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Geriatric nutritional risk index as a predictor of 28-day and 365-day mortality in patients with heart failure complicated by sepsis: A retrospective cohort study using the MIMIC-IV database

Yameng Wang^{1,▽}, Maosheng Wang^{2,3,▽}, Ling Wang^{2,3}, Qi Tang^{1,4}, Yuanping Wang^{5,6}, Xiangyun Teng^{7,8,✉}, Lili Jin^{5,6,✉}

¹Graduate School, The Eighth Clinical Medical College, Guangzhou University of Chinese Medicine, Foshan, China

²Department of Intensive Care Unit, The Fourth Clinical Medical College, Guangzhou University of Chinese Medicine, Shenzhen, China

³Department of Intensive Care Unit, Shenzhen Traditional Chinese Medicine Hospital, Shenzhen, China

⁴Emergency Medicine Center, Foshan Hospital of Traditional Chinese Medicine, Foshan, China

⁵Department of Cardiology, The Fifth Clinical Medical College, Guangzhou University of Chinese Medicine, Guangzhou, China

⁶Department of Cardiology, Guangdong Second Traditional Chinese Medicine Hospital, Guangzhou, China

⁷Baiyun Hospital of the First Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China

⁸Medical Laboratory Center, Maoming Hospital of Guangzhou University of Chinese Medicine, Maoming, China

ABSTRACT

Objective: To evaluate the association between the Geriatric Nutritional Risk Index (GNRI) at ICU admission and mortality in patients with heart failure complicated by sepsis, a high-risk population in which the prognostic value of this validated malnutrition risk assessment tool remains underexplored.

Methods: Patients with heart failure and sepsis were identified from the Medical Information Mart for Intensive Care (MIMIC-IV) database and stratified into four GNRI groups. The primary endpoints were 28-day and 365-day all-cause mortality. Survival analysis used Kaplan-Meier curves and Cox proportional hazards models. Linearity was assessed using restricted cubic splines (RCS), while GNRI's predictive performance was evaluated using receiver operating characteristic (ROC) curves.

Results: Altogether, 1713 patients with heart failure complicated by sepsis were identified in the present study. Kaplan-Meier analysis revealed 28-day mortality rates of 40.44% (high-risk) vs. 25.27% (no-risk) ($P<.001$), with a similar trend for 365-day mortality (63.75 % vs. 43.96%, $P<.001$). RCS confirmed a linear inverse relationship between GNRI and mortality. Cox regression demonstrated that each unit GNRI increase reduced 28-day

(hazard ratio [HR], 0.99; 95% confidence interval [CI] 0.98–1.00) and 365-day mortality risk (HR, 0.98; 95% CI 0.98–0.99). ROC analysis indicated a moderate predictive value of GNRI for 28-day all-cause mortality (AUC=0.58, sensitivity=66.61%, specificity=45.62%, $P<.001$) and 365-day all-cause mortality (AUC=0.60, sensitivity=66.52%, specificity=51.28%, $P<.001$). Furthermore, the addition of GNRI significantly enhanced the predictive performance of the SAPSII (AUC increased from 0.69

▽ These authors contributed equally to this work.

✉Co-corresponding author: Jin LL, E-mail: jinlili991@163.com; Teng XY, E-mail: driftcloudxy@outlook.com

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to 0.70, $P=.02$), SOFA (AUC increased from 0.73 to 0.74, $P=.02$), and LODS (AUC increased from 0.67 to 0.68, $P=.03$) scores, with these improvements achieving statistical significance.

Conclusions: Admission GNRI is an independent risk factor for in-hospital mortality in ICU patients with heart failure complicated by sepsis. GNRI scores serve as a valuable prognostic indicator for assessing mortality risk in this patient population.

KEYWORDS: Geriatric nutritional risk index; MIMIC-IV database; Heart failure; Sepsis

Summary

Question: What is the prognostic value of the Geriatric Nutritional Risk Index (GNRI) at ICU admission for predicting mortality in high-risk patients with heart failure complicated by sepsis?

Findings: In this retrospective cohort study, a lower GNRI was significantly and independently associated with increased 28-day and 365-day all-cause mortality. Each unit increase in GNRI was linked to a reduced mortality risk, demonstrating its value as an independent risk factor. The association was linear, and integrating GNRI with established severity scores significantly improved prognostic accuracy.

Meaning: GNRI at admission is a critical, independent prognostic indicator for patients with heart failure and sepsis, underscoring the pivotal role of early nutritional assessment in the ICU. It provides clinicians with a simple, validated tool to identify high-risk patients promptly, thereby facilitating proactive nutritional and clinical interventions to improve survival outcomes.

1. Introduction

Heart failure (HF), a global epidemic characterized by high morbidity and mortality, affects over 64 million individuals worldwide and significantly impairs patients' quality of life[1,2]. It is a clinical syndrome resulting from structural or functional abnormalities of the heart, leading to reduced cardiac output and systemic or pulmonary circulatory congestion[3]. Sepsis, a life-threatening organ dysfunction caused by a dysregulated host response to infection, is a common and critical complication in patients with heart failure, accounting for approximately one-quarter of all heart failure-related deaths[4]. Reports indicate that in 2017, sepsis was associated with 11 million deaths globally, representing 19.7% of total global mortality[5]. The co-occurrence of HF and sepsis presents a complex clinical challenge, with mortality rates reaching as high as 90% in patients with both

conditions[6]. The interplay between HF and sepsis creates a vicious cycle, where HF exacerbates the risk and severity of sepsis, and sepsis, in turn, worsens cardiac function and overall prognosis[7].

Nutritional disorders, such as malnutrition, cachexia and sarcopenia, are common and often under-recognized problem in patients with HF, further complicating their clinical course and increasing mortality risk[8]. Research indicates that the prevalence of malnutrition in heart failure patients ranges from 15% to 90%, depending on clinical conditions and the severity of heart failure, with elderly patients being particularly vulnerable[8,9]. In a contemporary, real-world, multicenter study of patients with severe heart failure, malnutrition was commonly observed and independently associated with an elevated mortality risk, with estimated 1-year all-cause mortality rates of 22.4% and 41.1% for patients without and with malnutrition, respectively[10]. Malnutrition leads to detrimental impacts on clinical outcomes, including prolonged hospital stays, increased risk of infections, impaired immune function, and ultimately, higher mortality[11]. Therefore, assessing nutritional status in HF patients is crucial for risk stratification and implementing appropriate interventions to improve outcomes.

Geriatric Nutritional Risk Index (GNRI) serves as a tool to identify patients with malnutrition and associated risks of morbidity and mortality, offering a simple yet comprehensive assessment based on ideal and actual body weight, height, and serum albumin concentration[12,13]. A meta-analysis involving 10,589 elderly patients with heart failure revealed that for each 1-unit decrease in the GNRI, the risk of all-cause mortality in heart failure patients significantly increased by 6%[14]. Despite the established prognostic value of GNRI in HF and other conditions, limited research has explored its utility in predicting outcomes in HF patients complicated by sepsis. Sepsis can significantly alter the metabolic and nutritional status of patients, leading to increased catabolism, protein breakdown, and depletion of micronutrients[15]. In this context, GNRI may serve as a valuable tool for identifying vulnerable patients who are at higher risk of adverse outcomes, including mortality.

