Research Article

Predictive Value of Arterial Blood Lactic Acid Concentration on the Risk of in-Hospital All-Cause Death in Patients with Acute Heart Failure

Weiwei Hu,1 Lei Yuan,2 Xiaotong Wang,3 Baohe Zang,1 Yang Zhang,1 Xianliang Yan,4 Wenjing Zhao,1 and Yali Chao1

1Department of Critical Care Medicine, The Affiliated Hospital of Xuzhou Medical University, Xuzhou 221000, Jiangsu, China
2Department of Interventional Vascular Surgery, Xuzhou Cancer Hospital, Xuzhou 221005, Jiangsu, China
3Department of Cardiology, The Affiliated Hospital of Xuzhou Medical University, Xuzhou 221000, Jiangsu, China
4Department of Emergency Medicine, The Affiliated Hospital of Xuzhou Medical University, Xuzhou 221000, Jiangsu, China

Correspondence should be addressed to Yali Chao; chaoyali@126.com

Received 31 July 2022; Revised 15 October 2022; Accepted 25 October 2022; Published 16 November 2022

Academic Editor: Pietro Scicchitano

Copyright © 2022 Weiwei Hu et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The study aims to examine the predictive value of arterial blood lactic acid concentration for in-hospital all-cause mortality in the intensive care unit (ICU) for patients with acute heart failure (AHF). We retrospectively analyzed the clinical data of 7558 AHF patients in the Medical Information Mart for Intensive Care IV (MIMIC-IV) database. The exposure variable of the present study was arterial blood lactic acid concentration and the outcome variable was in-hospital all-cause death. The patients were divided into those who survived (n = 6792) and those who died (n = 766). The multivariate logistic regression model, restricted cubic spline (RCS) plot, and subgroup analysis were used to evaluate the association between lactic acid and in-hospital all-cause mortality. In addition, receiver operating curve (ROC) analysis also was performed. Finally, we further explore the association between NT-proBNP and lactic acid and in-hospital all-cause mortality. Compared with the lowest quartiles, the odds ratios with 95% confidence intervals for in-hospital all-cause mortality across the quartiles were 1.46 (1.07–2.00), 1.48 (1.09–2.00), and 2.36 (1.73–3.22) for lactic acid, and in-hospital all-cause mortality was gradually increased with lactic acid levels increasing (P for trend < 0.05). The RCS plot revealed a positive and linear connection between lactic acid and in-hospital all-cause mortality. A combination of lactic acid concentration and the Simplified Acute Physiology Score (SAPS) II may improve the predictive value of in-hospital all-cause mortality in patients with AHF (AUC = 0.696). Among subgroups, respiratory failure interacted with an association between lactic acid and in-hospital all-cause mortality (P for interaction < 0.05). The correlation heatmap revealed that NT-proBNP was positively correlated with lactic acid (r = 0.07) and positively correlated with in-hospital all-cause mortality (r = 0.18). There was an inverse L-shaped curve relationship between NT-proBNP and in-hospital all-cause mortality, respectively. Mediation analysis suggested that a positive relationship between lactic acid and in-hospital all-cause death was mediated by NT-proBNP. For AHF patients in the ICU, the arterial blood lactic acid concentration during hospitalization was a significant independent predictor of in-hospital all-cause mortality. The combination of lactic acid and SAPS II can improve the predictive value of the risk of in-hospital all-cause mortality in patients with AHF.

1. Introduction

Acute heart failure (AHF) is a frequent clinical critical condition that is mostly represented by cardiogenic shock and acute pulmonary edema [1]. Due to the quick onset and progression of AHF, it is critical to provide prompt and appropriate treatment [2]. Thus, quick and precise evaluation and treatment of AHF patients may improve patient outcomes. People have begun to pay more attention to the prediction of early AHF death as a result of the recent increase in AHF patient mortality [3]. At the moment, N-terminal B-type natriuretic peptide precursor (NT-
proBNP) is a frequently utilized indicator for clinical assessment of heart failure patients’ prognosis, although its sensitivity and specificity are restricted [4]. Therefore, identifying biomarkers with a high degree of sensitivity and specificity is critical for assessing the prognosis of patients with AHF.

