RESEARCH

Open Access



The impact of the lactate-to-albumin ratio on long-term mortality risk in patients with severe heart failure and type 2 diabetes

Yanyan Dong^{1,2}, Xiaoyu Shi¹, Chenghao Wang³, Yinqin Hu⁴, Junxiong Li⁵, Hong Luo⁶, Maoping Zhu⁷, Fan Hu⁸ and Quangen Chu^{1,2*}

Abstract

Background Heart failure (HF) combined with diabetes is highly prevalent and is associated with more severe left ventricular dysfunction and a higher mortality rate. Early prediction of prognosis in such patients is crucial. This study aims to investigate the relationship between the lactate-to-albumin ratio (LAR) and outcomes in critically ill patients diagnosed with HF and diabetes.

Methods Data on critically ill HF patients with diabetes were retrospectively collected from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database. Restricted cubic spline (RCS) analysis identified a threshold value of 0.44, dividing patients into low-LAR (< 0.44) and high-LAR (\geq 0.44) groups. Least Absolute Shrinkage and Selection Operator (LASSO) regression with tenfold cross-validation identified variables associated with mortality. RCS, Kaplan–Meier curves, and Cox regression analyses were employed to evaluate the association between LAR and mortality. Subgroup analyses were conducted to validate the robustness of the findings.

Results A total of 3,774 patients were included, with a determined LAR cutoff value of 0.44. RCS analysis revealed a positive correlation between LAR and all-cause mortality at 90 days, 180 days, and 1 year. Cox regression analysis showed that both low-LAR and high-LAR groups were independent risk factors for all-cause mortality at 90 days, 180 days, and 1 year in HF patients with diabetes (*P* < 0.05). Kaplan–Meier survival curves demonstrated that the cumulative survival rates at 90 days, 180 days, and 1 year were lower in the low-LAR group compared to the high-LAR group. Subgroup analyses confirmed the stability of the association between LAR and all-cause mortality at all time points.

Conclusion In summary, LAR is a reliable and independent predictor of increased mortality in critically ill HF patients with diabetes. However, additional comprehensive prospective studies are needed to validate these findings.

Keywords LAR, Heart failure, Diabetes, Prognosis, MIMIC-IV

*Correspondence: Quangen Chu chuquangen@ahtcm.edu.cn Full list of author information is available at the end of the article



© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

Introduction

Heart failure (HF) refers to a clinical syndrome caused by structural and functional abnormalities of the myocardium, resulting in impaired pumping and filling capacity of the heart. It is a significant public health concern, particularly among the elderly, with a prevalence exceeding 10% in individuals over 70 years old [1]. Heart failure in older adults is often caused by coronary artery disease, degenerative valvular disease, or hypertension. Common symptoms include shortness of breath, fatigue, and fluid retention. Severe heart failure is diagnosed when symptoms persist even at rest [2]. Advanced heart failure is characterized by significant myocardial remodeling, with medication offering limited benefit in slowing disease progression. Older patients with compromised cardiovascular function and reduced heart performance face higher mortality rates during hospitalization [3]. Chronic conditions such as hypertension, hyperglycemia, and severe metabolic disorders can lead to advanced heart failure. Patients may experience a sudden decrease in cardiac output, reduced effective circulatory volume, activation of neuroendocrine and renal pathways, and kidney failure, contributing to multi-organ dysfunction and worse prognoses [4]. Many heart failure patients present with comorbid conditions, with a significant proportion also having type 2 diabetes [5]. Heart failure patients with type 2 diabetes often develop kidney dysfunction earlier and have worse clinical outcomes [6]. Diabetes adversely affects myocardial function, leading to diabetic cardiomyopathy. Additionally, as diabetes is prevalent in middleaged and older adults, it is a key risk factor for coronary artery disease and other cardiac conditions [7]. Abnormal glucose metabolism has early detrimental effects on both macrovascular and microvascular systems, directly damaging myocardial cells and interstitium, accelerating atherosclerosis, and hastening the progression of heart failure [8]. Lactate serves as a sensitive marker of tissue hypoperfusion and cellular hypoxia [9]. Clinically, blood lactate levels are dynamically monitored to assess tissue perfusion, metabolism, and mitochondrial function [10]. Albumin, synthesized in the liver, plays a crucial role in binding and transport, maintaining plasma oncotic pressure, and mitigating inflammatory responses. It also protects against microcirculation and tissue damage associated with inflammation [11]. Lactate and albumin are readily obtainable clinical markers commonly used for prognostic evaluation in various diseases. Their ratio may hold even greater predictive value. Research has revealed that lactate and albumin levels can fluctuate in inflammatory diseases, with the lactate-to-albumin ratio emerging as a prognostic marker for critically ill ICU patients [12]. The lactate-to-albumin ratio has been shown to predict the occurrence of multiple organ dysfunction syndrome (MODS) [13]. Previous studies have demonstrated that the lactate-to-albumin ratio can predict short- and long-term mortality in critically ill heart failure patients [14]. However, its predictive value in severe heart failure patients with coexisting type 2 diabetes remains unclear. This study aims to evaluate the prognostic value of the lactate-to-albumin ratio in predicting long-term mortality risk in patients with severe heart failure and type 2 diabetes. By identifying a more effective biomarker for prognostic assessment, the study seeks to enhance diagnostic accuracy and prognostic evaluation, guide clinical management, and ultimately improve patient outcomes.

Methods

Source of data

This retrospective study utilized data from the publicly accessible Medical Information Mart for Intensive Care IV (MIMIC-IV, version 2.2) database. MIMIC-IV is an enhanced version of its predecessor, MIMIC-III, featuring updated data and modifications to table structures. The dataset includes clinical information on over 190,000 unique hospital admissions at Beth Israel Deaconess Medical Center (BIDMC) in Boston, Massachusetts, USA, between 2008 and 2019. The database provides comprehensive details on patient demographics, vital signs, medications, laboratory tests, surgical procedures, diagnoses, treatment plans, and survival outcomes. To access this data, we completed the National Institutes of Health (NIH) Human Research Participant Protection Training and passed the Collaborative Institutional Training Initiative (CITI) exam (ID: 13,921,063). Since the database does not contain any protected health information and all patient data is anonymized, a waiver of informed consent was granted.]

Study design and population

This study focused on patients with heart failure (HF) and type 2 diabetes (T2D) who were admitted to the intensive care unit (ICU) for the first time. A cohort of 6,686 patients with HF and T2D was identified using the search terms "Heart Failure" and "Type 2 Diabetes" within the International Classification of Diseases, Ninth (ICD-9) and Tenth Revision (ICD-10) diagnostic codes. Exclusion criteria were established to ensure data accuracy and relevance: (1) Multiple ICU admissions, with only the first admission included in the analysis; (2) Patients younger than 18 years old; (3) ICU stays of less than 24 h; (4) Data on patients' serum lactate or serum albumin at ICU admission were missing; (5) Missing outcome measures, including survival status at 90 days, 180 days, and 1 year. Based on these criteria, patients were categorized

into two groups according to the LAR index cutoff values for further analysis (Fig. 1).

Data extraction

Data were extracted from the MIMIC-IV database using PostgreSQL (version 16.3) and Structured Query Language (SQL). The following data were collected: (1) Demographic information: age, gender, race, marital status, and BMI; (2) Laboratory results from the first day of ICU admission, including serum calcium, albumin, lactate, creatinine, glucose, bilirubin, serum potassium, HbA1c, alanine aminotransferase, Aspartate Aminotransferase, white blood cells, lymphocytes, serum uric acid, and hemoglobin; (3) Vital signs: blood pressure, respiratory rate, body temperature, and heart rate; (4) Comorbidities: diabetes, hypertension, stroke, anemia, congestive heart failure, malignancies, ventricular fibrillation, atrial fibrillation, and hyperlipidemia; (5) Medications: aspirin, ACE inhibitors, ARBs, β -blockers, metformin, insulin, α -glucosidase inhibitors, thiazolidinediones, and insulin secretagogues; (6) Scoring systems: Glasgow Coma Scale (GCS), O'Neill Acute Severity Index Score (OASIS), Simplified Acute Physiology Score II (SAPS II), Systemic Inflammatory Response Syndrome (SIRS), Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation III (APS III); (7) Interventions: mechanical ventilation and continuous renal replacement therapy.

Outcomes

This study focused on evaluating all-cause mortality outcomes in heart failure patients with comorbid type 2 diabetes from the MIMIC-IV database at different time intervals. The primary outcome was defined as long-term all-cause mortality at 180 days. Secondary outcomes included long-term all-cause mortality at 90 days and 1 year.

LAR Composite Index calculation

The formula for calculating LAR is as follows: Lac/Alb.

Statistical analysis

In the baseline characteristics table, the Shapiro–Wilk test was used to assess the distribution of continuous variables. If they followed a normal distribution, they are presented as mean \pm SD; if they did not, they are presented as median [inter quartile range (IQR)]. The comparison of continuous variables was performed using either the Student's t-test or the Mann–Whitney test, depending on their distribution. Categorical variables are presented as frequencies and percentages. Significant



Fig. 1 Study Flowchart. *A total of 6,686 patients were diagnosed with heart failure and diabetes. MIMIC-IV: Medical Information Mart for Intensive Care IV; ICU: Intensive Care Unit

differences were assessed using the Pearson chi-square test or Fisher's exact test.

Kaplan-Meier (K-M) curves were used to stratify the evaluation of the occurrence of outcome events based on LAR. LASSO regression with tenfold cross-validation was performed to further identify variables associated with 1-year, 90-day, and 180-day outcomes. The variables selected by LASSO analysis were included in Cox regression analysis to examine the relationship between LAR and mortality at 180 days, 90 days, and 1 year. The final model variables were selected based on the availability of event data. Model 1 was unadjusted, Model 2 was adjusted for age, BMI, and marital status, and Model 3 was further adjusted for AST, calcium, white blood cell count, atrial fibrillation, stroke, angiotensin-converting enzyme inhibitor, continuous renal replacement therapy, mechanical ventilation, Acute Physiology and Chronic Health Evaluation III, Simplified Acute Physiology Score II, and Sequential Organ Failure Assessment. Additionally, restricted cubic splines (RCS) were used to examine LAR as a continuous variable to elucidate the relationship between this index and the risk of outcome events. In cases of nonlinear correlation, recursive algorithms identified the threshold point between LAR and longterm all-cause mortality. Furthermore, stratified analyses and interaction tests were performed based on age, gender, atrial fibrillation, heart failure, hyperlipidemia, hypertension, stroke, ventricular fibrillation, dapagliflozin, insulin therapy, alpha-glucosidase inhibitors, angiotensin II receptor blocker, beta-adrenergic blockers, angiotensin-converting enzyme inhibitor, metformin, thiazolidinediones, insulinotropic agents, continuous renal replacement therapy, and mechanical ventilation. All statistical analyses were performed using R software (version 4.3.1, Austria). All analyses were two-tailed, with p < 0.05 considered statistically significant.

Result

Baseline characteristics of study individuals

In this study, among the 6,686 heart failure patients with diabetes identified in the MIMIC-IV database, 3,774 met the inclusion criteria and were subsequently analyzed (the screening process is shown in Fig. 1).

The average age of the participants was 69 years (IQR: 61–77 years). Among the total sample, 2,135 were male patients, comprising 56.6% of the cohort, and 2,508 were Caucasian, making up 66.5%; 1,050 were single, comprising 27.8% of the cohort, 872 were divorced/ widowed, comprising 23.1% of the cohort, 1,852 were married, comprising 49.1% of the cohort; 2225 were have atrial fibrillation, comprising 59.0% of the cohort; 2983 were have hyperlipidemia, comprising 79.0% of the cohort; 2348 were have hypertension, comprising

62.2% of the cohort; 777 were have stroke, comprising 20.6% of the cohort; 104 were have ventricular fibrillation, comprising 2.76% of the cohort. The average CPR value was 0.44 (IQR: 0.32-0.62). (The baseline is shown in Table 1).

Cutoff values and RCS analysis

In the RCS analysis, a cutoff value of 0.44 for LAR was determined based on a hazard ratio (HR) of 1. The patients were then divided into two groups: low LAR (<0.44, n = 1899) and high LAR (≥ 0.44 , n = 1875). The results of the RCS analysis, shown in Fig. 2, indicated a general positive correlation between LAR and the risk of all-cause mortality at 90 days, 180 days, and 1 year (P for all < 0.001). Notably, there was a nonlinear association between LAR and 1-year all-cause mortality (P for nonlinear = 0.022), while no such nonlinear trend was observed for the 90-day and 180-day all-cause mortality risks (P for nonlinear > 0.05).

