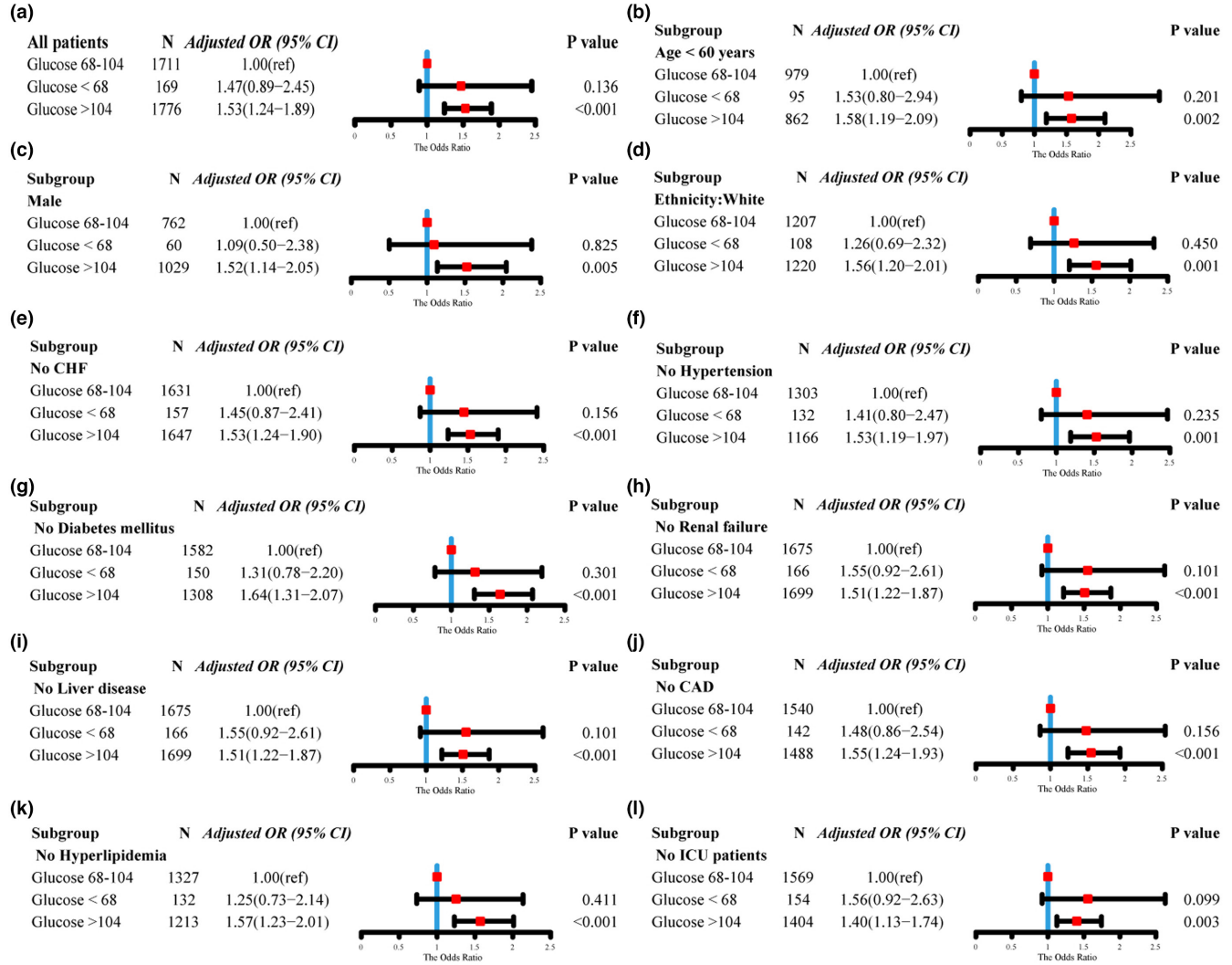

FIGURE 3 Results of subgroup analyses of POBG and a hospital LOS greater than or equal to 2 days according to clinical characteristics (Created using RStudio software version 1.4.1106). (a) All patients; (b) age less than 60 years group; (c) male group; (d) White group; (e) no CHF group; (f) no hypertension group; (g) no diabetes mellitus group; (h) no renal failure; (i) no liver disease group; (j) no CAD group; (k) no hyperlipidemia group; (l) no ICU group. CAD, coronary artery disease; CHF, chronic heart failure; CI, confidence interval; ICU, intensive care unit; LOS, length of stay; OR, odds ratio; POBG, pre-operative blood glucose.

