BMC Pulmonary Medicine

RESEARCH

Open Access

Association and risk of blood urea nitrogen-to-creatinine ratio with congestive heart failure in critically ill COPD patients

Jinjun Sun[1], Weiwei Chen[1] and Hongli Xu[1*]

Abstract

Objective Chronic obstructive pulmonary disease (COPD) is a leading cause of global morbidity and death. The blood urea nitrogen-to-creatinine ratio (BCR) is recognized as a crucial marker to assess renal function and cardiovascular risk. Nevertheless, the effects of BCR on COPD patients suffering comorbid congestive heart failure (CHF) is not clarified. This study aims to elucidate the association between BCR and CHF risk in the COPD population.

Methods Data from COPD patients meeting the eligibility criteria were from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database. The cumulative incidence curve was utilized for examining the link of BCR to CHF. Kaplan-Meier (KM) analysis was carried out for evaluating the relation of BCR to in-hospital mortality(IHM). Multivariable Cox regression assisted in assessing the correlation of BCR with CHF risk. Restricted cubic splines (RCS) were leveraged for unraveling the association of BCR (as a continuous variable) with CHF.

Results Our study included 2,840 COPD patients in the intensive care unit for the first time, with hospital stays exceeding 24 h. The incidence of CHF was 57.18% among these patients. Cumulative incidence curve analysis demonstrated a notably increased CHF incidence in patients having higher BCR ($18.889 < BCR \leq 92.5$) in contrast to those with lower BCR ($2.877 \leq BCR \leq 18.889$) ($p < 0.0001$). KM survival analysis indicated a markedly elevated IHM risk in patients with higher BCR in comparison to those with lower BCR ($p < 0.0001$). Multivariable Cox regression and RCS analysis further confirmed that higher BCR was linked to a risen likelihood of CHF [hazard ratio (HR) = 1.28, 95% confidence interval (CI, 1.15–1.44), $p < 0.001$]. Subgroup analysis revealed a higher risk of CHF [HR = 1.41, 95% CI (1.13–1.76), $p = 0.002$] in patients with diabetes than those without [HR = 1.24, 95% CI (1.08–1.41), $p = 0.002$].

Conclusion Elevated BCR is an independent risk factor for CHF in critically ill COPD individuals and strongly related to a risen risk of CHF. The findings prove BCR as a reliable clinical predictor, facilitating risk stratification and personalized treatment for COPD patients with comorbid CHF.

Keywords BCR, CHF, COPD, MIMIC-IV, Risk factor

*Correspondence:
Hongli Xu
15268888233@163.com
[1]Department of Tuberculosis, Affiliated Hospital of Shaoxing University, No. 999 South Zhongxing Road, Shaoxing 312000, Zhejiang, China

Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent respiratory disorder attributed to prolonged exposure to harmful particles or gases [1]. COPD sufferers often exhibit systemic inflammation, hypoxemia, endothelial dysfunction, heightened sympathetic activation, as well as aortic stiffness, all of which can lead to microvascular damage, proteinuria, and renal function impairment [2]. As an intricate and heterogeneous disease, COPD is frequently correlated with multiple comorbidities, which contribute to higher morbidity and mortality rates compared to those caused by the respiratory disease alone [3]. COPD commonly coexists with heart failure (HF), and the risk of both conditions rises with age. Several studies have reported an elevated incidence of cardiac diseases among adults hospitalized for pulmonary diseases [4–6]. The COPD-HF syndrome has gained increasing attention due to its critical impact on key health outcomes [7]. Therefore, identifying risk factors associated with the prevalence of COPD and HF is essential for ameliorating the prognosis of these patients.

Renal involvement is a common complication in chronic respiratory conditions in clinical settings. A higher incidence of renal failure was noted in patients suffering primary pulmonary diseases, particularly in those with COPD [8–10]. Therefore, monitoring renal function in COPD patients may be crucial for prognostic evaluation [11]. The blood urea nitrogen-to-creatinine ratio (BCR) is a widely utilized marker for evaluating kidney function, particularly in cases of suspected renal impairment. An elevated BCR may indicate worse renal function, as blood urea nitrogen (BUN) tends to accumulate when kidney function is impaired, while creatinine (Cr) levels may decrease as the glomerular filtration rate (GFR) drops, so BCR possibly indicates renal function deterioration [12, 13]. Given the complex pathophysiological relationship between COPD and HF, BCR serves both as an indicator of renal function and a valuable tool for assessing fluid balance, cardio-renal interactions, and chronic disease management, providing reliable support for comprehensive clinical evaluation and the development of individualized treatment strategies.

Despite established associations between COPD and HF, and the recognized role of BCR in evaluating renal function, the relationship between BCR and congestive heart failure (CHF) in critically ill COPD patients remains inconclusive. There is a need to investigate whether BCR can serve as an effective prognostic stratification marker for critically ill COPD patients with CHF, thereby offering deeper insights into disease progression and outcomes. To address this issue, we analyzed data from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database and constructed a linear regression model for offering insights into the prognosis and monitoring of patients with this combined syndrome.

Materials and methods

Study population

This is a retrospective study undertaken by analyzing eligible patient data from the MIMIC-IV database from 2008 to 2019. Data on BCR, COPD, and CHF were collected through retrieval. The eligibility criteria are detailed as follows. Inclusion criteria: (1) patients diagnosed with COPD; (2) those aged 18 or above; and (3) those entering the intensive care unit (ICU) for the first time, with a hospital stay exceeding 24 h. Exclusion criterion: patients with the absence of BUN and Cr data. The use of MIMIC-IV data was approved by the Institutional Review Boards of Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology. Our screening process is outlined in Fig. 1.