Association between LAR and clinical outcomes in patients with heart failure and diabetes

All variables from the baseline table were included in the LASSO regression analysis, with tenfold crossvalidation, resulting in a λ value of 0.0140222 (Figs. 3 and 4). A total of 15 prognostic-related covariates were selected, including age, BMI, marital status, AST, calcium, white blood cell count, atrial fibrillation, stroke, ACE inhibitors, CRRT, mechanical ventilation, APSIII, SAPSII, and SOFA. Figure 5.

To explore the independent effect of LAR on longterm all-cause mortality in patients with heart failure and diabetes, we used three Cox proportional hazards regression models (Table 2). In Model 1, no adjustments were made for covariates. Model 2 adjusted for age, BMI, and marital status, while Model 3 further adjusted for AST, calcium, white blood cell count, atrial fibrillation, stroke, ACE inhibitors, CRRT, mechanical ventilation, APSIII, SAPSII, and SOFA.

In Model 3, we found that the hazard ratios (HR) and 95% confidence intervals (CI) for all-cause mortality at 90 days, 180 days, and 1 year were 1.27 (1.13–1.43), 1.25 (1.12–1.39), and 1.22 (1.10–1.35), respectively, with P-values all < 0.001, indicating statistically significant differences (Table 2).

We then used the low LAR group as a reference. The hazard ratios (HR) and 95% confidence intervals (CI) for all-cause mortality in the high LAR group at 90 days, 180 days, and 1 year were 1.24 (1.09-1.41), 1.23 (1.10-1.37), and 1.23 (1.12-1.36), respectively,

Table 1 Baseline data

	[ALL]	< 0.44	>=0.44	P.overall
	N=3774	N=1899	N=1875	
Status-90d	0.27 (0.44)	0.24 (0.43)	0.29 (0.45)	0.001
Time-90d	90.0 [75.4;90.0]	90.0 [90.0;90.0]	90.0 [59.4;90.0]	< 0.001
Status-180d	0.34 (0.47)	0.32 (0.47)	0.36 (0.48)	0.004
Time-180d	180 [75.4;180]	180 [97.3;180]	180 [59.4;180]	0.001
Status-1 year	0.44 (0.50)	0.41 (0.49)	0.46 (0.50)	0.001
Time-1 year	365 [75.4;365]	365 [97.3;365]	365 [59.4;365]	< 0.001
Age(years)	69.0 [61.0;77.0]	69.0 [60.0;76.0]	70.0 [62.0;78.0]	< 0.001
Body Mass Index(BMI)	30.7 [26.2;36.2]	30.4 [26.1;36.0]	31.1 [26.2;36.3]	0.049
Gender:				0.683
Male	2135 (56.6%)	1081 (56.9%)	1054 (56.2%)	
Female	1639 (43.4%)	818 (43.1%)	821 (43.8%)	
Marital_status:				0.78
Single	1050 (27.8%)	529 (27.9%)	521 (27.8%)	
Divorced/Widowed	872 (23.1%)	430 (22.6%)	442 (23.6%)	
Married	1852 (49.1%)	940 (49.5%)	912 (48.6%)	
Race:			, , , , , , , , , , , , , , , , , , ,	0.158
White	2508 (66.5%)	1241 (65.4%)	1267 (67.6%)	
NoWhite	1266 (33.5%)	658 (34.6%)	608 (32.4%)	
Diastolic Blood Pressure	130 [120:145]	132 [120:148]	130 [118:142]	< 0.001
Systolic Blood Pressure	70.0 [62.0:80.0]	70.0 [62.5:80.0]	70.0 [61.0:80.0]	0.011
Serum Albumin (a/dl.)	3 80 [3 32:4 20]	4 00 [3 50:4 30]	3 60 [3 10:4 10]	< 0.001
Alanine Aminotransferase (ILI/I)	21 0 [15 0:33 0]	20.0 [15.0.30.0]	22.0 [16.0.37.0]	< 0.001
Aspartate Aminotransferase $(U /)$	24.0 [18.0:36.0]	23.0 [17.0.32.0]	26.0 [19.0:41.0]	< 0.001
Serum Bilirubin (mg/dl.)	0.50 [0.30:0.70]	0.40 [0.30:0.60]	0.50 [0.30:0.80]	< 0.001
Serum Calcium (mg/dL)	9 10 [8 50.9 40]	9 10 [8 60:9 50]	9.00 [8.40.9.40]	< 0.001
Serum Creatinine (mg/dL)	1 10 [0.90.1 60]	1 20 [0 90.1 70]	1 10 [0 90.1 60]	0.002
Easting Blood Glucose (mg/dL)	139 [107-196]	131 [104.182]	149 [112.210]	< 0.002
Hemoglobin Concentration (g/dL)	123 [108:136]	122[108.136]	125 [108.137]	0.13
Serum Lactate (mmol/L)	1 60 [1 20:2 20]	1 30 [1 00:1 50]	2 20 [1 90.2 90]	< 0.001
Lymphocyte (%)	186 [11.4.26.8]	199[130.274]	171 [950:259]	< 0.001
Serum Potassium (mEq.(1.)	4 30 [4 00:4 70]	4 30 [4 00:4 70]	4 40 [4 00:4 80]	0.059
White Blood Cell Count (K/ul.)	8 10 [6 50:10 4]	7 80 [6 30:9 50]	8.60 [6.70:11.6]	< 0.001
Atrial Fibrillation:	0.10 [0.50,10.7]	7.00[0.30,7.30]	0.00 [0.70,11.0]	0.263
No	1549 (41.0%)	762 (40.1%)	787 (42.0%)	0.205
Voc	2225 (59.0%)	1137 (50 0%)	1088 (58.0%)	
Hyperlinidemia	2223 (39.070)	1157 (55.576)	1000 (30.070)	0.023
No	791 (21.0%)	360 (10.4%)	122 (22 5%)	0.025
Vos	2083 (70.0%)	1530 (80.6%)	422 (22.370)	
Hypertension:	2903 (79.070)	1550 (00.070)	1455 (77.570)	0.013
No.	1426 (27.9%)	600 (25 00%)	746 (20,90%)	0.015
Voc	1420 (37.8%)	1210 (64 204)	1120 (60 20%)	
Stroke	2348 (02.2%)	1219 (04.2%)	1129 (00.2%)	0549
No.	2007 (70.4%)	1516 (70.90%)	1/01 (70.00%)	0.546
No	2997 (79.470)	1010(79.0%)	1401 (79.0%)	
Vontricular fibrillation:	/// (20.0%)	JOJ (ZU.Z%)	J94 (∠1.U%)	0 227
venucular iibriilation:	2670 (07 20/)	1052 (07 50/)	1010 (07 00/)	0.337
NU Voc	20/U (97.2%)	1032 (97.3%)	1010 (97.U%)	
	104 (2.70%)	4/ (2.4/%)	37 (3.04%)	1
Dapagiiiiozin:				I

Table 1 (continued)

	[ALL]	<0.44	>=0.44	P.overall
No	3773 (100.0%)	1898 (99.9%)	1875 (100%)	
Yes	1 (0.03%)	1 (0.05%)	0 (0.00%)	
Insulin Therapy:				0.021
No	96 (2.54%)	60 (3.16%)	36 (1.92%)	
Yes	3678 (97.5%)	1839 (96.8%)	1839 (98.1%)	
Alpha-glucosidase Inhibitors:				0.312
No	3759 (99.6%)	1889 (99.5%)	1870 (99.7%)	
Yes	15 (0.40%)	10 (0.53%)	5 (0.27%)	
Angiotensin II Receptor Blocker:				< 0.001
No	2593 (68.7%)	1214 (63.9%)	1379 (73.5%)	
Yes	1181 (31.3%)	685 (36.1%)	496 (26.5%)	
Beta-Adrenergic Blocker:				< 0.001
No	220 (5.83%)	72 (3.79%)	148 (7.89%)	
Yes	3554 (94.2%)	1827 (96.2%)	1727 (92.1%)	
Angiotensin-Converting Enzyme Inhibitor:				0.01
No	1599 (42.4%)	765 (40.3%)	834 (44.5%)	
Yes	2175 (57.6%)	1134 (59.7%)	1041 (55.5%)	
Metformin : No	3774 (100%)	1899 (100%)	1875 (100%)	1
Thiazolidinediones:				0.013
No	3658 (96.9%)	1827 (96.2%)	1831 (97.7%)	
Yes	116 (3.07%)	72 (3.79%)	44 (2.35%)	
Insulin Secretagogue:				1
No	3656 (96.9%)	1840 (96.9%)	1816 (96.9%)	
Yes	118 (3.13%)	59 (3.11%)	59 (3.15%)	
Continuous Renal Replacement Therapy:				0.064
No	3342 (88.6%)	1663 (87.6%)	1679 (89.5%)	
Yes	432 (11.4%)	236 (12.4%)	196 (10.5%)	
Mechanical Ventilation:				< 0.001
No	1343 (35.6%)	617 (32.5%)	726 (38.7%)	
Yes	2431 (64.4%)	1282 (67.5%)	1149 (61.3%)	
Acute Physiology and Chronic Health Evaluation III	46.0 [36.0;59.0]	46.0 [35.0;59.0]	47.0 [36.0;59.0]	0.539
Glasgow Coma Scale	15.0 [15.0;15.0]	15.0 [15.0;15.0]	15.0 [15.0;15.0]	0.007
O'Neill Acute Severity Index Score	2.00 [2.00;3.00]	2.00 [2.00;3.00]	3.00 [2.00;3.00]	0.003
Simplified Acute Physiology Score II	37.0 [30.0;45.0]	37.0 [29.0;45.0]	37.0 [30.0;45.0]	0.19
Systemic Inflammatory Response Syndrome	2.00 [2.00;3.00]	2.00 [2.00;3.00]	3.00 [2.00;3.00]	0.003
Sequential Organ Failure Assessment	5.00 [3.00;8.00]	5.00 [3.00;8.00]	5.00 [3.00;8.00]	0.071
LAR	0.44 [0.32;0.62]	0.32 [0.26;0.38]	0.62 [0.51;0.83]	< 0.001

* HR Hazard Ratio

with P-values all < 0.001, indicating statistically significant differences.

Survival analysis of LAR in patients with heart failure and diabetes

We conducted a Kaplan–Meier (K-M) curve analysis to assess the long-term survival of patients with heart failure and diabetes based on LAR. The results showed changes in all-cause mortality (ACM) at 90 days, 180 days, and 1 year between the high and low LAR groups (Fig. 4).

Notably, the long-term survival rate of patients in the low LAR group was higher than that of patients in the high LAR group, regardless of the risk of mortality at 90 days, 180 days, or 1 year. The corresponding P-values were as follows: primary outcome at 180 days: 0.0016; secondary outcomes at 90 days: 0.00074 and 1 year: 0.00043, all of which were statistically significant.



Fig. 2 RCS Curve of LAR and Long-term Mortality Risk. A. RCS Curve in 90-day; B. RCS Curve in 180-day; C. RCS Curve in 1-year



Fig. 3 LASSO Regression Analysis

Furthermore, we stratified LAR into quartiles and performed Kaplan–Meier (K-M) curve analysis. The results demonstrated that, irrespective of the time points at 90 days, 180 days, or 1 year, the survival rates of heart failure patients with diabetes were inversely proportional to LAR values, with statistically significant differences observed (P < 0.001) (Fig. 4).

Subgroup analysis

This study also performed stratified analysis and interaction tests based on variables such as age (≤ 65 or > 65), gender, atrial fibrillation, heart failure, hyperlipidemia, hypertension, stroke, ventricular fibrillation, dapagliflozin, insulin, alpha, ARBs, beta blockers, ACE inhibitors, metformin, thiazolidinediones, insulinotropic agents, CRRT, and mechanical ventilation (MV).

The results showed that, for the 90-day mortality risk, LAR interacted with gender, stroke, insulin, beta blockers, ACE inhibitors, thiazolidinediones, CRRT, and MV (interaction *P*-values < 0.05).

For the 180-day mortality risk, LAR interacted with age, gender, stroke, insulin, beta blockers, ACE inhibitors, thiazolidinediones, CRRT, and MV (interaction P-values < 0.05).

For the 1-year mortality risk, LAR interacted with age, gender, stroke, ACE inhibitors, CRRT, and MV (interaction *P*-values < 0.05).

