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Impact of Sodium-Glucose Co-Transporter 2 Inhibitor on the Development and Progression of Sepsis-Associated Acute Kidney Injury

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ABSTRACT

Background: Sodium-glucose co-transporter 2 inhibitors, which improve heart and kidney health in those with diabetes, show hope for lowering the risk of AKI. Even so, it is still not clear how SA-AKI affects the timing or final health of patients. This case-control study aimed to see if SGLT2i therapy prior to diagnosis with SA-AKI influenced the occurrence of SA-AKI in critically ill patients with sepsis.

Methods: In all, 664 patients were studied, with 361 having SA-AKI and 303 diagnosed with sepsis syndromes.

Results: Among those enrolled, SGLT2i had a significant and elevated effect on the risk of SA-AKI, with an HR of 10.812 (95% CI: 7.535–15.516, p < 0.001). After checking for other risk factors in a statistical model, giving SGLT2i treatment was still linked to SA-AKI (HR = 6.311, 95% CI: 4.388–9.076, p < 0.001).

Conclusions: Overall, the study found that patients who had used SGLT2i before might be more likely to experience SA-AKI if they also had sepsis syndromes.

Trial Registration: The Clinicaltrials.gov number for this trial is NCT06902493.

Keywords: Kidney injuries, sepsis, sepsis with kidney complications, and SGLT2i

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BACKGROUND

In critically ill patients, sepsis is linked to 25–75% of reported acute kidney injury (AKI) cases. Though nobody has agreed on a unique definition for SA-AKI, it has been suggested to happen when sepsis, based on the Sepsis-3 criteria and AKI, described by the KDIGO guidelines, exists at the same time (Zarbock et al., 2023). Even though SA-AKI is found most often in the most severe cases, measuring its actual incidence and prevalence is hard. There is no commonly accepted explanation for SA-AKI, and each study generally uses a different way to diagnose sepsis and AKI, which prevents straightforward generalization of results. A review of 47 observational studies on SA-AKI pointed out this issue, because three definitions for AKI and three ways to diagnose sepsis or septic shock were included (Liu et al., 2020). Besides, a combination of many elements can cause AKI in critically sick patients. Because the clinical environment changes, patient groups are not the same, and reporting key outcomes differs; this creates more difficulty in understanding what causes SA-AKI.

Finally figuring out the exact reason sepsis leads to AKI is still a challenge. Initial research thought that S-AKI was mainly caused by a drop in blood flow to the kidneys. Despite earlier knowledge, scientists now find that the blood flow to the kidneys can be increased or not change in many cases of sepsis (Shi et al., 2024). Instead, new studies emphasize that problems with the small blood vessels, inflammation of blood vessel walls, and abnormal immune system reactions can lead to S-AKI. As a result of the inflammation in sepsis, cytokines are released in large numbers, neutrophils become active, and the mitochondria are not working correctly, all helping to injure the kidneys.

A special feature of SGLT2i is that they help lower blood sugar in a way that other drugs do not. SGLT2 inhibitors prevent glucose and sodium from being taken back into the body and result in higher

urine levels of both substances for those with T2DM. Using SGLT2 inhibitors for glucose control has been shown to significantly lower the odds of cardiac complications and reduce the risk of dying from heart disease (Donnan et al., 2019). Moreover, these results apply to patients with or without diabetes and both heart failure types, as they protect reduced and preserved ejection fraction (EF). Most of these medicines' health advantages for the heart come from their ability to increase sodium and sugar excretion. Such activities improve blood pressure control and decrease oxidative stress and inflammation.

Researchers found that SGLT2i use in people with long-term diseases such as T2DM or CKD is linked to a 22% reduction in AKI (Risk Ratio [RR] = 0.78, 95% CI: 0.67–0.89). In patients with CKD, SGLT2 inhibitors prevented AKI by a proportion of 19% (RR = 0.81, 95% CI: 0.69–0.97) (Wang et al., 2024). However, in patients with HF, no significant increase or decrease in AKI risk was observed with the use of SGLT2 inhibitors, suggesting a neutral effect on kidney outcomes in this group.

