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Ten-Year Clinical Outcomes in MINOCA: A Clinical Framework for Long-Term Risk Stratification

MINOCA'da On Yıllık Klinik Sonuçlar: Uzun Dönem Risk Sınıflaması için Klinik Bir Çerçeve

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ABSTRACT

Objective: This study aimed to design and validate myocardial infarction with non-obstructive coronary arteries (MINOCA), a practical bedside prognostic tool for evaluating the long-term risk profiles of patients experiencing myocardial infarction (MI) with MINOCAs.

Methods: A retrospective cohort analysis was carried out at Gazi University between January 2013 and December 2018. MINOCA was diagnosed based on standard biochemical and clinical MI criteria, alongside angiographic evidence of stenosis of <50% in the epicardial arteries. We extracted baseline clinical, laboratory, and echocardiographic data from electronic registries. The primary endpoint was major adverse cardiovascular events (MACEs), defined as a composite of cardiovascular death, non-fatal MI, stroke, and hospitalization for heart failure; outcomes were tracked up to June 2025. Predictor variables were assessed via logistic regression, and the multivariable coefficients were used to assign point values for the PRO-MINOCA score. Statistical evaluations included receiver operating characteristic curves for discrimination, Kaplan-Meier survival curves, and Cox proportional hazards models for survival analysis.

Results: The cohort comprised 658 subjects (mean age 59.2 ± 11.6 years; 52.4% women). During the extended follow-up, 158 individuals (24%) experienced MACE. Multivariable analysis identified several independent risk factors: age ≥65 years, hypertension, diabetes, left ventricular ejection fraction (EF) <50%, estimated glomerular filtration rate <60 mL/min/1.73 m², elevated levels of C-reactive protein, troponin, and N-terminal pro-brain natriuretic peptide (NT-proBNP), incident atrial fibrillation, and a history of peripheral

ÖZ

Amaç: Bu çalışmada, obstrüktif olmayan koroner arterlerle seyreden miyokard infarktüsü (MINOCA) hastalarında uzun dönem kardiyovasküler riskin öngörülmesi için klinik pratikte kolaylıkla kullanılabilecek PRO-MINOCA skorunun geliştirilmesi ve doğrulanması amaçlandı.

Yöntemler: Ocak 2013-Aralık 2018 tarihleri arasında Gazi Üniversitesi'nde MINOCA tanısı alan hastalar retrospektif olarak değerlendirildi. MINOCA tanısı, miyokard infarktüsüne ait klinik ve biyokimyasal kriterlerin varlığına ek olarak koroner anjiyografide epikardiyal koroner arterlerde <%50 darlık saptanması ile konuldu. Hastaların başvuru sırasındaki klinik özellikleri, laboratuvar bulguları ve ekokardiyografik verileri hastane kayıtlarından elde edildi. Birincil sonlanım noktası kardiyovasküler ölüm, ölümcül olmayan miyokard infarktüsü, inme ve kalp yetersizliği nedeniyle hastaneye yatıştan oluşan majör advers kardiyovasküler olay (MACE) olarak belirlendi. Klinik sonlanımlar Haziran 2025'e kadar takip edildi. PRO-MINOCA skorunu oluşturmak için öngördürücü değişkenler lojistik regresyon analizi ile değerlendirildi ve çok değişkenli analizde bağımsız belirleyici olarak saptanan parametreler puanlama sistemine dahil edildi. Skorun ayırt edici gücü alıcı işletim karakteristiği eğrisi analiziyle, uzun dönem prognostik değeri ise Kaplan-Meier sağkalım analizi ve Cox regresyon modeliyle değerlendirildi.

