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ORIGINAL RESEARCH

Prognostic utility of the inflammatory burden index for early mortality prediction in heart failure: a retrospective cohort study using the MIMIC-IV database

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Abstract

Background: Systemic inflammation a key factor in the progression of heart failure (HF). The inflammatory burden index (IBI) has prognostic value in different conditions; however, its impact on short-term mortality in patients with HF remains uncertain. This study aimed to assess the association between IBI and mortality risk in patients with HF. **Methods**: In this retrospective study, 600 patients with HF from the Medical Information Mart for Intensive Care IV database (2008–2022) were examined and divided into three groups according to the log-transformed IBI (LnIBI). The main outcome measured was 28-day mortality in the intensive care unit (ICU). We used multivariable Cox and logistic regression to assess the independent effect of LnIBI on mortality, after adjustment for confounders. The dose-response relationship was modeled using restricted cubic splines. Predictive performance was compared using receiver operating characteristic curves, and Kaplan-Meier analysis was used to assess survival differences;subgroup analyses were conducted. **Results**: The cohort included 342 males (57.0%), with a median age of 71.0 years. The 28-day ICU mortality rates were 17.2% (103/600). In adjusted models, higher LnIBI independently predicted an elevated risk (for example, 28-day mortality after ICU admission: Hazard ratio (HR): 1.24, 95% confidence interval (CI): 1.09–1.41, $p = 0.001$; highest versus lowest tertile: HR: 1.99, 95% CI: 1.20–3.29, $p = 0.008$). Restricted cubic splines confirmed the linear dose-response relationship. LnIBI showed a superior area under the curve compared with C-reactive protein (CRP) for most endpoints (for example, 0.643 versus 0.595 for 28-day mortality after ICU admission, $p = 0.032$). Kaplan-Meier curves indicated poorer survival in the higher LnIBI tertiles ($p < 0.05$). **Conclusions**: Elevated IBI is independently associated with increased short-term mortality risk in critically ill patients with HF, outperforming CRP in predictive accuracy.

Keywords

Heart failure; Inflammatory burden index; Mortality; MIMIC-IV; Prognosis

1. Introduction

Heart failure (HF) is a substantial global health issue, marked by elevated morbidity, mortality, and healthcare costs [1, 2]. Although HF has been traditionally viewed as a hemodynamic disorder, increasing evidence suggests that systemic inflammation is crucial in its pathophysiology and progression [3, 4]. Chronic inflammation leads to negative changes in heart structure and heart muscle damage, which worsen patient prognosis [5]. Therefore, several inflammatory biomarkers, including C-reactive protein (CRP) and interleukin-6, have been studied as prognostic markers [6, 7]. Nonetheless, these specific markers can be affected by transient conditions and may not entirely reflect the complex, cumulative nature of systemic inflammation.

The inflammatory burden index (IBI), which combines various inflammatory markers into one comprehensive score, has emerged as a promising tool [8, 9]. IBI has demonstrated prognostic potential in various chronic diseases [10, 11], and emerging evidence suggests an association with HF itself [12]. Despite these findings, there is a significant lack of understanding about its specific role in predicting short-term mortality in critically ill patients with HF.

This study aimed to evaluate the association between IBI and short-term mortality in critically ill patients with HF using data from the large-scale Medical Information Mart for Intensive Care IV (MIMIC-IV) database.

2. Methods

2.1 Data source

This retrospective cohort study used data extracted from the MIMIC-IV database (version 3.1). This extensive, publicly available database includes de-identified electronic health records of patients admitted to the intensive care unit (ICU) at Beth Israel Deaconess Medical Center from 2008 to 2022. The study protocol was approved by the Institutional Review Board of Beth Israel Deaconess Medical Center (BIDMC), which waived the requirement for individual patient consent due to the de-identified nature of the data. Therefore, additional ethical approval was not required. One of the authors (ZTZ) obtained certified access to the database (certificate number: 47608458).

2.2 Participant selection

The study cohort was selected from the MIMIC-IV database according to the following criteria:

The inclusion criteria were as follows:

1. Age $\geq$18 years.

2. A recorded diagnosis of HF was identified using the relevant International Classification of Diseases, Ninth or Tenth Revision codes.

The exclusion criteria included the following:

1. Patients with an ICU length of stay of $<$24 h, including those who died within the first 24 h after ICU admission.

2. For patients with multiple ICU admissions during a single hospitalization, only the initial ICU admission was considered for analysis.

3. Patients with missing laboratory values for any of the components required to calculate the IBI (IBI = CRP $\times$ neutrophil count/lymphocyte count) [13] within the first 24 h of ICU admission.

2.3 Clinical outcomes

The primary outcome was 28-day all-cause mortality following ICU admission, which explicitly included deaths occurring after discharge from the ICU within 28 days. Secondary outcomes included 28-day in-hospital mortality, ICU (death during ICU stay), and in-hospital mortality (death during the entire hospital stay).

2.4 Data collection and variables

Data were extracted using PostgreSQL, including various variables collected within the first 24 h of each ICU admission for each patient. These variables included the following: (1) baseline characteristics, including demographics (age, gender, race, and weight), comorbidities (hypertension and diabetes), and the Charlson Comorbidity Index (CCI); (2) clinical assessments, which included initial vital signs (heart rate, systolic blood pressure, diastolic blood pressure, respiratory rate, temperature, and pulse oxygen saturation (SpO_2)), acute kidney injury (AKI) presence, and a suite of severity-of-illness scores (Sequential Organ Failure Assessment (SOFA), Acute Physiology Score III (APS III), Simplified Acute Physiology Score II (SAPS II), Oxford Acute Severity of Illness Score (OASIS), and the Glasgow Coma Scale (GCS)); (3) laboratory parameters, including hematological profiles (white blood cell (WBC) count, neutrophil count, lymphocyte count, platelet count, hemoglobin, hematocrit, red blood cell count, and red cell distribution width (RDW)), the inflammatory marker CRP, metabolic and renal function tests (serum creatinine, blood urea nitrogen (BUN), glucose, anion gap (AG), and electrolytes, including sodium, potassium, chloride, calcium, and magnesium), liver function indicators (total bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST)), and coagulation profiles (prothrombin time (PT) and partial thromboplastin time (PTT)); (4) in-hospital interventions, including the use of key medications (beta-blockers and diuretics), vasoactive agents (norepinephrine, dopamine, dobutamine, and milrinone), and organ support therapies (continuous renal replacement therapy (CRRT) and mechanical ventilation).

