Insulin Treatment Is Associated With Increased Mortality in Critically Ill Patients With Type 2 Diabetes in the Intensive Care Unit

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Research

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Abstract

Aims: Although insulin treatment is widely used in critically ill patients with type 2 diabetes mellitus in the intensive care unit (ICU), the clinical outcomes of insulin treatment remain unclear. This retrospective study aimed to explore the impact of insulin treatment on mortality and ICU stay among patients with type 2 diabetes.

Methods: We consecutively recruited 578 ICU patients with type 2 diabetes, from 2011 to 2021. According to their medication history regarding insulin use before and after ICU admission, these patients were categorized into three groups: N-N (treated without insulin before and after ICU admission), N-I (treated without insulin before and with insulin after ICU admission) and I-I (treated with insulin before and after ICU admission). Clinical characteristics were analyzed, and clinical outcomes including mortality and the length of ICU stay were compared between the groups. Propensity score matching was performed to obtain comparable subpopulation and the Kaplan-Meier survival curves were graphed to describe the survival trend of different groups.

Results: Compared with the N-N group, the N-I and I-I groups had significantly higher ICU mortality rates [20.0% (N-I) and 24.6% (I-I) *vs.* 0.0% (N-N); $p < 0.001$; respectively] and longer lengths of ICU stay [8.5 (N-I), 9 (I-I) vs. 6 (N-N), $p < 0.05$, respectively]. After propensity score matching, the N-I group had a significantly higher ICU mortality (15.4% *vs.* 0.0%, $p = 0.025$) and poorer survival rates (log-rank $p = 0.040$) than the N-N group. The length of ICU stay was significantly longer in the I-I group than in the N-N group (10 *vs.* 7, $p = 0.026$).

Conclusions: Insulin treatment was associated with increased ICU mortality rate and longer length of ICU stay among critically ill patients with type 2 diabetes. Caution is warranted for the regular application of insulin in critical patients with type 2 diabetes.

Introduction

Diabetes has the fastest increasing incidence of all the disease worldwide, and it poses a major threat to global health [1, 2]. The proportion of patients with type 2 diabetes admitted to the intensive care unit (ICU) is also growing [3]. One study reported a mortality rate of 36.0% in ICU patients with type 2 diabetes, compared with 29.1% in those without diabetes, which indicated that critically ill patients with type 2 diabetes tend to have worse outcomes and prognoses [4]. Thus, glycemic care of critically ill patients with type 2 diabetes is an important part of treatment besides regulating their homeostatic function and stress response [5, 6]. Suitable glucose control in critically ill patients was recommended for a better clinical outcome, and insulin is widely used as a classic, direct, and effective anti-diabetic agent [7, 8]. Traditionally, insulin treatment was always applied in type 2 diabetes patients when the function of pancreatic islet beta cells fail to compensate for the ongoing insulin resistance [9] and patients have complicated comorbidities such as chronic kidney disease [10]. Along with the definition of “intensive insulin therapy,” the time of insulin initiation is getting earlier, even in newly diagnosed type 2 diabetes

patients [11–13]. A recent notable publication, the *guideline for the prevention and treatment of type 2 diabetes mellitus in China (2020edition)*, indicated that insulin could be used when the level of glycosylated hemoglobin (HbA1c) exceeds 7.0%, even when the pancreatic islet function was existent at that time [14].

Although previous studies demonstrated that insulin therapy for critical illness decreased mortality in certain patients [15, 16], some research reported that insulin was also related to an increased cardiovascular risk as well as worsened mortality rates [17–19]. A large randomized trial found that intensive glucose control increased mortality in adults admitted in the ICU, compared with conventional blood glucose control [20]. Other similar studies also found that insulin-treated diabetes was associated with a significantly worse prognosis in patients with advanced heart failure [21]. Our previous study has demonstrated that insulin treatment for patients with coronavirus disease 2019 (COVID-19) and type 2 diabetes was associated with a significant increase in mortality and enhanced systemic inflammation in the ICU [22]. Therefore, in critically ill patients, it is still inconclusive whether insulin treatment has adverse consequences in addition to its beneficial effect in lowering blood glucose.

Accordingly, we conducted a retrospective, observational, exploratory study to assess the effect of insulin treatment on clinical outcomes in patients with type 2 diabetes admitted to the ICU. We investigated whether insulin treatment was associated with adverse clinical outcomes such as mortality and length of ICU stay in patients with type 2 diabetes. This would enable clinicians to have a better understanding of insulin treatment in patients with type 2 diabetes in the ICU.

Methods

Study design

This retrospective study investigated 791 patients with type 2 diabetes from 4005 patients admitted to the ICU between March 2011 and February 2021 in Tongji Hospital Wuhan, China. After excluding the patients who met the exclusion criteria, further analysis was conducted on 578 critically ill patients with type 2 diabetes, whose clinical information was well detailed (Fig. 1**)**. Type 2 diabetes was diagnosed according to a self-reported medical history or the use of anti-diabetic agents or insulin as chronic medication. Alternatively, newly diagnosed type 2 diabetes was based on HbA1c ≥ 6.5% and/or random plasma glucose ≥ 11.1 mmol/L [14] and clearly classified as type 2 diabetes in the medical record system. Considering that critically ill patients are prone to having stress-induced hyperglycemia, we did not enroll patients with only a random plasma glucose ≥ 11.1 mmol/L, but HbA1c < 6.0% and without a history of diabetes. Patients diagnosed with iatrogenic diabetes during hospitalization were not enrolled in this study. This study was approved by the institutional review board of Tongji Hospital (IRBID: TJ-IRB20200229).

Patients' information

Patients were admitted under the following inclusion criteria: (1) age ≥ 18 years; (2) length of ICU stay ≥ 3 days. Patients were excluded under the following exclusion criteria: (1) age ≥ 85 years; (2) previous

glycemic control methods were unknown; (3) missing all or almost all data on laboratory characteristics and clinical characteristics; and (4) type 1 diabetes mellitus. Patients were categorized based on glycemic control methods before and after ICU admission. The previous glycemic control methods were based on a self-reported medication history or a prescription record. Patients receiving treatment without insulin (oral anti-diabetic agents, lifestyle intervention, or without any intervention) before and after ICU admission were defined as the N-N group (n = 50). Patients undergoing treatment without insulin before ICU admission but treated with insulin after admission were defined as the N-I group (n = 300). Patients receiving insulin treatment before and after ICU admission were defined as the I-I group (n = 228). The flowchart of study design is shown in Fig. 1.

Data collection and endpoints definitions

We reviewed the clinical records and laboratory data of all the patients. Data was collected and checked independently by two study investigators. We extracted demographic data, medical history, laboratory findings, and data on in-hospital therapies through the electronic medical records. The glycemic control methods before and after ICU admission were shown in **Supplementary Table 1 (Additional file 1)**. Laboratory test results included blood routine, liver and renal function, random blood glucose, glycated hemoglobin, blood electrolyte, coagulation function, myocardial marker. All laboratory values were based upon the first measurement on ICU admission. If serum chemistry measurements were not tested on ICU admission, then the most recent values measured close to the first day of ICU admission were used. The endpoints were defined as all-cause death during hospitalization and the length of ICU stay. All the data mentioned above were compared among the three groups.

Data analyses

Categorical variables were calculated as frequencies and percentages. Continuous variables were described as mean (standard deviation), and skewed data were described as median (interquartile range). The three groups were compared using the *Pearson's chi-square* or the *Fisher's exact test* for categorical variables, and the continuous data were analyzed with the *one-way ANOVA*, independent *t* test, or *Mann-Whitney* test. The baseline characteristics and clinical outcomes were compared among all patients before propensity score matching (PSM). Then, the clinical outcomes were further analyzed in the propensity score matched sub-population. The age, gender; diabetic complications; histories of hypertension, coronary heart disease, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, sepsis, cancer, COVID-19, shock, acute myocardial infarction (AMI), smoking, and drinking; and the baseline levels of eGFR, albumin (ALB), and C-reactive protein (CRP) were used for PSM analysis. Calipers of 0.05 on the propensity score scale were used between the N-N and N-I group as well as between the N-I and I-I group. To obtain more matching people for more reliable results, the matching caliper value between N-N and I-I group was adjusted to 0.1. The survival curves were graphed to describe the survival status of each group of patients. Statistical analyses were conducted with *SPSS* (version 26.0) software. Figures were plotted with GraphPad Prism 8. $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics and clinical outcomes of ICU patients with type 2 diabetes.