C adjusted for all variables revealed a 53% higher risk of LOS greater than or equal to 2 days (aOR = 1.53, 95% CI 1.24–1.89, $p < 0.001$; Figure 3a), 114% higher risk of LOS greater than or equal to 5 days (aOR = 2.14, 95% CI 1.86–2.47, $p < 0.001$; Figure 4a), and 130% higher risk of LOS greater than or equal to 7 days (aOR = 2.30, 95% CI 1.97–2.69, $p < 0.001$; Figure 5a) in patients with glucose levels greater than 104 mg/dl than patients with glucose levels 68–104 mg/dl. A significantly high risk due to low blood glucose occurred only at LOS greater than or equal to 7 days, where patients with glucose less than 68 mg/dl had a 45% higher risk of LOS greater than 7 days than patients with glucose levels of 68–104 mg/dl (aOR = 1.45, 95% CI 1.02–2.05, $p = 0.040$). In addition, we observed similar results in many subgroups (Figure 3b-l, Figure 4b-l, and Figure 5b-l).

DISCUSSION

In this retrospective study, we included clinical data of 3656 inpatients with AP from the MIMIC-III database, and used RCS dose–response curve analysis, univariate, and multifactorial logistic regression analyses to explore the relationship between blood glucose levels and LOS. We found that there was a significant nonlinear relationship between blood glucose levels and LOS greater than or equal to 2 days, LOS greater than or equal to 5 days, and LOS greater than or equal to 7 days (all $p < 0.001$). In addition, we also validated this in our own clinical sample and found a significant nonlinear U-shaped relationship between blood glucose levels and LOS greater than or equal to 5 days and LOS greater than or equal to7 days (Figure S1). Moreover, either blood glucose less than 68 mg/dl or blood glucose greater than 104 mg/dl significantly

