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Diagnostic Value of RDW-Albumin Ratio for the Prediction of Mortality in Sepsis Associated Nonthyroidal Illness Syndrome Patients: A Retrospective Cohort Study

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Background: The correlation between RAR is linked to negative outcomes in sepsis, but it remains uncertain if RAR is connected to prognosis in patients with sepsis-related NTIS. So we investigated it in this study.

Methods: Patients with sepsis-associated NTIS admitted to Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, between March 2013 and April 2017 were included in the study. Participants were divided into two groups according to the optimal threshold value for RAR determined by the receiver operating characteristic curve. Cox proportional hazards regression and graphed with Kaplan–Meier curves examined the relationship between RAR and survival in patients with sepsis-associated NTIS. To account for potential confounding variables, a propensity score matching method was conducted to verify the relationship. Subgroup analysis was performed for different sex, age, comorbidities, infection location and other scores.

Results: A total of 328 patients with sepsis-related NTIS were analyzed in our study. The univariate and multivariate regression analysis indicated that RAR was a significant risk factor for 30-day mortality (HR 1.039(1.012, 1.067), p = 0.004). However, subgroup analysis suggested that RAR may not be an independent risk factor for 30-day mortality in sepsis patients with NTIS combined with tumor or urogenital infection. ROC analysis demonstrated that RAR had a high discriminatory ability for predicting 30-day mortality (AUC 0.751, p < 0.001). Kaplan-Meier curve analysis indicated increased 30-day mortality in the higher RAR group. Following PSM, 108 pairs of patients with matched scores were created. The multivariate regression model demonstrated that RAR was an independent factor associated with 30-day mortality risk (HR 1.049 (1.015, 1.085), p = 0.005). ROC analysis revealed that RAR was a strong discriminator for the 30d-mortality (AUC: 0.695, 95% CI: (0.598–0.792)).

Conclusion: A strong correlation was found between RAR and unfavorable clinical results in sepsis-related NTIS, where a greater RAR was linked to increased 30-day and in-hospital death rates.

Keywords: sepsis, red blood cell distribution width, albumin, nonthyroidal illness syndrome, prognosis

Introduction

Sepsis is a complex clinical syndrome characterized by organ dysfunction resulting from an inadequate host response to infection, involving physiological, pathological, and biochemical abnormalities.[1] Even with advancements in treatment choices, sepsis continues to pose a substantial threat of death in the intensive care units (ICU), because sepsis may result in various complications, such as shock, disseminated intravascular coagulation (DIC), and multiple organ dysfunction syndrome (MODS).[2,3] It was reported that the hospital mortality rate caused by sepsis is 20–30% and 40–60% by septic shock.[4,5]

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RDW and RDW fluctuation can help predict sepsis-related DIC morbidity and prognosis in patients with sepsis.[6] Albumin concentration is an important marker of nutritional status and the inflammatory response. The integration of these 2 markers may reflect inflammation, malnutrition, and other abnormalities. The published article revealed that higher RAR levels were associated with increased risks of all-cause and cause-specific mortality.[7] So we further explore the predictive value of RAR values in sepsis associated NTIS.

Almost all hormonal axes can be affected when patients develop sepsis, and if immune–hypothalamic–pituitary–adrenal axis is inhibited, triiodothyronine (T3) may abruptly decrease and reverse T3 (rT3) increase. This was attributed to the oxidative stress-related compensatory and the metabolic adaptation by reducing protein breakdown and energy expenditure in the acute stage of sepsis. Therefore, it is frequently observed low serum concentrations of T3 and thyroxine among ICU patients, along with thyroid-stimulating hormone (TSH) levels that are within the normal range or slightly decreased, which is known as non-thyroidal illness syndrome (NTIS).[8,9] Previous research has reported that nearly 50% sepsis patients may coexist with NTIS, with higher mortality rates.[10–13]

Given the worse prognosis induced by sepsis-related NTIS, numerous biomarkers have been suggested, aiming to achieve accurate and early prediction to improve prognosis, but none are deemed suitable for regular clinical application.[14] In 2022, Xu et al discovered the significant correlation between the red blood cell distribution width (RDW)-to-albumin ratio (RAR) and adverse clinical outcomes among sepsis patients. Their study showed that increased RAR level was related to increased mortality rates at 28 days, 90 days, and during hospitalization.[15] However, there are few studies utilizing this indicator to make survival predictions among patients suffering from sepsis-related NTIS. Our study aimed to investigate the potential relationship between RAR and survival in patients with sepsis-related NTIS, expecting early prognostic prediction to improve the outcomes.

Methods

Participants

This retrospective study included adult patients (≥18 years) diagnosed with sepsis-related NTIS between March 2013 and April 2017, who were admitted to either the ICU or emergency ward at Xinhua Hospital, affiliated with Shanghai Jiao Tong University School of Medicine. Sepsis was diagnosed based on the Sepsis-3 criteria,[1] and the NTIS was diagnosed in the presence of low serum free T3 (FT3) level (<3.5pmol/L) with normal/low TSH level (< 4.78μIU/mL). Patients without thyroid hormone test within 24 hours of admission, being in the active stage of malignant disease, with histological evidence in autoimmune disease, from the surgical intensive care unit, with thyroidal or pituitary disorders and using drugs that interfere with the hypothalamic-pituitary-thyroid axis before laboratory measurements were excluded. The study design was approved by the Ethics Committee at Xinhua Hospital (No. XHEC-D-2024-058) with informed consent being waived as the research involves no more than minimal risk to subjects. The study also conformed to the ethical guidelines of the Declaration of Helsinki.