Previous research has shown that elevated arterial blood lactic acid concentration is connected with an increased risk of morbidity and death in some severe illnesses, implying that lactic acid is a crucial predictor of prognosis in critically sick patients [5]. Research by Robert et al. has shown that elevated blood lactic acid on admission is common in AHF patients and is associated with markers of a worse prognosis [6]. Some studies also suggest that lactic acid can predict the prognosis of patients with AHF [7–9]. The association between the levels of lactic acid and nosocomial all-cause mortality in patients with AHF, especially in the critical care unit, has yet to be determined. In critical care medicine, the Medical Information Mart for Intensive Care IV (MIMIC-IV) database is a comprehensive single-center database that contains demographic and clinical data on all patients admitted to the ICU between 2008 and 2019 [10]. In this study, we searched for and analyzed clinical data from AHF patients admitted to the MIMIC-IV database to determine if lactic acid is associated with in-hospital all-cause mortality in patients with AHF after admission.

2. Materials and Methods

2.1. Data Source. The MIMIC-IV database, a publicly available critical care database, was used for all the research [11]. Between 2008 and 2019, the MIMIC-IV database contains clinical data on patients admitted to the intensive care unit (ICU) at Beth Israel Deaconess Medical Center (BIDMC), including demographics and infections, birth and death, ICU admission and discharge, vital signs, laboratory data, and body fluid balance, as well as reports, medications, and nursing records. After passing the Protection of Human Research Participants Examination and the NIH online training course, we were able to access the MIMIC-IV database and harvest data (certification number: 50141059). SQL (structured query language) was used to get all data from the MIMIC-IV database. In addition, we also included AHF patients from the Department of Critical Care Medicine, Affiliated Hospital of Xuzhou Medical University between 2018 and 2022 to verify the association between arterial blood lactic acid concentration and in-hospital all-cause mortality.

2.2. Study Population. We retrieved and extracted patients with AHF from the MIMIC-IV database between 2008 and 2019. The inclusion criteria were as follows: 10919 AHF patients were enrolled, of which 2679 AHF patients were excluded due to not being admitted to the hospital and ICU for the first time. Of the remaining 8240 AHF patients, 622 AHF patients were excluded because of the age of less than 18 and severely missing data. Finally, 7558 AHF patients were included in the present study. Medical records of the patient’s baseline data including the patient’s age, gender, ethnicity, body mass index (BMI), height, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), serum anion gap (SAP), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, serum creatinine (Scr), glucose, serum sodium, serum potassium, hematocrit, hemoglobin (Hb), platelet (Plt), red blood cell (RBC), C reactive protein (CRP), length of stay (LOS), albumin, lactic acid, white blood cell (WBC), N terminal pro B type natriuretic peptide (NT-proBNP), Simplified Acute Physiology Score (SAPS) II, sequential organ failure assessment (SOFA) score, and history of drug use of cardiotonic, nitro-glycerine, furosemide, hypoglycaemic, and infection-fighting. In addition, we also collected patient-related complications such as chronic obstructive pulmonary disease (COPD), hypertension, diabetes mellitus (DM), malignancy, respiratory failure (RF), septicaemia, ventricular fibrillation (VF), atrial fibrillation (AF), liver cirrhosis, acute myocardial infarction (AMI), chronic kidney disease (CKD). The mean lactic acid levels throughout hospitalization were utilized and the other blood test results were all the results of the patient’s initial examination in the ICU. When patients were hospitalized in the ICU more than once, the clinical data from the initial admission were used. In addition, according to the above inclusion and exclusion criteria, we enrolled 322 patients with AHF in the Intensive Care Unit of the Affiliated Hospital of Xuzhou Medical University.

2.3. Grouping and the End-Point. AHF patients were grouped according to survivors and deaths. The end-point was defined as in-hospital all-cause death that occurred in patients with AHF.

