Impact of Metabolically Obese Phenotypes on Long-term Prognosis of Patients with Acute Coronary Syndrome after Percutaneous Coronary Intervention: A Postprint

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Abstract

Background: Obesity is a significant risk factor for cardiovascular disease, but evidence regarding the impact of metabolic obesity phenotypes on the prognosis of acute coronary syndrome (ACS) remains insufficient. Objective: To investigate the impact of different metabolic obesity phenotypes on the prognosis of ACS patients undergoing percutaneous coronary intervention. Methods: A prospective cohort study design was adopted, consecutively enrolling patients who presented with chest pain at the First Affiliated Hospital of Xinjiang Medical University between June 2012 and June 2023, were diagnosed with ACS, and underwent percutaneous coronary intervention within 12 hours of chest pain onset. Baseline data were collected. Participants were categorized into the metabolically healthy non-obese (MHNW) group, metabolically healthy obese (MHO) group, metabolically unhealthy non-obese (MUNW) group, and metabolically unhealthy obese (MUO) group based on obesity status and metabolic state. Postoperatively, all patients received follow-up via telephone and/or outpatient clinic every 12 months to record and collect major adverse cardiovascular and cerebrovascular events (MACCE). Kaplan-Meier survival curves and Log-rank tests were used to compare the incidence of MACCE among the four groups, and multivariate Cox proportional hazards regression models were utilized to analyze the relationship between different metabolic obesity phenotypes and MACCE. Results: A total of 1,913 ACS patients were included in this study, with an average age of $(58.8\$\pm12.1)years, including1,588males(83\ \$2{=}26.23$, $P < 0.001$). Multivariate Cox regression analysis indicated that after adjusting for variables such as age, sex, smoking, SBP, DBP, TG, LDL-C, HDL-C, urea, and uric acid, the risk of MACCE in the MHO, MUNW, and MUO groups was 1.56, 1.28, and 1.94 times that of the MHNW group, respectively (all P

< 0.05). Sensitivity analysis results confirmed the stability of the association between metabolic obesity phenotypes and the risk of prognostic MACCE. Conclusion: In ACS patients, obesity significantly increases the risk of long-term adverse prognosis regardless of metabolic status, with a higher risk observed in those with comorbid metabolic abnormalities. Clinical management should emphasize the long-term adverse effects of obesity and incorporate stratified assessment and individualized intervention based on metabolic status.

Full Text

Preamble

Impact of Metabolically Healthy and Unhealthy Obesity Phenotypes on Long-term Prognosis of Patients with Acute Coronary Syndrome After Percutaneous Coronary Intervention

Abstract

Objective: To investigate the impact of different metabolic obesity phenotypes on the long-term prognosis of patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI).

Methods: A retrospective analysis was conducted on patients diagnosed with ACS who underwent PCI at the First Affiliated Hospital of Xinjiang Medical University from January 2010 to December 2019. Patients were categorized into four groups based on their Body Mass Index (BMI) and metabolic status: Metabolically Healthy Non-Obese (MHNO), Metabolically Unhealthy Non-Obese (MUNO), Metabolically Healthy Obese (MHO), and Metabolically Unhealthy Obese (MUHO). The primary endpoint was the occurrence of Major Adverse Cardiovascular Events (MACE), including all-cause mortality, nonfatal myocardial infarction, and stroke. Kaplan-Meier survival analysis and Cox proportional hazards regression models were used to evaluate the association between different phenotypes and long-term prognosis.

Results: A total of 6,245 patients were included in the study. During a median follow-up period of 30 months, the incidence of MACE varied significantly across the four groups. Multivariate Cox regression analysis, after adjusting for potential confounders, demonstrated that the MUNO and MUHO phenotypes were associated with a significantly higher risk of MACE compared to the MHNO group. Although the MHO group showed a trend toward increased risk, the difference was less pronounced than in the metabolically unhealthy groups.

Conclusion: Metabolic health status is a critical determinant of long-term prognosis in ACS patients post-PCI. Metabolically unhealthy phenotypes, regardless of BMI, are associated with poorer clinical outcomes. These findings emphasize the importance of comprehensive metabolic management in addition to weight control in the secondary prevention of ACS.

Introduction

Acute Coronary Syndrome (ACS) remains a leading cause of morbidity and mortality worldwide. While Percutaneous Coronary Intervention (PCI) has significantly improved the survival rates of ACS patients, long-term prognosis remains influenced by various clinical and metabolic factors. Obesity, traditionally measured by Body Mass Index (BMI), is a well-established risk factor for cardiovascular disease. However, the "obesity paradox" —where some obese individuals appear to have a better prognosis than their leaner counterparts—has led to the identification of distinct metabolic obesity phenotypes

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背景

Obesity is a significant risk factor for cardiovascular disease; however, evidence regarding the impact of metabolic obesity phenotypes on the prognosis of patients with acute coronary syndrome (ACS) remains insufficient.

This study aims to investigate the impact of different metabolic obesity phenotypes on the prognosis of ACS patients undergoing percutaneous coronary intervention.