In another two meta-analyses, the safety of SGLT2i was evaluated in patients with T2DM. Results showed that using SGLT2i was associated with a decreased risk of AKI (17). SGLT2i, compared to other glucose-lowering drugs, was associated with a lower risk of AKI (OR = 0.50, 95% CI 0.38–0.66, I^2 = 96%). Furthermore, they demonstrated a significant reduction in the incidence of AKI hospitalization (OR = 0.54, 95% CI 0.43–0.68, I^2 = 92.0%) (18). In another meta-analysis, 25,172 HF patients were included from 16 RCTs. SGLT2i led to a 28% reduction in the risk of AKI progression (RR = 0.72, 95% CI 0.61-0.85, p<0.0001) (19). However, these analyses primarily focused on non-septic populations, and the results may not be generalized to septic patients.

Several mechanisms that may explain the renal protective effects of SGLT2 inhibitors. These drugs reduce sodium reabsorption in the proximal convoluted tubules, activating the tubuloglomerular feedback mechanism and leading to vasoconstriction of the afferent arteriole, lowering intraglomerular pressure (Liang et al., 2025). Additionally, they improve renal cortical oxygenation by decreasing metabolic demand and increasing erythropoietin production. This class also induces metabolic reprogramming, reducing oxidative stress, inflammation, and kidney hypoxia.

This study aims to investigate the impact of the prior use of SGLT2i on the incidence of SA-AKI in critically ill patients with sepsis syndromes.

METHODS

This study was initiated after ethical approval (AFHSRMREC/2024/Pharmacy/751) from the Armed Forces Hospitals Southern Region-Institutional Review Board (AFHSR-IRB) SA (registration

number, H-06-KM-001), waived informed consent, and protocol registration on clinicaltrials.gov (NCT06902493, protocol ID: SGLT2I-AKI).

According to the literature, the reported AKI incidence in septic shock is 51% to 64%. Assuming alpha (α) of 0.05 (5% significance level, two-tailed) and power (1-β) of 80% (0.80). To detect a 20% relative reduction in AKI incidence (detectable difference), the minimum required sample size is 292 per group. This sample size is calculated using the Cochran-Armitage equation. All adult (≥ 18 years) patients who were admitted to the ICU with sepsis syndromes (sepsis or septic shock), according to the sepsis-3 definition, were assessed for enrollment if they met the eligibility criteria (Anker et al., 2021). Records of the critical care units of Armed Forces Hospitals Southern Region (AFHSR) from April 1, 2024, to March 1, 2025, were reviewed. The exclusion criteria were missing data, renal transplant or tumor, solitary kidney, established CKD, obstructive uropathy, renal artery stenosis, and pregnancy.

In this single-center case-control study, data collection involved the following: history taking, initial clinical examination, sequential organ failure assessment (SOFA), acute physiology and chronic health evaluation (APACHE II), source of sepsis, and admission laboratory investigations, including serum creatinine, blood urea nitrogen, electrolytes, coagulation profile, and inflammatory markers. Medication history was also recorded, especially the use of SGLT2 inhibitors.

The patients were categorized according to their primary outcome into the SA-AKI (cases) and the non-SA-AKI (control) group. AKI was defined according to the "Kidney Disease Improving Global Outcomes" (KDIGO) criteria as "increase in serum creatinine: ≥ 0.3 mg/dL within 48 hours or an increase to ≥ 1.5 times baseline or urine output reduction: < 0.5 mL/kg/hour for ≥ 6 hours" (Cannon et al., 2020). The primary outcome is the odds of SA-AKI in patients with prior use of SGLT2. The secondary outcomes were vasopressor use, ICU length of stay, 7-day mortality, and 28-day all-cause mortality. This study was conducted and reported according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).

STATISTICAL ANALYSIS

The data were entered into a computer and analyzed using the IBM SPSS (IBM Corp., Armonk, NY, USA) version 26.0. Qualitative variables are described using numbers and percentages." Quantitative variables are described using means or medians. Normally distributed variables are described as the mean ± standard deviation (SD). Non-normally distributed variables are presented as the median ± interquartile range (IQR). The results' significance was judged at the 5% (Boorsma et al., 2021). The chi-square test,

Fisher's exact test, the Monte Carlo correction, the Mann–Whitney test, and Student's t test were used. The Hosmer–Lemeshow goodness-of-fit test was used in multivariate adjusted regression analysis.