Variable extraction

The extracted variables were: demographic information (age, gender, race, marital status), vital signs [heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), temperature, oxygen saturation (SpO_2)], common comorbidities [diabetes, cerebrovascular disease, severe liver disease, CHF), systemic inflammatory response syndrome (SIRS), laboratory parameters (red blood cell (RBC), white blood cell (WBC), Cr, BUN, BCR, red cell distribution width (RDW), estimated GFR (eGFR), hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), international normalized ratio (INR), prothrombin time (PT), partial thromboplastin time (PTT)], medications and interventions (antibiotics, PDE4 inhibitors, glucocorticoids, beta-2 agonists, anticholinergics), as well as other relevant variables.

The eGFR was calculated as follows (multiplied by 1 for males):

eGFR (ml/min/1.73 m^2) = 186 × (Scr)^-1.154 × (age)^-0.203 × (0.742 for females).

All comorbidities were identified as per the International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) codes (Relevant codes for COPD and CHF are detailed in Tables S1 and S2). Data from the first 24 h after ICU entry were extracted via PostgreSQL 14.2. Our study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies.

Definitions of exposure variables and outcomes

The primary exposure variable was the BCR of COPD patients: the ratio of BUN to Cr. All patients underwent systematic imaging, medical history review, physical examination, and medication therapy during

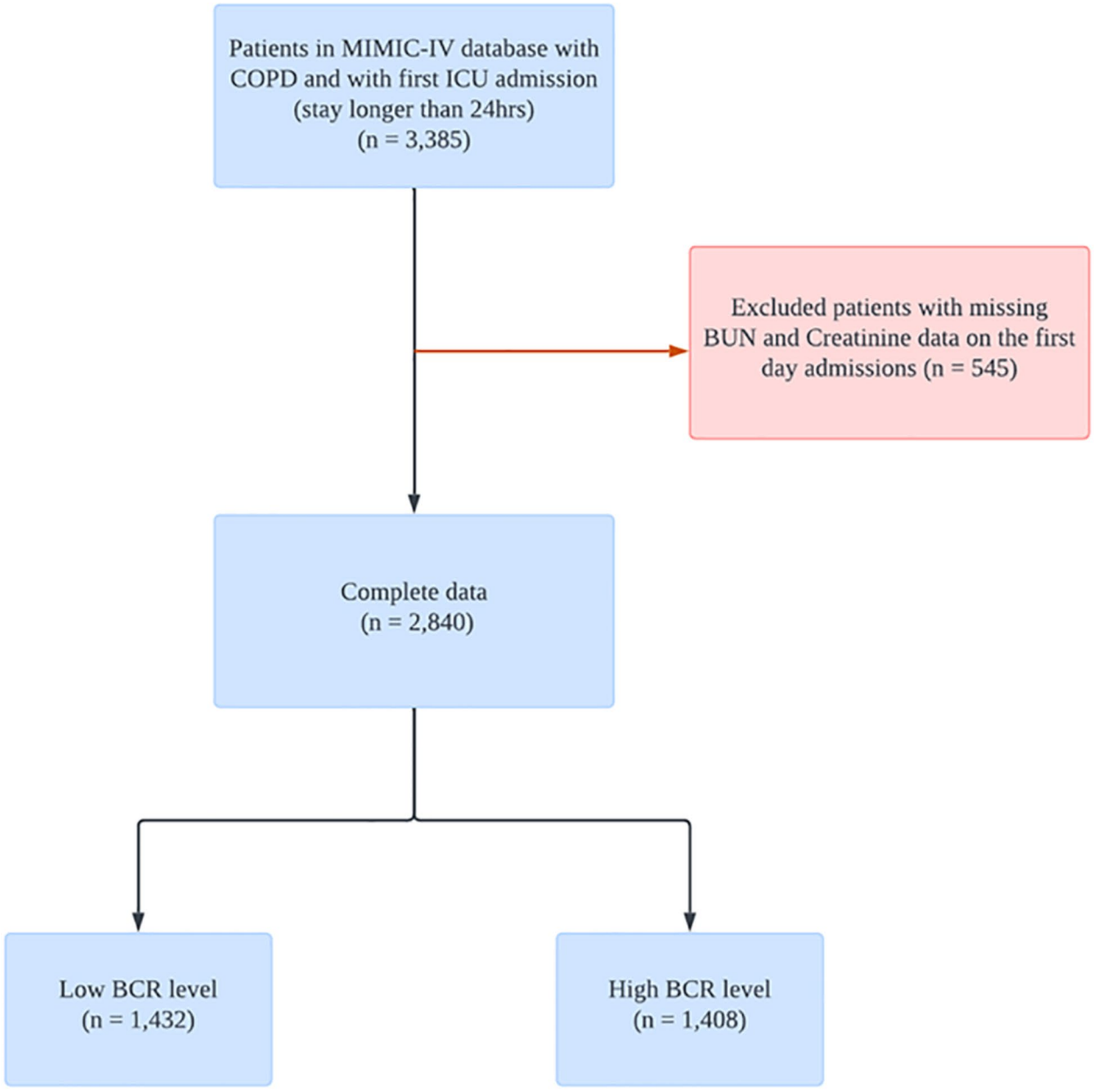

Fig. 1 Data screening flow chart

hospitalization, with intravenous administration determined based on clinical indications. Laboratory measurements were carried out upon admission, and subsequent tests were scheduled by the attending physician. The primary outcome was CHF incidence in COPD patients. The secondary outcome was the all-cause in-hospital mortality (IHM) among COPD patients. The short-term outcome was in-hospital prognosis, while the long-term outcome was follow-up data after discharge.

