İSTANBUL UNIVERSITY PRESS

Journal of İstanbul Faculty of Medicine
İstanbul Tıp Fakültesi Dergisi,
J Ist Faculty Med 2025, 88 (4): 296–304

https://doi.org/10.26650/IUITFD.1683309

Submitted: 28.04.2025
Revision Requested: 26.06.2025
Last Revision Received: 21.07.2025
Accepted: 13.08.2025
Published Online 18.09.2025

Journal of İstanbul Faculty of Medicine
İstanbul Tıp Fakültesi Dergisi

Research Article

Open Access

IRISIN IN PREDICTING MAJOR ADVERSE CARDIAC EVENTS AFTER MYOCARDIAL INFARCTION IN OBESE HYPERTENSIVE PATIENTS WITH TYPE 2 DIABETES MELLITUS

İRİSİNİN, OBEZ HİPERTANSİF TİP 2 DİYABET HASTALARINDA MİYOKARD ENFARKTÜSÜNDEN SONRA MAJÖR KARDİYAK ADVERS OLAYLARI ÖNGÖRMEDEKİ ROLÜ

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Abstract

Objective: Cardiovascular diseases (CVDs), particularly ST-elevation myocardial infarction (STEMI), remain the leading causes of mortality and disability worldwide. This study aimed to evaluate the relationship between serum irisin levels and the development of major adverse cardiovascular events (MACE) in high-risk patients with hypertension, type 2 diabetes mellitus (T2DM), and obesity following STEMI.

Material and Methods: A prospective observational study included 238 hypertensive patients with T2DM and obesity (BMI>30 kg/m²) admitted with a first STEMI. Patients were divided into MACE (n=117) and non-MACE (n=121) groups. Serum irisin was measured by ELISA. MACE was assessed over 12 months and included recurrent myocardial infarction, stroke, cardiovascular death, and hospitalisation for heart failure.

Results: Irisin levels were significantly lower in the MACE group (121.57±15.86 ng/mL) than in the non-MACE group (129.31±17.93 ng/mL; p=0.0005). Patients with MACE had a significantly longer duration of hypertension and T2DM. A non-dipper blood pressure profile was more frequent in the MACE group (41.88% vs. 26.44%; p=0.0121). Multivariate logistic regression revealed that lower irisin levels (OR: 0.911; 95% CI: 0.417–0.991; p=0.041) and non-dipper BP profile were independent predictors of MACE.

Öz

Amaç: Kardiyovasküler hastalıklar (KVH), özellikle ST-yükselmeli miyokard enfarktüsü (STEMI), dünya çapında ölüm ve sakatlıkların önde gelen nedeni olmaya devam etmektedir. Bu çalışma, STEMI sonrası hipertansiyon, tip 2 diabetes mellitus (T2DM) ve obezitesi olan yüksek riskli hastalarda serum irisin seviyeleri ile majör advers kardiyovasküler olayların (MACE) gelişimi arasındaki ilişkiyi değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntemler: Prospektif gözlemsel bu çalışmaya, ilk STEMI ile başvuran T2DM ve obezitesi (VKİ>30kg/m²) olan 238 hipertansif hasta dahil edildi. Hastalar MACE (n=117) ve MACE olmayan (n=121) gruplara ayrıldı. Serum irisin düzeyleri ELISA ile ölçüldü. MACE 12 ay boyunca tekrarlayan miyokard enfarktüsü, inme, kardiyovasküler ölüm ve kalp yetmezliği nedeniyle hastaneye yatışı kapsayan bir değerlendirme yapıldı.

Bulgular: İrisin düzeyleri MACE grubunda (121,57±15,86 ng/mL), MACE olmayan gruba (129,31±17,93 ng/mL; p=0,0005) kıyasla anlamlı derecede düşüktü. MACE hastalarında hipertansiyon ve T2DM süresi anlamlı derecede daha uzundu. Non-dipper kan basıncı profili MACE grubunda daha sıktı (%41,88'e karşı %26,44; p=0,0121). Çok değişkenli lojistik regresyon, düşük irisin düzeylerinin (OR: 0,911; %95 GA: 0,417-0,991; p=0,041) ve non-dipper kan basıncı profilinin MACE'nin bağımsız öngörücüleri olduğunu ortaya koydu.