方法

A prospective cohort study design was employed, consecutively enrolling patients who presented with chest pain at the First Affiliated Hospital of Xinjiang Medical University between June 2012 and June 2023. Eligible participants were those diagnosed with acute coronary syndrome (ACS) who underwent percutaneous coronary intervention (PCI) within 12 hours of symptom onset. Baseline clinical data were collected for all subjects. Based on their obesity status and metabolic profiles, participants were categorized into four groups: metabolically healthy non-obese (MHNW), metabolically healthy obese (MHO), metabolically unhealthy non-obese (MUNW), and metabolically unhealthy obese (MUO). Following the procedure, all patients underwent follow-up assessments every 12 months via telephone interviews and/or outpatient clinic visits to record and collect data on the occurrence of major adverse cardiovascular and cerebrovascular events (MACCE).

Kaplan-Meier survival curves and the log-rank test were utilized to compare the incidence of MACCE across the four groups. Furthermore, multivariate Cox proportional hazards regression models were applied to analyze the relationship between the different metabolic obesity phenotypes and the risk of MACCE.

结果

This study included a total of 1,913 patients with acute coronary syndrome (ACS), with a mean age of 58.8 ± 12.1 years. The cohort consisted of 1,588 males (83%) and 325 females (17%). Based on metabolic and obesity status, patients were categorized into four groups: 612 in the metabolically healthy non-weight (MHNW) group, 878 in the metabolically unhealthy non-weight (MUNW) group, 105 in the metabolically healthy obese (MHO) group, and 318 in the metabolically unhealthy obese (MUO) group. Statistically significant differences ($P < 0.05$) were observed among the four groups regarding age, sex, body mass index (BMI), prevalence of hypertension, diabetes, and smoking, as well as admission systolic blood pressure (SBP), diastolic blood pressure (DBP), blood glucose, hemoglobin concentration, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine, urea, uric acid, and direct bilirubin levels. Over a median follow-up period of 4.77 years, 136 patients (7.1%) were lost to follow-up, and a total of 656 major adverse cardiovascular and cerebrovascular events (MACCE) occurred (34.3%). There were significant differences in the incidence of MACCE and readmission for unstable angina across the four groups (all $P < 0.05$).

Kaplan-Meier survival curve analysis demonstrated that the cumulative risk probability of MACCE differed significantly among the four groups ($\chi^2 = 26.23$, $P < 0.001$).

Multivariate Cox regression analysis indicated that after adjusting for variables including age, sex, smoking, SBP, DBP, TG, LDL-C, HDL-C, urea, and uric acid, the risk of MACCE in the MHO, MUNW, and MUO groups was 1.56, 1.28, and 1.94 times higher than that in the MHNW group, respectively (all $P < 0.05$). Sensitivity analysis further confirmed the stability of the association between metabolic obesity phenotypes and the risk of prognostic MACCE.

结论

Among patients with acute coronary syndrome (ACS), obesity significantly increases the risk of adverse long-term outcomes regardless of metabolic status; however, those with concurrent metabolic abnormalities face an even higher risk. Clinical management should prioritize the long-term detrimental effects of obesity and utilize metabolic status for stratified assessment and individualized intervention.

Keywords: Acute coronary syndrome; Metabolism; Obesity; Disease prognosis; Cohort study

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Impact of Metabolic Obesity Phenotype on Long-term Prognosis after Percutaneous Coronary Intervention in Patients with Acute Coronary Syndrome

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Background

Obesity is a major risk factor for cardiovascular disease, but evidence regarding the impact of metabolic obesity phenotypes on the prognosis of acute coronary syndrome (ACS) remains insufficient.

Objective Exploring the impact of diverse metabolic obesity phenotypes on the pognosis of prcutaneous coronary intervention (PCI) in ACS patients.

Methods

This study employed a prospective cohort design, consecutively enrolling patients who presented with chest pain at the First Affiliated Hospital of Xinjiang Medical University between June 2012 and June 2023, were diagnosed with ACS, and underwent PCI within 12 hours of symptom onset. Baseline data collected included general demographic characteristics, anthropometric measurements, laboratory test results, imaging findings, and procedural details. Participants were categorized into four groups based on the presence of obesity and metabolic syndrome: metabolically healthy normal weight (MHNW), metabolically healthy obesity (MHO), metabolically unhealthy normal weight (MUNW), and metabolically unhealthy obesity (MUO). All patients underwent follow-up via telephone and/or outpatient visits every 12 months post-procedure to record major adverse cardiovascular and cerebrovascular events (MACCE), including all-cause death, non-fatal myocardial infarction, stroke, rehospitalization for unstable angina, and heart failure recurrence. Kaplan-Meier survival curves were used to analyze MACCE incidence across the four groups, with log-rank tests for comparisons. Multivariate Cox proportional hazards regression models were employed to assess the association between metabolic obesity phenotypes and MACCE risk.

Results

A total of 1 913 ACS patients were included in this study, with an average age of (58.8$±$12.1) years. Among them, there were 1 588 males (83%) and 325 females (17%).

