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Effects of Type 2 Diabetes on Mortality and Immunity Responses in Sepsis Patients: A Retrospective Cohort Study

Qingxia Du, Xuelian Yin, Jibing Li, Yi zheng, Hong Zhao, Jing Zhang, Qiumei Cao**

ABSTRACT

Background: The study aimed to investigate the association between comorbid Type 2 diabetes mellitus (T2DM) and sepsis outcomes with new evidence and compare the immunity responses of sepsis patients with T2DM and non-diabetics.

Methods: We conducted a retrospective data collection from consecutive patients diagnosed with sepsis. Utilizing propensity score matching (PSM), we matched T2DM patients with non-diabetics. We subsequently performed a comparative analysis of immune markers and primary clinical outcomes.

Results: 801 sepsis patients (322 with T2DM and 475 non-T2DM) were included. Following the PSM, sepsis patients with comorbid T2DM exhibited a reduced risk of 28-day (odds ratio (OR): 0.62; 95% confidence interval (CI): 0.41-0.94; P=0.031) and 90-day (OR: 0.64; 95% CI: 0.45-0.89; P=0.010) in-hospital mortality. There were no statistically significant differences in acute lung injury (OR: 0.80, 95% CI: 0.52-1.22, P=0.328), acute kidney injury (OR: 0.86, 95% CI: 0.56-1.32, P=0.510), the length of hospital stays between the groups (Table 2). Notably, T2DM patients showed elevated levels of lymphocytes and C4, while their IGM and IGG levels were lower than non-diabetics.

Conclusion: T2DM is associated with a reduced risk of 28-day, 90-day in-hospital mortality in sepsis. The risk of acute lung injury, or acute kidney injury and length of hospital stay was similar among T2DM and non-diabetics. Sepsis patients with comorbid T2DM exhibit enhanced levels of lymphocytes and C4 but reduced levels of IGG and IGM compared to non-diabetics.

INTRODUCTION

Sepsis is a life-threatening organ dysfunction stemming from disordered host reaction to infection and poses a crucial global healthcare challenge due to its high mortality rates and substantial medical costs. Type 2 diabetes (T2DM) frequently coexists with sepsis and is characterized by chronic low-grade inflammation Costantini et al. (2021). Notably, T2DM represents a condition with greater importance for long-term sepsis risk Lee et al. (2021). Both sepsis and T2DM disrupt immune pathways Costantini et al. (2021), rendering sepsis infections more intricate in individuals with T2DM. Although it is well-established that T2DM patients are more susceptible to infections and sepsis Carey et a1. 2018, there is a lack of consensus concerning the association between comorbid T2DM and sepsis outcomes. Studies by Zoppini et al. (2018) and Bertoni et al. (2001) found an increased mortality rate among individuals with diabetes suffering Conversely, other studies Chao et al. (2017) Sathananthan Et al. (2020). demonstrated that T2DM is not correlated with increased mortality, and some even Lin et al. (2021), de Miguel-Yanes et al. (2015), Esper et al. (2009), Moss et al. (2000), reported a decreased mortality rate among sepsis patients with T2DM.

Moreover, the impact of diabetes on the risk of acute lung injury and acute kidney injury in sepsis patients remains a topic of debate. Nonetheless, several investigations have indicated similar cytokine patterns Stegenga et a1. (2010), Moss et al. (2000) and reactive vascular endothelium in critically ill sepsis patients, regardless of pre-existing diabetes mellitus. Despite this, there remains a paucity of research examining changes in immunoglobulin levels among sepsis patients with T2DM The primary objectives of our study are to investigate: (1) the effects of T2DM on mortality rates, duration of hospitalization, and the risk of acute lung injury and acute kidney injury in sepsis patients; (2) the impact of T2DM on the immune responses of

Department of Emergency, the Affiliated Tongren Hospital of Capital Medical University, Beijing, China

Correspondence to: Jing Zhang, Department of Emergency, the Affiliated Tongren Hospital of Capital Medical University, Beijing, China

E-mail: zhangjing68519@sohu.com

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individuals with sepsis. This will involve a comparative analysis of various leukocyte counts and the levels of immunoglobulins, complements, and C-reactive protein (CRP) between those with and without T2DM.

