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Prognostic implications of system inflammation response index in atrial fibrillation patients with type 2 diabetes mellitus

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Systemic inflammation plays a crucial role in the pathogenesis and prognosis of diabetes and cardiovascular diseases. System inflammation response index (SIRI), is an emerging biomarker designed to assess the extent of systemic inflammation. We aimed to delineate the prognostic significance of SIRI in patients with both AF and type 2 diabetes mellitus (T2DM). Utilizing the Medical Information Mart for Intensive Care IV (MIMIC-IV) (v2.2) repository, subjects divided into three groups based on the SIRI index. The primary endpoint of our study was all-cause mortality during hospitalization, with one-year mortality serving as the secondary endpoint. A cohort of 2054 AF and T2DM patients participated. COX regression analysis revealed elevated SIRI levels as an independent risk factor for both in-hospital and 1-year mortality. 192 patients died during hospitalization, and 265 died during the follow-up of 1 year. When treating the SIRI as a continuous variable, a higher SIRI was significantly associated with increased all-cause mortality both in-hospital [hazard ratio (HR) 1.015, 95%CI 1.010–1.020, $P = 0.015$] and 1-year (HR 1. 016, 95%CI 1.008–1.015, $P = 0.012$). Additionally, compared to patients with the lowest tertiles of SIRI, those with the highest tertiles of SIRI possessed significantly higher all-cause mortality both in-hospital and 1-year after multivariable adjustment, and this relationship remained pronounced in AF and T2DM patients [in-hospital mortality (HR: 1.863, 95% CI 1.189–2.918, $P = 0.007$); one-year mortality (HR: 2.143, 95% CI 1.621–2.831, $P < 0.001$)]. Our RCS analyses indicated a pronounced linear association between SIRI and mortality in T2DM (p-value for non-linear < 0.001). In AF patients with T2DM, high SIRI is an independent predictor of poor survival and may be helpful for patient's risk stratification.

Keywords Atrial fibrillation, Type 2 diabetes mellitus, Systemic immune-inflammation index, MIMIC-IV, Prognostic indicator, Restricted cubic spline

Diabetes is a pressing global health issue, with its prevalence among adults escalating each year[1]. Recent data indicates a climb in the frequency of complications arising from diabetes[2,3]. Without adequate management, diabetes can lead to severe chronic conditions that not only diminish the health outlook for those affected but also increase health care costs[4]. Hence, pinpointing individuals at elevated risk is essential for effective diabetes management and the mitigation of its complications. Atrial fibrillation (AF) is the most type of heart arrhythmia, which is a major risk factor for ischemic stroke and provokes important economic burden along with significant morbidity and mortality[5]. Research has demonstrated that Type 2 diabetes mellitus (T2DM) acts as a standalone risk factor for AF occurrence[6]. Individuals with diabetes exhibit a greater incidence of AF than those without diabetes[7,8]. Moreover, diabetic individuals with AF face an escalated risk of experiencing stroke, heart failure, and mortality from any cause, compared to their counterparts without diabetes[9].

In this context, the system inflammation response index [SIRI, (neutrophil-count* monocyte-count)/ lymphocyte-count], emerges as a novel inflammatory marker with predictive capabilities across various disease spectrums including diabetes, acute ischemic stroke, kidney diseases, and increased cardiovascular disease risk[10–14]. Recent findings have established a connection between AF and the inflammatory responses and endothelial dysfunction in the heart, attributed to systemic inflammation[15]. This chain of events fosters

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a pro-inflammatory state that contributes to heart remodeling and dysfunction. Recent research highlights the strong correlation between various systemic inflammatory markers including C-reactive protein (CRP), neutrophil count, monocyte count, neutrophil-to-lymphocyte ratio (NLR), lymphocyte count, systemic immune-inflammation index (SII), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR), and the development of AF, ventricular arrhythmias (VA), and bradyarrhythmias[16]. Another study showed that SIRI can independently predict AF in patients with ST-Elevation Myocardial Infarction (STEMI) after post-percutaneous coronary intervention (PCI), with being positively correlated to worsened outcomes[17]. Chronic low-grade inflammation is increasingly recognized as a core pathological element in the cardiovascular manifestations of Diabetes Mellitus (DM), alongside hyperglycemia, hyperlipidemia and hypertension[18]. Within the DM context, dysfunctional adipose tissues release pro-inflammatory cytokines while the secretion of anti-inflammatory adipokines diminishes, leading to vascular endothelial damage, myocardial injury, oxidative stress, and thrombosis[19]. Furthermore, inflammation is implicated as a mediator of insulin resistance, creating a link to obesity, DM, and cardiovascular diseases (CVD)[20]. A recent study further shows that heightened levels of SIRI are independently linked to an elevated risk of CVD among the DM cohort with a high body mass index (BMI > 24 kg/m2), asserting its clinical importance over high-sensitivity C-reactive protein (hs-CRP)[21].

SIRI is a novel systemic inflammation index that was suggested in predicting poor outcomes of diabetic cardiovascular complications. Distinguished as a novel biomarker, SIRI has demonstrated superior predictive capabilities compared to other inflammatory markers, suggesting enhanced predictions for cardiovascular disease risks and all-cause mortality[22]. However, the correlation between SIRI and AF in diabetic patients remains unclear. Predominantly, the diabetic population is comprised of individuals diagnosed with T2DM. This study aims to explore the association between the SIRI and the in-hospital as well as 1-year mortality in patients with AF and T2DM admitted to the intensive care unit (ICU). The outcomes of this study are expected to contribute to the development of timely diagnostic and therapeutic strategies, thereby improving the prognosis for this patient group. Furthermore, this study seeks to shed light on the prognostic significance of SIRI in predicting patient outcomes, offering critical insights that could guide clinical decision-making.

Methods

Data source and ethics statement

This study utilized a retrospective observational design, drawing upon data from the publicly accessible MIMIC-IV database, which contains medical records of more than 70,000 patients admitted to the intensive care unit (ICU) of Beth Israel Deaconess Medical Center from 2008 to 2019. As the dataset adheres to protocols that ensure patient confidentiality, informed consent for data collection was not required. The analysis was performed using version 2.2 of the database, the latest version available at the time of the study. For access to the required datasets, author Yang Chen completed the Collaborative Institutional Training Initiative (CITI) program and subsequently extracted the necessary variables for this manuscript (name ID: 9652605, record ID: 60069524). The research was conducted in strict accordance with the ethical principles outlined in the Declaration of Helsinki.

Inclusion and exclusion criteria

This study concentrated on a subset of 2,054 individuals from the MIMIC-IV database, all of whom were diagnosed with both AF and T2DM upon admission. AF was diagnosed using ICD-9 code 42,731 or ICD-10 codes I4891, I480, I482, I481, I4820, I4819, I4821, and I4811. And T2DM was identified using ICD-9 code 2500, 2501, 2502, 2503, 2508, 2509, 2504, 2505, 2506, 2507 or ICD-10 codes E110, E111, E116, E118, E119, E120, E121, E126, E128, E129, E130, E131, E136, E138, E139, E140, E141, E146, E148, E149, E102, E103, E104, E105, E107, E112, E113, E114, E115, E117, E122, E123, E124, E125, E127, E132, E133, E134, E135, E137, E142, E143, E144, E145 and E147. Patients lacking documented diagnoses of both conditions at the time of admission were excluded from the analysis. Further exclusion criteria encompassed individuals with a history of hematologic diseases (such as thrombocytosis and granulocytopenia) and autoimmune disorders. We also excluded patients with an ICU stay shorter than 6 h, those under the age of 18, or those whose records were missing more than 30% of the data. For individuals with multiple hospital admissions, only data from the initial admission were considered. Figure 1 offers a detailed visual representation of the patient selection process, illustrating the precise inclusion and exclusion criteria applied.

Data extraction

For data extraction purposes, our methodology utilized Structured Query Language (SQL) alongside Navicat software (version 15). When addressing clinical parameters recorded multiple times throughout a patient's hospitalization, average values were calculated and integrated into our analysis. The primary indicator of interest, the SIRI, was determined using the equation: neutrophil count * monocyte count / lymphocyte count. Our investigation covered a comprehensive range of potential clinical parameters, including patient demographics, existing comorbidities, laboratory blood tests, vital statistics, prognostic scoring systems, administered medications, interventions and clinical events. The key outcome measured was in-hospital all-cause mortality, covering deaths in both ICU and general ward environments. Furthermore, we evaluated mortality outside the hospital through a one-year follow-up period, serving as the secondary endpoint of our study.