Citation: Shelest B, Babycheva O, Sadovenko O, Kalmykov O, Rodionova I, Avdieienko O, et al. Irisin in predicting major adverse cardiac events after myocardial infarction in obese hypertensive patients with type 2 diabetes mellitus. Journal of İstanbul Faculty of Medicine 2025;88(4):296-304. https://doi.org/10.26650/IUITFD.1683309

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Conclusion: Lower irisin levels and abnormal circadian BP rhythm are associated with increased MACE risk after STEMI in patients with T2DM and obesity. Irisin may serve as a valuable biomarker for early risk stratification in such high-risk populations.

Keywords Irisin · myocardial infarction · hypertension · obesity · diabetes mellitus

Sonuç: Düşük irisin düzeyleri ve anormal sirkadiyen kan basıncı ritmi, T2DM ve obezitesi olan hastalarda STEMI sonrası artmış MACE riski ile ilişkilidir. İrisin, bu tür yüksek riskli popülasyonlarda erken risk sınıflandırması için değerli bir biyobelirteç olarak görev alacağı öngörülmektedir.

Anahtar Kelimeler İrisin · miyokard enfarktüsü · hipertansiyon · obezite · diyabet mellitus

INTRODUCTION

Cardiovascular diseases (CVDs) continue to be a major global health concern, representing one of the leading causes of death and disability. Among the most critical manifestations is ST-elevation myocardial infarction (STEMI), which is associated with significant mortality and the risk of complications such as heart failure, arrhythmias, and major adverse cardiovascular events (MACE). The presence of comorbid conditions such as hypertension, type 2 diabetes mellitus, and obesity further increases the likelihood of these adverse outcomes. Consequently, identifying early predictors of such complications is essential for improving preventive and therapeutic strategies in high-risk patients.

In recent years, increasing attention has been directed towards the role of biomarkers in predicting cardiovascular complications (1, 2). Irisin, a myokine discovered in 2012, has emerged as a promising candidate due to its involvement in metabolic regulation—particularly through its ability to promote the browning of white adipose tissue and enhance energy expenditure (3). Altered irisin levels have been observed in metabolic disorders including obesity, hypertension, and diabetes (4, 5). Additionally, irisin is known to influence mitochondrial function, endothelial integrity, and inflammatory pathways, all of which are relevant to the development of cardiovascular disease (6).

Studies investigating irisin in the setting of acute coronary syndromes, such as STEMI, have highlighted its potential protective effects—especially its ability to mitigate endothelial dysfunction and inflammation during the early phase of myocardial injury (7). Paradoxically, elevated irisin levels during the post-infarction period have been linked to a higher risk of subsequent adverse cardiovascular events (8).

Given its metabolic and cardiovascular regulatory roles, irisin is gaining recognition as a potential biomarker for predicting MACE. Low irisin concentrations may reflect disrupted energy metabolism and heightened inflammation, both of which are key contributors to atherosclerosis and cardiovascular complications. This is particularly relevant for patients with multiple comorbidities such as diabetes, obesity, and hypertension. Despite its potential, the precise function of irisin throughout different stages of cardiovascular disease and its viability as a therapeutic target remain subjects of ongoing investigation.

The aim of this study was to investigate the relationship between irisin levels and the subsequent development of MACE in patients with hypertension, type 2 diabetes, obesity, and STEMI.

MATERIAL AND METHODS

Study design and patient population

This prospective observational study was conducted in the Cardiology Department of the Kharkiv Regional Clinical Hospital and the Cardiology Department of the City Clinical Hospital of Urgent and Emergency Medical Care in Kharkiv, Ukraine. The study was conducted between December 6, 2021, and July 31, 2024, including patient enrolment, follow-up, and data analysis. A total of 238 hypertensive patients were enrolled in the study. Patients were categorised into two groups, namely group MACE (n=117), with the presence of MACE and group non-MACE (n=121, without the MACE).