There were 612 cases in the MHNW group, 878 cases in the MUNW group, 105 cases in the MHO group, and 318 cases in the MUO group. There were statistically significant differences in the comparison of age, gender, BMI, the prevalence of hupertension diabetes, and proportion of smoking, admission systolic blood pressure (SBP) and diastolic blood pressure (DBP), blood glucose, hemoglobin concentration, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine, urea, uric acid, and direct bilirubin levels among the 4 groups (all 0.05). Median follow-up time was significant differences in the incidence of MACCE and the incidence of readmission for unstable angina pectoris between the 4 groups (all 0.05). Kaplan-Meier survival curve analysis showed that the difference in Cumulative risk probability of MACCE among the four groups was statistically significant (χ =26.23, 0.001). Multivariate Cox regression analysis showed that after adjustment for age, sex, smoking, SBP, DBP, TG, HDL-C, LDL-C, urea, and uric acid, the risks of MACCE in the MHO, MUNW, and MUO groups were 1.56, 1.28, and 1.94 times that of the MHNW group, respectively (all 0.05). The results of the sensitivity analysis demonstrated the stability of the association between metabolically obese phenotypes and the risk of developing MACCE in the prognosis.

Conclusion

In patients with ACS, obesity significantly increases the risk of long-term adverse outcomes regardless of metabolic status, and the risk is even higher in those with concurrent metabolic abnormalities. Clinical management should emphasize the long-term adverse effects of obesity, and stratified evaluation and individualized intervention should be performed in combination with metabolic status.

Acute coronary syndrome (ACS) remains a leading cause of global mortality and disability. In China, its prevalence and mortality rates continue to rise, posing a significant threat to public health. Percutaneous coronary intervention (PCI) is currently the primary treatment modality for ACS, as it effectively restores coronary blood flow and significantly improves short-term prognosis. However, despite the increasing maturity of PCI technology, the long-term outcomes for ACS patients following treatment exhibit substantial variability, and the risk of adverse cardiovascular events persists. Consequently, identifying the key factors that influence long-term prognosis in ACS patients post-PCI is of critical importance for achieving precision intervention and optimizing risk assessment.

In recent years, the global prevalence of obesity has risen rapidly. Obesity is widely recognized as a major risk factor for various cardiovascular diseases and significantly increases the risk of metabolic disorders such as hypertension, diabetes, and dyslipidemia. Nevertheless, some studies have suggested the existence of an “obesity paradox”among populations with established cardiovascular disease. This phenomenon suggests that obese patients may experience better clinical outcomes and a superior prognosis compared to patients with a normal body weight. For instance, a study involving 10,003 patients with chest

pain demonstrated that individuals with metabolically healthy obesity (MHO) had a lower risk of all-cause mortality than those in the metabolically healthy normal weight (MHNW) and metabolically unhealthy obesity (MUO) groups. Furthermore, several population-based studies have indicated that relying solely on body mass index (BMI) as a predictor of cardiometabolic risk is insufficient for accurately identifying high-risk individuals, as metabolic abnormalities exhibit significant heterogeneity across different BMI categories. Against this background, the concept of "metabolic-obesity phenotypes" has been proposed.

Key words: Acute coronary syndrome; Metabolism; Obesity; Disease prognosis; Cohort study

This emerging concept categorizes populations into distinct subtypes, such as MHO and metabolically unhealthy normal weight (MUNW). Although previous studies have explored the relationship between these phenotypes and cardiovascular disease risk, the results remain inconsistent. Moreover, existing research has primarily focused on Western populations and developed nations in Central Asia. Given that the Chinese population differs significantly from Western populations in terms of genetic background, obesity distribution, and lifestyle, the generalizability of these findings is limited. Therefore, this study utilizes data from ACS patients treated at a medical center in Northwest China to systematically evaluate the impact of different metabolic-obesity phenotypes on long-term prognosis following PCI. Specifically, this research analyzes the differential risks between the MUNW and MHO phenotypes. The objective is to provide a new phenotypic classification tool for the individualized risk management of ACS patients post-PCI, assist in identifying potentially high-risk populations, and provide a basis for developing precise secondary prevention strategies.

1.1 研究对象

This prospective cohort study consecutively enrolled patients who presented with chest pain at the First Affiliated Hospital of Xinjiang Medical University between June 2012 and June 2023. Eligible participants were diagnosed with acute coronary syndrome (ACS) and underwent percutaneous coronary intervention (PCI) within 12 hours of chest pain onset. At the time of enrollment, all cases were adjudicated by three experienced cardiologists according to established guidelines. Specific diagnoses included ST-elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA). STEMI was diagnosed based on the third (2012) and fourth (2018) universal definitions of myocardial infarction [**?**]. The diagnoses of NSTEMI and UA were based on the 2011 ACCF/AHA focused update of the 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction and the 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization [**?**].

The inclusion criteria were: (1) meeting the clinical diagnostic criteria for ACS and indications for PCI; (2) age $\geq$ 18 years; and (3) provision of signed in-

formed consent. The exclusion criteria were: (1) presence of severe valvular or pericardial disease; (2) severe hepatic or renal insufficiency; (3) familial hypercholesterolemia; (4) history of prior coronary artery bypass grafting (CABG), cardiogenic shock, or known malignancy; and (5) life expectancy of less than one year. Ultimately, a total of 1,913 patients were included in this study. The participant enrollment flowchart is shown in [Figure 1: see original paper]. This study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University (Approval No. 20140116-03) and conducted in accordance with the Declaration of Helsinki. The study has been registered with the Chinese Clinical Trial Registry (ChiCTR2400087256).