Therefore, this study aims to investigate the association between GNRI and mortality in patients with heart failure complicated by sepsis, utilizing a large-scale retrospective cohort derived from the Information Mart for Intensive Care IV (MIMIC-IV) database. The primary focus is to evaluate the predictive value of GNRI for 28-day and 365-day all-cause mortality in this high-risk population. The findings may offer novel insights into early identification and prognostic improvement strategies for these patients.

2. Methods

2.1. Source of data

This retrospective study utilized patient data extracted from version 3.1 of the MIMIC-IV database[16]. This comprehensive, publicly available, and de-identified database encompasses clinical information from 94,458 patients admitted to the intensive care units of Beth Israel Deaconess Medical Center between 2008 and 2019. The dataset includes demographic details, vital signs, disease diagnoses, medication records, laboratory results, surgical records, nursing notes, and follow-up survival data. Established with approval from the Beth Israel Deaconess Medical Center Institutional Review Board, the database's creation included a waiver of informed consent. One of the study authors completed the requisite training and certification provided by the National Institutes of Health and the Collaborative Institutional Training Initiative program, subsequently obtaining authorized access to the database (Record ID: 68716674). This study adheres to the reporting guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology statement and the principles outlined in the Declaration of Helsinki[17].

2.2. Study design and population

Patients with heart failure and sepsis were included based on the International Classification of Diseases, Ninth and Tenth Revisions (ICD-9 and ICD-10), and the Sepsis-3.0 criteria. Relevant ICD-9 and ICD-10 codes are provided in Supplementary Table 1. The diagnosis of sepsis per the Sepsis-3.0 definition[18] required an increase of 2 or more points in the Sequential Organ Failure Assessment (SOFA) score from baseline, coupled with confirmed or suspected infection. In this study, patients with sepsis were identified using the sepsis extraction code provided by the MIMIC code repository[19], which is fully compliant with the Sepsis-3.0 definition. Specifically, sepsis was defined as suspected or confirmed infection accompanied by a Sequential Organ Failure Assessment (SOFA) score ≥ 2 within the first 24 hours after ICU admission.

The exclusion criteria for the study population were as follows: (1) patients admitted to the ICU more than once; (2) patients with an ICU stay of less than 24 hours; (3) patients who could not be diagnosed with both HF and sepsis; and (4) patients lacking serum albumin, height, or weight data within 24 hours of ICU admission.

2.3. Data extraction

This study employed Navicat Premium (version 16.3.2) software to execute Structured Query Language (SQL) for retrieving and

extracting clinical data from the included patients. The extracted variables encompassed: (1) Demographics: age, sex, height, weight, and Body Mass Index (BMI); (2) Comorbidities: cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, mild liver disease, severe liver disease, diabetes, renal disease, and malignant tumors; (3) Vital Signs: body temperature, heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, and SpO₂; (4) Disease Severity Scores: Acute Physiology Score III (APS III), Simplified Acute Physiology Score II (SAPS II), Sequential Organ Failure Assessment (SOFA), and Logistic Organ Dysfunction Score (LODS); (5) Laboratory Tests: white blood cell count, red blood cell count, platelet count, hemoglobin, red cell distribution width, hematocrit, albumin, alanine aminotransferase, aspartate aminotransferase, total bilirubin, blood urea nitrogen, creatinine, sodium, potassium, magnesium, calcium, glucose, prothrombin time, partial thromboplastin time, and international normalized ratio; (6) Interventions: invasive ventilation, continuous renal replacement therapy (CRRT), and renal replacement therapy (RRT); (7) Outcomes: survival status at various time points and length of hospital stay. Laboratory parameters included in the analysis were averaged from measurements obtained within the first 24 hours of ICU admission. Missing data for variables were imputed using the median imputation method.

2.4. Defining of nutritional status and outcomes

GNRI is employed to assess the nutritional status of elderly patients upon ICU admission and is generally positively correlated with nutritional condition. It is calculated using the formula: $GNRI = [14.89 \times \text{serum albumin (g/dL)}] + [41.7 \times \text{actual BMI/ideal BMI}]$, where the ideal BMI is defined as 22 kg/m². When the ratio of actual BMI to ideal BMI exceeds 1, this ratio is capped at 1[20]. Patients were categorized into four GNRI risk groups (<82, 82–92, 92–98, and ≥ 98), which have been widely used in previous studies to represent severe, moderate, mild, and no nutritional risk, respectively[21–23]. The GNRI cut-off values applied in this study were not arbitrarily defined but were derived from previously published literature and clinical practice, facilitating comparability with existing studies[13]. In addition, GNRI was also analyzed as a continuous variable using restricted cubic spline models, which yielded consistent results and further supported the robustness of our findings.

2.5. Outcomes

The primary endpoint of this study was all-cause mortality at 28 days and 365 days.

2.6. Statistical analysis

Variables with missing data exceeding 20% were initially excluded, and missing values for the remaining variables were imputed using the median. For continuous data, normality was assessed using the skewness test. Variables conforming to a normal distribution were expressed as mean±standard deviation ($\bar{x}\pm s$), with intergroup differences evaluated using the t-test or one-way analysis of variance, depending on the grouping structure. For non-normally distributed data, values were presented as median (interquartile range), and intergroup comparisons were conducted using the Wilcoxon rank-sum test or Kruskal-Wallis test, as appropriate for the grouping. Categorical variables were reported as percentages, with intergroup differences analyzed using the chi-square test or Fisher's exact test, selected based on the expected frequency.

By systematically assessing the influence of all possible GNRI cutoff values on 365-day mortality, we identified the point yielding the maximum log-rank test statistic as the optimal cutoff. This threshold was employed to differentiate between the high-GNRI and low-GNRI groups. Kaplan-Meier survival curves were constructed based on GNRI risk stratification and the optimal cutoff, with the log-rank test employed to evaluate intergroup survival differences, assessing the impact of varying GNRI levels on the incidence of 28-day and 365-day all-cause mortality. Restricted cubic spline (RCS) curves were used to analyze GNRI as a continuous variable, elucidating its linear or nonlinear relationship with endpoint events; this preliminary analysis was unadjusted for confounders. Subsequently, four Cox proportional hazards models were constructed to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for GNRI as both a continuous and ordinal variable in relation to mortality, evaluating its association