The basic characteristics and clinical outcomes of all 578 patients are shown in Table 1. Among the ICU patients with type 2 diabetes, 372 (64.4%) were male and 206 (35.6%) were female. The average age was 62.2 years. The proportions of males, prevalence of coronary heart disease, and AMI in the N-I and I-I groups were significantly lower than those in the N-N group ($p < 0.05$ for both). The proportions of those with sepsis and shock in the N-I and I-I groups were both significantly higher than those in the N-N group ($p < 0.05$ for both). The duration of diabetes in the I-I group was significantly longer than those in the N-N and N-I groups [10 (7–20) vs. 3.5 (0-8.25) and 10 (7–20) vs. 4 (0–10); $p < 0.001$ for both]. The prevalence of chronic kidney disease in the I-I group was significantly higher than that in the N-N group ($p < 0.001$). The prevalence rates of diabetic nephropathy, diabetic cardiovascular disease, diabetic peripheral neuropathy, coronary heart disease, chronic kidney disease in the I-I group were significantly higher than those in the N-I group (all $p < 0.05$).

Table 1
Baseline characteristics, laboratory parameters and clinical outcomes of ICU patients with T2DM before propensity score matching.

Variable	Total population (*n* = 578)	N-N (*n* = 50)	N-I (*n* = 300)	I-I (*n* = 228)	*p* value
Baseline characteristics					
Age	62.24 ± 12.15	60.76 ± 10.77	61.99 ± 12.67	62.91 ± 11.73	0.459
Age range (≧ 60), *n* (%)	351 (60.7)	30 (60.0)	177 (59.0)	144 (63.2)	0.622
Gender, male	372 (64.4)	41 (82.0)	190 (63.3)†	141 (61.8) ‡	0.023
Duration of diabetes (years)	7 (2–10)	3.5 (0-8.25)	4 (0–10)	10 (7–20) ‡,§	< 0.001
Diabetic complications, n (%)					
Diabetic nephropathy	92 (15.9)	2 (4.0)	28 (9.3)	62 (27.2) ‡,§	< 0.001
Diabetic retinopathy	19 (3.3)	0 (0.0)	9 (3.0)	10 (4.4)	0.308
Diabetic cardiovascular disease	19 (3.3)	2 (4.0)	3 (1.0)	14 (6.1)§	0.003
Diabetic peripheral neuropathy	43 (7.4)	2 (4.0)	16 (5.3)	25 (11.0)§	0.036
DKA	26 (4.5)	0 (0.0)	14 (4.7)	12 (5.3)	0.272
HHS	9 (1.6)	0 (0.0)	5 (1.7)	4 (1.8)	1.000
Original comorbidities, *n* (%)					
Hypertension	351 (60.7)	33 (66.0)	174 (58.0)	144 (63.2)	0.353
Coronary heart disease	231 (40.0)	42 (84.0)	96 (32.0) †	93 (40.8) ‡,§	< 0.001
COPD	31 (5.4)	1 (2.0)	16 (5.3)	14 (6.1)	0.572
Chronic kidney disease	145 (25.1)	4 (8.0)	52 (17.3)	89 (39.0) ‡,§	< 0.001

Variable	Total population (*n* = 578)	N-N (*n* = 50)	N-I (*n* = 300)	I-I (*n* = 228)	*p* value
Chronic liver disease	87 (15.1)	11 (22.0)	46 (15.3)	30 (13.2)	0.280
Sepsis	72 (12.5)	1 (2.0)	41 (13.7) †	30 (13.2) ‡	0.063
Cancer	50 (8.7)	1 (2.0)	32 (10.7)	17 (7.5)	0.086
COVID 19	29 (5.0)	1 (2.0)	19 (6.3)	9 (3.9)	0.335
Shock	49 (8.5)	0 (0.0)	28 (9.3) †	21 (9.2) ‡	0.045
AMI	103 (17.8)	26 (52.0)	44 (14.7) †	33 (14.5) ‡	< 0.001
Smoker, *n* (%)	195 (33.7)	25 (50.0)	104 (34.7) †	66 (28.9) ‡	0.015
Drinker, *n* (%)	100 (17.3)	14 (28.0)	54 (18.0)	32 (14.0) ‡	0.055
Laboratory parameters					
Routine blood test					
White-cell count, $\times 10^9$ /L	10.01 (7.19–4.09)	9.13 (7.65–12.28)	10.19 (7.20-14.65)	10.02 (6.93–14.21)	0.597
Neutrophil count, $\times 10^9$ /L	8.17 (5.43–12.27)	7.11 (5.46–10.15)	8.25 (5.53–12.74)	8.41 (5.28–12.20)	0.226
Lymphocyte count, $\times 10^9$ /L	0.98 (0.60–1.46)	1.32 (0.90–1.90)	0.96 (0.60–1.49) †	0.95 (0.54–1.39) ‡	< 0.001
Monocyte count, $\times 10^9$ /L	0.56 (0.35–0.82)	0.65 (0.38–0.82)	0.57 (0.34–0.81)	0.53 (0.37–0.82)	0.387
Platelet count, $\times 10^9$ /L	178.00 (118.00-236.00)	217.00 (184.25-268.25)	164 (105–228) †	179.00 (115.00-238.00) ‡	< 0.001
Hemoglobin, g/L	111.30 ± 28.62	129.74 ± 18.40	113.89 ± 28.31†	103.82 ± 28.52‡,§	< 0.001
Blood biochemistry					
ALT, U/L	21 (13–38)	29.50 (18.75-48.00)	22.00 (14.00-40.25)	18.00 (11.00-34.75) ‡,§	< 0.001

Variable	Total population (*n* = 578)	N-N (*n* = 50)	N-I (*n* = 300)	I-I (*n* = 228)	*p* value
AST, U/L	29.00 (19.00–60.00)	35.50 (22.50–150.00)	31.00 (20.00–69.00)	26.00 (18.00–47.00) ‡,§	0.002
Albumin, g/L	33.05 ± 7.16	40.46 ± 4.15	32.52 ± 7.45†	32.11 ± 6.34‡	< 0.001
Total bilirubin, μmol/L	9.35 (6.00 -15.55)	10.10 (7.40–14.60)	10.75 (6.73–17.90)	7.90 (4.80–12.70) ‡,§	< 0.001
Direct bilirubin,mmol/L	3.90 (2.50–6.68)	4.15 (3.03–6.10)	4.50 (2.55–7.80)	3.30 (2.20–5.35) ‡,§	0.001
Total cholesterol, mmol/L	3.60 (2.73–4.43)	4.08 (3.38–4.75)	3.63 (2.66–4.47) †	3.48 (2.71–4.36) ‡	0.007
Triglyceride, mmol/L	1.34 (0.97–2.07)	1.20 (0.80–1.71)	1.41 (0.98–2.22) †	1.33 (1.00-1.93)	0.105
HDL, mmol/L	0.80 ± 0.35	0.98 ± 0.29	0.75 (0.52–0.98) †	0.80 ± 0.35‡	< 0.001
LDL, mmol/L	2.02 (1.30–2.82)	2.57 (2.11–3.39)	2.00 (1.18–2.82) †	1.83 (1.28–2.53) ‡	< 0.001
CK,U/L	144.50 (59.00-437.25)	525.50 (85.75–2107.00)	148.00 (61.00-508.00) †	128.00 (54.50-296.50) ‡	0.001
LDH,U/l	288.00 (209.00-441.75)	302.00 (208.50–528.00)	288.00 (209.00-505.00)	280.00 (213.00-403.00)	0.507
UA,umol/L	341.15 (249.25–476.00)	341.15 (287.75–470.00)	325.20 (225.20-463.50)	362.00 (259.00-492.20)	0.238
Creatinine, μmol/L	101.00 (68.00-208.50)	76.50 (64.75–97.25)	88.00 (63.00-168.00) †	134.50 (81.25–298.50) ‡, c	< 0.001
Blood urea nitrogen, mmol/L	8.80 (5.50-15.21)	5.15 (4.36–5.95)	8.27 (5.15–13.65) †	10.91 (6.91–19.24) ‡,§	< 0.001
eGFR mL/min	61.90 (26.18–93.18)	90.95 (72.95–97.88)	70.25 (33.18–97.85) †	42.05 (15.38–75.30) ‡,§	< 0.001
PCT,ng/mL	1.00 (0.26–7.35)	0.06 (0.04–25.15)	0.95 (0.24–7.64) †	1.06 (0.37–6.59) ‡	0.069

