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DIAGNOSTIC VALUE OF COMBINED SERUM PROTEIN CARBONYL, 8-HYDROXY-2'-DEOXYGUANOSINE, AND PGC-1α DETECTION FOR MYOCARDIAL ENERGY METABOLISM DISORDER IN ISCHEMIC CARDIOMYOPATHY

DIJAGNOSTIČKA VREDNOST KOMBINOVANOG ODREĐIVANJA SERUMSKIH PROTEINA KARBONILA, 8-HIDROKSI-2'-DEOKSIGUANOZINA I PGC-1α U OTKRIVANJU POREMEĆ AJA ENERGETSKOG METABOLIZMA MIOKARDA KOD ISHEMIJSKE KARDIOMIOPATIJE

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Summary

Background: Patients with ischemic cardiomyopathy (ICM) often have abnormalities in myocardial energy metabolism, whereas conventional cardiac function indices, such as left ventricular ejection fraction (LVEF) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), may not capture metabolic injury with sufficient sensitivity. This study aimed to evaluate the diagnostic value of the combined detection of serum protein carbonyl (PC), 8-hydroxy-2'-deoxyguanosine (8-OHdG), and peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) for myocardial energy metabolism disorder in patients with ICM.

Methods: In this single-centre retrospective study, a total of 167 patients with ICM from June 2024 to October 2025 were enrolled. According to myocardial energy metabolism status, they were divided into an energy metabolism disorder group (n=78) and a non-disorder group (n=89). Serum PC, 8-OHdG, and PGC-1α levels were measured. Clinical data, cardiac function indices, and serum biomarker levels were compared between the two groups. A combined diagnostic model was then constructed using logistic regression, and receiver operating characteristic (ROC) curves were used to evaluate the diagnostic performance of single indicators and combined detection.

Kratak sadržaj

Uvod: Pacijenti sa ishemijskom kardiomiopatijom (ICM) često imaju poremećaje energetskog metabolizma miokarda, dok konvencionalni pokazatelji srčane funkcije, kao što su ejekciona frakcija leve komore (LVEF) i N-terminalni pro-B-tip natriuretskog peptida (NT-proBNP), možda nisu dovoljno osetljivi za otkrivanje metaboličkog oštećenja. Cilj ove studije bio je da se proceni dijagnostička vrednost kombinovanog određivanja serumskih proteina karbonila (PC), 8-hidroksi-2'-deoksiguanozina (8-OHdG) i koaktivatora 1 alfa receptora aktiviranog proliferatorom peroksizoma gama (PGC-1a) za otkrivanje poremećaja energetskog metabolizma miokarda kod pacijenata sa ICM.

Metode: U ovu retrospektivnu studiju sprovedenu u jednom centru uključeno je ukupno 167 pacijenata sa ICM u periodu od juna 2024. do oktobra 2025. godine. Na osnovu statusa energetskog metabolizma miokarda, ispitanici su podeljeni u grupu sa poremećajem energetskog metabolizma (n=78) i grupu bez poremećaja (n=89). Određivani su serumski nivoi PC, 8-OHdG i PGC-1a. Upoređeni su klinički podaci, pokazatelji srčane funkcije i nivoi serumskih biomarkera između dve grupe. Zatim je primenom logističke regresije konstruisan kombinovani dijagnostički model, a za procenu dijagnostičkih performansi pojedinačnih pokazatelja i njihove kombinacije korišćene su ROC krive.

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Results: Compared with the non-disorder group, the energy metabolism disorder group showed increased PC and 8-OHdG levels and decreased PGC-1α levels; specifically, PC increased by approximately 38%, 8-OHdG increased by approximately 41%, and PGC-1α decreased by approximately 24%, with statistically significant differences (P<0.001). Multivariate logistic regression showed that PC, 8-OHdG, and PGC-1α were independently associated with myocardial energy metabolism disorder. ROC analysis showed that the areas under the curve (AUCs) of PC, 8-OHdG, and PGC-1α alone were 0.806, 0.791, and 0.772, respectively. The AUC of the combined diagnostic score increased to 0.884, with a sensitivity of 87.18% and a specificity of 79.78%, and the AUC of the combined model was higher than that of every single indicator.
Conclusion: Increased serum PC and 8-OHdG levels and decreased PGC-1α levels are closely related to myocardial energy metabolism disorder in patients with ICM. Combined detection of the three indicators demonstrates good diagnostic performance. It may provide laboratory evidence for early-stage auxiliary identification and risk stratification of myocardial energy metabolism disorders.

Keywords: ischemic cardiomyopathy, myocardial energy metabolism disorder, oxidative stress, protein carbonyl, 8-hydroxy-2′-deoxyguanosine, PGC-1α

Rezultati: U poređenju sa grupom bez poremećaja, grupa sa poremećajem energetskog metabolizma imala je više nivoe PC i 8-OHdG, kao i niže nivoe PGC-1a; konkretno, nivo PC bio je viši za približno 38%, nivo 8-OHdG za približno 41%, dok je nivo PGC-1a bio niži za približno 24%, pri čemu su razlike bile statistički značajne (P<0,001). Multivarijantna logistička regresija pokazala je da su PC, 8-OHdG i PGC-1a nezavisno povezani sa poremećajem energetskog metabolizma miokarda. ROC analiza pokazala je da su površine ispod krive (AUC) za PC, 8-OHdG i PGC-1a pojedinačno iznosile 0,806, 0,791 i 0,772. AUC kombinovanog dijagnostičkog skora poveć ao se na 0,884, uz senzitivnost od 87,18% i specifičnost od 79,78%, a AUC kombinovanog modela bio je veći od površine ispod krive svakog pojedinačnog pokazatelja.
Zaključak: Povišeni serumski nivoi PC i 8-OHdG, kao i sniženi nivoi PGC-1a, usko su povezani sa poremećajem energetskog metabolizma miokarda kod pacijenata sa ICM. Kombinovano određivanje ova tri pokazatelja pokazuje dobre dijagnostičke performanse i može pružiti laboratorijske dokaze za rano pomoćno prepoznavanje i stratifikaciju rizika poremećaja energetskog metabolizma miokarda.