Statistical analysis

Baseline characteristics were assessed and compared between the survivor and non-survivor groups. Continuous variables were presented as means ± standard deviations or as medians accompanied by interquartile ranges. Differences among these were evaluated using Student's t-tests. Categorical variables were expressed as

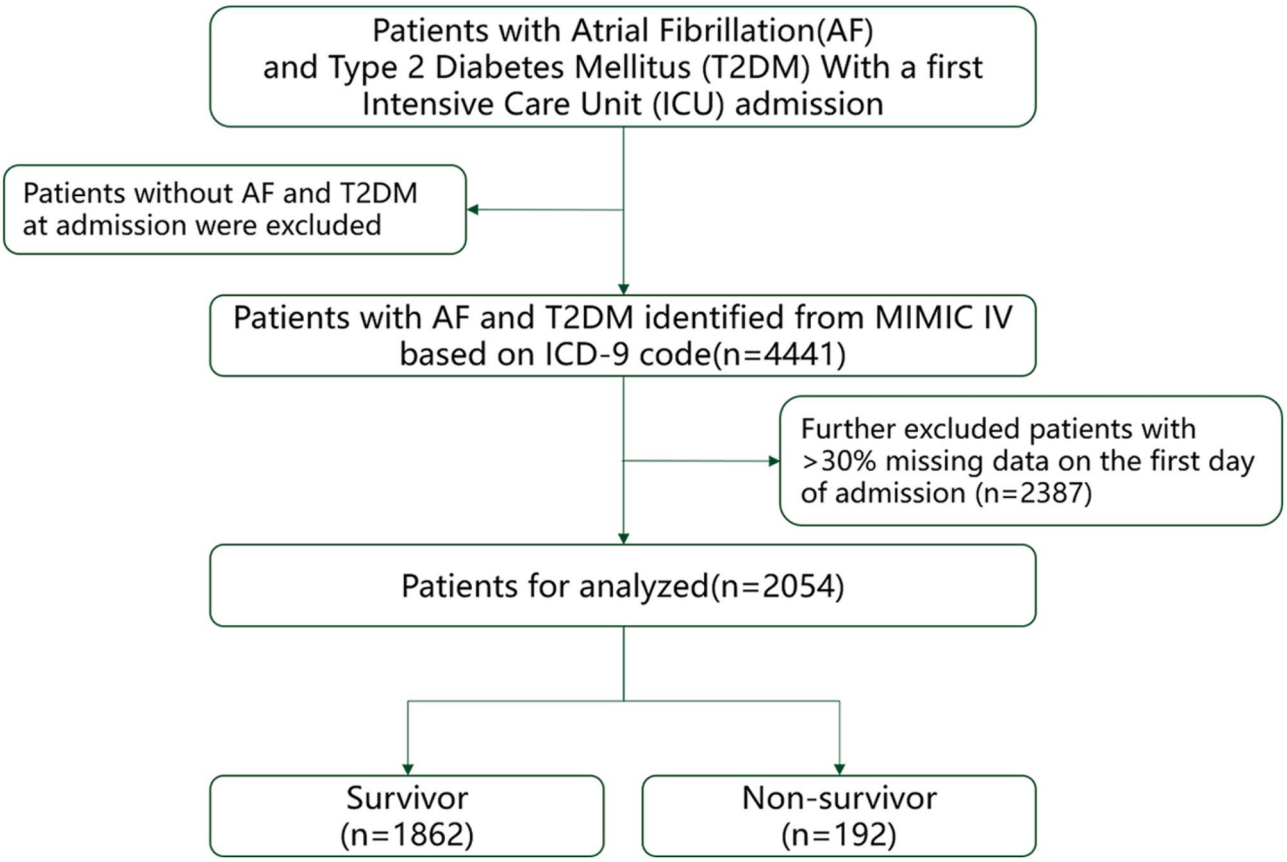

Fig. 1. Selection Flowchart for Patient Analysis: The MIMIC-IV database (version 2.2) holds detailed medical records of 299,712 patients covering 431,243 hospital admissions and 73,181 ICU stays. Within this comprehensive dataset, 4441 patients were diagnosed with both AF and T2DM. From these, individuals who met the exclusion criteria were carefully filtered out, resulting in a total of 2387 patients being removed from the study. The study ultimately included 2054 patients, of which 192 succumbed during the observation period.

frequencies and percentages, with group comparisons conducted using Pearson's chi-square test or Fisher's exact test, depending on appropriateness. The distribution of the SIRI was segmented into tertiles (Tertile 1 < 2.591, Tertile 2 2.591–5.701, Tertile 3 > 5.701).

The multivariate model included the following clinical and prognostic variables: age, gender, body mass index (BMI), hypertension (HBP), stroke, acute myocardial infarction (AMI), respiratory failure (RF), heart failure (HF), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), white blood cell count (WBC), levels of lactate, creatinine, phosphorus, glucose (GLU), hemoglobin A1c (HbA1c), low-density lipoprotein (LDL), high-density lipoprotein (HDL), partial pressure of oxygen (PaO2), the Sequential Organ Failure Assessment (SOFA) score, Acute Physiology Score III (APSIII), angiotensin-converting enzyme inhibitors (ACEIs) use, digoxin, diuretics, antiplatelet agents, albumin, continuous renal replacement therapy (CRRT), invasive ventilation.

The predictive power of SIRI alongside other indices such as Monocyte to Lymphocyte Ratio (MLR), Systemic Immune-Inflammation Index (SII), Systemic Inflammatory Response Syndrome (SIRS), SOFA, Simplified Acute Physiology Score II (SAPS II), and APS III for both in-hospital and one-year patient mortality were evaluated using Receiver Operating Characteristic (ROC) curves. Sensitivity and specificity for each index were determined, alongside the area under the curve (AUC). The optimal threshold for SIRI was derived using Youden's index.

Kaplan-Meier survival curves were constructed, and differences between groups were analyzed using the log-rank test. Hazard ratios (HR) for in-hospital mortality were recalculated using the adjusted Cox model.

Statistical significance was set at a p-value of less than 0.05, with all tests conducted as two-tailed. Youden's index and the optimal cutoff value were computed utilizing SPSS software (version 21), while ROC, Restricted Cubic Splines (RCS), Kaplan-Meier analyses and graphical representations were executed using Stata software (version 16).

Results

Baseline feature

In our study, utilizing data from the MIMIC-IV database, we initially identified 4,441 patients diagnosed with both AF and T2DM. Following the application of predefined exclusion criteria, 2,387 patients were excluded

from further analysis. This resulted in a final analytical cohort of 2,054 hospitalized patients with concurrent AF and T2DM. Within this cohort, 192 patients (representing 9.3% of the total) passed away during their hospital stay, while 1,862 patients survived, as shown in Fig. 1.

Baseline characteristics showed that non-surviving patients had higher SIRI values

Table 1 illustrates the baseline characteristics between survivors and non-survivors during the hospitalization period. Among those assessed, 63.68% were male, with an average age of 67.76 ± 11.54 years. It was observed that non-surviving patients exhibited significantly higher SIRI values compared to the survivor group [9.75 (4.46–17.56) vs. 3.6 (2.04–6.44); $P < 0.001$]. Additionally, marked differences were apparent between the two groups across a range of parameters. Notable divergences were found in the incidence of comorbid conditions such as hypertension, acute myocardial infarction (AMI), chronic kidney disease (CKD), and respiratory failure (RF), alongside variations in laboratory parameters; these included lactate, albumin, creatinine, calcium, magnesium, phosphorus, partial pressure of oxygen (PaO2), hemoglobin, white blood cell count (WBC), platelet count (PLT), neutrophil, lymphocyte, monocyte levels, serum sodium, glucose, total cholesterol (TC), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). Discrepancies were also observed in the scoring assessments, which comprised SOFA, SAPS II, APS III, and Glasgow Coma Scale (GCS). The implementation of CRRT, invasive ventilation, and the utilization of medications (ACE inhibitors, β-blockers, diuretics, antiplatelets, and albumin infusions) exhibited differences across the two groups. Furthermore, the length of hospital stays (LOS) demonstrated variation between the surviving and non-surviving groups.

Elevated SIRI levels serve as a prognostic indicator for mortality in AF and T2DM patients

The analysis demonstrated that high SIRI levels during hospitalization are significant predictors of mortality in patients with AF and T2DM. When analyzed as a continuous variable, SIRI was consistently identified as a significant risk factor for in-hospital mortality across all models: unadjusted [Hazard Ratio (HR) 1.020, 95% Confidence Interval (CI) 1.016–1.024, $P < 0.001$], partially adjusted [HR 1.021, 95% CI 1.017–1.025, $P < 0.001$], and fully adjusted [HR 1.015, 95% CI 1.010–1.020, $P = 0.015$]. This trend persisted in analyses predicting one-year mortality, further establishing SIRI as a significant prognostic marker. Moreover, when categorizing SIRI levels into tertiles, patients within the highest SIRI tertile (Tertile 3) exhibited significantly greater rates of in-hospital and one-year mortality compared with those in the lower tertiles (Tertiles 1 and 2), as evidenced by all P values from log-rank tests being below 0.05. In fully adjusted Cox regression models, using the lowest SIRI tertile as a reference, the highest SIRI tertile displayed a significant positive correlation with both in-hospital all-cause mortality (HR: 1.863, 95% CI 1.189–2.918, $P = 0.007$) and one-year mortality (HR: 2.143, 95% CI 1.621–2.831, $P < 0.001$). These findings, summarized in Table 2, underscore a strong link between elevated SIRI levels and increased mortality risks both during hospitalization and over a one-year period post-discharge in AF and T2DM patients. In Table 2, Cox regression analysis revealed several variables associated with mortality. Regarding in-hospital mortality, multivariate Cox regression analysis indicated that advanced age (HR, 1.012; 95% CI, 1.010–1.017; $p < 0.001$), increased WBC count (HR, 1.011; 95% CI, 1.006–1.026; $p = 0.005$), hyperglycemia (HR, 1.013; 95% CI, 1.010–1.020; $p < 0.001$), and higher SOFA score (HR, 1.188; 95% CI, 1.121–1.259; $p < 0.001$) were significant factors affecting in-hospital mortality. Conversely, higher PaO2 levels (HR, 0.994; 95% CI, 0.990–0.998; $p = 0.005$), as well as the use of ACEI (HR, 0.498; 95% CI, 0.315–0.787; $p = 0.003$) and antiplatelet agents (HR, 0.546; 95% CI, 0.384–0.779; $p = 0.001$), were associated with a protective effect. Similar results were observed for 1-year follow-up mortality, with the notable exception that the use of ACEI did not achieve the expected protective effect in this population (HR, 0.832; 95% CI, 0.660–1.048; $p = 0.118$).