MATERIALS AND METHODS

This study, conducted between January 2023 and September 2023, entails a retrospective, observational cohort analysis of consecutive patients admitted to various departments, including the Emergency ward, Emergency Care Unit, Geriatric ward, and Intensive Care Unit. The study population comprised individuals admitted for sepsis from January 2015 to January 2022, and their data were continuously retrieved through the electronic medical record system of Beijing Tongren Hospital, affiliated with Capital Medical University. The study protocol received approval from the Institutional Review Board of Tongren Hospital (TREC2022-KY133). The research procedures in this study were conducted in accordance with the principles of Helsinki Declaration. Due to the retrospective and anonymous nature of the data collection, the patient consent was waived. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines was used for designing this cohort study.

Moreover, the patients were categorized as having pre-existing T2DM based on information available in their medical records, which determined the sample size for this investigation. Patients meeting the following criteria were included in this study: a) strict adherence to the 2016 Sepsis 3 definition criteria, including septic shock; b) age equal to or above 18 years; c) individuals of any gender. Exclusion criteria comprised: a) age below18 years; b) incomplete medical records or hospital stays lasting less than or equal to 24 hours; c) pregnancy; d) history of injury; e) presence of specific notifiable disease (such as HIV infection, tuberculosis, severe liver or kidney dysfunction, among others.); f) presence of other types of diabetes; g) recent use of immunosuppressant agents, chemotherapy, or radiotherapy within 30 days prior to the onset of sepsis. Relevant demographic data, medical histories, and Sequential Organ Failure Assessment (SOFA) scores were extracted from the clinical information systems for analysis.

The main objectives of this study were to assess the 28-day and 90-day in-hospital mortality rates following admission, serving as the primary outcome. The second outcome encompassed the duration of hospitalization, as well as the occurrences of acute lung injury and acute kidney injury. As mentioned in previous studies Bellomo et a1. (2004), Ranieri VM et a1. (2012) acute lung and acute kidney injuries were defined based on established criteria. The assessment of immune responses involved measuring total leukocyte counts, various leukocyte subsets, complement levels, C-reactive protein (CRP), and immunoglobulin concentrations Peripheral venous blood samples were collected via venipuncture as part of routine patient care, specifically in the early morning within 24 hours of hospital admission. These samples were promptly sent to our clinical laboratory and processed per standardized approaches. Complete blood cell counts, encompassing total leukocyte count and differential leukocyte count, were performed using certified techniques. Additionally, levels of complements (C3, C4), CRP, and immunoglobulins (IGA, IGM, IGG, and IGE) were determined using immuno-enzymatic methods (Roche diagnostics). Both external and internal quality control procedures were implemented daily in our laboratory to ensure the accuracy and reliability of the results. All data on immunity parameters were extracted from the patient records.

The propensity scores were calculated to account for and match the following baseline potential confounding covariates, including age, sex, SOFA score, and modified Charlson's co-morbidity index (mCCI, excluding the contribution of T2DM). The propensity score matching (PSM) was performed with a caliper width set at 0.02 of the standard deviation of the logit. Following the matching process, the outcomes and immunity parameters were compared between the subjects matched based on propensity scores, including sepsis patients with and without T2DM.

Patient characteristics in both the original and matched cohorts were analyzed as follows: Categorical data were expressed as numbers and percentages (%), and comparisons between cohorts were carried out using chi-square tests. Quantitative variables were presented either as mean ± standard deviation (SD) or as median with interquartile range (IRQ) and were analyzed using the Mann-Whitney U test. The normality of quantitative data was assessed using the Kolmogrov-Smirnov test. Statistical significance was determined with a p-value of < 0.05.

RESULTS

In this study, 801 sepsis patients (322 with T2DM and 475 non-T2DM) sepsis patients were included. Among the T2DM group were 178 males and 144 females, while the non-T2DM group consisted of 248 males and 227 females.

No statistically significant differences were observed in terms of age, sex, medical history, hemoglobin levels, and serum albumin levels between the two cohorts.

However, sepsis patients with T2DM demonstrated higher modified Charlson's co-morbidity index (mCCI) and SOFA scores than non-diabetics (Table 1).