RESULTS

In this case-control study, 1,149 sepsis/septic shock patients were screened for eligibility. Of them, 485 were excluded according to the following: established CKD (413), obstructive uropathy (22), solitary kidney (5), renal transplant or tumor (4), and pregnancy (6). Finally, 664 patients were involved in the analysis: patients with SA-AKI (case group, n = 361) and those with sepsis syndromes without AKI (control group, n = 303). The baseline characteristics revealed several significant differences between the two groups. Patients in the case group (n = 361) were more likely to have a higher median SOFA score (7 vs. 5, $p < 0.001$) and a higher APACHE II score (20 vs. 20, $p < 0.001$), indicating greater severity of illness. Pneumonia was the most common source of sepsis (42.5%), followed by UTI (13%) (Uchimido et al., 2019). Additionally, the case group had a significantly higher prevalence of medical comorbidities, including hypertension (48.2% vs. 34.0%, $p < 0.001$), DM (41.6% vs. 24.8%, $p < 0.001$), and atrial fibrillation (25.5% vs. 16.8%, $p = 0.008$). Furthermore, a significantly higher proportion of patients in the case group were prescribed SGLT2i before hospital admission than the control group (79.2% vs. 26%, $p < 0.001$). (Table 1)

Regarding lab investigations, the results revealed several significant differences in key laboratory parameters. Patients in the case group had notably higher levels of BUN, serum creatinine, potassium, sodium, and procalcitonin. Both groups demonstrated similar elevated arterial lactate levels, indicating ongoing tissue hypoperfusion and metabolic distress. (Table2)

Regarding secondary outcomes, results revealed significant differences in several key clinical measures. Patients in the case group had a higher rate of vasopressor use, with 38.5% requiring vasopressors compared to 19.1% in the control group ($p = 0.001$). Furthermore, mortality rates were significantly higher in the case group across the two measured time points (Ince C et al., 2016). The 7-day mortality rate was 20.2% in the case group versus 12.2% in the control group ($p = 0.006$), indicating an increased risk of early death associated with AKI (McGuire et al., 2021). Similarly, the case group's 28-day mortality rate was substantially elevated at 46.8%, compared to 13.9% in the control group ($p < 0.001$). Despite these differences in mortality, there was no statistically significant difference in the median length of ICU stay between the two groups (case group: 7 days; control group: 8 days; $p = 0.966$). (Table 3)

In a univariate regression analysis, prior use of SGLT2i emerged as a strong and statistically significant predictor of SA-AKI among the enrolled patients, with a hazard ratio (HR) of 10.812 (95%

confidence interval: 7.535–15.516, $p < 0.001$) (Rahil et al., 2025). This association remained robust after adjusting for potential confounding variables in a multivariate regression model, where SGLT2i use was identified as an independent risk factor for SA-AKI, showing a strong effect size with an HR of 6.311 (95% CI: 4.388–9.076, $p < 0.001$). (Table 5)

DISCUSSION

Sepsis-associated acute kidney injury (SA-AKI) is a critical complication that significantly impacts the prognosis of patients suffering from sepsis. This condition occurs when organ-wide inflammation associated with an infection rapidly reduces kidney function. SA-AKI occurs as a result of kidney damage caused by renal hypoperfusion, inflammation, and excess oxidative stress.

Because of SA-AKI, people experience serious results such as staying in the hospital for a long time, facing higher healthcare costs, and their risk of death increases (Uchimido et al., 2019). Due to the growing rate of sepsis and its related complications, new preventive and treatment options are urgently required.

SGLT2i has dramatically changed how T2DM is treated and benefits the kidneys. It helps slow the advancement of CKD and lowers a person's risk of AKI.

It was studied whether treatment with SGLT2i influences SA-AKI occurrence in patients with sepsis. To achieve this aim, the study included adult patients given a sepsis syndrome diagnosis as the control group and those with SA-AKI as the case group (Peerapornratana et al., 2019). The information used in the data was extracted from patients' medical records, including their details, symptoms, and lab results. As we know, this study is the first to consider whether SGLT2i use might affect SA-AKI outcomes.