2.4. Statistical Analyses. Continuous variables were represented as mean ± standard deviation or median (25th quartile, 75th quartile) and categorical variables are presented as a percentage. Continuous variables were compared between groups using the T-test and Wilcoxon test, and categorical comparisons between groups were performed using the X2 test. Model 1 was not adjusted for variables. Model 2 was adjusted for age, gender, ethnicity. Model 3 was adjusted for age, ethnicity, BMI, weight, SBP, the history of AF, liver cirrhosis, AMI, CKD, RF, COPD, VF, DM, and septicemia, SAP, bicarbonate, BUN, serum calcium, serum creatinine, glucose, hematocrit, Hb, Plt, RBC, CRP, LOS, albumin, WBC, NT-proBNP, cardiotonic drugs, nitroglycerine drugs, furosemide drugs, infection-fighting drugs, SAPS II, and SOFA score. The restricted cubic spline (RCS) was used to evaluate the association between lactic acid and in-hospital all-cause mortality and the area under the receiver operating characteristic curve (AUC) was performed to assess the predictive value of lactic acid on the risk of in-hospital death. The subgroup analysis was performed by stratified multivariate logistic regression analysis under different COPD, hypertension, DM, RF, septicemia, VF, AF, AMI, and CKD. The purpose of mediation analysis is to determine which factors play a mediating role in the relationship between the exposure and the disease. All statistical analyses were performed using the software Stata 15 and R 4.13. All P value < 0.05 was significant.
3. Results

3.1. Baseline Characteristics. According to inclusion and exclusion criteria, this study included a total of 7558 AHF patients, with 6792 patients in the survival group and 766 patients in the death group. There is a flow diagram for our screening and grouping study shown in Figure 1. Compared with the survival group, patients in the death group were older and more likely to have liver cirrhosis, AMI, CKD, malignancy, RF, COPD, DM, and sepsicaemia, but less likely to have hypertension. In addition, the death group had lower levels of SBP, bicarbonate, calcium, hematocrit, RBC, hemoglobin, platelets and albumin, higher levels of SAP, glucose, CRP, BUN, Scr, WBC, NT-proBNP, SAPS score II and SOFA score, and longer LOS. Meanwhile, patients in death group also were easier to use cardiotropic drugs, vasoactive drugs, and infection-fighting drugs (P < 0.05, Table 1). The basic characteristics of the 322 participants from ICU of the Affiliated Hospital of Xuzhou Medical University are shown in Supplementary Table 1.

3.2. Association between Lactic Acid and the Risk of In-Hospital All-Cause Death. In a fully adjusted model III, compared with the lowest quartiles, the odds ratios (ORs) with 95% confidence intervals (CIs) for in-hospital all-cause death across the quartiles were 1.46 (1.07–2.00), 1.48 (1.09–2.00), and 2.36 (1.73–3.22) for lactic acid (Table 2). The RCS also showed a linear relationship and a positive correlation between lactic acid and in-hospital all-cause mortality (Figure 2). Using data from patients with AHF in ICU of the Affiliated Hospital of Xuzhou Medical University for validation, we found that the ORs with 95% CIs for in-hospital all-cause death across the quartiles were 0.52 (0.31, 0.87), 0.73 (0.43, 1.22), and 1.13 (0.68, 1.86) for lactic acid, compared with the lowest quartiles (Supplementary Table II). Meanwhile, there was also a linear correlation between lactic acid and in-hospital all-cause mortality (Supplementary Figure 1).

3.3. Diagnostic Value of Lactic Acid. As illustrated in Figure 3(a), the receiver operator characteristic curve constructed by the indicator variable lactic acid was able to predict in-hospital all-cause mortality and the AUC was 0.616 (sensitivity: 52.22% and specificity: 63.35%). The AUC of the lactic acid plus the SAPS II for the diagnosis of in-hospital all-cause death was 0.696, and the sensitivity and specificity were 61.88% and 65.89%, respectively. In addition, the AUC of the SOFA score in predicting the risk of in-hospital death was 0.646, while the AUC of lactic acid combined with the SOFA score was 0.661 (Figure 3(b)).

3.4. Subgroup Analysis. The present study based on a subgroup analysis of COPD, DM, hypertension, RF, sepsicaemia, VF, AF, AMI, and CKD, showed the relationship between arterial blood lactic acid and in-hospital all-cause death. Among subgroups, RF interacted with the association between arterial blood lactic acid and in-hospital all-cause death. Among subgroups, RF interacted with the association between arterial blood lactic acid and in-hospital all-cause death (P for interaction <0.05). Except for the subgroup of RF, the interaction of arterial blood lactic acid for COPD, DM, hypertension, sepsicaemia, VF, AF, AMI, and CKD with in-hospital all-cause death were not significant (Table 3).