Data Collection

Clinical variables are obtained from the patient's medical records, whether they are paper-based or electronic. Baseline information includes gender, age, comorbidities [cardiovascular-disease, heart failure (HF), renal insufficiency, cerebrovascular disease, acute ischemic stroke, tumor history, hypertension, diabetes, atrial fibrillation (AF), Deep Vein Thrombosis (DVT), and chronic obstructive pulmonary disease (COPD)]. Laboratory test measurements were collected including prothrombin time (PT), D-Dimer, FDP, WBC, Neutrophil percentage, Lymphocyte percentage, Platelet count, MBG, Lactate levels, Troponin levels, T-BIL, RDW, and albumin upon admission within 24 hours. Thyroid function tests, including TT3, FT3, TT4, FT4, TSH, and rT3 indices, were also collected. The above data are the first results within 24 hours of admission, all collected manually. Presumed sources of infection were classified into respiratory infection, urogenital, intra-abdominal, blood stream, skin-soft tissues, intracerebral infection and other unknown according to systems. Other baseline information included whether mechanical ventilation was used and length of hospitalization.

Outcomes

The primary outcome was 30-day mortality, defined as death within 30 days after admission. Hospital mortality was a secondary outcome.

Statistical Analysis

Continuous variables were analyzed by calculating the mean ± standard deviation (SD) or median interquartile range (IQR) according to whether variables were distributed normally. Between-group differences were analyzed using t or Mann–Whitney *U*-tests for continuous variables or chi-square tests for categorical variables. Standardized mean difference (SMD) value was calculated indicating difference of baseline characteristics between groups. Receiver operating characteristic (ROC) curve was used to determine the optimal cut-offs for the RAR indicator. Univariate and multivariate Cox proportional hazards models were performed to evaluate the risk difference for 30-day mortality between different RAR level groups and reported the hazard ratio (HR) values. Candidate variables for multivariate Cox regression models were chosen based on clinical significance and potential risk factors obtained in the univariate Cox regression analysis. Survival curve was plotted by the Kaplan–Meier (K-M) method, and a Log rank test determined whether hazard varied between different RAR level groups. A contrastive analysis was conducted with the prediction performance by RAR level, APACHE II and SOFA scores to screen the best predictor of classification performance identified by the ROC curve. To minimize the effects of potential confounding factors, propensity score matching (PSM) was conducted using a caliper width of 0.1 and SMD values greater than 0.2 are considered imbalanced. Subgroup analysis was conducted by examining whether the relationship remained between different subgroups, including sex, age, history of hypertension, diabetes, tumor, presumed source of infection, SOFA scores, and APACHE II scores. Significance was determined at $p < 0.05$ for all two-sided tests. Statistical analyses and plotting were performed using the IBM SPSS Statistics 26 and GraphPad Prism (version 9.5.0).

Results

The Baseline Characteristic Comparison Between the 30-Day Death Group and Survival Group

The patients' baseline clinical characteristics are shown in Table 1 of the study. A total of 328 patients with sepsis associated with NTIS were enrolled in the study, and 51 (15.5%) patients died at 30 days after admission. The patients' baseline clinical characteristics are compared in Table 1 according to their 30-day death or survival state. The median age of the survival group was 72 years (IQR: 61 to 82) and 170 were male (61.4%). The median age of patients in the death group was 81 (IQR: 67 to 85) and 27 of whom were male (52.9%). Patients in the death group had higher rates of cardiovascular disease, HF, kidney disease history, mechanical ventilation therapy, and with higher APACHE II scores (median score: 22 vs 13) and SOFA scores (7 vs 4) than those in the survival group. Respiratory infection was the primary cause of infection in the majority of cases (n = 153, 46.6%), with intra-abdominal infection (n = 102, 31.1%) and urogenital infection (n = 61, 18.6%) following closely behind. The non-survivors had higher levels of RDW than survivors (median: 14.5% vs 13.5%, $P < 0.001$), lower albumin (median: 28.8g/L vs 34.1g/L, $P < 0.001$) and higher RAR value (50.2 L/g vs 40.5 L/g, $P < 0.001$).

The Initial Characteristics Prior to Propensity Score Matching and Subsequent to Propensity Score Matching

Patients were categorized into two groups based on ROC analysis results, with one group having a high RAR value (RAR ≥ 42.66 L/g; n = 144) and the other group having a low RAR value (RAR < 42.66 L/g; n = 184). Table 2 displays noticeable variations in initial characteristics between the two groups. Patients in the low RAR group were younger and had lower sofa scores and APACHE II scores. Patients in the High RAR group were associated with more kidney disease (40.3% vs 21.7%, $p = 0.001$) and more heart failure (39.6% vs 19.6%, $p < 0.001$). Due to the uneven baseline characteristics among groups, a 1:1 ratio propensity score matching was conducted to address potential confounding variables, resulting in the creation of 108 pairs of matched patients. Table 3 displays the fundamental attributes of patients following PSM. Patients with low RAR levels exhibited elevated levels of T-BIL ($P = 0.001$) and Lactate ($P = 0.01$) compared to those in the high RAR group.