2.5 Statistical analysis

All continuous variables had skewed distributions; therefore, they were summarized using medians and interquartile ranges (IQR). However, categorical variables are presented as counts and percentages. To address the non-normal distribution, IBI was converted to LnIBI through a logarithmic transformation for later modeling and analysis (**Supplementary Fig. 1**) [11]. The study participants were divided into tertiles (T1, T2, and T3) based on their LnIBI scores. Participant profiles across these tertiles were compared using the Kruskal-Wallis H test for continuous variables and either the Chi-square or Fisher's exact test for categorical variables. Furthermore, demographic and clinical profiles of the included and excluded patients were analyzed to evaluate potential selection bias. Multivariable Cox regression models were employed to evaluate the association between LnIBI and time-dependent outcomes, including 28-day ICU mortality and 28-day in-hospital mortality. Additionally, multivariable logistic regression was used to analyze binary outcomes, specifically ICU mortality (death during ICU stay) and in-hospital mortality (death during the entire hospitalization). To enhance the precision of our estimates and ensure robust model building, covariates were objectively selected using the least absolute shrinkage and selection operator (LASSO) regression and the Boruta algorithm. The results are reported as hazard ratios (HRs) for Cox models and odds ratios (ORs) for logistic models, each accompanied by their respective 95% confidence intervals (CIs). Three incrementally refined models were created, with the absence of multicollinearity confirmed by a variance inflation factor (VIF) $<$5 [11]. To explore potential non-linear dose-response relationships, restricted cubic splines (RCS) were employed with four knots placed at the 5th, 35th, 65th, and 95th percentiles. The median value was designated as the reference point, and the Wald test was performed to assess the significance of non-linearity. To maintain data integrity, the full sample was utilized for these analyses without excluding extreme values. Receiver operating characteristic (ROC) curve analysis was used to compare the prognostic significance of LnIBI for mortality with CRP, neutrophil, and lymphocyte counts. Kaplan-Meier curves and log-rank tests were used to assess the survival differences across tertiles. Subgroup and interaction analyses were performed by stratifying the cohort according

to gender, race, comorbidities (including hypertension and diabetes), AKI status, and CRRT usage. Notably, these analyses were considered exploratory; therefore, no adjustment for multiplicity was applied. Variables with >10% missing data were excluded; however, those with ≤10% missing values underwent multiple imputation. The analyses were conducted using R (version 4.4.1), with statistical significance set at $p < 0.05$.

3. Results

3.1 Baseline characteristics

Information on 600 patients with HF was extracted from the MIMIC-IV database. Fig. 1 outlines the criteria for patient inclusion and exclusion. Details on missing data, which accounted for 1.16%–6.13% of the variables, including PT and PTT (**Supplementary Table 1**). The cohort consisted of 342 males, representing 57.0% of the participants, with a median age of 71 years (IQR, 62–80) (Table 1). The overall mortality rates were 17.2% (103/600) for 28-day mortality after ICU admission, 16.0% (96/600) for 28-day in-hospital mortality, 9.3% (56/600) for in-ICU mortality, and 17.5% (105/600) for in-hospital mortality (Table 2). The patients were stratified into three tertiles (T1, T2, and T3) based on their LnIBI values. Patients in the lower LnIBI tertiles (T1–T2) typically had higher lymphocyte counts and higher serum calcium, chloride, and sodium levels than those in the highest tertile (T3). Conversely, the T3 group had markedly higher inflammatory markers (CRP, WBC, and neutrophil counts) levels, elevated markers of organ dysfunction (AG, BUN, and serum creatinine), higher heart rate, and higher severity scores (SOFA, APS III, SAPS II, OASIS, and CCI). Moreover, the T3 group had substantially higher rate of CRRT use and experienced considerably worse outcomes for every primary and secondary mortality endpoint ($p < 0.05$). Compared with the excluded patients, individuals in the final study cohort were younger, exhibited marginally higher illness severity scores (APS III, SAPS II, and OASIS), and showed differences in comorbidity patterns and racial distribution ($p < 0.05$) (**Supplementary Table 2**).

3.2 Association of IBI with short-term mortality

LASSO regression identified 15 candidate predictors, while the Boruta algorithm identified 9. The intersection of these two methods yielded six robust covariates for the final model. The final selected variables were: age at admission, RDW, urine output, GCS score, beta-blocker use, and CRRT (**Supplementary Fig. 2**). Additionally, all final variables exhibited VIF values <5 (**Supplementary Table 3**).

Three logistic regression models were created to study the association between IBI and mortality: a non-adjusted model, model I (age-adjusted), and model II (adjusted for all selected covariates). In the fully-adjusted model II, LnIBI, as a continuous variable, was a significant independent predictor of the primary endpoint, 28-day mortality after ICU admission (HR: 1.24, 95% CI: 1.09–1.41, $p = 0.001$) (Table 3). This association remained significant for in-ICU mortality (OR: 1.21, 95% CI: 1.01–1.45, $p = 0.046$) (Table 4).

The LnIBI analysis as a categorical variable (tertiles) yielded similar results. Patients in the highest tertile (T3) had a significantly higher risk of 28-day mortality after ICU admission compared to those in the lowest tertile (T1) in the fully-adjusted model (HR: 1.99, 95% CI: 1.20–3.29, $p = 0.008$). Moreover, a significant upward trend in 28-day mortality after ICU admission was observed across increasing LnIBI tertiles (p for trend = 0.008) (Table 3).