3.5. Association between NT-proBNP, Lactic Acid, and the Risk of In-Hospital All-Cause Death. In the full adjusted multivariate logistic regression model, NT-proBNP was an independent predictor of in-hospital all-cause death and compared with the lowest quartile, the ORs with 95% CIs for
association of NT-proBNP with in-hospital all-cause death in the fourth quartiles was 13.39 (9.52–18.83) ($P < 0.001$) (Table 4). The correlation heatmap of NT-proBNP, lactic acid, and in-hospital all-cause death revealed that NT-proBNP was positively related with lactic acid ($r = 0.07$) and NT-proBNP were positively related with in-hospital all-cause mortality ($r = 0.18$) (Figure 4(a)). The RSC showed an inverse L-shaped curve relationship between NT-proBNP and in-hospital all-cause mortality (Figure 4(b)). Mediation analysis was undertaken to assess if the association between NT-proBNP and in-hospital all-cause death was mediated by lactic acid. The NT-proBNP was estimated to explain 3.74%
of the association between the lactic acid levels and in-hospital all-cause death (IE: $\beta = 0.001132$, $P < 0.001$; TE: $\beta = 0.029307$, $P < 0.001$; and DE: $\beta = 0.028176$, $P < 0.001$) (Figure 4(c)).

4. Discussion

AHF is a group of clinical syndromes characterized by abnormal cardiac structure and function, resulting in a sharp decline in cardiac displacement, hypoperfusion of tissues and organs, and acute blood stasis, with higher mortality and rehospitalization rates than that of chronic heart failure [12]. Lactic acid levels in the circulation are an important indicator of the availability of oxygen to the tissues, metabolism, and perfusion of the body’s cells [13]. A rise in arterial blood lactic acid concentrations occurs when the body is under oxygen-depleted conditions. As a result, the arterial blood lactic acid levels may be utilized in clinical practice to evaluate the microcirculation function of tissues and organs [14]. Findings from this study show that high lactic acid levels are a significant risk factor for in-hospital all-cause mortality in patients with AHF. Our results are consistent with previous studies, suggesting that arterial blood lactic acid concentration plays an important role in determining the prognosis of heart failure [5].

Lactic acid levels are associated with the prognosis of a variety of diseases [15–17]. We performed a subgroup analysis by disease type, allowing for possible interference from other comorbidities. Finally, elevated lactic acid levels were linked with AHF mortality independent of the presence or absence of COPD, DM, hypertension, RF, septicaemia, VF, AF, AMI, and CKD. Notably, lactic acid levels in the first three quartiles were not significantly associated with all-cause mortality in patients without respiratory failure,
whereas there was a significant association between lactic acid levels and mortality in patients with respiratory failure. Previous studies have demonstrated that lactic acid levels are associated with outcomes in patients with RF [18]. This suggests that the prognosis of respiratory failure is more sensitive to arterial lactic acid levels than AHF, however, after the exclusion of RF, arterial lactic acid at Q4 levels is still significantly associated with all-cause death in AHF. For this reason, we expected that higher lactic acid levels were related to an increased risk of all-cause mortality within 28 days of admission for AHF patients.

Patients with AHF are unable to provide appropriate oxygenation and perfusion of tissues and organs owing to infection, decreased cardiac function, coronary artery stenosis, and other factors, increasing in anaerobic glycolysis and lactic acid build-up [19]. Narang et al. revealed that the cardiac index decreases when lactic acid levels rise in individuals with acute decompensated heart failure [7]. Li et al. found that as lactic acid levels climbed, inhospital mortality in patients with heart failure increased proportionately [20]. Kawase et al. discovered that blood lactic acid levels were linked to in-hospital mortality in patients with acute heart failure without acute coronary syndrome, and that serum lactic acid levels might assist in predicting the risk of early death in individuals with acute decompensated heart failure [21]. In addition, lactic acid levels have been proven to be an independent predictor of death in hospitalized patients with heart failure. When the lactic acid levels in acutely decompensated heart failure patients exceed 3.2 mmol/L, the hospital mortality rate increases [22, 23]. Once significant amounts of blood lactic acid and its metabolites are stored in the body, patients will gradually progress into severe metabolic acidosis, which will eventually result in PH decline, hyperkalaemia, and a decrease in the ventricular fibrillation threshold, further increasing the incidence of sudden cardiac death [24]. In the study of Kapur et al. lactic acid levels were also added to the classification criteria for cardiogenic shock. Therefore, we speculate that blood lactic acid is a very useful clinical parameter for assessing the severity and prognosis of AHF [25]. The association between NT-proBNP and in-hospital all-cause rate was finally identified as a nearly inverse L-shaped curve. In addition, the effect of lactic acid on in-hospital all-cause mortality was influenced by NT-proBNP. As mentioned above, higher lactic acid concentrations were associated with higher in-hospital all-cause mortality in patients with AHF. A recent