The Ethics Committee of Kharkiv National Medical University has approved the study (Date: 03.11.2021, No: 3). The work was carried out in accordance with the requirements of the Declaration of Helsinki, the Charter of the Ukrainian Association for Bioethics, and the Good Clinical Practice (GCP) standards (1992), according to the requirements and norms of the ICH GCP, and the model provisions on ethics of the Ministry of Health of Ukraine No. 66 dated 13/02/2006. All patients provided written informed consent before inclusion in the study and were fully informed about the methods and scope of the research.

Inclusion criteria were age between 40 and 75 years; confirmed diagnosis of type 2 diabetes mellitus according to the World Health Organisation (WHO) and European Cardiology Society (ESC) Guidelines on diabetes criteria. Type 2 diabetes mellitus was confirmed based on fasting plasma glucose levels ≥7.0 mmol/L (126 mg/dL) on two separate occasions. HbA1c levels ≥6.5% on two separate tests, previous documentation of diabetes diagnosis and ongoing treatment with oral hypoglycaemic agents or insulin. Body mass index (BMI) over 30 kg/m² (classified as Class I or II obesity by WHO standards); diagnosis of essential hypertension according

to ESC; admission to the hospital with a first-time STEMI diagnosis.

Exclusion criteria: type 1 diabetes mellitus or other specific types of diabetes; previous history of myocardial infarction, stroke, or revascularization procedures; presence of severe comorbidities such as chronic kidney disease (stage IV or V), hepatic failure, or active cancer; inability or refusal to provide informed consent.

STEMI was diagnosed on the basis of the ESC criteria (9). The diagnosis required the following: clinical symptoms of acute myocardial ischaemia (e.g., chest pain lasting more than 20 min); new ST-segment elevation at the J-point in two or more contiguous leads on a 12-lead electrocardiogram (ECG), with the following cut-off points: ≥0.2 mV (2 mm) in men or ≥0.15 mV (1.5 mm) in women in leads V2-V3; ≥0.1 mV (1 mm) in other contiguous chest leads or limb leads; detection of elevated cardiac biomarkers (troponin I or T levels) above the 99th percentile upper reference limit, confirming myocardial necrosis. All ECGs were interpreted by two independent cardiologists to ensure diagnostic accuracy. In cases of disagreement, a third cardiologist was consulted.

Data collection and measurements

Weight and height were measured using standardised equipment. BMI was calculated as weight (kg) divided by height squared (m^2); Blood Pressure (BP) Measurement: Systolic and diastolic BPs were measured using a calibrated sphygmomanometer (Omron M6 Comfort, Japan) after the patient had rested for at least 5 min. The average of two readings was recorded. 24-Hour Ambulatory BP Monitoring (ABPM): ABPM was performed using the Meditech ABPM-04 device (Meditech Ltd., Hungary). Patients were classified as "dippers" or "non-dippers" based on nocturnal BP patterns according to standard criteria (a nocturnal systolic BP decrease of less than 10% was considered non-dipping); blood samples were collected upon admission to assess: glucose levels; glycated haemoglobin (HbA1c); lipid profile (total cholesterol, HDL, LDL, triglycerides); serum creatinine; and cardiac enzymes (troponin I/T). Serum irisin levels were measured using an enzyme-linked immunosorbent assay (ELISA) kit from R&D Systems (Minneapolis, MN, USA), following the manufacturer's instructions, on an enzyme immunoassay analyser Labline-90 (Austria).

Echocardiographic Evaluation

The ejection fraction (EF) and other cardiac functions were assessed using transthoracic echocardiography (TTE) performed by experienced sonographers. The examinations were conducted using a Medison SonoAce X6 ultrasound machine (Samsung Medison, South Korea) with a 2–5 MHz transducer. The procedures followed the guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging (10). The echocardiographer was blinded to the patients' clinical data.

Data on hypertension and diabetes duration: The duration of essential hypertension and diabetes mellitus was obtained from patient medical records and patient interviews.

Follow-up and outcome assessment

Patients were followed for one year to monitor for the occurrence of MACE, which included: recurrent myocardial infarction, stroke, cardiovascular death, hospitalisation for heart failure.