Data analysis

Statistical analysis was undertaken via R 4.3.1. Continuous variables in normal distribution were shown in mean ± standard deviation (x ± s), whereas non-normally distributed ones were in median and interquartile range [M (QL, QU)], with differences across groups detected through the Mann-Whitney U test. Categorical data were displayed as percentages (%), and differences between groups were evaluated via the chi-square test. Low BCR was defined as $2.877 \leq BCR \leq 18.889$, and high BCR was

defined as 18.889 < BCR ≤ 92.5. Kaplan-Meier (KM) survival and cumulative incidence curves were used for assessing the relationship between BCR and CHF survival, with differences between groups evaluated through the log-rank test. Cox proportional hazards models were utilized for examining the risk relationship of the observed outcomes with COPD.

Our multivariable Cox regression model included the following confounders: age, gender, race, marital status, heart rate, DBP, SBP, MBP, temperature, SpO_2, diabetes, cerebrovascular disease, severe liver disease, myocardial infarction, BUN, Cr, RBC count, WBC count, RDW, hemoglobin, hematocrit, MCV, MCH, eGFR, SIRS, sequential organ failure assessment (SOFA), and use of medications like beta-blockers, angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor-neprilysin inhibitor (ARNI), angiotensin receptor blocker (ARB), nitroglycerin, statins, beta-2 agonists, anticholinergics, and PDE4 inhibitors. Trend tests were undertaken, and hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were measured for quantifying the effects of BCR on these outcomes. Restricted cubic spline (RCS) curves were leveraged for exploring the nonlinear link of BCR (as a continuous variable) to CHF. The intricate relation of BCR to CHF across subgroups were clarified via subgroup analyses, with results visualized accordingly. The baseline table was generated using the tableone package. The receiver operating characteristic (ROC) curve analysis was executed through the riskRegression and survival packages. KM analysis was performed via the survival and survminer packages. Cox regression was performed using the survival and rms packages. RCS were plotted through ggplot2 and plotRCS. Subgroup analysis was conducted using the jstable package. The forest plot was created using the forestplot package. Variance inflation factor (VIF) was employed for examining multicollinearity in all independent variables, and no multicollinearity was detected. Additionally, sensitivity analysis was carried out to evaluate reault reliability. All descriptive analyses were undertaken with two-sided tests, and $p < 0.05$ signified statistical significance.

Results

Baseline characteristics

2,840 critically ill COPD patients were encompassed, among which 53.13% were male, 71.09% were White, and the average age was 71. The majority of patients were married (38.84%), and the incidence of CHF was 57.18%. Their anthropometric characteristics and biochemical results, stratified by BCR, are presented in Table S3. Notable differences were found across groups with regard to age, gender, race, marital status, BUN, Cr, BCR, DBP, MBP, eGFR, hemoglobin, and CHF ($p < 0.0001$) The baseline characteristics, split by CHF comorbidity, are detailed in Table S4.

KM cumulative incidence and survival curves

The cumulative incidence curve illustrates the probability of CHF occurrence in COPD patients. The results from the log-rank test indicate that as hospital stay duration increases, patients with higher BCR tend to develop CHF in comparison to those having lower BCR, with marked differences noted across groups ($p < 0.0001$) (Fig. 2A). The KM survival curve, further aiding in examining the relation of BCR to IHM risk in COPD individuals, revealing that survival rates decrease over time, with higher BCR associated with worse survival outcomes ($p = 0.0027$). Additionally, the number of survivors at each time point is lower in the high-BCR cohort in contrast to the low-BCR cohort (Fig. 2B). The close relation of BCR to IHM risk in COPD sufferers with comorbid CHF is further shown in Supplementary Fig. 1. These findings highlight the significant role of BCR in risk stratification for COPD patients with comorbid CHF.

Multivariable Cox regression model

In the unadjusted Model 1, in comparison to the low-BCR cohort, the high-BCR cohort was shown to have a 1.28-fold higher CHF risk [HR = 1.28, 95% CI (1.15–1.44), $p < 0.001$]. In Model 2, after adjustments of age, gender, race, as well as marital status, the high-BCR group continue to exhibit an elevated likelihood of CHF in contrast to the low-BCR cohort[HR = 1.21, 95% CI (1.08–1.36), $p < 0.001$]. After all factors were adjusted in Model 3, similar results were noted, with BCR also being linked to an elevated risk of CHF [HR = 1.20 95% CI (1.04–1.39), $p = 0.014$] (Table 1).

RCS curve analysis

RCS analysis was conducted for Model 1, Model 2, and Model 3 to elucidate the continuous relationship between BCR and CHF. The results, shown in Fig. 3, indicate a nonlinear relationship between BCR and CHF in Model 1 (*p for nonlinear* < 0.001). However, no significant linear relationship was revealed in Model 2 and Model 3 (*p for nonlinear* = 0.015 and *p for nonlinear* = 0.131). Additionally, HR < 1 in some cases may be related to variables such as medications or other factors, which might reduce the risk of CHF at low BCR. However, as BCR increases, the risk of CHF also increases (HR > 1).

