Association of Metabolic Score for Insulin Resistance with Adverse Prognosis in Patients with Chronic Heart Failure: Postprint

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Abstract

Background Insulin resistance (IR) is closely associated with the occurrence and development of cardiovascular disease. Currently, multiple studies have confirmed that IR is highly prevalent in patients with heart failure (HF) and is related to adverse cardiovascular outcomes. However, the association between the indicator reflecting IR—metabolic score for insulin resistance (Mets-IR)—and adverse prognosis in patients with chronic heart failure (CHF) remains unclear. Objective To analyze the correlation between Mets-IR and adverse prognosis in CHF patients. Methods This was a retrospective study. A total of 313 patients diagnosed with CHF in the Department of Cardiology of The Second Affiliated Hospital of Zhengzhou University from January 2020 to January 2021 were selected as study subjects. Patients were divided into two groups according to the occurrence of all-cause death: the all-cause death group (61 cases) and the control group (252 cases). Mets-IR was analyzed as a categorical variable and divided into two categories based on the median: low-level Mets-IR (Mets-IR<37.28) and high-level Mets#2;IR (Mets#2;IR $\geq$ 37.28). Baseline data were collected, including Mets-IR, age, serum biomarkers, and echocardiographic parameters. Follow-up was conducted until December 31, 2022. Patient prognosis was collected through the hospital' s electronic medical record system or telephone follow-up. The primary endpoint was all-cause death, and the secondary endpoint was readmission due to HF. Survival curves for all-cause death and HF readmission in patients with different Mets-IR levels were analyzed using Kaplan-Meier curves and Log-rank test. Cox proportional hazards regression model was applied to analyze the correlation between Mets-IR and the risk of all-cause death and HF readmission. Receiver operating characteristic (ROC) curves were constructed to analyze the predictive value of Mets-IR for all-cause death and HF readmission risk in CHF patients. Results The median follow-up duration was 25.0 (9.0, 28.5) months. Among the 313 CHF patients, 61

cases (19.5%) experienced all-cause death and 121 cases (38.7%) experienced readmission due to HF. Patients in the all-cause death group had higher age, fasting plasma glucose, Mets#2;IR, N-terminal pro-B-type natriuretic peptide, serum uric acid, neutrophil count, red cell distribution width, atrial fibrillation, hypertension, diuretics, aldosterone receptor antagonists, and New York Heart Association (NYHA) class than the control group, while diastolic blood pressure, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, albumin, hemoglobin, serum sodium, left ventricular ejection fraction, and angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB)/angiotensin receptor-neprilysin inhibitors (ARNI) were lower than the control group (P<0.05). Log-rank test results showed that patients with high-level Mets#2;IR had higher all-cause mortality and HF readmission rates than those with low-level Mets-IR (P<0.001). After adjusting for multiple confounding factors, Cox proportional hazards regression analysis showed that compared with low-level Mets-IR patients, high-level Mets-IR patients had increased risk of all-cause death (HR=2.90, 95%CI=1.51~5.54, P=0.001) and HF readmission risk (HR=1.55, 95%CI=1.04~2.30, P=0.030). The area under the ROC curve for Mets-IR in predicting all-cause death risk and HF readmission risk was 0.68 (95%CI=0.62~0.75) and 0.62 (95%CI=0.55~0.68), respectively. Conclusion Elevated Mets-IR levels may increase the risk of all-cause death and HF readmission in CHF patients and can be used for risk stratification in CHF patients.

Full Text

Introduction

Heart failure (HF) is a complex clinical syndrome that imposes an increasingly heavy burden on healthcare costs due to its high mortality rate and frequent hospitalizations. It is estimated that 64 million people worldwide suffer from HF, and this number continues to rise due to population growth and aging [1]. Therefore, early identification of high-risk patients is necessary to implement individualized interventions of varying intensity. Studies have shown that metabolic syndrome increases the risk of developing HF by twofold [2]. Insulin resistance (IR), a component of metabolic syndrome, is highly prevalent in HF patients (up to 60%) and is associated with adverse cardiovascular outcomes [3-4]. In the setting of IR, the myocardium utilizes free fatty acids rather than glucose [5], and this metabolic irregularity increases vulnerability to pressure overload or ischemia. Furthermore, IR leads to increased activation of angiotensin II-stimulated extracellular signal-regulated kinases 1 and 2 [6]. The hyperinsulinemic-euglycemic clamp technique is the gold standard for diagnosing IR; however, its time-consuming nature, high cost, and complexity make it difficult to apply in real-world clinical settings and large-scale studies [7]. Researchers from Mexico have developed a novel tool called the Metabolic Score for Insulin Resistance (Mets-IR) to assess insulin sensitivity [8]. Currently, few studies have evaluated the association between Mets-IR and adverse prognosis in chronic heart failure (CHF) patients. Therefore, this study aims to assess the

relationship between Mets-IR and adverse prognosis in CHF patients, with the goal of reducing the incidence of adverse outcomes and providing a theoretical basis for individualized risk stratification management.