Researchers matched patients who had SA-AKI to individuals with sepsis or septic shock but who did not have AKI. The study involved 361 people with SA-AKI and 303 people without renal injury. Analysis of baseline characteristics revealed that patients in the SA-AKI group scored higher in SOFA and APACHE II, suggesting they were more ill at the onset. Infection from the lungs was the leading cause of sepsis for both groups, making up 42.5% of the cases, more so than infection of the urinary tract, at 13%. Those diagnosed with SA-AKI more commonly had problems such as hypertension, DM, and atrial fibrillation (Post EH et al., 2017). Significant numbers of people in the SA-AKI group received SGLT2 inhibitors prior to being admitted to the hospital.

As seen by laboratory tests, BUN, serum creatinine, potassium, sodium, and procalcitonin were higher in the SA-AKI group than in the control group. The arterial lactate was the same between the two groups, meaning their tissues lacked enough blood and were still struggling metabolically. The report

indicates that patients with SA-AKI often have more serious changes in the body, which could lead to more problems with AKI during sepsis (Heyman et al., 2024). Compared to the DA-AKI group, the SA-AKI group was more likely to require vasopressors (38.5% vs. 19.1%), had greater mortality at day 7 (20.2% vs. 12.2%) and day 28 (46.8% vs. 13.9%) (Solomon et al., 2022). Even though mortality was higher in the group with COVID-19, the median time spent in the ICU was the same in both groups. It appears that SA-AKI can lead to greater early mortality, but it does not usually extend the duration of ICU treatment for septic patients.

Based on the analysis, past use of SGLT2i was shown to have a strong and independent effect on SA-AKI. Compared to patients who were not prescribed SGLT2i, people who had used SGLT2i before were 10.812 times more likely to contract SA-AKI, according to univariate analysis. Correcting for hypertension, DM, atrial fibrillation, hepatic disease, and the diagnosis of septic shock raises the hazard ratio to 6.311 (Xiang et al., 2021). This means the link between SGLT2i use and SA-AKI does not weaken when other factors relevant to the outcome are considered. According to these results, patients with sepsis taking SGLT2i drugs may experience SA-AKI and therefore should be watched closely and offered alternate therapies if they are at high risk.

Inhibiting SGLT2 can result in extra sodium in the distal nephron, so the oxygen requirement of the thick ascending loop of Henle is also raised. Myoglobin contributes to the hypoxia of the kidney's inner part, which is thought to lead to AKI. SGLT2i worsens medullary hypoxia that is already part of diabetic kidney disease (Zaitoun et al., 2024). Medicines known as SGLT2i result in excessive sugar in the urine and loss of sodium, which can cause dehydration, mainly in elderly patients, those using diuretics or RAAS inhibitors, and those eating less or with gastrointestinal problems.

Despite what we learn from this study, it is important to recognize its flaws. Since all patients were treated in one center, some findings might not reflect what could happen in other healthcare settings. Also, because facts about previous SGLT2i were collected after the event, there can be bias in how these drugs and their aftereffects are interpreted. Future multicenter, prospective studies are needed to validate these findings and explore the underlying mechanisms by which SGLT2i may influence renal outcomes in the context of sepsis.

CONCLUSION

Scientists learned from close examination of 664 critically ill patients who had sepsis syndromes that receiving SGLT2 inhibitors potentially increased the risk of sepsis-associated acute kidney injury (SA-

AKI). Patients who had taken SGLT2 inhibitors earlier were 6.311 times more likely to develop SA-AKI, once adjusting for other variables, as found by the study. SA-AKI developed in 361 out of 1323 patients, and 79.2% of these had taken SGLT2i drugs, while only 26% in the control group did. The group of patients also had more serious disease, demanded additional vasopressor treatment, and had a higher death rate within 7 days (20.2% compared to 12.2%) as well as 28 days (46.8% vs. 13.9%).

They suggest that, although SGLT2 inhibitors are thought to protect from kidney damage in stable patients, in critically ill septic patients, they may carry a new risk. The authors propose that SGLT2 inhibitors may cause the kidney's thick ascending loop to require more oxygen, leading to increased hypoxia and a risk of AKI during sepsis. In addition, drugs that increase urine can lead to worse dehydration in those most at risk of sepsis. The research faces some limitations, such as being a retrospective study and potentially bias-driven, but it is the first to study how SGLT2 inhibitors affect SA-AKI outcomes. The findings suggest that clinicians treating septic patients who use SGLT2i should take action immediately, and then multicenter studies are needed to confirm and explore these observations.