with mortality under multifactorial confounding. Model 1 was unadjusted; Model 2 adjusted for demographic characteristics and vital signs, including age, sex, systolic blood pressure, diastolic blood pressure, SpO₂, temperature, heart rate, and respiratory rate; Model 3 further adjusted for severity scores and laboratory parameters, such as APS III, SAPS II, SOFA, LODS, white blood cell count, red blood cell count, platelet count, hemoglobin, red cell distribution width, creatinine, urea nitrogen, prothrombin time, international normalized ratio, alanine aminotransferase, aspartate aminotransferase, total bilirubin, potassium, sodium, and magnesium; Model 4 additionally adjusted for comorbidities, including cerebrovascular disease, chronic pulmonary disease, diabetes, severe liver disease, renal disease, malignant tumors, dementia, and rheumatic disease. All models used the high nutritional risk group (GNRI < 82) as the reference, with trend tests performed for GNRI categorical variables. Furthermore, receiver operating characteristic (ROC) curve analysis was conducted to assess GNRI's predictive performance for mortality. The area under the curve (AUC) quantified GNRI's predictive value for 28-day and 365-day mortality. Combined prediction models integrating GNRI with APS III, SAPS II, SOFA, and LODS scores were developed, and the DeLong test was used to compare AUC differences between combined models and original scores, evaluating the statistical significance of GNRI's incremental value. Finally, to clarify GNRI's prognostic value across subgroups, we performed subgroup analyses based on age, sex, receipt of RRT, CRRT, or invasive ventilation, and presence of cerebrovascular disease, diabetes, mild liver disease, severe liver disease, chronic pulmonary disease, malignant tumors, renal disease, and dementia. All data analyses were conducted using R software (version 4.4.2), with statistical significance defined as $P < .05$.

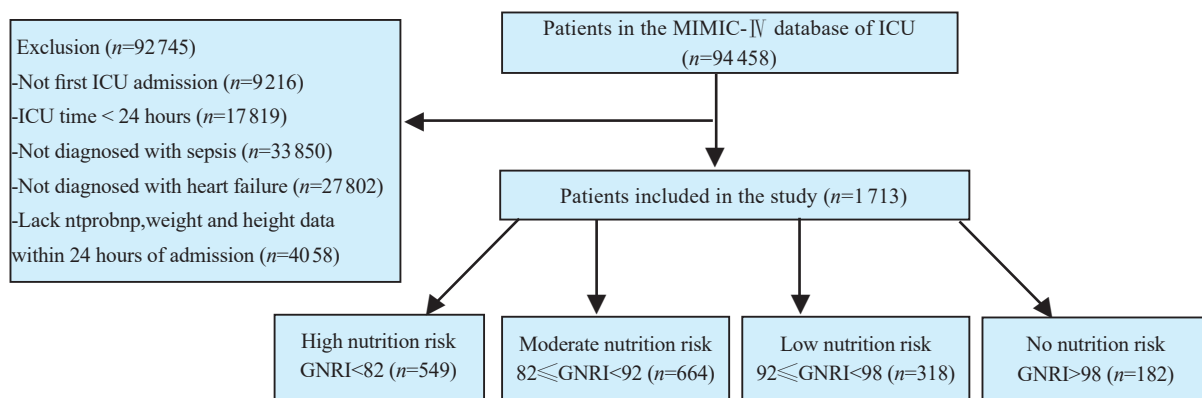


Figure 1. Flowchart of study population selection from the MIMIC-IV v3.1 database.

Table 1. Baseline characteristics and Pain Intensity Scores by treatment group.

Characteristic	High nutrition risk GNRI<82	Moderate nutrition risk 82≤GNRI<92	Low nutrition risk 92≤GNRI<98	No nutrition risk GNRI≥98	F/ χ^2	P
Number, <i>n</i>	549	664	318	182		
Age, year	69.65±14.36	70.63±13.07	70.09±13.11	69.04±14.08	0.89	.44
Sex						
Female	218 (39.71%)	261 (39.31%)	131 (41.19%)	62 (34.07%)	2.61	
Male	331 (60.29%)	403 (60.69%)	187 (58.81%)	120 (65.93%)		
Cerebrovascular disease	95 (17.3%)	103 (15.51%)	43 (13.52%)	25 (13.74%)	2.74	.43
Dementia	33 (6.01%)	35 (5.27%)	16 (5.03%)	8 (4.4%)	0.87	.83
Chronic pulmonary disease	167 (30.42%)	231 (34.79%)	119 (37.42%)	61 (33.52%)	4.97	.17
Mild liver disease	88 (16.03%)	77 (11.6%)	40 (12.58%)	21 (11.54%)	5.87	.12
Diabetes	273 (49.73%)	319 (48.04%)	139 (43.71%)	89 (48.9%)	3.05	.38
Renal disease	243 (44.26%)	316 (47.59%)	148 (46.54%)	89 (48.9%)	1.84	.61
Malignant cancer	85 (15.48%)	76 (11.45%)	25 (7.86%)	12 (6.59%)	16.92	< .001
Severe liver disease	45 (8.2%)	45 (6.78%)	20 (6.29%)	17 (9.34%)	2.45	.48
Invasive Vent	451 (82.15%)	511 (76.96%)	223 (70.13%)	129 (70.88%)	20.29	< .001
CRRT	133 (24.23%)	136 (20.48%)	49 (15.41%)	34 (18.68%)	10.08	.02
RRT	166 (30.24%)	179 (26.96%)	68 (21.38%)	41 (22.53%)	9.75	.02
28-day mortality, <i>n</i> (%)						
Yes	222 (40.44%)	202 (30.42%)	90 (28.3%)	46 (25.27%)	23.86	< .001
No	327 (59.56%)	462 (69.58%)	228 (71.7%)	136 (74.73%)		
365-day mortality, <i>n</i> (%)						
Yes	350 (63.75%)	363 (54.67%)	136 (42.77%)	80 (43.96%)	44.68	< .001
No	199 (36.25%)	301 (45.33%)	182 (57.23%)	102 (56.04%)		

Note: GNRI, geriatric nutritional risk index; CRRT, continuous renal replacement therapy; RRT, renal replacement therapy