Ključne reči: ishemijska kardiomiopatija, poremećaj energetskog metabolizma miokarda, oksidativni stres, proteinski karbonili, 8-hidroksi-2′-deoksiguanozin, PGC-1a.

Introduction

Ischemic cardiomyopathy (ICM) is an important clinical entity that develops after long-term progression of coronary atherosclerotic heart disease. Its main pathological basis includes persistent or recurrent myocardial ischemia, cardiomyocyte injury, ventricular remodelling, and impaired systolic function. This disease is not only an important cause of chronic heart failure, but also one of the major reasons for cardiovascular death and repeated hospitalisation (1). Epidemiological data show that cardiovascular disease remains the leading cause of death worldwide, causing approximately 19.8 million deaths in 2022; among these deaths, ischemic heart disease was the leading single cause, accounting for approximately 9 million deaths in 2021, or about 13% of all global deaths (2, 3). With population ageing, the growing burden of metabolic disorders, and improved long-term survival among patients with coronary heart disease, the clinical and public health burden caused by ICM continues to increase (4). However, disease progression in these patients is not determined solely by the degree of coronary stenosis or by left ventricular ejection fraction. Many patients have already developed abnormalities in cardiomyocyte energy production and utilisation before overt deterioration of cardiac function becomes apparent (5). Therefore, relying solely on symptom classification, cardiac structural parameters, or natriuretic peptide levels may fail to reflect early myocardial metabolic injury promptly.

Cardiomyocytes are highly dependent on energy supply, and normal contraction, relaxation, and ion homeostasis all require a continuous and stable supply of adenosine triphosphate (ATP) (6). Under ischemic injury, insufficient coronary blood supply restricts mitochondrial oxidative phosphorylation, disrupts the balance between fatty acid oxidation and glucose utilisation, and increases the production of reactive oxygen species (ROS). Sustained oxidative stress can further damage proteins, lipids, and nucleic acids, leading to mitochondrial dysfunction and reduced efficiency of energy generation (7); this energy metabolism disorder is not merely a secondary change, but may contribute to the continuing process of myocardial fibrosis, ventricular dilation, and systolic dysfunction (8). Some imaging and metabolic assessment techniques can more directly evaluate myocardial energy metabolism. Among them, 31P magnetic resonance spectroscopy can noninvasively reflect myocardial high-energy phosphate metabolism. However, its clinical use remains limited by equipment availability, testing costs, and technical complexity. Among them, 31P magnetic resonance spectroscopy can noninvasively reflect myocardial high-energy phosphate metabolism, but its clinical use is still limited by equipment availability, testing costs, and technical complexity; it cannot be performed at the bedside, requires a long examination time, and demands high patient cooperation (9). At present, commonly used clinical indicators such as N-terminal pro-B-type natriuretic peptide (NT-proBNP), troponin, and creatine kinase

isoenzyme mainly focus on assessing myocardial stretch, necrosis, or acute injury. They provide limited information on oxidative stress burden, mitochondrial injury, and metabolic adaptability under chronic ischemic conditions (10, 11).

Protein carbonyl (PC), 8-hydroxy-2'-deoxyguanosine (8-OHdG), and peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) are associated with three key processes: protein oxidative damage, DNA oxidative damage, and mitochondrial biogenesis regulation. PC is a relatively stable product formed by the oxidative modification of proteins. It can reflect the degree of damage to structural and enzymatic proteins in an oxidative stress environment (12). 8-OHdG is a well-established marker of oxidative DNA damage. It is closely related to mitochondrial DNA damage, cumulative oxidative stress, and impaired cellular function (13). PGC-1α is an important regulator of mitochondrial biogenesis, oxidative metabolism, and energy homeostasis, and abnormal levels may indicate reduced metabolic adaptability in cardiomyocytes (14). From a biochemical perspective, these three indicators do not repeat the same pathological information. Rather, they characterise myocardial metabolic stress along three dimensions: oxidative damage, genetic injury, and mitochondrial metabolic regulation. Compared with a single indicator, their combined detection may be more useful for identifying occult or early myocardial energy metabolism disorder in patients with ICM.

Existing studies on ICM have focused more on cardiac function classification, the extent of coronary artery disease, the degree of ventricular remodelling, and the risk of adverse cardiovascular events. In contrast, the diagnostic value of serum biochemical markers for myocardial energy metabolism disorder remains relatively underexplored. Although previous studies on oxidative stress markers have suggested their association with cardiovascular injury, single indicators are easily affected by age, glucose metabolism status, renal function, inflammation level, and drug therapy, and a single indicator can only reflect one pathological aspect of myocardial energy metabolism, which limits their diagnostic stability and clinical interpretability (15). At present, the combined distribution characteristics of PC, 8-OHdG, and PGC-1α in patients with ICM have not been fully clarified; whether these three indicators are continuously associated with myocardial energy metabolism parameters and cardiac function indices remains to be systematically evaluated. More importantly, whether the combined detection of these three serum indicators can improve the identification of myocardial energy metabolism disorder still needs to be verified in clinical samples. Based on this, this study aimed to measure PC, 8-OHdG, and PGC-1α levels in patients with ICM, compare their differences between patients with and without myocardial energy metabolism disorder, and analyse their relationships with myocardial energy metabolism and cardiac function-related indices, and further evaluate the diagnostic performance of single indicators and combined detection for myocardial energy metabolism disorder, with the construction of a simplified serum-based combined diagnostic model. This strategy may provide a simple, reproducible, and clinically accessible biochemical assessment method for the early identification of myocardial metabolic abnormalities in patients with ICM. It may serve as a reference for subsequent risk stratification, treatment decision-making, and dynamic follow-up.