Statistical analysis

Statistical analyses were performed using the JASP software, Version 0.19.0. Continuous variables were expressed as mean±standard deviation (SD) and compared using the Student's t-test or Mann–Whitney U test, as appropriate. Categorical variables were presented as frequencies and percentages, and comparisons were made using the chi-square test or Fisher's exact test. The normality of the data distribution was assessed using the Kolmogorov-Smirnov test. Correlation analyses were performed using Pearson's or Spearman's correlation coefficients, depending on the data distribution. Univariate and multivariate logistic regression analyses were conducted to identify the independent predictors of MACE. A p-value <0.05 was considered statistically significant.

RESULTS

All patients enrolled in this study were hospitalised with a diagnosis of STEMI and diabetes mellitus and had a BMI over 30 kg/m^2. All subjects exhibited increased BMI within the range of 30.0–39.9 kg/m^2 (Class I–II obesity according to the WHO classification). Patients were divided into the MACE group (n=117) and the non-MACE group (n=121). During the 1-year follow-up period, in the MACE group, the following events occurred: recurrent myocardial infarction in 23 patients (19.7%), stroke in 15 patients (12.8%), and hospitalisation due to heart failure in 79 patients (67.5%). Cardiovascular death was not observed in this cohort (0%). The baseline characteristics are presented in Table 1.

Gender distribution and the average age were approximately equal in both groups, with about half of the subjects being male: 48.7% vs 49.6% in the MACE group and non-MACE group respectively, p=0.8922; the average age was statistically equal in the both groups (56.89±9.03 years vs 55.02±10.17

Table 1. Baseline characteristics of the participants

Characteristics	MACE (n=117)	Non MACE (n=121)	p
Mean age, years	56.89±9.03	55.02±10.17	0.1354
Males, n (%)	57 (48.7%)	60 (49.6%)	0.8922
Body mass index, kg/m²	36.18±5.83	34.87±4.88	0.061
Hypertension duration, years	21.05±8.83	18.72±7.95	**0.0333**
Diabetes duration, years	7.93±3.11	6.53±2.73	**0.0003**
History of smoking, n (%)	45 (38.5%)	43 (35.5%)	0.6324
Systolic blood pressure, mmHg	157.31±11.03	154.77±12.01	0.0909
Diastolic blood pressure, mmHg	95.53±9.71	94.32±8.89	0.3168
Non-dipper BP profile (disrupted circadian rhythm), n (%)	49 (41.88%)	32 (26.44%)	**0.0121**
Serum glucose, mg/dL	135.75±30.48	134.51±31.83	0.7593
HbA1c, %	7.63±2.97	7.11±2.57	0.1495
Serum creatinine, mg/dL	0.91±0.25	0.90±0.31	0.7848
Total cholesterol, mg/dL	211.65±56.93	207.97±38.21	0.5533
Triglyceride, mg/dL	138.55 ± 25.91	140.23 ± 34.45	0.6719
HDL-C, mg/dL	49.85±8.34	47.91±9.65	0.0989
LDL-C, mg/dL	123.89 ± 37.58	121.46 ± 35.71	0.6095
LVMI, g/m²	133.15±20.46	129.86±24.71	0.2652
hs-cTnI, ng/ml	74.53 ±15.31	77.19±16.84	0.2040
LVEF, %	55.32±7.53	56.29±6.92	0.3016
Irisin, ng/mL	121.57±15.86	129.31±17.93	**0.0005**

p: p-value, MACE: Major adverse cardiovascular events, HDL-C: High-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, LVMI: Left ventricular mass index, hs-cTnI: High sensitive cardiac troponin I, LVEF: Left ventricle ejection fraction