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Conflicts of interest/Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could influence the work reported in this research.

Availability of data and material

The data and material are available at reasonable requests from the corresponding author.

Code availability

N/A

Authors' contributions

The corresponding author, M. A. Alshrahili, formulated the research question, collected administrative approvals, performed the screening process, and participated in writing this article. H. S. Almfalh, S. A. Alqahtani, A. Salawi, A M Alfageeh, Z. H Alshehri, A. M. Ayyasy, K Q. Ghazwani, T. A. Albarqi, N. A. Shahar, F. O. Zaylaee, F. A. Shahhar and H. S. Alahmari participated in data collection and editing this article. The author, I. Ahmed designed the statistical plan and performed the statistical analysis.

Ethics approval

This study was approved by the Armed Forces Hospitals Southern Region-Institutional Review Board

(AFHSR-IRB, H-06-KM-001), Saudi Arabia (AFHSRMREC/2024/Pharmacy/751).

Consent to participate

Waived by AFHSR-IRB, H-06-KM-001.

Consent for publication

N/A

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Table 1: The baseline characteristics of the two groups studied

	Overall (n = 664)	**Control Group (n = 303)**	**Case Group (n = 361)**	***p* value**
Sex (Male)	337 (54.1)	176 (58.1)	183 (50.7)	0.061
Age (years)	56 (9.0)	56 (7.5)	57 (7.0)	0.336
Glasgow coma scale	13 (3)	13 (3)	13 (3)	0.224
SOFA score	6 (4)	5 (3)	7 (5)	<0.001*
APACHE II score	22 (9)	20 (6)	26 (10)	<0.001*
Sepsis	403 (60.7)	226 (74.6)	177 (49.0)	<0.001*
Septic shock	261 (39.3)	77 (25.4)	184 (51.0)	
Medical history				
Hypertension	277 (41.7)	103 (34.0)	174 (48.2)	<0.001*
Diabetes	225 (33.9)	75 (24.8)	150 (41.6)	<0.001*
Atrial fibrillation	143 (21.5)	51 (16.8)	92 (25.5)	0.008*
Stroke	129 (19.4)	58 (19.1)	71 (19.7)	0.922
Hepatic	125 (18.8)	73 (24.1)	52 (14.4)	0.002*
Heart failure	116 (17.5)	56 (18.5)	60 (16.6)	0.540
Recent Surgery	75 (11.3)	32 (10.6)	43 (11.9)	0.624
Obstructive lung disease	57 (8.6)	29 (9.6)	28 (7.8)	0.408
Malignancy	47 (7.1)	20 (6.6)	27 (7.5)	0.762
Source of sepsis				
Pneumonia	282 (42.5)	132 (43.6)	150 (41.6)	0.636
UTI	86 (13.0)	33 (10.9)	53 (14.7)	0.164
Mixed	82 (12.3)	45 (14.9)	37 (10.2)	0.077
SBP	65 (9.8)	42 (13.9)	23 (6.4)	0.002*
CRBSI	46 (6.9)	18 (5.9)	28 (7.8)	0.443
Cellulitis	34 (5.1)	9 (3.0)	25 (6.9)	0.022*
Abdomen	35 (5.3)	10 (3.3)	25 (6.9)	0.054
DFI	34 (5.1)	14 (4.6)	20 (5.5)	0.724
Systolic B.P (mmHg)	75.6 ± 31	82.0 ± 27	69.5 ± 33	<0.001*
Diastolic B.P (mmHg)	45.4 ± 22	49.9 ± 18	41.5 ± 24	<0.001*
Heart rate (beats/min)	113.4 ± 20	112.6 ± 21	114.0 ± 20	0.387
Temperature (°C)	38.1 ± 0.9	38.2 ± 0.8	38.0 ± 1.0	0.027*
Respiratory rate (cycles/min)	26.8 ± 7.2	25.5 ± 7.3	27.8 ± 7.0	<0.001*
Urine output				
Anuria	33 (4.9)	-	33 (9.1)	<0.001*
Less than 0.3	159 (23.9)	-	159 (44)	
Less than 0.5	169 (25.5)	-	169 (46.8)	
More than 0.5	303 (45.6)	303 (100)	-	
SGLT2i				
Prior use	365 (55)	79 (26)	286 (79.2)	<0.001*
Dapagliflozin	305 (46)	54 (17.8)	251 (69.5)	
Empagliflozin	60 (9)	25 (8.2)	35 (9.7)	