Discussion

Diabetes is one of the common etiological factors of heart failure (HF) [15], and glucose metabolism abnormalities lead to microvascular damage, cardiomyocyte apoptosis, and cardiac fibrosis, which result in structural and functional changes in the heart [16]. Studies have shown that the prevalence of diabetes in heart failure patients is high [17] (Type 2 Diabetes Mellitus and Heart Failure, A Scientific Statement From the American Heart Association and Heart Failure Society of America), and patients with diabetes and HF show more severe left ventricular dysfunction and higher mortality rates [18]. This retrospective study provides strong evidence for the Lactate/



Fig. 4 Kaplan–Meier Curve of LAR and Long-term Mortality Risk. A. 90-day overall Kaplan–Meier curve; B. 180-day overall Kaplan–Meier curve; C.1-year overall Kaplan–Meier curve; D. 90-day subgroup Kaplan–Meier curve; B. 180-day subgroup Kaplan–Meier curve; C.1-year subgroup Kaplan–Meier curve; B. 180-day subgroup Kaplan–Meier curve; C.1-year subgroup Kaplan–Meier curve; B. 180-day subgroup Kaplan–Meier curve; C.1-year subgroup Kaplan–Meier curve; B. 180-day subgroup Kaplan–Meier curve; C.1-year subgroup Kaplan–Meier curve; B. 180-day subgroup Kaplan–Meier curve; C.1-year subgroup Kaplan–Meier curve; B. 180-day subgroup Kaplan–Meier curve; C.1-year subgroup Kaplan–Meier curve; B. 180-day subgroup Kaplan–Meier curve; C.1-year subgroup Kaplan–Meier curve; B. 180-day subgroup Kaplan–Meier curve; C.1-year subgroup Kaplan–Meier curve; B. 180-day subgroup Kaplan–Meier curve; C.1-year subgroup Kaplan–Meier curve; B. 180-day subgroup Kaplan–Meier curve; C.1-year subgroup Kaplan–Meier curve; B. 180-day subgroup Kaplan–Meier curve; C.1-year subgroup Kaplan–Meier curve; B. 180-day subgroup Kaplan–Meier curve; C.1-year subgroup Kaplan–Meier curve; B. 180-day subgroup Kaplan–Meier curve; B. 180-day subgroup Kaplan–Meier curve; B. 180-day subgroup Kaplan–Meier curve; C.1-year subgroup Kaplan–Meier curve; B. 180-day subgroup Kaplan–Meier curve; C.1-year subgroup Kaplan–Meier curve; B. 180-day subgroup Kaplan–Meier curve; C.1-year subgroup Kaplan–Meier curve; B. 180-day subgroup

Albumin Ratio (LAR) as a predictive factor for diabetes in combination with heart failure. It also establishes a critical threshold of LAR (0.44) for risk stratification in patients with diabetes and heart failure. The study results indicate that, compared to the low-LAR group, the longterm survival rate of patients with diabetes and heart failure in the high-LAR group significantly decreases. As LAR increases, the risk of all-cause mortality at 90 days, 180 days, and 1 year also increases. Notably, LAR shows a nonlinear correlation with the 1-year all-cause mortality risk.

The predictive ability of the Lactate-to-Albumin Ratio (LAR) is associated with lactate and albumin levels. Lactate is a product of anaerobic glycolysis of glucose in the body, primarily produced in skeletal muscles through glycolysis and pyruvate metabolism [19]. It is a sensitive marker of tissue perfusion levels and whether the body is in a hypoxic state [20]. Diabetes induces and promotes tissue hypoxia [21], which in turn promotes lactate production. Lactate is closely associated

with most cardiovascular diseases. After excluding confounding factors such as arteriosclerosis and insulin resistance, a study still found an independent correlation between elevated lactate levels at rest and heart failure, highlighting the critical role of lactate as a marker of reduced oxidative capacity in heart failure [22]. Serum albumin levels reflect the body's nutritional status and the extent of liver synthesis impairment. Furthermore, changes in vascular permeability and protein loss due to kidney dysfunction may also lead to lower albumin levels [23]. Albumin levels also represent the body's antioxidant capacity [24], as it can bind with metal ions like copper and zinc to inhibit their catalytic effects on free radicals, thereby reducing free radical production. Albumin also forms chelates with transition metals, preventing their reaction with oxygen and the generation of reactive oxygen species, thus exerting antioxidant effects. The thiol group on the cysteine residue (especially Cys-34) can bind with free radicals to neutralize their activity and protect cells from oxidative