Subgroup analysis

Subgroup analysis was undertaken to clarify the complex correlation between BCR and CHF across different subpopulations (Fig. 4). Although no significant interaction was noted for diabetes, patients with diabetes[HR = 1.41, 95%CI(1.13,1.76), $p = 0.002$] exhibited

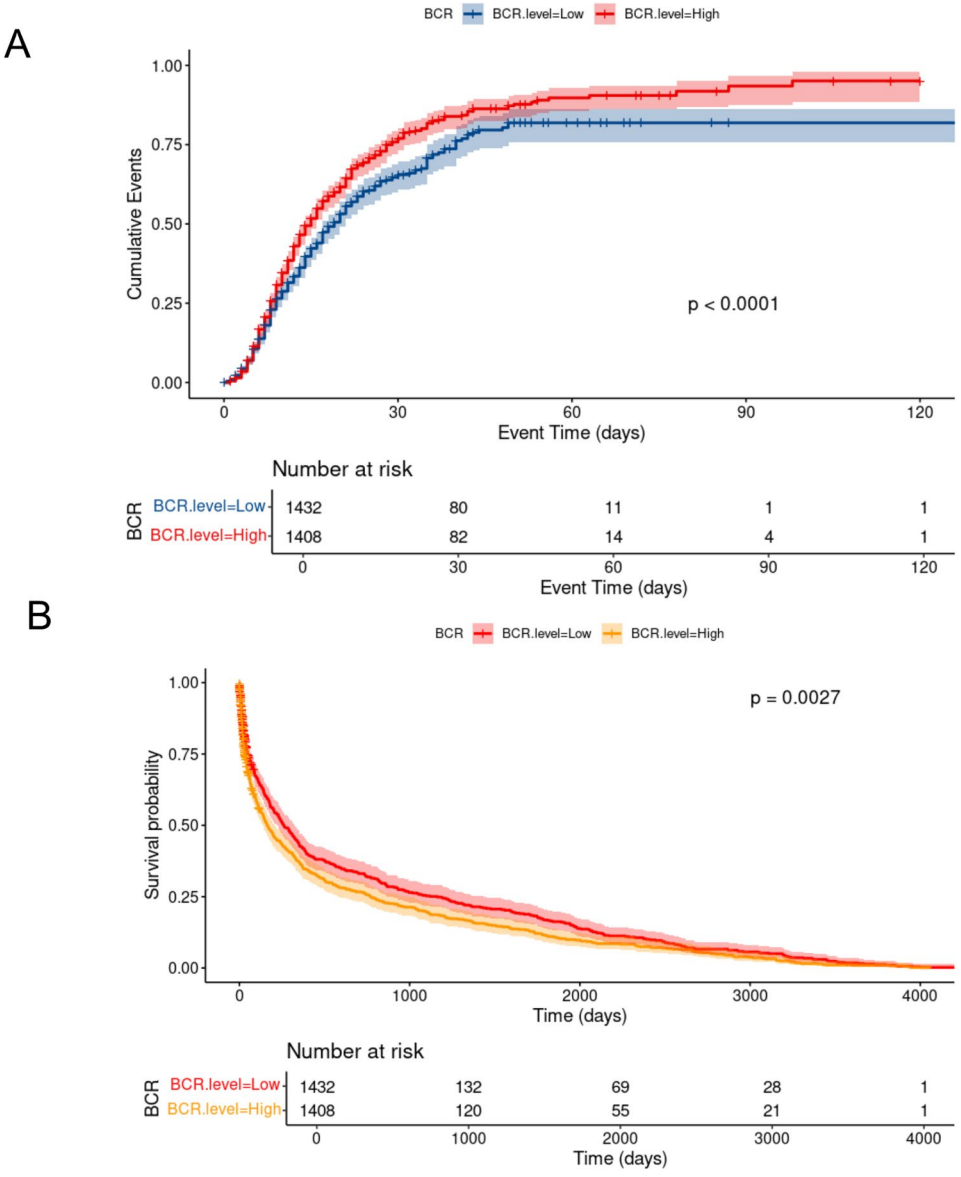

Fig. 2 KM cumulative incidence and survival curve analysis. **A**: Cumulative incidence curve of CHF in relation to BCR levels. **B**: Survival curve for COPD patients

Table 1 Cox regression analysis of CHF risk in COPD patients based on BCR levels

BCR levels	Model 1		Model 2		Model 3	
	HR (95%CI)	*P*-value	HR (95%CI)	P-value	HR (95%CI)	*P*-value
Short-term mortality						
Low	Ref.		Ref.		Ref.	
High	1.28 (1.15–1.44)	< 0.001	1.21 (1.08–1.36)	0.001	1.20 (1.04–1.39)	0.014

Model 1: unadjusted model; Model 2: adjusted by Age and Gender, Race, Marital status; Model 3: adjusted by Age, Gender, Race, Marital status, Heart rate, DBP, SBP, MBP, Temperature, SPO2, Diabetes, Cerebrovascular disease, Severe liver disease, Myocardial infarction, BUN, Creatinine, RBC, WBC, RDW, Hemoglobin, Hematocrit, MCV, MCH, eGFR, SIRS, SOFA, Beta blocker, ACEI, ARNI, ARB, Nitroglycerin, Statin, Beta2.agonists, Anticholinergics, PDE4.inhibitors