\[ \text{Figure 3: Receiver operating characteristic curve for predicting the risk of in-hospital all-cause death in patients with acute heart failure. (a), The } \text{AUC of lactic acid} = 0.616, \text{with a sensitivity of} 52.22\% \text{and a specificity of} 63.35\%. \text{The AUC of SAPS II} = 0.681, \text{with a sensitivity of} 67.75\% \text{and a specificity of} 57.80\%. \text{The AUC of lactic acid combined with SAPS II} = 0.696, \text{with a sensitivity of} 61.88\% \text{and a specificity of} 65.89\%. (b). The AUC of SOFA score} = 0.646, \text{with a sensitivity of} 64.60\% \text{and a specificity of} 63.74\%. \text{The AUC of lactic acid combined with SOFA score} = 0.661, \text{with a sensitivity of} 76.37\% \text{and a specificity of} 48.13\%. \text{Note: The x axis represents the false-positive rate, while the y axis shows the true-positive rate. Abbreviations: ROC, Receiver operating characteristic; AUC, the area under ROC curve; SAPS II, Simplified acute physiology score II; and SOFA, Sequential organ failure assessment.} \]
study showed that NT-proBNP is independent predictors of all-cause and cardiovascular-related mortality in patients with acute decompensated heart failure [26]. Therefore, further research is needed to determine how lactic acid and BNP are related.

In conclusion, it is important to note that in patients with AHF, dynamic arterial blood lactic acid levels, which may help determine the illness severity and prognosis, can be found. In addition, the study had a number of flaws. To begin with, this is a retrospective study, which creates a bias in the selection of subjects. Second, the sample size was not large enough, especially for the death group. After the subgroup analysis, the sample size of each subgroup was different, for the analysis of some concomitant diseases, the sample size

\[\text{Table 3: Subgroup analysis for the levels of lactic acid predicting in-hospital mortality.}\]

| Variables | Q1 | Q2 | Q3 | Q4 | \(P\) for interaction |
|-----------|----|----|----|----|------------------------|
| COPD      |    |    |    |    |                        |
| No        | Ref. | 1.59 (1.20–2.11) *** | 1.74 (1.31–2.30) *** | 2.93 (2.23–3.84) *** | 0.201 |
| Yes       | Ref. | 1.74 (0.89–3.39) | 1.93 (0.98–3.80) | 1.76 (0.86–3.61) |                        |
| DM        |    |    |    |    |                        |
| No        | Ref. | 1.54 (1.16–2.05) *** | 1.63 (1.23–2.17) ** | 2.60 (1.97–3.43) *** | 0.856 |
| Yes       | Ref. | 2.02 (1.05–3.86) * | 2.44 (1.27–4.69) ** | 3.55 (1.85–6.78) *** |                        |
| Hypertension |    |    |    |    |                        |
| No        | Ref. | 1.64 (1.26–2.15) *** | 1.85 (1.42–2.41) *** | 2.76 (2.13–3.58) *** | 0.777 |
| Yes       | Ref. | 1.39 (0.48–4.03) | 0.51 (0.13–1.96) | 2.59 (0.91–7.39) |                        |
| RF        |    |    |    |    |                        |
| No        | Ref. | 1.14 (0.73–1.82) | 0.97 (0.61–1.57) | 2.17 (1.43–3.38) *** | 0.030 |
| Yes       | Ref. | 1.99 (1.44–2.78) *** | 2.72 (1.99–3.82) *** | 4.66 (3.35–6.57) *** |                        |
| Septicaemia |    |    |    |    |                        |
| No        | Ref. | 1.66 (1.26–2.21) *** | 1.73 (1.31–2.30) *** | 2.57 (1.96–3.41) *** | 0.133 |
| Yes       | Ref. | 1.47 (0.74–3.04) | 1.98 (1.03–4.02) | 3.56 (1.93–7.03) *** |                        |
| VF        |    |    |    |    |                        |
| No        | Ref. | 1.79 (1.37–2.37) *** | 2.00 (1.53–2.64) *** | 2.94 (2.26–3.87) *** | 0.437 |
| Yes       | Ref. | 1.47 (0.74–3.04) | 1.98 (1.03–4.02) | 3.56 (1.93–7.03) *** |                        |
| AF        |    |    |    |    |                        |
| No        | Ref. | 2.01 (1.35–3.05) *** | 1.83 (1.21–2.82) ** | 3.30 (2.24–4.98) *** | 0.129 |
| Yes       | Ref. | 1.25 (0.89–1.76) | 1.47 (1.06–2.07) * | 2.16 (1.56–3.04) *** |                        |
| AMI       |    |    |    |    |                        |
| No        | Ref. | 1.64 (1.24–2.17) *** | 1.67 (1.26–2.22) *** | 2.54 (1.94–3.36) *** | 0.321 |
| Yes       | Ref. | 1.28 (0.64–2.76) | 2.03 (1.02–4.34) * | 3.29 (1.69–6.93) *** |                        |
| CKD       |    |    |    |    |                        |
| No        | Ref. | 1.59 (1.12–2.31) * | 1.67 (1.17–2.42) *** | 2.70 (1.91–3.89) ** | 0.660 |
| Yes       | Ref. | 1.69 (1.17–2.47) *** | 1.93 (1.34–2.83) *** | 2.83 (1.99–4.11) *** |                        |