Variable	Total population (*n* = 578)	N-N (*n* = 50)	N-I (*n* = 300)	I-I (*n* = 228)	*p* value
NT-ProBNP, pg/mL	2251.50 (500.75-8283.75)	620.50 (158.50-2258.25)	1552.00 (388.00-6992.50) †	4476.00 (1144.00-15565.50) ‡,§	< 0.001
cTnI, pg/mL	41.05 (3.80-839.25)	2648.95 (20.28-41559.20)	34.70 (3.65-607.38) †	33.30 (2.63-475.25) ‡	< 0.001
Myoglobin, μg/L	179.65 (67.88-534.65)	147.60 (44.25-1200.10)	167.95 (65.63-566.38)	201.20 (82.70-496.40)	0.870
CK-MB, ng/mL	3.05 (1.20–9.53)	17.40 (1.15-148.85)	3.45 (1.30–8.93) †	2.50 (1.10-7.00) ‡	0.009
Glucose, mmol/L	11.89 (8.97–15.82)	10.14 (8.65–11.45)	11.38 (8.75–15.73) †	12.79 (9.96–16.50) ‡,§	< 0.001
Lactate, mmol/L	2.22 (1.44–3.52)	1.00 (0.77–7.25)	2.48 (1.50–3.71)	1.97 (1.45–3.10)	0.069
HbA1c, %	7.50 (6.50–9.30)	6.90 (6.30-8.00)	7.80 (6.60–9.60) †	7.55 (6.43–9.40)	0.024
Potassium (mmol/L)	4.13 (3.73–4.65)	3.97 (3.70–4.16)	4.07 (3.67–4.63)	4.35 (3.84–4.87) ‡,§	< 0.001
Sodium (mmol/L)	138.50 (135.58–141.40)	138.60 (136.43-140.68)	138.70 (135.83–142.00)	138.10 (135.00-140.80)	0.204
Chloride (mmol/L)	100.60 (96.70-104.60)	99.90 (98.00-102.45)	101.00 (96.73-105.08)	100.60 (96.50-103.98)	0.395
Calcium (mmol/L)	2.13 (2.00-2.25)	2.24 (2.15–2.31)	2.12 (1.99–2.25) †	2.12 (1.98–2.23) ‡	< 0.001
Bicarbonate (mmol/L)	21.10 (17.40–24.00)	23.20 (20.65–25.70)	21.00 (17.25-24.00) †	20.80 (16.68-24.00) ‡	0.001
Coagulation function					
PT, Sec	14.85 (13.80–16.60)	14.20 (13.10–15.00)	14.90 (13.80-16.78) †	14.90 (13.90–17.10) ‡	0.001
INR	1.17 (1.07–1.33)	1.10 (0.99–1.17)	1.18 (1.07–1.37) †	1.18 (1.08–1.37) ‡	< 0.001

Variable	Total population (*n* = 578)	N-N (*n* = 50)	N-I (*n* = 300)	I-I (*n* = 228)	*p* value
FIB,g/L	4.45 (3.21–5.92)	3.46 (2.93–4.14)	4.55 (3.12–5.94) †	4.60 (3.40–6.13) ‡	0.001
APTT, Sec	41.90 (36.60–50.80)	40.50 (35.78–172.20)	41.95 (36.60-50.75)	41.90 (37.65–49.20)	0.765
TT, Sec	16.90 (15.90–18.80)	16.95 (16.08–240.10)	16.70 (15.73–18.38)	17.10 (15.90–18.80)	0.119
D-dimer, ug/mL	1.73 (0.63–4.05)	0.41 (0.26–0.80)	2.09 (0.70–5.47) †	1.73 (0.77–3.81) ‡	< 0.001
Infection-related indices					
C-reactive protein, mg/L	47.80 (8.23–133.80)	6.70 (2.10–17.50)	59.40 (11.70-162.08) †	54.80 (12.30-130.25) ‡	< 0.001
ESR,mm/H	22.50 (8.00-49.25)	10.00 (4.00-19.50)	23.00 (7.50–41.00) †	37.00 (12.00–64.00) ‡,§	< 0.001
IL-6,pg/ml	63.45 (21.92–150.10)	14.95 (9.66–33.57)	64.84 (25.17-165.63) †	70.28 (22.54-123.99) ‡	0.034
Hypoglycemia at ICU stay, *n* (%)					
Blood glucose ≤ 3.9 mmol/L	60 (10.4)	1 (2.0)	26 (8.7)	33 (14.5) ‡,§	0.012
Blood glucose ≤ 3.0 mmol/L	27 (4.7)	0 (0.0)	14 (4.7)	13 (5.7)	0.236
Clinical outcomes					
Length of ICU stay (days)	8 (5–14)	6 (4–8)	8.5 (5–14) †	9 (5-15.75) ‡	0.001
Mortality, *n* (%)	116 (20.1)	0 (0.0)	60 (20.0) †	56 (24.6) ‡	< 0.001

Variable	Total population (n = 578)	N-N (n = 50)	N-I (n = 300)	I-I (n = 228)	p value
Data were presented as n (%), mean ± SD, and median (interquartile range). N-N group was composed of patients received treatment without insulint before and after ICU admission. N-I group was composed of patients received treatment without insulin before ICU admission but received insulin treatment after ICU admission. I-I group was composed of patients received insulin treatment before and after ICU admission. Abbreviations: DKA, diabetic ketoacidosis; HHS, hyperglycemic hyperosmolar state; COPD, chronic obstructive pulmonary disease; AMI, acute myocardial infarction. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; LDH, lactate dehydrogenase; UA, uric acid; PCT, procalcitonin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; cTnI, cardiac troponin I; CK-MB, creatinine kinase MB; PT, prothrombin time; INR, international normalized ratio; FIB, fibrinogen; APTT, activated partial thromboplastin time; TT, thrombin time; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; NA, not applicable.					
The p value indicates differences among the N-N, N-I and I-I groups.					
† indicates significant differences among the N-I group *vs.* the N-N group.					
‡ indicates significant differences among the I-I group *vs.* the N-N group.					
§ indicates significant differences among the I-I group *vs.* the N-I group.					
p < 0.05 was considered statistically significant.					

The laboratory parameters on ICU admission were also recorded. The levels of lymphocyte count, hemoglobin, albumin, total cholesterol, eGFR, cardiac troponin I were significantly lower in the N-I and I-I groups than in the N-N group (p < 0.05 for both). In contrast, the levels of creatinine, amino-terminal pro-brain natriuretic peptide (NT-ProBNP), CRP, erythrocyte sedimentation rate (ESR), and serum IL-6 in the N-I and I-I groups were significantly higher than those in the N-N group (p < 0.05 for both). The levels of triglyceride, glucose, HbA1c were significantly higher in the N-I group than in the N-N group (p < 0.05). The I-I group had lower levels of ALT, AST, total bilirubin, and higher levels of potassium than the N-N and N-I groups (p < 0.05). The I-I group had lower levels of hemoglobin, ALT, AST, total bilirubin, eGFR and higher levels of creatinine, blood urea nitrogen, NT-ProBNP, glucose, potassium, ESR than the N-I group (p < 0.05). During hospitalization, the incidence of hypoglycemia was higher in the I-I group than in the N-N and N-I groups [14.5% (33/228) *vs.* 2.0% (1/50) and 14.5% (33/228) *vs.* 8.7% (26/300); p < 0.05 for both].

The clinical outcomes are shown at the bottom of Table 1. Compared with the N-N group, the N-I and I-I groups had longer length of ICU stay [8.5 (5–14) *vs.* 6 (4–8) and 9 (5-15.75) *vs.* 6 (4–8); p < 0.05 for both] and significantly increased mortality rates [20.0% (60/300) vs. (0.0% (0/50) and 24.6% (56/228) vs. (0.0% (0/50); p < 0.001 for both]. The *Kaplan-Meier survival analysis* showed a significantly poorer survival in the N-I and I-I groups than in the N-N group (log-rank p = 0.024 for N-N vs. N-I group and log-rank p = 0.010 for N-N vs. I-I group) (Fig. 2a).

Compared with the N-N group, the N-I group had higher mortality after PSM

To investigate the clinical outcomes between the N-I and N-N groups, PSM was performed to avoid bias. The N-I and N-N groups were defined as the N-N-PSM group and the N-I-PSM group after PSM was performed. Except for some variables (platelet count, blood urea nitrogen, INR, D-dimer) that differed, the baseline characteristics were comparable between these two groups (all $p > 0.05$) (Table 2). There were no markedly differences in the length of ICU stay between the N-I-PSM and N-N-PSM groups [7 (5–9) *vs.* 6 (4–8), $p = 0.172$]. Mortality rate was significantly higher [15.4% (6/39) vs. 0.0% (0/39), $p = 0.025$] in the N-I-PSM group than in the N-N-PSM group (Table 2). The *Kaplan-Meier survival analysis* showed a significantly poorer survival in the N-I-PSM group than in the N-N-PSM group (log-rank $p = 0.040$) (Fig. 2b). Since there was no event in the N-N group, the hazard ratio was not calculated.