Orwall9774•1 34(12.4)•1 23(1.4)•1 23(1.4)0.0010.011 <t< th=""><th>Variable</th><th>Count</th><th>90_day</th><th>OR.95.CI</th><th>P.for.interaction</th><th>180_0</th><th>day</th><th>OR.95.CI.1</th><th>P.for.interaction.1</th><th>1ye</th><th>ar</th><th>OR.95.CI.2</th><th>P.for.interaction.2</th></t<>	Variable	Count	90_day	OR.95.CI	P.for.interaction	180_0	day	OR.95.CI.1	P.for.interaction.1	1ye	ar	OR.95.CI.2	P.for.interaction.2
app <b< td=""><td>Overall</td><td>3774</td><td>1.1*</td><td>1.34(1.2-1.49)</td><td></td><td>: 1</td><td></td><td>1.28(1.16_1.42)</td><td></td><td>1</td><td></td><td>1.25(1.14_1.37)</td><td></td></b<>	Overall	3774	1.1*	1.34(1.2-1.49)		: 1		1.28(1.16_1.42)		1		1.25(1.14_1.37)	
eds 121 Image: 1000 (27-12) Image: 1000 (27-12) <thimage: (27-12)<="" 1000="" th=""> Image: 10000 (27-12)<</thimage:>	age				0.117				0.03	1			0.001
b-e6 0.421 0.422 0.44 0.422 0.44 0.42 0.43 0.44 Male 1.55 1.55 0.42 0.42 0.42 0.42 Male 1.55 1.55 0.41 0.42 0.43 0.44 See 1.55 0.11 0.42 0.42 0.42 Male 1.32(1.51.58) 1.17(0.11.42) 1.15(1.01.14) 0.42 No 1.32(1.51.58) 1.22(1.61.42) 1.22(1.61.43) 1.22(1.61.43) No 74 4 1.32(1.51.51) 0.644 1.22(1.01.44) 0.42 No 1.22(1.01.43) 1.22(1.01.43) 1.22(1.01.43) 1.22(1.01.43) 1.22(1.01.43) No 1.24 1.22(1.01.43) 1.22(1.01.43) 1.22(1.01.43) 1.22(1.01.43) No 1.24 1.22(1.01.43) 1.22(1.01.43) 1.22(1.01.43) 1.22(1.01.43) No 1.24 1.22(1.01.43) 1.22(1.01.43) 1.22(1.01.43) 1.22(1.01.43) No 1.24(1.21.50) 1.2	<65	1321	-	1.06(0.78-1.45)		-	-	0.98(0.74_1.29)			-	0.86(0.66_1.12)	
gender0.0420.0420.0230.0430.0430.041Female19891 22(155(1.31-8)1 4 (477.7)1 14(10.1.32)1 14(10.1.32)1 14(10.1.32)No15401 34(1.31-16)0.730.7191 12(10.1.32)1 12(10.1.32)No15401 34(1.31-16)1 22(1.05,1.41)1 12(1.01,1.32)1 12(1.01,1.32)No15401 34(1.21-16)1 22(1.05,1.42)1 12(1.01,1.32)No7141 34(1.21-16)1 22(1.01,1.42)0.4330.721No7141 34(1.21-16)1 22(1.01,1.42)0.4330.721No7141 34(1.21-16)1 22(1.01,1.42)0.4330.721No7141 34(1.21-16)1 22(1.01,1.42)0.4330.721No7141 22(1.01,1.42)0.410.410.41No7141 22(1.01,1.42)0.410.410.41No1 22(1.01,1.42)0.051 12(1.01,1.33)1 12(1.01,1.32)No1 22(1.01,1.42)1 12(1.01,1.32)1 12(1.01,1.32)0.65No20774 12(1.21,1.32)1 12(1.01,1.32)1 12(1.01,1.32)No20874 12(1.01,1.42)1 12(1.01,1.32)1 12(1.01,1.32)No10001 12(1.01,1.32)1 12(1.01,1.32)1 12(1.01,1.32)No20971 12(1.01,1.32)1 12(1.01,1.32)1 12(1.01,1.32)No37374 12(1.21,1.32)1 12(1.01,1.32)1 12(1.01,1.32)No37374 134(1.21.49)1 12(1.01,1.32)<	>=65	2453	-	1.39(1.23-1.57)		1		1.37(1.22_1.53)		1		1.37(1.23_1.52)	
Main P136 + 1 49(132,173) I 1 49(132,173) I 1 49(132,163) Bernake D37 D37 <thd37< th=""> D37 D37 D</thd37<>	gender				0.042				0.029				0.041
ferma 100 110(10] 110(10] 0.073 0.718 0.718 0.042 No 1540 134(115.156) 0.718 0.718 0.718 0.718 0.42 No 134(115.156) 134(117.150) 132(115_152) 132(115_152) 132(115_162) 132(115_162) 0.43 No 774 133(115.150) 132(115_152) 0.413 0.718 0.718 0.714 0.711 0.711 0.711 0.711 0.711 0.721<	Male	2135		1.56(1.31-1.86)			-8-	1.49(1.27_1.75)		1		1.42(1.22_1.64)	
arial fermionon0.873 <td>Female</td> <td>1639</td> <td>-</td> <td>1.23(1.05-1.43)</td> <td></td> <td></td> <td>-</td> <td>1.17(1.01_1.36)</td> <td></td> <td>1</td> <td></td> <td>1.15(1.01_1.32)</td> <td></td>	Female	1639	-	1.23(1.05-1.43)			-	1.17(1.01_1.36)		1		1.15(1.01_1.32)	
No 1540 + 1.24(1.15.1-5.6) + 1.27(1.0.6, 1.40) + 1.22(1.0.5, 1.41) No 30(1.17.1-5.6) + 1.32(1.15_1.5.2) + 1.22(1.0.5, 1.41) No 371 + 1.33(1.15.1-5.0) + 1.23(1.15_1.142) + 1.22(1.0.5, 1.41) No 771 + 1.33(1.15.1-5.0) + 1.23(1.10, 1.40) + 1.22(1.0.1, 1.42) No 2833 + 1.33(1.15.1-5.0) + 1.23(1.10, 1.40) + 1.22(1.0.1, 1.42) No 2436 + 1.44(1.27.46) + 1.23(1.10, 1.40) + 1.23(1.11, 1.42) No 2437 + 1.44(1.27.46) + 1.23(1.10, 1.43) + 1.23(1.11, 1.42) State 777 + 1.10(7.1-4) 0.045 + 1.23(1.12, 1.30) 0.014 No 3771 + 1.34(1.2.1.6) + 1.23(1.12, 1.30) 0.022 0.014 No 3771 + 1.34(1.2.1.6) + <	atrial fibrillation				0.873				0.719	1			0.482
Yes 2225 4 139(117.158) 4 132(115_152) 4 13(115_14) Non 701 4 134(12.149) 4 128(1.0_115_163) 4 128(1.0_116_163) 4 128(1.0_116_163) 4 128(1.0_116_163) 4 128(1.0_116_163) 4 128(1.0_116	No	1549	-	1.34(1.13-1.58)		1	-	1.27(1.08 1.49)		1		1.22(1.05 1.41)	
beart_alure	Yes	2225	-	1.36(1.17-1.58)			-	1.32(1.15 1.52)		1		1.3(1.15 1.48)	
No Yes	heart failure									1			
vise 3774 * 1.34(1.2.1.49) * 1.28(1.16_1.142) * 1	No		1			1				1			
pyperipidemia no. 0.919 no. 0.43 no. 0.721 No 711 1.34(1.12.16) 1.12(1.01_1.52) 1.12(1.01_1.52) 1.12(1.01_1.43) hyperina 0.084 0.17 0.42 0.42 No 1.36(1.51.53) 1.13(1.51.53) 1.13(1.51.53) 1.13(1.51.53) 0.17 0.42 No 2.87 1.14(1.21.16) 1.13(1.01.17.13) 1.13(1.01.17.13) 1.33(1.51.25) 0.014 No 2.97 1.14(5.128.165) 1.13(1.01.17.13) 1.33(0.42.125) 0.014 No 2.977 1.10(8.71.34) 1.22(1.10.1.33) 1.33(0.42.125) 0.014 Vers 0.771 1.10(8.71.34) 1.22(1.11.13.13) 1.23(1.12.16) 0.13(0.42.125) 0.014 Vers 1.10(8.71.24) 1.13(1.01.14) 1.22(1.12.13) 0.055 0.13(0.42.125) 0.014 No 3.67 1.34(1.21.49) 1.22(1.14.14) 1.22(1.14.13) 1.22(1.14.13) 1.22(1.14.13) Vers 3.67 1.34(1.21.49) 1.22(1.12.13)<	Yes	3774		1.34(1.2-1.49)		1		1.28(1.16 1.42)		1		1.25(1.14 1.37)	
No. 791 * 134(1,12,16) * 128(10,1,152) * 122(10,4,14) Yes 283 * 133(1,15,153) * 128(10,1,162) * 127(11,142) No 1426 * 14(12,71,66) * 137(12,156) * 137(12,163) No 1266 * 127(10,13,142) * 137(12,156) * 137(12,163) Stoke 0.014 * 137(12,156) * 137(12,156) 0.018 No 287 * 145(12,31,65) * 137(12,156) 0.014 No 3870 * 143(12,21,50) 0.055 133(0,22,13) * 125(1,14,13) Vest 104 * 177(0,45,07) * 0.222 0.055 No 3873 * 134(12,149) * 126(1,14,141) 125(1,14,130) imagintoxim 0.046 0.046 0.046 0.022 0.046 0.22 No 377 * 13	hyperlipidemia		1		0.919	1			0.943	1			0 721
No 283 + 1 33(11:51:33) + 1 22(11.31,14) - 1 27(11.31,14) Npertension . 0.084 . 0.17 0.42 No 124 1 44(127:165) + 1 37(12,153) + 1 37(12,153) + 1 37(12,153) 0.42 No 297 + 1 44(12:51:55) + 1 37(12,153) + 1 37(12,152) 0.014 No 297 + 1 47(12:51:55) + 1 37(12,153) 0.014 Versi 773 + 1 34(12:14) + 1 22(11.61:143) 0.65 0.673 0.65 No 373 + 1 34(12:14) + 1 22(11.61:142) + 1 22(11.61:14) 1 22(11.61:14) 1 22(11.61:14) 1 22(11.61:14) 1 22(11.61:14) 1 22(11.61:14) 1 22(11.61:14) 1 22(11.61:14) 1 22(11.61:14) 1 22(11.61:14) 1 22(11.61:14) 1 22(11.61:14) 1 22(11.61:14) 1 22(11.61:14) 1 22(11.61:14) 1 22(11.61:14) 1 22(11.61:14) 1 22(11.61:14) 1 22(11.61:14) </td <td>No</td> <td>791</td> <td></td> <td>1 34(1 12-1 6)</td> <td>0.010</td> <td></td> <td></td> <td>1 28(1 07 1 52)</td> <td>0.010</td> <td>1</td> <td>-</td> <td>1 22(1 04 1 44)</td> <td>0.121</td>	No	791		1 34(1 12-1 6)	0.010			1 28(1 07 1 52)	0.010	1	-	1 22(1 04 1 44)	0.121
Instruction Instruction <thinstruction< th=""> <thinstruction< th=""></thinstruction<></thinstruction<>	Yes	2983	-	1 33(1 15-1 53)				1.29(1.13, 1.46)		1		1 27(1 13 1 42)	
No. 1428 1 1 1.6(1, 12, 1, 6, 6) 1.7(1, 12, 1, 5, 6) 1.3(1, 14, 1, 4) 0.2(1, 14, 1, 4) Yes 2448 4 1.2(1, 14, 14, 3) 4 1.3(1, 12, 1, 5) 0.019 0.014 No 2997 4 1.45(1, 22, 15, 2) 1.03(0, 82, 1, 3) 4 1.03(0, 82, 1, 3) 1.03(0, 82, 1, 3) Vers 777 4 1.3(1, 14, 14, 7) 0.019 0.019 0.014 No 3670 4 1.3(1, 12, 15, 0) 4 1.3(1, 62, 13) 4 1.03(0, 82, 13, 0) 1.03(0, 82, 13, 0) 0.655 No 3670 4 1.3(1, 12, 16) 0.99(0, 41, 23) 4 1.28(1, 14, 13) 0.655 No 3676 4 1.3(1, 12, 14) 4 1.28(1, 14, 14) 4 1.28(1, 14, 13) 0.552 No 3759 4 3.53(1, 35, 924) 4 1.28(1, 14, 14) 4 1.28(1, 14, 14) 4 1.28(1, 14, 14) 4 1.28(1, 14, 14) 4 1.28(1, 14, 14) 4 1.28(1, 14, 14)	hypertension	2000		1.00(1.10 1.00)	0.084			1.20(1.10_1.10)	0.17	1		1.27(1.10_1.12)	0.42
No. 1248 Image: April 12 (10, 12, 13, 0) Image: April 12 (10, 12, 13, 0) Image: April 12 (10, 12, 13, 0) stroke 0.045 0.019 0.019 0.014 No 3670 1.45(12, 21, 5) 1.30(0, 02, 13, 0) 1.30(0, 02, 13, 0) 1.30(0, 02, 13, 0) No 3670 1.34(1, 21, 5) 1.30(0, 02, 13, 0) 1.30(0, 02, 13, 0) 1.30(0, 02, 13, 0) No 3670 1.34(1, 21, 5) 1.32(1, 16, 1, 43) 1.30(0, 02, 13, 0) 1.30(0, 02, 13, 0) Ves 1.4 1.34(1, 21, 15) 1.32(1, 16, 1, 43) 1.30(0, 02, 13, 0) 1.30(0, 02, 13, 0) msuin 0.373 1.34(1, 12, 14, 9) 1.32(1, 16, 14, 2) 1.22(1, 14, 1, 37) 2.22(0, 66, 5, 73) res 378 1.32(1, 15, 14, 9) 1.32(1, 13, 14, 0) 1.32(1, 12, 14, 17) 1.22(1, 14, 1, 37) res 378 1.32(1, 12, 149) 1.32(1, 12, 149) 1.32(1, 13, 130) 1.23(1, 13, 130) res 378 1.34(1, 12, 149) 1.32(1, 13, 140) 1.32(1, 14, 137) 1.22(1, 14, 137) 0.655 res 378 1.34(1, 12, 149) 1.32(1, 12, 143) 1.23(1, 13, 130) 1.23(1, 14, 137)<	No	1426	-	1 46(1 27-1 66)	0.004		-	1 37(1 2 1 56)	0.11	1		1 3(1 14 1 47)	0.42
index Description Description <thdescription< th=""> <</thdescription<>	Vec	2348		1.2(1.01-1.43)		1		1 19(1 02 1 39)		1		1.2(1.05 1.38)	
