Insulin for hyperglycemia prevention and management during postgastrectomy nutrition support in gastric cancer: Reduced complications in a retrospective cohort study in China

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ABSTRACT

Background and Objectives: To evaluate the effectiveness of insulin addition to the total nutrition admixture (TNA) for glycemic control among patients with gastric cancer (GC) receiving supplementary parenteral nutrition (SPN) after gastrectomy. **Methods and Study Design:** A retrospective cohort study was conducted among 208 noncritical ill patients who underwent gastrectomy for GC from 2017 to 2019 at a tertiary teaching hospital in Lanzhou, China. All the included patients received individualized SPN and enteral nutrition treatment after gastrectomy. The patients were randomly divided into insulin and noninsulin groups based on the TNA composition. Blood glucose (BG) measurements, glycemic fluctuation, and hypoglycemia incidence during SPN were compared between the two groups. The postoperative comprehensive complications index (CI) and infections were compared according to insulin regimen and postoperative glycemic status. **Results:** The mean BG was significantly low and fluctuated less in the insulin group than in the noninsulin group (p<0.05). One unit of insulin per 6 g of parenteral nutrition glucose addition to TNA did not increase hypoglycemia incidence (p>0.05). Comparing CI and the infection rate, no significance was observed between the insulin and noninsulin groups, but a higher infection incidence was observed in patients with hyperglycemia than in euglycemic patients (p<0.05). **Conclusions:** Appropriate insulin addition to TNA has an overall positive effect on glycemic management in patients with noncritical GC who received SPN after gastrectomy. Postoperative glycemic status was associated with the incidence of relevant complications. Further research is needed for conclusive recommendations.

Key Words: gastrectomy, supplementary parenteral nutrition, hyperglycemia, insulin, blood glucose fluctuation

INTRODUCTION

Gastric cancer (GC) is the fifth most common type of tumor and the third leading cause of cancer-related death worldwide.[1] Radical gastrectomy is an effective treatment option for patients with GC. Although the enhanced recovery after surgery concept is commonly promoted perioperatively, many nondiabetic patients present with hyperglycemia (HG) due to the long operation time, large postoperative trauma, nutritional support, and possible anxiety. Poor control of perioperative blood glucose (BG) is closely associated with an increased chance of postoperative complications and mortality in patients who underwent major

abdominal surgeries,[2-4] and nondiabetic patients who experience HG have an increased risk of infection.[2]

Insulin therapy is the best method of glycemic control in the hospitalization setting. For non–intensive care unit (ICU) patients who receive parenteral nutrition (PN), direct insulin addition to total nutrition admixture (TNA) has been recommended in some studies,[5-7] as it is a simple and less painful procedure. Nevertheless, according to the Chinese consensus for PN compounding, prophylactic insulin should not be administered to euglycemic patients who receive PN.[8] In practice, however, we observed the increased occurrence of HG and pertinent complications in nondiabetic patients undergoing surgery who did not receive insulin therapy while on PN. Regarding this topic, we reviewed relevant studies and found that some recommend 1 unit of insulin per 4–10 g of PN glucose to be routinely added to the TNA for nondiabetic PN patients for glycemic control.[9,10]

Currently, solid evidence of the effects of insulin in TNA on glycemic control is still lacking, particularly among patients with postoperative cancer. To optimize the glycemic management protocol for our patient population, in this retrospective cohort study, we assessed the safety and efficacy of insulin addition to TNA through the analysis of postoperative BG concentrations and the complication incidence among 208 patients with GC who received supplementary parenteral nutrition (SPN) after gastrectomy.

MATERIALS AND METHODS

Study design and participants

In total, 208 nondiabetic patients with GC received surgical intervention in our surgical oncology department between March 2017 and September 2019. Participant inclusion criteria were as follows: (1) histologically confirmed diagnosis of gastric adenocarcinoma; (2) underwent elective radical gastrectomy and D2 lymphadenectomy; and (3) at nutritional risk, with nutritional risk screening (2002) score ≥3. Patients with the following criteria were excluded: (1) preexisting diabetes or diabetes diagnosis during hospitalization (i.e., admission random venous plasma glucose [VPG] >11.1 mmol/L [200 mg/dL]); (2) coexistence of other malignancy; (3) systemic glucocorticoid treatment within 3 months before admission or during hospitalization; (4) patient directly transferred to ICU after surgery; (5) incomplete postoperative BG data; and (6) HG occurrence after infection onset. Clinical data, including BMI, surgical method, pathological stage, postoperative BGs, and postoperative complications, were evaluated. The study was performed according to the Declaration of

Helsinki and was approved by the Ethics Committee of the First Hospital of Lanzhou University (Ethical approval number: LDYYLL-2021-272).