Materials and Methods

Study design

This was a single-centre retrospective clinical data analysis. The study subjects were patients hospitalised in the Department of Cardiology at our hospital from June 2024 to October 2025 and diagnosed with ICM. All data were derived from previous hospitalisation records, the laboratory information system, imaging databases, and test results from remaining archived serum samples. The study was approved by the Ethics Committee of our hospital (approval No. 2024k017), and all study subjects signed informed consent.

Study subjects

After a case-by-case review of diagnoses, examination data, serum sample status, and the completeness of key variables, a total of 167 patients were included. According to the myocardial energy metabolism assessment results obtained during hospitalisation, they were divided into the myocardial energy metabolism disorder group (n=78) and the non-disorder group (n=89).

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) age 18–85 years; (2) meeting the diagnostic criteria for ICM, defined as left ventricular systolic dysfunction in the presence of documented coronary artery disease, previous myocardial infarction, or objective evidence of ischemic myocardial scar according to the 2021 ESC guideline-based diagnostic framework for heart failure and ischemic aetiology (16); (3) completion of routine laboratory tests, echocardiography, and myocardial energy metabolism-related assessment during hospitalisation; (4) availability of remaining archived serum samples that met testing requirements or complete serum biomarker test re-

cords; and (5) complete main clinical data sufficient for grouping, correlation analysis, and diagnostic performance analysis. The exclusion criteria were as follows: (1) acute myocardial infarction, unstable angina, or acute decompensated heart failure within 4 weeks before admission; (2) dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, myocarditis, congenital heart disease, or moderate or severe valvular regurgitation or stenosis confirmed by echocardiography; (3) severe hepatic dysfunction, defined as alanine aminotransferase or aspartate aminotransferase exceeding 3 times the upper limit of the normal reference range; (4) severe renal dysfunction, defined as estimated glomerular filtration rate <30 mL/(min·1.73 m^2) or ongoing maintenance dialysis; (5) active infection, autoimmune disease, malignant tumours, recent severe trauma, or major surgery; (6) long-term use of systemic glucocorticoids, immunosuppressants, or high-dose antioxidant agents; (7) serum samples with obvious haemolysis, lipemia, contamination, unclear records of repeated freeze-thaw cycles, or insufficient volume; and (8) inability to determine myocardial energy metabolism status, or missing key clinical variables.

Data extraction

Study data were collected by two researchers who had received uniform training. The extracted information included general data, ICM-related medical history, comorbidities, medication use, routine laboratory indicators, echocardiographic parameters, myocardial energy metabolism indicators, and serum biomarker test results.

Source and storage of serum samples

The serum samples used in this study were residual serum samples collected during routine clinical diagnosis and treatment during the index hospitalisation. Samples were collected from 07:00 to 09:00 on the morning after admission, and patients remained fasting before blood collection. Blood samples were placed in BD Vacutainer® serum separator tubes with clot activator (catalogue No. 366408; BD, Franklin Lakes, NJ, USA), allowed to stand at room temperature for 30 min, and then centrifuged at 3000 r/min, approximately 1505 ×g, for 10 min at 4 °C using a refrigerated centrifuge (Eppendorf). After centrifugation, serum was separated and aliquoted into enzyme-free cryotubes according to the hospital biobank management procedure, with 300 μL per tube, and then stored in an ultra-low-temperature freezer at -80 °C (Thermo Fisher Scientific). Before testing, samples were slowly thawed at 4 °C, mixed thoroughly, and centrifuged at 10000 r/min for 5 min at 4 °C; the supernatant was collected for analysis.

PC detection

PC was measured using a protein carbonyl content assay kit (Abcam). Before testing, serum samples were diluted 1:10 with phosphate-buffered saline. The derivatisation reaction was performed at 22±2 °C in the dark for 45 min, followed by protein precipitation and washing. After redissolution, absorbance was read at 375 nm using a microplate reader (BioTek). Total protein concentration was measured using a bicinchoninic acid protein assay kit (Beyotime), with a reading wavelength of 562 nm. The validated quantitative linear range was 0.05–20.00 nmol/mg protein, and the analytical lower limit of detection was 0.02 nmol/mg protein. Blank, quality control, and duplicate sample wells were included in each batch. When the coefficient of variation between duplicate wells was ≤10%, the mean value was used as the final result; samples with a coefficient of variation >10% were retested.

8-OHdG detection

Serum 8-OHdG was measured using a human 8-OHdG enzyme-linked immunosorbent assay kit (Cayman Chemical). Serum samples were thawed at 4 °C and mixed thoroughly, and then diluted at a ratio of 1:4. The standard curve concentration range was 0.125–20.0 ng/mL. Standards, quality controls, and diluted serum samples were all tested in duplicate, with 50 μL added to each well. The plate was incubated at 4 °C for 18 h. After washing, the substrate solution was added, and colour development was performed at room temperature in the dark for 90 min. Absorbance was read at 412 nm using a microplate reader (BioTek), and sample concentrations were calculated by fitting the standard curve with a four-parameter logistic model. Low-, medium-, and high-concentration quality control samples were included on each assay plate. The coefficient of determination of the standard curve was required to be >0.990, and quality control results were required to fall within the allowable range.