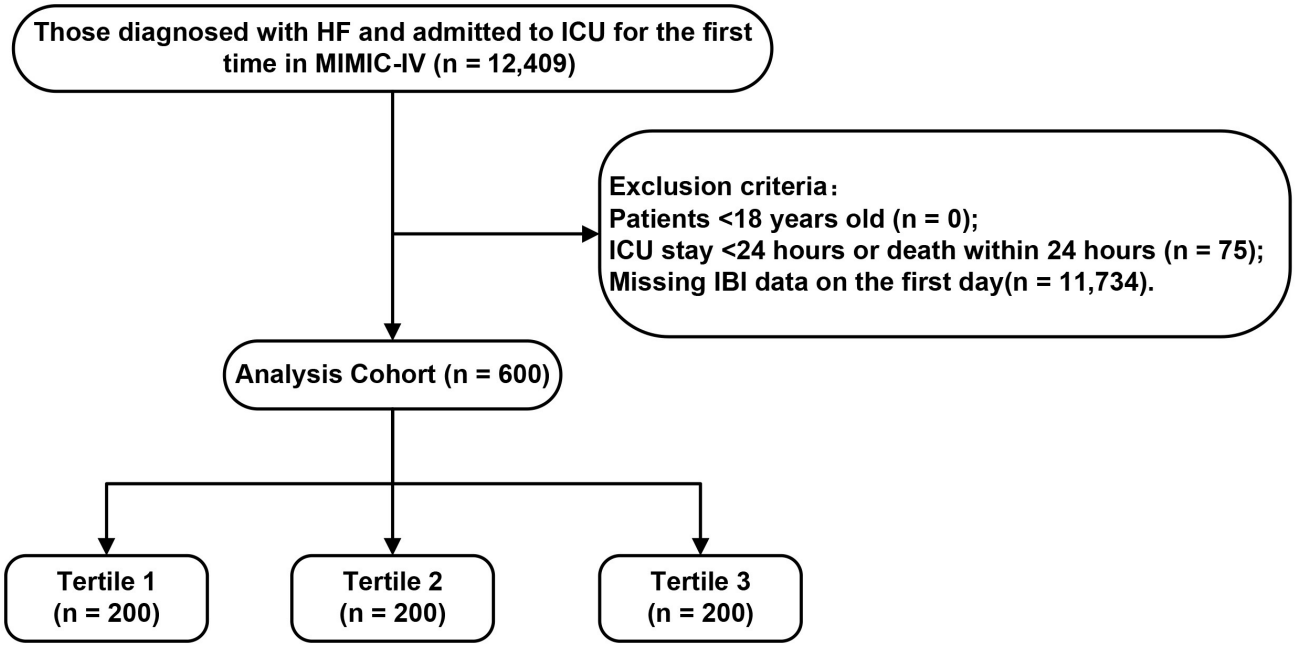

FIGURE 1. Flow diagram of the study. ICU, intensive care unit; MIMIC, medical information mart for intensive care; HF, heart failure; IBI, inflammatory burden index.

TABLE 1. Baseline characteristics of the HF patients included in the study.

	Overall n = 600	T1 (0.83–5.94) n = 200	T2 (5.94–7.27) n = 200	T3 (7.27–10.22) n = 200	*p*-value
Baseline characteristics					
- Gender					
Male	342 (57%)	106 (53%)	107 (53.5%)	129 (64.5%)	0.032
Female	258 (43%)	94 (47%)	93 (46.5%)	71 (35.5%)	
- Age at admission (yr)	71.0 (62.0, 80.0)	72.0 (62.0, 79.5)	71.0 (62.0, 80.0)	72.0 (62.5, 80.0)	0.80
- Race					
White	341 (56.8%)	121 (60.5%)	113 (56.5%)	107 (53.5%)	0.36
Other	259 (43.2%)	79 (39.5%)	87 (43.5%)	93 (46.5%)	
- Weight (kg)	83.8 (68.8, 103.1)	81.2 (66.2, 103.8)	85.1 (70.9, 106.6)	83.7 (70.2, 101.2)	0.64
Comorbidities					
Hypertension	51 (8.5%)	22 (11%)	19 (9.5%)	10 (5%)	0.081
Diabetes	145 (24.2%)	48 (24%)	40 (20%)	57 (28.5%)	0.13
Complications					
AKI	532 (88.7%)	180 (90%)	173 (86.5%)	179 (89.5%)	0.49
Vital signs					
Heart rate (bpm)	89.0 (75.0, 104.0)	83.0 (72.0, 98.0)	90.0 (78.0, 109.0)	90.5 (77.5, 106.0)	<0.001
SBP (mmHg)	116.0 (102.0, 134.0)	119.0 (103.0, 139.0)	116.0 (102.5, 133.0)	113.5 (100.0, 133.5)	0.12
DBP (mmHg)	69.0 (58.0, 82.0)	70.0 (58.0, 82.0)	69.0 (58.5, 83.0)	68.0 (58.0, 80.0)	0.82
Respiratory rate (bpm)	21.0 (17.0, 25.0)	20.0 (17.0, 24.0)	20.0 (17.0, 25.5)	21.0 (17.0, 26.0)	0.41
Temperature (°C)	36.8 (36.5, 37.1)	36.8 (36.5, 37.0)	36.8 (36.5, 37.1)	36.8 (36.5, 37.1)	0.75
SpO_2 (%)	97.0 (94.0, 99.0)	97.0 (95.0, 100.0)	97.0 (94.5, 99.0)	96.0 (93.0, 99.0)	0.16
Laboratory tests					
Neutrophil counts (K/μL)	9.7 (6.6, 13.9)	7.6 (4.9, 10.8)	9.4 (6.9, 13.1)	12.5 (8.9, 17.8)	<0.001
lymphocyte counts (K/μL)	1.0 (0.6, 1.6)	1.3 (0.8, 1.9)	1.2 (0.7, 1.8)	0.6 (0.4, 1.0)	<0.001
CRP (mg/L)	85.8 (32.7, 168.4)	15.6 (6.9, 43.6)	96.2 (67.8, 160.0)	171.7 (108.7, 223.6)	<0.001
WBC (K/μL)	11.9 (8.6, 17.1)	10.4 (7.9, 14.7)	12.0 (8.5, 16.3)	14.2 (9.7, 19.2)	<0.001
PLT (K/μL)	194.5 (139.5, 274.0)	188.0 (140.0, 269.5)	207.0 (139.0, 273.5)	188.5 (138.0, 278.0)	0.38
Hematocrit (%)	31.9 (26.7, 37.3)	33.8 (27.2, 38.1)	30.9 (26.4, 36.9)	31.6 (26.4, 36.5)	0.08
Hemoglobin (g/L)	10.1 (8.4, 11.9)	10.5 (8.5, 12.1)	9.9 (8.2, 11.8)	9.9 (8.2, 11.6)	0.18
Red blood cell count (m/μL)	3.5 (2.9, 4.2)	3.6 (3.0, 4.4)	3.4 (2.9, 4.1)	3.4 (2.9, 4.1)	0.11
RDW (%)	15.4 (14.0, 17.2)	15.1 (13.9, 17.6)	15.2 (14.0, 17.1)	15.5 (14.2, 17.0)	0.68
AG (mmol/L)	15.0 (12.0, 18.0)	14.0 (12.0, 17.0)	14.0 (12.0, 17.0)	16.0 (13.0, 19.0)	0.003
Blood urea nitrogen (mg/dL)	28.0 (18.0, 47.0)	24.0 (16.0, 42.0)	25.0 (18.0, 45.0)	36.0 (21.0, 59.0)	<0.001
Serum calcium (mg/dL)	8.4 (7.9, 8.9)	8.6 (8.1, 9.1)	8.4 (8.0, 8.8)	8.4 (7.8, 8.8)	<0.001
Serum chloride (mmol/L)	102.0 (97.0, 106.0)	102.0 (98.0, 106.0)	102.0 (98.0, 106.0)	100.0 (96.0, 105.0)	0.018
Serum sodium (mmol/L)	138.0 (134.0, 141.0)	139.0 (136.0, 142.0)	138.0 (134.5, 141.0)	137.0 (133.0, 140.5)	<0.001
Serum potassium (mmol/L)	4.3 (3.9, 4.8)	4.3 (3.8, 4.7)	4.3 (3.8, 4.7)	4.4 (3.9, 4.9)	0.20
Serum creatinine (mg/dL)	1.3 (0.9, 2.3)	1.2 (0.9, 1.9)	1.3 (0.9, 2.0)	1.6 (1.0, 3.2)	<0.001