Interventions

All the 208 included patients underwent radical gastrectomy (proximal gastrectomy, distal gastrectomy, or total gastrectomy) with D2 lymphadenectomy. Postoperative pathological staging was performed according to the American Joint Committee on Cancer, eighth edition, staging system.

Patients were allowed to sip water or were provided nasojejunal tube feeding (NJTF) of 5% glucose sodium chloride solution up to 300 mL from postoperative day 1 (POD1). From POD2, patients without gastrointestinal symptoms, including diarrhea, abdominal pain, abdominal distension, and vomiting, were initiated on an oral liquid diet or NJTF (Fresubin), which provided 25% of the estimated total energy expenditure (TEE) calculated using Harris Benedict equation. Feeding was adjusted based on the patient's tolerance and oral intake. All patients received individualized SPN through central venous access from POD1 until the total enteral nutrition reached 60% of the TEE to prevent progressive malnutrition. SPN was formulated daily in accordance with the relevant guidelines[11] to ensure the total nutritional intake meet at least 60% of the TEE. Individualized dosages of vitamins, minerals, and trace elements were added to solutions. All TNAs were timely compounded in the Pharmacy Intravenous Admixture Services center of the hospital.

BG monitoring and evaluation

The BG data of all recruited patients were recorded, including admission random VPG, capillary blood glucose (CBG) after returning to the ward on the operation day (recorded as pre-SPN CBG), POD1 VPG (at 07:00), and during SPN CBG (four times daily at 06:00, 12:00, 18:00, and 00:00).

The collected BG data were statistically evaluated based on the following indictors. Blood glucose control rate (BGCR): the ratio of BG values within 3.9–10 mmol/L (70–180 mg/dL). Hypoglycemia incidence: the number and proportion of hypoglycemia (BG <2.8 mmol/L [50 mg/dL]) in each subgroup. HG incidence: the number and proportion of patients with HG (BG >11.1 mmol/L [200 mg/dL]) more than twice[12] in each subgroup. Coefficient of variation (CV): the ratio of glycemic standard deviation to the mean. Fasting capillary glucose -CV (FCG-CV):[13] the ratio of the standard deviation of fasting CBG (collected daily at 06:00 AM).

The largest amplitude of glycemic excursions (LAGE): the difference between the maximum and minimum BG values during SPN.

Postoperative complications

Postoperative comprehensive complications index (CI)[14] within 30 days after surgery was determined. Postoperative infections were graded according to the Clavien-Dindo Classification[15] and included superficial and deep wound infection, organ/space infection, urinary tract infection, pneumonia, sepsis, and septic shock.[16]

Statistical analysis

The experimental data were recorded in a Microsoft Excel (version 2010) spreadsheet and were statistically analyzed and visually processed using SPSS (version 26.0) and GraphPad Prism (version 8.0), respectively. All continuous variables were examined using the normal distribution test. The independent t test (normally distributed, mean ± standard deviation) and Mann–Whitney U test (not normally distributed, median [interquartile range: Q1, Q3]) were performed for between-group comparisons. The chi-square test and Fisher's exact test were used for categorical data analysis (n [%]). Two-tailed p values of <0.05 were considered statistically significant.

RESULTS

In total, 208 patients (158 men and 50 women) with a mean age of 59.4 years were enrolled into this study (Figure 1). The insulin and noninsulin groups consisted of 89 (42.8%) and 119 (57.2%) patients, respectively. We obtained 3254 BG measurements (average of 15.64 measurements per subject) at different time points of assessment from the two groups. The demographic (age, sex, BMI) and clinical characteristics (history of hypertension, neoadjuvant chemotherapy, admission VPG, and pathological tumor–node–metastasis stage) were comparable (p>0.05) between the two groups (Table 1).