years, respectively, p=0.1354). Systolic and diastolic BP levels were comparable between the groups with and without MACE: 157.31±11.03 mmHg vs. 154.77±12.01 mmHg (p=0.0909), and 95.53±9.71 mmHg vs. 94.32±8.89 mmHg (p=0.3168), respectively. Other clinical, anthropometric, laboratory, and instrumental parameters were also statistically comparable between the two groups. The proportion of smokers was similar: 45 subjects (38.5%) in the MACE group vs. 43 subjects (35.5%) in the non-MACE group (p=0.6324). Serum glucose levels were 135.75±30.48 mg/dL in the MACE group vs. 134.51±31.83 mg/dL in the non-MACE group (p=0.7593). HbA1c levels were 7.63±2.97% vs. 7.11±2.57% (p=0.1495). Serum creatinine levels were 0.91±0.25 mg/dL vs. 0.90±0.31 mg/dL (p=0.7848). The lipid profile indices, including high-density lipoprotein (HDL) cholesterol (49.85±8.34 mg/dL vs. 47.91±9.65 mg/dL, p=0.0989), triglycerides (138.55 ± 25.91 mg/dL vs 140.23 ± 34.45 mg/dL, p=0.6719), and total cholesterol (211.65±56.93 mg/dL vs. 207.97±38.21 mg/dL, p=0.2262), did not differ significantly between the groups. The left ventricular ejection fraction was also similar: 55.32±7.53 % in the MACE group vs. 56.29±6.92 % in the non-MACE group (p=0.3016).

In contrast, we found that irisin levels were significantly decreased in the MACE group compared with the non-MACE group (121.57±15.86 ng/mL vs. 129.31±17.93 ng/mL, p=0.0005). The duration of essential hypertension was significantly longer in the MACE group (21.05±8.83 years vs. 18.72±7.95 years, p=0.0333). Similarly, the duration of diabetes mellitus was significantly longer in the MACE group (7.93±3.11 years vs. 6.53±2.73 years, p=0.0003). Additionally, the percentage of patients with an abnormal 24-hour ABPM profile (classified as "non-dippers," including over-dippers and night-peakers) was significantly higher in the MACE group (49 patients, 41.88%) compared to the non-MACE group (32 patients, 26.44%; p=0.0121). BMI was not significantly higher in the MACE group (36.18±5.83 kg/m² vs. 34.87±4.88 kg/m², p=0.061).

We also observed a negative correlation between irisin levels and the Global Registry of Acute Coronary Events (GRACE) risk score (r=–0.281, p=0.039), as well as between irisin levels and the duration of essential hypertension (r=–0.351, p=0.044).

In the next phase of our study, we performed univariate logistic regression analysis to identify the independent predictors of MACE development. Lower irisin levels were associated with an increased risk of MACE, with an odds ratio (OR) of 0.930 (95% confidence interval [CI]: 0.863–0.995, p=0.021). Other significant factors identified were the duration of essential hypertension (OR: 1.935, 95% CI: 1.032–

Table 2. Univariate and multivariate logistic analysis of the influence of the studied factors on the MACE in STEMI patients with EH, DM and obesity

Indices	Univariate logistic regression OR (95% CI)		Multivariate logistic regression OR (95% CI)	
		p		p
Irisin	0.930 (0.863–0.995)	**0.021**	0.911 (0.417–0.991)	**0.041**
Disrupted circadian rhythm	2.944 (1.392–6.235)	**0.001**	2.176 (1.745–5.763)	**0.044**
SBP, mm Hg	1.122 (0.976–2.451)	0.673		
DBP, mm Hg	1.413 (0.718–3.357)	0.459		
Gender (M/F)	4.005 (0.497–7.302)	0.816		
Age, years	0.917 (0.783–2.153)	0.738		
BMI, kg/m²	1.498 (0.689–3.215)	0.596		
Smoking	3.034 (0.765–7.395)	0.815		
TC, mg/dL	0.876 (0.587–3.109)	0.698		
HDL-C, mg/dL	0.617 (0.284–1.871)	0.109		
LDL-C, mg/dL	2.013 (0.691–3.054)	0.271		
Triglyceride, mg/dL	3.135 (0.844–4.742)	0.784		
Duration EH, years	1.935 (1.032–3.945)	**0.029**	—	—
Duration DM, years	1.121 (1.005–3.542)	**0.035**	—	—
Serum glucose, mg/dL	1.948 (0.803–6.055)	0.317		
HbA1c, %	1.645 (0.867–3.649)	0.093		
Serum creatinine, mg/dL	2.158 (0.788–9.467)	0.899		
LVEF, %	1.745 (0.835–3.903)	0.458		

p: p-value, CI: Confidence interval, OR: Odds ratio, BMI: Body mass index; MACE: Major adverse cardiovascular events, EH: Essential hypertension, DM: Diabetes mellitus, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, TC: Total cholesterol, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, LVMI: Left ventricular mass index, LVEF: Left ventricular ejection fraction