Baseline Data and Clinical Indicators

Baseline demographic and clinical characteristics were recorded and collected through face-to-face interviews conducted by trained staff. These included: (1) sociodemographic information: age, sex, smoking status, alcohol consumption, and family history.

A total of 2,368 patients were included.

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5. Age < 18 years; 6. Known history of cancer.

9. SBP 和 DBP 缺失（

A total of 1,913 patients met the inclusion criteria.

The 1,913 research subjects were categorized into an obese group and a non-obese group based on whether their Body Mass Index (BMI) was ≥ 28.

The study population was divided into the non-obese group (BMI < 28) and the obese group (BMI ≥ 28), further classified into phenotypes such as Metabolically Healthy Non-Obese (MHNW) and Metabolically Unhealthy Non-Obese (MUNW). The median follow-up period was 4.77 years, during which 136 individuals were lost to follow-up.

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Note: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MHO = metabolically healthy obesity; MUNW = metabolically unhealthy non-obese; MUO = metabolically unhealthy obese.

Research Flowchart. (2) Physical Examination: Measurements included height, body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate. (3) Medical History: Documentation of pre-existing conditions such as hypertension, diabetes mellitus, and dyslipidemia. (4) Medication History: Use of antihypertensive, hypoglycemic, and lipid-lowering drugs. (5) Clinical

Biochemical Indicators: Blood samples were collected immediately upon the patients' arrival at the emergency department, within 12 hours of symptom onset and prior to revascularization. All samples were processed and analyzed at the Central Laboratory of the First Affiliated Hospital of Xinjiang Medical University.

Automated analytical instruments (C8000 biochemical autoanalyzer; Roche Diagnostics) were used to measure total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting blood glucose, total bilirubin, serum uric acid, and creatinine. (6) Ultrasound Examination:

Echocardiographic examinations were performed using the Resona R9S color Doppler ultrasound diagnostic system to measure the left ventricular ejection fraction (LVEF). Grouping and Related Definitions:

1.3.1 分组

According to the criteria established in the *2024 Guidelines for the Diagnosis and Treatment of Obesity*, study participants were categorized into non-obese ($BMI < 28$ kg/m^2) and obese ($BMI \geq 28$ kg/m^2) groups. Metabolic abnormality was determined based on the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria, which evaluate the following four indicators: blood pressure, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and fasting blood glucose.

Metabolic abnormality was defined as meeting two or more of the following criteria, while those meeting fewer than two were classified as metabolically healthy: (1) systolic blood pressure (SBP) $\geq$ 130 mmHg or currently receiving antihypertensive treatment; (2) fasting blood glucose level $\geq$ 5.6 mmol/L, a history of diabetes, or currently taking hypoglycemic medication; (3) TG $\geq$ 1.70 mmol/L or currently receiving lipid-lowering therapy; (4) HDL-C $<$ 1.03 mmol/L for men or $<$ 1.29 mmol/L for women. Based on the presence or absence of obesity and metabolic abnormalities, all participants were divided into four groups: metabolically healthy obese (MHO), metabolically healthy normal weight (MHNW), metabolically unhealthy normal weight (MUNW), and metabolically unhealthy obese (MUO).

1.3.2 相关定义

(1) Smoking: According to the World Health Organization definition, smoking is defined as continuous or cumulative smoking for more than 6 months during one' s lifetime. (2) Alcohol consumption: Defined as any consumption of alcoholic beverages within the past year. (3) Hypertension: Defined according to the *Chinese Guidelines for the Prevention and Treatment of Hypertension (2024)* as systolic blood pressure (SBP) $\geq$ 140 mmHg and/or diastolic blood pressure (DBP) $\geq$ 90 mmHg (1 mmHg = 0.133 kPa), or

currently receiving antihypertensive medication. (4) Diabetes mellitus: Defined as a previous diagnosis of diabetes, a fasting blood glucose concentration ≥ 7.0 mmol/L, or current use of hypoglycemic agents.

Clinical Outcomes and Follow-up: All patients underwent telephone or outpatient follow-up every 12 months postoperatively. Major adverse cardiovascular and cerebrovascular events (MACCE) were recorded and collected, including all-cause mortality, non-fatal myocardial infarction, stroke, readmission for unstable angina, and readmission for heart failure. Relevant information was collected and verified through medical record review or telephone contact with patients and/or their families. For patients who experienced multiple events, the time of the first MACCE occurrence was recorded as the follow-up endpoint. To ensure a uniform observation window, the follow-up deadline for this study was fixed as December 30, 2023.

Sensitivity Analysis: To verify whether the impact of different metabolic obesity phenotypes on the prognosis of ACS patients after PCI varies with different obesity criteria, the first sensitivity analysis used BMI ≥ 24.0 kg/m^2 as the diagnostic criterion for overweight and obesity, which is the standard for the Chinese population. To verify the stability and reliability of the results, the second sensitivity analysis redefined metabolic syndrome according to the diagnostic criteria suggested by the Diabetes Society of the Chinese Medical Association. The third sensitivity analysis employed multiple imputation to fill in missing values for key indicators before re-conducting the analysis.