PGC-1α detection

Serum PGC-1α was measured using a human PGC-1α enzyme-linked immunosorbent assay kit (Cusabio). Serum samples were diluted 1:2 before loading. The standard curve concentration range was 15.6–1000.0 pg/mL. Standards, quality controls, and samples were all tested in duplicate, with 100 μL added to each well. Samples were incubated with the coated antibody at 37 °C for 120 min. After washing, biotinylated detection antibody was added and incubated at 37 °C for 60 min; after another wash, horseradish peroxidase-labelled streptavidin was added and incubated at 37 °C for

30 min. Subsequently, 3,3',5,5'-tetramethylbenzidine substrate was added, and colour development was performed at room temperature in the dark for 15 min. After the reaction was stopped, absorbance was measured at 450 nm using a microplate reader (BioTek), and PGC-1α concentration was calculated from a four-parameter logistic standard curve and expressed as pg/mL. Low-, medium-, and high-concentration quality control samples were included in each batch, and the coefficient of determination of the standard curve was required to be >0.990; when the coefficient of variation between duplicate wells was ≤10%, the mean value was used, whereas samples with a coefficient of variation >10% were retested.

Construction of the combined serum diagnostic model

Subsequently, a binary logistic regression model was constructed with the presence or absence of myocardial energy metabolism disorder as the dependent variable and the three serum biomarkers as independent variables. Because the units and numerical ranges of the three indicators differed, all variables were standardised as Z values before modelling. The Z value was calculated as $Z = (X - \mu) / \sigma$, where X represents the raw value, μ represents the mean value of that variable in the study population, and σ represents the standard deviation. A clinically adjusted model was further constructed. The adjustment variables included age, sex, body mass index, diabetes mellitus, estimated glomerular filtration rate, left ventricular ejection fraction, and NT-proBNP.

Risk stratification analysis

Based on tertiles of the predicted probability from the combined serum diagnostic model, patients were divided into low-, intermediate-, and high-risk groups. The detection rate of myocardial energy metabolism disorder, left ventricular ejection fraction, NT-proBNP, myocardial energy expenditure, and indexed myocardial energy expenditure were compared among the different risk groups.

Statistical analysis

SPSS 27.0 (IBM) and R 4.3.2 (R Foundation) were used for statistical analysis. The distribution of continuous variables was first assessed using the Shapiro-Wilk test combined with histograms and Q-Q plots. Normally distributed continuous variables were expressed as mean ± standard deviation, and between-group comparisons were performed using the independent-samples t-test; non-normally distributed continuous variables were expressed as median with interquartile range, denoted as M (P25–P75), and between-group comparisons were performed using the Mann-Whitney U test. Categorical variables were expressed as numbers and percentages, and between-group comparisons were performed using the χ^2 test or Fisher's exact test. Binary logistic regression was used to analyse factors associated with myocardial energy metabolism disorder. Variables with P<0.10 in univariate analysis and clinically meaningful variables were included in multivariate analysis, and the results were expressed as odds ratios and 95% confidence intervals. Model fit was evaluated using the Hosmer-Lemeshow goodness-of-fit test, with P>0.05 indicating no evidence of poor fit, and the goodness of fit of different logistic models was compared using the Akaike information criterion and the Bayesian information criterion. ROC curves were used to evaluate the diagnostic performance of PC, 8-OHdG, PGC-1α, and the combined serum diagnostic score for myocardial energy metabolism disorder, and the area under the curve and 95% confidence interval were calculated. The maximum Youden index was used to determine the optimal cut-off value, and sensitivity and specificity were calculated. The areas under the curve of different indicators were compared using the DeLong test. Correlation analyses were reported as correlation coefficients with corresponding P values; 95% confidence intervals were not calculated because these analyses were exploratory. All tests were two-sided, and P<0.05 was considered statistically significant.

Results

Quality control of serum biomarker detection

The assays for PC, 8-OHdG, and PGC-1α showed acceptable analytical stability (*Table I*), supporting the repeatability of serum biomarker measurements in this study.

Comparison of clinical data

There were no statistically significant differences between the two groups in sex, body mass index, smoking history, hypertension, previous percutaneous coronary intervention, or major medication use (P>0.05), suggesting that the baseline treatment status of the two groups was generally comparable. Compared with the non-disorder group, the myocardial energy metabolism disorder group had a longer disease course, a higher proportion of diabetes mellitus, and a higher frequency of three-vessel coronary artery disease (P<0.05). In terms of cardiac structure and function, the disorder group showed more pronounced cardiac dysfunction and ven-

Table I Analytical characteristics and quality control parameters for serum biomarker assays.

Indicator	Detection method	Sample dilution ratio	Linear range	Lower detection limit	Intra-assay CV (%)	Inter-assay CV (%)	Recovery (%)	Standard curve R^2
PC	DNPH derivatisation colourimetry	1:10	0.05–20.00 nmol/mg protein	0.02 nmol/mg protein	6.4±1.1	9.2±1.4	96.3±4.8	0.996±0.002
8-OHdG	Competitive ELISA	1:04	0.125–20.000 ng/mL	0.05 ng/mL	6.7±1.4	10.6±1.8	97.1±5.2	0.995±0.003
PGC-1α	Double-antibody sandwich ELISA	1:02	15.6–1000.0 pg/mL	5.0 pg/mL	7.1±1.3	11.2±1.6	95.8±5.6	0.997±0.002

Table II Baseline clinical characteristics of patients with and without myocardial energy metabolism disorder.