SIRI exhibits a good prognostic utility for predicting mortality in AF patients with T2DM

The ROC curves for SIRI, along with other indicators such as MLR, SII, SIRS, SOFA, SAPS II, and APS III, in forecasting in-hospital and one-year mortality are depicted in Fig. 2 SIRI outperformed MLR (in-hospital mortality: 0.731 vs. 0.669, $p < 0.001$; one-year mortality: 0.715 vs. 0.694, $p = 0.007$) and SII (in-hospital mortality: 0.731 vs. 0.651, $p < 0.001$; one-year mortality: 0.715 vs. 0.653, $p < 0.001$) in predicting mortality for both time frames. Notably, SIRI's AUC values were superior to those of SAPS II, SIRS, and SOFA in predicting one-year mortality (0.715 vs. 0.649, $p < 0.001$; 0.715 vs. 0.568, $p < 0.001$; and 0.715 vs. 0.625, $p < 0.001$, respectively), as confirmed by the DeLong test. This underscores SIRI's predictive advantage. The optimal cut-off value for predicting in-hospital mortality using SIRI was established at 7.336, achieving a sensitivity of 59.9% and a specificity of 79.7% (maximum Youden's index), which indicates greater validity and significant prognostic value (Table 3).

Elevated mean SIRI significantly correlates with increased mortality rates both in-hospital and one-year post-discharge

Figure 3 shows the KM survival curves which demonstrate the relationship between varying tertiles of SIRI levels and the incidence of in-hospital and one-year mortality. The Log-rank test reveals a distinct pattern: an increase in the SIRI index corresponds with a heightened risk of mortality both during the hospital stay and one year after discharge. This correlation between higher SIRI levels and increased mortality rates within the hospital and one-year post-discharge is statistically significant, as evidenced by a Log-rank p-value of less than 0.001. Further illustrating this point, relationships between SIRI and all-cause death were plotted using RCS. The HR curves presented in Fig. 4 depict a rising trend, signifying that the risk of mortality elevates in association with increasing SIRI values, with a p-value for nonlinearity below 0.001.

Variables	All patients	Survivor	Non-survivor	*P*-value
Patients	*n* = 2054	*n* = 1862	*n* = 192	-
Demographics				
Age (years)	67.76 ± 11.54	67.50 ± 11.53	70.34 ± 11.27	**0.001**
Gender (male, n[%])	1308(63.68%)	1195(64.18%)	113(58.85%)	0.144
BMI (Kg/m2)	28.77(24.87–33.51)	28.69(24.83–33.24)	29.48(24.99–37.27)	**< 0.001**
Comorbidities				
Hypertension (n[%])	1406(68.45%)	1314(70.57%)	92(47.92%)	**< 0.001**
Stroke (n[%])	639(31.11%)	588(31.58%)	51(26.56%)	0.153
AMI (n[%])	501(24.39%)	454(24.38%)	47(24.48%)	**< 0.001**
HF(n[%])	1239(60.32%)	1139(61.17%)	100(52.08%)	0.014
RF (n[%])	975(47.47%)	817(43.88%)	158(82.29%)	**< 0.001**
CKD (n[%])	909(44.26%)	837 (44.95%)	72(37.50%)	**0.048**
COPD (n[%])	409(19.91%)	364(19.55%)	45(23.44%)	0.199
Laboratory variables				
SIRI index	3.81(2.10–7.08)	3.60(2.04–6.44)	9.75(4.46–17.56)	**< 0.001**
Lactate (mmol/L)	1.91(1.52–2.45)	1.88(1.50–2.39)	2.32(1.70–3.77)	**< 0.001**
Albumin (g/dL)	3.55 ± 0.69	3.61 ± 0.55	3.02 ± 0.69	**< 0.001**
Creatinine (mg/dL)	1.15(0.88–1.69)	1.13(0.86–1.61)	1.55(1.06–2.24)	**< 0.001**
Calcium (mg/dL)	8.70 ± 0.50	8.73 ± 0.46	8.42 ± 0.69	**< 0.001**
Magnesium (mg/dL)	2.11 ± 0.18	2.11 ± 0.18	2.14 ± 0.21	**0.009**
Phosphorus (mg/dL)	3.65 ± 0.70	3.61 ± 0.62	4.03 ± 1.18	**< 0.001**
PaO_2 (mmHg)	151.95 ± 67.66	156.56 ± 68.32	107.29 ± 38.99	**< 0.001**
$PaCO_2$ (mmHg)	41.63 ± 7.13	41.57 ± 6.98	42.16 ± 8.45	0.277
Hemoglobin (g/dL)	10.51 ± 1.58	10.59 ± 1.56	9.72 ± 1.54	**< 0.001**
WBC (K/uL)	10.55 ± 5.69	10.10 ± 5.16	14.86 ± 8.20	**< 0.001**
PLT (K/uL)	215.57 ± 80.26	219.44 ± 78.89	178.04 ± 83.89	**< 0.001**
Neutrophil (K/uL)	7.16(5.10–9.89)	6.95(5.01–9.37)	11.02(7.48–15.79)	**< 0.001**
Lymphocyte (K/uL)	1.31(0.92–1.78)	1.34(0.94–1.80)	0.98(0.72–1.45)	**< 0.001**
Monocyte (K/uL)	0.71(0.54–0.93)	0.70(0.54–0.92)	0.81(0.58–1.11)	**< 0.001**
Serum Sodium (mmol/L)	138.70 ± 3.01	138.63 ± 2.84	139.37 ± 4.30	**< 0.001**
Serum Potassium (mmol/L)	4.24 ± 0.28	4.24 ± 0.27	4.25 ± 0.41	0.706
Glucose (mg/dL)	133.07 ± 33.25	130.95 ± 29.98	153.57 ± 51.56	**< 0.001**
TC (mg/dL)	154.81 ± 43.55	156.53 ± 42.56	138.19 ± 49.31	**< 0.001**
TG (mg/dL)	123.13(88.00-173.00)	122.00(88.00-171.00)	129.50(88.50-206.50)	0.059
LDL (mg/dL)	81.50 ± 33.03	82.42 ± 32.67	72.59 ± 35.12	**< 0.001**
HDL (mg/dL)	45.42(35.15–56.79)	46.31(35.93–57.45)	39.48(25.07–47.59)	**< 0.001**
HbA1c(%)	6.24 ± 1.30	6.23 ± 1.25	6.33 ± 1.75	0.340
Vital signs				
SBP (mmHg)	115.75 ± 13.67	116.11 ± 13.48	112.24 ± 14.93	**< 0.001**
DBP (mmHg)	57.16 ± 9.47	57.40 ± 9.42	54.78 ± 9.56	**< 0.001**
Heart Rate (bpm)	84.80 ± 11.77	83.30 ± 11.50	89.67 ± 13.23	**< 0.001**
Scoring systems				
SOFA	4.55 ± 2.75	4.29 ± 2.47	7.12 ± 3.78	**< 0.001**
SIRS	2.58 ± 0.76	2.55 ± 0.75	2.87 ± 0.77	**< 0.001**
SAPSII	40.55 ± 13.29	39.55 ± 12.74	50.31 ± 14.56	**< 0.001**
APSIII	47.00 ± 21.26	45.26 ± 20.00	63.91 ± 25.41	**< 0.001**
GCS	14.55 ± 0.70	14.57 ± 0.68	14.34 ± 0.85	**< 0.001**
Prescription				
ACEI (n[%])	634(30.87%)	610(32.76%)	24(12.50%)	**< 0.001**
Digoxin (n[%])	366(17.82%)	334(17.94%)	32(16.67%)	0.192
Beta blocker (n[%])	1905(92.75%)	1753(94.15%)	152(79.17%)	**< 0.001**
Diuretic (n[%])	1889(91.97%)	1723(92.53%)	166(86.46%)	**0.003**
Anti-platelet (n[%])	1759(85.64%)	1650(88.61%)	109(56.77%)	**< 0.001**
Albumin infusion (n[%])	1246(60.66%)	1147(61.60%)	99(51.56%)	**0.007**
Treatments				
Continued				

Variables	All patients	Survivor	Non-survivor	*P*-value
CRRT (n[%])	194(9.44%)	136(7.30%)	58(30.21%)	**< 0.001**
Invasive ventilation (n[%])	1841(89.63%)	1657(89.00%)	184(95.83%)	**0.003**
Events				
Hospital-LOS (days)	5.67(2.20-11.99)	5.31(2.05–10.84)	12.12(5.19–22.85)	**< 0.001**

Table 1. The characteristic of the population. P-values less than 0.05 are indicated in bold. BMI, body mass index; AMI, acute myocardial infarction; HF, heart failure; RF, respiratory failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; WBC, white blood cell; PLT, Platelets; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; HDL, high density lipoprotein; HbA1c, hemoglobin A1c; SBP, systolic blood pressure; DBP, diastolic blood pressure; SOFA, sequential organ failure assessment; SIRS, systemic inflammatory response syndrome; SAPSII, simplified acute physiology score II; APSIII, acute physiology score III; GCS, glasgow coma scale; ACEI, angiotensin-converting-enzyme inhibitors; CRRT, continuous renal replacement therapy; LOS length of stay.