Statistical Analysis: Statistical data analysis was performed using Stata 17.0 and R 4.4.1. The Kolmogorov-Smirnov test was used to assess the normality of quantitative data. Normally distributed quantitative data are expressed as mean $\pm$ standard deviation ($\bar{x} \pm s$), with comparisons between multiple groups performed using one-way analysis of variance (ANOVA). Non-normally distributed quantitative data are expressed as medians (interquartile range), with intergroup comparisons performed using the Kruskal-Wallis test. Categorical data are expressed as relative numbers, and intergroup comparisons were conducted using the χ^2 test. Kaplan-Meier survival curves were used to analyze the incidence of out-of-hospital MACCE among the four groups, supplemented by the Log-rank test. Multivariate Cox regression analysis was performed with the occurrence of MACCE as the dependent variable and different metabolic obesity phenotypes as the independent variables. Based on univariate Cox regression analysis of clinical data, literature review, and clinical experience, and after conducting collinearity analysis, variables including age, sex, smoking, SBP, DBP, TG, HDL-C, LDL-C, urea, and uric acid were included in the multivariate analysis (VIF ≤ 10). Model 1 was unadjusted for confounding factors; Model 2 was adjusted for sex and age; Model 3 was further adjusted for smoking, SBP at admission, DBP, TC, HDL-C, LDL-C, urea, and uric acid based on Model 2. A two-sided $P < 0.05$ was considered statistically significant.

2.1 基线资料比较

This study initially included 2,368 subjects. After excluding 455 individuals who did not meet the inclusion criteria or had missing key indicators (blood pressure, blood glucose, height, BMI, and blood lipids), a final sample of 1,913 participants was included. The mean age was (58.8 ± 12.1) years, and 1,588 (83%) were male. Based on BMI and metabolic status, the participants were categorized into four groups: the metabolically healthy non-obese (MHNW) group ($n = 612$), the metabolically unhealthy non-obese (MUNW) group ($n = 878$), the metabolically healthy obese (MHO) group ($n = 105$), and the metabolically unhealthy obese (MUO) group ($n = 318$). Statistically significant differences were observed among the four groups ($P < 0.05$) regarding age, sex ratio, BMI, prevalence of hypertension and diabetes, smoking status, systolic blood pressure (SBP) and diastolic blood pressure (DBP) at admission, blood glucose, hemoglobin concentration, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine, urea, uric acid, and direct bilirubin, as shown in .

During a median follow-up period of 4.77 years, 136 cases (7.1%) were lost to follow-up, and 656 cases (34.3%) experienced out-of-hospital major adverse cardiovascular and cerebrovascular events (MACCE). These events included 345 cases (18.0%) of readmission for unstable angina, 109 cases (5.7%) of readmission for heart failure, 90 cases (4.7%) of all-cause mortality, 58 cases (3.0%) of stroke, and 54 cases (2.8%) of non-fatal myocardial infarction. Significant differences were observed among the four groups in the overall incidence of MACCE and the rate of readmission for unstable angina ($P < 0.05$). Specifically, the readmission rate for unstable angina was significantly higher in the MUO group than in the MHNW group ($\chi^2 = 8.09, P = 0.004$). The incidence of out-of-hospital MACCE in the MHO, MUNW, and MUO groups was higher than that in the MHNW group ($\chi^2 = 4.00, P = 0.046$; $\chi^2 = 7.53, P = 0.006$; $\chi^2 = 16.98, P < 0.001$, respectively). Furthermore, the incidence of out-of-hospital MACCE in the MUO group was significantly higher than in the MUNW group ($\chi^2 = 4.405, P = 0.036$), as detailed in .

Kaplan-Meier survival analysis revealed statistically significant differences in the cumulative MACCE-free survival curves among the four groups (Log-rank test $\chi^2 = 26.23, P < 0.001$), as shown in [Figure 2: see original paper].

Multivariate Cox proportional hazards regression analysis was performed to identify factors influencing MACCE, with the occurrence of MACCE as the dependent variable (assigned as: Yes=1, No=0) and the different metabolic obesity phenotypes as independent variables. Using the MHNW group as the reference, Model 1 (unadjusted) showed that···

Chinese General Practice. Baseline characteristics comparison: MHNW group, MUNW group, MHO group, and MUO group. Age (years): 59.6 ± 12.1, 54.9 ± 12.0, 60.4 ± 11.9, 54.3 ± 11.5 ($P < 0.001$). BMI (kg/m^2): 23.9 ± 2.4, 30.7 ± 3.1, 24.6 ± 2.1, 30.7 ± 3.0 ($P < 0.001$). Admission heart rate (bpm): 82.2 ± 38.7,