No 2997 1.45(1.22.1.65) 1.45(1.22.1.65) 1.36(1.22.1.52) Yes 777 1.10.87.1.4) 1.30.08.2.1.3) 1.30.08.2.1.25) No 870 1.34(1.2.1.5) 1.30.08.2.1.3) 1.30.08.2.1.25) Yes 104 1.30.04.5.2.36 1.30.04.5.2.36 Yes 104 1.34(1.2.1.4) 1.30.04.5.2.36 Yes 104 1.32(1.14_1.3.3) 1.33(0.45_2.36) Yes 104 1.32(1.14_1.3.3) 1.33(0.45_2.36) Yes 1.31.15.9.2.4) 1.22(1.14_1.41) 1.32(1.14_1.3.3) Yes 3678 1.32(1.18-1.48) 3.28(1.27, 247) 2.220.66, 73) Yes 3678 1.32(1.18-1.48) 1.22(1.14_1.41) 1.22(1.14_1.3.3) Yes 150 0.44(0.398.94) 0.41(0.398.94) 0.41(0.398.94) Yes 151 0.41(0.3439.85) 0.41(0.398.94) 0.41(0.398.94) Yes 151 0.014(0.3439.85) 0.127 0.004 No 2503 1.32(1.13.1.41,41) 1.22(1.13.1.30) 1.25(1.14_1.3.3) <td>ctroko</td> <td>2040</td> <td></td> <td>1.2(1.01-1.43)</td> <td>0.045</td> <td>1</td> <td></td> <td>1.15(1.02_1.55)</td> <td>0.010</td> <td>1</td> <td></td> <td>1.2(1.00_1.00)</td> <td>0.014</td>	ctroko	2040		1.2(1.01-1.43)	0.045	1		1.15(1.02_1.55)	0.010	1		1.2(1.00_1.00)	0.014
No 289 1 14(12-1.4) 1 13(12-1.5) 1 13(12-1.5) Vesticular_ficitizion 0.055 0.373 1 13(24.1.2.1.5) No 3670 1 134(1.2.1.5) 0.390(.4.1.2.35) 1 134(1.2.1.4.3) Vesticular_ficitizion 1 134(1.2.1.6) 0.390(.4.1.2.35) 1 134(1.2.1.4.3) No 3773 1 134(1.2.1.6) 0.390(.4.1.2.35) 1 134(1.2.1.4.3) No 3773 1 134(1.2.1.49) 0.390(.4.1.2.35) 1 134(1.2.1.4.3) No 3773 1 134(1.2.1.49) 1 128(1.16_1.42) 1 125(1.14_1.137) Yes 3778 1 134(1.2.1.49) 1 124(1.15_1.40) 1 124(1.15_1.40) No 3759 1 134(1.2.1.49) 1 124(1.16_1.42) 1 124(1.15_1.40) No 3759 1 134(1.2.1.49) 1 122(0.11.5_1.44) 1 124(1.14_1.37) Yes 3554 1 13(1.16-1.47) 1 122(0.91.065) 1 132(0.91.50) adb 0.627 0.140_398.49 1 122(0.12.01) 1 132(0.2.15) Yes 159 1 13(1.16-1.47) 1 122(0.11.5.14) 1 122(1.12.11) No 2554 1 128(1.32.1.44) 1 122(1.12.2.	No	2007		1 45/1 29 1 65)	0.045	1	-	1 41/1 25 1 50)	0.015	1		1 26(1 22 1 52)	0.014
Hts 1.0001-1.97 1.0001-1.97 1.0001-1.97 1.0001-1.97 No 3870 4 1.34(1.2-1.5) 4 1.29(1.16,1.43) 4 1.25(1.41,1.33) Yes 104 1.17(0.45-3.07) 0.99(0.41,2.35) 4 1.25(1.41,1.33) Mo 973 4 1.34(1.2-1.49) 4 1.28(1.16,1.42) 4 1.25(1.41,1.37) Yes 1 3.13(1.2-1.49) 4 1.28(1.16,1.42) 4 1.25(1.41,1.37) Wo 973 4 1.34(1.2-1.49) 4 1.28(1.16,1.42) 4 2.22(0.86,5.73) Yes 3678 4 1.32(1.2-1.49) 4 1.28(1.16,1.42) 4 2.2(1.13,1.30) Yes 3678 4 1.32(1.2-1.49) 4 1.28(1.16,1.42) 4 2.2(1.13,1.30) Yes 158 4 1.34(1.2-1.49) 4 1.28(1.16,1.42) 4 1.28(1.16,1.42) 0.695 No 2583 4 1.34(1.2-1.49) 4 1.29(1.15,1.41) 0.14(0.398.94) 0.14(0.398.94) 0.14(0.398.94) 0.14(0.398.94) 0.14(0.398.94) 0.14(0.398.94)	No	2997		1.45(1.20-1.05)				1.41(1.25_1.59)		1	-	1.30(1.22_1.32)	
No Sero 1 34(12-11.5) 1 32(11.61.43) 1 125(1.14_1.13) 1 25(1.14_1.13) Yes 100 3773 + 1 34(12-11.6) + 1 22(1.16_1.43) + 1 25(1.14_1.13) +<	Tes	111		1.1(0.07-1.4)	0.905			1.03(0.82_1.3)	0.570	1	T	1.03(0.04_1.25)	0.65
No 36/0 -1.44(1.2-1.3) -1.24(1.1-6_1.43) -1.24(1.1-6_1.43) Yes 104 -1.17(0.45.3.07) -0.990.041_2.35) -1.130.045_2.26) Mo 3773 +1.34(1.2-1.49) +1.22(1.16_1.42) +1.25(1.14_1.37) Yes 10 -0.046 -0.046 -0.046 -0.22 No 96 -3.53(1.35-9.24) +1.22(1.14_1.41) +1.24(1.13_1.36) Yes 3678 +1.32(1.18-1.48) +1.22(1.14_1.41) +1.24(1.13_1.36) aipha -0.695 -0.581 -0.9(0.90.22) 0.552 No 3759 +1.34(1.2-1.49) +1.22(1.16_1.42) +1.25(1.13_1.36) Yes 159 -0.14(0-13438.85) -0.14(0.398.94) -0.14(0.398.94) -0.14(0.1343.85) arb 0.0527 -0.064 -0.0751 0.0695 -0.627 No 2593 +1.31(1.16-1.47) +1.22(1.15_1.44) +1.25(1.13_1.30) +1.126(1.14_2.137) Yes 1181 +1.42(1.14.4) +1.22(1.13_1.42) +1.25(1.13_1.43) +1.25(1.14_1.47) Yes 3535 +1.28(1.14.147) +1.212(1.14.141) +1.22(1.14_1.47) </td <td>ventricular_nonliation</td> <td>0070</td> <td></td> <td>104/1015</td> <td>0.805</td> <td>1</td> <td></td> <td>1 00/1 10 1 10</td> <td>0.573</td> <td>1</td> <td></td> <td>4.05/4.44.4.00</td> <td>0.65</td>	ventricular_nonliation	0070		104/1015	0.805	1		1 00/1 10 1 10	0.573	1		4.05/4.44.4.00	0.65
Tris 1.04 - 1.17(1.53-5.07) - 1.03(1.72,53) - 1.03(1.72,53) No 373 + 1.34(1.2-1.49) + 1.28(1.16_1.42) + 1.25(1.14_1.37) Yes 3678 + 1.32(1.8-1.48) - 0.046 0.046 0.22 No 96 - 3.53(1.35-9.24) - 3.28(1.27, 8.47) + 2.22(0.86, 5.73) Yes 3678 + 1.34(1.2-1.49) - 1.28(1.16_1.42) + 1.24(1.13_1.36) apha 0.695 0.581 0.552 0.581 0.552 arb 0.14(0-13439.85) 0.14(0-13439.85) 0.751 0.19(0.90.20) arb 1.34(1.2-1.49) + 1.29(1.15_1.44) + 1.25(1.13_1.14) seta_blocker 0.019 0.027 0.084 - 0.001 - 0.001 - 0.001 - 0.001 - 0.001 - 0.001 - 0.001 - 0.001 - 0.001 - 0.001 - 0.001 - 0.001 - 0.001 </td <td>NO</td> <td>3670</td> <td></td> <td>1.34(1.2-1.5)</td> <td></td> <td></td> <td>-</td> <td>1.29(1.16_1.43)</td> <td></td> <td>1</td> <td>Ľ.,</td> <td>1.25(1.14_1.38)</td> <td></td>	NO	3670		1.34(1.2-1.5)			-	1.29(1.16_1.43)		1	Ľ.,	1.25(1.14_1.38)	
adapaginozin 1,34(1,2-1,49) 1,28(1,16_1,42) 1,28(1,14_1,137) Yes 1 0.046 0.046 0.22 No 96 3,53(1,35-9,24) 1,22(1,14_1,14) 1,22(1,14_1,13,136) yes 3673 1,32(1,18-1,48) 1,22(1,14_1,14) 1,22(1,14_1,13,136) apha 0.695 0.561 0.561 0.562 No 3759 1,34(1,2-1,49) 1,28(1,16_1,142) 1,25(1,14_1,137) Yes 151 0.1(40-1343.85) 0.14(0,368.84) 0.751 0.695 No 3759 1,31(1,16.1,47) 1,22(0,91,165,144) 1,25(1,14_1,2,130) 1,25(1,14_2,13,138) Yes 1181 0.14(0,1438.84) 0.140(36.84) 0.0751 0.064 No 2523 1,31(1,16.1,47) 1,22(0,91,165) 0.027 0.064 No 128(1,31,144) 0.142(315,2.30) 1,22(1,1_1,35) 0.004 Yes 3554 1,28(1,16_1,42) 1,22(1,1_1,35) 0.004 No 3656 1,91(1,62,2.26) 1,07(0,91,126) 1,25(1,14_1,137) 1,25(1,14_1,137) Yes 1,32(1,18,147) <td>Yes</td> <td>104</td> <td></td> <td>> 1.17(0.45-3.07)</td> <td></td> <td></td> <td></td> <td>0.99(0.41_2.35)</td> <td></td> <td>1 -</td> <td></td> <td>1.03(0.45_2.36)</td> <td></td>	Yes	104		> 1.17(0.45-3.07)				0.99(0.41_2.35)		1 -		1.03(0.45_2.36)	
No 3/73 * 1.34(1,21.49) * 1.29(1.16_1.42) * 1.29(1.16_1.42) insuin 0.046 0.046 0.046 0.046 0.22 0.22(0.86_5.73) Ves 3678 * 1.32(1.18-1.48) * 1.27(1.14_1.41) * 1.24(1.13_1.36) alpha 0.695 0.581 0.581 0.552 No 375 * 1.34(1.21.49) * 1.28(1.16_1.42) * 1.24(1.13_1.36) Ves 15 0.14(-013439.85) * 1.28(1.16_1.42) * 1.28(1.13_1.36) No 253 1.31(1.16-1.47) * 1.29(1.15_1.44) * 1.29(1.15_1.44) * 1.29(1.15_1.44) Ves 11810 * 1.38(1.36.2.49) * 1.29(1.15_1.43) * 1.29(1.12_1.35) Sold * 1.29(1.15_1.44) * 1.29(1.15_1.42) * 1.29(1.12_1.35) Ves 3554 * 1.38(1.36.2.49) * 1.23(1.1_1.38) * 1.29(1.5_1.42_1.91) Ves 159(1.62.2.6) * 1.11(0.93.1.32) * <	dapagliflozin		1			1				-			
Yes 1 1 0.046 0.046 0.046 0.22 No 96 3.53(1.35-9.24) -> 3.28(1.27_8.47) -> 2.22(0.86_5.73) 2.22(0.86_5.73) Yes 367 -> 1.32(1.18-1.48) -> 1.27(1.14_1.14) -> 2.22(0.86_5.73) 0.552 No 3759 -> 1.34(1.2.1.49) -> 1.28(1.16_1.42) -> 1.25(1.14_1.37) 0.552 No 3759 -> 1.34(1.2.1.49) -> 1.28(1.16_1.42) -> 1.25(1.14_1.37) 0.695 No 2593 -> 1.31(1.16-1.47) -> 1.29(1.15_1.14) -> 1.25(1.131.38) 0.695 No 2593 -> 1.85(1.38-2.49) -> 1.73(1.31_2.3) +> 1.59(1.2_2.11) 1.25(1.131.38) Ves 128 -> 1.85(1.38-2.49) -> 1.73(1.31_2.3) +> 1.59(1.2_2.11) 0.004 No 220 -> 1.85(1.38-2.49) -> 1.173(1.31_2.3) +> 1.59(1.2_2.11) 1.25(1.13130) 0.001 No 1599 -> 1.91(1.62-2.26) -> 1.173(1.31_2.3) +> 1.59(1.2_2.11) 1.09(0.95125) 0.001 No 3774 -> 1.91(1.62-2.46) -> 1.25(1.16142) +> 1.25(1.13137) 1.25(1.13137) <td< td=""><td>No</td><td>3773</td><td>-</td><td>1.34(1.2-1.49)</td><td></td><td></td><td>*</td><td>1.28(1.16_1.42)</td><td></td><td>1</td><td>•</td><td>1.25(1.14_1.37)</td><td></td></td<>	No	3773	-	1.34(1.2-1.49)			*	1.28(1.16_1.42)		1	•	1.25(1.14_1.37)	
Insulin 0.046 0.046 0.046 0.22 0.22 No 96	Yes	1	1			1				1			
No 96	insulin				0.046				0.046	1			0.22
Yes 3678 1,2(1,18-1,48) 1,2(1,14_1,41) 1,24(1,13_1,136) 0.551 0.552 alpha 0.695 0.591 0.581 0.551 0.552 No 3759 1,34(1,2-1,49) 0.291 0.581 0.551 0.552 arb 0.627 0.751 0.99(0,90,22) 0.695 0.695 No 2593 1,31(1,16-1,47) 1,22(1,15_1,14,14) 1,25(1,13_1,13,0) 1.25(1,13_1,13,0) Yes 181 1,42(1,04-1,94) 1,22(1,12_1,15,5) 0.067 0.0751 0.695 No 220 1,85(1,38-2,49) 1,23(1,1_1,38) 1,59(1,2,2,11) 1,59(1,2,2,11) 1,59(1,2,2,11) Yes 3554 1,28(1,13,1.44) 1,23(1,1_1,38) 1,22(1,1_1,35) 0.001 0.027 0.001 No 1599 1,14(1,2-1,49) 1,28(1,16,1.42) 1,28(1,16,1.42,19) 1,28(1,16,1.42,19) 1,28(1,14,13,17) Yes 116 1,34(1,2-1,49) 1,28(1,15,1.42) 1,25(1,13,1.37) 1,25(1,13,1.37) No 3658 1,34(1,2-1,49) 1,28(1,16,1.42) 1,25(1,13,1.37) 2,25(1,13,1.37) <	No	96	-	> 3.53(1.35-9.24)				3.28(1.27_8.47)		1		2.22(0.86_5.73)	
alpha 0.695 0.581 0.581 0.552 No 3759 1.34(12-149) 1.28(1.16_1.42) 1.28(1.14_1.37) Yes 150 0.14(0-13439.85) 0.14(0_396.94) 0.18(0_3022) arb 0.13(1.16-147) 1.28(1.15_1.44) 1.28(1.15_1.44) 1.28(1.15_1.43) 1.28(1.15_1.43) bela_blocker 0.019 0.027 0.084 0.084 No 220 1.85(1.38-249) -1.73(1.31_2.3) +1.59(1.2_2.11) 0.084 acei 0.001 1.22(1.1_1.38) +1.22(1.1_1.35) 0.084 acei 0.001 1.23(1.12.3) +1.59(1.2_2.11) <0.084	Yes	3678		1.32(1.18-1.48)		1	*	1.27(1.14_1.41)		1	•	1.24(1.13_1.36)	
No 3759 $1.34(12-1.49)$ $1.28(1.16_{-1.42})$ $1.28(1.16_{-1.42})$ $1.28(1.16_{-1.42})$ Yes 15 $0.14(0.13439.85)$ $0.14(0.996.94)$ $0.19(0.90.22)$ arb 0.627 0.751 $0.995.94$ No 2593 $1.31(1.16-1.47)$ $1.22(1.15_{-1.44})$ $1.22(1.13_{-1.38})$ Yes 1181 $1.42(1.04-1.94)$ $1.22(1.15_{-1.44})$ $1.28(1.13.18)$ bela_blocker 0.019 0.027 0.084 No 220 $-1.85(1.38-2.49)$ $-1.73(1.31_{-2.3})$ $-1.59(1.2_{-2.11})$ Yes 3554 $1.28(1.13-1.44)$ $-1.23(1.1_{-1.38})$ $-1.22(1.1_{-1.35})$ acei 0.001 <0.001 <0.001 <0.001 <0.001 No 1.91(1.62-2.26) $-1.8(1.54_{-2.1})$ $+1.65(1.42_{-1.91})$ $+1.65(1.42_{-1.91})$ Yes 1.34(1.2-1.49) $+1.28(1.16_{-1.42})$ $+1.25(1.11_{-1.37})$ $-1.09(0.95_{-1.25})$ Intervolutioner <0.001 0.012 0.138 0.027 -0.013 No 3658 $1.34(12-1.49)$ $1.28(1.16_{-1.42})$ $1.25(1.$	alpha		1		0.695				0.581	1			0.552