TABLE 1. Continued.

	Overall n = 600	T1 (0.83–5.94) n = 200	T2 (5.94–7.27) n = 200	T3 (7.27–10.22) n = 200	*p*-value
Laboratory tests					
Serum glucose (mg/dL)	135.0 (108.0, 178.0)	132.5 (105.0, 172.0)	133.0 (109.0, 176.0)	140.5 (113.5, 186.0)	0.18
Serum magnesium (mg/dL)	2.0 (1.8, 2.3)	2.0 (1.8, 2.3)	2.0 (1.8, 2.3)	2.0 (1.8, 2.3)	0.93
PT (s)	14.9 (13.0, 17.9)	14.1 (12.6, 16.9)	15.6 (13.4, 18.1)	15.5 (13.4, 19.0)	<0.001
PTT (s)	31.6 (28.0, 39.6)	31.2 (27.4, 38.5)	31.5 (27.9, 39.2)	32.3 (28.4, 40.7)	0.19
Total bilirubin (mg/dL)	0.6 (0.4, 1.0)	0.6 (0.4, 0.9)	0.6 (0.4, 1.0)	0.7 (0.4, 1.1)	0.19
ALT (IU/L)	26.0 (15.0, 72.0)	24.0 (15.0, 58.5)	24.0 (14.0, 62.0)	32.5 (15.5, 98.5)	0.12
AST (IU/L)	38.0 (23.0, 86.0)	35.0 (22.5, 59.0)	35.5 (21.5, 87.0)	50.0 (26.0, 130.5)	<0.001
Treatment during hospitalization					
Beta-blocker	426 (71%)	139 (69.5%)	152 (76%)	135 (67.5%)	0.15
Diuretic	490 (81.7%)	162 (81%)	166 (83%)	162 (81%)	0.84
Dobutamine	24 (4%)	3 (1.5%)	10 (5%)	11 (5.5%)	0.08
Milrinone	17 (2.8%)	9 (4.5%)	6 (3%)	2 (1%)	0.11
Dopamine	8 (1.3%)	5 (2.5%)	1 (0.5%)	2 (1%)	0.19
Norepinephrine	176 (29.3%)	52 (26%)	54 (27%)	70 (35%)	0.09
CRRT	82 (13.7%)	18 (9%)	23 (11.5%)	41 (20.5%)	0.002
Ventilation	523 (87.2%)	166 (83%)	179 (89.5%)	178 (89%)	0.09
Score					
SOFA	5.0 (3.0, 8.0)	5.0 (3.0, 7.0)	4.5 (2.0, 8.0)	6.0 (4.0, 8.5)	<0.001
APS III	48.0 (37.0, 62.0)	44.5 (34.0, 54.5)	46.0 (35.0, 60.0)	55.0 (44.0, 69.0)	<0.001
SAPS II	39.5 (33.0, 48.5)	37.0 (31.0, 45.0)	38.0 (32.0, 47.0)	43.0 (35.5, 54.5)	<0.001
OASIS	33.0 (28.0, 39.0)	32.5 (27.0, 38.0)	32.0 (27.0, 38.5)	34.0 (29.0, 43.0)	0.003
GCS	15.0 (14.0, 15.0)	15.0 (14.0, 15.0)	15.0 (14.0, 15.0)	15.0 (14.0, 15.0)	0.63
CCI	7.0 (5.0, 9.0)	7.0 (5.0, 9.5)	6.0 (5.0, 8.0)	7.0 (5.5, 9.0)	<0.001
Output amount	1631.0 (916.0, 2695.0)	1750.0 (1034.5, 2501.5)	1730.0 (972.5, 2841.0)	1387.5 (725.0, 2622.5)	0.03

Data were presented as median (IQR), or n (%).
T, tertile; IQR, interquartile range; AKI, acute kidney injury; SBP, systolic blood pressure; DBP, diastolic blood pressure; SpO_2, pulse oxygen saturation; CRP, C-reactive protein; WBC, white blood cell; PLT, platelet; RDW, red cell distribution width; AG, anion gap; PT, prothrombin time; PTT, partial thromboplastin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRRT, continuous renal replacement therapy; SOFA, sequential organ failure assessment; APS, acute physiology score; SAPS, simplified acute physiology score; OASIS, oxford acute severity of illness score; GCS, Glasgow coma scale; CCI, Charlson comorbidity index.