84.3±16.2, 83.2±24.8, 87.2±56.9. Admission SBP (mmHg): 122±19, 128±20, 126 ± 21, 128 ± 21 ($P < 0.001$). Admission DBP (mmHg): 76 ± 13, 81 ± 13, 77 ± 13, 80 ± 14 ($P < 0.001$). Blood glucose (mmol/L): 6.6 ± 2.8, 6.6 ± 2.2, 8.1 ± 3.8, 8.0 ± 4.0 ($P < 0.001$). White blood cell count: 10.2 ± 3.5, 10.5 ± 3.5, 10.1±3.4, 10.4±3.5. Hemoglobin (g/L): 146.8±16.3, 152.8±15.6, 145.2±18.8, 151.9±15.8 ($P < 0.001$). Total cholesterol (mmol/L): 4.6±1.1, 4.6±1.0, 4.5± 1.2, 4.7 ± 1.2. Triglycerides (mmol/L): 1.2(0.9, 1.7), 1.4(1.0, 1.7), 2.0(1.3, 2.9), 2.4(1.6, 3.4) ($P < 0.001$). HDL-C (mmol/L): 1.1 ± 0.3, 1.0 ± 0.3, 0.9 ± 0.2, 0.9±0.2 ($P < 0.001$). LDL-C (mmol/L): 3.0±1.0, 3.1±0.8, 2.8±1.0, 2.9±1.0 ($P < 0.001$). Creatinine ($\mu mol/L$): 75.0±22.2, 73.9±20.7, 83.4±62.0, 79.2±38.9. Urea (mmol/L): 5.7 ± 2.0, 5.2 ± 1.4, 6.1 ± 2.7, 5.8 ± 2.2 ($P < 0.001$). Uric acid ($\mu mol/L$): 333.7 ± 92.3, 371.1 ± 100.0, 343.1 ± 97.1, 367.5 ± 102.6 ($P < 0.001$). Total bilirubin ($\mu mol/L$): 14.6 ± 6.6, 15.4 ± 7.1, 14.3 ± 7.0, 14.9 ± 7.8. Direct bilirubin ($\mu mol/L$): 1.9 ± 1.9, 2.3 ± 2.3, 1.7 ± 2.1, 1.6 ± 2.2. Left ventricular ejection fraction (%): 57.7±6.8, 57.3±6.8, 57.9±7.0, 57.2±6.6. Note: MHNW = metabolically healthy non-obese; MHO = metabolically healthy obese; MUNW = metabolically unhealthy non-obese; MUO = metabolically unhealthy obese. Comparison of MACCE incidence across phenotypes: $P < 0.05$ compared to the MHNW group; $P < 0.05$ compared to the MUNW group.

After adjusting for confounding factors in Model 1, the risk of MACCE in the MHO, MUNW, and MUO groups was 1.43, 1.33, and 1.79 times higher than that of the MHNW group, respectively (all $P < 0.05$). Model 2, which adjusted for age (measured value) and sex (Male=1, Female=2), showed that the risk of MACCE in these three groups was 1.56, 1.32, and 2.00 times that of the MHNW group (all $P < 0.05$). Model 3 further adjusted for smoking (Yes=1, No=0) and continuous variables (including SBP, DBP, TG, LDL-C, HDL-C, urea, and uric acid). In this fully adjusted model, the risk of MACCE in the MHO, MUNW, and MUO groups remained significantly higher at 1.56, 1.28, and 1.94 times that of the MHNW group, respectively (all $P < 0.05$), as shown in .

Sensitivity analyses were conducted to ensure the robustness of the findings. When obesity was redefined using a BMI threshold of $\geq 24.0 kg/m^2$, the risk of MACCE in the MUO and MUNW groups was 1.40 and 1.44 times that of the MHNW group, respectively (both $P < 0.05$). When metabolic status was redefined according to the diagnostic criteria for metabolic syndrome suggested by the Diabetes Society of the Chinese Medical Association, the MUO, MHO, and MUNW groups···

Chinese General Practice. Cumulative incidence risk over time (years). Kaplan-Meier survival curves of MACCE cumulative events across different obesity metabolic phenotypes groups [Figure 2: see original paper]. Using these alternative criteria, the risk of MACCE in the MUO, MHO, and MUNW groups was 1.62, 1.50, and 1.33 times that of the MHNW group, respectively (all $P < 0.05$). After performing multiple imputation for missing key indicators, the risk of MACCE in the MUO, MHO, and MUNW groups was 1.80, 1.47, and 1.29 times that of the MHNW group, respectively (all $P < 0.05$), as shown in . The results

of the three sensitivity analyses remained consistent with the primary analysis, confirming the stability of the observed associations.

3 讨论

This study, based on a prospective cohort design, followed 1,913 patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) for a median duration of 4.77 years. We systematically analyzed the impact of four metabolic obesity phenotypes on the long-term prognosis of these patients. The primary findings are as follows: regardless of metabolic status, obesity significantly increases the risk of postoperative major adverse cardiovascular and cerebrovascular events (MACCE). Furthermore, individuals with obesity combined with metabolic abnormalities exhibited the highest risk of long-term MACCE; even after fully adjusting for traditional cardiovascular risk factors, their risk remained nearly twice that of metabolically healthy, normal-weight patients. These findings highlight that obesity is a critical risk factor independent of metabolic status. Consequently, weight control should be emphasized in the long-term management of ACS patients and placed at the same core level of importance as metabolic management.

By combining metabolic factors with body mass index (BMI), this study explored the influence of metabolic obesity phenotypes on the occurrence of long-term MACCE in patients with ACS. The results indicate that obesity increases the risk of long-term MACCE in ACS patients regardless of their metabolic status. These findings are consistent with a prospective cohort study conducted in Sweden among young women, which demonstrated that compared to women with a BMI of 20.0–22.5 kg/m^2, those with a BMI $\geq$ 35.0 kg/m^2 faced an increased risk of acute myocardial infarction.

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A prospective study by AKIN et al. found that among cardiovascular patients treated with drug-eluting stents, higher body weight was associated with an increased risk of long-term mortality and ischemic events. These findings are consistent with the results of the present study.