Bulgular: Çalışmaya toplam 658 hasta dahil edildi. Hastaların ortalama yaşı 59,2 ± 11,6 yıl olup %52,4'ü kadındı. Uzun dönem takipte 158 hastada (%24) MACE gelişti. Çok değişkenli analizde ≥65 yaş, hipertansiyon, diabetes mellitus, sol ventrikül ejeksiyon fraksiyonunun <%50 olması, tahmini glomerüler filtrasyon hızının <60 mL/dk/1,73

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ABSTRACT

arterial disease, MI, or prior stroke. The formulated PRO-MINOCA scale (ranging from 0 to 12 points; higher scores indicate greater risk) allocated 2 points each to reduced EF and elevated NT-proBNP and 1 point to the other parameters. The score demonstrated strong discriminative capacity [area under the curve: 0.781; 95% confidence interval (CI): 0.745–0.816; $p < 0.001$]. A threshold of ≥7 provided 74% sensitivity and 70% specificity. Individuals scoring ≥7 exhibited a profoundly reduced event-free survival rate (log-rank χ^2: 61.2; $p < 0.001$) and a more than twofold increase in MACE risk (hazard ratio: 2.67; 95% CI: 2.06-3.44).

CONCLUSION: The PRO-MINOCA score serves as a highly practical, purely clinical instrument that effectively identifies MINOCA patients who are at elevated long-term risk based on baseline diagnostic data. This tool can facilitate early, risk-adjusted management, particularly in environments lacking advanced cardiovascular imaging. Prospective and external validation studies are recommended.

Keywords: Myocardial infarction, non-obstructive coronary arteries, risk assessment, cardiac biomarkers, prognosis, chronic kidney disease

ÖZ

m² olması, yüksek C-reaktif protein, troponin ve N-terminal pro-beyin natriüretik peptid (NT-proBNP) düzeyleri, yeni gelişen atriyal fibrilasyon ve geçirilmiş periferik arter hastalığı, miyokard infarktüsü veya inme öyküsü uzun dönem MACE için bağımsız belirleyiciler olarak saptandı. Bu değişkenler temel alınarak oluşturulan PRO-MINOCA skoru 0 ile 12 puan arasında değişmekteydi. Azalmış ejeksiyon fraksiyonu ve yüksek NT-proBNP düzeyi ikişer puan, diğer değişkenler ise birer puan olarak skorlandı. PRO-MINOCA skoru MACE öngörüsünde iyi düzeyde ayırt edici performans gösterdi [eğri altında kalan alan: 0,781; %95 güven aralığı (GA): 0,745–0,816; p < 0,001]. ≥7 puan değeri %74 duyarlılık ve %70 özgüllük sağladı. PRO-MINOCA skoru ≥7 olan hastalarda olaysız sağkalım anlamlı olarak daha düşüktü (log-rank χ^2: 61,2; p < 0,001) ve MACE riski belirgin olarak artmıştı [hazard oranı: 2,67; %95 GA: 2,06–3,44].

Sonuç: PRO-MINOCA skoru, MINOCA hastalarında başvuru anında elde edilebilen klinik, laboratuvar ve ekokardiyografik verilerle uzun dönem kardiyovasküler riski öngörebilen pratik bir prognostik araçtır. İleri kardiyak görüntüleme yöntemlerine erişimin sınırlı olduğu klinik ortamlarda erken risk sınıflaması ve hasta yönetiminin planlanmasına katkı sağlayabilir. Skorun klinik kullanımını desteklemek için prospektif ve dış doğrulama çalışmalarına ihtiyaç vardır.

Anahtar Sözcükler: Miyokard infarktüsü, obstrüktif olmayan koroner arterler, risk değerlendirmesi, kardiyak biyobelirteçler, prognoz, kronik böbrek hastalığı

INTRODUCTION

Acute myocardial infarction (MI) remains a primary driver of global cardiovascular morbidity and mortality (1). While the traditional diagnosis of MI relies on identifying significant occlusions within the epicardial coronary vessels (2). MI with non-obstructive coronary arteries is characterized by the presence of MI signs despite the absence of obstructive lesions (defined as <50% stenosis) during coronary angiography. This unique clinical entity is estimated to occur in approximately 5% to 15% of all acute coronary syndrome presentations (3).

Although historically perceived as a relatively benign entity, contemporary research highlights that MINOCA is associated with a considerable long-term cardiovascular burden (3,4). Mortality rates at one year can approach 5%, while the five-year occurrence of major adverse cardiovascular events (MACEs) may hit 25% (5). Furthermore, extensive registry data, such as the SWEDEHEART study, indicate that the long-term prognostic profile of individuals with MINOCA closely mirrors that of patients suffering from obstructive MI (6).