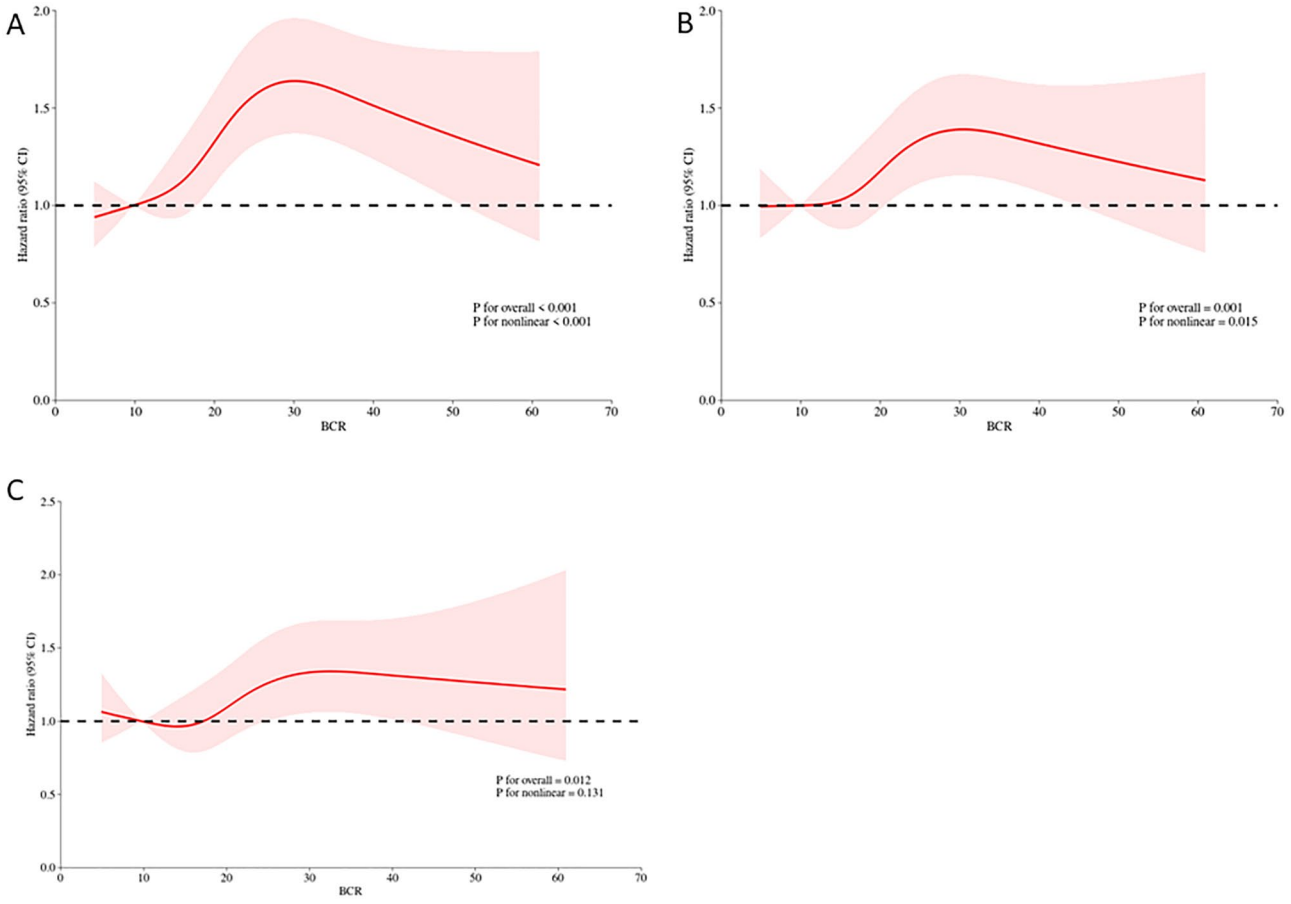

Fig. 3 RCS analysis. **A**: RCS curve based on Model (1) **B**: RCS curve based on Model (2) **C**: RCS curve based on Model 3
Model 1: unadjusted model; Model 2: adjusted for age, gender, race, marital status; Model 3: adjusted for age, gender, race, marital status, heart rate, DBP, SBP, MBP, temperature, SpO_2, diabetes, cerebrovascular disease, severe liver disease, myocardial infarction, BUN, Cr, RBC count, WBC count, RDW, hemoglobin, hematocrit, MCV, MCH, eGFR, SIRS score, SOFA score, beta blocker, ACEI, ARNI, ARB, nitroglycerin, statin, Beta2-agonists, anticholinergics, PDE4 inhibitors

an elevated likelihood of CHF in comparison to those without[HR = 1.24, 95%CI(1.08,1.41), $p = 0.002$]. Similar results were found in groups receiving glucocorticoid, beta-2 agonists, and anticholinergics, where, despite the lack of significant interaction, these medications were related to a risen likelihood of CHF in COPD individuals.

Discussion

Based on data from 2,840 critically ill COPD people in American MIMIC-IV database, our study investigated the prospect of BCR as a prognostic marker for risk stratification and unveiled the relationship between BCR, CHF comorbidity, and IHM.

Our findings demonstrate a notable link between higher BCR and a risen risk of CHF in the COPD population. Notably, even after adjustment for various confounders, high BCR remained strongly associated with an elevated CHF risk. This not only extends the clinical application of BCR as a marker of renal insufficiency but also suggests its potential in forecasting cardiovascular events, particularly in critically ill COPD individuals suffering multiple comorbidities. Moreover, higher BCR was linked to worse survival outcomes in the COPD cohort, corroborateing the conclusion from previous research that BCR may serve as an important indicator of poor prognosis.