SOFA: sequential organ failure assessment score, APACHE II: acute physiology and chronic health evaluation version II score, SBP: spontaneous bacterial peritonitis, B.P.: Blood pressure.
Categorical variables are expressed as numbers (percentages) and compared using the Chi-square test.
Normally distributed continuous variables are expressed as mean ± standard deviation and compared using Student's t-test.
Non-normally distributed continuous variables are expressed as median (interquartile range) and compared using Mann-Whitney's test.
**: Statistically significant at p ≤ 0.05*

Table 2: The initial laboratory investigations in the two groups studied

	Overall (n = 664)	Control Group (n = 303)	Case Group (n = 361)	*p* value
Hemoglobin (g/dl)	10.3 (3.4)	10.8 (3.4)	10.1 (3.3)	0.280
WBCs (x10^3 cells/ µl)	17 (13)	14 (12)	17 (11.5)	0.057
Platelets (x10^3/µl)	218 (138)	211 (162)	228 (134)	0.002*
INR	1.35 (0.38)	1.35 (0.4)	1.37 (0.35)	0.249
C-reactive protein (mg/l)	114.3 (80)	116.8 (77)	112.6 (83)	0.662
Procalcitonin (ng/ml)	2.3 (1.9)	2.3 (2)	2.4 (1.9)	0.027*
Arterial lactate (mmol/l)	5.7 ± 2.1	5.6 ± 2.2	5.7 ± 2.1	0.795
BUN (mg/dl)	95.8 (90.6)	60.3 (34.4)	146.5 (82.8)	<0.001*
Serum creatinine (mg/dl)	2 (4.3)	0.9 (0.3)	5.0 (5)	<0.001*
Serum Na (mmol/l)	133 (12)	132 (12)	134 (13)	0.016*
Serum K (mmol/l)	4 (1.4)	3.9 (1.1)	4.2 (1.2)	0.004*

WBCs: white blood cell count, INR: international normalized ratio, BUN: blood urea nitrogen.
Normally distributed continuous variables are expressed as mean ± standard deviation and compared using Student's t-test.
Non-normally distributed continuous variables are expressed as median (interquartile range) and compared using Mann-Whitney's test.
**: Statistically significant at p ≤ 0.05*

Table 3: The secondary outcomes in the two groups studied

	Overall (n = 664)	Control Group (n = 303)	Case Group (n = 361)	*p* value
Vasopressor use	197 (29.7)	58 (19.1)	139 (38.5)	0.001*
ICU length of stay	8 (7)	8 (7)	7 (7)	0.966
7-day mortality	110 (16.6)	37 (12.2)	73 (20.2)	0.006*
28-day mortality	211 (31.7)	42 (13.9)	169 (46.8)	< 0.001*

SGLT2i: Sodium-glucose co-transporter 2 inhibitor.
Non-normally distributed continuous variables are expressed as median (interquartile range) and compared using Mann-Whitney's test.
**: Statistically significant at p ≤ 0.05*

Table (4): Multivariate Adjusted Regression Analysis of Risk Factors for Sepsis-Associated Acute Kidney Injury

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*p value*	HR (95%CI)	*p value*
Prior use of SGLT2i	10.812 (7.535–15.516)	<0.001*	6.311 (4.388–9.076)	<0.001*
Hypertension	1.807 (1.319–2.475)	<0.001*	0.627 (0.450–0.873)	0.006
Diabetes	2.161 (1.547–3.020)	<0.001*	0.880 (0.617–1.256)	0.482
Hepatic disease	0.530 (0.357–0.787)	0.002*	0.202 (0.128–0.320)	<0.001*
Atrial fibrillation	1.774 (1.215–2.590)	0.003*	0.974 (0.643–1.475)	0.900
Septic shock	3.051 (2.192–4.248)	<0.001*	1.448 (0.999–2.099)	0.051

SGLT2i: Sodium-glucose co-transporter 2 inhibitor.
Hosmer–Lemeshow goodness-of-fit model.
HR: Hazard ratio, 95% CI: 95% confidence interval, LL: lower limit, UL: upper limit.
**: Statistically significant at p ≤ 0.05*