The clinical complexity of MINOCA stems from its diverse pathophysiological mechanisms, which encompass microvascular dysfunction, epicardial vasospasm, myocarditis, takotsubo syndrome, and thromboembolic events (7). To identify the precise underlying etiology, advanced imaging modalities—most notably cardiac magnetic resonance (CMR), optical coherence tomography (OCT), and intravascular ultrasound (IVUS)—are of paramount importance. However, the routine application of these modalities is frequently hindered by logistical barriers, limited availability, and high costs (4,8,9). Consequently, a significant proportion of MINOCA patients are managed clinically without a confirmed etiological diagnosis.

Because of these diagnostic hurdles, there is a clear imperative for an accessible, MINOCA-specific risk stratification instrument. Standard prognostic calculators like the GRACE and TIMI scores fail to adequately capture the distinct clinical profile of the MINOCA population (9-11). Currently, no specialized scoring system that relies entirely on standard laboratory and clinical parameters at the time of presentation has achieved widespread clinical integration.

To address this gap, our study sought to formulate and validate the PRO-MINOCA score, a novel prognostic model tailored to forecast long-term MACE in patients with angiographically verified MINOCAs. Using only baseline laboratory and clinical metrics collected at initial presentation, this tool enables rapid risk assessment without the need for advanced imaging or definitive etiological categorization. Ultimately, PRO-MINOCA delivers a pragmatic, real-world strategy to guide clinical decision-making for this complex patient cohort.

MATERIALS AND METHODS

Study Design and Setting

This research was conducted as a single-centre retrospective study at the Cardiology Department of the Gazi University Faculty of Medicine. Our primary aim was to establish a prognostic scoring tool to predict long-term outcomes for patients with non-obstructive MI, relying exclusively on baseline clinical and laboratory data available at admission.

Ethical Approval

The Institutional Ethics Committee of Gazi University Faculty of Medicine provided formal approval for the research (protocol code: 2025-1013, meeting number: 9, date: 27.05.2025). Due to the retrospective nature of this clinical registry analysis and the use of de-identified data, the committee waived the requirement for individual patient consent. The study's conduct strictly adhered to the ethical principles of the Declaration of Helsinki.

Study Population

We retrospectively evaluated all patients who underwent coronary angiography with a preliminary diagnosis of acute MI between January 2013 and December 2018. Of approximately 5,500 acute MI patients who were catheterized during the five-year window, 658 met the strict criteria for MINOCA and constituted our final study cohort.

The diagnosis of MINOCA requires clinical, biochemical, and electrocardiographic evidence of an acute infarction [e.g., elevated cardiac troponin, dynamic electrocardiography (ECG) alterations, ischemic chest pain] coupled with angiographic evidence of <50% stenosis in all major epicardial arteries. While some individuals underwent advanced imaging (such as CMR, OCT, or IVUS), these findings were not used to inform etiological subclassification in the present analysis. Inclusion depended strictly on the established angiographic criteria for non-obstructive MI. The entire eligible cohort within the specified timeframe was enrolled without an a priori sample size calculation, aiming to reflect real-world prognostic dynamics.

Data Collection

Patient data were extracted from the institutional electronic medical records and historical interventional logs. We documented presenting symptoms, baseline demographics, cardiovascular risk factors, ECG characteristics, comorbidities, and initial medical therapies. Routine laboratory values recorded at diagnosis—including estimated glomerular filtration rate (eGFR), creatinine, complete blood count, lipid profile, C-reactive protein (CRP), haemoglobin, and cardiac biomarkers (troponin and natriuretic peptides)—were integrated into the evaluation as potential prognostic indicators.

Thresholds for specific biomarkers were defined based on current literature and internal receiver operating characteristic (ROC) analyses. We established binary cut-offs of >1000 ng/L for peak high-sensitivity cardiac troponin T and >1000 pg/mL for and N-terminal pro-brain natriuretic peptide (NT-proBNP), reflecting their prognostic relevance demonstrated in prior research (12-15). Cut-off values of <60 mL/min/1.73 m² for eGFR and >10 mg/L for CRP were similarly adopted based on clinical guidelines and previous evidence (16).