Table 1 The Baseline Characteristics Compared Survivors with No-Survivors

Characteristics	Survivors (n=277)	No-survivors (n=51)	P value
Gender (%)			0.259
Male	170(61.4)	27 (52.9)	
Female	107(38.6)	24 (47.1)	
Age (years)	72(61, 82)	81 (67, 85)	0.001
Cardiovascular_disease (%)			<0.001
No	191 (69.0)	22 (43.2)	
ACS	26 (9.4)	17 (33.3)	
CAD	60 (21.6)	12 (23.5)	
HF (%)			<0.001
No	211 (76.2)	24 (47)	
Acute	14 (5)	8 (15.7)	
Chronic	52 (18.8)	19 (37.3)	
Kidney_disease (%)			<0.001
No	208 (75.1)	22 (43.1)	
AKI	46(16.6)	23 (45.1)	
CKD	23(8.3)	6 (11.8)	
Cerebral_vascular_disease (%)			<0.001
No	214(77.3)	35 (68.6)	
Acute Ischemic Stroke	12(4.3)	7 (13.7)	
Stroke History	51(18.4)	9 (17.7)	
Tumor (%)			0.255
No	264(95.3)	46 (90.2)	
Yes	13(4.7)	5 (9.8)	
Hypertension (%)			0.137
No	140(50.5)	20 (39.2)	
Yes	137(49.5)	31 (60.8)	
Diabetes (%)			0.253
No	161(58.1)	34 (66.7)	
Yes	116(41.9)	17 (33.3)	
AF (%)			0.345
No	237(85.6)	41 (80.4)	
Yes	40(14.4)	10 (19.6)	
DVT (%)			0.346
No	252(91)	49 (96.1)	
Yes	25(9)	2 (3.9)	
COPD (%)			0.767
No	260(93.9)	49 (96.1)	
Yes	17(6.1)	2 (3.9)	
Mechanical_ventilation (%)			<0.001
No	222(80.1)	22 (43.1)	
Yes	55(19.9)	29 (56.9)	
Presumed_source_of_infection (%)			<0.001
Respiratory Infection	113(40.8)	40 (78.4)	
Urogenital	57(20.5)	4 (7.8)	
Intra-abdominal	99(35.7)	3 (5.9)	
Blood Stream	3(1.1)	0 (0)	
Skin-soft tissues	1(0.4)	2 (3.9)	
Intracerebral Infection	1(0.4)	1 (2)	
Other Unknown	3(1.1)	1 (2)	
Hospital_time (days)	11(8, 16)	8 (4, 15)	0.004
APACHEII	13(10, 19)	22 (16, 28)	<0.001

(*Continued*)

Table 1 (Continued).

Characteristics	Survivors (n=277)	No-survivors (n=51)	P value
SOFA	4(2, 6)	7 (5, 10)	<0.001
PT (s)	13.1(11.8, 14.75)	13.6 (11.9, 15.3)	0.255
D-Dimer (mg/L)	0.89(0.51, 1.37)	1.28 (0.83, 4.12)	0.002
FDP (g/L)	8.62(4.14, 18.205)	13.28 (7.03, 43.73)	0.007
WBC (*10^9/L)	12.83(8.8, 17.685)	13.1 (8.5, 17.8)	0.85
Neutrophil_percentage (%)	87.9(82.2, 92)	89 (82.9, 91.8)	0.838
Lymphocyte_percentage (%)	6.1(3.7, 10)	6.2 (3.8, 9.7)	0.939
Platelet (*10^9/L)	137(100, 191)	156 (86, 214)	0.795
MBG (mmol/L)	9.1(6.9, 13.3)	9.3 (6.6, 13.2)	0.978
Lactate (mmol/L)	2(1.5, 3.2)	2.8 (1.8, 4.2)	0.008
Troponin (ng/mL)	0.04(0.02, 0.134)	0.19 (0.046, 1.255)	<0.001
T_BIL (umol/L)	18.6(12.65, 27.45)	18.8 (9.1, 27.4)	0.676
TT3 (nmol/L)	0.69(0.51, 0.9075)	0.52 (0.38, 0.66)	<0.001
TT4 (nmol/L)	86.1(66.4, 104.5)	70.4 (51.4, 83.7)	<0.001
FT3 (pmol/L)	2.53(2.015, 2.945)	2.12 (1.86, 2.57)	0.001
FT4 (pmol/L)	14.83(12.865, 17.095)	15.24 (11.86, 17.93)	0.677
TSH (uIU/mL)	0.83(0.34, 1.625)	0.55 (0.29, 1.31)	0.184
rT3 (ng/mL)	0.29(0.2, 0.39)	0.27 (0.16, 0.36)	0.266
RDW (%)	13.5(12.9, 14.3)	14.5 (13.3, 15.4)	<0.001
Albumin (g/L)	34.1(29.9, 39.15)	28.8 (25.4, 32.3)	<0.001
RAR (1/g/L)	40.5028(34.2204, 46.7292)	50.1946 (43.7309, 58.6572)	<0.001

Abbreviations: IQR, interquartile range; ACS, acute coronary syndrome; CAD, coronary artery disease; HF, heart failure; AKI, acute kidney injury; CKD, chronic kidney diseases; AF, atrial fibrillation; DVT, deep venous thrombosis; COPD, chronic obstructive pulmonary disease; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation; PT, prothrombin time; FDP, fibrinogen degradation products; WBC, white blood cell count; MBG, mean blood glucose; T-BIL, total bilirubin.

Table 2 The Baseline Characteristics Before Propensity Score Matching

Characteristics	Low RAR group (n=184)	High RAR group (n=144)	P value	SMD
Gender (%)			0.308	0.12
Male	115(62.5)	82 (56.9)		
Female	69(37.5)	62 (43.1)		
Age (years)	69.5(59,80)	77.5 (67,83)	<0.001	0.42
Cardiovascular_disease (%)			0.214	0.17
No	127(69)	86 (59.7)		
ACS	21(11.4)	22 (15.3)		
CAD	36(19.6)	36 (25)		
HF (%)			<0.001	0.41
No	148(80.4)	87 (60.4)		
Acute	8(4.3)	14 (9.7)		
Chronic	28(15.3)	43 (29.9)		
Kidney_disease (%)			0.001	0.4
No	144(78.3)	86 (59.7)		
AKI	30(16.3)	39 (27.1)		
CKD	10(5.4)	19 (13.2)		
Cerebral_vascular_disease (%)			0.703	0.04
No	142(77.2)	107 (74.3)		
Acute Ischemic Stroke	9(4.9)	10 (6.9)		

(*Continued*)

Table 2 (Continued).