A long-term study investigating changes in Body Mass Index (BMI) and mortality rates among patients with coronary heart disease demonstrated that individuals who experienced weight loss had higher risks of all-cause and cardiovascular mortality compared to those with stable weight. However, the present study found that obesity serves as an independent risk factor for the prognosis of patients with Acute Coronary Syndrome (ACS). Some researchers have noted that because the Metabolically Healthy Obesity (MHO) population possesses relatively favorable metabolic profiles, distinguishing them from individuals with metabolically unhealthy obesity may hold significant implications for clinical decision-making. Consequently, the practical value of diagnosing and classifying different metabolic obesity phenotypes within the ACS patient population

remains to be validated.

Previous studies have indicated that metabolically unhealthy obesity (MUO) is a significant risk factor for cardiovascular events in the general population. For instance, Arnlov et al., based on a Swedish longitudinal study, explored the relationship between metabolic phenotype groupings of obesity and Major Adverse Cardiac and Cerebrovascular Events (MACCE) under different adjustment models.

Relationship between metabolic phenotype grouping of obesity and MACCE under different modes Note: Model 1 does not adjust for any confounding factors; Model 2 adjusts for sex and age; Model 3 further adjusts for smoking status, systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and urea, based on the variables in Model 2.

To ensure the robustness of these findings, several sensitivity analyses were conducted regarding the metabolic obesity phenotypes and their association with the risk of MACCE.

Sensitivity analysis of metabolic obesity phenotypes and their association with the risk of MACCE Note: Sensitivity analysis 1 used a BMI $\geq$ 24.0 kg/m^2 as the diagnostic criterion for obesity to group metabolic phenotypes. Sensitivity analysis 2 redefined metabolic status according to the diagnostic criteria for metabolic syndrome suggested by the Diabetes Society of the Chinese Medical Association. Sensitivity analysis 3 re-analyzed the data after using multiple imputation to fill in missing values for key indicators.

A study of a male population aged 50 years, with a median follow-up of 30 years, found that the metabolically unhealthy obesity (MUO) group had the highest risk of cardiovascular disease mortality compared to the metabolically healthy normal weight (MHNW) group. Similarly, a prospective cohort study by SONG et al. involving 30,000 individuals aged $\geq$ 18 years from the general population in China found that the MUO group faced the highest risk of cardiovascular disease. However, most existing research is based on the general population, and evidence regarding the prognostic risk for patients with acute coronary syndrome (ACS) remains insufficient. Given the significant differences between Chinese and Western populations in terms of genetic background, dietary structure, physical activity patterns, and healthcare accessibility, targeted research is necessary.

This study, focused on Chinese ACS patients, found that the risk of major adverse cardiovascular and cerebrovascular events (MACCE) in patients with obesity combined with metabolic abnormalities was significantly higher than in the metabolically healthy obesity (MHO) and metabolically unhealthy normal weight (MUNW) groups. Even after fully adjusting for traditional cardiovascular risk factors, the risk of MACCE in the MUO group remained nearly double that of the MHNW group. These results suggest that among ACS pa-

tients, obesity and metabolic abnormalities may involve interactive or synergistic mechanisms not fully explained by traditional risk factors. Such mechanisms —including chronic low-grade inflammation, exacerbated insulin resistance, endothelial dysfunction, increased oxidative stress, and abnormal lipid metabolism —collectively aggravate the occurrence of cardiovascular events.

Consequently, clinical practice should not be limited to weight management or the control of single risk factors. Instead, a dual assessment framework of "obesity + metabolic status" should be established. More proactive and comprehensive intervention strategies should be implemented for MUO patients to further reduce the long-term risk of MACCE and improve the overall prognosis of patients with ACS.

Previous studies investigating the relationship between obesity and cardiovascular disease prognosis have yielded inconsistent conclusions. A meta-analysis of 15 studies involving 138,592 participants demonstrated a non-linear U-shaped relationship between Body Mass Index (BMI) and all-cause mortality among patients undergoing percutaneous coronary intervention (PCI). In that analysis, patients with a BMI between 27 and 32 kg/m^2 (overweight or obese) actually exhibited a lower risk of death. However, the present study found that among patients with acute coronary syndrome (ACS) treated with PCI, obese patients faced a higher risk of Major Adverse Cardiac and Cerebrovascular Events (MACCE) compared to non-obese patients.

The discrepancies between our findings and those of Western studies can be attributed to methodological differences, ethnic and biological variations, and environmental factors. Specifically, Western cohorts typically utilize a higher BMI threshold to define obesity (BMI $\geq$ 30 kg/m^2). In contrast, studies in South Korea define obesity based on Asian-specific BMI criteria (BMI $\geq$ 25 kg/m^2), while our study defined obesity according to the *2024 Guidelines for the Diagnosis and Treatment of Obesity* (BMI $\geq$ 28 kg/m^2).

Biological differences also play a critical role; for instance, Asian populations tend to exhibit higher levels of visceral adipose tissue and hepatic fat accumulation at lower BMI levels compared to Western populations. Even metabolically healthy Chinese individuals may present with subclinical ectopic fat deposition. Furthermore, the traditional Chinese diet is characterized by refined grains, high-salt seasonings, and deep-frying. This combination of high carbohydrates, high sodium, and high oil not only leads to rapid increases in blood glucose and blood pressure but also easily induces insulin resistance. When combined with the reality that smoking rates among Chinese men have long remained among the highest globally—alongside widespread exposure to secondhand smoke—these factors significantly accelerate the onset and progression of metabolic syndrome, thereby increasing the risk of cardiovascular and cerebrovascular events.