Baseline echocardiographic measurements were obtained from digital archives. Extended clinical follow-up was tracked via national death registries, hospital databases, and digital records, and concluded in June 2025. The primary endpoint was the occurrence of MACEs, defined as a composite of cardiovascular death, non-fatal MI, stroke, and hospitalization for heart failure. All laboratory parameters were measured using standardized institutional assays, and the cohort was analyzed without predefined experimental grouping.

Statistical Analysis

Continuous data are presented as medians with interquartile ranges or means ± standard deviations, depending on data distribution, and were compared using the Mann-Whitney U test or Student's t-test. Categorical variables are presented as frequencies and percentages and analyzed using Fisher's exact test or the chi-square test, as dictated by the data.

To identify predictors of MACE, we initially conducted univariable logistic regression analyses for all potential biochemical, clinical, and echocardiographic variables. Candidate predictors achieving a univariable p-value <0.10 were advanced to a forward stepwise multivariable logistic regression model. Because of their inherent prognostic weight, sex and age were maintained as forced covariates in the multivariable analysis, irrespective of their univariable significance. We confirmed the absence of significant multicollinearity by ensuring that variance inflation factors remained below 2 for all predictors.

Variables that maintained independent associations with MACE in the final multivariable construct were selected to form the PRO-MINOCA score. Point values were allocated based on the relative magnitude of the adjusted odds ratios and on clinical relevance. Variables that had stronger independent associations with MACE, particularly reduced left ventricular ejection fraction (LVEF) and elevated NT-proBNP, were assigned 2 points, whereas the remaining independent predictors were assigned 1 point each, to preserve the simplicity and bedside applicability of the score. The model's discriminative capacity was evaluated using ROC curves, reporting the area under the curve (AUC) alongside 95% confidence intervals. The optimal scoring threshold was identified via the Youden index. Survival dynamics were visualized through Kaplan-Meier curves and assessed with the log-rank test, while hazard ratios were derived from Cox proportional hazards models. A two-tailed p-value below the 0.05 threshold was used to determine statistical significance for all comparative analyses. Data processing and statistical computations were conducted using the SPSS software suite, version 26.0 (IBM Corp., Armonk, NY).

RESULTS

Screening of 5,500 patients who underwent coronary angiography for suspected acute MI was performed. From this initial pool, 658 individuals met the specific inclusion criteria for MINOCA and constituted the final study population. Through systematic linkage with national registries, long-term outcome data were successfully obtained for 100% of the participants. The median follow-up duration was 10.5 years with follow-up extending through June 2025. The study group had a mean age of 59.2 ± 11.6 years, with a female representation of 52.4%. During the clinical observation period, MACE was recorded in 158 patients (24%), while the remaining 500 patients (76%) did not experience any primary endpoints.

Detailed baseline clinical, laboratory, and echocardiographic characteristics, categorized by the occurrence of MACE, are presented in Table 1. Comparative analysis revealed that patients in the MACE (+) group were generally older and demonstrated a higher prevalence of cardiovascular risk factors, including diabetes mellitus, hypertension, hyperlipidemia, and active tobacco use. Furthermore, this group exhibited significantly lower LVEF, larger left atrial diameters, and markedly higher baseline concentrations of CRP, creatinine, troponin, and NT-proBNP. Clinical histories of prior MI, peripheral artery disease (PAD), stroke, and new-onset atrial fibrillation were also more frequent among those who experienced MACE (all $p < 0.05$) (Table 2).

Table 1. Baseline clinical, laboratory and echocardiographic characteristics of the study population according to MACE status.