Abbreviation: Q1, 0.3–1.1 mmol/L; Q2, 1.1–1.6 mmol/L; Q3, 1.6–2.3 mmol/L; and Q4, 2.3–4.3 mmol/L. ***\(P<0.001\), **\(P<0.01\), and *\(P<0.05\); Model 1 was not adjusted for variables. Model 2 was adjusted for age, sex, ethnicity. Model 3 was adjusted for age, ethnicity, body mass index, weight, systolic blood pressure, the history of atrial fibrillation, liver cirrhosis, acute myocardial infarction, chronic kidney disease, respiratory failure, chronic obstructive pulmonary disease, ventricular fibrillation, diabetes mellitus, septicaemia, anion gap, bicarbonate, blood urea nitrogen, calcium, serum creatinine, glucose, hematocrit, hemoglobin, platelet, red blood cells, C reactive protein, length of stay, albumin, white blood cells, N terminal pro B type natriuretic peptide, cardiotonic drugs, nitro-glycerine drugs, furosemide drugs, infection-fighting drugs, Simplified Acute Physiology Score II, and sequential organ failure assessment.

\[\text{Table 4: Association between NT-proBNP and the risk of in-hospital deaths.}\]

| NT-proBNP | Model 1 | Model 2 | Model 3 |
|-----------|---------|---------|---------|
| Q1, pg/ml | Ref.    | Ref.    | Ref.    |
| Q2, pg/ml | 0.66 (0.44–1.01) * | 0.62 (0.41–0.95) * | 0.40 (0.25–0.64) *** |
| Q3, pg/ml | 1.09 (0.75–1.58) | 0.98 (0.67–1.42) | 0.71 (0.47–1.07) ** |
| Q4, pg/ml | 16.01 (12.05–21.27) *** | 14.59 (10.96–19.42) *** | 13.39 (9.52–18.83) *** |

Abbreviation: NT-proBNP, N terminal pro B type natriuretic peptide; Q1, 122–3589 pg/ml; Q2, 3590–8367 pg/ml; Q3, 8368–11382 pg/ml; Q4, 11383–52201 pg/ml. ***\(P<0.001\), **\(P<0.01\), *\(P<0.05\); Model 1 was not adjusted for variables. Model 2 was adjusted for age, sex, ethnicity. Model 3 was adjusted for age, ethnicity, body mass index, weight, systolic blood pressure, the history of atrial fibrillation, liver cirrhosis, acute myocardial infarction, chronic kidney disease, respiratory failure, chronic obstructive pulmonary disease, ventricular fibrillation, diabetes mellitus, and septicaemia, anion gap, bicarbonate, blood urea nitrogen, serum calcium, serum creatinine, glucose, hematocrit, hemoglobin, platelet, red blood cells, C reactive protein, length of stay, albumin, white blood cells, lactic acid, cardiotonic drugs, nitro-glycerine drugs, furosemide drugs, infection-fighting drugs, simplified Acute Physiology Score II, and sequential organ failure assessment.
was too small to produce potential bias, and our results may have been impacted by other unknown variables, even though we adjusted for certain factors.