Before SPN was initiated, no statistical difference was observed in POD1 VPG and HG incidence between the groups (Table 1). During SPN, the mean BG concentrations and HG incidence in the insulin group were significantly lower than those in the noninsulin group (p<0.05; Table 2). Furthermore, >25% of the patients in the insulin group achieved the BGCR, which was significantly higher than that in the noninsulin group. Adding 1 unit of insulin per 6 g of PN glucose in TNA did not significantly increase the incidence of hypoglycemic events (Table 2). The BG values before and during SPN were analyzed. Patients with pre-SPN HG

were categorized into persistent HG (HG appearing before and during SPN) and improved HG (pre-SPN HG resolved while receiving SPN) groups. Patients without pre-SPN HG were categorized into late-onset HG (BG was normal before SPN, and HG developed while on SPN) and non-HG (BG within normal limit before and during SPN) groups. During SPN, we observed numerous patients with late-onset HG in the noninsulin group (46.2% vs 15.7%, $p<0.05$) (Table 2). Regarding patients with pre-SPN HG, 62.5% (5/8) of the BG measurements in the insulin group normalized during SPN compared with 40% (2/5) in the noninsulin group.

Glycemic fluctuation is a risk factor for increased postoperative complications and mortality.[17] We listed the mean and highest BGs from POD1 to POD3 in Figure 2, and we calculated the amplitude and CV (LAGE, CV, and FCG-CV) to evaluate the glycemic status while patients were on SPN. As shown in the results, the CV and LAGE calculated according to days indicate unstable BGs during SPN, and insulin addition to TNA had a positive effect on glycemic maintenance (Table 2).

Although the incidence of grade III–V infection observed in the noninsulin group ($p > 0.05$) was more than that observed in the insulin group, the postoperative CI and infection rates were not statistically different between the groups (Table 3). However, considering the effect of HG, CI ($p<0.05$) and the incidence of infection were significantly higher in patients with postoperative HG than in euglycemic patients (Table 4). In subgroup analysis, the infection rate and CI were statistically significantly higher in patients with persistent HG, improved HG, and late-onset HG than in euglycemic patients, irrespective of insulin therapy (Table 5). Among the subgroups, the incidence of grade III–V infection was the highest in the late-onset HG group (Table 5). No statistical difference was observed in infection complications, and a few infection cases were caused by surgical complications that were irrelevant to the glycemic status. We observed three infectious cases in the non-HG group that were caused by abdominal bleeding, anastomotic leakage, and adhesive intestinal obstruction; two patients in the late-onset HG group presented with sepsis shock due to pulmonary infection and severe incision suppuration, respectively.

DISCUSSION

Several studies have revealed that HG is closely related to the prognosis of patients postoperatively. This retrospective study investigated the glycemic effects of insulin addition (1 unit/6 g glucose) to TNA among nondiabetic patients with GC who received SPN after elective radical gastrectomy. Our study suggested that the postoperative CI and infection rate

were significantly higher in patients with HG than in euglycemic patients, and insulin addition to TNA efficiently reduced the postoperative BG concentrations and fluctuation. Furthermore, this insulin dosage in TNA did not increase hypoglycemia occurrence.

Several studies have shown that HG may impair immune function through the reduction of phagocytic activity of macrophages, chemotaxis disruption of polymorphonuclear neutrophils, increase in adhesion molecule expression, and free radical production in immune cells, leading to lipid peroxidation and an increase in cardiovascular inflammatory markers, which ultimately increase infection risk and in-hospital complications.[18-20] Steve Kwon et al found that perioperative HG, regardless of whether the patient was diagnosed with diabetes, was associated with nearly twofold risks of higher infection, in-hospital mortality, and operative complications.[2] The same study found that patients with HG but without diabetes had worse outcomes compared with patients with diabetes.[2] Claudio Fiorillo et al reviewed the glycemic status in 173 nondiabetic patients after gastrectomy and noted that postoperative HG was a risk factor for increased mortality and complication rates.[3] Ayami Yoneda et al supports that BG improvement prevents surgical site infection (SSI) in nondiabetic patients undergoing gastrointestinal surgery.[21] In our study, insulin therapy prevented HG during SPN, irrespective of HG occurrence before or during SPN, and the CI and infection rate were higher in HG patients than in euglycemic patients, confirming the findings of Claudio Fiorillo et al and Steve Kwon et al. This confirms that glycemic management is crucial in clinical nondiabetic patients.