Variable	Total group (n = 658)	MACE (+) (n = 158)	MACE (–) (n = 500)	p-value
Mean age (years)	59.2 ± 11.6	63.1 ± 10.2	57.8 ± 11.4	<0.001
Female sex, n (%)	345 (52.4%)	92 (58.2%)	253 (50.6%)	0.12
BMI (kg/m²)	27.3 ± 4.1	27.9 ± 4.5	27.0 ± 4.0	0.08
Hypertension, n (%)	308 (46.8%)	96 (60.8%)	212 (42.4%)	<0.001
Diabetes mellitus, n (%)	141 (21.5%)	47 (29.7%)	94 (18.8%)	0.002
Hyperlipidemia, n (%)	258 (39.2%)	73 (46.2%)	185 (37.0%)	0.03
Current smoking, n (%)	209 (31.7%)	65 (41.1%)	144 (28.8%)	0.005
LA diameter (mm)	38.5 ± 5.9	40.1 ± 5.7	38.0 ± 5.8	0.04
Enddiastolic LV diameter (mm)	49.8 ± 6.1	51.1 ± 6.4	49.4 ± 5.9	0.09
LV-EF (%)	53.4 ± 7.2	49.8 ± 8.1	54.9 ± 6.6	<0.001
Wall motion abnormality, n (%)	274 (41.6%)	92 (58.2%)	182 (36.4%)	<0.001
Admission troponin (ng/L)	512 (210–1165)	635 (310–1380)	489 (190–1100)	0.002
Peak troponin (ng/L)	1238 (605–2450)	1460 (740–2680)	1165 (580–2100)	<0.001
NT-proBNP (pg/mL)	1050 (410–2280)	1725 (860–3150)	870 (390–1980)	<0.001
Creatinine (mg/dL)	1.01 ± 0.21	1.21 ± 0.24	0.96 ± 0.18	<0.001
Sodium (mmol/L)	137.6 ± 3.5	137.2 ± 3.8	137.8 ± 3.3	0.38
Potassium (mmol/L)	4.2 ± 0.5	4.1 ± 0.6	4.2 ± 0.4	0.44
CRP (mg/L)	9.6 (4.3–22.1)	13.2 (6.1–30.5)	8.4 (3.8–18.5)	0.006
eGFR (mL/min/1.73 m²)	72.3 ± 18.7	64.2 ± 21.4	75.1 ± 17.2	<0.001
Hemoglobin (g/dL)	13.5 ± 1.7	12.8 ± 1.9	13.7 ± 1.6	0.001
Prior PAD, n (%)	60 (9.1%)	27 (17.1%)	33 (6.6%)	<0.001
Prior stroke or TIA, n (%)	44 (6.7%)	21 (13.3%)	23 (4.6%)	0.002
Onset AF, n (%)	51 (7.8%)	23 (14.6%)	28 (5.6%)	0.01
PRO-MINOCA score	5.6 ± 2.4	7.8 ± 1.8	4.9 ± 2.0	<0.001

Baseline demographic profile, comorbidities, laboratory findings, and echocardiographic measurements of the study cohort are displayed according to long-term MACE status. Data distribution determined the method of descriptive reporting: normally distributed variables are expressed as mean ± SD, whereas skewed variables are presented as median with interquartile range. Categorical parameters are reported as frequency and percentage. Group comparisons were performed using distribution-appropriate tests for continuous variables and contingency analysis for categorical data.
AF: Atrial fibrillation, BMI: Body mass index, CRP: C-reactive protein, eGFR: Estimated glomerular filtration rate, EF: Ejection fraction, Hb: Hemoglobin, HT: Hypertension, LA: Left atrium, LV: Left ventricle, MACE: Major adverse cardiovascular events, MINOCA: Myocardial infarction with non-obstructive coronary arteries, NT-proBNP: N-terminal pro-brain natriuretic peptide, PAD: Peripheral artery disease, TIA: transient ischemic attack, SD: Standard deviation.

In the initial univariable logistic regression, several factors were significantly linked to the development of MACE: age ≥65 years, hypertension, diabetes mellitus, diminished EF (EF <50%), renal impairment (eGFR <60 mL/min/1.73 m²), and elevated levels of troponin, NT-proBNP, and CRP. Additionally, new-onset atrial fibrillation and a history of PAD, MI, or stroke/transient ischemic attack (TIA) were identified as significant predictors. When these variables were entered into a multivariable model, each variable remained an independent predictor of adverse outcomes ($p < 0.05$).

Utilizing these regression coefficients, we constructed the PRO-MINOCA score, a novel clinical risk assessment tool. This scoring system ranges from 0 to 12 points. Elevated NT-proBNP and reduced LVEF, which showed the strongest adjusted associations with MACE and represent clinically established markers of myocardial dysfunction and adverse prognosis, were assigned 2 points each. The remaining independent predictors were each assigned 1 point to preserve the practical, bedside-oriented structure of the score. (Table 3). The average PRO-MINOCA score for the entire cohort was 5.6 ± 2.4. Notably, the MACE (+) group exhibited substantially higher mean scores compared to the event-free group (7.8 ± 1.8 vs. 4.9 ± 2.0, $p < 0.001$).