Clinically, the use of of BCR has been predominantly focused on evaluating renal function, particularly in acute kidney injury and chronic kidney disease [14]. While scoring systems such as SOFA and acute physiology and chronic health evaluation (APACHE) are extensively employed in ICU settings, BCR offers a simple and cost-effective biomarker derived from routine laboratory tests. It is less susceptible to time-related variability or inaccuracies. As a continuous variable, BCR significantly correlates with the likelihood of CHF in critically ill COPD people, providing a more detailed and dynamic risk stratification. This can facilitate the early detection of worsening renal and cardiovascular risks, enabling timely intervention. Increasing evidence in recent years suggests

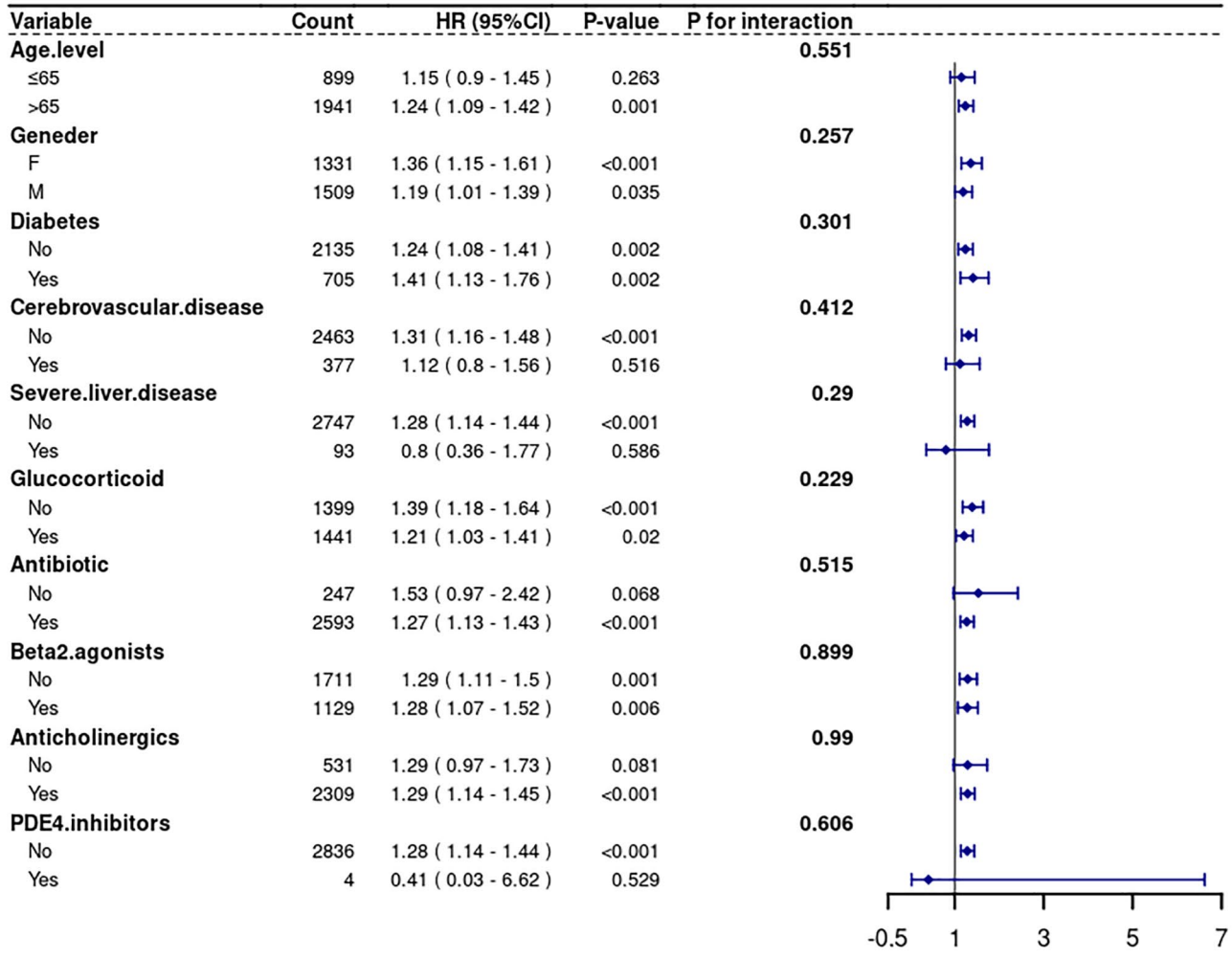

Fig. 4 Forest plot of subgroup analysis for CHF risk in COPD patients

that BCR-related indices are key prognostic factors for HF and other cardiovascular events. Moreover, congestion is a marker of poor prognosis in HF individuals, and BCR is often considered an indicator of "venous" congestion, making it increasingly recognized as a biomarker for assessing HF-related congestion [15]. Massari F et al. [16] noted that a BCR > 25 was linked to poor outcomes in HF sufferers. Saygitov R.T. et al. [17] identified elevated BUN or a concurrent rise in BUN and Cr as independent risk factors for mortality in acute coronary syndrome patients. Additionally, Takaya Y [14]. and Lin H [18]. confirmed the correlation between BCR and HF. This is especially relevant in critically ill COPD patients, who often present with multiple chronic conditions, such as HF and diabetes, which complicate disease management [19].

The association between BCR and COPD with CHF comorbidity is likely driven by complex pathophysiological mechanisms. COPD patients frequently experience chronic hypoxemia and systemic inflammatory responses. Hypoxemia induces endothelial dysfunction in the kidneys and disrupts the oxygen supply-demand balance in renal tubules, thereby exacerbating ischemic renal injury [20]. Furthermore, the systemic inflammatory response, regulated by pro-inflammatory cytokines-like tumor necrosis factor-αand interleukin-6, increases oxidative stress in the kidney, promotes fibrosis, as well as triggers endothelial dysfunction, further impairing renal function [21]. Under the combined effects of hypoxemia and inflammation, reduced renal blood flow diminishes the GFR, potentially inducing renal damage and chronic kidney disease [22]. This deterioration in renal function, reflected by elevated BCR, can increase cardiac load, ultimately promoting the development of CHF and negatively impacting patient survival [23].