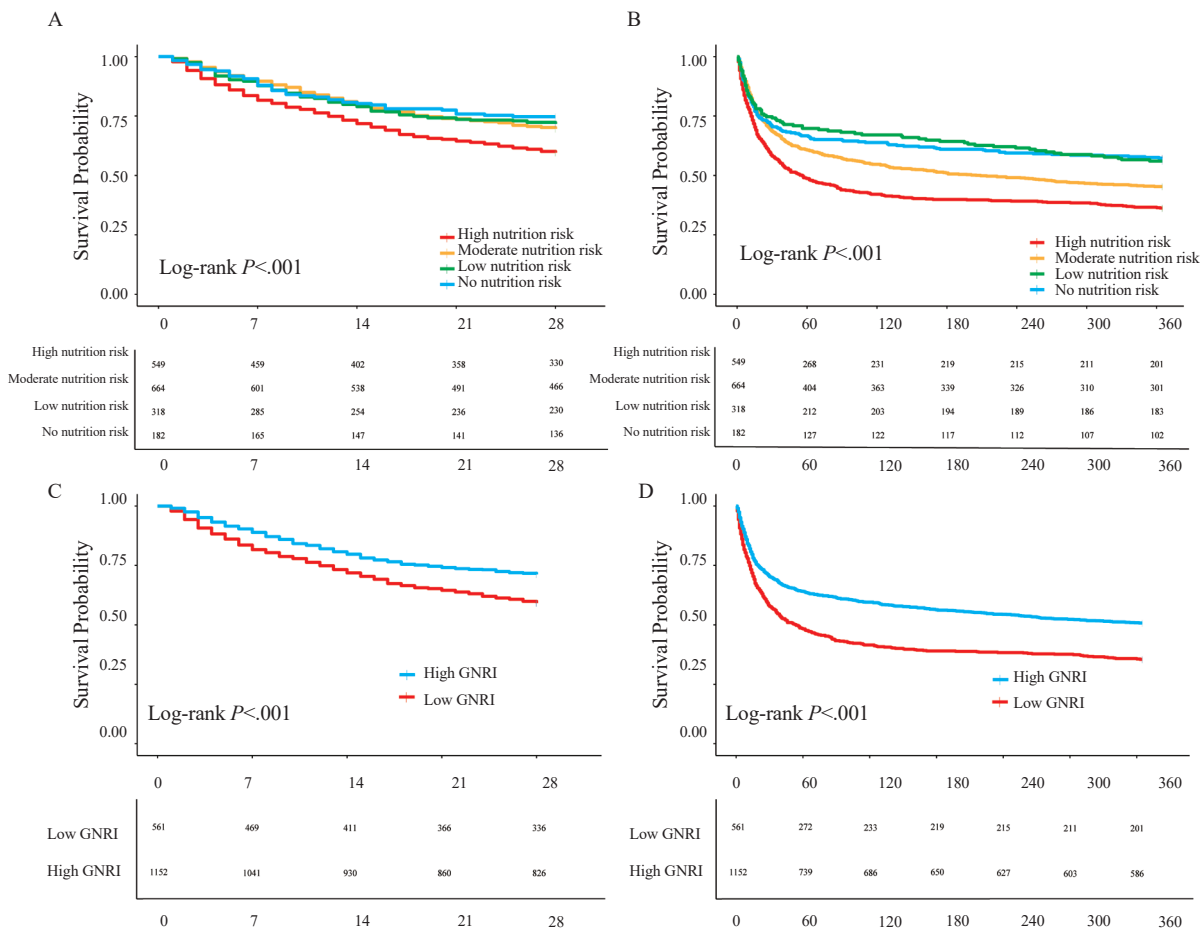


Figure 2. Kaplan-Meier survival analysis curves for all-cause mortality. A. Kaplan-Meier curves of 28-day all-cause mortality stratified by GNRI levels; B. Kaplan-Meier curves of 365-day all-cause mortality stratified by GNRI levels; C. Kaplan-Meier curves for 28-day mortality stratified by GNRI cutoff; D. Kaplan-Meier curves for 28-day mortality stratified by GNRI cutoff.

3. Results

3.1. Baseline characteristics of study individuals

This study enrolled 1713 patients diagnosed with heart failure complicated by sepsis, with the screening process detailed in Figure 1. Among them, 1041 were male and 672 were female, with an average age of 70.05 ± 13.61 years. Patients were stratified into four groups based on their GNRI scores: high nutritional risk group ($\text{GNRI} < 82$; $n=549$), moderate nutritional risk group ($82 \leq \text{GNRI} < 92$; $n=664$), low nutritional risk group ($92 \leq \text{GNRI} < 98$; $n=318$), and no nutritional risk group ($\text{GNRI} \geq 98$; $n=182$).

3.2. Survival analysis

The survival curves within 28 days of hospitalization for patients with heart failure complicated by sepsis exhibited a clear divergent trend, with the log-rank test further confirming statistically significant differences between groups ($P < .001$; Figure 2A). Consistent with the 28-day results, the survival curves for each group over 365 days also demonstrated significant differences at subsequent time points. The differences between groups were statistically significant ($P < .001$; Figure 2B). In addition, we used the maximum selection statistic method to determine the optimal cutoff point for the GNRI score as 83.2 (Supplementary Figure 1). Patients were divided into low and high GNRI groups based on this