Table 1: Demographic and clinical characteristics of patients stratified by diabetes the original cohort

Variables	All patients (N=801)	With T2DM (N=322)	Non-diabetics (N=479)	P value
age (years)	76.80±15.18	76.96±13.23	76.90±16.17	0.146
sex, n (%)				0.934
male	326 (40.70)	178 (55.28)	148 (30.96)	
female	267 (48.01)	144 (44. 72)	123(25.68)	
SOFA score	3.39±1.78	3.75±2.04	3.16±1.57	0.000*
mCCI	7.64±3.03	8.97±2.70	6.79±2.94	0.000*
lactic acid(mmol/L)	2.82±0.99	1.71±1.89	1.41±1.14	0.195
hemoglobin(g/L)	101.32±20.78	99.65±21.20	102.39±20.40	0.194
serum albumin(g/L)	29.84±5.41	29.55±5.45	30.04±5.61	0.403
glucose (mg/dL)	6.10 (5.10,8.31)	10.78±27.68	5.54 (4.82,6.60)	0.000*
white blood cell,10^9/	8.93±4.74	9.53±4.89	8.52±4.60	0.000*
neutrophil,109/	7.07±4.55	7.66±4.67	6.67±4.42	0.005*
monocyte,10^9/	0.57±0.41	0.58±0.32	0.57±0.46	0.22
lymphocyte ,10^9/L	1.12±0.73	1.13±0.74	1.12±0.73	0.537
CRP(U/L)	66.88 (21.19,135.15)	90.89±87.34	87.46±90.86	0.427
IGA (mg/dl)	261.90 (187.45,355.63)	73.30 (21.33,133.98)	260.25 (188.53,340.95)	0.449
IGG (mg/dl)	1131.33 (880.02,1409.25)	269.00 (186.20,365.00)	1160.40 (955.60,1425.75)	0.005*
IGM (mg/dl)	67.70 (46.00,105.20)	1091.33 (771.89,1381.77)	71.70 (46.24,117.25)	0.017*
IGE (mg/dl)	92.50 (23.80,278.16)	63.35 (42.25,96.28)	89.20 (25.8-,263.00)	0.496
complement C3(mg/dl)	99.10 (82.70,119.83)	111.66 (21.67,472.34)	99.10 (82.29,119.25)	0.996
Complement C4(mg/dl)	28.44 (21.03,35.07)	99.60 (83.10,121.50)	27.47 (20.31,34.45)	0.059
hospital stay (days)	19.57 ±16.32	22.10±19.41	17.94± 13.67	0.002*

mCCI, modified Charlson's comorbidity index; SOFA score, Sepsis Related Organ Failure Assessment score.

Applying propensity score matching made adjustments for the SOFA score and mCCI, resulting in a matched cohort of T2DM patients. The demographic and clinical characteristics of patients after propensity matching are detailed in Table 2. Following the PSM, no statistically significant differences were observed in SOFA score, mCCI, age, sex, hemoglobin levels, and serum albumin levels between the T2DM patients and their matched non-diabetic counterparts (Table 2). Following the PSM, no significant associations were found between T2DM and acute lung injury (OR: 0.80, 95% CI: 0.52-1.22, P=0.328) or acute kidney injury (OR: 0.86, 95% CI: 0.56-1.32, P=0.510). Notably, a decreased sepsis mortality risk was observed in subjects with T2DM. The odds ratios for T2DM concerning 28-day and 90-day in-hospital mortalities were 0.62 (95% CI, 0.41-0.94, P=0.031) and 0.64 (95% CI, 0.45-0.89, P=0.010), respectively (Table 3) There were no statistically significant differences in the length of hospital stay between the groups (Table 2). Regarding specific immune parameters, there were no notable distinctions between T2DM patients and their matched non-diabetics concerning blood leukocyte, neutrophil, or monocyte counts, as well as C3, IGA, IGE, and CRP levels.