TABLE 2. Clinical outcomes.

	Overall n = 600	T1 (0.83–5.94) n = 200	T2 (5.94–7.27) n = 200	T3 (7.27–10.22) n = 200	*p*-value
28-day mortality after ICU admission	103 (17.2%)	23 (11.5%)	28 (14%)	52 (26%)	<0.001
28-day in-hospital mortality	96 (16%)	22 (11%)	26 (13%)	48 (24%)	<0.001
In-ICU mortality	56 (9.3%)	12 (6%)	14 (7%)	30 (15%)	0.003
In-hospital mortality	105 (17.5%)	24 (12%)	32 (16%)	49 (24.5%)	0.004

T, tertile; ICU, intensive care unit.

TABLE 3. Relationship between LnIBI and 28-day mortality after ICU and in-hospital mortality in HF patients.

Exposure	Non-adjusted		Model I		Model II	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
28-day mortality after ICU admission						
LnIBI	1.33 (1.17–1.52)	<0.001	1.33 (1.17–1.52)	<0.001	1.24 (1.09–1.41)	0.001
T1	Ref		Ref		Ref	
T2	1.29 (0.74–2.23)	0.36	1.29 (0.74–2.23)	0.36	1.26 (0.73–2.19)	0.41
T3	2.34 (1.43–3.84)	<0.001	2.349 (1.43–3.84)	<0.001	1.99 (1.20–3.29)	0.008
p for trend		<0.001		<0.001		0.008
28-day in-hospital mortality						
LnIBI	1.13 (0.99–1.28)	0.05	1.13 (0.99–1.28)	0.05	1.08 (0.95–1.22)	0.20
T1	Ref		Ref		Ref	
T2	1.63 (0.97–2.75)	0.06	1.63 (0.97–2.75)	0.06	1.61 (0.95–2.71)	0.07
T3	1.62 (0.96–2.73)	0.07	1.62 (0.96–2.73)	0.07	1.42 (0.83–2.42)	0.19
p for trend		0.06		0.06		0.16

Non-adjusted models: None; Model I adjusted for: age at admission; Model II adjusted for: confounders in the minimally adjusted (Model I) + RDW, urine output, GCS score, beta-blocker use, CRRT.
T, tertile; HR, hazard ratio; CI, confidence intervals; IBI, inflammatory burden index; ICU, intensive care unit; GCS, Glasgow Coma Scale; RDW, red cell distribution width; CRRT, continuous renal replacement therapy; Ref, reference.

TABLE 4. Relationship between LnIBI and mortality after ICU and in-hospital mortality in HF patients.

Exposure	Non-adjusted		Model I		Model II	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
In-ICU mortality						
LnIBI	1.27 (1.06–1.52)	0.010	1.27 (1.06–1.52)	0.010	1.21 (1.01–1.45)	0.046
T1	Ref		Ref		Ref	
T2	1.95 (0.91–4.16)	0.08	1.95 (0.91–4.16)	0.08	1.99 (0.92–4.30)	0.08
T3	2.34 (1.12–4.93)	0.025	2.34 (1.11–4.92)	0.025	2.02 (0.94–4.34)	0.07
p for trend		0.023		0.023		0.06
In-hospital mortality						
LnIBI	1.14 (1.01–1.30)	0.046	1.14 (1.01–1.30)	0.047	1.11 (0.97–1.27)	0.11
T1	Ref		Ref		Ref	
T2	1.72 (1.01–2.93)	0.048	1.72 (1.01–2.93)	0.047	1.76 (1.03–3.03)	0.040
T3	1.52 (0.88–2.62)	0.13	1.52 (0.88–2.62)	0.13	1.39 (0.79–2.43)	0.24
p for trend		0.10		0.10		0.11

Non-adjusted models: None; Model I adjusted for: age at admission; Model II adjusted for: confounders in the minimally adjusted (Model I) + RDW, urine output, GCS score, beta-blocker use, CRRT.
T, tertile; OR, odds ratios; CI, confidence intervals; IBI, inflammatory burden index; ICU, intensive care unit; GCS, Glasgow Coma Scale; RDW, red cell distribution width; CRRT, continuous renal replacement therapy; Ref, reference.

3.3 Dose-response relationship between LnIBI and short-term mortality

Additionally, we used RCS regression to assess the dose-response relationship between the LnIBI and mortality outcomes. The RCS analysis demonstrated a significant and nearly linear association after adjusting for age, CCI score, RDW, WBC, and beta-blocker use (p for non-linear > 0.05). As depicted in Fig. 2, higher LnIBI levels were consistently associated with increased risks of 28-day mortality after ICU admission and in-ICU mortality.

3.4 ROC curve analysis

According to Fig. 3 and **Supplementary Table 4**, LnIBI demonstrated a better predictive ability for mortality than CRP in most cases. Specifically, the area under the curve (AUC) for LnIBI was significantly higher than that for CRP in predicting 28-day mortality after ICU admission (0.643 versus 0.595, $p = 0.032$), and in-ICU mortality (0.645 versus 0.592, $p = 0.047$). Conversely, the AUCs for LnIBI were not statistically different compared to neutrophil or lymphocyte counts across all mortality outcomes evaluated ($p > 0.05$).