Subgroup analysis explores the link between SIRI and mortality in patients with AF and T2DM

To further delve into the predictive power of SIRI levels, a subgroup analysis was performed focusing on its association with in-hospital and one-year mortality among patients diagnosed with AF and T2DM. The analysis encompassed various patient categories, including those differentiated by age, sex, BMI, HBP, stroke, AMI, HF, RF, CKD, COPD, use of serum albumin, invasive ventilation and CRRT.

In patients with AF and T2DM, elevated SIRI levels were significantly linked to an increased risk of hospital mortality, particularly in subgroups such as males [HR (95% CI) 2.648 (2.001–3.504)], those aged 75 years and older [HR (95% CI) 2.613 (2.010–3.396)], those with a history of stroke [HR (95% CI) 2.752 (1.793–4.225)], and those diagnosed with COPD [HR (95% CI) 2.631 (1.613–4.29)]. Notably, absence of AMI [HR (95% CI) 2.834 (2.216–3.624)] and RF [HR (95% CI) 3.611 (2.185–4.964)] also showed significant correlations with higher mortality rates (Fig. 5A).

Similarly, the analysis of one-year mortality revealed that higher SIRI levels significantly increased the risk of ICU mortality across various subgroups, including males [HR (95% CI) 2.352 (1.994–2.775)], those aged 75 years or above [HR (95% CI) 2.411 (2.044–2.845)], those with BMI of 25 kg/m2 or higher [HR (95% CI) 2.415 (2.071–2.817)], and those with CKD [HR (95% CI) 2.254 (1.874–2.710)]. The absence of stroke [HR (95% CI) 2.375 (2.038–2.767)], AMI [HR (95% CI) 2.486 (2.137–2.893)], and RF [HR (95% CI) 2.734 (2.135–3.501)], also indicated higher risks of mortality (Fig. 5B). Interestingly, SIRI showed a more pronounced predictive value in patients without AMI [in-hospital, HR (95% CI) without AMI 2.834 (2.216–3.624) vs. with AMI 1.873 (1.258–2.788), P for interaction < 0.001; one-year, HR (95% CI) without AMI 2.486 (2.137–2.893) vs. with AMI 1.743 (1.372–2.215), P for interaction = 0.021] or RF [in-hospital, HR (95% CI) without RF 3.611 (2.185–4.964) vs. with RF 1.770 (1.403–2.234), P for interaction < 0.001; one-year, HR (95% CI) without RF 2.734 (2.135–3.501) vs. with RF 1.646 (1.414–1.916), P for interaction < 0.001], highlighting its potential role as a critical marker in these subpopulations.

Discussion

In our investigation, SIRI was evaluated as a potential predictor of hospitalization and 1-year mortality rates among patients with AF and T2DM. The outcomes of this retrospective analysis indicated that an elevated SIRI level corresponded with higher rates of hospital and 1-year mortality in the population of AF patients with T2DM. Moreover, KM survival analysis showed that patients within the highest SIRI levels faced a significantly increased risk of mortality both during hospitalization and throughout the 1-year follow-up period when compared to those in the low SIRI category. Subgroup analysis further corroborated these findings, supporting SIRI's potential as a valuable prognostic resource for clinical decision-making.

SIRI and AF + T2DM patients' mortality

Recent advances in diabetes management and antihyperglycemic medication have significantly enhanced the control of diabetes-related complications over the past decades[23]. Previous literature indicates a decline in the rates of these complications between 1990 and 2010, primarily due to a marked reduction in myocardial infarction incidents[24]. Nevertheless, cardiovascular issues continue to be a predominant cause of morbidity and mortality among diabetic patients. It is worth noting that recent research has shown an increase in diabetes-related complications post-2010, particularly in low- and middle-income nations[25]. This resurgence may be attributed to the prolonged duration of diabetes in patients, correlating with increased life expectancies[26]. Thus, identifying high-risk populations is vital for efficient diabetes management and reducing healthcare expenditures.

The occurrence of AF in diabetic patients has been recognized as a significant risk factor for adverse outcomes[9]. A randomized controlled trial highlighted that T2DM patients who develop AF are at a substantially higher risk of adverse cardiovascular events, chronic kidney disease (CKD), and increased mortality[27]. Therefore, AF should be considered an indicator of particularly severe prognosis in diabetic patients, necessitating aggressive management of all associated risk factors. Early detection of at-risk patients with both AF and T2DM, through simple, efficient, and cost-effective measures, can facilitate timely interventions, thereby decreasing mortality risks.

Variables	Unadjusted Model			Adjusted Model 1			Adjusted Model 2		
	HR (95% CI)	P-value	P for trend	HR (95% CI)	P-value	P for trend	HR (95% CI)	P-value	P for trend
Hospital mortality									
Continuous SIRI index per 1 unit	1.020(1.016–1.024)	**< 0.001**		1.021(1.017–1.025)	**< 0.001**		1.015(1.010–1.020)	**0.015**	
Quartile			**< 0.001**			**< 0.001**			**0.002**
SIRI Tertile 1(N = 685) < 2.591	Ref			Ref			Ref		
SIRI Tertile 2(N = 685) 2.591–5.701	1.383(0.842–2.272)	0.2		1.363(0.830–2.239)	0.222		1.091 (0.781–1.810)	0.537	
SIRI Tertile 3(N = 684) > 5.701	5.116(3.378–7.749)	**< 0.001**		4.994(3.293–7.545)	**< 0.001**		1.863(1.189–2.918)	**0.007**	
Age	1.022(1.009–1.035)	**0.001**		-	-		1.012(1.010–1.017)	**< 0.001**	
Gender	0.808(0.606–1.078)	0.147		-	-		0.723(0.536–1.002)	0.05	
BMI	1.009(1.002–1.016)	**0.012**		-	-		1.005(0.998–1.018)	0.295	
Stroke	0.794(0.576–1.093)	0.158		0.757(0.549–1.044)	0.09		1.007(0.785–1.240)	0.563	
HF	0.705(0.531–1.369)	0.163		0.696(0.523–1.249)	0.124		0.805(0.579–1.120)	0.199	
WBC	1.018(1.011–1.025)	**< 0.001**		1.013(1.012–1.024)	**< 0.001**		1.011(1.006–1.026)	**0.005**	
PaO_2	0.983(0.980–0.987)	**< 0.001**		0.984(0.981–0.987)	**< 0.001**		0.994(0.990–0.998)	**0.005**	
Glucose	1.015(1.013–1.018)	**< 0.001**		1.016(1.013–1.019)	**< 0.001**		1.013(1.010–1.020)	**< 0.001**	
SOFA	1.315(1.265–1.366)	**< 0.001**		1.337(1.285–1.390)	**< 0.001**		1.188(1.121–1.259)	**< 0.001**	
APSIII	1.020(1.018–1.024)	**< 0.001**		1.017(1.015–1.025)	**< 0.001**		1.005(0.998–1.012)	0.184	
ACEI	0.306(0.200–0.470)	**< 0.001**		0.311(0.203–0.477)	**< 0.001**		0.498(0.315–0.787)	**0.003**	
Digoxin	0.913(0.625–1.335)	0.639		0.992(0.630–1.349)	0.676		1.004(0.718–1.376)	0.756	
Anti-platelet	0.193(0.145–0.257)	**< 0.001**		0.190(0.143–0.254)	**< 0.001**		0.546(0.384–0.779)	**0.001**	
Invasive ventilation	2.731(1.346–5.544)	**0.005**		2.520(1.240–5.122)	**0.011**		1.267(0.666–1.490)	0.552	
One-year mortality									
Continuous SIRI index per 1 unit	1.020(1.017–1.023)	**< 0.001**		1.021(1.018–1.024)	**< 0.001**		1. 016(1.008–1.015)	**0.012**	
Quartile			0.364			**0.001**			**< 0.001**
SIRI Tertile 1(N = 685) < 2.591	Ref			Ref			Ref		
SIRI Tertile 2(N = 685) 2.591–5.701	1.693(1.260–2.275)	**< 0.001**		1.665(1.239–2.238)	**0.001**		1.342(0.994–1.811)	0.055	
SIRI Tertile 3(N = 684) > 5.701	4.624(3.559–6.006)	**< 0.001**		4.411(3.393–5.734)	**< 0.001**		2.143(1.621–2.831)	**< 0.001**	
Age	1.024(1.022–1.041)	**0.001**		-	-		1.014(1.012–1.031)	**< 0.001**	
Gender	0.940(0.778–1.136)	0.524		-	-		0.853(0.696–1.046)	0.127	
BMI	1.000(0.993–1.009)	0.868		-	-		1.000(0.990–1.010)	0.944	
Stroke	0.916(0.749–1.120)	0.392		0.867(0.709–1.061)	0.166		1.022(0.827–1.263)	0.837	
HF	1.028(0.852–1.241)	0.771		1.011(0.837–1.221)	0.91		0.856(0.690–1.061)	0.155	
WBC	1.015(1.012–1.019)	**< 0.001**		1.019(1.016–1.029)	**< 0.001**		1.011(0.999–1.023)	0.065	
PaO_2	0.990(0.988–0.991)	**< 0.001**		0.989(0.988–0.991)	**< 0.001**		0.998(0.995–0.999)	**0.015**	
Glucose	1.011(1.009–1.013)	**< 0.001**		1.012(1.010–1.015)	**< 0.001**		1.012(1.008–1.015)	**< 0.001**	
SOFA	1.198(1.163–1.233)	**< 0.001**		1.215(1.180–1.252)	**< 0.001**		1.078(1.037–1.122)	**< 0.001**	
APSIII	1.017(1.014–1.019)	**< 0.001**		1.020(1.018–1.027)	**< 0.001**		1.006(1.001–1.011)	**0.014**	
ACEI	0.659(0.531–0.817)	**< 0.001**		0.669(0.540–0.830)	**< 0.001**		0.832(0.660–1.048)	0.118	
Digoxin	1.013(1.011–1.022)	0.005		1.017(1.012–1.037)	**0.002**		1.014(1.011–1.018)	**0.003**	
Anti-platelet	0.308(0.252–0.377)	**< 0.001**		0.294(0.240–0.360)	**< 0.001**		0.477(0.376–0.606)	**< 0.001**	
Invasive ventilation	1.341(0.962–1.869)	0.084		1.240(0.889–1.730)	0.206		0.874(0.619–1.232)	0.441	