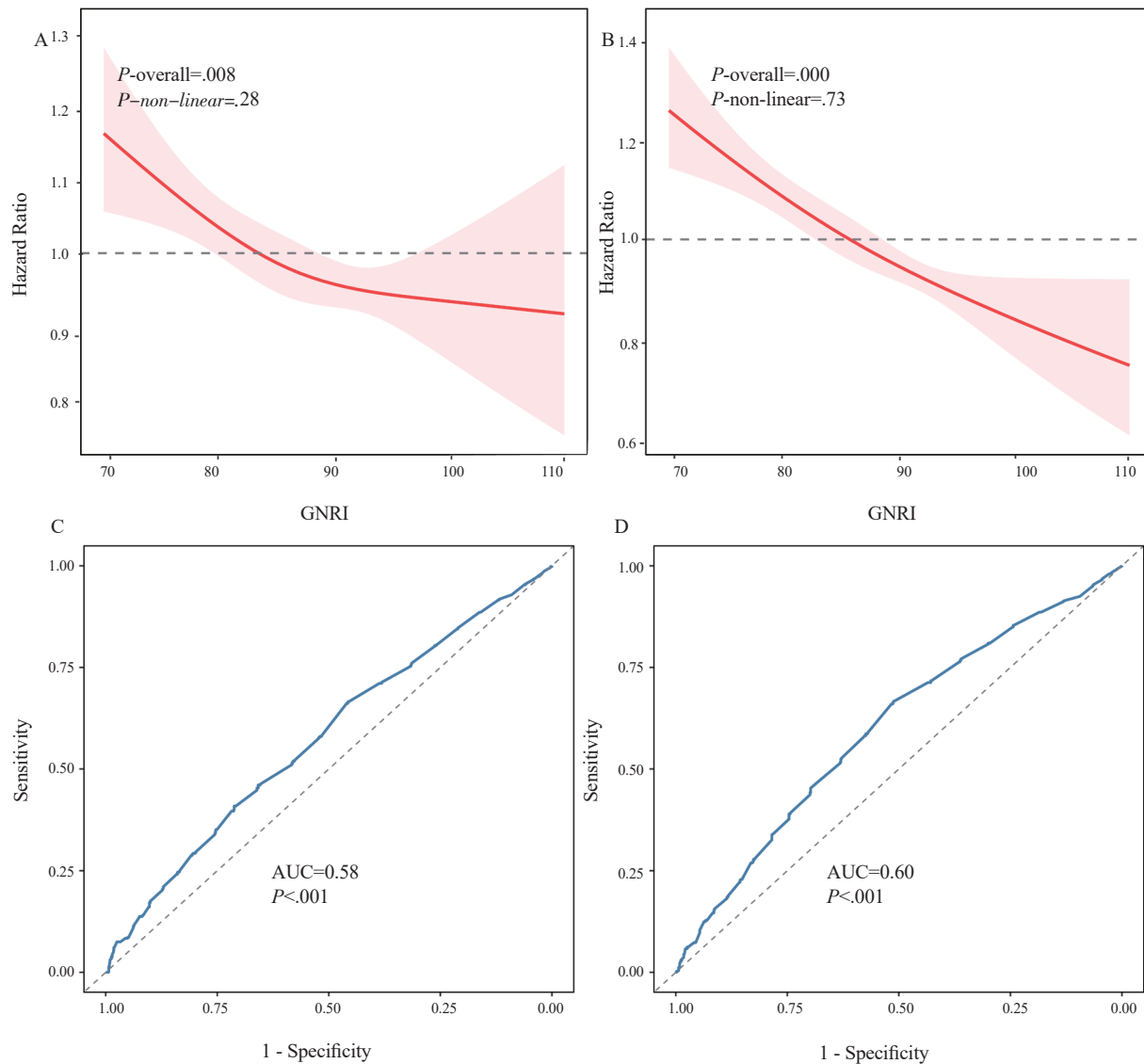


Figure 3. A. RCS of GNRI index with 28-day all-cause mortality; B. RCS of GNRI index with 365-day all-cause mortality; C. ROC curve of GNRI index for 28-day all-cause mortality; D. ROC curve of GNRI index for 365-day all-cause mortality.

Table 2. Cox proportional hazard models for 28-day and 365-day all-cause mortality.

Variable	Model 1 HR (95% CI)	P	Model 2 HR (95% CI)	P	Model 3 HR (95% CI)	P	Model 4 HR (95% CI)	P
All-cause mortality within 28 days								
GNRI	0.98 (0.97-0.99)	< .001	0.98 (0.97-0.99)	< .001	0.99 (0.98-1.00)	.006	0.99 (0.98-1.00)	.004
GNRI<82	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
82≤GNRI<92	0.69 (0.57-0.83)	< .001	0.70 (0.58-0.85)	< .001	0.77 (0.63-0.93)	.008	0.77 (0.63-0.94)	.009
92≤GNRI<98	0.65 (0.51-0.83)	< .001	0.66 (0.52-0.85)	.001	0.84 (0.65-1.08)	.18	0.82 (0.63-1.06)	.14
GNRI≥98	0.57 (0.42-0.79)	< .001	0.61 (0.44-0.84)	.002	0.76 (0.55-1.07)	.11	0.77 (0.55-1.08)	.13
P for trend		< .001		< .001		.06		.054
All-cause mortality within 365 days								
GNRI	0.98 (0.97-0.98)	< .001	0.98 (0.97-0.98)	< .001	0.98 (0.98-0.99)	< .001	0.98 (0.98-0.99)	< .001
GNRI<82	1 (Ref)		1 (Ref)		1(Ref)		1(Ref)	
82≤GNRI<92	0.75 (0.65-0.87)	< .001	0.74 (0.64-0.86)	< .001	0.78 (0.67-0.91)	.001	0.78 (0.67-0.91)	.002
92≤GNRI<98	0.56 (0.46-0.68)	< .001	0.55 (0.45-0.67)	< .001	0.68 (0.55-0.84)	< .001	0.69 (0.56-0.85)	< .001
GNRI≥98	0.56 (0.44-0.71)	< .001	0.57 (0.45-0.73)	< .001	0.75 (0.58-0.97)	.03	0.76 (0.59-0.98)	.04
P for trend		< .001		< .001		< .001		< .001

Model 1: no adjustment; Model 2: adjusted for Age, Sex, SBP, DBP, SpO₂, Temperature, Heart Rate, Respiratory Rate.; Model 3: further adjusted for APS III, SAPS II, SOFA, LODS, WBC, RBC, Platelet, Hemoglobin, RDW, Creatinine, Bun, PT, INR, ALT, AST, Bilirubin Total, Potassium, Sodium, Magnesium; Model 4: further adjusted for Cerebrovascular Disease, Chronic Pulmonary Disease, Diabetes, Severe Liver Disease, Renal Disease, Malignant Cancer, Dementia, Rheumatic Disease.

HR: hazard ratio; GNRI: geriatric nutritional risk index; SBP: systolic blood pressure; DBP: diastolic blood pressure; SpO₂: pulse blood oxygen saturation; APS III: acute physiology score; SAPS II: simplified acute physiology score; SOFA: sequential organ failure assessment; LODS: logistic organ dysfunction system; WBC: white blood cell; RBC: red blood cell; RDW: red blood cell distribution width; PT: prothrombin time; INR: international normalized ratio; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

cutoff for Kaplan-Meier survival curve analysis (Figure 2C, Figure 2D), which showed significantly higher mortality in the low GNRI group compared to the high GNRI group (log-rank<.001).

3.3. The detection of nonlinear relationships

The restricted cubic spline regression model revealed a significant linear association between the GNRI and 28-day and 365-day all-cause mortality in patients with heart failure complicated by sepsis (P -overall=.008, P -overall=.000). Higher nutritional risk (lower GNRI) was associated with poorer prognosis. Tests for nonlinearity did not reach statistical significance (P -non-linear=.28, P -non-linear=.73) (Figure 3A, Figure 3B).