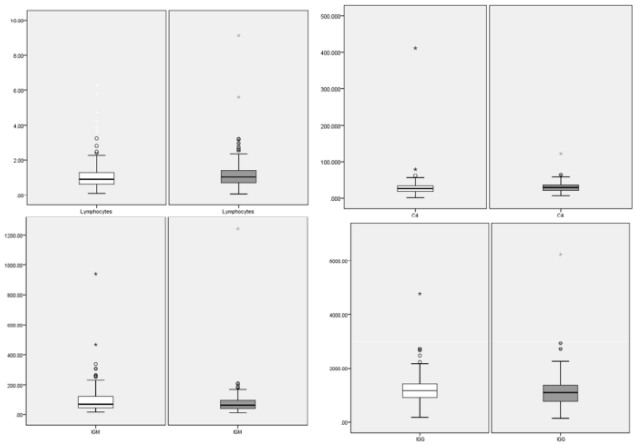
However, sepsis patients with T2DM illustrated significantly increased lymphocyte and plasma levels of C4, while their IGM and IGG plasma levels were substantially decreased compared to non-diabetic patients (Table 2; Fig 1).

Table 2: Demographic and clinical characteristics of the PSM cohort

Variables	All patients (N=593)	With T2DM (N=322)	Without T2DM (N=271)	P value
age (years)	76.87±14.30	76.96±13.22	76.76±15.76	0.372
sex, n (%)				0.934
male	326 (55.00)	178 (55.28)	148 (54.61)	
female	267 (45.00)	144 (44.72)	123(45.39)	
SOFA score	3.68±1.93	3.75±2.04	3.61±1.81	0.814
mCCI	7.57±3.06	7.59±3.09	7.54±3.03	0.958
lactic acid(mmol/L)	1.61±1.58	1.71±1.89	1.47±1.05	0.297
Hemoglobin (g/L)	100.88±21.36	99.65±21.20	102.36±21.51	0.12
serum albumin(g/L)	29.38±5.45	29.55±5.45	29.80±5.99	0.484
glucose (mg/dL)	6.66 (5.30,9.10)	8.28 (5.96,11.30)	5.76 (4.97,6.81)	0.000*
white blood cell,10^9/	9.53±5.00	9.53±4.89	9.53±5.13	0.998
neutrophil,109/	7.68±4.80	7.66±4.66	7.70±4.98	0.784
monocyte,10^9/	0.58±0.44	0.58±0.32	0.59±0.55	0.291
lymphocyte ,10^9/L	1.11±0.76	1.13±0.74	1.08±0.78	0.047*
CRP(U/L)	66.88 (21.19,135.15)	73.30 (21.33,133.98)	60.40 (20.50,140.60)	0.785
IGA (mg/dl)	263.60 (182.90,363.90)	269.00 (186.20,365.00)	261.71 (179.60,348.81)	0.394
IGG (mg/dl)	1126.51 (839.57,285.75)	1091.33 (771.89,1381.77)	1170.39 (899. 60,1435.50)	0.018*
IGM (mg/dl)	65.70 (45.01,104.40)	63.35 (42.25,96.28)	70.00 (46.50,122.53)	0.048*
IGE (mg/dl)	98.72 (28.90,285.75)	111.66 (21.67,472.34)	95.20 (36.00,269.16)	0.938
Complement 3(mg/dl)	98.50 (82.30,119.30)	99.60 (83.10,121.50)	97.40 (81.35,117.85)	0.493
Complement 4(mg/dl)	28.85 (20.76,35.96)	30.00 (22.03,36.95)	27.20 (19.35,34.38)	0.054*
hospital stay (days)	19.57 (16.32)	22.10 (19.41)	19.67 (14.99)	0.242

mCCI, modified Charlson's comorbidity index; SOFA score, Sepsis Related Organ Failure Assessment score. *P < 0.05.

Figure 1:



Box-plot for serum lymphocytes (*109) and concentration of complement 4 (mg/dl), IGM (mg/dl), and IGG (mg/dl) on admission in sepsis patients with T2DM (the right gray boxes) and non-diabetics (the left white boxes). Boxes show medians (solid horizontal lines) and interquartile ranges.