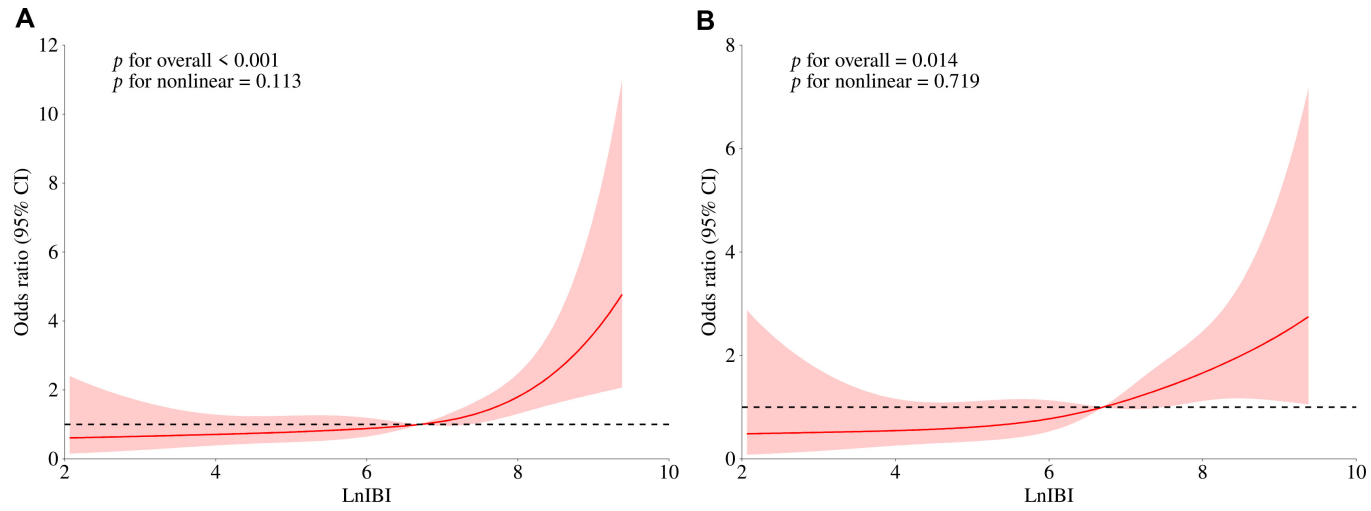

FIGURE 2. Relationship between LnIBI and short-term mortality. (A,B) correspond to the restricted cubic spline analyses for 28-day ICU and in-ICU mortality. Abbreviations: CI, confidence interval; LnIBI, log-transformed Inflammatory Burden Index.

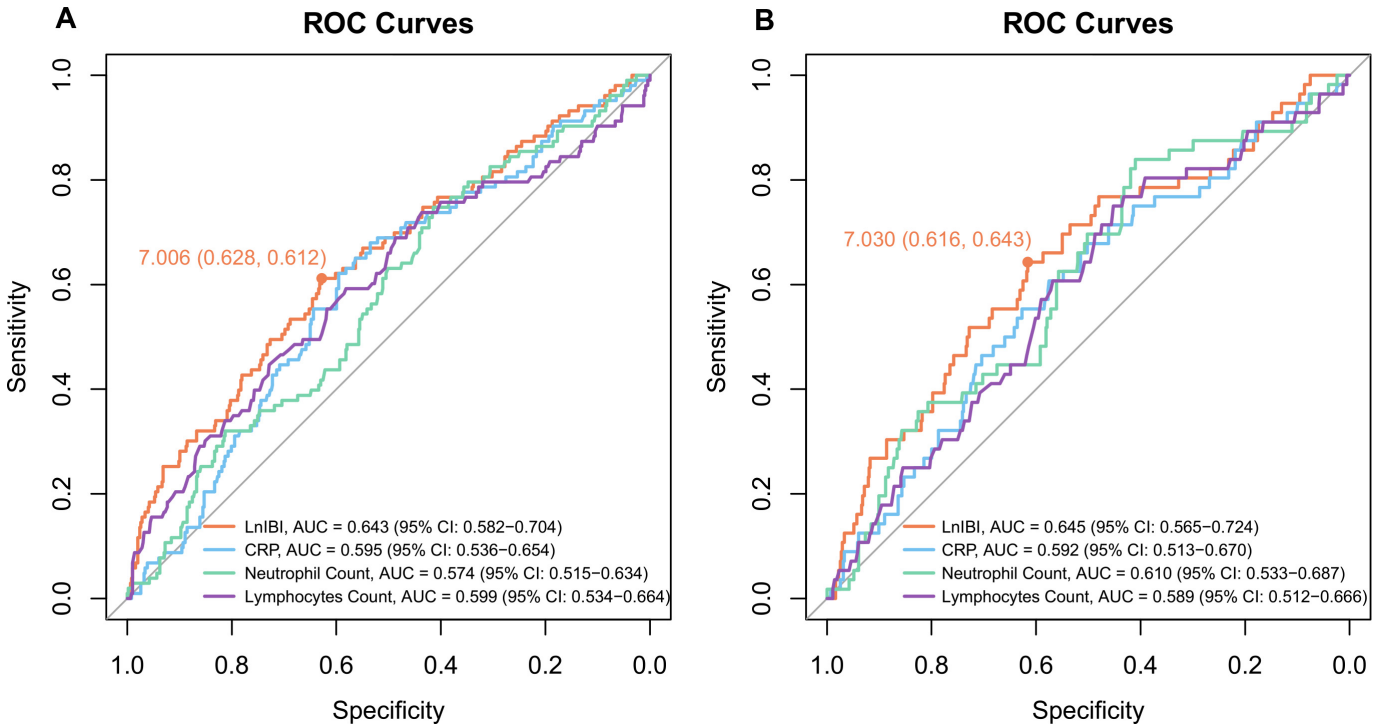

FIGURE 3. ROC curves. (A,B) Correspond to the ROC for 28-day ICU and in-ICU mortality. Abbreviations: CRP, C-reactive protein; ROC, Receiver Operating Characteristic; AUC, Area Under the Curve; LnIBI, log-transformed Inflammatory Burden Index; CI, confidence interval.

3.5 Kaplan-Meier survival curve

As illustrated in Fig. 4, patients in the lowest LnIBI tertile (T1) demonstrated the highest survival probability; whereas, those in the highest tertile (T3) had the poorest survival outcomes ($p < 0.05$).