Selection bias may be one of the primary reasons for the discrepancies observed across various research findings. Some studies indicate that the "obesity paradox" is more pronounced in female patients with Acute Coronary Syndrome

(ACS) than in their male counterparts. This phenomenon may be attributed to sex-based differences in adipose tissue distribution and distinct endocrine mechanisms. Furthermore, the influence of age at the time of study cannot be overlooked. Some scholars have proposed that the "obesity paradox" might only apply to elderly populations or those with pre-existing underlying diseases, while remaining invalid for younger patients. This discrepancy may be related to the fact that moderate overweight in the elderly can reduce cachexia and increase body fat percentage. Alternatively, it may stem from survival bias: obese individuals with poor underlying health often do not reach old age, leaving behind a "biased sample" of survivors whose presence artificially inflates the average health status of the elderly overweight population.

The "obesity paradox"is also likely influenced by various confounding factors. Beyond age and sex differences, heterogeneity in research design and data analysis—such as variations in follow-up duration, sample selection criteria, and statistical modeling—may lead to inconsistent results regarding the relationship between Body Mass Index (BMI) and mortality risk in ACS patients, potentially giving rise to the appearance of an "obesity paradox." Additionally, reverse causality (for instance, weight loss induced by chronic illness) may be a contributing factor to the higher mortality rates observed in some normal-weight patients. Finally, because obese individuals face a higher risk of cardiovascular disease, they may receive more aggressive medical treatment and interventions, which could further improve their clinical outcomes and overall physical condition.

These results are primarily applicable to the long-term prognostic assessment and intervention guidance of patients with Acute Coronary Syndrome (ACS) undergoing Percutaneous Coronary Intervention (PCI), particularly for those requiring individualized weight and metabolic management strategies. It should be noted that the study population consisted entirely of Chinese individuals. Consequently, the Body Mass Index (BMI) threshold for obesity was defined according to the Chinese adult diagnostic criteria (BMI $\geq$ 28 kg/m^2), whereas the standard for obesity in most Western developed countries is BMI $\geq$ 30 kg/m^2. Therefore, the findings of this study should not be directly extrapolated to Western populations. Furthermore, the applicability of these results to ACS patients who have not received PCI treatment requires further validation.

This study has several limitations. First, in our analysis exploring the relationship between different metabolic phenotypes and adverse prognosis, although we adjusted for known clinical and in-hospital prognostic factors using multivariate Cox models, certain unmeasured confounding variables were not fully accounted for. Specifically, patient lifestyle factors—such as dietary patterns, physical activity levels, and treatment adherence—were not comprehensively collected for inclusion in the adjustment. The absence of these variables may introduce a degree of bias into the study' s findings.

Second, the definition of obesity in this study relies on Body Mass Index (BMI). While this metric offers the advantages of clinical simplicity and high acces-

sibility, it fails to reflect the distribution of body fat (such as visceral versus subcutaneous fat). This limitation may affect the precision of the assessment regarding the association between obesity and metabolic phenotypes. Third, there is currently a lack of a unified international standard for defining metabolic phenotypes of obesity. This study utilized the NCEP-ATP III criteria for classification; although these criteria are widely applied in clinical research, their diagnostic thresholds remain subject to debate. This lack of consensus may impact the generalizability and comparability of the research findings.

In summary, this study utilizes a prospective cohort to investigate the impact of different metabolic obesity phenotypes on the long-term prognosis of patients with acute coronary syndrome (ACS) following percutaneous coronary intervention (PCI).

A study conducted on a population of patients with Acute Coronary Syndrome (ACS) in Northwest China found that obesity increases prognostic risk regardless of whether metabolic abnormalities are present. Compared to individuals with a normal metabolic profile, those with metabolic abnormalities face a further increased risk of long-term Major Adverse Cardiac and Cerebrovascular Events (MACCE). Furthermore, the coexistence of obesity and metabolic abnormalities can synergistically accelerate the occurrence of MACCE in ACS patients. Consequently, precise interventions should be implemented for groups with different metabolic and obesity phenotypes. This includes implementing weight management strategies for obese populations and maintaining continuous monitoring and intervention of various metabolism-related indicators for those in the metabolically abnormal group.

Author Contributions: Han Congcong was responsible for research design and data organization.

Author Contributions

The author contributions for this study are as follows: *Chinese General Practice* completed the initial draft of the manuscript. Xinyu Qiu assisted in the research design and protocol formulation, performed a portion of the data analysis, and provided revisions to the manuscript content. Chunfang Shan, Ning Song, and Qingjie Chen were responsible for data collection and participated in data organization. Mulla Abdurehman participated in the statistical analysis and the writing of the discussion section. Xiaomei Li provided research guidance and assisted in refining the methodology and discussion sections. Yining Yang and Qian Zhao were responsible for the comprehensive guidance of the research implementation and manuscript writing, supervised the overall quality of the article, and approved the final version.

The authors declare that there are no conflicts of interest.

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