The optimal target of postoperative BG has always been the focus of discussion. Several studies have indicated that intensive insulin therapy (IIT) targeting BG must be maintained at 4.4–6.1 mmol/L to improve clinical outcomes in different clinical settings.[22] In 2011, Cao et al demonstrated that IIT significantly reduced the postoperative short-term morbidity, but not mortality, among nondiabetic patients receiving PN after D2 gastrectomy, which may be related to insulin sensitivity improvement and increased human leukocyte antigen (HLA)-DR expression on monocytes.[23] Nevertheless, IIT is always associated with undesirable hypoglycemia.[23] As a consequence, most studies have suggested that the random BG of perioperative patients should be controlled within 10.0 mmol/L (180 mg/dL).[5,24] In this study, BGs at 3.9–10.0 mmol/L (70–180 mg/dL) were defined as the standard for effective BG control. BGs of >11.1 mmol/L (200 mg/dL) more than twice was defined as HG, referring to the recommended target value of American society of parenteral and enteral nutrition and the definition of stress-induced HG.[12]

In this study, we observed that nearly half of our patient population had developed HG during hospitalization, regardless of the treatment type. Gianotti et al studied the perioperative BG trend in nondiabetic patients undergoing major elective abdominal surgery and found that the maximum BGs were frequently observed at the end of the surgery.[4] We predict that HG occurrence in our patients was a comprehensive result of surgical stress, decreased physical activity, and SPN. Surgery and trauma increase the levels of counter regulatory hormones, such as glucagon, epinephrine, cortisol, and growth hormone, which collectively result in alterations in carbohydrate metabolism, including insulin resistance (IR), increased hepatic glucose production, impaired peripheral glucose utilization, and relative insulin deficiency.[18] These hormones in the stress setting lead to enhanced lipolysis and increased fatty acid concentration,[25] which also produce dose-dependent IR in peripheral tissues and increase hepatic glucose output in both diabetic and nondiabetic individuals.[12,26] Furthermore, bed rest has been demonstrated to diminish glucose uptake and insulin signaling by insulin-dependent tissues.[27] The patients in this study were on combined nutrition with oral intake and enteral and parenteral feeding. The individualized SPN provides up to 250 g/d of glucose and up to 30% of total calories from lipid emulsions, which may cause glucose overload and hypertriglyceridemia, which contribute to HG. Additionally, the infusion rate is another significant predictor of HG in patients during PN.[28] Although SPN improves patients' nutritional status, the exogenous infusion of glucose and fat emulsion may increase postoperative BG fluctuation.

Significant evidence indicates that both subcutaneous and intravenous insulin are effective in HG management during PN therapy.[28] The addition of insulin to TNA is physiologically convenient and less invasive.[5] However, research addressing the insulin dosage for PN-related HG management in nondiabetic patients is limited. Among these available studies, some suggest the use of 0.5 unit of insulin per 10 g of PN glucose for the management of perioperative HG.[6,29] One study recommended initiating 1 unit of insulin per 10 g of PN glucose when the patient was observed to have serum BG values >10 mmol/L (180 mg/dL) twice consecutively.[30] Insulin dosages were later titrated in increments of 0.05–0.1 unit per 1 g of PN glucose until BG become stable. Two randomized controlled trials have proposed determining the insulin dosage added to PN based on previous day readings and adjusting subcutaneous insulin according to correctional dosing protocol. Addition of insulin subcutaneously and directly had comparable efficacy in controlling BG in both critical and noncritical patients.[7,31] A retrospective study in noncritical adult patients who received general surgeries and postoperative PN recommended the regular addition of insulin to TNA rather

than long-acting insulin therapy for a high likelihood of achieving glycemic control.[32] However, robust practical evidence is still lacking to reach a consensus. This study tested the effectiveness of 1 unit of insulin per 6 g of glucose in PN, and this dosage was determined solely according to doctors' experience, which might be a common procedure in Chinese noncritical surgical departments, and the possibility of HG occurrence in perioperative patients has been ignored.