Table 2. Cox proportional hazard ratios for all-cause mortality. Model 1: adjusted for age, gender, BMI. Model 2: adjusted for age, gender, BMI, HBP, Stroke, AMI, HF, RF, CKD, COPD, WBC, Lactate, Creatinine, phosphorus, Glucose, HbA1c, LDL, HDL, PaO_2, SOFA, APSIII, ACEI, Digoxin, Diuretic, Antiplatelet, albumin infusion, CRRT, Invasive ventilation. P-values less than 0.05 are indicated in bold.

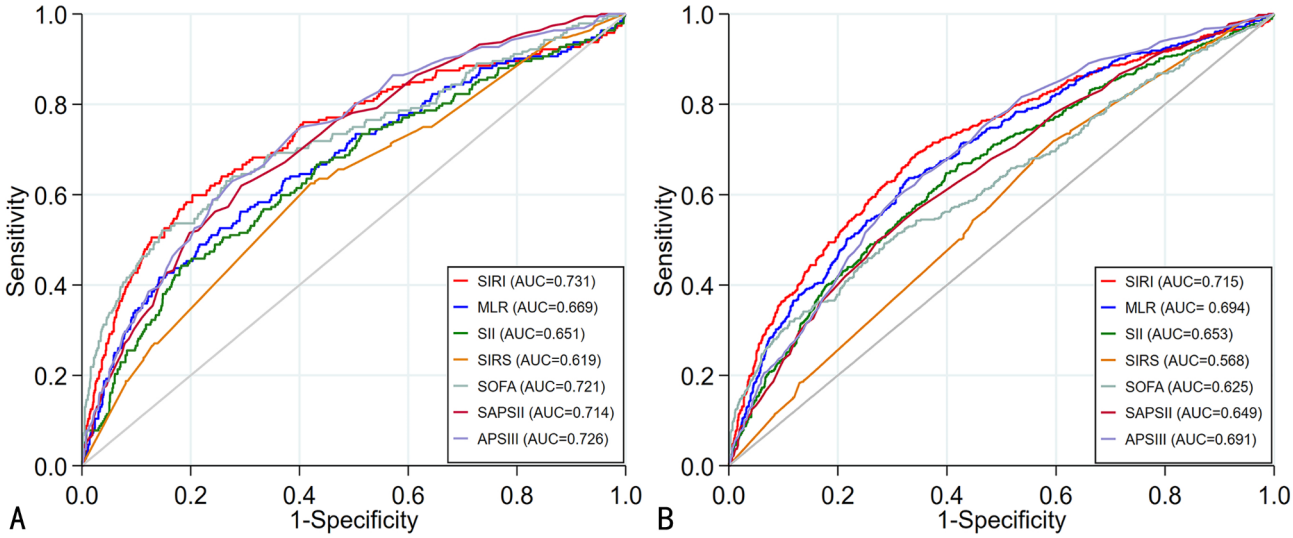

Fig. 2. ROC Curves for Predictors of In-Hospital and One-Year Mortality in Critical Patients: (A) In-hospital mortality; (B) 1-year mortality. The red solid line traces the ROC curve for the SIRI with its AUC indicating a comparatively good predictive performance in this study. The DeLong test outcomes indicate a superior AUC for the SIRI compared to the MLR (in-hospital mortality: 0.731 vs. 0.669, $p < 0.001$; 1-year mortality: 0.715vs. 0.694, $p = 0.007$) and SII (in-hospital mortality: 0.731 vs. 0.651, $p < 0.001$; 1-year mortality: 0.715 vs. 0.653, $p < 0.001$). The AUC value of SIRI was superior to SAPSII (0.715 vs. 0.649, $p < 0.001$), SIRS (0.715 vs. 0.568, $p < 0.001$) and SOFA (0.715 vs. 0.625, $p < 0.001$) for predicting one-year mortality.

Variables	AUC	95%CI	Cut-off value	Sensitivity	Specificity	Youden's index
SIRI	0.731	0.688–0.774	7.336	0.599	0.797	0.396
MLR	0.669	0.625–0.713	0.986	0.417	0.858	0.275
SII	0.651	0.607–0.694	2151.49	0.443	0.817	0.260
SIRS	0.619	0.577–0.660	2.970	0.625	0.579	0.204
SOFA	0.721	0.678–0.764	6.786	0.521	0.853	0.374
SAPSII	0.714	0.676–0.752	44.5	0.620	0.707	0.327
APSIII	0.726	0.688–0.764	52.5	0.630	0.723	0.353

Table 3. Information of ROC curves in Figure 2.

Inflammation plays a critical role in cardiac diseases, and systemic inflammation can be assessed by standard laboratory testing such as the white blood cell count, conducted routinely upon patient admission[28,29]. Recently, the systemic immune-inflammation index (SII) and monocyte to lymphocyte ratio (MLR) have emerged as significant inflammatory markers. These can be easily calculated using the white blood cell count data. Research by Jiachen Luo et al. demonstrated that a high SII independently predicts poor survival in patients with acute myocardial infarction (AMI) and diabetes, suggesting its utility in patient risk stratification[30]. Furthermore, a retrospective and cross-sectional study involving 386 patients showed that the neutrophil to lymphocyte ratio (NLR) was independently associated with left ventricular hypertrophy (LVH) in hypertensive patients, aligning with the diagnostic effectiveness of C-reactive protein (CRP) and B-type natriuretic peptide (BNP)[29]. Our study introduces a novel inflammatory marker, the SIRI, in patients with AF and T2DM. Composed of neutrophils, lymphocytes, and monocytes, SIRI offers enhanced sensitivity and specificity in predicting cardiovascular events and all-cause mortality when compared to SII and MLR[31].