The discriminative efficiency of the PRO-MINOCA score was confirmed via ROC analysis, which yielded an AUC of 0.781(95% CI: 0.745–0.816, $p < 0.001$). Based on the Youden index (0.44), the optimal diagnostic cut-off was determined to be ≥7, providing a sensitivity of 74% and a specificity of 70% (Figure 1).

Survival dynamics, visualized through Kaplan-Meier analysis, indicated a significantly lower event-free survival rate for patients with a PRO-MINOCA score of ≥7 (log-rank test: χ^2: 61.2, $p < 0.001$). The mean survival duration for those with scores <7 was 3738 days, contrasting with 3187 days in the high-risk group (≥7) (Figure 2). Median survival values followed similar trajectories (3842 vs. 3330 days).

Table 2. Univariate and multivariate logistic regression analysis of variables associated with MACE.

Variables	Univariable OR	p-value	95% confidence interval		Multivariable OR	p-value	95% confidence interval	
			Lower	Upper			Lower	Upper
Age ≥65	1.62	0.023	1.07	2.44	1.50	0.041	1.02	2.22
BMI	1.01	0.893	0.68	1.48	—	—	—	—
Diabetes mellitus	1.92	0.008	1.18	3.09	2.06	0.005	1.25	3.39
Hypertension	1.99	0.006	1.23	3.26	2.24	0.004	1.29	3.90
LV-EF <50%	2.72	<0.001	1.74	4.23	3.29	0.001	1.91	5.68
GFR <60	1.84	0.019	1.10	3.08	1.99	0.022	1.10	3.55
Elevated CRP	1.73	0.011	1.13	2.70	1.82	0.015	1.14	2.89
Onset AF	2.05	0.007	1.21	3.49	2.30	0.008	1.24	4.25
Elevated NT-proBNP	3.46	0.001	2.01	6.13	4.11	<0.001	2.15	7.79
Elevated troponin-T	2.48	0.002	1.40	4.42	2.77	0.001	1.58	4.88
Prior PAD/stroke or TIA	1.80	0.033	1.05	3.13	1.93	0.027	1.07	3.47

This table presents the results of univariable and multivariable logistic regression analyses evaluating predictors of major adverse cardiovascular events. Results are expressed as odds ratios with 95% confidence intervals and p-values. Variables with $p < 0.10$ in univariable analysis were considered for inclusion in the multivariable model. OR: Odds ratio, CI: Confidence interval, AF: Atrial fibrillation, BMI: Body mass index, CRP: C-reactive protein, eGFR: Estimated glomerular filtration rate, LVEF: Left ventricular ejection fraction, NT-proBNP: N-terminal pro-B-type natriuretic peptide, PAD: Peripheral artery disease, TIA: Transient ischemic attack.

Table 3. PRO-MINOCA score components, clinical definitions, odds ratios, and assigned points.

PRO-MINOCA component	Definition/clinical criteria	OR	Score
P – Prior stroke/TIA	History of stroke or TIA	1.93	1
R – Reduced EF	LV-EF <50%	3.29	2
O – Older age	Age ≥65 years	1.50	1
M – Myocardial injury	Peak high-sensitivity troponin T >1000 ng/L	2.77	1
I – Impaired renal function	eGFR <60 mL/min/1.73 m²	1.99	1
N – Natriuretic peptide elevated	NT-proBNP >1000 pg/mL	4.11	2
O – Onset atrial fibrillation	New-onset AF on admission	2.30	1
C – CRP elevation	CRP >10 mg/L	1.82	1
A – Additional comorbidity	Presence of diabetes mellitus	2.06	1
	Presence of hypertension	2.24	1

The PRO-MINOCA score is a composite risk tool developed to predict major adverse cardiac events (MACE) in patients diagnosed with myocardial infarction with non-obstructive coronary arteries (MINOCA). Each component of the acronym represents an independent predictor identified through multivariate logistic regression analysis. Variables were assigned points based on both their clinical relevance and statistical strength (odds ratio). Components with stronger associations (OR ≥3 or high clinical weight) were given 2 points, while others were assigned 1 point. The total score reflects the cumulative risk burden for each patient. AF: Atrial fibrillation, CRP: C-reactive protein, LV: Left ventricle, EF: Ejection fraction, eGFR: Estimated glomerular filtration rate, NT-proBNP: N-terminal pro B-type natriuretic peptide, OR: Odds ratio, TIA: Transient ischemic attack.