3.6 Subgroup analysis

As presented in Fig. 5A, the forest plots revealed that elevated LnIBI levels were consistently associated with a higher 28-day mortality risk after ICU admission in all subgroups analyzed (p for interaction > 0.05). Fig. 5B further illustrates that this positive association remained stable and statistically significant for in-ICU mortality.

4. Discussion

In this retrospective cohort study of patients with HF, we observed that IBI, a new composite score, is a predictor of short-term mortality. Our study identified a notable dose-response relationship, indicating that higher IBI levels were proportionally associated with an increased 28-day mortality

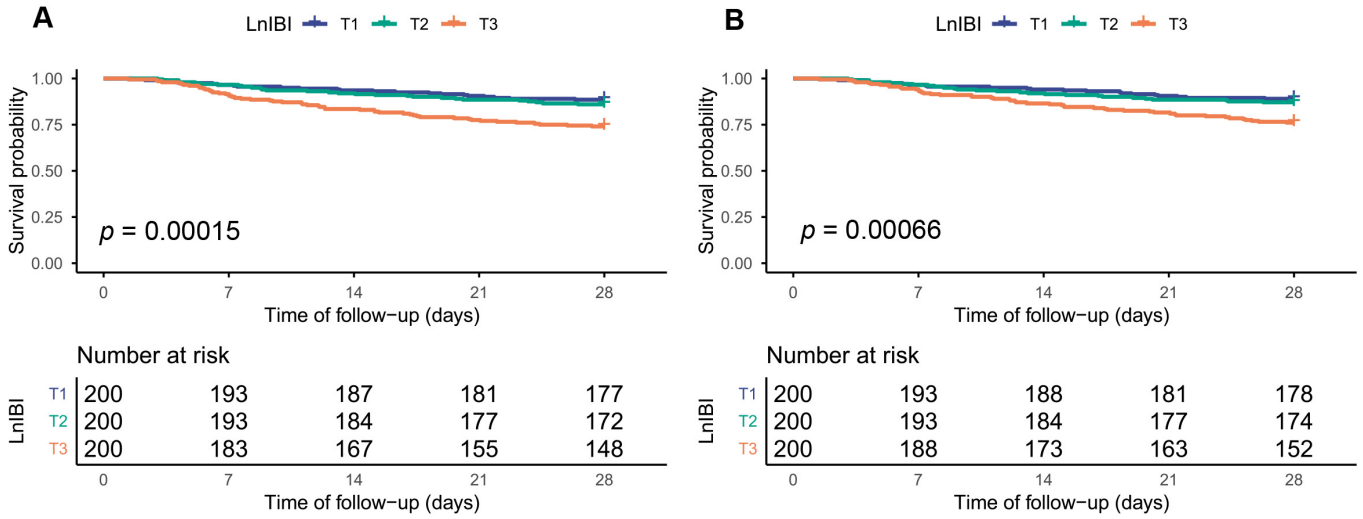

FIGURE 4. Kaplan-Meier curves. A and B depict Kaplan-Meier survival curves for 28day ICU and 28-day in-hospital mortality. LnIBI, log-transformed Inflammatory Burden Index; T, tertile.

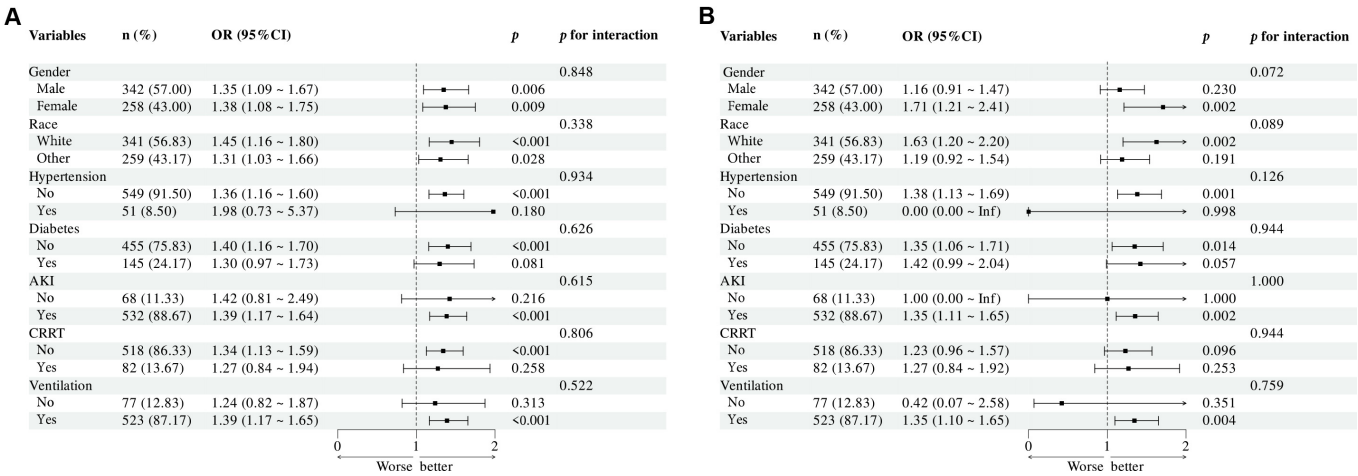

FIGURE 5. Subgroup analyses. (A,B) Correspond to subgroup analyses for 28-day ICU and in-ICU mortality. OR, odds ratio; CI, confidence interval; AKI, acute kidney injury; CRRT, continuous renal replacement therapy.

risk after ICU admission and in-ICU mortality. This association remained significant even after adjusting for numerous potential confounders, highlighting the independent prognostic value of the IBI in this high-risk cohort.