Related studies

Previous research has identified chronic inflammation as a significant risk factor for various diseases, including cancer, DM, and atherosclerotic disease[32]. As novel inflammatory markers, the SIRI indices have demonstrated high sensitivity to inflammatory status across a wide spectrum of diseases, making them both easily detectable and cost-effective. Recent studies have revealed that SIRI is significantly associated with all-cause mortality in populations with type 2 diabetes, obesity, and patients who have experienced acute myocardial infarction[13,33,34]. Additionally, SIRI has shown predictive relevance in complications associated with DM. A retrospective observational study indicated that SIRI levels in patients with T2DM and peripheral arterial disease (PAD) were significantly higher than those in T2DM patients without PAD, correlating with increased disease severity. In diabetic kidney disease (DKD) among T2DM patients, a high SIRI value was recognized as an independent

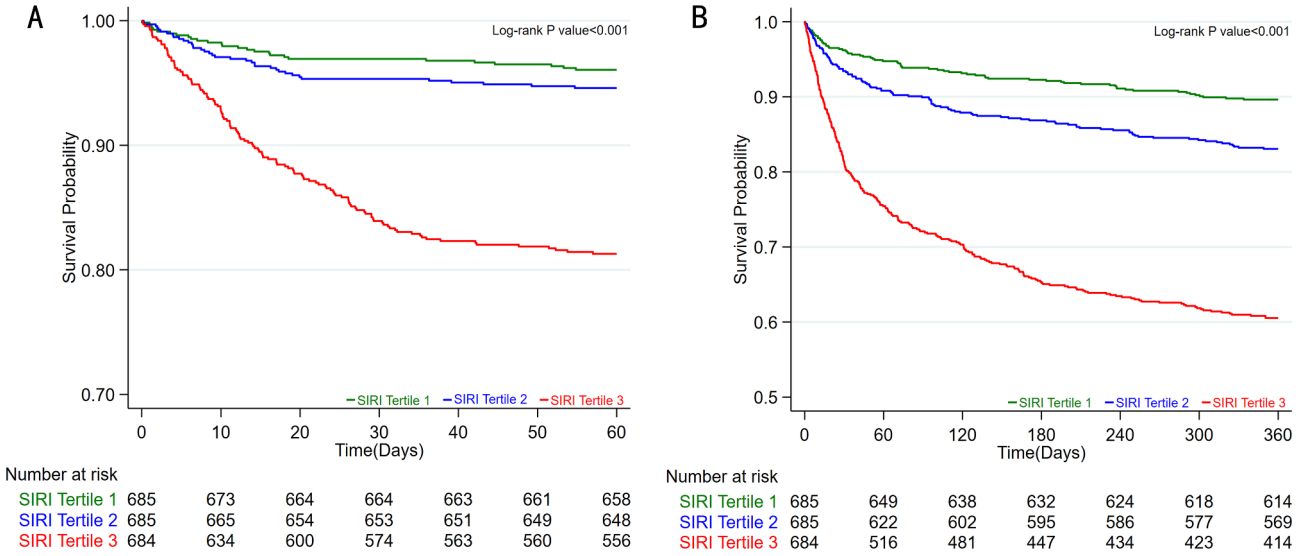

Fig. 3. Kaplan-Meier survival analysis curves for all-cause mortality. Footnote SIRI tertiles: Tertile1 < 2.591, Tertile2 2.591–5.701, Tertile3 > 5.701. Kaplan–Meier curves showing cumulative probability of all-cause mortality according to groups in hospital (A) and 1 year (B).

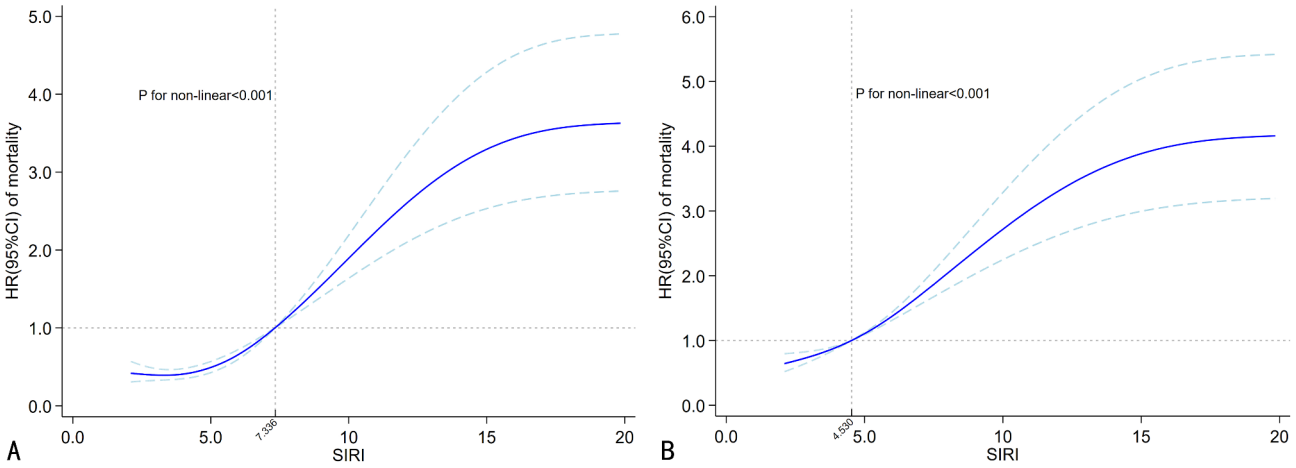

Fig. 4. Non-Linear Association Between SIRI and Mortality Shown via RCS Regression: (A) Hospitalization mortality; (B) 1-year follow-up mortality. The adjusted hazard ratios (HR) are denoted by solid blue lines, with 95% confidence intervals (CI) marked by blue dashed lines. The analysis demonstrates a non-linear correlation between SIRI and both hospitalization and one-year mortality rates. The hospital mortality risk map's cutoff value stood at 7.336, while it was 4.53 for the one-year mortality.

risk factor for DKD, while an elevated SII was linked to a higher risk of progressing kidney disease in biopsy-confirmed DKD cases[35].Consistent with previous findings, our analysis shows that a higher SIRI level remains an independent predictor of both in-hospital and long-term mortality after adjusting for multiple variables.

Another study demonstrated that SIRI was significantly linked to mortality risk in patients with chronic heart failure, possibly offering better prognostic value than C-reactive protein[36]. This observation underscores that individuals with elevated SIRI levels face a higher mortality risk. A retrospective study encompassing 616 ST-elevation myocardial infarction (STEMI) patients treated with percutaneous coronary intervention (PCI) found that SIRI independently predicts AF in post-PCI STEMI patients and is positively correlated with poorer outcomes[17]. In patients with ischemic stroke, SIRI values were significantly higher in AF patients than in in those without[37]. Runze Chi et al. reported that high SIRI values are associated with left ventricular remodeling and systolic function impairment in AF patients, suggesting that SIRI could serve as a reliable and straightforward inflammatory biomarker for detecting cardiac structural damage and systolic functional impairment[38]. Our RCS analysis further implied a linear association between SIRI and long-term mortality in patients with T2DM and AF, pointing to the potential clinical value of anti-inflammatory treatments in this high-risk group. In addition, non-channel blocking drugs with anti-inflammatory properties, such as renin-angiotensin system inhibitors,

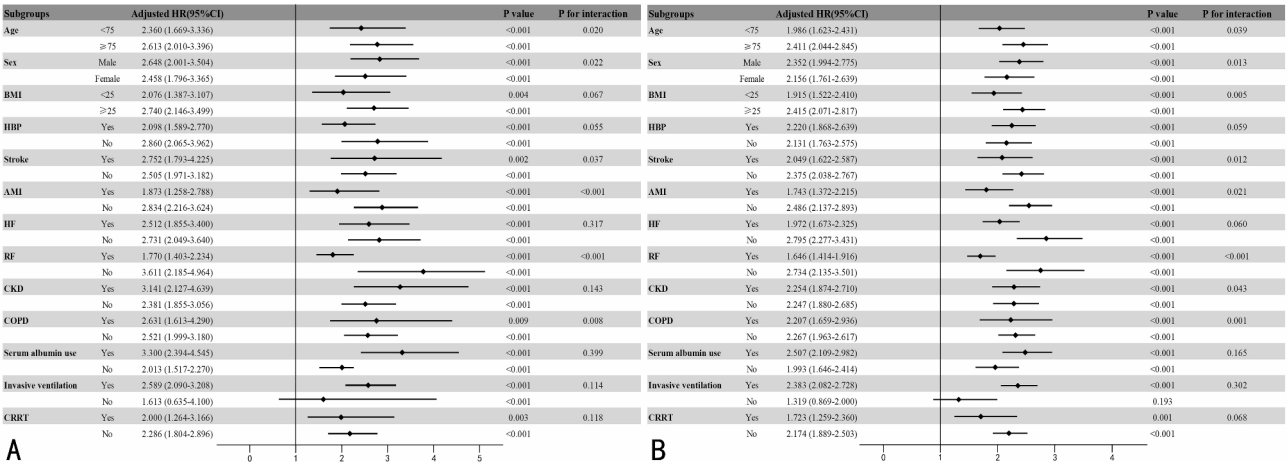

Fig. 5. Forest Plot of In-Hospital and One-Year Mortality Hazard Ratios Across Subgroups: This plot displays hazard ratios for in-hospital (A) and one-year (B) mortality, segmented by various subgroups, and includes an interaction analysis probing the influence of SIRI on in-hospital mortality and one-year mortality within these diverse cohorts.

statins, corticosteroids, omega-3 fatty acids, vitamin C and thiazolidinediones, have demonstrated beneficial effects in AF[39–41]. These findings suggest that early anti-inflammatory interventions could potentially prevent the onset of AF, thus reducing the incidence of cardiovascular diseases and premature mortality.