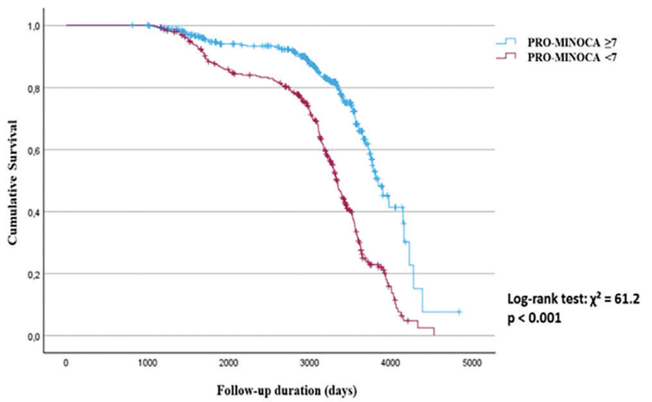

Figure 1. ROC curve of the PRO-MINOCA score for predicting major adverse cardiac events (MACE).

As illustrated by the ROC analysis, the PRO-MINOCA score exhibited significant discriminative ability, with a calculated AUC of 0.781 (95% CI: 0.745-0.816; p < 0.001). ROC: Receiver operating characteristic, MINOCA: Myocardial infarction with non-obstructive coronary artery, AUC: Area under the curve, CI: Confidence interval.

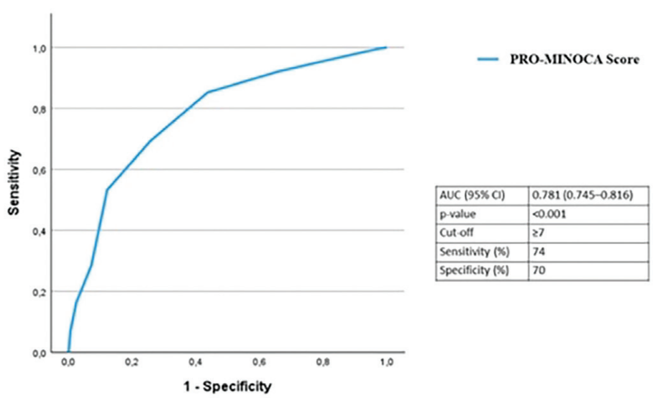

Figure 2. Kaplan-Meier survival curve for major adverse cardiac events (MACEs) stratified by the PRO-MINOCA score cut-off. Survival probabilities were estimated via Kaplan-Meier curves, revealing a substantial divergence in MACE-free survival between the two groups stratified by the PRO-MINOCA threshold (score <7 vs. ≥7). The median survival time was 3842 days in the lower-score group and 3330 days in the higher-score group. The difference was statistically significant according to the log-rank (Mantel-Cox) tes t(χ^2: 61.2, df: 1, p < 0.001). MINOCA: Myocardial infarction with non-obstructive coronary artery.

Finally, the univariable Cox proportional hazards model demonstrated that a PRO-MINOCA score of ≥7 was associated with a more than 2.6-fold increase in the risk of MACE (HR: 2.665; 95% CI: 2.064–3.442; p < 0.001). The model showed an excellent overall fit (likelihood ratio χ^2: 61.2, p < 0.001) in the cohort of 658 patients. These statistical findings confirm that the PRO-MINOCA score is a robust and straightforward clinical instrument for forecasting long-term cardiovascular risk in the MINOCA population.

DISCUSSION

This research aimed to develop and validate the PRO-MINOCA score, a straightforward and clinically reliable tool to predict long-term MACEs in patients with MINOCA. With a median observation period of 10.5 years (extending up to 12 years), our study provides one of the most extensive longitudinal datasets in this area. This prolonged follow-up reinforces the growing consensus that the clinical trajectory of MINOCA is far from benign.