It is noteworthy that CHF and renal insufficiency alone cannot fully explain the adverse effects of elevated BCR. Accelerated catabolic processes, which increase with age, may also lead to higher BCR in elderly patients [17]. Aging correlates with the progressive breakdown of proteins (albumin, hemoglobin, ferritin), leading to elevated

BUN and potentially higher BCR [24]. This finding aligns with our results, as the majority of COPD patients with CHF comorbidity were elderly (median [IQR] = 74, $p < 0.0001$), which may partially explain the higher BCR in this population. Moreover, CHF itself may further elevate BCR by causing impaired renal perfusion and inducing tubular dysfunction. This vicious cycle may be particularly evident in COPD patients with CHF. Therefore, closely monitoring of renal function in this patient population is essential [25, 26].

Furthermore, our study elucidated a significantly increased CHF risk in COPD patients with concurrent diabetes or those on other medications. The presence of vascular pathology and microvascular complications in patients with diabetes may exacerbate hypoxemia and kidney damage, thereby elevating the risk of CHF [27]. Additionally, while certain medications can mitigate clinical symptoms of COPD to some extent, they may increase the risk of CHF by negatively impacting the cardiovascular system, increasing cardiac workload or altering hemodynamics [28]. These findings reveal the necessity for closely monitoring COPD patients, especially those with concurrent diabetes or those receiving medications that may increase cardiac burden, to prevent adverse outcomes [29].

The strengths of this study are: (1) It firstly leveraged the U.S. MIMIC-IV database to examine the link of BCR to CHF in the critically ill COPD population, proving that elevated BCR can predict the underlying risk of CHF and are correlated with adverse outcomes in COPD; (2) The robustness of all findings were ensured via stratified and subgroup analyses, revealing that medication use and other comorbidities contribute to an increased risk of CHF. However, several limitations should be noted: (1) On account that this study is retrospective, while we adjusted for confounders in the analysis, some potential biases may still remain; (2) The retrospective design prevents the establishment of causality. It cannot be determined whether elevated BCR directly increases CHF risk or merely reflects a shared pathophysiological mechanism. Prospective studies and randomized controlled trials are essential to validate this association; (3) The study was conducted based solely on the MIMIC-IV database, which may influence the generalizability of our findings.

Conclusion

This study based on the MIMIC-IV database presents clinical evidence linking BCR to the risk of CHF and IHM in critically ill COPD people. BCR is an independent risk factor for CHF in the COPD population, with high BCR significantly related to poor prognosis, indicating that BCR can serve as an important prognostic marker for COPD patients. Therefore, clinical practice should emphasize monitoring BCR in COPD patients to note high-risk individuals early and offer timely interventions. These findings offer valuable clinical guidance for individualized management of COPD patients and contribute to understanding the potential pathological mechanisms leading to CHF in this population, providing a basis for developing more effective intervention strategies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-025-03556-6.

Supplementary Material 1

Acknowledgements
Not applicable.

Author contributions
Jinjun Sun and Hongli Xu designed the study, Jinjun Sun analyzed the data and wrote the manuscript, Weiwei Chen drew the images, and Hongli Xu checked with Jinjun Sun.

Funding
Not applicable.

Data availability
The datasets analysed during the current study are available in the MIMIC-IV database (MIMIC-IV v3.0 (physionet.org)).

Declarations

Ethics approval and consent to participate
The MIMIC-IV database has obtained approval from the Institutional Review Boards of Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Consent to participate
All participants agreed to participate.

Clinical trial number
Not applicable.

Received: 10 October 2024 / Accepted: 13 February 2025
Published online: 08 March 2025

References

1. Celli B, Fabbri L, Criner G, et al. Definition and nomenclature of Chronic Obstructive Pulmonary Disease: time for its Revision[J]. Am J Respir Crit Care Med. 2022;206(11):1317–25. https://doi.org/10.1164/rccm.202204-0671PP.
2. Sorino C, Scichilone N, Pedone C, et al. When kidneys and lungs suffer together[J]. J Nephrol. 2019;32(5):699–707. https://doi.org/10.1007/s40620-018-00563-1.
3. Huiart L, Ernst P, Suissa S. Cardiovascular morbidity and mortality in COPD[J]. Chest. 2005;128(4):2640–6. https://doi.org/10.1378/chest.128.4.2640.
4. Corrales-Medina VF, Musher DM, Shachkina S, et al. Acute pneumonia and the cardiovascular system[J]. Lancet. 2013;381(9865):496–505. https://doi.org/10.1016/S0140-6736(12)61266-5.