Characteristics	Low RAR group (n=184)	High RAR group (n=144)	P value	SMD
Stroke History	33(17.9)	27 (18.8)		
Tumor (%)			0.305	0.13
No	176(95.7)	134 (93.1)		
Yes	8(4.3)	10 (6.9)		
Hypertension (%)			0.107	0.18
No	97(52.7)	63 (43.8)		
Yes	87(47.3)	81 (56.2)		
Diabetes (%)			0.753	0.02
No	108(58.7)	87 (60.4)		
Yes	76(41.3)	57 (39.6)		
AF (%)			0.768	0.03
No	155(84.2)	123 (85.4)		
Yes	29(15.8)	21 (14.6)		
DVT (%)			0.037	0.25
No	174(94.6)	127 (88.2)		
Yes	10(5.4)	17 (11.8)		
COPD (%)			0.754	0.04
No	174(94.6)	135 (93.8)		
Yes	10(5.4)	9 (6.2)		
Mechanical_ventilation (%)			0.01	0.3
No	147(79.9)	97 (67.4)		
Yes	37(20.1)	47 (32.6)		
Hospital_time (days)	11(7,15)	11 (8,16)	0.55	0.09
APACHEII	13(9,19)	17 (12,22)	<0.001	0.47
SOFA	4(2,6)	5 (3,8)	<0.001	0.43
PT (s)	12.8 (11.6,14.2)	13.8 (12.05,15.475)	0.001	0.36
D-Dimer (mg/L)	0.825 (0.4375,1.2075)	1.08 (0.7,3.025)	<0.001	0.32
FDP (g/L)	7.615 (3.5125,16.24)	10.48(5.7325,28.4675)	<0.001	0.27
WBC (*10^9/L)	12.495 (8.5725,17.4)	13.75(8.8,17.8075)	0.26	0.12
Neutrophil_percentage (%)	87.85 (82.375,91.8)	88.3(81.825,92.2)	0.585	0.04
Lymphocyte_percentage (%)	6.05 (3.75,9.65)	6.15(3.625,10.275)	0.787	0.07
Platelet (*10^9/L)	139 (102.25,192)	138(85.25,192)	0.725	0.05
MBG (mmol/L)	9.4 (7.225,14)	8.55(6.4,12.75)	0.017	0.2
Lactate (mmol/L)	2.25 (1.6,3.3)	2(1.5,3.55)	0.283	0.01
Troponin (ng/mL)	0.038 (0.0155,0.12875)	0.071(0.02725,0.30225)	<0.001	0.34
T_BIL (umol/L)	20 (13.95,29.85)	16.7(10.85,25.075)	0.003	0.12
TT3 (nmol/L)	0.71(0.54,0.9175)	0.585(0.4425,0.8375)	0.001	0.35
TT4 (nmol/L)	88.5(66.4,106.975)	77.8(61.775,96.175)	0.005	0.28
FT3 (pmol/L)	2.625(2.05,2.9675)	2.325(1.9,2.7575)	0.003	0.32
FT4 (pmol/L)	14.9(13.035,17.1475)	14.725(12.215,17.1775)	0.326	0.15
TSH (uIU/mL)	0.7(0.295,1.4875)	0.87(0.37,1.74)	0.161	0.14
rT3 (ng/mL)	0.29(0.2025,0.39)	0.27(0.16,0.39)	0.188	0.11

Univariate and Multivariate Cox Regression Analysis Between RAR Levels and 30-Day Survival

A multivariate Cox regression analysis was performed by incorporating significant factors in the univariate Cox model. The multivariate Cox regression results are shown in Table 4, high RAR level was a significant risk factor for survival within 30 days after admission (HR 1.039, 95% CI 1.012–1.067, p = 0.004). Moreover, stroke history (HR 3.27 95% CI: 1.053, 10.152, p = 0.04), mechanical-ventilation (HR 2.694 95% CI: 1.378, 5.265, p = 0.004) and APACHE II scores