3.945, p=0.029), duration of diabetes mellitus (OR: 1.121, 95% CI: 1.005–3.542, p=0.035), and non-dipper BP profile on 24-hour ABPM (OR: 2.944, 95% CI: 1.392–6.235, p=0.001) (Table 2). the parameters of glycemic and lipid profiles, BMI, and BP levels did not show significance in these univariate analyses.

Subsequently, multivariate logistic regression analysis was conducted, incorporating variables with a p-value less than 0.1 from the univariate analysis. This revealed that irisin levels and non-dipper BP profile on 24-h ABPM remained significant predictors of MACE development in individuals with essential hypertension, diabetes mellitus, and obesity. Specifically, lower irisin levels (OR: 0.911; 95% CI: 0.417–0.991; p=0.041), and non-dipper BP profile (OR: 2.176; 95% CI: 0.745–5.763; p=0.044) continued to be associated with an increased risk of MACE (Table 2).

ROC curve analysis identified an optimal irisin cut-off level of 126.30 ng/mL for predicting MACE, with an area under the curve (AUC) of 0.68, sensitivity of 71%, and specificity of 65%.

DISCUSSION

Our study revealed that decreased irisin levels were significantly associated with a higher risk of MACE in patients with essential hypertension, diabetes mellitus, and obesity. Specifically, we found that with each unit reduction in serum irisin, the risk of developing MACE increased by approximately 21.1%. Our ROC curve analysis further supports the prognostic value of irisin, demonstrating that patients with irisin levels below the identified optimal cut-off (≤126.3 ng/mL) had a significantly higher likelihood of developing MACE. Although Kaplan-Meier survival analysis was not performed due to the absence of precise individual event timing data in our current dataset, the ROC analysis provides strong preliminary evidence for irisin's clinical utility as a biomarker. These findings underscore the potential of irisin for predicting adverse cardiovascular outcomes in obese hypertensive diabetic patients following myocardial infarction.

The inclusion of the non-dipper blood pressure profile evaluation provided additional insights into our study population, considering the recognised relationship between abnormal nocturnal blood pressure dipping and increased cardiovascular risk. Our study highlights a significant association between non-dipper BP profiles and MACE in patients with hypertension, diabetes, and obesity following myocardial infarction. Consistent with our findings, Pusuroglu et al. demonstrated that non-dipper

hypertension independently predicted MACE, highlighting a clear association between abnormal nocturnal BP patterns and increased cardiovascular risk (11). Similarly, Boos et al. identified elevated arterial stiffness and inflammation primarily in non-dippers, emphasising abnormal BP dipping patterns as significant markers of cardiovascular risk, aligning closely with our results (12).

Further supporting our observations, Manea et al. reported a high prevalence of non-dippers among diabetic hypertensive patients, linking this profile to increased mean arterial pressure and adverse metabolic outcomes (13). This indicates a shared pathophysiology with our patient cohort, underscoring disrupted nocturnal BP regulation as a key contributor to cardiovascular vulnerability (13). Additionally, Candemir et al. demonstrated a significant association between non-dipper BP patterns and prolonged hospital stays and adverse events in patients with decompensated heart failure, reinforcing the clinical importance of early identification of non-dipper profiles (14). Finally, Komori et al. provided insights into broader systemic implications of abnormal circadian BP rhythms, such as cerebral hypoperfusion and atherosclerosis, further reinforcing our findings regarding the detrimental cardiovascular impact of non-dipping BP profiles (15). Collectively, these results underline the critical importance of abnormal nocturnal BP dipping patterns as robust predictors of adverse cardiovascular outcomes, highlighting their value for early risk stratification and patient management in high-risk metabolic populations.