Indicator	Myocardial energy metabolism disorder group (n=78)	Non-disorder group (n=89)	Statistic	P
Age (years)	67.56±8.44	65.06±8.62	t=1.895	0.06
Male [cases (%)]	52 (66.67)	55 (61.80)	c2=0.428	0.513
BMI (kg/m^2)	25.50±3.10	25.00±3.00	t=1.056	0.293
ICM duration (years)	6.60±3.60	5.33±3.15	t=2.439	0.016
Smoking history [cases (%)]	40 (51.28)	39 (43.82)	c2=0.928	0.335
Hypertension [cases (%)]	54 (69.23)	55 (61.80)	c2=1.013	0.314
Diabetes mellitus [cases (%)]	35 (44.87)	26 (29.21)	c2=4.396	0.036
Dyslipidaemia [cases (%)]	48 (61.54)	43 (48.31)	c2=2.931	0.087
Previous myocardial infarction [cases (%)]	48 (61.54)	43 (48.31)	c2=2.931	0.087
Previous PCI [cases (%)]	42 (53.85)	43 (48.31)	c2=0.509	0.476
Three-vessel coronary artery disease [cases (%)]	36 (46.15)	27 (30.34)	c2=4.427	0.035
LVEF (%)	39.42±6.91	45.07±7.12	t=-5.185	<0.001
LVEDD (mm)	60.40±6.50	55.79±5.90	t=4.799	<0.001
GLS (%)	-10.39±2.61	-12.80±3.02	t=5.489	<0.001
NT-proBNP (pg/mL)	2179.65±941.65	1375.57±706.70	t=6.286	<0.001
Serum creatinine (mmol/L)	89.99±22.00	83.51±19.00	t=2.046	0.042
eGFR [mL/(min·1.73 m^2)]	76.80±18.50	84.00±17.20	t=-2.606	0.01
hs-CRP (mg/L)	5.43±2.86	3.94±2.18	t=3.815	<0.001
Fasting blood glucose (mmol/L)	7.00±2.00	6.42±1.75	t=1.976	0.05
LDL-C (mmol/L)	2.46±0.76	2.34±0.70	t=1.068	0.287
β-blockers [cases (%)]	62 (79.49)	76 (85.39)	c2=1.010	0.315
ACEI/ARB/ARNI [cases (%)]	61 (78.21)	73 (82.02)	c2=0.382	0.537
MRA [cases (%)]	52 (66.67)	48 (53.93)	c2=2.806	0.094
SGLT2 inhibitors [cases (%)]	34 (43.59)	31 (34.83)	c2=1.341	0.247
Statins [cases (%)]	70 (89.74)	82 (92.13)	c2=0.291	0.59

Table III Serum biomarkers, myocardial energy metabolism parameters, and cardiac function indices in patients with and without myocardial energy metabolism disorder.

Indicator	Myocardial energy metabolism disorder group (n=78)	Non-disorder group (n=89)	Statistic	P
PC (nmol/mg protein)	3.57±0.88	2.58±0.75	t=7.838	<0.001
8-OHdG (ng/mL)	12.44±3.48	8.81±2.80	t=7.476	<0.001
PGC-1a (pg/mL)	126.23±36.47	166.00±44.49	t=-6.264	<0.001
PCr/ATP	1.37±0.15	1.82±0.14	t=-20.156	<0.001
Myocardial energy expenditure	82.44±20.47	68.58±17.29	t=4.745	<0.001
Indexed myocardial energy expenditure	0.56±0.13	0.46±0.11	t=5.455	<0.001
LVEF (%)	39.42±6.91	45.07±7.12	t=-5.185	<0.001
GLS (%)	-10.39±2.61	-12.80±3.02	t=5.489	<0.001
NT-proBNP (pg/mL)	2179.65±941.65	1375.57±706.70	t=6.286	<0.001

Table IV Serum biomarker changes according to the severity of myocardial energy metabolism disorder.

Indicator	Non-disorder (n=89)	Mild disorder (n=26)	Moderate disorder (n=32)	Severe disorder (n=20)	Statistic	P
PCr/ATP	1.82±0.14	1.53±0.04	1.37±0.06	1.18±0.07	F=266.567	<0.001
PC (nmol/mg protein)	2.58±0.75	3.15±0.75	3.60±0.83	4.06±0.88	F=27.260	<0.001
8-OHdG (ng/mL)	8.81±2.80	11.00±3.00	12.51±3.19	14.20±3.79	F=24.014	<0.001
PGC-1α (pg/mL)	166.00±44.49	139.00±37.00	125.99±35.00	110.00±33.00	F=15.313	<0.001

tricular remodelling, higher serum creatinine and high-sensitivity C-reactive protein levels, and a lower estimated glomerular filtration rate (<0.05, *Table II*).

Comparison of serum PC, 8-OHdG, and PG C-1α levels

Compared with the non-disorder group, the disorder group had increased serum PC and 8-OHdG levels, whereas PGC-1α was decreased (P<0.05). At the same time, the myocardial energy metabolism disorder group had a lower phosphocreatine-to-adenosine triphosphate ratio (PCr/ATP) than the non-disorder group (P<0.001), while myocardial energy expenditure (MEE) and indexed MEE were both higher than those in the non-disorder group (P<0.001). These results were consistent with lower left ventricular ejection fraction and higher NT-proBNP levels in the disorder group, suggesting that abnormal myocardial energy metabolism and impaired cardiac function changed in parallel (*Table III*).

Changes in serum indicators according to the severity of myocardial energy metabolism disorder

The severity of myocardial energy metabolism disorder was graded according to the PCr/ATP ratio (17): non-disorder was defined as PCr/ATP≥1.60, mild disorder as 1.45≤PCr/ATP<1.60, moderate disorder as 1.25≤PCr/ATP<1.45, and severe disorder as PCr/ATP<1.25; the threshold of 1.60 was selected because previous 31P-MRS studies used PCr/ATP<1.60 to define reduced myocardial energy reserve and reported its prognostic relevance, whereas the lower thresholds were adopted to further stratify the abnormal PCr/ATP range in the present study (9, 27, 28). After stratification according to the severity of myocardial energy metabolism disorder, PCr/ATP gradually decreased as the disorder became more severe, whereas serum PC and 8-OHdG increased and PGC-1α decreased with increasing severity (P<0.001) (*Table IV*).