Table 3 The Baseline Characteristics After Propensity Score Matching

Characteristics	Low RAR group (n=108)	High RAR group (n=108)	p
Gender (%)			0.488
Male	67 (62)	62(57.4)	
Female	41 (38)	46(42.6)	
Age (years)	72 (60.5,81)	76(66,83)	0.051
Cardiovascular_disease (%)			0.497
No	68 (63)	68(63)	
ACS	16 (14.8)	11(10.1)	
CAD	24 (22.2)	29(26.9)	
HF (%)			0.891
No	76 (70.4)	73(67.6)	
Acute	7 (6.5)	7(6.5)	
Chronic	25 (23.1)	28(25.9)	
Kidney_disease (%)			0.636
No	78 (72.2)	74(68.5)	
AKI	22 (20.4)	22(20.4)	
CKD	8 (7.4)	12(11.1)	
Cerebral_vascular_disease (%)			0.847
No	81 (75)	83(76.9)	
Acute Ischemic Stroke	6 (5.6)	7(6.5)	
Stroke History	21 (19.4)	18(16.6)	
Tumor (%)			0.353
No	104 (96.3)	101(93.5)	
Yes	4 (3.7)	7(6.5)	
Hypertension (%)			0.496
No	57 (52.8)	52(48.1)	
Yes	51 (47.2)	56(51.9)	
Diabetes (%)			0.779
No	66 (61.1)	68(63)	
Yes	42 (38.9)	40(37)	
AF (%)			0.196
No	87 (80.6)	94(87)	
Yes	21 (19.4)	14(13)	
DVT (%)			0.653
No	98 (90.7)	96(88.9)	
Yes	10 (9.3)	12(11.1)	
COPD (%)			0.552
No	103 (95.4)	101(93.5)	
Yes	5 (4.6)	7(6.5)	
Mechanical_ventilation (%)			1
No	77 (71.3)	77 (71.3)	
Yes	31 (28.7)	31 (28.7)	
Hospital_time (days)	12 (8.25,17)	11(8,15)	0.182
APACHEII	15.5 (10,22)	15.5(11,20.75)	0.561
SOFA	5 (2.25,7.75)	5(3,7)	0.774
PT (s)	13.3 (12.125,15.05)	13.35(11.7,14.8)	0.638
D-Dimer (mg/L)	1.015 (0.605,1.9575)	1.01(0.6425,2.0975)	0.895
FDP (g/L)	10.505 (4.67,27.5025)	9.995(5.14,21.85)	0.582
WBC (*10^9/L)	11.7 (7.4925,17.35)	13.39(8.94,18.59)	0.186
Neutrophil_percentage (%)	88.2 (81.6,92.775)	88.6(81.825,92.45)	0.712
Lymphocyte_percentage (%)	5.8 (3.5,10.1)	6.3(3.325,10.025)	0.941

(*Continued*)

Table 3 (Continued).

Characteristics	Low RAR group (n=108)	High RAR group (n=108)	p
Platelet (*10^9/L)	125 (79.75,175.75)	139(88.75,194.5)	0.129
MBG (mmol/L)	9.4 (7.2,13.925)	8.6(6.625,13.1)	0.212
Lactate (mmol/L)	2.4 (1.8,3.5)	2(1.4,3.05)	0.01
Troponin (ng/mL)	0.05(0.02,0.151)	0.0575(0.02425,0.2245)	0.296
T_BIL (umol/L)	21.05(14.125,34.85)	16.05(10.125,23.75)	0.001
TT3 (nmol/L)	0.66(0.485,0.8075)	0.61(0.4925,0.87)	0.857
TT4 (nmol/L)	83.15(58.925,101.1)	80(64.925,99.975)	0.582
FT3 (pmol/L)	2.345(1.94,2.8475)	2.4(1.985,2.82)	0.908
FT4 (pmol/L)	14.645(12.895,16.4325)	14.94(12.2825,17.4925)	0.624
TSH (uIU/mL)	0.685(0.29,1.3175)	0.835(0.37,1.75)	0.137
rT3 (ng/mL)	0.26(0.1825,0.3775)	0.275(0.16,0.39)	0.84

Table 4 Univariate and Multivariate Analysis

Variable	Univariate analysis [HR (95% CI)]	P	Multivariate analysis[HR (95% CI)]	P
Before PSM				
CAD	2.75(1.313–5.759)	<0.001		
Stroke History	3.034 (1.129–8.151)	0.016	3.27 (1.053–10.152)	0.04
Age (years)	1.043 (1.017–1.069)	0.001		
Mechanical_ventilation	4.572 (2.605–8.022)	<0.001	2.694 (1.378–5.265)	0.004
APACHEII	1.124 (1.087–1.161)	<0.001	1.061 (1.01–1.115)	0.018
SOFA	1.216 (1.124–1.315)	<0.001		
D-Dimer (mg/L)	1.078 (1.02–1.14)	0.008		
Lactate (mmol/L)	1.12 (1.047–1.198)	0.001		
Troponin (ng/mL)	1.088 (1.045–1.133)	<0.001		
TT3 (nmol/L)	0.089 (0.029–0.27)	<0.001		
TT4 (nmol/L)	0.981 (0.972–0.991)	<0.001		
FT3 (pmol/L)	0.423 (0.261–0.684)	<0.001		
RAR (1/g/L)	1.066 (1.043–1.089)	<0.001	1.039 (1.012–1.067)	0.004
After PSM				
Variable	Univariate analysis [HR (95% CI)]	P	Multivariate analysis[HR (95% CI)]	P
CAD	2.968 (1.171,7.523)	0.002		
Age (years)	1.041(1.009,1.073)	0.011		
Mechanical_ventilation	3.780(1.894,7.543)	<0.001	2.547 (1.086, 5.975)	0.032
APACHEII	1.112(1.062,1.164)	<0.001		
SOFA	1.156 (1.046, 1.279)	0.005		
Troponin (ng/mL)	1.202 (1.092, 1.322)	<0.001		
TT3 (nmol/L)	0.190 (0.047, 0.769)	0.02		
TT4 (nmol/L)	0.986 (0.974, 0.999)	0.035		
FT3 (pmol/L)	0.546 (0.306, 0.975)	0.041		
rT3 (ng/mL)	0.584 (0.354, 0.961)	0.034		
RAR (1/g/L)	1.055 (1.024, 1.086)	<0.001	1.049 (1.015, 1.085)	0.005

(HR 1.061 95% CI: 1.01, 1.115, p = 0.018) were all independent risk factors. After PSM, RAR was also an independent risk factor for 30-day death (HR 1.049 95% CI: 1.015, 1.085, p = 0.005).