Emerging evidence supports the role of serum irisin as a valuable prognostic biomarker for cardiovascular outcomes. For instance, the study by Chai et al. examined the link between serum irisin levels and MACE in patients with acute myocardial infarction (AMI) undergoing percutaneous coronary intervention (PCI) (16). Their findings demonstrated that lower irisin levels upon hospital admission were significantly associated with MACE within a year following PCI. Differences in clinical features, such as Killip classification and left ventricular ejection fraction, were also noted between patients who experienced MACE and those who did not. These observations corroborate our results and reinforce the prognostic value of irisin in assessing outcomes in high-risk cardiovascular patients.

Furthermore, our study expands upon these findings by exploring the predictive role of irisin in a broader clinical context, including patients with combined metabolic disorders—specifically, those with hypertension, obesity, and type 2 diabetes. While both our research and the work of Chai et al. highlight the association between lower irisin levels and poor outcomes, our findings suggest that irisin may serve as a consistent prognostic marker across different populations and cardiovascular conditions. This aligns with the existing literature pointing out that irisin contributes to cardiovascular protection due to its anti-inflammatory and antioxidative properties (17).

Additional research supports the idea that reduced irisin levels correlate with greater cardiovascular risk. For example, studies have shown that patients with acute coronary syndrome (ACS) have significantly lower irisin levels than those with stable coronary artery disease (SCAD), non-obstructive CAD, or normal coronary arteries (18). Among these groups, patients with ACS showed the lowest irisin levels, and higher levels were associated with improved event-free survival post-PCI. These findings echo our results, designating that low irisin is a valuable indicator of poor prognosis in patients at high cardiovascular risk.

Ozturk et al. also demonstrated significantly lower irisin levels in patients with STEMI compared with controls (19). Their study identified an inverse relationship between irisin and cardiac troponin I levels, along with a correlation between low irisin and prolonged QTc interval—indicators of more severe myocardial damage and electrophysiological dysfunction. These results are in line with our study, further supporting the association between low irisin levels and increased MACE risk, particularly in patients with comorbid conditions such as diabetes and obesity.

Hsieh et al. also observed an association between altered irisin levels after STEMI and adverse cardiovascular outcomes (8). Although their study noted worse outcomes with elevated irisin levels, this discrepancy may reflect differences in the disease stage or patient characteristics. Our findings identify that low irisin levels may reflect metabolic insufficiency and chronic inflammation, contributing to worse outcomes.

Ho and Wang's review emphasises irisin's dual role in cardiovascular health (20). While irisin appears to be protective during the early stages of myocardial infarction by preserving endothelial function, our data show that reduced irisin levels may signal impaired metabolic activity and systemic inflammation in patients at an elevated risk of MACE.

Animal studies also reinforce the therapeutic potential of irisin. In a rat model of myocardial infarction, Bashar et al. demonstrated that irisin levels correlated with infarct size and that interventions such as physical exercise or recombinant irisin administration mitigated myocardial injury and oxidative stress (21). These findings support the hypothesis that irisin may act as both a biomarker and a therapeutic agent. Nevertheless, our data indicate

that persistently elevated irisin levels post-infarction may represent a compensatory mechanism in response to metabolic stress.

Grzeszczuk et al. have described the critical role of irisin in cardiomyocyte energy regulation and mitochondrial biogenesis, pointing to its high concentration in cardiac tissue (22). Their findings, which highlight the role of irisin in converting white to brown adipose tissue and enhancing mitochondrial activity, are consistent with our observations that lower irisin levels are associated with higher MACE risk. A deficiency in irisin may impair mitochondrial function and energy metabolism, contributing to the pathogenesis of cardiovascular complications in patients with hypertension, diabetes, and obesity.

In line with this, research on patients with congestive heart failure (CHF) has shown that reduced irisin levels, along with lower HDL cholesterol, are linked to adverse outcomes such as increased arterial stiffness and left ventricular hypertrophy (23). Although that study focused on CHF, our results allow us to assert that the prognostic value of irisin extends beyond heart failure, encompassing a wider spectrum of cardiometabolic disorders.