Table V Correlations of serum biomarkers with myocardial energy metabolism and cardiac function parameters.

Serum indicator	PCr/ATP	MEE	LVEF	NT-proBNP
PC	r=-0.511, P<0.001	r=0.366, P<0.001	r=-0.335, P<0.001	r=0.407, P<0.001
8-OHdG	r=-0.489, P<0.001	r=0.346, P<0.001	r=-0.331, P<0.001	r=0.390, P<0.001
PGC-1α	r=0.433, P<0.001	r=-0.279, P<0.001	r=0.320, P<0.001	r=-0.327, P<0.001

Table VI Multivariate logistic regression analysis of the combined diagnostic model based on serum PC, 8-OHdG, and PGC-1α.

Variable	β value	Standard error	OR (95%CI)	Statistic	P
PC Z value	0.824	0.273	2.279 (1.334–3.894)	Wald χ^2=9.085	0.003
8-OHdG Z value	1.052	0.274	2.865 (1.675–4.900)	Wald χ^2=14.767	<0.001
PGC-1α Z value	-0.677	0.243	0.508 (0.315–0.818)	Wald χ^2=7.752	0.005

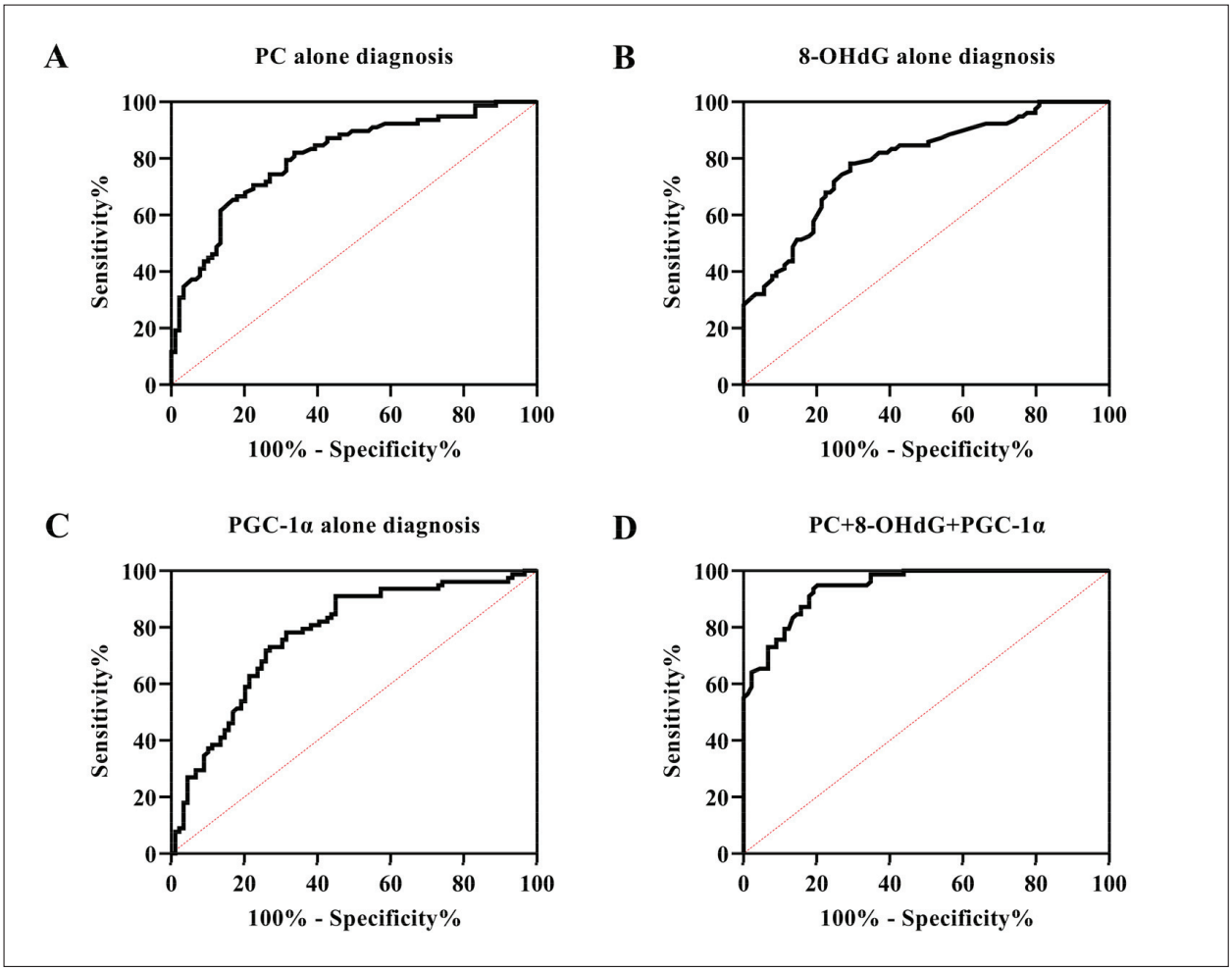

Figure 1 Representative image of AMR. (A) Angiogram before right coronary artery recanalization, (B) Automatic measurement of coronary lumen contour after right coronary artery recanalization, (C) Simulated three-dimensional coronary lumen contour.

Correlations of serum indicators with myocardial energy metabolism and cardiac function parameters

Correlation analysis showed that both PC and 8-OHdG were negatively correlated with PCr/ATP (r=-0.511 and -0.489, P<0.001), and positively correlated with myocardial energy expenditure and NT-proBNP (P<0.001). The correlation direction of PGC-1α was opposite to that of the oxidative damage indicators. PGC-1α was positively correlated with PCr/ATP and left ventricular ejection fraction (r=0.433 and 0.320, P<0.001), and negatively correlated with NT-proBNP (r=-0.327, P<0.001) (*Table V*).