Different models were utilized to analyze the diagnostic significance of RAR in sepsis-related NTIS patients, including unadjusted models, Model 1 adjusted for age and gender, and Model 2 adjusted for variables in Model 1,

Table 5 Association of RAR and Mortality in Different Models

Outcome	Variable	HR (95% CI)		
		Unadjusted	Model 1	Model 2
30d hospital mortality	RAR	1.066 (1.043, 1.089)	1.058 (1.034, 1.083)	1.041 (1.016, 1.065)
	RAR ≥ 42.6611	6.573 (3.193, 13.527)	5.656 (2.734 11.7)	4.193 (1.986, 8.854)
30d hospital mortality (After PSM)	RAR	1.055 (1.024, 1.086)	1.048 (1.016, 1.08)	1.044 (1.011, 1.077)
	RAR ≥ 42.6611	4.013 (1.741, 9.247)	3.69 (1.598, 8.521)	4.009 (1.708, 9.412)

Notes: Model 1 adjusted for age, gender. Model 2 adjusted for variables in Model 1, Cardiovascular_disease, cerebral_vascular_disease, APACHE II, mechanical_ventilation.

cardiovascular disease, cerebral vascular disease, APACHE II, and mechanical ventilation (Table 5). Patients exhibiting elevated RAR levels experienced increased mortality within 30 days. Following propensity score matching, the individual hazard ratios of Unadjusted, Model 1, and Model 2 for individuals with RAR ≥ 42.6611 L/g were 4.013 (95% CI 1.741–9.247, P < 0.05), 3.69 (95% CI 1.598–8.521, P < 0.05), and 4.009 (95% CI 1.708–9.412, P < 0.05).

RAR Significantly Improves Diagnostic Value of 30d-Mortality in Sepsis Associated Nonthyroidal Illness Syndrome Patients

To evaluate the prognostic significance of RAR for mortality in sepsis-associated NTIS, ROC analysis was conducted as shown in Figure 1. The AUC for RAR, APACHE II and SOFA was 0.751 (95% CI: 0.678–0.825), 0.764 (95% CI: 0.688–0.839), and 0.718 (95% CI: 0.645–0.791), respectively. The best threshold for RAR in sepsis-related NTIS was determined to be 42.66 1/g/L, achieving a sensitivity of 0.82 and a specificity of 0.629 (Figure 1A). Moreover, it was discovered that RAR exhibited a robust ability to differentiate in-hospital mortality, with an AUC of 0.736 and a significance level of less than 0.001. After PSM, the respective AUC for RAR, APACHE II and SOFA were 0.695 (95% CI: 0.598–0.792), 0.718 (95% CI: 0.616–0.820), and 0.671 (95% CI: 0.581–0.761) (Figure 1B). About the hospital mortality of patients, the AUC for RAR was 0.736 (95% CI: 0.658–0.813), the AUC for APACHE II and SOFA was 0.764 (95% CI: 0.689–0.838) and 0.723 (95% CI: 0.651–0.795) (Figure 1C). We created 30-day survival curves for sepsis patients with NTIS to evaluate overall survival at various RAR levels, u sing the optimal cutoff value of 42.66 1/g/L determined by ROC curves. The Kaplan-Meier analysis in Figure 2A indicated that individuals belonging to the low RAR category exhibited a notably greater 30-day survival rate compared to those in the high RAR group prior to PSM (95.1% vs 71.5%; p < 0.05). Similarly, comparable outcomes were seen following PSM (93.5% compared to 75.9%; p < 0.05) as depicted in Figure 2B.

Patient Characteristics and Results Vary Among Different Types of NTIS

Individuals with non-thyroidal illness syndrome (NTIS) are classified into two groups based on varying concentrations of FT3 and FT4, as shown in Figure 3. Type 1 exhibited low levels of FT3, independent of the FT4 levels. Type 2 exhibited decreased levels of FT3 and FT4. Figure 3 displays the results of ROC analysis conducted to evaluate the predictive capacity of RAR, revealing its significant discriminatory power for 30-day hospital mortality across various categories. In type 1, the AUC for RAR, APACHE II and SOFA was 0.737 (95% CI: 0.659–0.816), 0.755 (95% CI: 0.672–0.837), and 0.702 (95% CI: 0.618–0.785), respectively (Figure 3A). In type 2, the respective AUC for RAR, APACHE II and SOFA were 0.826 (95% CI: 0.638–1.000), 0.826 (95% CI: 0.646–1.000), and 0.752 (95% CI: 0.596–0.907) (Figure 3B).

Higher RAR Correlated with Higher 30-day Mortality in the Most Subgroups, in Addition to Combined Tumor or Urogenital Infection

Forest plots of subgroup analyses (Figure 4). Gender, age (divided into ≤70 years and >70 years), comorbidities of hypertension, comorbidities of diabetes, combined tumor, presumed different source of infection (including lower respiratory, urogenital, intra-abdominal), APACHE II scores and SOFA scores were included in subgroup analyses. Patients with elevated RAR levels showed a higher 30-day mortality rate in various subgroups, including those with