This study has several limitations that need to be taken care of in future research: First, we did not standardize the surgical procedures between the two groups because surgical approaches were determined based on the cancer type. To minimize variances, sensitivity analysis was performed. The relevant outcome indicators of patients undergoing open radical gastrectomy were analyzed, which did not change previous results. Furthermore, a logistic regression analysis of the patients with HG suggested that the choice of surgical procedure was not an independent factor. Second, glycated hemoglobin of patients with known diabetes history was not measured; thus, patients with preexisting diabetes or prediabetes were excluded based on BG at admission, which may not efficiently omit all patients with diabetes. In addition, patients with preexisting IR are more likely to experience HG compared with healthy individuals, irrespective of stress or PN status.[33] However, we were unable to evaluate the IR level of our patient population because of which we cannot rule out the possibility of IR-induced HG during hospitalization. Third, insulin treatment was determined by different attending doctors based on their experiences, as a standard treatment was absent. Therefore, this study was conducted to testify the effectiveness of the currently used therapy.

Conclusion

An increased risk of complications was observed in patients with perioperative HG, which therefore should be prevented carefully and managed effectively. The addition of 1 unit of insulin per 6 g of PN glucose to TNA can improve the overall BG control to a certain extent in patients with cancer receiving postoperative SPN. Further research is needed to make a confirmative recommendation on optimal insulin therapy in patients undergoing surgery for accurate glycemic control.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

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Table 1. Baseline characteristics of participants

	Noninsulin (n=119)	Insulin (n=89)	*p*-value
Sex [n (%)]			0.843†
Men	91 (76.5)	67 (75.3)	
Women	28 (23.5)	22 (24.7)	
Age [n (%)]			0.696†
< 65 years	78 (65.5)	56 (62.9)	
≥ 65 years	41 (34.5)	33 (37.1)	
BMI (kg/m^2)	21.94 ± 2.67	21.73 ± 3.16	0.615‡
Hypertension [n (%)]			0.282†
Yes	15 (12.6)	16 (18.0)	
No	104 (87.4)	73 (82.0)	
Admission VPG (mmol/L)	5.12 (4.75, 5.65)	5.07 (4.64, 5.73)	0.592§
Neoadjuvant chemotherapy [n (%)]			0.750†
Yes	44 (37.0)	31 (34.8)	
No	75 (63.0)	58 (65.2)	
pTNM [n (%)]			0.643†
I/II	63 (52.9)	50 (56.2)	
III/IV	56 (47.1)	39 (43.8)	
Operation approach [n (%)]			0.000†
Open gastrectomy	52 (43.7)	85 (95.5)	
Laparoscopic gastrectomy	67 (56.3)	4 (4.5)	
Surgery type [n (%)]			0.022†
Proximal gastrectomy	0	4 (4.5)	
Distal gastrectomy	59 (49.6)	51 (57.3)	
Total gastrectomy	60 (50.4)	34 (38.2)	
POD1 VPG (mmol/L)	5.91 (5.31, 6.78)	6.14 (5.45, 6.99)	0.228§
Pre-SPN HG [n (%)]			0.158†
Yes	5 (4.2)	8 (9.0)	
No	114 (95.8)	81 (91.0)	

VPG: venous plasma glucose; POD1: postoperative day 1; Pre-SPN HG: The returning to the ward capillary blood glucose to ≥11.1 mmol/L more than twice on the operation day; pTNM: pathological tumor – node – metastasis.
†Chi-square test.
‡Independent t-test.
§Mann-Whitney U test.

Table 2. BG concentrations and fluctuations during SPN

	Noninsulin (n=119)	Insulin (n=89)	*p*-value
Mean BGs during SPN (mmol/L)	8.35 (7.45, 9.14)	7.35 (6.67, 8.40)	0.000‡
Highest BGs during SPN (mmol/L)	12.3 (10.7, 14.5)	10.4 (8.8, 12.2)	0.000‡
BGCR (%)	75.0 (58.3, 90.9)	91.67 (83.3, 100)	0.000‡
During SPN Hypoglycemia [n (%)]			0.182§
Yes	0 (0)	2 (2.2)	
No	119 (100)	87 (97.8)	
During SPN HG [n (%)]			0.000¶
Yes	58 (48.7)	17 (19.1)	
No	61 (51.3)	72 (80.9)	
Classification of postoperative HG† [n (%)]			0.000§
Persistent	3 (2.5)	3 (3.4)	
Improved	2 (1.7)	5 (5.6)	
Late-onset	55 (46.2)	14 (15.7)	
Non-HG	59 (49.6)	67 (75.3)	
CV (%)	28.58 (23.06, 34.12)	21.14 (16.79, 26.29)	0.000‡
FCG-CV (%)	18.84 (12.24, 25.93)	14.43 (8.15, 20.31)	0.003‡
LAGE (mmol/L)	7.2 (5.7, 9.7)	5.0 (4.0, 6.7)	0.000‡

BG: blood glucose; SPN: supplementary parenteral nutrition; BGCR: blood glucose control rate; During-SPN HG: BG of ≥11.1 mmol/L more than twice during SPN; CV: coefficient of variation; FCG-CV: fasting capillary glucose-coefficient of variation; LAGE: largest amplitude of glycemic excursions.