Multivariate analysis of the combined diagnostic model based on the three serum indicators

After PC, 8-OHdG, and PGC-1α were included simultaneously in the multivariate logistic regression model, all three remained independently associated with myocardial energy metabolism disorder. Among them, increased PC was associated with a higher risk of disorder (OR=2.279, 95%CI: 1.334–3.894, Wald χ^2=9.085, P=0.003); the association of 8-OHdG Z value was stronger (OR=2.865, 95%CI: 1.675–4.900, Wald χ^2=14.767, P<0.001). A higher PGC-1α Z value was associated with a reduced risk (OR=0.508, 95%CI: 0.315–0.818, Wald χ^2=7.752, P=0.005). The model-fitting results showed that the Hosmer-Lemeshow test P-value for the three-serum-indicator model was 0.697. Based on this, the combined diagnostic model constructed using the three serum indicators was obtained as follows: Logit(P)=-0.166+0.824×PC Z value+1.052×8-OHdG Z value-0.677×PGC-1α Z value (*Table VI*).

Diagnostic performance of single and combined serum indicators

The AUCs of PC, 8-OHdG, and PGC-1α were 0.806, 0.791, and 0.772, respectively. After combining the three indicators, diagnostic performance

Table VII Diagnostic performance of serum PC, 8-OHdG, PGC-1a, and the combined diagnostic score for myocardial energy metabolism disorder.

Indicator/model	AUC (95%CI)	Optimal cut-off value	Sensitivity (%)	Specificity (%)
PC	0.806 (0.740–0.872)	3.27 nmol/mg protein	66.67	82.02
8-OHdG	0.791 (0.723–0.859)	9.90 ng/mL	78.21	70.79
PGC-1α	0.772 (0.700–0.844)	145.80 pg/mL	78.21	68.54
Combined diagnostic score of the three indicators	0.884 (0.834–0.934)	0.45	87.18	79.78

Note: combined model vs PC, AUC difference=0.078, Z=2.135, P=0.033; combined model vs 8-OHdG, AUC difference=0.093, Z=2.343, P=0.019; combined model vs PGC-1α, AUC difference=0.112, Z=3.291, P<0.001.

Table VIII Metabolic and cardiac functional characteristics across risk groups stratified by the combined diagnostic score.

Indicator	Low-risk group (n=56)	Intermediate-risk group (n=55)	High-risk group (n=56)	Statistic	P
Predicted probability of the combined model	0.20±0.08	0.44±0.09	0.72±0.11	F=440.153	<0.001
Myocardial energy metabolism disorder [cases (%)]	10 (17.86)	24 (43.64)	44 (78.57)	χ^2=41.776	<0.001
PCr/ATP	1.77±0.17	1.60±0.27	1.47±0.25	F=23.216	<0.001
Myocardial energy expenditure	68.78±17.15	74.69±19.38	81.68±21.51	F=6.185	0.003
Indexed myocardial energy expenditure	0.46±0.10	0.50±0.12	0.55±0.13	F=7.691	<0.001
LVEF (%)	45.38±6.98	42.22±7.59	39.69±7.10	F=8.691	<0.001
GLS (%)	-12.92±2.98	-11.70±2.92	-10.40±2.82	F=10.526	<0.001
NT-proBNP (pg/mL)	1203.68±603.98	1686.49±775.99	2362.07±940.09	F=30.726	<0.001
hs-CRP (mg/L)	3.53±1.92	4.57±2.55	5.81±2.82	F=12.112	<0.001

improved further. The AUC of the combined diagnostic score was 0.884 (95% CI: 0.834–0.934), with a sensitivity of 87.18% and a specificity of 79.78%; the positive predictive value and negative predictive value were 79.07% and 87.65%, respectively. The AUC of the combined model was higher than that of every single indicator, indicating that the combined detection of the three serum indicators was more useful for identifying myocardial energy metabolism disorder in patients with ICM than any single indicator alone (*Figure 1, Table VII*).

Simplified combined diagnostic model and risk stratification results

After further stratification by the combined diagnostic score, the detection rates of myocardial energy metabolism disorder in the low-, intermediate-, and high-risk groups were 17.86%, 43.64%, and 78.57%, respectively (χ^2=41.776, P<0.001). As the risk level increased, PCr/ATP gradually decreased, myocardial energy expenditure, NT-proBNP, and high-sensitivity C-reactive protein gradually increased, and left ventricular ejection fraction and global longitudinal strain gradually decreased (P<0.05) (*Table VIII*).

Discussion

This study found that, when patients with ICM were complicated by myocardial energy metabolism disorder, serum PC and 8-OHdG levels increased, whereas PGC-1α levels decreased; after the three indicators were combined, their ability to identify myocardial energy metabolism disorder was better than that of any single indicator. Further stratified analysis showed that an increased combined diagnostic score was consistent with decreased PCr/ATP, increased myocardial energy expenditure, and aggravated cardiac dysfunction. These findings suggest that myocardial energy metabolism disorder in patients with ICM is not caused by an abnormality in a single pathway but may be accompanied by protein and DNA oxidative damage and reduced mitochondrial metabolic regulatory capacity.