3.4. Cox regression of GNRI and 28-day and 365-day mortality

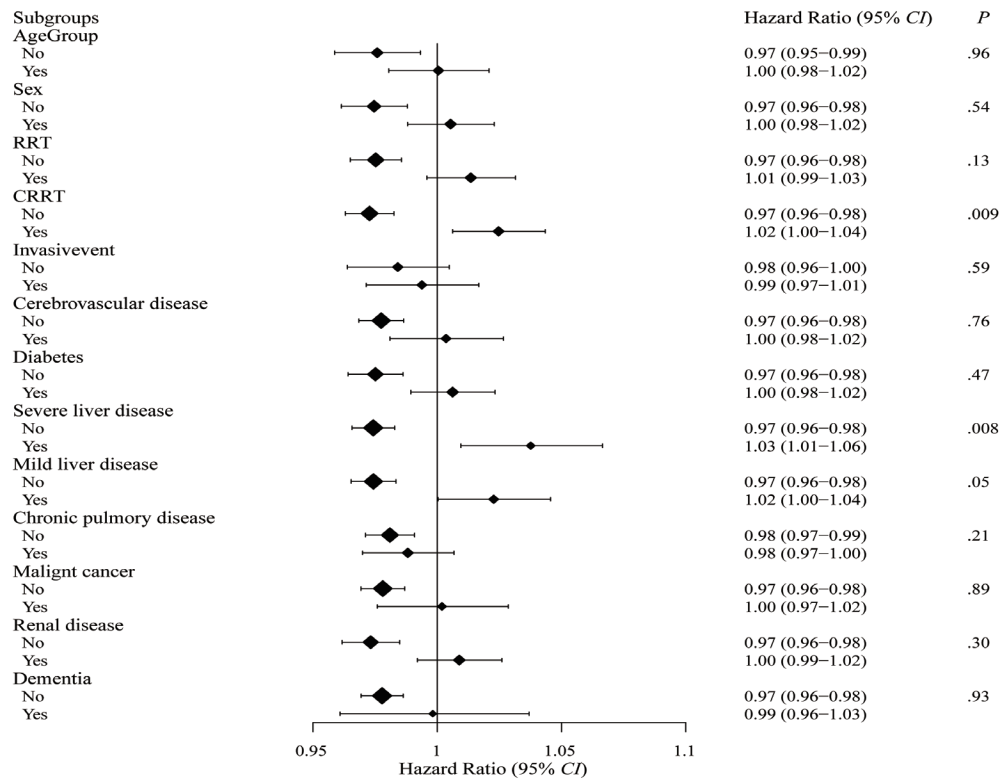
Table 2 presents the results of Cox proportional hazard models evaluating the association between the GNRI and all-cause mortality at 28 days and 365 days across four models with progressive adjustments. In the unadjusted Model 1, higher GNRI levels were associated with significantly reduced mortality risk at both 28 days (HR 0.98, 95% CI 0.97–0.99, P <.001) and 365 days (HR 0.98, 95% CI 0.97–0.98, P <.001). Compared to the reference group (GNRI<82), patients with GNRI scores of 82–92, 92–98, and >98 exhibited progressively lower hazard ratios for 28-

day mortality (HR 0.69, 0.65, and 0.57, respectively, all P <.001) and 365-day mortality (HR 0.75, 0.56, and 0.56, respectively, all P <.001), with a significant trend (P for trend <.001). In Model 2, the associations remained robust (28-day: HR 0.98, 95% CI 0.97–0.99, P <.001; 365-day: HR 0.98, 95% CI 0.97–0.98, P <.001). Further adjustments in Model 3 for additional laboratory parameters slightly attenuated the hazard ratios, particularly for the GNRI>98 group at 28 days (HR 0.76, 95% CI 0.55–1.07, P =.11) and 365 days (HR 0.75, 95% CI 0.58–0.97, P =.03), though the overall trend remained significant (P for trend =.06 and <.001, respectively). In Model 4, which further adjusted for comorbidities, the results were consistent, with GNRI retaining its protective effect (28-day: HR 0.99, 95% CI 0.98–1.00, P =.004; 365-day: HR 0.98, 95% CI 0.98–0.99, P <.001). The GNRI > 98 group showed a non-significant reduction in 28-day mortality (HR 0.77, 95% CI 0.55–1.08, P =.13) but a significant reduction in 365-day mortality (HR 0.76, 95% CI 0.59–0.98, P =.04). These findings suggest that higher GNRI levels are independently associated with improved survival outcomes, even after accounting for a wide range of clinical and laboratory covariates..

3.5. Predictive value and incremental effect of GNRI

To investigate the predictive performance of the GNRI for short-term and long-term mortality, receiver operating characteristic (ROC) curves were constructed, and the area under the curve

A



B

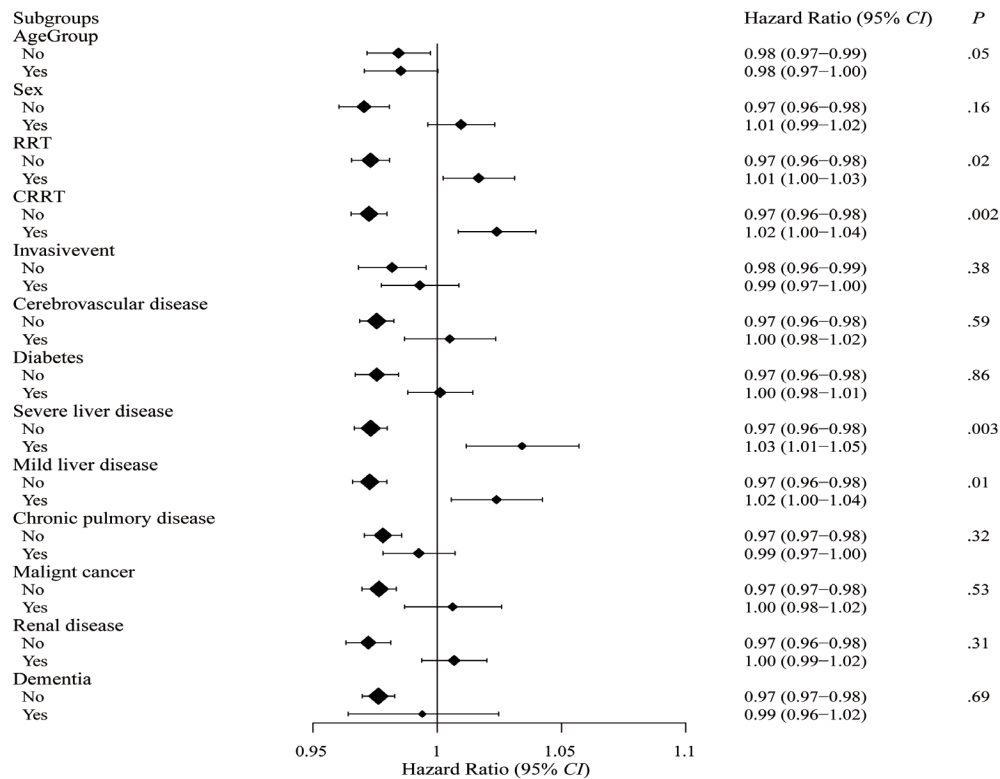


Figure 4. A. Forest plots of stratified analyses of GNRI index and 28-day all-cause mortality; B. Forest plots of stratified analyses of GNRI index and 365-day all-cause mortality. CRRT, continuous renal replacement therapy; RRT, renal replacement therapy.

(AUC) was used to quantify predictive value. The results (Figure 3C, Figure 3D) demonstrated that GNRI had moderate predictive value for 28-day and 365-day all-cause mortality, with corresponding AUC values of 0.58 (sensitivity=66.61%, specificity=45.62%, $P<.001$) and 0.60 (sensitivity=66.52%, specificity=51.28%, $P<.001$), respectively. Furthermore, upon incorporating the GNRI index into the APS III, SAPS II, SOFA, and LODS scoring systems (Supplementary Figure 2), an incremental effect was observed. Specifically, the addition of GNRI significantly enhanced the predictive performance of SAPS II (0.69 vs. 0.70, $P=.02$), SOFA (0.73 vs. 0.74, $P=.02$), and LODS (0.67 vs. 0.68, $P=.03$) scores, with these improvements achieving statistical significance.