Table 2
Comparison of baseline characteristics, laboratory parameters and clinical outcomes between the N-N-PSM and N-I-PSM groups.

Variable	Total population (*n* = 78)	N-N-PSM (*n* = 39)	N-I-PSM (*n* = 39)	*p* value
Baseline characteristics				
Age	61.64 ± 11.99	61.05 ± 10.54	62.23 ± 13.40	0.667
Age range (≥ 60), *n* (%)	46 (59.0)	23 (59.0)	23 (59.0)	1.000
Gender, male	20 (25.6)	9 (23.1)	11 (28.2)	0.604
Duration of diabetes (years)	2.00 (0.00–6.00)	3.00 (0.00–10.00)	1.50 (0.00-5.75)	0.370
Diabetic complications, n **(%)**				
Diabetic nephropathy	1 (1.3)	1 (2.6)	0 (0.0)	1.000
Diabetic retinopathy	0 (0.0)	0 (0.0)	0 (0.0)	NA
Diabetic peripheral neuropathy	3 (3.8)	2 (5.1)	1 (2.6)	1.000
DKA	0 (0.0)	0 (0.0)	0 (0.0)	NA
HHS	0 (0.0)	0 (0.0)	0 (0.0)	NA
Original comorbidities, n **(%)**				
Hypertension	47 (60.3)	24 (61.5)	23 (59.0)	0.817
Coronary heart disease	59 (75.6)	31 (79.5)	28 (71.8)	0.429
COPD	1 (1.3)	1 (2.6)	0 (0.0)	1.000
Chronic kidney disease	9 (11.5)	4 (10.3)	5 (12.8)	1.000
Chronic liver disease	15 (19.2)	7 (17.9)	8 (20.5)	0.774

Data were presented as *n* (%), mean ± SD, and median (interquartile range). The N-N-PSM and N-I-PSM groups were propensity score matched sub-populations between the N-N and N-I groups. The N-N group was composed of patients treated without insulin before and after ICU admission. The N-I group was composed of patients received treatment without insulin before ICU admission but received insulin treatment after ICU admission. Abbreviations: DKA, diabetic ketoacidosis; HHS, hyperglycemic hyperosmolar state; COPD, chronic obstructive pulmonary disease; AMI, acute myocardial infarction. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; LDH, lactate dehydrogenase; UA, uric acid; PCT, procalcitonin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; cTnI, cardiac troponin I; CK-MB, creatinine kinase MB; PT, prothrombin time; INR, international normalized ratio; FIB, fibrinogen; APTT, activated partial thromboplastin time; TT, thrombin time; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; NA, not applicable.

Variable	Total population (n = 78)	N-N-PSM (n = 39)	N-I-PSM (n = 39)	p value
Sepsis	2 (2.6)	1 (2.6)	1 (2.6)	1.000
Cancer	2 (2.6)	1 (2.6)	1 (2.6)	1.000
COVID 19	3 (3.8)	1 (2.6)	2 (5.1)	1.000
Shock	0 (0.0)	0 (0.0)	0 (0.0)	NA
AMI	38 (48.7)	19 (48.7)	19 (48.7)	1.000
Smoker, *n* (%)	40 (51.3)	20 (51.3)	20 (51.3)	1.000
Drinker, *n* (%)	9 (23.1)	9 (23.1)	9 (23.1)	1.000
Laboratory parameters				
Routine blood test				
White-cell count, ×10 ^{9} /L	10.33 ± 4.63	10.09 ± 3.64	10.56 ± 5.49	0.659
Neutrophil count, ×10 ^{9} /L	7.97 ± 4.26	7.83 ± 3.55	8.12 ± 4.91	0.764
Lymphocyte count, ×10 ^{9} /L	1.30 (0.90–1.79)	1.21 (1.00-1.80)	1.50 (0.80–1.79)	0.897
Monocyte count, ×10 ^{9} /L	0.65 (0.44–0.85)	0.69 (0.38–0.84)	0.62 (0.46–0.89)	0.893
Platelet count, ×10 ^{9} /L	207.00 (162.75-270.25)	223.00 (185.00-275.00)	190.00 (145.00-270.00)	0.033
Hemoglobin, g/L	130.00 (116.50-139.50)	133.00 (115.00-139.00)	129.00 (117.00-144.00)	0.865
Blood biochemistry				
ALT, U/L	29.50 (17.75-48.00)	30.00 (18.00–48.00)	29.00 (17.00–49.00)	0.865

Data were presented as *n* (%), mean ± SD, and median (interquartile range). The N-N-PSM and N-I-PSM groups were propensity score matched sub-populations between the N-N and N-I groups. The N-N group was composed of patients treated without insulin before and after ICU admission. The N-I group was composed of patients received treatment without insulin before ICU admission but received insulin treatment after ICU admission. Abbreviations: DKA, diabetic ketoacidosis; HHS, hyperglycemic hyperosmolar state; COPD, chronic obstructive pulmonary disease; AMI, acute myocardial infarction. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; LDH, lactate dehydrogenase; UA, uric acid; PCT, procalcitonin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; cTnI, cardiac troponin I; CK-MB, creatinine kinase MB; PT, prothrombin time; INR, international normalized ratio; FIB, fibrinogen; APTT, activated partial thromboplastin time; TT, thrombin time; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; NA, not applicable.

Variable	Total population (n = 78)	N-N-PSM (n = 39)	N-I-PSM (n = 39)	p value
AST, U/L	34.00 (21.00-134.00)	29.00 (20.00-144.00)	34.00 (22.00-107.00)	0.686
Albumin, g/L	40.59 ± 4.93	40.12 ± 4.50	41.06 ± 5.34	0.400
Total bilirubin, μmol/L	10.00 (7.08–16.15)	10.20 (7.50–14.60)	9.70 (7.00-16.60)	0.624
Direct bilirubin,mmol/L	4.30 (2.80-6.00)	4.50 (3.10–6.40)	3.80 (2.50–5.70)	0.223
Total cholesterol, mmol/L	4.16 ± 1.41	4.05 ± 1.05	4.28 ± 1.71	0.487
Triglyceride, mmol/L	1.24 (0.82–2.03)	1.20 (0.81–1.61)	1.30 (0.82–2.43)	0.316
HDL, mmol/L	0.96 ± 0.30	0.97 ± 0.30	0.95 ± 0.30	0.819
LDL, mmol/L	2.64 ± 1.23	2.62 ± 0.90	2.65 ± 1.51	0.902
CK,U/L	247.00 (79.00-1451.00)	415.50 (77.25-2006.50)	192.00 (79.00-634.00)	0.425
LDH,U/l	279.00 (208.00-442.00)	273.00 (193.00-516.00)	284.50 (208.75–397.00)	0.863
UA,umol/L	348.15 (282.10-476.93)	343.70 (284.00-477.00)	357.40 (276.40-476.90)	0.956
Creatinine, μmol/L	95.69 ± 62.88	90.05 ± 60.05	101.33 ± 65.87	0.432
Blood urea nitrogen, mmol/L	5.70 (4.42–7.47)	5.11 (4.29–6.10)	6.40 (5.10–9.20)	0.008
eGFR mL/min	85.00 (67.13–95.53)	90.20 (68.40–97.60)	84.20 (62.50–92.10)	0.267
PCT,ng/mL	0.20 (0.05–0.91)	0.12 (0.03–37.57)	0.29 (0.08–0.91)	0.289
NT-ProBNP, pg/mL	764.00 (184.50–2595.00)	764.00 (151.50–2554.00)	766.50 (192.50-3565.70)	0.774
cTnI, pg/mL	589.40 (20.03-9653.30)	840.00 (18.70-38329.70)	139.30 (20.20–5724.00)	0.342

Data were presented as n (%), mean ± SD, and median (interquartile range). The N-N-PSM and N-I-PSM groups were propensity score matched sub-populations between the N-N and N-I groups. The N-N group was composed of patients treated without insulin before and after ICU admission. The N-I group was composed of patients received treatment without insulin before ICU admission but received insulin treatment after ICU admission. Abbreviations: DKA, diabetic ketoacidosis; HHS, hyperglycemic hyperosmolar state; COPD, chronic obstructive pulmonary disease; AMI, acute myocardial infarction. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; LDH, lactate dehydrogenase; UA, uric acid; PCT, procalcitonin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; cTnI, cardiac troponin I; CK-MB, creatinine kinase MB; PT, prothrombin time; INR, international normalized ratio; FIB, fibrinogen; APTT, activated partial thromboplastin time; TT, thrombin time; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; NA, not applicable.