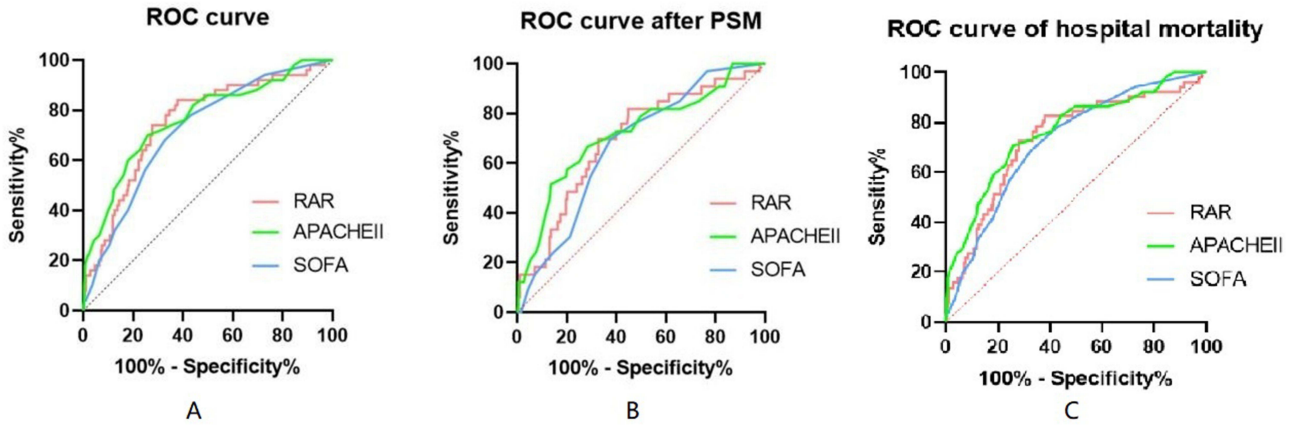

Figure 1 Comparison of RAR and different ratings for assessing prognosis in sepsis patients with NTIS.
Notes: (**A**) ROC curve for predicting 30-day mortality. (**B**) ROC curve for predicting 30-day mortality after PSM. (**C**) ROC curve for predicting hospital mortality.

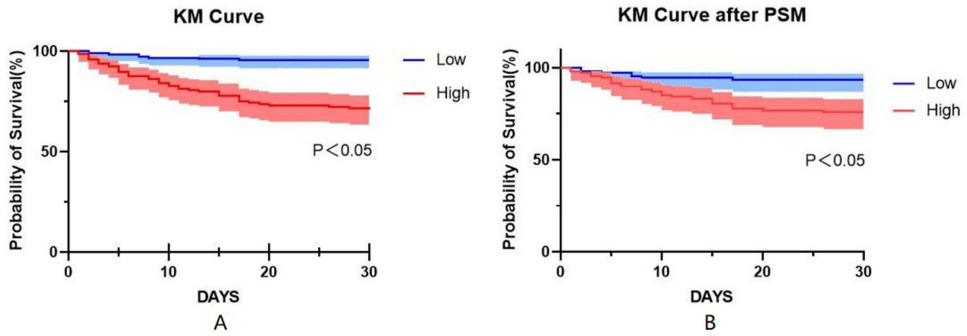

Figure 2 Kaplan-Meier survival curves for cumulative survival in different RAR groups.
Notes: (**A**) Kaplan-Meier survival curve of 30d. (**B**) Kaplan-Meier survival curve of 30d after PSM.

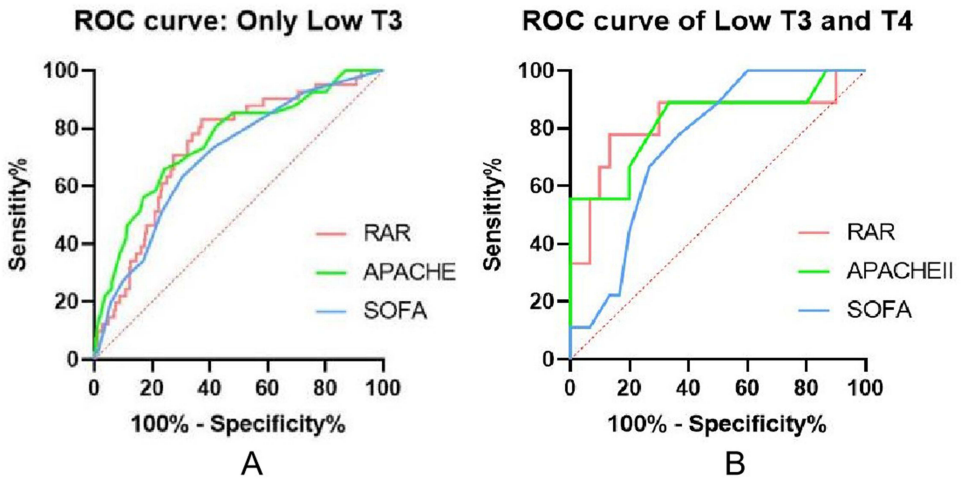

Figure 3 Comparison of RAR and different ratings for assessing prognosis in sepsis patients with different types of NTIS.
Notes: (**A**) Patients with sepsis combined with low T3 only. (**B**) Patients with sepsis combined with low T3 and T4.

Variable	HR (95%)	P for interaction
Male	1.077 (1.043-1.112)	<0.001
Female	1.053 (1.021-1.086)	
Age≤70	1.083 (1.035-1.133)	<0.001
Age>70	1.055 (1.028-1.082)	
Hypertension no	1.048 (1.011-1, 087)	0.001
Hypertension yes	1.076 (1.045-1.108)	
Diabetes no	1.043 (1.015-1.072)	0.508
Diabetes yes	1.117 (1.07-1.165)	
Tumor no	1.065 (1.041-1.09)	0.089
Tumor yes	1.06 (0.96-1.17)	
Lower Respiratory	1.053 (1.026-1.081)	0.409
Urogenital	1.062 (0.986-1.145)	
Intra-abdominal	1.097 (1.005-1.198)	
APACHEII≤20	1.065 (1.028-1.103)	<0.001
APACHEII>20	1.046 (1.017-1.077)	
SOFA≤4	1.094 (1.038-1.152)	<0.001
SOFA>4	1.045 (1.02-1.071)	

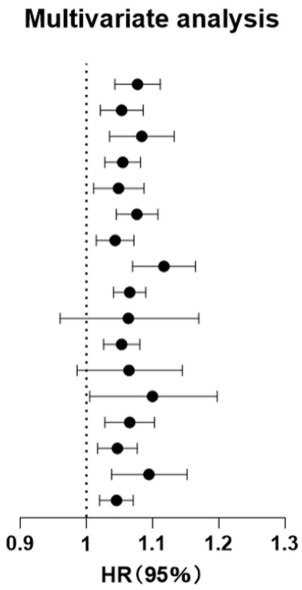

Figure 4 Subgroup analysis performed for different sex, age, comorbidities, infection location and other scores.

combined tumors (HR 1.06, 95% CI 0.96–1.17) or urogenital infections as the suspected source of infection (HR 1.06, 95% CI 0.96–1.17).