Yes 15 0.14(0-13439.85) 0.14(0_396.94) 0.19(0_90.22) arb 0.627 0.751 0.095 No 2593 1.31(1.16-1.47) 1.29(1.15_1.44) 1.25(1.13_1.3.8) Yes 1181 1.42(1.04-1.94) 0.019 0.027 0.084 beta_blocker 0.019 0.027 0.084 0.096 No 220 1.85(1.38-2.49) 1.23(1.1_1.38) 1.25(1.12_1.3) 1.25(1.12_1.13) acei .0.001 .001 .001 .0001 .0001 .00001 .00001 .00001 .00001 .00001 .00001 .000005 .0001 .000005 .0001 .000005 .0001 .00005 .0001 .00005 .0001 .00005 .0001 .00005 .0001 .00005 .0001 .00005 .0001 .00005 .0001 .0012 .0.0138 .0001 .0012 .0.0138 .0.026 .0.026 .0.026 .0.026 .0.026 .0.026 .0.026 .0.026 .0.026 .0.026 .0.026 .0.026 .0.026 .0.026 .0.027 .0.011 .0.0	No	3759		1.34(1.2-1.49)			+	1.28(1.16_1.42)		1	•	1.25(1.14_1.37)	
arb 0.627 0.627 0.751 0.695 No 2593 4 1.31(1.61.47) 4 1.29(1.15_1.44) 1.25(1.13_1.38) yes 1181 4 1.42(1.04.1.94) 4 1.29(0.15_1.65) 4 1.29(0.9_1.65) beta_blocker 0.019 0.027 0.027 0.084 No 220 4 1.8(1.31.4.4) 4 1.23(1.1_1.38) 4 1.59(1.211) Yes 3554 1 1.29(1.13_1.4.4) 4 1.23(1.1_1.38) 4.0001 0.001 No 1599 1 1.91(1.62-2.26) 4 1.8(1.54_2.1) 4 1.65(1.42_1.91) Yes 2175 1.11(0.93-1.32) 1.10(0.91_1.26) 4 1.65(1.42_1.91) Yes 1.34(1.21.49) 1.28(1.16_1.42) 4 1.25(1.14_1.37) 9 Yes 116 1.34(12.1.47) 1.28(1.15_1.42) 4 1.25(1.13_1.37) Yes 116 1.34(1.21.49) 1.28(1.16_1.42) 4 1.25(1.13_1.37)	Yes	15	-	* 0.14(0-13439.85)		-		0.14(0_396.94)		-		0.19(0_90.22)	
No 2593 $+$ 1.31(1,16.1.47) $+$ 1.22(1,15_1.44) $+$ 1.25(1.13_1.38) Yes 1.11 $+$ 1.22(0.91_1.65) $+$ 1.18(0.9_1.55) 0.084 beta_blocker 0.019 0.027 0.084 No 220 $-+$ 1.85(1.38-2.49) $-+$ 1.73(1.31_2.3) $+$ 1.59(1.2_2.11) Yes 3554 $+$ 1.28(1.13-1.44) $-+$ 1.23(1.1_1.38) $-+$ 1.22(1.1_1.35) acei $$ 0.001 $$ 0.001 $$ 0.001 $$ 0.001 $$ 0.001 $$ 0.001 $$ 0.001 $$ 0.001 $$ 0.001 $$ 0.001 $$ 0.001 $$ 0.001 $$ 0.001 $$ 0.001 0.001 0.012 0.138 Mo 3658 $+$ $1.32(1.18-1.47)$ $+$ $1.28(1.16_1.42)$ $ 1.25(1.13_1.37)$ $ 2.5(1.10.4.08)$ Insultationtopic $ 0.694$ 0.694 0.557 0.326	arb				0.627				0.751	1			0.695
Yes 1181 \bullet 1.42(1.04-1.94) \bullet 1.22(0.91_1.65) \bullet 1.18(0.9_1.55) 0.034 beta_blocker 0.019 0.027 0.084 No 220 \bullet 1.85(1.38-2.49) \bullet 1.73(1.31_2.3) \bullet 1.59(1.2_2.11) acei <0.001 \bullet 1.22(1.1_1.35) \bullet 1.22(1.1_1.35) acei <0.001 \bullet 1.23(1.1_2.8) \bullet 1.22(1.1_1.35) acei <0.001 \bullet 1.22(1.1_1.35) \bullet 0.001 \bullet 1.22(1.1_1.35) wetformin 1.91(1.62-2.26) \bullet 1.8(1.54_2.1) \bullet 1.65(1.42_1.91) \bullet 1.09(0.91.25) metformin 1.34(1.2-1.49) \bullet 1.28(1.16_1.42) \bullet 1.25(1.13_1.37) Yes 116 4.58(2.2-9.3) \bullet 1.28(1.15_1.42) \bullet 1.25(1.13_1.37) \bullet 1.25(1.13_1.37) Yes 118 \bullet 1.34(1.2-1.49) \bullet 1.28(1.16_1.42) \bullet 1.25(1.13_1.37) \bullet 2.51(1.04.6.08) 0.326 0.326 0.326	No	2593	•	1.31(1.16-1.47)			*	1.29(1.15_1.44)		1	•	1.25(1.13_1.38)	
beta_blocker Image: method is a start of the star	Yes	1181	-	- 1.42(1.04-1.94)		-	-	1.22(0.91_1.65)		1	-	1.18(0.9_1.55)	
No 220 \bullet 1.85(1.38-2.49) \bullet 1.73(1.31_2.3) \bullet 1.59(1.2_11) Yes 3554 \bullet 1.28(1.13-1.44) \circ	beta_blocker				0.019	1			0.027	1			0.084
Yes 3554 1.28(1.13-1.44) 1.23(1.1_1.38) 1.22(1.1_1.35) acei <0.001	No	220	-	1.85(1.38-2.49)				1.73(1.31_2.3)		-		1.59(1.2_2.11)	
acei <td>Yes</td> <td>3554</td> <td>-</td> <td>1.28(1.13-1.44)</td> <td></td> <td>1</td> <td>•</td> <td>1.23(1.1_1.38)</td> <td></td> <td>1</td> <td>•</td> <td>1.22(1.1_1.35)</td> <td></td>	Yes	3554	-	1.28(1.13-1.44)		1	•	1.23(1.1_1.38)		1	•	1.22(1.1_1.35)	
No 1599 - 1.91(1.62-2.26) - 1.8(1.54_2.1) - 1.65(1.42_1.91) Yes 2175 1.11(0.93-1.32) 1.07(0.91_1.26) 1.09(0.95_1.25) metformin - 1.34(1.2-1.49) 1.28(1.16_1.42) 1.25(1.14_1.37) Yes - 1.34(1.2-1.49) 1.28(1.16_1.42) 1.25(1.14_1.37) Yes 1 - 1.32(1.18-1.47) - 1.28(1.15_1.42) 1.25(1.13_1.37) No 3658 1.32(1.18-1.47) - 1.28(1.16_1.42) 1.25(1.13_1.37) 2.51(1.04_6.08) Insulinotropic 0.694 0.557 0.326 0.326 No 3656 1.34(1.2-1.49) 1.28(1.16_1.42) 1.25(1.13_1.37) 2.23(0.69_7.14) Yes 118 1.82(0.39-8.58) - 1.33(0.5_7.36) - 1.25(1.13_1.37) Yes 3342 1.47(1.3-1.66) 0.008 0.002 1.41(1.27_1.56) 0.027 No 3342 1.48(1.34-2.58) - 1.69(1.24_2.31) 1.65(1.26_2.16) 0.027 No 1343 1.27(1.13-1.43) 1.23(1.1_1.37) 1.19(1.08_1.32)	acei		1		<0.001	1			<0.001	1			<0.001
Yes 2175 1.11(0.93-1.32) 1.07(0.91_1.26) 1.09(0.95_1.25) metformin No 3774 1.34(1.2-1.49) 1.28(1.16_1.42) 1.25(1.14_1.37) Yes 1.32(1.18-1.47) 1.28(1.15_1.42) 1.25(1.13_1.37) Yes 1.32(1.18-1.47) 1.28(1.15_1.42) 1.25(1.13_1.37) Yes 1.35(2.25-9.33) 3.49(1.61_7.55) 2.51(1.04_6.08) insulinotropic 0.694 0.557 0.326 No 3656 1.34(1.2-1.49) 1.28(1.16_1.42) 1.25(1.13_1.37) Yes 118 1.32(0.39-8.58) 0.694 0.557 0.326 crrt 0.008 0.002 2.23(0.69_7.14) 2.23(0.69_7.14) No 3342 1.47(1.3-1.66) 4.143(1.27_1.6) 4.143(1.27_1.6) 4.141(1.27_1.56) Yes 432 0.96(0.71-1.28) 0.034 0.053 0.027 No 1343 1.27(1.13-1.43) 1.23(1.1_1.37) 1.91(1.08_1.32)	No	1599	-	1.91(1.62-2.26)			-40	1.8(1.54_2.1)		1	-	1.65(1.42_1.91)	
metformin No 3774 Image: state s	Yes	2175	-	1.11(0.93-1.32)			F	1.07(0.91_1.26)		1	•	1.09(0.95_1.25)	
No 3774 + 1.34(1.2-1.49) + 1.28(1.16_1.42) + 1.25(1.14_1.37) Yes 0.012 0.012 0.013 0.138 No 3658 + 1.32(1.18-1.47) + 1.28(1.15_1.42) + 1.25(1.13_1.37) Yes 16 4.58(2.25-0.33) - 1.28(1.16_1.42) + 1.25(1.13_1.37) Yes 118 - 0.694 0.557 0.326 - 0.326 No 3656 + 1.34(1.2-1.49) + 1.28(1.16_1.42) + 1.25(1.13_1.37) Yes 118 - 1.34(1.2-1.49) + 1.28(1.16_1.42) + 1.25(1.13_1.37) Yes 118 - 1.34(1.2-1.49) + 1.28(1.16_1.42) + 1.25(1.13_1.37) Yes 118 - 1.36(0.39-8.58) - 1.28(1.16_1.42) + 1.25(1.13_1.37) Wo 3342 + 1.47(1.3-1.66) - 0.607(.65_1.16) - 1.41(1.27_1.56) 0.027 No 1343 - 1.86(1.34-2.58) - 1.69(1.24	metformin									1			
Yes Image: state st	No	3774		1.34(1.2-1.49)		1	*	1.28(1.16_1.42)		1	•	1.25(1.14_1.37)	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Yes		1							1			
No 3658 • $1.32(1.18-1.47)$ • $1.28(1.15_1.42)$ • $1.25(1.13_1.37)$ Yes 116 $4.58(2.25-9.33)$ • $3.49(1.61_7.55)$ • $2.51(1.04_6.08)$ No 3656 • $1.34(1.2-1.49)$ • $1.28(1.16_1.42)$ • $1.25(1.13_1.37)$ Yes 118 • $1.34(1.2-1.49)$ • $1.28(1.16_1.42)$ • $1.25(1.13_1.37)$ Yes 118 • $1.34(1.2-1.49)$ • $1.28(1.16_1.42)$ • $1.25(1.13_1.37)$ Yes 118 • $1.32(0.39-8.58)$ • $1.28(1.16_1.42)$ • $1.25(1.13_1.37)$ No 3342 • $1.47(1.3-1.66)$ • $1.43(1.27_1.6)$ • $1.41(1.27_1.56)$ Yes 432 0.96(0.71-1.28) • 0.034 0.053 0.027 No 1343 • $1.27(1.13-1.43)$ • $1.69(1.24_2.31)$ • $1.65(1.26_2.16)$ Yes 2431 $1.27(1.13-1.43)$ • $1.23(1.1_1.37)$ • $1.29(1.08_1.32)$	thiazolidinediones				<0.001				0.012	1			0.138
Yes 116 4.58(2.25-9.33) -> 3.49(1.61_7.55) -> 2.51(1.04_6.08) insulinotropic 0.694 0.557 0.326 No 3656 • 1.34(1.2-1.49) • 1.28(1.16_1.42) • 1.25(1.13_1.37) Yes 118 • 1.82(0.39-8.58) • 1.93(0.5_7.36) • 2.23(0.69_7.14) No 3342 • 1.47(1.3-1.66) • 1.43(1.27_1.6) • 1.41(1.27_1.56) Yes 432 • 0.96(0.71-1.28) • 0.0034 0.053 0.027 No 1343 • 1.86(1.34-2.58) • 1.69(1.24_2.31) • 1.65(1.26_2.16) Yes 2431 • 1.27(1.13-1.43) • 1.23(1.1_1.37) • 1.19(1.08_1.32)	No	3658	-	1.32(1.18-1.47)		1	*	1.28(1.15_1.42)		1	•	1.25(1.13_1.37)	
insulinotropic 0.694 0.557 0.326 No 3656 1.34(1.2-1.49) 1.28(1.16_1.42) 1.25(1.13_1.37) Yes 118 1.82(0.39-8.58) 1.93(0.5_7.36) 2.23(0.69_7.14) crrt 0.008 0.002 <0.001	Yes	116		4.58(2.25-9.33)		1	->	3.49(1.61_7.55)		1		2.51(1.04_6.08)	
No 3656 • 1.34(1.2-1.49) • 1.28(1.16_1.42) • 1.25(1.13_1.37) Yes 118 • 1.82(0.39-8.58) • 1.93(0.5_7.36) • 2.23(0.69_7.14) crrt 0.008 0.002 <0.001	insulinotropic		1		0.694	1			0.557	1			0.326
Yes 118 1.82(0.39-8.58) 1.93(0.5_7.36) 2.23(0.69_7.14) crrt 0.008 0.002 <0.001	No	3656		1.34(1.2-1.49)				1.28(1.16_1.42)		1	-	1.25(1.13_1.37)	
crrt 0.008 0.002 <0.001 No 3342 + 1.47(1.3-1.66) + 1.43(1.27_1.6) + 1.41(1.27_1.56) Yes 432 - 0.96(0.71-1.28) - 0.87(0.65_1.16) - 0.77(0.58_1.03) mv 0.034 0.053 0.027 No 1343 - 1.86(1.34-2.58) - 1.69(1.24_2.31) - 1.65(1.26_2.16) Yes 2431 1.27(1.13-1.43) - 1.23(1.1_1.37) - 1.9(1.08_1.32)	Yes	118		1.82(0.39-8.58)		-	-	1.93(0.5_7.36)		-		2.23(0.69_7.14)	
No 3342 + 1.47(1.3-1.66) + 1.43(1.27_1.6) + 1.41(1.27_1.56) Yes 432 - 0.96(0.71-1.28) - 0.87(0.65_1.16) - 0.77(0.58_1.03) mv 0.034 0.053 0.027 - 1.65(1.26_2.16) 1.19(1.08_1.32) Yes 2431 - 1.27(1.13-1.43) - 1.23(1.1_1.37) - 1.19(1.08_1.32)	crrt				0.008	1			0.002	1			<0.001
Yes 432 0.96(0.71-1.28) 0.87(0.65_1.16) 0.77(0.58_1.03) mv 0.034 0.053 0.027 No 1343 - 1.86(1.34-2.58) - 1.69(1.24_2.31) - 1.65(1.26_2.16) Yes 2431 1.27(1.13-1.43) - 1.23(1.1_1.37) 1.19(1.08_1.32)	No	3342	+	1.47(1.3-1.66)		1	+	1.43(1.27_1.6)		1		1.41(1.27_1.56)	
mv 0.034 0.053 0.027 No 1343	Yes	432	-	0.96(0.71-1.28)		-8		0.87(0.65_1.16)		-		0.77(0.58_1.03)	
No 1343 1.86(1.34-2.58) 1.69(1.24_2.31) 1.65(1.26_2.16) Yes 2431 1.27(1.13-1.43) 1.23(1.1_1.37) 1.19(1.08_1.32)	mv				0.034	1			0.053	1			0.027
Yes 2431 1.27(1.13-1.43) 1.23(1.1_1.37) 1.19(1.08_1.32)	No	1343	-	1.86(1.34-2.58)		1	-	1.69(1.24 2.31)		1		1.65(1.26 2.16)	
	Yes	2431		1.27(1.13-1.43)			*	1.23(1.1_1.37)		1		1.19(1.08_1.32)	
0051152 0051152 0051152			005115	2		0.054	15	2		00 5	11 5	2	