What does our current work add to existing knowledge

The literature on the association between the SIRI and mortality in patients with AF comorbid with T2DM is limited. Our study provides evidence that an elevated SIRI, particularly within specific subgroups of patients, is associated with an increase in both in-hospital and 1-year mortality rates. This finding suggests the significant potential of SIRI as a tool for risk stratification and customized management in this clinically vulnerable population. Given the widespread impact of DM and AF worldwide, these findings assume heightened importance. They facilitate the early identification of patients at higher risk of mortality, enabling more precise clinical interventions to reduce the likelihood of subsequent cardiac events and mortality. Notably, our data clearly demonstrate a significant linear relationship between SIRI and mortality rates (both in-hospital and within 1-year post-discharge) in AF patients with T2DM, even upon rigorous adjustment for potential confounders. SIRI is a viable tool for high mortality risk detection in critically ill AF and T2DM patients. Also, ROC analysis revealed that SIRI provided higher AUC levels, demonstrating superior discriminative ability compared to MLR and SII for predicting both in-hospital and 1-year mortality. Interestingly, SIRI outperformed the SAPS II, SIRS, and SOFA in predicting one-year mortality, reinforcing its utility as a tool for assessing long-term mortality risk in this patient group.

Furthermore, our study delves into the risk stratification of various patient subgroups. Subgroup analysis indicated the consistent value of SIRI in predicting mortality within one year and in-hospital for patients receiving treatments like serum albumin, invasive ventilation, or CRRT. Interestingly, the predictive significance of SIRI, for in-hospital mortality, appeared more pronounced in individuals without AMI and RF (P for interaction < 0.05), suggesting that treatments for these conditions may significantly influence SIRI's predictive accuracy for all-cause mortality. One-year subgroup analysis showed a more evident predictive value of SIRI in patients without stroke, AMI, and RF (P for interaction < 0.05). Another finding of the present study was that the association between SIRI and mortality seemed to be more significant in older patients, male and those BMI ≥ 25 kg/m^2. These findings highlight a need for increased attention to these groups due to their higher mortality risk.

In summary, our analysis suggests that SIRI should not be regarded as a sole diagnostic tool, but should be used as a substitute along with other clinical and laboratory parameters for a more comprehensive risk stratification and assessment of clinical outcomes, such as mortality, in the management of critically ill patients.

Possible mechanisms

From the mechanism perspective, activated neutrophils release a variety of proteolytic enzymes, especially, granule proteins released after neutrophil activation have been suggested to involve in the process of myocardial injury[42]. The neutrophil-derived enzyme myeloperoxidase (MPO) is increasingly recognized as a significant contributor to oxidative damage during reperfusion, as well as to vascular dysfunction, adverse ventricular remodeling, and atrial fibrillation[43]. In contrast, lymphocytes play a role in regulating inflammation, helping to curb excessive immune responses and reduce damage to the heart muscle. Activated platelets release various proinflammatory chemokines and cytokines, which exacerbate atherosclerosis and contribute to intimal hyperplasia and plaque instability, often leading to poor cardiovascular outcomes[44]. Additionally, studies on single-cell transcriptomes from human atria have shown an increase in inflammatory monocytes and macrophages in cases of atrial fibrillation, with blocking monocyte migration shown to reduce arrhythmia in animal studies[45].

Despite their established roles in affecting individuals with AF, under diabetic conditions, neutrophils tend to produce more superoxide and inflammatory cytokines, leading to tissue damage[46]. Additionally, several non-channel-blocking drugs with anti-inflammatory effects have shown to be beneficial in managing AF. Neutrophils produce excessive ROS, inducing neutrophils form extracellular traps (NETs) within the cells, which fills surrounding tissues with ROS and induces tissue damage[47]. Another study showed that NETs by releasing decondensed chromatin lined with cytotoxic proteins which can also induce tissue damage[48]. NETs play a crucial role in facilitating pathological thrombosis, worsening cardiovascular, inflammatory, and thrombotic diseases[49], which could be particularly significant in driving DM-related cardiovascular complications. Moreover, the risk of diabetes has been linked to increased levels of circulating monocytes. Diabetic mice display higher numbers of circulating neutrophils and monocytes, a reflection of hyperglycemia-induced proliferation and expansion of bone marrow myeloid progenitors, along with the release of monocytes into the bloodstream[50]. The SIRI is a novel biomarker used to measure systemic inflammation, which is evaluated using neutrophils, monocytes and lymphocytes. Thus, SIRI can provide insights into the progression and severity of AF in patients with T2DM. Targeting inflammation could be a viable therapeutic strategy to improve outcomes for AF patients with diabetes. Further research is needed to explore this approach further.

Strengths and limitations

The strengths of our study lie in its comprehensive examination of the prognostic status of patients with T2DM and AF during hospitalization and follow-up for one year, highlighting important clinical implications:

(1) We found that higher levels of the SIRI were associated with an increased risk of death. This suggests that using the SIRI index for risk stratification can help identify high-risk individuals, and its economic and practical value in clinical practice for indicating mortality risk is significant.
(2) In the MMIC-IV database, the multivariate regression model demonstrated that the SIRI index has good predictive value for the in-hospital and one-year prognosis of patients with T2DM and AF.
(3) Our study results indicate that using the SIRI index to assess inflammation may facilitate early pharmacological intervention in high-risk individuals, which may help reduce the risk of death.

The present study also has several limitations. Firstly, we did not investigate the association of dynamic changes in the SIRI level with mortality rates, which needs to be further addressed. Secondly, despite our retrospective analysis providing strong evidence, we must recognize the potential for hidden confounding factors that are difficult to fully exclude. The lack of data on prior use of medications such as steroids and antibiotics could affect the evaluation of SIRI, making it hard to establish a definite cause-and-effect relationship in our findings. Thirdly, the use of ACEI seems to provide a protective effect only for in-hospital patients. Multivariate regression analysis suggests that its use in 1-year follow-up patients did not achieve the expected outcome ($P=0.118$), which needs further investigation.

Conclusions

In summary, this investigation broadened the assessment of the SIRI to include a cohort of critically ill patients with AF and T2DM. We found that a high SIRI is a critical prognostic marker for both in-hospital and one-year mortality among these patient groups. Moreover, we identified a significant linear relationship between increased SIRI levels and a higher risk of all-cause mortality in patients with AF also suffering from T2DM. Given the adverse prognostic effects of a heightened inflammatory response in both AF and T2DM, further research is needed to explore whether SIRI can be effectively utilized in the risk stratification of AF patients with diabetes and in guiding the use of anti-inflammatory therapies.

Data availability

The data generated and analyzed during the current study are available from the corresponding author on reasonable request.

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References

1. Magliano, D. J., Boyko, E. J. & committee, I. D. F. D. A. t. e. s. in *Idf diabetes atlas* (International Diabetes Federation © International Diabetes Federation, 2021). (2021).
2. Geiss, L. S. et al. Resurgence of diabetes-related nontraumatic Lower-Extremity Amputation in the Young and Middle-aged adult U.S. Population. *Diabetes Care*. **42**, 50–54 (2019).
3. Gregg, E. W., Hora, I. & Benoit, S. R. Resurgence in diabetes-related complications. *Jama* **321**, 1867–1868 (2019).
4. Abushanab, D. et al. Projecting the Health and Economic Burden of Cardiovascular Disease among people with type 2 diabetes, 2022–2031. *Pharmacoeconomics* **41**, 719–732 (2023).
5. Lippi, G., Sanchis-Gomar, F. & Cervellin, G. Global epidemiology of atrial fibrillation: an increasing epidemic and public health challenge. *Int. J. Stroke*. **16**, 217–221 (2021).
6. Huxley, R. R., Filion, K. B., Konety, S. & Alonso, A. Meta-analysis of cohort and case-control studies of type 2 diabetes mellitus and risk of atrial fibrillation. *Am. J. Cardiol.* **108**, 56–62 (2011).
7. Huxley, R. R. et al. Type 2 diabetes, glucose homeostasis and incident atrial fibrillation: the atherosclerosis risk in communities study. *Heart* **98**, 133–138 (2012).
8. Aksnes, T. A. et al. Impact of new-onset diabetes mellitus on development of atrial fibrillation and heart failure in high-risk hypertension (from the VALUE Trial). *Am. J. Cardiol.* **101**, 634–638 (2008).
9. Du, X. et al. Risks of cardiovascular events and effects of routine blood pressure lowering among patients with type 2 diabetes and atrial fibrillation: results of the ADVANCE study. *Eur. Heart J.* **30**, 1128–1135 (2009).