Discussion

The study revealed that patients suffering from sepsis-related NTIS with higher RAR levels had worse survival prognosis within both 30 days after admission and hospitalization. The ROC curves indicated that RAR indicator had superior prediction performance for 30-day mortality than other classical indexes. The results of univariate Cox regression analysis among PSM cohorts and subgroup analysis further verified the above findings. To date, our study is the first to investigate the relationship and prediction efficacy of RAR with survival among patients with sepsis-related NTIS, aiding in the early identification of survival state and providing the possibility for individualized interventions.

Sepsis affecting the hematopoietic system can significantly impact health, with certain research indicating the importance of red blood cell distribution width for diagnosing and predicting outcomes in sepsis.[16–21] In a prior investigation, our team discovered that variations in RDW levels can be used to forecast the development and outcome of sepsis-associated DIC in sepsis patients.[6] In ICU patients who are critically ill, there is typically a significant decrease in serum albumin levels, which has been linked to increased mortality rates, more frequent ICU admissions, and longer hospital stays.[22–28] RAR is a combination of RDW and albumin, which has been researched in relation to diabetes, heart conditions, and inflammatory disorders.[29–31] A recent study indicates that patients with sepsis have a worse clinical outlook when their RAR levels are higher.[15] NTIS is common in the majority of severely ill patients, with those requiring extended care in the ICU often displaying lower levels of plasma T3 and T4.[9] Ning et al stated that nearly half of septic patients experienced complications related to NTIS. Patients with sepsis and non-thyroidal illness syndrome (NTIS) exhibit significantly increased 30-day in-hospital mortality rates.[10]

There are few studies on the biomarkers of the prediction of mortality in sepsis associated NTIS, our study is the first associated study, which is innovative. Our current research found a correlation between elevated RAR levels and increased SOFA and APACHE II scores in patients. The study findings indicate a potential link between RAR and disease severity in ICU patients with sepsis-related NTIS. Upon further examination of subgroups, it is evident that in most cases, a higher RAR is associated with increased 30-day mortality rates. Patients diagnosed with both tumor and urogenital infection displayed a correlation with RAR in terms of 30-day mortality, indicating that RAR could serve as a significant indicator for forecasting the outcome of individuals with sepsis-related NTIS. We approach subgroup analyses with caution due to the potential impact of population heterogeneity on the results. The AUC for RAR was

observed to be higher than SOFA and just lower than APACHE II in our research, given that RDW and albumin are routinely tested in ICUs, which is easy for clinicians to obtain and easier to evaluate. Additional research is needed to confirm these findings.

There were certain constraints in our research. Due to the retrospective nature of the study, the population consisted of a diverse mix of infection causes. Despite attempts to account for potential confounders and conduct subgroup analyses, it was challenging to eliminate selection and confounding biases, which are inherent limitations of retrospective studies. There is currently no method available for the longitudinal and dynamic measurement of thyroid hormone levels, as they, along with RDW and albumin levels, fluctuate during the sepsis process. Furthermore, this study was conducted retrospectively at a single center, and the findings should be validated by larger multicenter clinical studies due to the constraints of the limited sample size. Additionally, certain underlying conditions, like long-term liver and kidney issues, can impact the levels of thyroid hormones, RDW, and albumin in the body. Subgroup analyses were conducted on these groups to confirm the strength of the findings. Our findings indicate that RAR is linked to negative clinical outcomes in patients with sepsis-related NTIS. We think that it is necessary to conduct a well-planned, prospective study involving multiple centers in order to confirm the validity of our findings.

Conclusions

Regardless of the type of NTIS, RAR is a potential prognostic indicator for patients with sepsis associated with NTIS and is associated with a poor clinical prognosis. Increased RAR is associated with higher rates of mortality within 30 days and during hospitalization.

Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Patient Data Confidentiality Disclaimer

We hereby affirm our commitment to the strict confidentiality of patient data. We understand the sensitive nature of this information and the trust placed in us by our patients. To ensure the highest level of data protection, we adhere to the following principles:

Compliance with Laws and Regulations: We strictly followed the "Declaration of Helsinki", "International Ethical Guidelines for Research Involving Human Health" and other medical ethics standards, and fully respect the subjects' rights to know and privacy, and effectively protect the subjects' rights and well-being.

Limited Access and Use: We restrict access to patient data to authorized personnel who require it for legitimate business purposes, such as providing medical care or managing patient records. We ensure that such personnel are appropriately trained on data privacy and confidentiality practices.

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Minimization of Data Collection: We collect only the minimum amount of patient data necessary to fulfill our legitimate business purposes. We regularly review our data collection practices to ensure that they remain necessary and appropriate.

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Patient Rights: We respect the rights of patients to access, correct, and request the deletion of their personal information in accordance with applicable laws and regulations.

By adhering to these principles, we strive to maintain the trust of our patients and to ensure the confidentiality and security of their data.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The researchers affirm that the study was carried out without any business or monetary affiliations that could be interpreted as a possible clash of interests.

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