Fig. 5 Forest plot of Subgroup Analysis

damage [25]. High lactate levels and low albumin levels are key determinants of the lactate-to-albumin ratio (LAR), with their ratio reflecting the complex and close relationship between antioxidant capacity and hypoxic

conditions. In a physiological setting, hypoxic conditions trigger adaptive responses that enhance antioxidant capacity. However, prolonged high lactate levels, indicating sustained hypoxia, lead to the production of

Variable Model-I H		95% Cl	P-value	Model-II HR	95% Cl	P-value	Model-III HR	95% Cl	P-value	
1-year mortality							·			
LAR	1.25	1.14, 1.37	< 0.001	1.21	1.10, 1.34	< 0.001	1.22	1.10, 1.35	< 0.001	
LAR < 0.44	1			1			1			
LAR≥0.44	1.19	1.08, 1.31	< 0.001	1.18	1.07, 1.30	< 0.001	1.23	1.12, 1.36	< 0.001	
90-day mortality										
LAR	1.34	1.20, 1.49	< 0.001	1.29	1.15, 1.44	< 0.001	1.27	1.13, 1.43	< 0.001	
LAR < 0.44	1			1			1			
LAR≥0.44	1.24	1.09, 1.40	< 0.001	1.21	1.07, 1.38	0.002	1.24	1.09, 1.41	< 0.001	
180-day mortality										
LAR	1.28	1.16, 1.42	< 0.001	1.24	1.12, 1.38	< 0.001	1.25	1.12, 1.39	< 0.001	
LAR < 0.44	1			1			1			
LAR≥0.44	1.19	1.07, 1.33	0.002	1.18	1.06, 1.32	0.003	1.23	1.10, 1.37	< 0.001	

Table 2 Cox Analysis of LAR and Long-term Mortality Risk

* LAR lactate-to-albumin ratio, HR Hazard Ratio

reactive oxygen species (ROS) and other free radicals, inducing inflammation. This, in turn, reduces the liver's ability to synthesize albumin, alters vascular permeability, increases protein loss, and further diminishes the body's antioxidant capacity, exacerbating oxidative stress and systemic inflammation. Compared to isolated albumin or lactate levels, LAR is more sensitive to subtle changes in the body and has stronger prognostic capabilities in certain specific diseases. In recent years, many researchers have used the LAR model to predict the risk of rehospitalization in heart failure patients [26]. LAR levels at admission in out-of-hospital cardiac arrest patients have also been used to predict clinical outcomes and neurological prognosis [27, 28].

After adjusting for confounding factors, our findings remained statistically significant. Subgroup analysis revealed strong interactions between mortality risk at 90 days, 180 days, and one year with factors such as age, gender, stroke history, ACEI use, CRRT, and mechanical ventilation. The study found that male patients and those aged 65 years or older exhibited a higher risk associated with elevated LAR levels, which aligns with findings from previous epidemiological studies [29, 30]. Stroke is a risk factor for diabetes complicated by heart failure, consistent with findings from another study showing that a history of stroke combined with diabetes increases the incidence of stroke in heart failure patients without atrial fibrillation [31]. We also observed that in patients not receiving angiotensin-converting enzyme inhibitors (ACEIs), high LAR was associated with increased mortality risk in HF-DM patients. Studies have shown that ACEI/ARB therapy significantly reduces the risk of new-onset diabetes in non-HF patients, improves glycemic control, and slows diabetes progression [32]. We also observed a significant association between high LAR and mortality risk in HF-DM patients not receiving CRRT treatment. This may be attributed to progressive renal function decline, leading to albumin loss and consequently elevated LAR levels.

Furthermore, at both the 90-day and 180-day time points, the LAR in HF-DM patients showed an interaction with the use of insulin, β -blockers, and thiazolidinediones. Insulin resistance can impair the physiological effects of insulin, hinder glucose uptake and utilization, and negatively affect cardiac contractility, leading to structural and functional abnormalities in the heart [33]. The hyperglycemia caused by pancreatic dysfunction often necessitates insulin therapy, aligning with our observation that insulin use is also a risk factor. β -blockers, a first-line treatment for heart failure, are not explicitly contraindicated for diabetic patients in current guidelines. However, studies have shown that β -blocker use in diabetic patients is associated with increased cardiovascular risk. Among patients with coronary artery disease or heart failure, those using $\beta\text{-blockers}$ have a significantly higher cumulative incidence of cardiovascular events compared to non-users [34]. This may be due to β-blockers masking hypoglycemia symptoms such as tachycardia or their potential direct hypoglycemic effects [35]. We observed that among patients not using thiazolidinediones, higher LAR was significantly associated with reduced 90-day and 180-day mortality risk in HF-DM patients. This finding aligns with reports indicating that thiazolidinediones may increase the risk of heart failure [36, 37].

Strengths and limitations

This study has several strengths. To date, no research has focused on the prognostic role of LAR levels in ICU patients with HF-DM. Our findings provide evidence supporting LAR as an independent predictor of 90-day, 180-day, and one-year mortality in HF-DM patients. However, there are also limitations. First, this study relied entirely on data retrieved from electronic medical records in the MIMIC-IV database, which may introduce selection bias. Additionally, the study did not incorporate data from multiple regions worldwide. Due to inherent limitations of the database, we were unable to include comprehensive baseline characteristics, detailed diagnostic information, or socioeconomic factors for patients with diabetes and heart failure, which could have influenced the results and introduced potential bias.

Conclusion

In conclusion, this study conducted a detailed investigation of the association between the lactate-to-albumin ratio (LAR) and 90-day, 180-day, and one-year mortality risks in a cohort of patients with diabetes and heart failure. The findings revealed that an elevated LAR is an independent predictor of overall mortality in this patient population, demonstrating a nonlinear relationship. This association remained statistically significant even after adjusting for potential confounders. Future studies are needed to validate the exact relationship between LAR and all-cause mortality in patients with diabetes and heart failure, aiming to enhance our understanding and management of this complex condition.

Acknowledgements

I would like to extend my sincere gratitude to the corresponding author of this study, Quangen Chu, for his instructive advice and useful suggestions on this study. I am deeply grateful of his funding and help in the completion of this study.

Authors' contributions

Dong Y.Y. and Hu Y.Q. designed the study, Dong Y.Y. and Shi X.Y. wrote the first draft of the manuscript and verified the underlying data. Hu Y.Q. and Wang C.H. conducted the statistical analysis, Dong Y.Y., Li J.X., Luo H. and Wang C.H. played a role in the acquisition of the data and analyses, and participated in data interpretation. Hu F. and Zhu M.P. edited the figures and tables. Chu Q.G. directed the study design and funded the study. All authors revised and approved the final manuscript. The guarantor (Chu Q.G.) confirms that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

Funding

This study was supported by the (1) National Natural Science Foundation of China (81774189); (2) Anhui Province Excellent Research and Innovation Team Project for Universities (2022AH010037); (3) Humanity and Social Science Research Project of Anhui Educational Committee (SK2021A0324); (4) Collaborative Innovation Project of Anhui Educational Committee (GXXT-2020-036).

Data availability

All data are publicly available in MIMIC-IV.

Declarations

Ethics approval and consent to participate

The data used in this study are all from the publicly available MIMIC-IV database. Because the database does not contain any protected health information and patients remain anonymous, a waiver of informed consent was obtained.

Consent for publication

Not applicable, this study did not contain any details, images, or videos relating to an individual person.

Competing interests

The authors declare no competing interests.

Author details

¹School of Traditional Chinese Medicine, Anhui University of Chinese Medicine, Anhui Hefei, China. ²Key Laboratory of Xinan Medicine, Ministry of Education, Anhui University of Chinese Medicine, Anhui Hefei, China. ³Jiangxi University of Traditional Chinese Medicine, Nanchang Jiangxi, China. ⁴Department of Cardiovascular Disease, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China. ⁵Department of Acupuncture and Moxibustion, Huadong Hospital Affiliated to Fudan University, Shanghai, China. ⁶Department of Rehabilitation, Chongqing Liangping District Hospital of Traditional Chinese Medicine, Zhabei Central Hospital, Jing 'an District, Shanghai, China. ⁸Department of Rehabilitation, Putuo Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China.

Received: 28 November 2024 Accepted: 27 February 2025 Published online: 29 March 2025

References

- Jackson AM, Jhund PS, Anand IS, Düngen HD, Lam CSP, Lefkowitz MP, Linssen G, Lund LH, Maggioni AP, Pfeffer MA, Rouleau JL, Saraiva JFK, Senni M, Vardeny O, Wijkman MO, Yilmaz MB, Saito Y, Zile MR, Solomon SD, McMurray JJV. Sacubitril-valsartan as a treatment for apparent resistant hypertension in patients with heart failure and preserved ejection fraction. Eur Heart J. 2021Sep 21;42(36):3741–52. https://doi.org/10.1093/ eurhearti/ehab499.PMID:34392331;PMCID:PMC8455346.
- Taniguchi T, Shiomi H, Morimoto T, Watanabe H, Ono K, Shizuta S, Kato T, Saito N, Kaji S, Ando K, Kadota K, Furukawa Y, Nakagawa Y, Horie M, Kimura T. Incidence and Prognostic Impact of Heart Failure Hospitalization During Follow-Up After Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction. Am J Cardiol. 2017Jun 1;119(11):1729–39. https://doi.org/10.1016/j.amjcard.2017.03.013. (Epub 2017 Mar 22 PMID: 28407886).
- Takeda A, Martin N, Taylor RS, Taylor SJ. Disease management interventions for heart failure. Cochrane Database Syst Rev. 2019:1(1):CD002752. https://doi.org/ 10.1002/14651858.CD002752.pub4. PMID: 30620776; PMCID: PMC6492456.
- 4. Writing Committee; Maddox TM, Januzzi JL Jr, Allen LA, Breathett K, Butler J, Davis LL, Fonarow GC, Ibrahim NE, Lindenfeld J, Masoudi FA, Motiwala SR, Oliveros E, Patterson JH, Walsh MN, Wasserman A, Yancy CW, Youmans QR. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021;77(6):772–810. https://doi.org/10.1016/j.jacc.2020.11. 022. Epub 2021 Jan 11. PMID: 33446410.
- 5. Dunlay SM, Givertz MM, Aguilar D, Allen LA, Chan M, Desai AS, Deswal A, Dickson VV, Kosiborod MN, Lekavich CL, McCoy RG, Mentz RJ, Piña IL; American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; and the Heart Failure Society of America. Type 2 Diabetes Mellitus and Heart Failure: A Scientific Statement From the American Heart Association and the Heart Failure Society of America: This statement does not represent an update of the 2017 ACC/AHA/HFSA heart failure guideline update. Circulation. 2019 Aug 13;140(7):e294-e324. https://doi.org/10.1161/CIR.00000000000091. Epub 2019 Jun 6. Erratum in: Circulation. 2019:140(12):e692. https://doi.org/10.1161/CIR.00000 0000000735. PMID: 31167558.
- Palanca A, Castelblanco E, Perpiñán H, Betriu À, Soldevila B, Valdivielso JM, Bermúdez M, Duran X, Fernández E, Puig-Domingo M, Groop PH, Alonso N, Mauricio D. Prevalence and progression of subclinical atherosclerosis in patients with chronic kidney disease and diabetes. Atherosclerosis. 2018Sep;276:50–7. https://doi.org/10.1016/j.atherosclerosis.2018.07.018. (Epub 2018 Jul 19 PMID: 30032025).