Methods

1.1 Study Subjects

We selected 313 patients diagnosed with CHF in the Department of Cardiovascular Medicine at the Second Affiliated Hospital of Zhengzhou University between January 2020 and January 2021 as study subjects. Inclusion criteria were: (1) meeting the diagnostic criteria of the "2018 Chinese Guidelines for the Diagnosis and Treatment of Heart Failure" [9]; (2) age $\geq$ 18 years; and (3) complete clinical data. Exclusion criteria were: (1) absence of fasting triglycerides (TG), fasting blood glucose (FBG), or high-density lipoprotein cholesterol (HDL-C); (2) CHF acute episode with stable condition <1 week; (3) severe hepatic or renal insufficiency, congenital heart disease, pulmonary heart disease, severe infection, or malignant tumor. This study was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Zhengzhou University (approval number: 2023206), and all CHF patients provided informed consent.

1.2 Data Collection

Clinical data were collected through the hospital' s electronic medical record system or telephone follow-up, including inpatient, emergency, and outpatient records.

1.2.1 Clinical Data We collected patient demographics (sex, age, height, weight), blood pressure (systolic blood pressure [SBP], diastolic blood pressure [DBP]), and serum biomarkers measured from venous blood samples collected after 8-10 hours of fasting at first admission, including N-terminal pro-B-type natriuretic peptide (NT-proBNP), serum creatinine (Scr), serum uric acid (SUA), low-density lipoprotein cholesterol (LDL-C), HDL-C, TG, total cholesterol (TC), and calculated body mass index (BMI) and Mets-IR. The formulas were: (1) BMI = weight (kg)/height^2 (m^2); (2) Mets-IR = Ln[2×FBG (mg/dL) + TG (mg/dL)] × BMI (kg/m^2)/Ln[HDL-C (mg/dL)].

1.2.3 Medication Use and Cardiac Function Classification Medication data included β-blockers, angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB)/angiotensin receptor-neprilysin inhibitors (ARNI), diuretics, aldosterone receptor antagonists, and lipid-lowering drugs. Cardiac function classification was based on the New York Heart Association (NYHA) functional classification system [9].

1.3 Follow-up and Grouping

Patients were followed up every 6 months through the electronic medical record system or telephone until December 31, 2022, with a median follow-up duration of 25.0 (9.0, 28.5) months. The primary endpoint was all-cause mortality, and the secondary endpoint was readmission due to HF. For the secondary endpoint, only the first HF readmission event during follow-up was analyzed. Patients were divided into two groups based on all-cause mortality: the all-cause mortality group (61 cases) and the control group (252 cases). Mets-IR was analyzed as a categorical variable, dichotomized by the median into low-level Mets-IR (Mets-IR $<$ 37.28) and high-level Mets-IR (Mets-IR $\geq$ 37.28).

1.4 Statistical Analysis

Statistical analysis was performed using SPSS 25.0 and GraphPad Prism 8.0. The Kolmogorov-Smirnov test was used to assess normality of continuous variables. Normally distributed variables were expressed as mean $\pm$ standard deviation and compared between groups using independent samples t-test. Non-normally distributed variables were expressed as median (P25, P75) and compared using Mann-Whitney U test. Categorical variables were expressed as frequencies and percentages and compared using ^{2} test or Fisher' s exact test. Survival curves for all-cause mortality and HF readmission across different Mets-IR levels were analyzed using Kaplan-Meier plots and log-rank tests. Cox proportional hazards regression models were applied to analyze the association between Mets-IR and risks of all-cause mortality and HF readmission. Variables with P $<$ 0.05 or clinical significance were included in the Cox model, and multicollinearity was tested with a variance inflation factor threshold of $<$4. Receiver operating characteristic (ROC) curves were constructed to evaluate the predictive value of Mets-IR for all-cause mortality and HF readmission. P $<$ 0.05 was considered statistically significant.