Our study also underscores the relevance of irisin in vascular health. Wang et al. reported that irisin not only predicts vascular calcification but also inhibits its progression by improving endothelial function and preventing phenotypic changes in vascular smooth muscle cells (24). Because vascular calcification is common in chronic diseases such as diabetes and hypertension, these findings support the broader cardiovascular significance of irisin. While our work focuses on MACE prediction, these complementary findings highlight irisin's potential in protecting vascular structure and function.

However, the role of irisin remains controversial. According to a review by Ou-Yang et al., conflicting data and measurement inconsistencies complicate our understanding of irisin in coronary heart disease (CHD) (25). Despite evidence supporting its metabolic benefits, further studies—especially those using gene knockout models or recombinant irisin—are needed to clarify its precise mechanisms and therapeutic implications.

Li et al. have emphasised irisin's potential role in heart failure, where impaired energy production and metabolic remodelling are common features (26). The fact that irisin is produced both by the skeletal muscle and the heart highlights its systemic and local significance. Although its mechanisms in heart failure remain under investigation, the growing evidence supports its therapeutic potential.

Our findings align with those of the study by González D et al., emphasising the cardioprotective role of irisin, including its association with metabolic and cardiovascular parameters (27). Both studies confirm an inverse relationship between irisin levels and cardiovascular risk, but our research uniquely extends these observations, demonstrating the prognostic significance of irisin specifically for predicting MACE in obese hypertensive diabetic patients following myocardial infarction. Additionally, while their study identified diastolic blood pressure as positively correlated with irisin, we further identified a significant association between non-dipper blood pressure profiles and reduced irisin levels as predictors of cardiovascular events.

Although our findings are clinically relevant, several limitations must be acknowledged. First, the sample size was relatively small, and larger cohort studies are required to validate these associations. Second, we did not assess baseline irisin levels in relation to other established cardiac biomarkers. Third, our single-centre design may limit the generalizability of the results to other populations or healthcare settings. Additionally, we did not fully account for confounding factors such as comorbidities and treatment regimens, which may have influenced survival outcomes. Due to the absence of precise individual event timing data, Kaplan–Meier survival analysis was not feasible in this study. Future studies should address these limitations to further elucidate the role of irisin in cardiovascular risk stratification and management.

CONCLUSION

Thus, the study presents that irisin is a marker of altered metabolic activation and inflammatory processes that contribute to the progression of cardiovascular complications. Low irisin levels in patients with myocardial infarction, diabetes, and obesity may signal insufficient activation of protective mechanisms, ultimately increasing the risk of MACE.

Further investigations are necessary to elucidate the essential mechanisms and therapeutic potential of irisin in cardiovascular disease, focusing on the adequate therapeutic level of irisin in myocardial infarction, the optimal timing of irisin administration, and whether irisin acts as a trigger or consequence in heart failure repair mechanisms. With more evidence, irisin may be established not only as a biomarker but also as a potential therapeutic target in cardiovascular disease management.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Kharkiv National Medical University (Date: 03.11.2021, No: 3).

Informed Consent: Consent was obtained from all patients who participated in the study.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- B.S., O.B., O.S., O.K., I.R., O.A., Y.K., O.S.; Data Acquisition- B.S., O.B., O.S., O.K., I.R., O.A., Y.K., O.S.; Data Analysis/Interpretation – B.S., O.B., O.S., O.K., I.R., O.A., Y.K., O.S.; Drafting Manuscript- B.S., O.B., O.S., O.K., I.R., O.A., Y.K., O.S.; Critical Revision of Manuscript- B.S., O.B., O.S., O.K., I.R., O.A., Y.K., O.S.; Final Approval and Accountability- B.S., O.B., O.S., O.K., I.R., O.A., Y.K., O.S.; Technical or Material Support- B.S., O.B., O.S., O.K., I.R., O.A., Y.K., O.S.; Supervision- B.S., O.B., O.S., O.K., I.R., O.A., Y.K., O.S.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: Authors declared no financial support.

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