3.6. Subgroup analysis

In addition, we conducted risk subgroup analysis and interaction analysis of outcomes in patients with heart failure complicated by sepsis, stratified by sex, age (<65 years or ≥ 65 years), receipt of RRT, CRRT, or invasive ventilation, as well as the presence of comorbidities including cerebrovascular disease, diabetes, mild liver disease, severe liver disease, chronic lung disease, malignant tumors, kidney disease, and dementia. In most subgroups, lower GNRI levels were significantly associated with an increased risk of mortality at 28 days (Figure 4A) and 365 days (Figure 4B). However, in subgroups receiving CRRT and those with severe liver disease, higher GNRI levels were significantly associated with an increased risk of mortality at both 28 days and 365 days. Similarly, in subgroups with mild liver disease and those receiving RRT, higher GNRI levels were significantly associated with an increased risk of mortality at 365 days.

4. Discussion

This study investigated the association between GNRI and 28-day and 365-day mortality in patients with heart failure complicated by sepsis. Our findings demonstrated that reduced GNRI levels were a significant independent risk factor for both short- and long-term all-cause mortality in this population, even after adjusting for potential confounders. A linear inverse relationship between GNRI and mortality was identified. Furthermore, incorporating GNRI into existing risk prediction models significantly enhanced their prognostic accuracy for clinical outcomes. These results suggest that GNRI, as a simple and practical nutritional assessment tool, holds potential as a novel prognostic biomarker in heart failure complicated by sepsis patients. While consistent with existing evidence on GNRI's predictive value in heart failure and sepsis individually, this study is the first to focus on its role in the context

of their synergistic interaction.

GNRI is a specialized metric designed to evaluate nutrition-related morbidity and mortality risks in hospitalized older adults. Higher GNRI values indicate better nutritional status, whereas lower values signify poorer nutritional health. Existing research has established GNRI's prognostic utility in HF patients. A meta-analysis encompassing nine studies and 7659 participants demonstrated that high- and moderate-risk GNRI levels were associated with increased all-cause mortality in older HF patients[24]. Similarly, a retrospective cohort study[25] reported a negative correlation between GNRI and 6-month rehospitalization in older HF patients, underscoring the critical role of nutritional status in HF outcomes. In the context of sepsis, a clinical study involving 401 older sepsis patients identified GNRI <87 as an independent predictor of 28-day in-hospital mortality, with a mortality rate of 12.7%[25]. In contrast, the present study observed a higher 28-day mortality rate (4.44%) at a GNRI threshold of <82, likely reflecting the compounded complexity of HF and sepsis. This suggests that GNRI prognostic thresholds may vary across patient populations. Collectively, these findings endorse GNRI's value as a simple, practical nutritional assessment tool in critically ill patients.

In the management of patients with HF complicated by sepsis, nutritional status serves as a critical determinant of overall health and significantly influences prognosis. Malnutrition in HF patients is associated with a marked increase in in-hospital mortality, prolonged hospital stays, and heightened risks of severe complications such as cardiogenic shock and cardiac arrest[26]. HF patients often experience impaired absorption and digestion due to reduced cardiac function and congestion in related organs, such as the liver and gastrointestinal tract, predisposing them to malnutrition. Malnutrition not only exacerbates cardiac contractile dysfunction but also significantly elevates mortality and complication risks[27]. In HF, elevated levels of inflammatory markers, such as TNF- α and CRP, are common, and malnutrition can further promote the production of these inflammatory factors, accelerate the progression of cardiac cachexia and create a vicious cycle[15,28]. In patients with concurrent sepsis, malnutrition intensifies these risks due to the combined effects of catabolic stress, inflammation, and organ dysfunction[18]. Furthermore, malnutrition compromises immune function, increasing the risk of infections and other complications, which prolongs hospitalization and worsens prognosis[29]. A retrospective study[30] found that malnourished HF patients face a threefold higher mortality risk compared to well-nourished patients, with mortality rates of approximately 9% in the malnourished group versus 3% in the non-malnourished group. Consequently, nutritional status is of paramount importance in the management of HF patients with

sepsis, impacting disease progression, inflammatory responses, and adverse clinical outcomes. Scientific nutritional assessment and early individualized nutritional support are indispensable components of sepsis treatment, contributing to improved survival rates and quality of life.

This study demonstrates that GNRI serves as a valuable prognostic factor in patients with sepsis and concomitant HF, facilitating the identification of individuals at elevated risk of adverse outcomes. Furthermore, incorporating GNRI into existing severity scores (*e.g.*, SOFA and SAPS II) significantly enhanced predictive accuracy. GNRI's straightforward calculation, requiring only serum albumin and body weight data, renders it a practical bedside tool, potentially aiding early identification of high-risk patients for targeted interventions. Clinically, these findings suggest that GNRI can inform nutritional support strategies for HF patients with sepsis, particularly those with GNRI<82, who may benefit from aggressive nutritional interventions to mitigate mortality risk. However, the modest improvement in predictive models (AUC<.80) indicates limited translational impact for individual prognostication, necessitating integration with other biomarkers (*e.g.*, inflammatory markers) for comprehensive risk stratification.

Interestingly, a reversal of the association between GNRI and mortality was observed in certain high-risk subgroups, particularly among patients receiving CRRT and those with severe liver disease. This finding does not suggest a protective effect of higher GNRI, but rather indicates that the physiological meaning of GNRI components may be altered in these clinically complex populations. In patients undergoing renal replacement therapy, mortality risk is predominantly driven by disease severity, systemic inflammation, and multiorgan dysfunction[31]. In addition, body weight and serum albumin levels in these patients are substantially influenced by fluid overload, rapid volume shifts, and extracorporeal albumin loss, which may compromise the validity of GNRI as a surrogate of nutritional status. Consequently, higher GNRI values in this context may reflect non-nutritional factors rather than true nutritional reserve. Similarly, patients with liver disease frequently exhibit impaired hepatic albumin synthesis, fluid retention, and metabolic disturbances, and are at increased risk of cardiovascular and malignant complications[32]. Non-nutritional weight gain and hypoalbuminemia driven by liver dysfunction may therefore distort GNRI calculations and attenuate its prognostic accuracy. Taken together, these findings suggest that GNRI should be interpreted with caution in patients with advanced organ failure, and that the observed association reversal in these subgroups should be regarded as hypothesis-generating rather than indicative of a causal relationship.

This study has several limitations. First, its retrospective design, relying on the MIMIC-IV database, limits causal inference. Unadjusted confounders, including dietary habits, physical activity,

and detailed cardiac function data (*e.g.*, echocardiographic results), may bias outcomes due to database constraints. Second, the findings' generalizability may be restricted to U.S. ICU populations, given the demographic and geographic scope of MIMIC-IV. Third, while GNRI enhanced predictive models, its incremental benefit was modest, indicating limited clinical utility for individual prognosis. Lastly, despite GNRI's simplicity as a nutritional assessment tool, it may not fully capture patients' comprehensive nutritional status. Future research should focus on prospective cohort studies or randomized controlled trials to validate GNRI's predictive value and evaluate whether nutrition-targeted interventions (*e.g.*, optimized feeding protocols) improve outcomes in heart failure patients with sepsis. Furthermore, investigating GNRI's interactions with other biomarkers (*e.g.*, inflammatory or cardiac function markers) could refine risk stratification. Longitudinal studies across diverse populations are critical to assess generalizability and establish clinically relevant thresholds.