5. Conclusion

The levels of arterial blood lactic acid were an independent predictor of all-cause death of admission for AHF patients in the ICU. The combination of lactic acid and SAPS II may increase the accuracy of predicting the likelihood of in-hospital all-cause death in AHF patients. There was a positive relationship between lactic acid and in-hospital all-cause death was mediated by NT-proBNP.

Data Availability

The MIMIC-IV database is available in the PhysioNet (https://physionet.org/content/mimiciv/0.4/), and the data can also be obtained from the corresponding authors upon reasonable request.
Ethical Approval

The MIMIC-IV database was approved by the Institutional Review Boards (IRB) of the Massachusetts Institute of Technology, and the informed consent has been waived as they do not contain protected health information.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

Weiwei Hu and Xiaotong Wang contributed to hypothesis development and manuscript preparation. Yang Zhang contributed to study design. Lei Yuan and Xianliang Yan undertook data collection and statistical analysis. Baobei Zhang and Wenjing Zhao made great contributions to charts modifications and the full-text format adjustments. Weiwei Hu and Yali Chao drafted and revised the manuscript. All authors approved the final draft of the manuscript for publication. Weiwei Hu, Lei Yuan, and Xiaotong Wang contributed equally to this work.

Acknowledgments

Thanks to Zhang Jing (Shanghai Tongren Hospital) for his work on the Mimic database. This study was funded by the Key Research and Development Plan of Xuzhou, Jiangsu Province (KC17172) to Yali Chao.

Supplementary Materials

Supplementary Figure 1: restricted cubic spline plots of associations between lactic acid levels and in-hospital all-cause mortality. Supplementary Table 1: baseline characteristics of the AHF patients on admission. Supplementary Table 2: association between lactic acid levels and the risk of in-hospital mortality. (Supplementary Materials)