10. Wang, S., Pan, X., Jia, B. & Chen, S. Exploring the correlation between the systemic Immune inflammation index (SII), systemic inflammatory response index (SIRI), and type 2 Diabetic Retinopathy. *Diabetes Metab. Syndr. Obes.* **16**, 3827–3836 (2023).
11. Wang, N., Wang, L., Zhang, M., Deng, B. & Wu, T. Correlations of 2 Novel Inflammation Indexes With the Risk for Early Neurological Deterioration in Acute Ischemic Stroke Patients After Intravenous Thrombolytic Therapy. *Neurologist* (2024).
12. Dong, W. et al. A combined analysis of TyG index, SII index, and SIRI index: positive association with CHD risk and coronary atherosclerosis severity in patients with NAFLD. *Front. Endocrinol. (Lausanne)*. **14**, 1281839 (2023).
13. Kong, F. et al. System inflammation response index: a novel inflammatory indicator to predict all-cause and cardiovascular disease mortality in the obese population. *Diabetol. Metab. Syndr.* **15**, 195 (2023).
14. Yildiz, E. G. et al. Can System inflammation response index or systemic Immune inflammation index predict gestational diabetes mellitus in the first trimester? A prospective observational study. *Int. J. Gynaecol. Obstet.* **166**, 837–843 (2024).
15. Qin, D., Mansour, M. C., Ruskin, J. N. & Heist, E. K. Atrial fibrillation-mediated cardiomyopathy. *Circ. Arrhythm. Electrophysiol.* **12**, e007809 (2019).
16. Yang, X. et al. Systemic inflammation indicators and risk of incident arrhythmias in 478,524 individuals: evidence from the UK Biobank cohort. *BMC Med.* **21**, 76 (2023).
17. Wang, J., Hu, S., Liang, C. & Ling, Y. The association between systemic inflammatory response index and new-onset atrial fibrillation in patients with ST-elevated myocardial infarction treated with percutaneous coronary intervention. *BMC Cardiovasc. Disord.* **22**, 525 (2022).
18. Tancredi, M. et al. Excess mortality among persons with type 2 diabetes. *N Engl. J. Med.* **373**, 1720–1732 (2015).
19. Hajer, G. R., van Haeften, T. W. & Visseren, F. L. Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. *Eur. Heart J.* **29**, 2959–2971 (2008).
20. Savage, D. B., Petersen, K. F. & Shulman, G. I. mechanisms of insulin resistance in humans and possible links with inflammation. *Hypertension* **45**, 828–833 (2005).
21. Lin, K., Lan, Y., Wang, A., Yan, Y. & Ge, J. The association between a novel inflammatory biomarker, systemic inflammatory response index and the risk of diabetic cardiovascular complications. *Nutr. Metab. Cardiovasc. Dis.* **33**, 1389–1397 (2023).
22. Jin, Z. et al. The associations of two novel inflammation indexes, SII and SIRI with the risks for Cardiovascular diseases and all-cause mortality: a ten-year Follow-Up study in 85,154 individuals. *J. Inflamm. Res.* **14**, 131–140 (2021).
23. Kwon, S. et al. Association between Atrial Fibrillation and Diabetes-Related complications: a Nationwide Cohort Study. *Diabetes Care*. **46**, 2240–2248 (2023).
24. Gregg, E. W. et al. Changes in diabetes-related complications in the United States, 1990–2010. *N Engl. J. Med.* **370**, 1514–1523 (2014).
25. Ali, M. K., Pearson-Stuttard, J., Selvin, E. & Gregg, E. W. Interpreting global trends in type 2 diabetes complications and mortality. *Diabetologia* **65**, 3–13 (2022).
26. Muschik, D. et al. Change in life expectancy with type 2 diabetes: a study using claims data from lower Saxony, Germany. *Popul. Health Metr.* **15**, 5 (2017).
27. Geng, T. et al. Associations of New-Onset Atrial Fibrillation with risks of Cardiovascular Disease, chronic kidney Disease, and Mortality among patients with type 2 diabetes. *Diabetes Care*. **45**, 2422–2429 (2022).
28. Scott, L. Jr., Li, N. & Dobrev, D. Role of inflammatory signaling in atrial fibrillation. *Int. J. Cardiol.* **287**, 195–200 (2019).
29. Yu, X. et al. NLR-A simple Indicator of inflammation for the diagnosis of left ventricular hypertrophy in patients with hypertension. *Int. Heart J.* **61**, 373–379 (2020).
30. Luo, J. et al. Prognostic implications of systemic immune-inflammation index in myocardial infarction patients with and without diabetes: insights from the NOAFCAMI-SH registry. *Cardiovasc. Diabetol.* **23**, 41 (2024).
31. Wang, P. et al. Monocyte-to-high-density lipoprotein ratio and systemic inflammation response index are associated with the risk of metabolic disorders and cardiovascular diseases in general rural population. *Front. Endocrinol. (Lausanne)*. **13**, 944991 (2022).
32. Fullerton, J. N. & Gilroy, D. W. Resolution of inflammation: a new therapeutic frontier. *Nat. Rev. Drug Discov.* **15**, 551–567 (2016).
33. Zhang, J. et al. Association between inflammatory biomarkers and mortality in individuals with type 2 diabetes: NHANES 2005–2018. *Diabetes Res. Clin. Pract.* **209**, 111575 (2024).
34. Chen, Y., Xie, K., Han, Y., Xu, Q. & Zhao, X. An Easy-to-Use Nomogram based on SII and SIRI to predict in-hospital mortality risk in Elderly patients with Acute myocardial infarction. *J. Inflamm. Res.* **16**, 4061–4071 (2023).
35. Liu, W., Zheng, S. & Du, X. Association of systemic Immune-inflammation index and systemic inflammation Response Index with Diabetic kidney disease in patients with type 2 diabetes Mellitus. *Diabetes Metab. Syndr. Obes.* **17**, 517–531 (2024).
36. Zhu, D. et al. The associations of two novel inflammation biomarkers, SIRI and SII, with mortality risk in patients with chronic heart failure. *J. Inflamm. Res.* **17**, 1255–1264 (2024).
37. Lin, K. B. et al. Systemic immune inflammation index and system inflammation response index are potential biomarkers of atrial fibrillation among the patients presenting with ischemic stroke. *Eur. J. Med. Res.* **27**, 106 (2022).
38. Chi, R. et al. Association between systemic inflammatory response index and left ventricular remodeling and systolic dysfunction in atrial fibrillation patients. *BMC Cardiovasc. Disord.* **23**, 377 (2023).
39. Murray, K. T., Mace, L. C. & Yang, Z. Nonantiarrhythmic drug therapy for atrial fibrillation. *Heart Rhythm*. **4**, S88–90 (2007).
40. Liu, T., Li, G. P. & Huang, T. G. Anti-inflammatory therapies in atrial fibrillation. *Int. J. Cardiol.* **104**, 359–360 (2005).
41. Liu, T., Korantzopoulos, P., Li, G. & Li, J. The potential role of thiazolidinediones in atrial fibrillation. *Int. J. Cardiol.* **128**, 129–130 (2008).
42. Zhang, N., Aiyasiding, X., Li, W. J. & Liao, H. H. Tang, Q. Z. Neutrophil degranulation and myocardial infarction. *Cell. Commun. Signal.* **20**, 50 (2022).
43. El Kazzi, M. et al. Neutrophil-mediated cardiac damage after Acute myocardial infarction: significance of defining a new target cell type for developing cardioprotective drugs. *Antioxid. Redox Signal.* **33**, 689–712 (2020).
44. Totani, L. & Evangelista, V. Platelet-leukocyte interactions in cardiovascular disease and beyond. *Arterioscler. Thromb. Vasc Biol.* **30**, 2357–2361 (2010).
45. Hulsmans, M. et al. Recruited macrophages elicit atrial fibrillation. *Science* **381**, 231–239 (2023).
46. Karima, M. et al. Enhanced superoxide release and elevated protein kinase C activity in neutrophils from diabetic patients: association with periodontitis. *J. Leukoc. Biol.* **78**, 862–870 (2005).
47. Johnson, J. et al. Oxidative stress in neutrophils: implications for Diabetic Cardiovascular complications. *Antioxid. Redox Signal.* **36**, 652–666 (2022).
48. Wong, S. L. et al. Diabetes primes neutrophils to undergo NETosis, which impairs wound healing. *Nat. Med.* **21**, 815–819 (2015).
49. Njeim, R. et al. NETosis contributes to the pathogenesis of diabetes and its complications. *J. Mol. Endocrinol.* **65**, R65–r76 (2020).
50. Nagareddy, P. R. et al. Hyperglycemia promotes myelopoiesis and impairs the resolution of atherosclerosis. *Cell. Metab.* **17**, 695–708 (2013).

Author contributions

W.L. and Y.C. conceptualized and designed this study. W.L. and Y.C. performed data extraction and initial analysis. C.P., Y.L. and B.Z. assisted in the data cleaning, data proofreading, and statistical analysis. W.L. and Y.C. contributed to figure plotting. W.L .wrote the main manuscript text. Y.L. and B.Z. participated in the critical revision of the manuscript. C.P. supervised the study. All authors reviewed the manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
This research was carried out in strict conformity with the ethical principles outlined in the Declaration of Helsinki (revised in 2013) and received the endorsement of the Institutional Review Boards at both Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology. Data access was granted to an investigator post completion of an online National Institutes of Health course and successful passing of the associated human research participant protection exam (Application No. 60069524). As the MIMIC-IV database is publicly available, there was no requirement for additional ethical approval or informed consent for this particular study.

Additional information
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