Variable	Total population (n = 78)	N-N-PSM (n = 39)	N-I-PSM (n = 39)	p value
Myoglobin, μg/L	117.85 (52.60-918.20)	96.35 (37.33-1051.55)	201.75 (64.88–918.20)	0.378
CK-MB, ng/mL	4.30 (1.20–52.00)	3.40 (0.03–37.57)	5.40 (1.20–29.20)	0.842
Glucose, mmol/L	10.54 (8.65–12.24)	9.88 (8.37–11.40)	11.55 (8.98–14.49)	0.063
Lactate, mmol/L	1.43 (1.02–8.49)	1.00 (0.77–7.25)	2.65 (1.34–8.49)	0.131
HbA1c, %	7.30 (6.53–8.78)	7.00 (6.35–8.60)	7.40 (6.80–9.60)	0.133
Potassium (mmol/L)	3.99 (3.78–4.30)	3.97 (3.70–4.19)	4.07 (3.87–4.44)	0.265
Sodium (mmol/L)	138.75 (136.95-141.05)	138.60 (136.50-140.60)	139.30 (137.00 -141.40)	0.390
Chloride (mmol/L)	100.30 (96.50-102.70)	99.70 (96.80-102.40)	100.40 (95.50-102.70)	0.905
Calcium (mmol/L)	2.24 ± 0.13	2.22 ± 0.12	2.25 ± 0.14	0.391
Bicarbonate (mmol/L)	22.80 (20.25–24.63)	22.90 (20.40–26.00)	22.60 (18.00-24.60)	0.215
Coagulation function				
PT, Sec	14.25 (13.20-15.03)	14.10 (13.10–14.90)	14.40 (13.70–15.60)	0.163
INR	1.10 (1.01–1.18)	1.08 (0.99–1.16)	1.11 (1.05–1.26)	0.046
FIB,g/L	3.87 ± 1.40	3.94 ± 1.48	3.81 ± 1.34	0.688
APTT, Sec	39.95 (35.98–56.85)	39.60 (34.60-171.80)	40.70 (36.60–48.60)	0.988
TT, Sec	17.00 (16.00-25.43)	16.70 (16.00-40.10)	17.10 (16.10–19.40)	0.892
D-dimer, ug/mL	0.51 (0.34–1.58)	0.42 (0.28–0.80)	0.66 (0.41–2.04)	0.011

Data were presented as n (%), mean ± SD, and median (interquartile range). The N-N-PSM and N-I-PSM groups were propensity score matched sub-populations between the N-N and N-I groups. The N-N group was composed of patients treated without insulin before and after ICU admission. The N-I group was composed of patients received treatment without insulin before ICU admission but received insulin treatment after ICU admission. Abbreviations: DKA, diabetic ketoacidosis; HHS, hyperglycemic hyperosmolar state; COPD, chronic obstructive pulmonary disease; AMI, acute myocardial infarction. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; LDH, lactate dehydrogenase; UA, uric acid; PCT, procalcitonin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; cTnI, cardiac troponin I; CK-MB, creatinine kinase MB; PT, prothrombin time; INR, international normalized ratio; FIB, fibrinogen; APTT, activated partial thromboplastin time; TT, thrombin time; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; NA, not applicable.

Variable	Total population (n = 78)	N-N-PSM (n = 39)	N-I-PSM (n = 39)	p value
Infection-related indices				
C-reactive protein, mg/L	7.35 (2.50–22.40)	7.40 (2.40–21.20)	7.30 (2.50–31.00)	0.976
ESR,mm/H	11.00 (5.00-22.50)	10.00 (4.50–21.00)	13.00 (5.00–24.00)	0.730
IL-6,pg/ml	15.10 (11.13–43.80)	14.95 (9.66–33.57)	25.07 (11.79–47.87)	0.631
Hypoglycemia at ICU stay, n (%)				
Blood glucose ≤ 3.9 mmol/L	1 (1.3)	0 (0.0)	1 (2.6)	1.000
Blood glucose ≤ 3.0 mmol/L	0 (0.0)	0 (0.0)	0 (0.0)	NA
Clinical outcomes				
Length of ICU stay (days)	7 (4–8)	6 (4–8)	7 (5–9)	0.172
Mortality, n (%)	6 (7.7)	0 (0.0)	6 (15.4)	0.025

Data were presented as n (%), mean ± SD, and median (interquartile range). The N-N-PSM and N-I-PSM groups were propensity score matched sub-populations between the N-N and N-I groups. The N-N group was composed of patients treated without insulin before and after ICU admission. The N-I group was composed of patients received treatment without insulin before ICU admission but received insulin treatment after ICU admission. Abbreviations: DKA, diabetic ketoacidosis; HHS, hyperglycemic hyperosmolar state; COPD, chronic obstructive pulmonary disease; AMI, acute myocardial infarction. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; LDH, lactate dehydrogenase; UA, uric acid; PCT, procalcitonin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; cTnI, cardiac troponin I; CK-MB, creatinine kinase MB; PT, prothrombin time; INR, international normalized ratio; FIB, fibrinogen; APTT, activated partial thromboplastin time; TT, thrombin time; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; NA, not applicable.

Compared with the N-N group, the I-I group had longer length of ICU stay

To investigate the clinical outcomes between the N-N and I-I groups, PSM was performed to avoid bias. The N-N and I-I groups were defined as the N-N-PSM and I-I-PSM groups after PSM was performed. Except for some variables (duration of diabetes, blood urea nitrogen, calcium) that differed, the baseline characteristics were comparable between the N-N-PSM and I-I-PSM groups (all $p > 0.05$) (Table 3). The length of ICU stay was notably longer in the I-I-PSM group than in the N-N-PSM group [10 (6–14) vs. 7 (4–8), $p = 0.026$]. Mortality rate seemed to be higher in the I-I-PSM group than in the N-N-PSM group [16.0% (4/25) vs. 0.0% (0/25), $p = 0.110$], but the statistical difference was not significant. (Table 3) The *Kaplan-Meier survival analysis* did not show an obviously poorer survival rate in the I-I-PSM group than in the N-

N-PSM group (log-rank $p = 0.370$) (Fig. 2c). Since there was no event in the N-N group, the hazard ratio was not calculated.

Table 3
Comparison of baseline characteristics, laboratory parameters and clinical outcomes between the N-N-PSM and I-I-PSM groups.

Variable	Total population (*n* = 50)	N-N-PSM (*n* = 25)	I-I-PSM (*n* = 25)	*p* value
Baseline characteristics				
Age	61.00 ± 10.92	60.64 ± 11.55	61.36 ± 10.48	0.818
Age range (≥ 60), *n* (%)	29 (58.0)	15 (60.0)	14 (56.0)	0.774
Gender, male	36 (72.0)	17 (68.0)	19 (76.0)	0.529
Duration of diabetes (years)	6.50 (3.00-10.75)	4.00 (2.00–10.00)	10.00 (6.00–20.00)	0.016
Diabetic complications, n **(%)**				
Diabetic nephropathy	3 (6.0)	2 (8.0)	1 (4.0)	1.000
Diabetic retinopathy	0 (0.0)	0 (0.0)	0 (0.0)	NA
Diabetic cardiovascular disease	3 (6.0)	1 (4.0)	2 (8.0)	1.000
Diabetic peripheral neuropathy	3 (6.0)	2 (8.0)	1 (4.0)	1.000
DKA	1 (2.0)	0 (0.0)	1 (4.0)	1.000
HHS	0 (0.0)	0 (0.0)	0 (0.0)	NA
Original comorbidities, n **(%)**				
Hypertension	34 (68.0)	17 (68.0)	17 (68.0)	1.000
Coronary heart disease	37 (74.0)	19 (76.0)	18 (72.0)	0.747
COPD	1 (2.0)	1 (4.0)	0 (0.0)	1.000
Chronic kidney disease	9 (18.0)	3 (12.0)	6 (24.0)	0.463

Data were presented as *n* (%), mean ± SD, and median (interquartile range). The N-N-PSM and I-I-PSM groups were propensity score matched sub-populations between the N-N and I-I groups. The N-N group was composed of patients treated without insulin before and after ICU admission. The I-I group was composed of patients treated with insulin before and after ICU admission. Abbreviations: DKA, diabetic ketoacidosis; HHS, hyperglycemic hyperosmolar state; COPD, chronic obstructive pulmonary disease; AMI, acute myocardial infarction. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; LDH, lactate dehydrogenase; UA, uric acid; PCT, procalcitonin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; cTnI, cardiac troponin I; CK-MB, creatinine kinase MB; PT, prothrombin time; INR, international normalized ratio; FIB, fibrinogen; APTT, activated partial thromboplastin time; TT, thrombin time; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; NA, not applicable.