Results

Baseline Characteristics

Among the 313 CHF patients, 184 (58.8%) were male and 129 (41.2%) were female, with a mean age of 68.0 $\pm$ 13.3 years. There were no significant differences between groups in sex, admission heart rate, BMI, SBP, TC, aspartate aminotransferase (AST), alanine aminotransferase (ALT), Scr, blood urea nitrogen (BUN), serum potassium (K), left ventricular end-diastolic diameter (LVEDD), coronary artery disease (CAD), diabetes, smoking history, β-blocker use, or lipid-lowering drug use (P $>$ 0.05). However, the all-cause mortality group had significantly higher age, FBG, Mets-IR, NT-proBNP, SUA, neutrophil count, red cell distribution width (RDW), atrial fibrillation (AF), hypertension, diuretic use, aldosterone receptor antagonist use, and NYHA classification, and significantly lower DBP, TG, HDL-C, LDL-C, albumin (ALB), hemoglobin (HB), serum sodium (Na), left ventricular ejection fraction (LVEF),

and ACEI/ARB/ARNI use compared to the control group ($P < 0.05$) .

2.2.1 Survival Curve Analysis

During follow-up, 61 patients (19.5%) experienced all-cause mortality (16 in low-level Mets-IR group, 45 in high-level Mets-IR group) and 121 patients (38.7%) had at least one HF readmission (46 in low-level Mets-IR group, 75 in high-level Mets-IR group). Kaplan-Meier survival analysis showed that patients with high-level Mets-IR had significantly higher rates of all-cause mortality and HF readmission compared to those with low-level Mets-IR ($P < 0.001$) [Figure 1: see original paper].

2.2.2 Association Between Mets-IR and All-Cause Mortality Risk

Using all-cause mortality as the dependent variable (yes = 1, no = 0) and Mets-IR category as the independent variable (low-level = 0, high-level = 1), univariate Cox regression analysis showed that high-level Mets-IR was associated with increased all-cause mortality risk (HR = 3.23, 95%CI = 1.82-5.71, $P < 0.001$). After adjusting for confounders including age, NT-proBNP, ALB, SUA, neutrophil count, RDW, HB, serum Na, LVEF (all as continuous variables), NYHA classification (Class I-II = 0, Class III-IV = 1), AF, hypertension, ACEI/ARB/ARNI, diuretics, and aldosterone receptor antagonists (all yes = 1, no = 0), high-level Mets-IR remained independently associated with increased all-cause mortality risk (HR = 2.90, 95%CI = 1.51-5.54, P = 0.001) .

2.2.3 Association Between Mets-IR and HF Readmission Risk

Using HF readmission as the dependent variable (yes = 1, no = 0) and Mets-IR category as the independent variable, univariate Cox regression analysis showed that high-level Mets-IR was associated with increased HF readmission risk (HR = 1.86, 95%CI = 1.29-2.68, P = 0.001). After adjusting for confounders including age, NT-proBNP, ALB, SUA, RDW, HB, serum K, LVEF, LVEDD (all continuous), NYHA classification, AF, CAD, hypertension, ACEI/ARB/ARNI, diuretics, and aldosterone receptor antagonists, high-level Mets-IR remained independently associated with increased HF readmission risk (HR = 1.55, 95%CI = 1.04-2.30, P = 0.030) .

2.3 Predictive Value of Mets-IR for All-Cause Mortality and HF Readmission

ROC curve analysis showed that Mets-IR predicted all-cause mortality with an area under the curve (AUC) of 0.68 (95%CI = 0.62-0.75), optimal cutoff value of 37.19, sensitivity of 75.4%, and specificity of 55.6% [Figure 2: see original paper]. For HF readmission prediction, Mets-IR had an AUC of 0.62 (95%CI = 0.55-0.68), optimal cutoff value of 37.73, sensitivity of 62.0%, and specificity of 39.1% [Figure 3: see original paper].

Discussion

Insulin resistance is closely associated with cardiovascular disease and has been shown to predict cardiovascular events in multiple clinical studies. Mets-IR is a novel IR index with high accuracy for detecting IR, validated against the euglycemic-hyperinsulinemic clamp with an AUC of 0.84 (95%CI = 0.78-0.90) [8]. Qian et al. [10] conducted a prospective cohort study demonstrating that Mets-IR was significantly positively associated with the risk of new-onset cardiovascular disease/stroke/heart disease, independent of age, sex, smoking, alcohol consumption, and sleep duration. Han et al. [11] found that Mets-IR levels were positively associated with prehypertension or hypertension among Japanese subjects with normal glucose levels. In a longitudinal Korean cohort of adults without diabetes, elevated Mets-IR was positively associated with incident ischemic heart disease [12]. A Swedish study of 1,187 patients without prior HF found that IR predicted HF development independent of all established risk factors, including diabetes itself [13]. However, to our knowledge, no study has evaluated the association between Mets-IR and adverse prognosis in CHF patients. Therefore, this study aimed to assess this relationship to enable early identification of high-risk patients for individualized intervention.