- Assar ME, Angulo J, Rodríguez-Mañas L. Diabetes and ageing-induced vascular inflammation. J Physiol. 2016:594(8):2125–46. https://doi.org/10. 1113/JP270841. Epub 2015 Nov 2. PMID: 26435167; PMCID: PMC4933100.
- Park JJ. Epidemiology, Pathophysiology, Diagnosis and Treatment of Heart Failure in Diabetes. Diabetes Metab J. 2021:45(2):146–157. https:// doi.org/10.4093/dmj.2020.0282. Epub 2021 Mar 25. Erratum in: Diabetes Metab J. 2021 Sep;45(5):796. https://doi.org/10.4093/dmj.2021.0239. PMID: 33813813; PMCID: PMC8024162.
- De Backer D, Cecconi M, Chew MS, Hajjar L, Monnet X, Ospina-Tascón GA, Ostermann M, Pinsky MR, Vincent JL. A plea for personalization of the hemodynamic management of septic shock. Crit Care. 2022Dec 1;26(1):372. https://doi. org/10.1186/s13054-022-04255-y.PMID:36457089;PMCID:PMC9714237.
- Kruse O, Grunnet N, Barfod C. Blood lactate as a predictor for in-hospital mortality in patients admitted acutely to hospital: a systematic review. Scand J Trauma Resusc Emerg Med. 2011Dec;28(19):74. https://doi.org/10. 1186/1757-7241-19-74.PMID:22202128;PMCID:PMC3292838.
- Kuten Pella O, Hornyák I, Horváthy D, Fodor E, Nehrer S, Lacza Z. Albumin as a Biomaterial and Therapeutic Agent in Regenerative Medicine. Int J Mol Sci. 2022Sep 12;23(18):10557. https://doi.org/10.3390/ijms231810557.PMID:361 42472;PMCID:PMC9502107.
- Gharipour A, Razavi R, Gharipour M, Mukasa D. Lactate/albumin ratio: An early prognostic marker in critically ill patients. Am J Emerg Med. 2020Oct;38(10):2088–95. https://doi.org/10.1016/j.ajem.2020.06.067. (Epub 2020 Jun 27 PMID: 33152585).
- Butt W. The Lactate-Albumin Ratio Predicts Multiple Organ Dysfunction Syndrome and Death, But Is It Ready to Use? Pediatr Crit Care Med. 2023Sep 1;24(9):785–7. https://doi.org/10.1097/PCC.00000000003317. (Epub 2023 Sep 5 PMID: 37668501).
- Guo W, Zhao L, Zhao H, Zeng F, Peng C, Guo W, Yan H. The value of lactate/ albumin ratio for predicting the clinical outcomes of critically ill patients with heart failure. Ann Transl Med. 2021Jan;9(2):118. https://doi.org/10. 21037/atm-20-4519.PMID:33569420;PMCID:PMC7867948.
- Perrone-Filardi P, Paolillo S, Costanzo P, Savarese G, Trimarco B, Bonow RO. The role of metabolic syndrome in heart failure. Eur Heart J. 2015Oct 14;36(39):2630–4. https://doi.org/10.1093/eurheartj/ehv350. (Epub 2015 Aug 4 PMID: 26242711).
- Marsico F, Gargiulo P, Marra AM, Parente A, Paolillo S. Glucose Metabolism Abnormalities in Heart Failure Patients: Insights and Prognostic Relevance. Heart Fail Clin. 2019Jul;15(3):333–40. https://doi.org/10.1016/j.hfc.2019.02. 002. (Epub 2019 Apr 5 PMID: 31079691).
- Matsue Y, Suzuki M, Nakamura R, et al. Prevalence and prognostic implications of pre-diabetic state in patients with heart failure[J]. Circ J. 2011;75(12):2833–9.
- Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JJ, Swedberg KB, Ostergren J, Michelson EL, Pieper KS, Granger CB. Predictors of mortality and morbidity in patients with chronic heart failure. Eur Heart J. 2006Jan;27(1):65–75. https:// doi.org/10.1093/eurheartj/ehi555. (Epub 2005 Oct 11 PMID: 16219658).
- Crawford SO, Ambrose MS, Hoogeveen RC, Brancati FL, Ballantyne CM, Young JH. Association of lactate with blood pressure before and after rapid weight loss. Am J Hypertens. 2008Dec;21(12):1337–42. https://doi.org/10. 1038/ajh.2008.282. (Epub 2008 Sep 18 PMID: 18802433).
- Masyuk M, Wernly B, Lichtenauer M, Franz M, Kabisch B, Muessig JM, Zimmermann G, Lauten A, Schulze PC, Hoppe UC, Kelm M, Bakker J, Jung C. Prognostic relevance of serum lactate kinetics in critically ill patients. Intensive Care Med. 2019Jan;45(1):55–61. https://doi.org/10.1007/s00134-018-5475-3. (Epub 2018 Nov 26 PMID: 30478622).
- Pokorski M, Pozdzik M, Antosiewicz J, Dymecka A, Mazzatenta A, Di Giulio C. Hypoxic Ventilatory Reactivity in Experimental Diabetes. Adv Exp Med Biol. 2015;860:123–32. https://doi.org/10.1007/978-3-319-18440-1_14. (PMID: 26303474).
- Matsushita K, Williams EK, Mongraw-Chaffin ML, Coresh J, Schmidt MI, Brancati FL, Hoogeveen RC, Ballantyne CM, Young JH. The association of plasma lactate with incident cardiovascular outcomes: the ARIC Study. Am J Epidemiol. 2013:178(3):401–9. https://doi.org/10.1093/aje/kwt002. Epub 2013 Jun 30. PMID: 23817916; PMCID: PMC3727342.
- Chien SC, Chen CY, Lin CF, Yeh HI. Critical appraisal of the role of serum albumin in cardiovascular disease. Biomark Res. 2017Nov;10(5):31. https:// doi.org/10.1186/s40364-017-0111-x.PMID:29152305;PMCID:PMC5681838.
- Arques S. Human serum albumin in cardiovascular diseases. Eur J Intern Med. 2018Jun;52:8–12. https://doi.org/10.1016/j.ejim.2018.04.014. (Epub 2018 Apr 19 PMID: 29680174).

- Colombo G, Clerici M, Giustarini D, Rossi R, Milzani A, Dalle-Donne I. Redox albuminomics: oxidized albumin in human diseases. Antioxid Redox Signal. 2012Dec 1;17(11):1515–27. https://doi.org/10.1089/ars.2012.4702. (Epub 2012 Jun 25 PMID: 22587567).
- Xia X, Tan S, Zeng R, Ouyang C, Huang X. Lactate dehydrogenase to albumin ratio is associated with in-hospital mortality in patients with acute heart failure: Data from the MIMIC-III database. Open Med (Wars). 2024Mar 19;19(1):20240901. https://doi.org/10.1515/med-2024-0901.PMID:3858482 2;PMCID:PMC10996934.
- Kong T, Chung SP, Lee HS, Kim S, Lee J, Hwang SO, Shin SD, Song KJ, Cha KC, You JS; Korean Cardiac Arrest Research Consortium (KoCARC) Investigators. The Prognostic Usefulness of the Lactate/Albumin Ratio for Predicting Clinical Outcomes in Out-of-Hospital Cardiac Arrest: a Prospective, Multicenter Observational Study (koCARC) Study. Shock. 2020:53(4):442–451. https:// doi.org/10.1097/SHK.00000000001405. PMID: 31306348.
- Chen DL, Chung CM, Wang GJ, Chang KC. Lactate-to-albumin ratio and cholesterol levels predict neurological outcome in cardiac arrest survivors. Am J Emerg Med. 2024Sep;83:9–15. https://doi.org/10.1016/j.ajem.2024.06. 029. (Epub 2024 Jun 25 PMID: 38943710).
- Feng J, Zhang Y, Zhang J. Epidemiology and Burden of Heart Failure in Asia. JACC Asia. 2024Mar 19;4(4):249–64. https://doi.org/10.1016/j.jacasi.2024.01. 013.PMID:38660101;PMCID:PMC11035951.
- Bozkurt B, Ahmad T, Alexander K, Baker WL, Bosak K, Breathett K, Carter S, Drazner MH, Dunlay SM, Fonarow GC, Greene SJ, Heidenreich P, Ho JE, Hsich E, Ibrahim NE, Jones LM, Khan SS, Khazanie P, Koelling T, Lee CS, Morris AA, Page RL 2nd, Pandey A, Piano MR, Sandhu AT, Stehlik J, Stevenson LW, Teerlink J, Vest AR, Yancy C, Ziaeian B; WRITING COMMITTEE MEMBERS. HF STATS 2024: Heart Failure Epidemiology and Outcomes Statistics An Updated 2024 Report from the Heart Failure Society of America. J Card Fail. 2024:S1071–9164(24)00232-X. https://doi.org/10.1016/j.cardfail.2024.07.001. Epub ahead of print. PMID: 39322534.
- Pullicino PM, McClure LA, Howard VJ, Wadley VG, Safford MM, Meschia JF, Anderson A, Howard G, Soliman EZ. Identifying a high stroke risk subgroup in individuals with heart failure. J Stroke Cerebrovasc Dis. 2013:22(5):620–6. https://doi.org/10.1016/j.jstrokecerebrovasdis.2011.10.012. Epub 2011 Dec 3. PMID: 22142776; PMCID: PMC3326204.
- Wang R, Ye H, Zhao Y, Wei J, Wang Y, Zhang X, Wang L. Effect of sacubitril/ valsartan and ACEI/ARB on glycaemia and the development of diabetes: a systematic review and meta-analysis of randomised controlled trials. BMC Med. 2022Dec 17;20(1):487. https://doi.org/10.1186/s12916-022-02682-w. PMID:36527023;PMCID:PMC9758945.
- Shimizu I, Minamino T, Toko H, Okada S, Ikeda H, Yasuda N, Tateno K, Moriya J, Yokoyama M, Nojima A, Koh GY, Akazawa H, Shiojima I, Kahn CR, Abel ED, Komuro I. Excessive cardiac insulin signaling exacerbates systolic dysfunction induced by pressure overload in rodents. J Clin Invest. 2010;120(5):1506–14. https://doi.org/10.1172/JCI40096. Epub 2010 Apr 19. PMID: 20407209; PMCID: PMC2860916.
- Tsujimoto T, Sugiyama T, Shapiro MF, Noda M, Kajio H. Risk of Cardiovascular Events in Patients With Diabetes Mellitus on β-Blockers. Hypertension. 2017;70(1):103–110. https://doi.org/10.1161/HYPERTENSIONAHA.117.09259. Epub 2017 May 30. PMID: 28559400; PMCID: PMC5739105.
- Paolillo S, Dell'Aversana S, Esposito I, Poccia A, Perrone FP. The use of β-blockers in patients with heart failure and comorbidities: Doubts, certainties and unsolved issues. Eur J Intern Med. 2021 Jun;88:9–14. https://doi.org/ 10.1016/j.ejim.2021.03.035. (Epub 2021 Apr 30 PMID: 33941435).
- Arnold SV, Inzucchi SE, Echouffo-Tcheugui JB, Tang F, Lam CSP, Sperling LS, Kosiborod M. Understanding Contemporary Use of Thiazolidinediones. Circ Heart Fail. 2019Jun;12(6): e005855. https://doi.org/10.1161/CIRCHEARTF AILURE.118.005855. (PMID: 31129998).
- Filion KB, Joseph L, Boivin JF, Suissa S, Brophy JM. Thiazolidinediones and the risk of incident congestive heart failure among patients with type 2 diabetes mellitus. Pharmacoepidemiol Drug Saf. 2011Aug;20(8):785–96. https://doi. org/10.1002/pds.2165. (Epub 2011 Jun 13 PMID: 21671441).

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.