Variable	Total population (*n* = 50)	N-N-PSM (*n* = 25)	I-I-PSM (*n* = 25)	*p* value
Chronic liver disease	10 (20.0)	4 (16.0)	6 (24.0)	0.480
Sepsis	2 (4.0)	1 (4.0)	1 (4.0)	1.000
Cancer	3 (6.0)	1 (4.0)	2 (8.0)	1.000
COVID 19	2 (4.0)	0 (0.0)	2 (8.0)	0.490
Shock	0 (0.0)	0 (0.0)	0 (0.0)	NA
AMI	20 (40.0)	10 (40.0)	10 (40.0)	1.000
Smoker, *n* (%)	25 (50.0)	13 (52.0)	12 (48.0)	0.777
Drinker, *n* (%)	9 (18.0)	4 (16.0)	5 (20.0)	1.000
Laboratory parameters				
Routine blood test				
White-cell count, $\times 10^9$ /L	10.49 ± 5.62	9.86 ± 3.85	11.12 ± 6.99	0.431
Neutrophil count, $\times 10^9$ /L	8.01 ± 5.31	7.38 ± 3.62	8.64 ± 6.60	0.407
Lymphocyte count, $\times 10^9$ /L	1.52 ± 0.94	1.64 ± 0.77	1.41 ± 1.08	0.386
Monocyte count, $\times 10^9$ /L	0.56 (0.37–0.73)	0.65 (0.37–0.81)	0.49 (0.36–0.68)	0.165
Platelet count, $\times 10^9$ /L	213.50 (164.75-274.25)	222.00 (176.00-272.00)	190.00 (128.00-279.50)	0.367
Hemoglobin, g/L	123.30 ± 20.62	124.92 ± 17.09	121.68 ± 23.88	0.584
Blood biochemistry				
ALT, U/L	25.00 (13.75-45.00)	29.00 (16.50–46.00)	21.00 (12.50–46.00)	0.221

Data were presented as *n* (%), mean ± SD, and median (interquartile range). The N-N-PSM and I-I-PSM groups were propensity score matched sub-populations between the N-N and I-I groups. The N-N group was composed of patients treated without insulin before and after ICU admission. The I-I group was composed of patients treated with insulin before and after ICU admission. Abbreviations: DKA, diabetic ketoacidosis; HHS, hyperglycemic hyperosmolar state; COPD, chronic obstructive pulmonary disease; AMI, acute myocardial infarction. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; LDH, lactate dehydrogenase; UA, uric acid; PCT, procalcitonin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; cTnI, cardiac troponin I; CK-MB, creatinine kinase MB; PT, prothrombin time; INR, international normalized ratio; FIB, fibrinogen; APTT, activated partial thromboplastin time; TT, thrombin time; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; NA, not applicable.

Variable	Total population (*n* = 50)	N-N-PSM (*n* = 25)	I-I-PSM (*n* = 25)	*p* value
AST, U/L	28.50 (17.75–52.50)	29.00 (17.00–54.00)	28.00 (17.50–60.00)	0.741
Albumin, g/L	38.74 ± 5.22	39.38 ± 4.92	38.10 ± 5.52	0.388
Total bilirubin, μmol/L	7.90 (5.88–14.28)	8.90 (6.15–15.40)	7.50 (4.75–12.60)	0.260
Direct bilirubin,mmol/L	3.35 (2.60–5.85)	4.10 (2.75–6.10)	3.10 (2.55–5.40)	0.285
Total cholesterol, mmol/L	3.70 (2.90–4.56)	3.71 (3.27–4.44)	3.48 (2.73–4.93)	0.313
Triglyceride, mmol/L	1.25 (0.95–2.01)	1.20 (0.92–2.09)	1.44 (0.94–2.01)	0.800
HDL, mmol/L	0.92 ± 0.35	0.92 ± 0.27	0.92 ± 0.43	0.950
LDL, mmol/L	2.41 ± 0.98	2.52 ± 0.91	2.28 ± 1.06	0.403
CK,U/L	103.00 (53.00-325.00)	277.00 (58.00-1549.00)	97.50 (36.50-219.75)	0.064
LDH,U/l	246.00 (193.00-431.00)	246.00 (187.00-442.00)	247.00 (194.00-393.25)	0.992
UA,umol/L	355.65 (277.25–476.00)	328.60 (279.50-506.70)	377.00 (269.00-464.65)	0.907
Creatinine, μmol/L	96.00 (66.00-148.00)	79.00 (59.50-111.50)	111.00 (70.50-196.50)	0.109
Blood urea nitrogen, mmol/L	6.90 (4.98–10.64)	5.19 (4.22–7.78)	8.85 (6.02–13.18)	0.001
eGFR mL/min	70.45 (37.50–94.90)	76.20 (56.15-95.00)	63.20 (28.30-96.35)	0.273
PCT,ng/mL	1.26 (0.16–5.02)	0.20 (0.03-50.00)	3.12 (1.11–3.92)	0.180
NT-ProBNP, pg/mL	1156.00 (275.00-4709.00)	823.50 (144.75-4789.25)	1304.00 (388.00-4259.50)	0.522

Data were presented as *n* (%), mean ± SD, and median (interquartile range). The N-N-PSM and I-I-PSM groups were propensity score matched sub-populations between the N-N and I-I groups. The N-N group was composed of patients treated without insulin before and after ICU admission. The I-I group was composed of patients treated with insulin before and after ICU admission. Abbreviations: DKA, diabetic ketoacidosis; HHS, hyperglycemic hyperosmolar state; COPD, chronic obstructive pulmonary disease; AMI, acute myocardial infarction. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; LDH, lactate dehydrogenase; UA, uric acid; PCT, procalcitonin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; cTnI, cardiac troponin I; CK-MB, creatinine kinase MB; PT, prothrombin time; INR, international normalized ratio; FIB, fibrinogen; APTT, activated partial thromboplastin time; TT, thrombin time; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; NA, not applicable.

Variable	Total population (*n* = 50)	N-N-PSM (*n* = 25)	I-I-PSM (*n* = 25)	*p* value
cTnI, pg/mL	73.35 (6.48-4645.35)	234.20 (12.15-14202.70)	33.70 (4.00-905.75)	0.233
Myoglobin, μg/L	82.50 (33.40-262.10)	76.60 (32.15–762.90)	89.35 (41.43-239.98)	0.942
CK-MB, ng/mL	1.80 (0.90–17.40)	2.20 (0.90-34.55)	1.35 (0.83–5.53)	0.248
Glucose, mmol/L	10.55 (7.60-12.77)	9.88 (7.53–11.50)	11.53 (7.65-17.00)	0.146
Lactate, mmol/L	1.02 (0.70–3.10)	1.00 (0.77–7.25)	2.17 (0.42–3.10)	1.000
HbA1c, %	7.40 (6.40–9.20)	7.00 (6.30–8.70)	7.45 (6.60–9.55)	0.367
Potassium (mmol/L)	4.09 (3.72–4.40)	3.96 (3.69–4.20)	4.18 (3.78–4.68)	0.073
Sodium (mmol/L)	138.20 (135.60-140.20)	138.90 (136.65–140.80)	137.70 (134.45–140.00)	0.290
Chloride (mmol/L)	99.78 ± 3.91	100.06 ± 3.92	99.50 ± 3.96	0.618
Calcium (mmol/L)	2.20 ± 0.14	2.24 ± 0.12	2.16 ± 0.14	0.047
Bicarbonate (mmol/L)	22.03 ± 4.42	23.12 ± 4.03	20.94 ± 4.59	0.080
Coagulation function				
PT, Sec	14.00 (13.20–14.90)	13.70 (12.95–14.70)	14.30 (13.45–15.05)	0.093
INR	1.09 (1.01–1.16)	1.04 (0.99–1.14)	1.14 (1.04–1.19)	0.058
FIB,g/L	3.46 (2.87–4.78)	3.45 (2.93–4.92)	3.62 (2.71–4.84)	0.771
APTT, Sec	39.90 (35.40-54.43)	39.10 (33.85–56.55)	42.00 (37.35–53.75)	0.268
TT, Sec	17.30 (16.18–21.38)	16.70 (15.75–20.15)	17.80 (16.45–23.50)	0.259
D-dimer, ug/mL	0.65 (0.30–1.86)	0.47 (0.30–0.89)	1.19 (0.32–2.86)	0.120

Data were presented as *n* (%), mean ± SD, and median (interquartile range). The N-N-PSM and I-I-PSM groups were propensity score matched sub-populations between the N-N and I-I groups. The N-N group was composed of patients treated without insulin before and after ICU admission. The I-I group was composed of patients treated with insulin before and after ICU admission. Abbreviations: DKA, diabetic ketoacidosis; HHS, hyperglycemic hyperosmolar state; COPD, chronic obstructive pulmonary disease; AMI, acute myocardial infarction. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; LDH, lactate dehydrogenase; UA, uric acid; PCT, procalcitonin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; cTnI, cardiac troponin I; CK-MB, creatinine kinase MB; PT, prothrombin time; INR, international normalized ratio; FIB, fibrinogen; APTT, activated partial thromboplastin time; TT, thrombin time; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; NA, not applicable.