5. O'Meara ES, White M, Siscovick DS, et al. Hospitalization for pneumonia in the Cardiovascular Health Study: incidence, mortality, and influence on longer-term survival[J]. J Am Geriatr Soc. 2005;53(7):1108–16. https://doi.org/10.1111/j.1532-5415.2005.53352.x.
6. Ramirez J, Aliberti S, Mirsaeidi M, et al. Acute myocardial infarction in hospitalized patients with community-acquired pneumonia[J]. Clin Infect Dis. 2008;47(2):182–7. https://doi.org/10.1086/589246.
7. Fisher KA, Stefan MS, Darling C, et al. Impact of COPD on the mortality and treatment of patients hospitalized with acute decompensated heart failure: the Worcester Heart failure Study[J]. Chest. 2015;147(3):637–45. https://doi.org/10.1378/chest.14-0607.
8. Gjerde B, Bakke PS, Ueland T, et al. The prevalence of undiagnosed renal failure in a cohort of COPD patients in western Norway[J]. Respir Med. 2012;106(3):361–6. https://doi.org/10.1016/j.rmed.2011.10.004.
9. van Gestel YR, Chonchol M, Hoeks SE, et al. Association between chronic obstructive pulmonary disease and chronic kidney disease in vascular surgery patients[J]. Nephrol Dial Transpl. 2009;24(9):2763–7. https://doi.org/10.1093/ndt/gfp171.
10. Incalzi RA, Corsonello A, Pedone C, et al. Chronic renal failure: a neglected comorbidity of COPD[J]. Chest. 2010;137(4):831–7. https://doi.org/10.1378/chest.09-1710.
11. Sandelowsky H, Weinreich UM, Aarli BB, et al. COPD - do the right thing[J]. BMC Fam Pract. 2021;22(1):244. https://doi.org/10.1186/s12875-021-01583-w.
12. Lindenfeld J, Schrier RW. Blood urea nitrogen a marker for adverse effects of loop diuretics?[J]. J Am Coll Cardiol. 2011;58(4):383–5. https://doi.org/10.1016/j.jacc.2011.01.054.
13. Schrier RW. Blood urea nitrogen and serum creatinine: not married in heart failure[J]. Circ Heart Fail. 2008;1(1):2–5. https://doi.org/10.1161/CIRCHEARTFAILURE.108.770834.
14. Takaya Y, Yoshihara F, Yokoyama H, et al. Risk stratification of Acute kidney Injury using the Blood Urea Nitrogen/Creatinine Ratio in patients with Acute Decompensated Heart Failure[J]. Circ J. 2015;79(7):1520–5. https://doi.org/10.1253/circj.CJ-14-1360.
15. Parrinello G, Torres D, Testani JM, et al. Blood urea nitrogen to creatinine ratio is associated with congestion and mortality in heart failure patients with renal dysfunction. Intern Emerg Med. 2015;10(8):965–72. https://doi.org/10.1007/s11739-015-1261-1.
16. Massari F, Scicchitano P, Iacoviello M, et al. Multiparametric approach to congestion for predicting long-term survival in heart failure. J Cardiol. 2020;75(1):47–52. https://doi.org/10.1016/j.jjcc.2019.05.017.
17. Saygitov RT, Glezer MG, Semakina SV. Blood urea nitrogen and creatinine levels at admission for mortality risk assessment in patients with acute coronary syndromes[J]. Emerg Med J. 2010;27(2):105–9. https://doi.org/10.1136/emj.2008.068155.
18. Lin HJ, Chao CL, Chien KL, et al. Elevated blood urea nitrogen-to-creatinine ratio increased the risk of hospitalization and all-cause death in patients with chronic heart failure[J]. Clin Res Cardiol. 2009;98(8):487–92. https://doi.org/10.1007/s00392-009-0025-1.
19. Miravitlles M. Improving outcomes of Chronic Obstructive Pulmonary Disease through the treatment of comorbidities: one step Beyond[J]. Am J Respir Crit Care Med. 2023;208(10):1017–9. https://doi.org/10.1164/rccm.202309-1546ED.
20. Polverino F, Laucho-Contreras ME, Petersen H, et al. A pilot study linking endothelial Injury in lungs and kidneys in Chronic Obstructive Pulmonary Disease[J]. Am J Respir Crit Care Med. 2017;195(11):1464–76. https://doi.org/10.1164/rccm.201609-1765OC.
21. Lu Z, Van Eeckhoutte HP, Liu G, et al. Necroptosis Signaling promotes inflammation, Airway Remodeling, and Emphysema in Chronic Obstructive Pulmonary Disease[J]. Am J Respir Crit Care Med. 2021;204(6):667–81. https://doi.org/10.1164/rccm.202009-3442OC.
22. Wang B, Li ZL, Zhang YL, et al. Hypoxia and chronic kidney disease[J]. EBioMedicine. 2022;77:103942. https://doi.org/10.1016/j.ebiom.2022.103942
23. House AA, Wanner C, Sarnak MJ et al. Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference[J]. Kidney Int, 2019,95(6):1304–1317.https://doi.org/10.1016/j.kint.2019.02.022
24. Fehrman-Ekholm I, Skeppholm L. Renal function in the elderly (> 70 years old) measured by means of iohexol clearance, serum creatinine, serum urea and estimated clearance[J]. Scand J Urol Nephrol. 2004;38(1):73–7. https://doi.org/10.1080/00365590310015750.
25. Szlagor M, Dybiec J, Młynarska E, et al. Chronic kidney disease as a Comorbidity in Heart Failure[J]. Int J Mol Sci. 2023;24(3):2988. https://doi.org/10.3390/ijms24032988
26. Kuan V, Denaxas S, Patalay P, et al. Identifying and visualising multimorbidity and comorbidity patterns in patients in the English National Health Service: a population-based study[J]. Lancet Digit Health. 2023;5(1):e16–27. https://doi.org/10.1016/S2589-7500(22)00187-X.
27. Lyssenko V, Vaag A. Genetics of diabetes-associated microvascular complications[J]. Diabetologia. 2023;66(9):1601–13. https://doi.org/10.1007/s00125-023-05964-x.
28. Hatlen G, Romundstad S, Hallan SI. The accuracy of predicting cardiovascular death based on one compared to several albuminuria values[J]. Kidney Int. 2014;85(6):1421–8. https://doi.org/10.1038/ki.2013.500.
29. Krishnaswami A, Steinman MA, Goyal P, et al. Deprescribing in older adults with Cardiovascular Disease[J]. J Am Coll Cardiol. 2019;73(20):2584–95. https://doi.org/10.1016/j.jacc.2019.03.467.

Publisher's note