†The classification of postoperative HG was determined according to HG occurrence before and during SPN.

‡Mann–Whitney U test.

§Fisher's exact test.

¶Chi-square test

Table 3. Postoperative complications

	Noninsulin (n=119)	Insulin (n=89)	*p*-value
CI	0 (0, 8.66)	0 (0, 12.25)	0.761†
Postoperative infection			0.608‡
No	97 (81.5)	68 (76.4)	
Grade I–II	19 (16.0)	19 (21.3)	
Grade III–V	3 (2.5) §	2 (2.2)¶	

CI: comprehensive complications index.
†Mann–Whitney U test.
‡Fisher's exact test.
§The three patients were sepsis shock induced by pulmonary infection, severe incision suppuration, and adhesive intestinal obstruction, respectively.
¶The severe infection complications of these two patients were due to abdominal bleeding and anastomotic leakage

Table 4. Hyperglycemia (HG) and postoperative complications

	HG (n=82)	Non-HG (n=126)	*p*-value
CI	8.66 (0, 20.92)	0 (0, 8.66)	0.002†
Postoperative infection			0.324‡
No	61 (74.4)	104 (82.5)	
Grade I–II	19 (23.2)	19 (15.1)	
Grade III–V	2 (2.4)	3 (2.4)	

CI: comprehensive complications index.
†Mann–Whitney U test.
‡Fisher's exact test

Table 5. Relationships between different classifications of postoperative hyperglycemia and complication rates

	Persistent HG (n=6)	Improved HG (n=7)	Late-onset HG (n=69)	Non-HG (n=126)	*p*-value
CI	8.66(0, 14.20)	0 (0, 22.64)	8.66 (0, 20.92)	0 (0, 8.66)	0.024†
Postoperative infection					0.585‡
No	4 (66.7)	5 (71.4)	52 (75.4)	104 (82.5)	
Grade I–II	2 (33.3)	2 (28.6)	15 (21.7)	19 (15.1)	
Grade III–V	0	0	2 (2.9) §	3 (2.4) ¶	

CI: comprehensive complications index; HG: hyperglycemia.
†Mann–Whitney U test.
‡Fisher's exact test.
§The two patients had sepsis shock due to pulmonary infection and severe incision suppuration, respectively.
¶The severe infection complications of these three patients were due to abdominal bleeding, anastomotic leakage, and adhesive intestinal obstruction