Variable	Total population (n = 50)	N-N-PSM (n = 25)	I-I-PSM (n = 25)	p value
Infection-related indices				
C-reactive protein, mg/L	6.65 (2.18–24.45)	7.10 (2.25–23.35)	6.20 (1.95–28.90)	0.938
ESR,mm/H	14.00 (5.75–31.75)	14.00 (4.00-30.50)	12.00 (6.75–40.25)	0.415
IL-6,pg/ml	20.21 (12.21–48.52)	16.25 (12.21–43.40)	27.09 (10.75-3758.49)	0.624
Hypoglycemia at ICU stay, *n* (%)				
Blood glucose ≤ 3.9 mmol/L	2 (4.0)	0 (0.0)	2 (8.0)	0.490
Blood glucose ≤ 3.0 mmol/L	1 (2.0)	0 (0.0)	1 (4.0)	1.000
Clinical outcomes				
Length of ICU stay (days)	8 (5.75–11.25)	7 (4–8)	10 (6–14)	0.026
Mortality, *n* (%)	4 (8.0)	0 (0.0)	4 (16.0)	0.110

Data were presented as *n* (%), mean ± SD, and median (interquartile range). The N-N-PSM and I-I-PSM groups were propensity score matched sub-populations between the N-N and I-I groups. The N-N group was composed of patients treated without insulin before and after ICU admission. The I-I group was composed of patients treated with insulin before and after ICU admission. Abbreviations: DKA, diabetic ketoacidosis; HHS, hyperglycemic hyperosmolar state; COPD, chronic obstructive pulmonary disease; AMI, acute myocardial infarction. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; LDH, lactate dehydrogenase; UA, uric acid; PCT, procalcitonin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; cTnI, cardiac troponin I; CK-MB, creatinine kinase MB; PT, prothrombin time; INR, international normalized ratio; FIB, fibrinogen; APTT, activated partial thromboplastin time; TT, thrombin time; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; NA, not applicable.

Compared with the N-I group, the length of ICU stay and mortality rate in the I-I group had no significant difference

To investigate the clinical outcomes between the N-I and I-I groups, PSM was performed to avoid bias. The N-I and I-I groups were defined as the N-I-PSM and I-I-PSM groups after PSM was performed. Except for several variables (duration of diabetes, total bilirubin, blood urea nitrogen, NT-ProBNP, CK-MB, glucose, ESR) that differed, the baseline characteristics were comparable between the N-I-PSM and I-I-PSM groups (all $p > 0.05$). During hospitalization, the incidence of hypoglycemia was significantly higher in the I-I-PSM group than in the N-I-PSM group [15.7% (22/140) vs. 5.0% (7/140); $p = 0.003$] **(Supplementary Table 2) (Additional file 2)**. There were no significant differences in the mortality rate [22.9% (32/140) vs. 19.3% (27/140), $p = 0.464$] and the length of ICU stay [9 (5–16) vs. 8 (5–13), $p = 0.389$] in the I-I-PSM group

compared with those in the N-I-PSM group **(Supplementary Table 2) (Additional file 2)**. The survival curves between the N-I-PSM and I-I-PSM groups were still presented for an intuitive survival trends, although the Log-rank test could not be performed; consequently, the related parameter was not given (Fig. 2d).

Discussion

In this study, we included 578 ICU patients with type 2 diabetes to explore the association of insulin treatment with clinical outcomes. Our study found that insulin treatment was not only associated with increased mortality rate but also related to longer length of ICU stay. These results suggested that insulin treatment might lead to worse clinical outcomes in ICU patients with type 2 diabetes.

Compelling evidence indicated that insulin treatment leads to an increased risk of mortality [18, 22, 23]. A study which included 7401 patients with diabetes has suggested that insulin-treated diabetes was associated with a higher mortality rate and a longer length of hospital stay [23], meanwhile, our previous study also observed a similar increased in-hospital mortality in patients treated with insulin during hospitalization, compared with those treated without insulin [22]. Our present work found that ICU patients with type 2 diabetes who received treatment without insulin before but received insulin treatment after admission had higher mortality rates and longer lengths of ICU stay. The explanation for this finding might be as follows. First, the insulin doses were difficult to adjust to match the actual need for patients using insulin for the first time whether these patients were in the ICU or not. Second, hyperglycemia and insulin resistance were the hallmarks of an altered metabolism from the release of cortisol induced by stress response in critically ill patients [24, 25], which led to the control of insulin doses becoming more complicated. Therefore, initiating insulin therapy in critically ill patients with type 2 diabetes must be done with caution. Third, an investigation reported that the quality-adjusted life years index of patients using insulin was reported as being lower than that of those using metformin, and this was evident in subjects who switched from metformin to insulin [26, 27]. The proportion of patients who used metformin before admission and then changed to insulin after admission in our study was 18.0% (54/300), and 29.6% (16/54) of these patients died. This data may indicate that changing glycemic control methods is a potential risk factor for mortality in critically ill type 2 diabetes patients.

In this study, some patients did not change their glycemic control method, which involved insulin treatment or oral agent treatment, during the whole stay in ICU. A surprising result occurred after comparing the ending points of above two groups, demonstrating that insulin treatment did not increase mortality rate but prolonged the length of stay in ICU. Insulin treatment is likely to be used in critically ill patients in clinical practice [28]. Although PSM was performed for a comparable condition between these two groups of ICU patients with type 2 diabetes, the state of illness of ICU patients with type 2 diabetes who received insulin treatment before and after admission may be more complicated. In addition to glucose control, insulin is involved in various metabolisms in the body such as the promotion of protein synthesis, *de novo* lipogenesis, inhibition of lipolysis, and other defense mechanisms [29]. Moreover, insulin can modify inflammation [30, 31]. At the onset of critical illness, organs in the body experience

drastic pathophysiological changes, and insulin may be involved in the regulation mechanism of this process as a pro-inflammatory factor [32]. It is possible, nevertheless, that insulin administration might contribute to a chronic inflammation status, which enhances adaptation to the inflammation situation. This status might protect type 2 diabetes patients in the ICU who use insulin away from the inflammation site. We also observed an increased preference for a longer length of ICU stay in insulin-treated patients. To our knowledge, insulin therapy will more or less likely increase the risk of widely fluctuating blood glucose level [33]. Thus, we speculate that insulin play a crucial role in the longer length of ICU stay in this study.

Moreover, there were no differences in the mortality rate and the length of ICU stay in patients who received insulin injection in the ICU regardless of whether they received insulin treatment or oral agents before admission. The present data support the view that insulin treatment in the ICU would lead to higher mortality rates and longer lengths of ICU stay. It remains unclear whether insulin treatment in ICU is a cause or a consequence of the adverse outcomes. Recognizing that more caution should be paid to ICU patients with type 2 diabetes who received insulin treatment after ICU admission is of great importance.

The present study has some limitations. First, the sample size was relatively small for the ICU patients with type 2 diabetes who received treatment without insulin before and after ICU admission because ICU patients generally received insulin treatment after admission, and oral medication was often replaced. Second, as the dynamic observation of biochemical values including inflammation indicators was limited, we failed to evaluate the development of clinical conditions in the patients and explore the relationship between insulin treatment and system inflammation. Further research is required on a larger sample size of ICU patients with type 2 diabetes who received various anti-diabetic treatments.

Conclusion

Insulin treatment of patients with type 2 diabetes in ICU is associated with increased mortality rate and longer length of stay, regardless of whether they received insulin treatment before ICU admission. Clinicians should be more concerned about type 2 diabetes patients in ICU.