Our results demonstrate a significant association between Mets-IR and adverse prognosis risk in CHF patients, consistent with previous research. Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and triglyceride-glucose (TyG) index are also reliable surrogate markers for insulin sensitivity. A prospective study of 156 non-diabetic patients hospitalized for acute HF confirmed that HOMA-IR predicted the composite endpoint of death and readmission at 90 days [14]. Previous studies have also reported that TyG index is associated with adverse clinical outcomes in HF patients [15]. Unlike these studies, we used Mets-IR, a novel insulin resistance index that has been shown to have better diagnostic performance than non-insulin IR indices such as TG/HDL and TyG [8]. Zhang et al. [16] conducted a retrospective cohort study evaluating whether Mets-IR predicts adverse outcomes in ischemic cardiomyopathy patients with diabetes, finding that hazard ratios for adverse outcomes during follow-up increased with Mets-IR quartiles, even after adjusting for general HF risk factors. Similarly, our study found that patients who experienced all-cause mortality or HF readmission had significantly higher Mets-IR than control patients. Previous research has shown that HF patients with IR have more severe left ventricular dysfunction and higher mortality than those without IR [16]. Our results also identified age, SUA, RDW, LVEF, and LVEDD as independent risk factors for all-cause mortality or HF readmission in CHF patients, consistent with previous findings [17-18].

This study demonstrates that Mets-IR is a potential independent predictor of all-cause mortality and HF readmission risk in CHF patients, even after adjusting for baseline characteristics and HF risk factors. In cardiovascular disease patients, the utility of Mets-IR may be influenced by diabetes and hyperlipidemia to some extent, and these factors should be controlled to establish its value as a

biomarker. Therefore, future studies should evaluate mean changes in Mets-IR during cardiovascular disease progression and follow-up, and further investigate the potential benefits of Mets-IR-targeted therapies in cardiovascular disease patients. Additionally, future HF prognostic models could incorporate Mets-IR for comprehensive risk assessment. Finally, the pathological role of Mets-IR in different types of cardiovascular disease requires further investigation.

Although the pathophysiological mechanisms linking HF and IR require further study, potential mechanisms by which IR leads to adverse prognosis in HF may include: First, under IR conditions, the myocardium utilizes free fatty acids and reduces glucose uptake and oxidation, leading to glucolipid metabolic disorder that induces immune cell infiltration into adipose tissue and macrophage activation, triggering chronic inflammation and reducing myocardial response to injury, thereby increasing cardiovascular disease risk [19]. Additionally, IR alters the systemic neurohumoral environment, causing changes in cardiac metabolism and signaling pathways that affect the cardiovascular system and participate in CVD development [5]. IR activates the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS), increasing reactive oxygen species and oxidative stress, which in turn exacerbates IR and impairs vascular function [20]. IR impairs calcium signaling, leading to compromised myocardial contractility, reduced cardiac energy efficiency, cardiomyocyte death, and cardiac fibrosis [21]. Second, IR causes subcellular abnormalities including oxidative stress, mitochondrial dysfunction, and endoplasmic reticulum stress [22]. Meanwhile, HF may induce myocardial and systemic IR, creating a vicious cycle [23].

This study established a prediction model incorporating Mets-IR and confirmed its significant predictive value for adverse prognosis in CHF patients. The increasing complexity and healthcare costs of HF management drive the need for useful markers for patient risk stratification and prognosis. Mets-IR is readily available in clinical practice and can be routinely monitored during patient management to enable early intervention in high-risk patients and improve outcomes. This study has several limitations. First, as a retrospective study, the causal relationship between Mets-IR and adverse prognosis in CHF patients requires confirmation through large-scale multicenter prospective studies. Second, since Mets-IR was assessed only at admission without dynamic monitoring, we could not evaluate whether reducing Mets-IR improves patient outcomes. Finally, despite including as many clinically relevant variables as possible in the multivariate analysis, potential confounders may remain.

In conclusion, elevated Mets-IR levels may increase the risk of all-cause mortality and HF readmission in CHF patients. Mets-IR can serve as a predictor of all-cause mortality and HF readmission risk and is independently associated with adverse prognosis in CHF patients, showing promise as a risk stratification tool for poor outcomes in this population.

Author Contributions: Yin Qiuguo conceived and designed the study, supervised its implementation, and wrote the manuscript. Yin Qiuguo, Qin Xintong,

Zhang Yidan, and Jiang Peng collected and organized the data. Yin Qiuguo, Guo Ping, and Jia Xingtai revised the manuscript. Jian Liguo was responsible for quality control and review of the research process and coordinated the overall progress of the article.

Conflict of Interest: The authors declare no conflict of interest.

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Note: Figure translations are in progress. See original paper for figures.