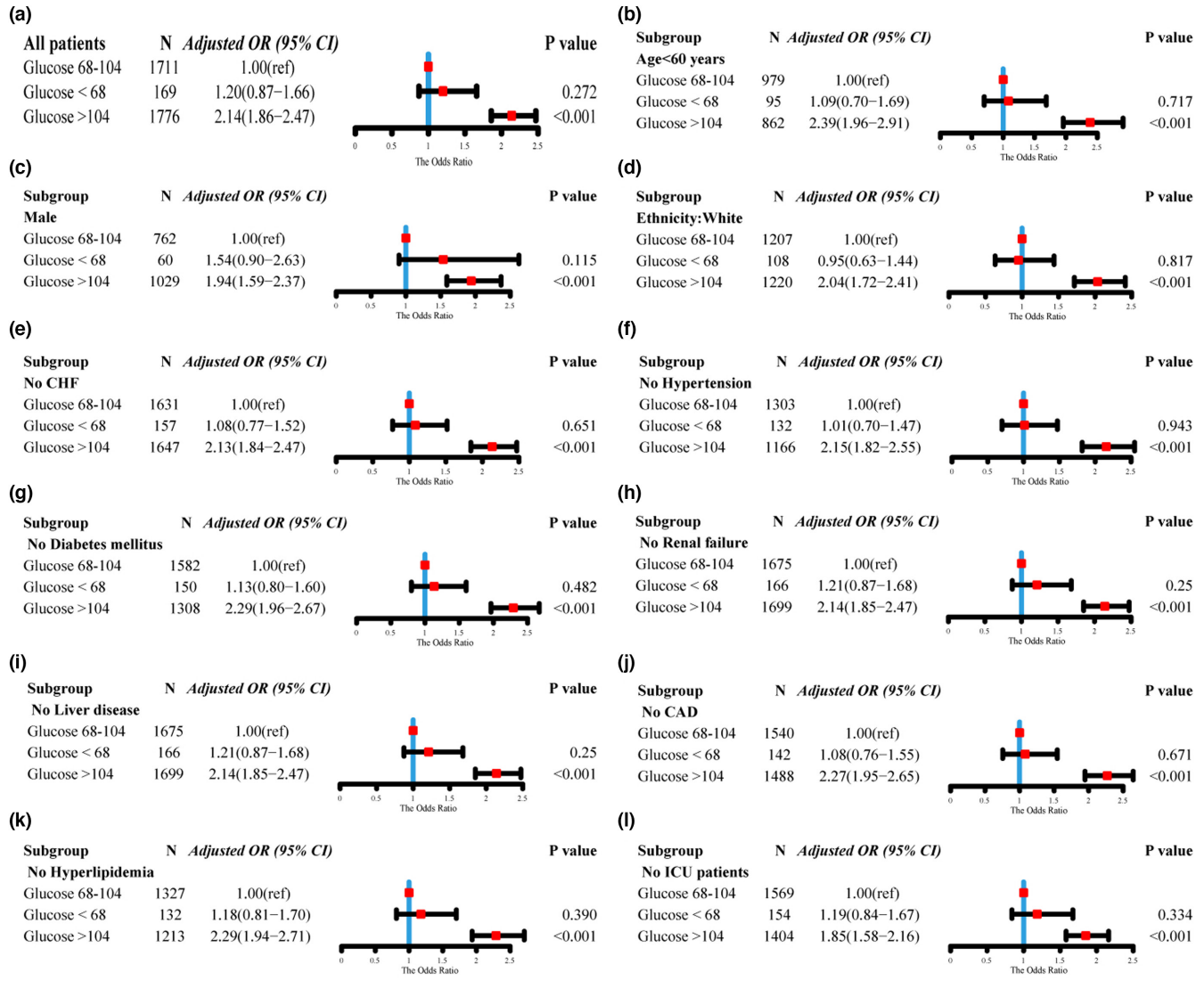

FIGURE 4 Results of subgroup analyses of POBG and a hospital LOS greater than or equal to 5 days according to clinical characteristics (created using RStudio software version 1.4.1106). (a) All patients; (b) age less than 60 years group; (c) male group; (d) White group; (e) no CHF group; (f) no hypertension group; (g) no diabetes mellitus group; (h) no renal failure; (i) no liver disease group; (j) no CAD group; (k) no hyperlipidemia group; (l) no ICU group. CAD, coronary artery disease; CHF, chronic heart failure; CI, confidence interval; ICU, intensive care unit; LOS, length of stay; OR, odds ratio; POBG, pre-operative blood glucose.

increased the risk of LOS. Moreover, multivariate logistic regression analysis showed that patients with blood glucose greater than 104 mg/dl had a significantly higher risk of LOS greater than or equal to 2 days, LOS greater than or equal to 5 days, and LOS greater than or equal to 7 days than those with blood glucose levels 68–104 mg/dl. Patients with blood glucose less than 68 mg/dl had a higher risk of LOS greater than or equal to 7 days than those with blood glucose levels 68–104 mg/dl (all statistically significant).

In early development of AP, various inflammatory cells of the body are activated, releasing various cytokines and inflammatory mediators that trigger a systemic response syndrome in the organism.[17,18] It has been found that hyperglycemia can trigger the release of inflammatory cytokines, and thus cause a series of inflammatory reactions that can lead to rapid development of multi-organ functional damage.[19] Another study found that hyperglycemic state serves as an important indicator of multi-organ failure and poor prognosis in patients with SAP, by comparing blood glucose levels with organ failure rate, ICU transfer rate, and mortality rate.[20,21] In addition, Yan et al.[22] found that Glucose_max, Glucose_mean, Glucose_SD, and Glucose_CV were associated with mortality of patients hospitalized with AP. Interestingly, Yildirim et al.[23] demonstrated that anti-inflammatory and antioxidant therapy can alleviate the condition of patients with AP and hinder further progression. These results suggest that blood glucose level is closely related to inflammatory response in AP, can influence the development of the disease by stimulating inflammatory response in the body,