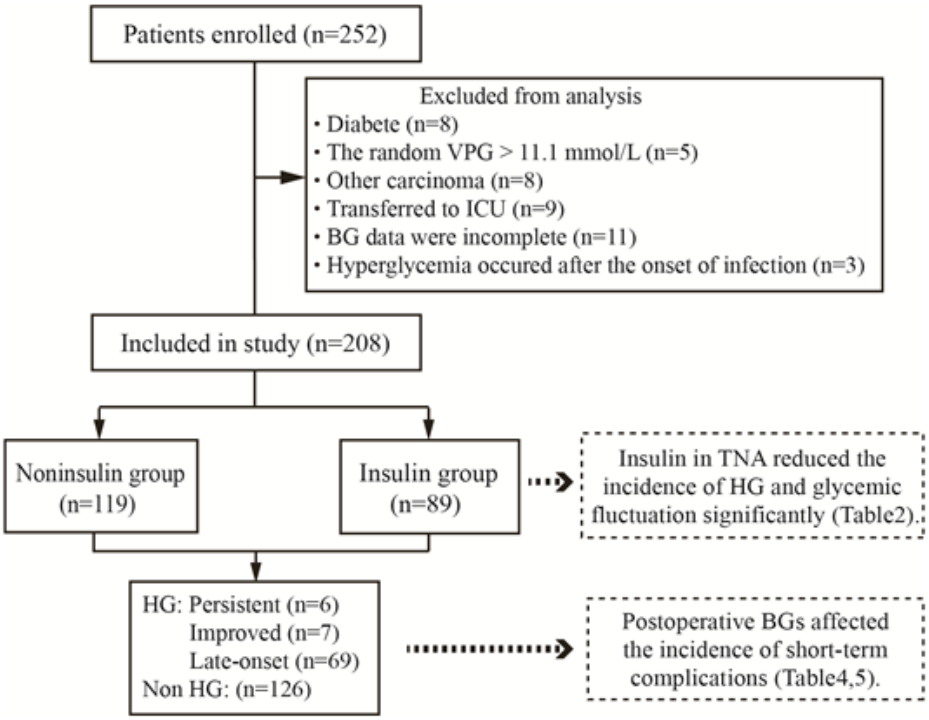

Figure 1. Flowchart of patient selection.

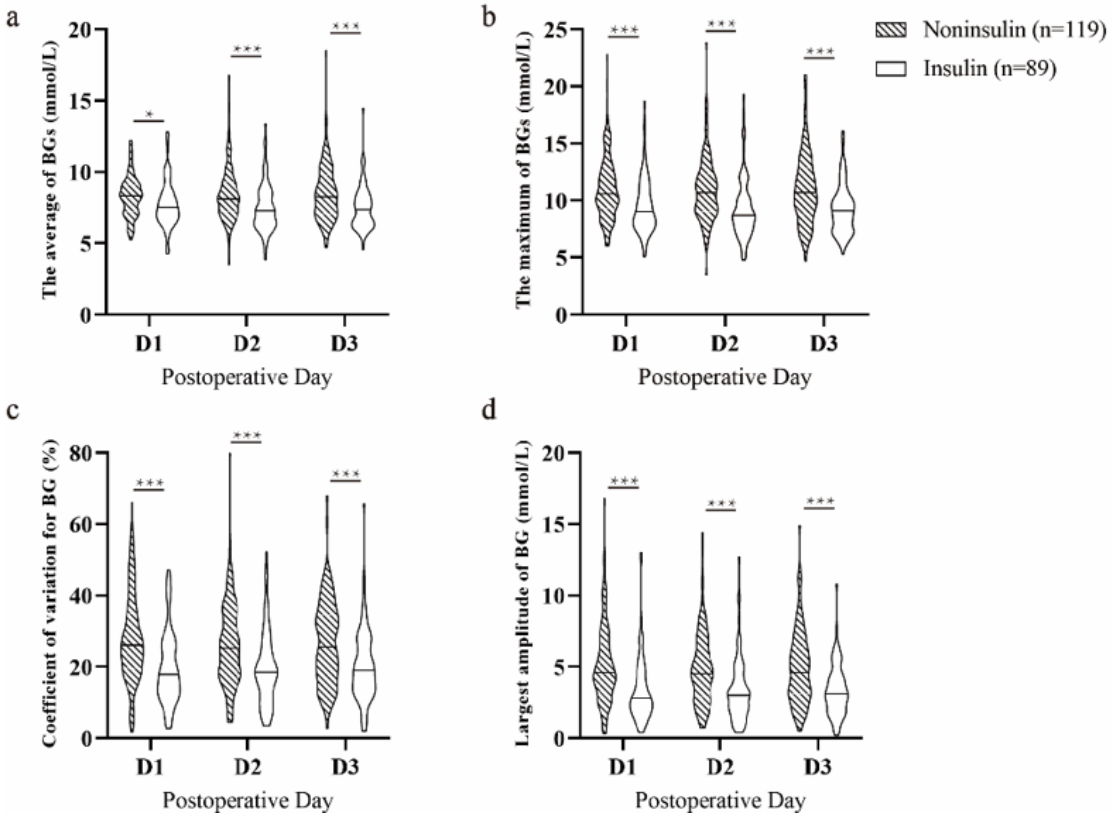

Figure 2. The (a) mean blood glucose (BG), (b) highest BG, (c) coefficient of variation, and (d) fluctuation range on days 1–3 of the supplementary parenteral nutrition period. The violin diagrams show all values, where the black line represents the median. $^{*}p<0.05$, $^{***}p<0.001$.