Table 3: The odds ratio of clinical outcomes of diabetes mellitus and sepsis before and after PSM

outcome	All patients	T2DM group	non-T2DM group	Odds risk(95%CI)	P value
Before PSM	N=801	N=322	(N=479)		
Acute lung injury	128(15.98)	51 (15.84)	77 (16.08)	0.97(0.66-1.43)	0.922
Acute kidney injury	113(14.10)	51 (15.84)	62 (12.94)	1.25(0.84-1.87)	0.301
28-day in-hospital mortality	108 (13.48)	47 (14.60)	61 (12.73)	1.17 (0.76-1.76)	0.462
90-day in-hospital mortality	216(26.97)	101 (31.37)	115 (24.01)	1.44(1.05-1.98)	0. 023*
After PSM	N=593	N=322	N=271		
Acute lung injury	103(17.37)	51 (15.84)	52 (49.46)	0.80(0.52-1.22)	0.328
Acute kidney injury	100 (5.25)	51 (15.84)	49 (18.01)	0.86(0.56-1.32)	0.51
28-day in-hospital mortality	106 (17.94)	47 (14.60)	59 (21.77)	0.62(0.41-0.94)	0.031*
90-day in-hospital mortality	215 (36.38)	101 (31.56)	114 (42.07)	0.64(0.45-0.89)	0.010*

DISCUSSION

The main results of our cohort study allow us to further characterize the impact of T2DM on the outcomes and immunity responses among patients with sepsis from the following three aspects. First and foremost, sepsis patients with comorbid T2DM exhibited a reduced risk of 28-day, 90-day in-hospital mortality. However, having comorbid T2DM did not increase the risk of extended hospital stay, acute lung injury, or acute kidney injury. Second, regarding the immunity response, T2DM patients displayed significantly higher levels of lymphocytes and C4 concentration, while plasma IGM and IGG levels were significantly lower compared to those without T2DM.

plasma IGM and IGG levels were significantly lower compared to those without T2DM.

In previous studies, the conflicting outcomes in sepsis patients with comorbid T2DM might be attributed to variations in the control of confounders across different research, such as age, sepsis severity, and co-morbidities. Propensity-score matching, a popular analytical method, helps mitigate selection bias by accounting for the effects of these confounding factors commonly encountered in observational studies. Austin et al. (2011). We applied a multivariate logistic regression to calculate the propensity score, allowing us to match participants based on age, gender, disease severity (SOFA score), and co-morbidities (mCCI). To the best of our knowledge, our findings align with the initial study on this topic that utilized propensity score matching, indicating a dramatically lower 28-day mortality rate for sepsis patients comorbid with diabetes. Lin et al. (2021). Our observations were corroborated through the meta-analysis by Wang et al. (2017), illustrating that diabetes is associated with a marginally lower mortality rate and comparable incidence of respiratory dysfunction in cases of sepsis.

The precise mechanism underlying the impact of T2DM on sepsis outcomes remains elusive. Given that inflammation constitutes the most critical pathogenic basis of sepsis, it has been posited by several researchers that T2DM may mitigate septic inflammation by attenuating cytokine release and impairing neutrophil function Moss. Moss et al. (2000) proposed that a blunted inflammatory response, deficient neutrophil function, and altered neutrophil-endothelial interaction could produce a protective effect on diabetic patients, resulting in a decreased risk of acute respiratory distress syndrome compared to individuals without a history of diabetes. Our cohort study observed significantly higher lymphocyte levels alongside strikingly lower IGM and IgG levels in patients with T2DM compared to those without diabetics. Lymphocytes play a vital role in developing metabolic inflammation and insulin resistance in T2DM Xia et al. (2017). Studies have also indicated increased lymphocyte counts Otton et al. (2004) and altered proportion of T lymphocyte subsets in T2DM patients Zhao et al. (2014), linking T2DM to perturbations in the immune system Hameed et al. (2015). Hyperglycemia and hyperinsulinemia disturbadenosine metabolism and transport, as well as