The relationship between inflammation and the pathophysiology and progression of HF is widely accepted [14, 15]. Nonetheless, numerous studies have depended on individual biomarkers, including CRP, which can be affected by temporary conditions and might not entirely reflect the complexity of systemic inflammation [16]. In our study, IBI, through its combination of multiple inflammatory markers, was associated with the prediction of short-term mortality in patients with HF. This is consistent with emerging evidence from other areas, where IBI has been identified as a useful prognostic tool for various diseases. For example, a comprehensive study using data from the National Health and Nutrition Examination Survey (NHANES) involving 15,325 people with cardiovascular disease (CVD) observed a significant positive association between IBI levels and CVD (OR: 1.43, 95% CI: 1.16–1.76; $p < 0.001$) [17]. A retrospective analysis of 27,495 adults with chronic inflammatory airway diseases revealed that individuals in the highest IBI quartile had a significantly greater risk of all-cause mortality than those in the lowest quartile [18]. In the context of oncology, a retrospective study involving 2428 patients with non-small cell lung cancer identified IBI as an independent prognostic factor for patient survival (HR: 1.229, 95% CI: 1.131–1.335; $p < 0.001$) [19].

Beyond these disease-specific associations, contemporary epidemiological data highlight that the overall burden of HF is steadily increasing globally, with substantial effects on morbidity, mortality, and healthcare utilization [1]. In this context, composite inflammatory indices, including IBI, may be particularly valuable for early risk stratification and for identifying high-risk patients who could benefit from closer monitoring and timely intervention [20]. For example, in a cohort of 4423 patients with HF, those with high-sensitivity CRP levels of 10 mg/L or more had a significantly higher risk of all-cause death compared to those with levels <2 mg/L (HR: 2.49, 95% CI: 2.19–2.84; $p < 0.001$) [21]. Furthermore, a large meta-analysis including 15,995 patients with HF revealed that a

high neutrophil-to-lymphocyte ratio (NLR) was a substantial predictor of in-hospital mortality (HR: 1.54, 95% CI: 1.18–2.00; $p < 0.001$) and long-term all-cause mortality (HR: 1.61, 95% CI: 1.40–1.86; $p < 0.001$) compared to a low NLR [22]. The IBI uniquely integrates systemic inflammation and immune status markers by integrating CRP, neutrophil, and lymphocyte counts. Therefore, it provides a more complete and cohesive assessment of the complex interaction between inflammation and HF compared to any single biomarker.

A comparison of the AUC revealed that the IBI outperformed CRP in predicting 28-day mortality after ICU admission (AUC: 0.643 versus 0.595, $p = 0.032$) and in-ICU mortality (AUC: 0.645 versus 0.592, $p = 0.047$). IBI, which can be easily derived from routine laboratory data, shows promise as a reliable and accessible tool to evaluate risk inpatients with HF at ICU admission. This potential is further supported by our finding that patients in the highest IBI tertile (T3) were more likely to receive CRRT more frequently. As CRRT is clinically recognized as a method for clearing inflammatory mediators [23], whether high IBI may benefit from early interventions, such as CRRT or anti-inflammatory therapies, remains a hypothesis for future prospective validation.

Although this study has several strengths, it also has important limitations. First, the retrospective design of the study allows identification of associations; however, it cannot confirm causation. Moreover, as the findings are sourced from the MIMIC-IV database, they are limited to one academic medical center in the United States, potentially affecting their generalizability. Third, although we adjusted for numerous confounders, the possibility of residual confounding from unmeasured variables remains. Fourth, a high proportion of missing data for key HF-specific measures, including echocardiographic parameters and N-terminal pro-B-type natriuretic peptide (NT-proBNP), limited our ability to perform comparative analyses or robust phenotype classification. Fifth, differences in demographic and clinical characteristics between patients included in the final cohort and those excluded based on the inclusion/exclusion criteria may have introduced selection bias. Lastly, the biological pathways underlying the IBI remain undefined and require clarification in future studies.

5. Conclusions

Our findings indicate that IBI is an independent indicator of short-term mortality in individuals with HF. It provides better prognostic value than CRP and offers a more comprehensive assessment of the inflammatory status of patients. Future studies should prospectively validate IBI across multiple centers.

ABBREVIATIONS

AG, Anion Gap; AKI, Acute Kidney Injury; ALT, Alanine Aminotransferase; APS III, Acute Physiology Score III; AST, Aspartate Aminotransferase; AUC, Area Under the Curve; BIDMC, Beth Israel Deaconess Medical Center; BUN, Blood Urea Nitrogen; CCI, Charlson Comorbidity Index; CRRT, Continuous Renal Replacement Therapy; CRP, C-reactive Protein; CVD, Cardiovascular Disease; DBP, Diastolic Blood Pressure; GCS, Glasgow Coma Scale; HF, Heart Failure; IBI, Inflammatory Burden Index; ICU, Intensive Care Unit; NLR, Neutrophil-to-Lymphocyte Ratio; OASIS, Oxford Acute Severity of Illness Score; PLT, Platelet; PT, Prothrombin Time; PTT, Partial Thromboplastin Time; RDW, Red Cell Distribution Width; SAPS II, Simplified Acute Physiology Score II; SBP, Systolic Blood Pressure; SOFA, Sequential Organ Failure Assessment; SpO_2, Pulse Oxygen Saturation; WBC, White Blood Cell; CI, Confidence Interval; HR, Hazard ratio; IQR, interquartile ranges; LASSO, least absolute shrinkage and selection operator; LnIBI, log-transformed Inflammatory Burden Index; MIMIC, Medical Information Mart for Intensive Care; NHANES, the National Health and Nutrition Examination Survey; OR, odds ratios; RCS, restricted cubic splines; ROC, Receiver Operating Characteristic; T, Tertile; VIF, Variance Inflation Factor; Ref, Reference; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

AVAILABILITY OF DATA AND MATERIALS

This data can be found here: https://mimic.physionet.org/.

AUTHOR CONTRIBUTIONS

QL and ZTZ—contributed to the conceptualization, data analysis, and writing. Both authors participated in editing and reviewing the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study used deidentified data from the MIMIC-IV database (version 3.1). The protocol was approved by the Institutional Review Board of Beth Israel Deaconess Medical Center, with informed consent waived. One author (ZTZ) has certified database access (No. 47608458).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.

com/mre-signavitae/article/2085594804576501760/attachment/Supplementary%20material.docx.

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