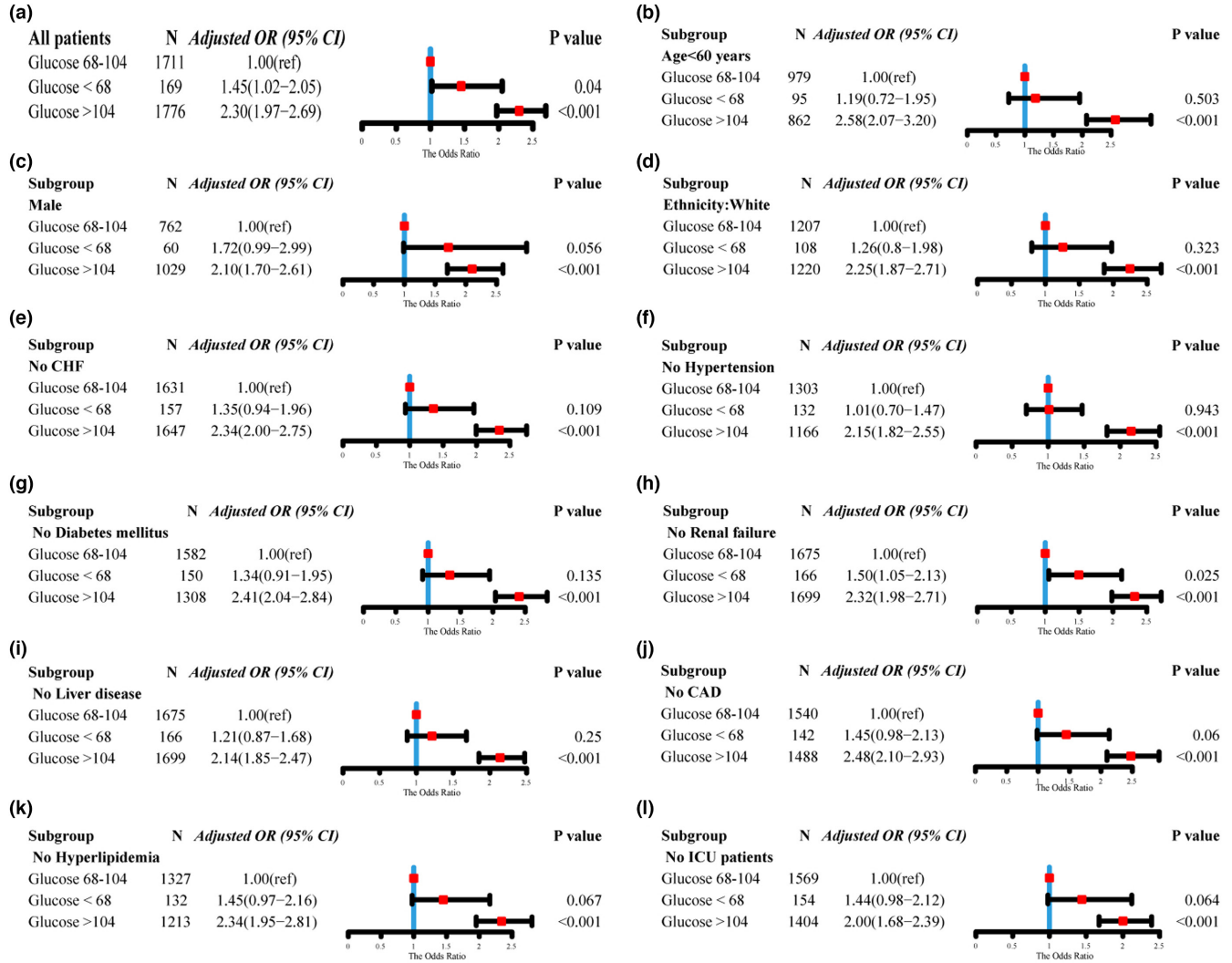

FIGURE 5 Results of subgroup analyses of POBG and a hospital LOS greater than or equal to 7 days according to clinical characteristics (created using RStudio software version 1.4.1106). (a) All patients; (b) age less than 60 years group; (c) male group; (d) White group; (e) no CHF group; (f) no hypertension group; (g) no diabetes mellitus group; (h) no renal failure; (i) no liver disease group; (j) no CAD group; (k) no hyperlipidemia group; (l) no ICU group. CAD, coronary artery disease; CHF, chronic heart failure; CI, confidence interval; ICU, intensive care unit; LOS, length of stay; OR, odds ratio; POBG, pre-operative blood glucose.

and hyperglycemia status can be used as one of the clinical reference indicators to assess the severity of AP.[24]