the expression of adenosine receptors in T and B lymphocytes Sakowicz-Burkiewicz et al. (2011). These changes lead to dysfunctional B and T lymphocytes, resulting in lowered proliferative potential and decreased immunoglobulin synthesis by B cells in response to antigenic stimulation Hameed et al. (2015). The most compelling evidence for humoral immunodeficiency in diabetic patients comes from vaccination studies Koh et a1. 2012. People with diabetes not only exhibit weaker antibody responses to various vaccines Richardson et al. (1933), Muszkat et a1. (2003), Bouter et a1. (1992), Alavian et al (2010), but they also experience a shorter duration of sero-protection after some vaccination Tamer et al. (2005), Kiliç et al. (2003). In non-infectious conditions, previous studies have shown significantly higher levels of IGA and IGG in diabetics compared to non-diabetics Ardawi et al. (1994), Rodriguez-Segade et al. (1996), Asare-Anane et al. (2018), serum IGM levels do not show significant differences. Our research showed a significant decrease in IGM and IGG levels in sepsis patients with T2DM compared to non-diabetics. These indicates that T2DM patients might experience lymphocyte dysfunction and humoral immunodeficiency, potentially weakening the exaggerated inflammatory cascade and representing a beneficial adaptive reaction in the case of sepsis.

Research has demonstrated that individuals with T2DM typically exhibit elevated levels of C4, C3, McMillan et al. (1980) C2, and Factor B Moin et al. (2021) at baseline. Additionally, hepatocytes are well-documented to produce relatively high levels of CRP in patients with T2DM. The elevated levels of components Shim et al. (2020) and CRP Stanimirovic et a1. (2022) have been correlated with the development of T2DM. In our study, we observed higher plasma concentrations of C4 in diabetic patients, whereas the plasma levels of C3 and CRP remain unchanged. These changes might be influenced by the interplay of underlying inflammation in both T2DM and sepsis. The potential significance of these changes warrants further research and exploration. The discrepancies between our findings and others in non-infectious conditions could be linked to the immune pathological process specific to sepsis in the context of T2DM. A recent study reported that elevated levels of endogenous IGA and IGG on the first day of diagnosis were associated with reduced 90-day survival in sepsis patients Alagna et al. (2021). However, there was no association found between IGM levels and survival. Our cohort study focused on sepsis, T2DM, immunity, and their impact on mortality to explain the interplay between them. Our study has several strengths: Our analysis includes a broad spectrum of various departments' patients with different sepsis severities, and our results may have implications for initial decisions of therapeutic options and allocation of health care resources. Unlike most prior studies, potential confounders such as age, sepsis severity, and co-morbidities were measured and accounted for PSM in our cohort, which increased the credibility of the results. The results of our study will benefit the design of clinical trials for sepsis outcomes and stimulate fundamental medical investigation. Future research is essential to explore the exact biological etiology of this association in epidemiology.

Limitations

Despite employing PSM to address potential confounders, our study had several limitations. First, our retrospective single-center design limited access to crucial information regarding the duration, severity, pre-hospitalization anti-diabetic medication history in T2DM patients, and the degree of glycemic control during their hospital stay. Second, existing study has shown a positive impact on mortality reduction in patients whose treatment for antiglycemic, antihypertensive, and lipid management aligns with recommended models Sun et al. (2021); however, we lacked data on the long-term control of blood pressure, blood lipids, and blood glucose preceding hospital admission of patients within our cohort, thus hindering an assessment of the influence of these factors on the study outcomes. Third, selection bias may arise in this study owing to its retrospective and single-center nature.

CONCLUSIONS

Our study contributes to the growing body of evidence suggesting that sepsis patients may experience benefits when they have comorbid T2DM. Specifically, we observed that T2DM patients with sepsis had a reduced risk of 28-day and 90-day in-hospital mortality compared to non-diabetics. This observation suggests that T2DM itself might lead to a more favorable prognosis and outcomes in sepsis cases. These findings hold significant implications for the current clinical evaluation and management of sepsis.

Moreover, our study indicated that T2DM patients might have dysfunctional lymphocytes, potentially dampening the uncontrolled systemic response during sepsis. To unravel the underlying mechanisms responsible for the protective effect of T2DM in sepsis, further research combining animal models, in vitro studies, and epidemiologic investigations is crucial. Identifying these potential mechanisms and screening appropriate immunomodulatory agents could be immensely valuable in enhancing the prognosis of sepsis.

DECLARATIONS

Data Availability

The data are available on reasonable request to the corresponding authors with permission of Beijing Tongren Hospital.

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