First, the increased PC and 8-OHdG levels observed in patients with myocardial energy metabolism disorder are consistent with the pathological characteristics of persistent oxidative damage under chronic ischemic conditions: patients with ICM have long-term myocardial hypoperfusion and microcirculatory dysfunction, and once mitochondrial oxidative phosphorylation is restricted, the efficiency of the electron transport chain declines and reactive oxygen species production increases (18). Excessive accumulation of reactive oxygen species can induce oxidative modification of protein side chains and form relatively stable carbonylated products; meanwhile, DNA, especially mitochondrial DNA, is close to the site of reactive oxygen species production and has relatively limited protective mechanisms, making it more susceptible to oxidative damage and the generation of 8-OHdG (19, 20). Therefore, the elevation of these two indicators not only reflects enhanced systemic oxidative stress but may also suggest an increased oxidative burden accompanying impaired high-energy phosphate metabolism in cardiomyocytes. Previous studies on coronary heart disease, heart failure, and metabolic abnormalities, including recent studies on oxidative stress and cardiovascular injury, have generally suggested that oxidative stress is associated with worsening cardiac function (21, 22). This study further links these serum oxidative damage indicators to decreased PCr/ATP, thereby clarifying their significance in myocardial energy metabolism disorders. Unlike PC and 8-OHdG, PGC-1α showed a decreasing trend in patients with myocardial energy metabolism disorder, mainly because PGC-1α is an important regulator of mitochondrial biogenesis and oxidative metabolism and can affect the expression of nuclear respiratory factors, mitochondrial transcription factor A, and fatty acid oxidation-related genes (23). During chronic ischemia and ventricular remodelling, cardiomyocytes require mitochondrial compensation to maintain ATP supply; if the PGC-1α-related pathway is suppressed, mitochondrial quantity, oxidative phosphorylation capacity, and substrate utilisation flexibility may decline, and the myocardium's ability to adapt to ischemia and pressure overload may also be weakened (24). In this study, the decrease in PGC-1α was consistent with lower PCr/ATP, lower left ventricular ejection fraction, and higher NT-proBNP levels, suggesting that it may reflect insufficient mitochondrial metabolic adaptation. Previous basic studies have shown that downregulation of PGC-1α expression is associated with reduced ATP generation, myocardial metabolic reprogramming, and progression of ventricular remodelling (23, 24), further supporting our interpretation. However, serum PGC-1α is not derived specifically from the myocardium. Skeletal muscle metabolic status, inflammatory response, and the systemic energy metabolic environment may all affect its level, which also explains why PGC-1α alone had limited diagnostic performance.

On the other hand, we also observed that the three indicators changed continuously as myocardial energy metabolism disorder became more severe. PC and 8-OHdG gradually increased, indicating that the oxidative damage burden increased with the progression of metabolic disorder; PGC-1α gradually decreased, suggesting that mitochondrial compensation and metabolic regulation were further limited. When these two types of changes coexist, cardiomyocytes may be in a state of increased

oxidative damage and insufficient compensatory capacity, ultimately presenting as decreased PCr/ATP and reduced energy utilisation efficiency (25). Previous studies on the relationship between single oxidative stress markers and cardiac function or prognosis have not been entirely consistent. Some studies observed only weak correlations (26), and some did not identify a clear association (27). These differences may be related to study population, disease stage, specimen type, and control of confounding factors. For example, diabetes mellitus, renal dysfunction, and chronic inflammation can all affect circulating levels of oxidative stress-related indicators. Compared with single indicators, this study jointly analysed oxidative damage and mitochondrial regulatory indicators, covering multiple biochemical links involved in myocardial energy metabolism disorder, and therefore was more likely to obtain stable correlation results. The superior performance of the combined diagnostic model also underscores this point. Clinical studies have shown that PC mainly reflects protein oxidative damage (19), 8-OHdG primarily indicates DNA oxidative damage (20), and PGC-1α is associated with mitochondrial biogenesis and regulation of energy metabolism (23). The biochemical information represented by the three indicators is not redundant. Still, it corresponds to damage formation, genetic material injury, and insufficient metabolic repair capacity. Single indicators are more easily affected by non-myocardial factors and have limited diagnostic stability; combined detection can, to some extent, integrate information from different pathological processes and may therefore provide more stable diagnostic performance.

Finally, the risk stratification results further strengthened the clinical interpretability of the combined model, indicating that combined detection does not merely reflect differences in laboratory values but corresponds well to myocardial metabolic status and cardiac functional impairment. For patients with ICM, a higher combined serum score may suggest a greater oxidative damage burden and weaker mitochondrial metabolic adaptability. It may therefore serve as a reference for further cardiac imaging, metabolic assessment, or intensified follow-up. However, it must be emphasised that this model should be positioned as an auxiliary identification tool and cannot replace PCr/ATP, echocardiography, or other cardiac functional examinations.

This study also has several limitations. First, this was a single-centre retrospective analysis with a relatively small sample size (n=167), and case selection, data completeness, and potential unmeasured confounders may affect the stability of the results. In addition, serum samples were derived from archived samples. Although quality control was performed before testing, storage time, freeze-thaw process, and batch differences may still have affected the test results. Third, PC, 8-OHdG, and PGC-1α are not myocardial-specific markers, and diabetes mellitus, renal function status, chronic inflammation, and medication use may affect their circulating levels. In addition, myocardial-specific oxidative stress markers, such as myocardium-derived PC or 8-OHdG, were not measured in this study, and future studies should explore cardiomyocyte-specific exosomal biomarkers to more accurately distinguish myocardial oxidative injury from systemic oxidative stress. Fourth, this study did not include an independent validation cohort, and the generalizability of the combined diagnostic model still needs to be further evaluated in larger samples and multicentre populations.

Conclusion

Myocardial energy metabolism disorder in patients with ICM is closely associated with increased serum PC and 8-OHdG levels and decreased PGC-1α levels. These three indicators reflect myocardial metabolic stress from the perspectives of protein and DNA oxidative damage and mitochondrial metabolic regulation, respectively, and their combined detection shows better diagnostic performance than single indicators. The simplified combined diagnostic model constructed using the three serum indicators has a certain level of clinical biochemical accessibility and may serve as a reference for the auxiliary identification and risk stratification of myocardial energy metabolism disorders in patients with ICM.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Consent to publish

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Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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