In recent years, numerous studies have reported that blood glucose level affects LOS in hospitalized patients. Chiang et al.[13] retrospectively analyzed clinical data of 4025 patients who underwent appendectomy and 4266 patients who underwent laparoscopic cholecystectomy from 2005–2016, and found that the higher pre-operative blood glucose (POBG) level was significantly associated with prolonged LOS. Sun et al.[25] also found that a higher POBG level was significantly associated with longer LOS, by analyzing data of 310 patients with kidney stones who underwent percutaneous nephrolithotomy. He et al.[16] investigated the relationship between POBG and LOS in 338 patients with renal cell carcinoma, who underwent laparoscopic nephrectomy, and found that POBG was positively associated with the risk of LOS greater than or equal to 2 weeks and LOS greater than or equal to 3 weeks. These studies collectively indicate that hyperglycemia increases LOS in hospitalized patients, which may be because hyperglycemia increases the risk of surgical site infection, prolongs wound healing time, and thus increases the LOS in the hospital.[26,27] In addition, Lankish et al.[28] found that hyperglycemia (>125 mg/dl) was associated with prolonged hospitalization in patients with AP, and Rajaratnam et al.[29] found that patients with glucose levels greater than or equal to 8.3 mmol/L had a higher mean LOS compared with patients with gallstone pancreatitis with serum glucose levels below 8.3 mmol/L on admission (17.9 days vs. 7.1 days, $p < 0.001$).

Interestingly, in the current study, we found that among 169 hospitalized patients with blood glucose less than 68 mg/dl, the risk of LOS gradually increased as the blood glucose

level decreased. It was found that the blood glucose level is regulated by multiple factors, such as the liver, nervous system, and endocrine system. Moreover, complex pathological changes occur in the body in the AP state, and blood glucose level does not reflect the function of pancreatic islet secretion system well, and fluctuation of blood glucose values is finally attributed to pancreatic endocrine hormone disorder.[30,31] Due to abnormal release of glucose metabolism regulating hormones, mainly insulin and glucagon, the glycogen storage in the liver is reduced or the metabolism is changed, resulting in a decrease in the output of sugar from the liver and thus hypoglycemia.[32] Hypoglycemia has a great impact on the nervous system, especially on the sympathetic nerves. The main source of energy for the brain is glucose, and the amount of glucose stored in the brain is very limited.[33] In the early stage of hypoglycemia, patients may experience congestion of brain tissue, and as the duration of hypoglycemia increases, punctate necrosis of brain tissue or cerebral edema may occur, eventually leading to necrosis of nerve cells and even death.[34] Therefore, when severe hypoglycemia occurs, it can cause irreversible damage to the brain tissue as well as nerves, which may also be the reason why hypoglycemia increases LOS.[35,36] In the present study, we found that blood glucose levels and LOS in patients with AP were significantly correlated, with either hyperglycemia or hypoglycemia increasing LOS in patients with AP. For hospitalized patients with AP, controlling blood glucose at 68–104 mg/dl minimized the LOS and reduced the burden on patients and hospitals.

Limitations

There are several limitations to this study. (1) The MIMIC-III database is a single-center US database, and the majority of the patients are American, limiting the applicability of these findings to other regions and ethnicities. (2) The MIMIC-III database is a retrospective public database, which has its own limitations. (3) The data in the MIMIC-III database are relatively old and lack data on comorbidities and other treatments, which adds complexity to the analysis results, and introduces bias in the results. Therefore, a multicenter study with a large sample is needed to further validate these findings.

CONCLUSIONS

In conclusion, our findings suggest that for patients hospitalized with AP, blood glucose level and LOS were significantly correlated, and either hyperglycemia or hypoglycemia increases LOS. Optimal blood glucose levels of 68–104 mg/dl can significantly improve LOS in patients with AP.

AUTHOR CONTRIBUTIONS

D.W., J.L., and P.Z. wrote the manuscript. D.W., Z.H., and Y.S. designed the research. P.Z., Z.H., and Y.S. performed the research. D.W., J.L., Z.H., and Y.S. analyzed the data.

ACKNOWLEDGMENTS

The authors thank Dong Wang from Zhongda Hospital (Nanjing, China) for his technical guidance. We also thank Bullet Edits for editing this manuscript.

FUNDING INFORMATION

This study was supported by the Key Subdiscipline Construction Project of Pudong Health Committee of Shanghai (Grant No. PWZy2020-05); and the Medical Discipline Construction Project of Pudong Health Committee of Shanghai (Grant No. PWYgf2021-08).

CONFLICT OF INTEREST

We declare that there are no conflicts of interest between authors.

ETHICAL APPROVAL

This study is an analysis of a public database. The methodology of this study was approved by National Health Protection Human Research Institute (certification number 44274909).

DECLARATION OF FIGURES AUTHENTICITY

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wang D, Lu J, Zhang P, Hu Z, Shi Y. Relationship between blood glucose levels and length of hospital stay in patients with acute pancreatitis: An analysis of MIMIC-III database. *Clin Transl Sci*. 2023;16:246-257. doi: 10.1111/cts.13445