The underlying pathophysiology of MINOCA is notoriously diverse, and the absence of clear obstructive coronary lesions often makes the diagnostic pathway more complex (17). Consequently, there is an urgent clinical requirement for early-stage risk assessment instruments. While CMR imaging is essential for identifying specific etiologies, its routine application in daily practice remains hindered by cost, limited access, and institutional differences in expertise (18-20). This underscores the necessity for non-invasive, accessible, and user-friendly scoring models.

Various established risk scores—including HEART, GRACE, ACEF, and TIMI—have been evaluated in MINOCA cohorts; however, most were originally developed and calibrated for different clinical contexts, such as surgical candidates or patients with general acute coronary syndromes (21,22). Research by Fedele et al. (11) indicated that while the ACEF and GRACE scores can predict one-year mortality in MINOCA, their discriminative performance is only moderate for this specific subset and they lack precision for long-term forecasting. Similarly, Gao et al. (23) explored the ACEF score's utility in MINOCA, but its limited focus on only three variables (age, creatinine, and EF) restricts its overall clinical sensitivity.

To address these gaps, our PRO-MINOCA model integrates variables specific to the MINOCA demographic that are derived entirely from clinical parameters and validated through rigorous multivariable analysis. The components—including age ≥65, prior stroke/TIA, EF <50%, eGFR <60, elevated CRP, new-onset atrial fibrillation, and elevated biomarkers (troponin and NT-proBNP)—have all been previously identified as prognostic markers in MINOCA literature and were strongly linked to MACE in our cohort (17,24-29).

The PRO-MINOCA score demonstrated strong discriminative ability, with an AUC of 0.781 (95% CI: 0.745–0.816). Utilizing the Youden index, we identified ≥7 as the optimal threshold, providing 74% sensitivity and 70% specificity for MACE prediction. This was further validated by Kaplan-Meier analysis, which showed a marked decline in survival for patients whose scores exceeded this threshold. A key advantage of PRO-MINOCA is its reliance on data immediately available at the time of diagnosis, allowing for seamless integration into clinical workflows. Consequently, in clinical settings where advanced modalities like CMR are unavailable, PRO-MINOCA offers a robust and pragmatic alternative for early risk stratification (30).

This study introduces one of the most comprehensive clinical scoring systems for MINOCA, supported by substantial long-term data. The PRO-MINOCA score serves as a vital guide for clinicians, helping to refine risk assessment and inform more personalized management strategies from the moment of diagnosis.

Study Limitations

Several limitations warrant mention. First, the retrospective, single-center framework may limit the generalizability of the findings and preclude causal inferences. While we minimized selection and information bias through standardized electronic records and national registry linkage, these inherent risks remain. Second, the lack of systematic CMR data prevented an etiological subclassification of MINOCA, meaning we could not assess whether the score's performance varied across different subtypes (e.g., myocarditis vs. plaque rupture). Third, although the statistical validation is robust, the score's direct impact on clinical outcomes and decision-making requires evaluation in prospective, randomized trials. Future multicenter investigations are needed to further validate the PRO-MINOCA score in diverse populations.

CONCLUSION

W e propose the PRO-MINOCA score as a novel, pragmatic instrument based purely on clinical parameters to predict long-term adverse outcomes in MINOCA patients. Our model demonstrated strong statistical performance and clinical relevance, supported by a large patient cohort and an extended follow-up. PRO-MINOCA represents an effective alternative for early risk stratification, particularly in resource-limited settings where advanced cardiac imaging is not readily accessible.

Ethics

Ethics Committee Approval: The Institutional Ethics Committee of Gazi University Faculty of Medicine provided formal approval for the research (protocol code: 2025–1013, meeting number: 9, date: 27.05.2025).

Informed Consent: Due to the retrospective nature of this clinical registry analysis and the use of de-identified data, the committee waived the requirement for individual patient consent.

Footnotes

Authorship Contributions

Concept: Y.B.Ş., S.Ü., Design: Y.B.Ş., S.Ü., Data Collection or Processing: Y.B.Ş., Analysis or Interpretation: Y.B.Ş., S.Ü., Literature Search: Y.B.Ş., Ö.S., Writing: Y.B.Ş.

Conflict of Interest: No conflict of interest was declared by the authors.

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