In conclusion, this study underscores the potential of GNRI as a significant prognostic indicator in patients with heart failure and sepsis. Reduced GNRI was significantly associated with increased 28-day and 365-day all-cause mortality in this cohort. GNRI should be considered a critical factor in clinical management. This research highlights the pivotal role of nutritional assessment in critical care, providing clinicians with evidence to facilitate early identification of high-risk patients, thereby enabling proactive interventions to mitigate severe disease outcomes effectively.

Conflict of interest statement

The authors report no conflict of interest.

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Data availability statement

The data supporting this bibliometric analysis are publicly available from the Web of Science Core Collection. Any additional details can be obtained from the corresponding authors upon reasonable request.

Authors' contributions

WYM: Data curation, Formal analysis, Writing and original draft. WMS: Methodology, Software, Writing and original draft. WL: Resources, Software, Methodology and original draft. TQ: Conceptualization, Data curation, Writing and original draft. WYP: Supervision, Project administration, Writing and original draft. TYX: Investigation, Supervision, Writing and review. JLL: Conceptualization, Supervision, Writing review and editing.

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Geriatric nutritional risk index as a predictor of 28-day and 365-day mortality in patients with heartfailure complicated by sepsis: A retrospective cohort study using the MIMIC-IV database

Yameng Wang^{1▽}, Maosheng Wang^{2,3▽}, Ling Wang^{2,3}, Qi Tang^{1,4}, Yuanping Wang^{5,6},
Xiangyun Teng^{7,8✉}, Lili Jin^{5,6✉}

Affiliations

¹Graduate School, The Eighth Clinical Medical College, Guangzhou University of Chinese Medicine, Foshan, China

²Department of Intensive Care Unit, The Fourth Clinical Medical College, Guangzhou University of Chinese Medicine, Shenzhen, China

³Department of Intensive Care Unit, Shenzhen Traditional Chinese Medicine Hospital, Shenzhen, China

⁴Emergency Medicine Center, Foshan Hospital of Traditional Chinese Medicine, Foshan, China

⁵Department of Cardiology, The Fifth Clinical Medical College, Guangzhou University of Chinese Medicine, Guangzhou, China

⁶Department of Cardiology, Guangdong Second Traditional Chinese Medicine Hospital, Guangzhou, China

⁷Baiyun Hospital of the First Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China

⁸Medical Laboratory Center, Maoming Hospital of Guangzhou University of Chinese Medicine, Maoming, China

Co-corresponding author:

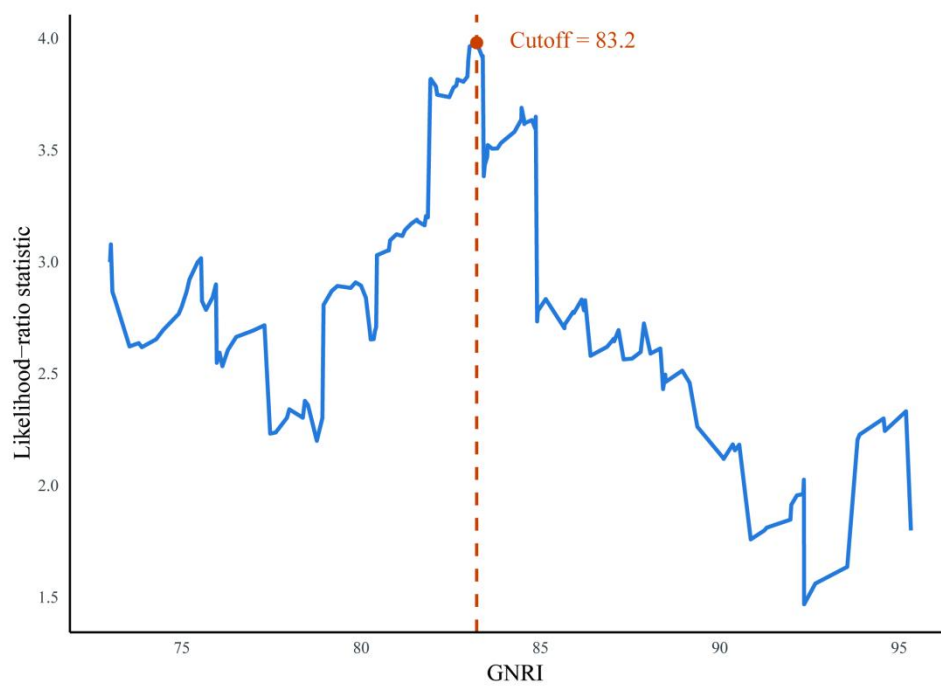
Jin LL, E-mail: jinlili991@163.com; Teng XY, E-mail: driftcloudxy@outlook.com

Supplementary Table 1. ICD codes for heart failure included in the diagnosis.

ICD-codes	long title
ICD-9	
42840	Combined systolic and diastolic heart failure, unspecified
42841	Acute combined systolic and diastolic heart failure
42842	Chronic combined systolic and diastolic heart failure
42843	Acute on chronic combined systolic and diastolic heart failure
4289	Heart failure, unspecified
ICD-10	
I50	Heart failure
I501	Left ventricular failure, unspecified
I5020	Unspecified systolic (congestive) heart failure
I5021	Acute systolic (congestive) heart failure
I5022	Chronic systolic (congestive) heart failure
I5023	Acute on chronic systolic (congestive) heart failure
I5030	Unspecified diastolic (congestive) heart failure
I5031	Acute diastolic (congestive) heart failure
I5032	Chronic diastolic (congestive) heart failure
I5033	Acute on chronic diastolic (congestive) heart failure
I5040	Unspecified combined systolic (congestive) and diastolic (congestive) heart failure
I5041	Acute combined systolic (congestive) and diastolic (congestive) heart failure
I5042	Chronic combined systolic (congestive) and diastolic (congestive) heart failure
I5043	Acute on chronic combined systolic (congestive) and diastolic (congestive) heart failure
I50810	Right heart failure, unspecified
I50811	Acute right heart failure
I50812	Chronic right heart failure
I50813	Acute on chronic right heart failure
I50814	Right heart failure due to left heart failure

15082	Biventricular heart failure
15083	High output heart failure
15084	End stage heart failure
15089	Other heart failure
1509	Heart failure, unspecified

Supplementary Figure 1. Optimal Cutoff Analysis for GNRI.



Supplementary Figure 2. ROC curve analysis of the incremental effect of GNRI on 365-day all-cause mortality. A APSIII score + GNRI; B SAPSII score + GNRI; C SOFA score + GNRI; D LODS score + GNRI.