Declarations

Ethical approval and consent to participate

This study was approved by the institutional review board of Tongji Hospital (IRBID: TJ-IRB20200229). The consent to participate was not applicable.

Consent for publication

Not applicable.

Availability of supporting data

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

All authors declared no conflict of interest.

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Authors' contributions

YY and DW conceived and designed the study. RF and YY wrote the manuscript. RF, XP, BY, and JH performed the literature review. YY and DW secured the study's funding. RF, XP, BY, JH and XY acquired and analyzed the data. All authors reviewed and approved the final version of the manuscript.

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Figures

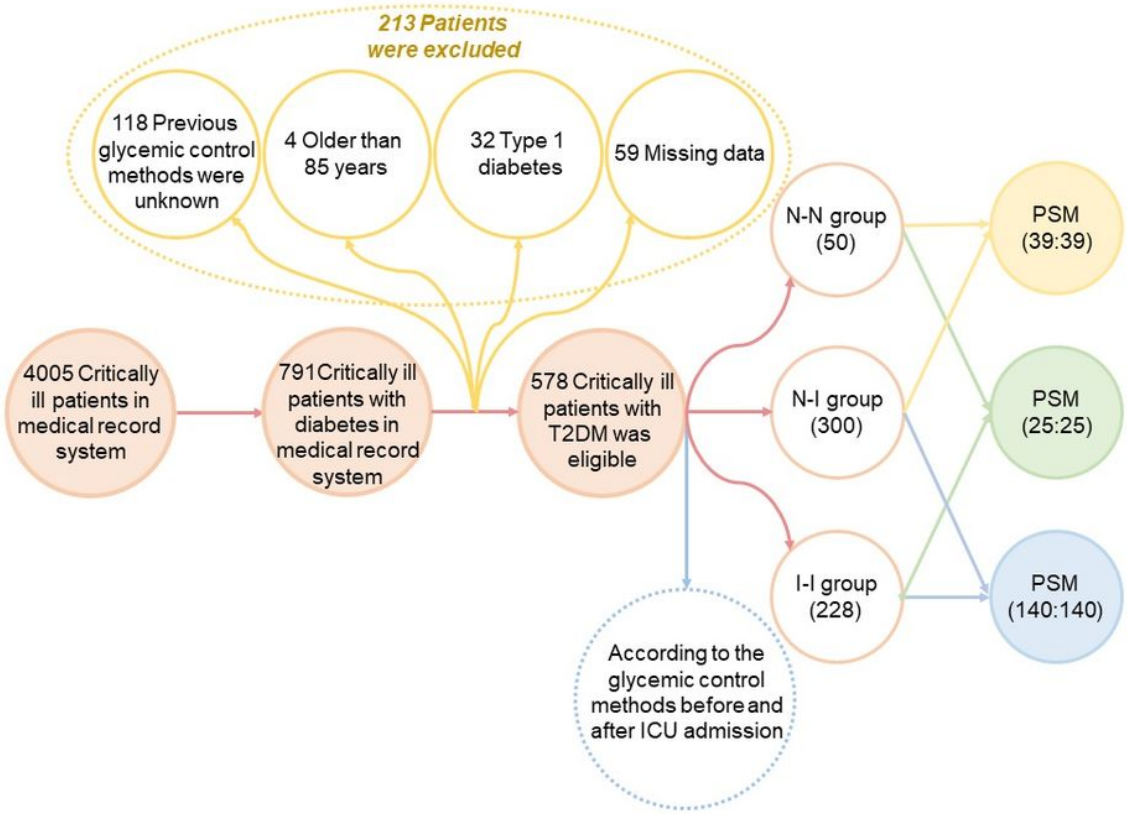

Figure 1

The flowchart of study design. N-N = patients receiving treatment without insulin before and after ICU admission. N-I = patients undergoing treatment without insulin before ICU admission but treated with insulin after admission. I-I = patients receiving insulin treatment before and after ICU admission. PSM = propensity score matching.

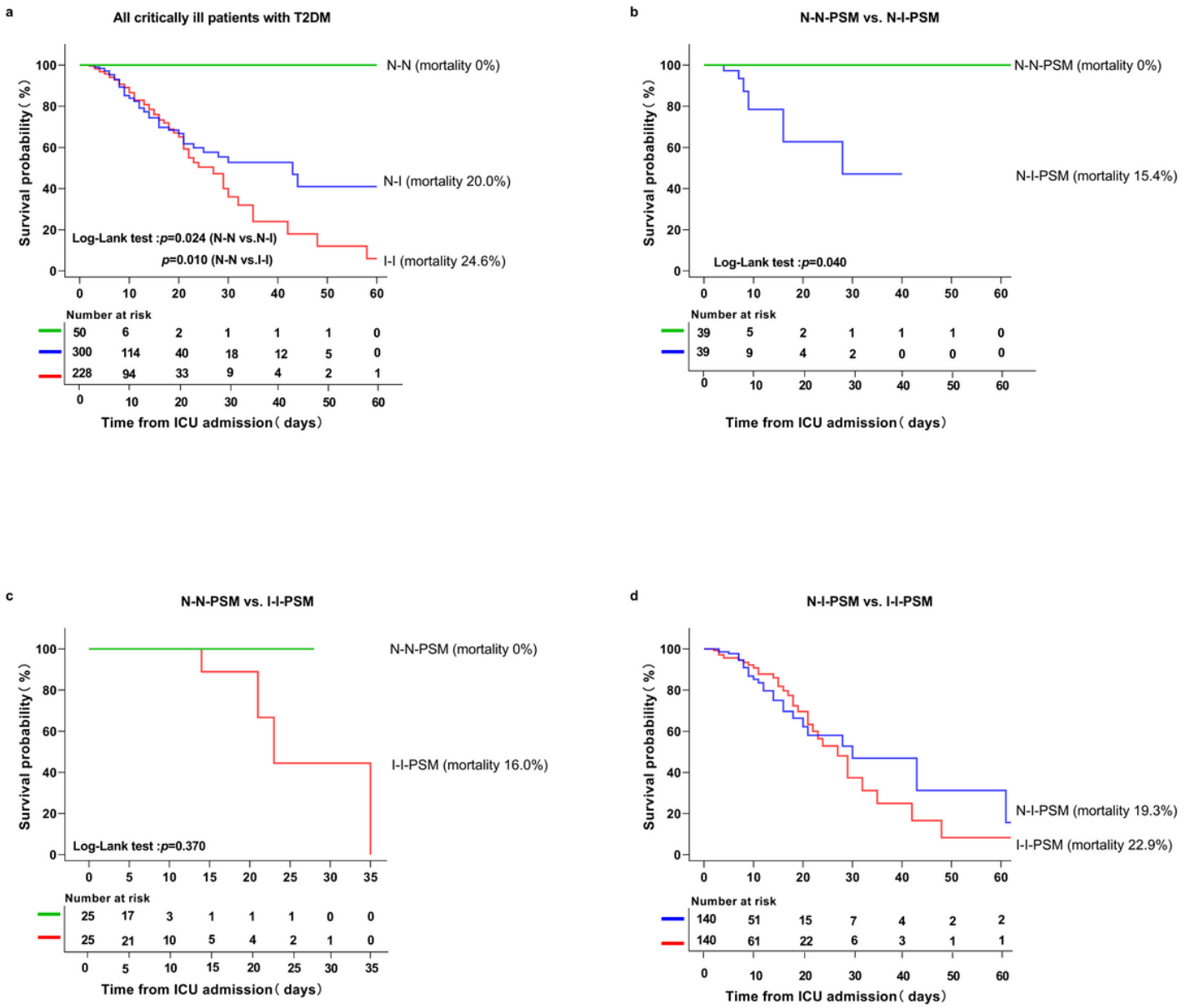

Figure 2

Kaplan-Meier survival curve for critically ill patients with type 2 diabetes. (a). Kaplan-Meier survival curve for 578 critically ill patients with type 2 diabetes; (b). Kaplan-Meier survival curve for ICU patients with type 2 diabetes in the N-N and N-I groups after PSM; (c). Kaplan-Meier survival curve for ICU patients with type 2 diabetes in the N-N and I-I groups after PSM; Log-rank $p < 0.05$ indicated statistical significance. (d). The survival curves between the N-I-PSM and I-I-PSM groups were presented for an intuitive survival trends, not for Log-rank test, the related parameter was not given. N-N = patients receiving treatment without insulin before and after ICU admission. N-I = patients undergoing treatment without insulin before ICU admission but treated with insulin after admission. I-I = patients receiving insulin treatment before and after ICU admission. PSM = propensity score matching.

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