References

[1] C. Peña-Gil, V. González-Salvado, and J. Figueras-Bellot, “Acute heart failure. The quintessential cardiac emergency,” Revista espanola de cardiology (English ed), vol. 75, pp. 9–11, 2021.
[2] T. S. Metkus, J. Lindsley, L. Fair et al., “Quality of heart failure care in the intensive care unit,” Journal of Cardiac Failure, vol. 27, no. 10, pp. 1111–1125, 2021.
[3] G. C. Fonerow, K. F. Adams, W. T. Abraham, C. W. Yancy, and W. J. Boscardin, “Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis,” JAMA, vol. 293, no. 5, pp. 572–580, 2005.
[4] P. Llacé, M. Á Gallardo, P. Palau et al., “Comparison between CA125 and NT-proBNP for evaluating congestion in acute heart failure,” Medicina Clinica, vol. 156, no. 12, pp. 589–594, 2021.
[5] F. di Grezia, E. A. di Panzillo, S. Russo et al., “Prognostic role of lactate on mortality in younger and older patients with cardio-respiratory failure admitted to an acute intensive care unit,” Aging Clinical and Experimental Research, vol. 28, no. 3, pp. 407–412, 2016.
[6] R. Zymlinski, J. Biegus, M. Sokolski et al., “Increased blood lactate is prevalent and identifies poor prognosis in patients with acute heart failure without overt peripheral hypoperfusion,” European Journal of Heart Failure, vol. 20, no. 6, pp. 1011–1018, 2018.
[7] N. Narang, M. Dela Cruz, T. Imamura et al., “Discordance between lactic acidemia and hemodynamics in patients with advanced heart failure,” Clinical Cardiology, vol. 44, no. 5, pp. 636–645, 2021.
[8] H. B. Cetinkaya and H. Gunes, “Use of shock index and lactate to predict mortality in acute heart failure patients in emergency department,” Journal of the College of Physicians and Surgeons Pakistan: JCPSP, vol. 31, no. 3, pp. 262–266, 2021.
[9] H. Uyar, E. Yesil, M. Karadeniz et al., “The effect of high lactate level on mortality in acute heart failure patients with reduced ejection fraction without cardiogenic shock,” Cardiovascular Toxicology, vol. 20, no. 4, pp. 361–369, 2020.
[10] A. E. W. Johnson, D. J. Stone, L. A. Celli, and T. J. Pollard, “The MIMIC Code Repository: enabling reproducibility in critical care research,” Journal of the American Medical Informatics Association, vol. 25, no. 1, pp. 32–39, 2018.
[11] A. L. Goldberger, L. A. N. Amaral, L. Glass et al., “PhysioBank, PhysioToolkit, and PhysioNet: components of a new research resource for complex physiologic signals,” Circulation, vol. 101, no. 23, pp. E215–E220, 2000.
[12] R. Brandon Stacey, M. Meng, G. V. Byrum Iii et al., “Clinical outcomes in different types of aortic stenosis as assessed by Doppler echocardiography,” Journal of Heart Valve Disease, vol. 25, no. 6, pp. 672–678, 2016.
[13] A. Fizel and A. Fizelova, “Cardiac hypertrophy and heart failure: dynamics of changes in high-energy phosphate compounds, glycolen and lactic acid,” Journal of Molecular and Cellular Cardiology, vol. 2, no. 3, pp. 187–192, 1971.
[14] K. Wasserman, “The peripheral circulation and lactic acid metabolism in heart, or cardiovascular, failure,” Circulation, vol. 80, no. 4, pp. 1084–1086, 1989.
[15] M. Kahyaoglu, A. Karaduman, Ç Geçmen et al., “Serum lactate level may predict the development of acute kidney injury in acute decompensated heart failure,” Turk Kardiyojoloji Dernegi Arsivi, vol. 48, no. 7, pp. 683–689, 2020.
[16] F. Gao, X. L. Huang, M. X. Cai et al., “Prognostic value of serum lactate kinetics in critically ill patients with cirrhosis and acute-on-chronic liver failure: a multicenter study,” Aging (Albany NY), vol. 11, no. 13, pp. 4446–4462, 2019.
[17] G. M. Kubiak, W. Jacheć, C. Wojciechowska et al., “Handheld capillary blood lactate analyzer as an accessible and cost-effective prognostic tool for the assessment of death and heart failure occurrence during long-term follow-up,” Disease Markers, vol. 2016, pp. 1–7, 2016.
[18] Y. Lu, H. Guo, X. Chen, and Q. Zhang, “Association between lactate/albumin ratio and all-cause mortality in patients with acute respiratory failure: a retrospective analysis,” PLoS One, vol. 16, no. 8, Article ID e0255744, 2021.
[19] S. M. Forsythe and G. A. Schmidt, “Sodium bicarbonate for the treatment of lactic acidosis,” Chest, vol. 117, no. 1, pp. 260–267, 2000.
[20] F. Li, H. Xin, J. Zhang, M. Fu, J. Zhou, and Z. Lian, “Prediction model of in-hospital mortality in intensive care unit patients with heart failure: machine learning-based, retrospective analysis of the MIMIC-III database,” BMJ Open, vol. 11, no. 7, Article ID e044779, 2021.
[21] T. Kawase, M. Toyofuku, T. Higashihara et al., “Validation of lactate level as a predictor of early mortality in acute decompensated heart failure patients who entered intensive care unit,” *Journal of Cardiology*, vol. 65, no. 2, pp. 164–170, 2015.

[22] J. Biegus, R. Zymliński, M. Sokolski, E. A. Jankowska, W. Banasiak, and P. Ponikowski, “Elevated lactate in acute heart failure patients with intracellular iron deficiency as identifier of poor outcome,” *Kardiologia Polska*, vol. 77, no. 3, pp. 347–354, 2019.

[23] J. Biegus, R. Zymliński, M. Sokolski, P. Gajewski, W. Banasiak, and P. Ponikowski, “Clinical, respiratory, haemodynamic, and metabolic determinants of lactate in heart failure,” *Kardiologia Polska*, vol. 77, no. 1, pp. 47–52, 2019.

[24] P. Safaei, G. Khadjeh, M. R. Tabandeh, and K. Asasi, “Role of cardiac hypoxia in the pathogenesis of sudden death syndrome in broiler chickens - a metabolic and molecular study,” *Acta Veterinaria Hungarica*, vol. 69, no. 1, pp. 43–49, 2021.

[25] N. K. Kapur, M. Kanwar, S. S. Sinha et al., “Criteria for defining stages of cardiogenic shock severity,” *Journal of the American College of Cardiology*, vol. 80, no. 3, pp. 185–198, 2022.

[26] P. L. Santaguida, A. C. Don-Wauchope, M. Oremus et al., “BNP and NT-proBNP as prognostic markers in persons with acute decompensated heart failure: a systematic review,” *Heart Failure Reviews*, vol. 19, no. 4, pp. 453–470, 2014.