HELLENIC JOURNAL OF CARDIOLOGY VOL. 77, 2024: 13-26

ORIGINAL ARTICLE

The impact of renal function on the three-year outcomes in patients with myocardial infarction with nonobstructive coronary arteries

Yong Hoon Kim,[1,†] Ae-Young Her,[1,†] Seung-Woon Rha,[2] Cheol Ung Choi,[2] Byoung Geol Choi,[3] Soohyung Park,[2] Dong Oh Kang,[2] Jung Rae Cho,[4] Ji Young Park,[5] Sang-Ho Park,[6] Myung Ho Jeong[7]

ABSTRACT

BACKGROUND Due to limited data availability, we compared the 3-year outcomes of patients with acute myocardial infarction (AMI) and nonobstructive coronary arteries (MINOCA) and those with obstructive coronary arteries (MIOCA) according to renal function.

METHODS From a final cohort of 10,774 patients with AMI were classified into 2 groups: the chronic kidney disease (CKD) group (estimated glomerular filtration rate <60 mL/min/1.73 m^2, 2,854 patients; MINOCA, 123; MIOCA, 2,731) and the non-CKD group (7,920 patients; MINOCA, 256; MIOCA, 7,664). The primary outcome was the 3-year all-cause death rate, and the secondary outcomes included cardiac death (CD), non-CD death (NCD), recurrent myocardial infarction (MI), and any revascularization.

RESULTS In both the CKD and non-CKD groups, the adjusted in-hospital mortality, 3-year all-cause death, CD, and recurrent MI rates were similar between the MINOCA and MIOCA groups, but the adjusted 3-year any revascularization rates were significantly higher in the MIOCA group than in the MINOCA group. Characteristically, in the CKD group, the adjusted 3-year NCD rate (P = 0.032) was higher in the MINOCA group than in the MIOCA group, and sepsis was the main cause of NCD in this group. In both the MINOCA and MIOCA groups, all-cause death and NCD were significantly higher in the CKD group than in the non-CKD group.

CONCLUSIONS Regardless of renal function, the MINOCA and MIOCA groups had comparable mortality rates. However, patients with MINOCA and CKD had higher NCD rates. Close monitoring of renal function and enhanced strategies are required to reduce mortality in patients with MINOCA. (Hellenic Journal of Cardiology 2024;77:13-26)

[1]Division of Cardiology, Department of Internal Medicine, Kangwon National University College of Medicine, Kangwon National University School of Medicine, 24289, Chuncheon, Republic of Korea
[2]Cardiovascular Center, Korea University Guro Hospital, 08308, Seoul, Republic of Korea
[3]Cardiovascular Research Institute, Korea University College of Medicine, 02841, Seoul, Republic of Korea
[4]Cardiology Division, Department of Internal Medicine, Kangnam Sacred Heart Hospital, Hallym University College of Medicine, 0744, Seoul, Republic of Korea
[5]Division of Cardiology, Department of Internal Medicine, Cardiovascular Center, Nowon Eulji Medical Center, Eulji University, 01830, Seoul, Republic of Korea
[6]Cardiology Department, Soonchunhyang University Cheonan Hospital, 31151, Cheonan, Republic of Korea
[7]Department of Cardiology, Cardiovascular Center, Chonnam National University Hospital, 61469, Gwangju, Republic of Korea
†Yong Hoon Kim and Ae-Young Her contributed equally to this work.
Peer review under responsibility of Hellenic Society of Cardiology.

Manuscript received July 7, 2023; revised manuscript received July 31, 2023, accepted August 1, 2023. Available online August 8, 2023

ISSN 1109-9666 https://doi.org/10.1016/j.hjc.2023.08.001

1. INTRODUCTION

It was found that nearly 90% of patients with ST-segment elevation myocardial infarction (STEMI) had a blocked coronary artery.[1] In cases of patients without STEMI, only 26% displayed an occluded coronary artery.[2] Moreover, 1-13% of acute myocardial infarctions (AMIs) occur in the absence of obstructive coronary artery disease (CAD) (≥50% diameter stenosis in a major epicardial vessel), and this condition has been termed myocardial infarction with nonobstructive coronary arteries (MINOCA). MINOCA can be difficult to differentiate from stress-induced cardiomyopathy, myocarditis, and type 2 myocardial infarction (MI).[3] Additionally, the precise mechanisms underlying myocardial damage, the pathophysiology and outcomes of MINOCA, as well as optimal treatment strategies, have not been well established.[3] Although patients with MINOCA may not exhibit significant blockages or narrowing in their coronary arteries, they still face a substantial risk of adverse outcomes.[4] The rates of major adverse cardiovascular events in MINOCA are as high as those observed in myocardial infarction with obstructive coronary arteries (MIOCA).[5] A reduction of 10 ml/min/1.73 m^2 in the glomerular filtration ratio (GFR) is accompanied by a 5-6% additional rise in the rates of cardiovascular mortality[6], and chronic kidney disease (CKD) is associated with all-cause death and cardiovascular mortality in patients with AMI.[7] However, published data that focus on the comparative clinical outcomes between MINOCA and MIOCA in patients with or without CKD are limited.[8] In this study, we compared the 3-year clinical outcomes between these 2 groups (MINOCA and MIOCA) according to the presence or absence of CKD.

2. METHODS

2.1. STUDY POPULATION. The dataset for this cohort study was collected from the Korea Acute Myocardial Infarction Registry-National Institute of Health (KAMIR-NIH), which is a multicenter prospective registry.[9] A total of 13,104 patients who were at least 18 years old at the time of enrollment and diagnosed with AMI were registered in the KAMIR-NIH from November 2011 to December 2015. Fig. 1 illustrates the exclusion criteria. Of the 13,104 patients, a subset of individuals was excluded from the analysis, including those who did not undergo coronary angiography (CAG) (n = 209, 1.6%); patients who previously experienced MI, percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) (n = 1608, 12.3%); those with incomplete laboratory results (n = 361, 2.8%); and those who could not be followed up (n = 152, 1.2%). Ultimately, a total of 10,774 patients diagnosed with AMI were enrolled and stratified into 2 groups: the chronic kidney disease (CKD) group (estimated GFR [eGFR] <60 mL/min/1.73 m^2), consisting of 2854 patients (26.5%), and the non-CKD group (eGFR ≥60 mL/min/1.73 m^2), comprising 7920 patients (73.5%). The CKD and non-CKD groups were further classified into subgroups based on the presence or absence of MINOCA or MIOCA. Subgroups A (n = 123) and C (n = 256) included MINOCA cases, whereas subgroups B (n = 2731) and D (n = 7664) included MIOCA cases (Fig. 1). Approval for this nonrandomized study was obtained from the Ethics Committee of each participating center, including the Chonnam National University Hospital Institutional Review Board Ethics Committee (CNUH-2011-172), in compliance with the ethical guidelines of the 2004 Declaration of Helsinki. Before enrollment, written informed consent was obtained from all the 10,774 patients involved in the study. A comprehensive 3-year clinical follow-up was successfully completed for these patients, using various methods, such as in-person visits, telephone tracking, and a comprehensive examination of their medical records. Data were collected by independent clinical research coordinators using a web-based case report form integrated into an Internet-based Clinical Research and Trial management system (iCReaT). The iCReaT Study number C110016, established by the Centers for Disease Control and Prevention, Ministry of Health and Welfare, Republic of Korea, functions as a data management system. The processes for event adjudication have been documented and explained in a prior publication, and an independent committee responsible for event adjudication within the KAMIR-NIH carefully monitored and evaluated the occurrence of all events.[9]

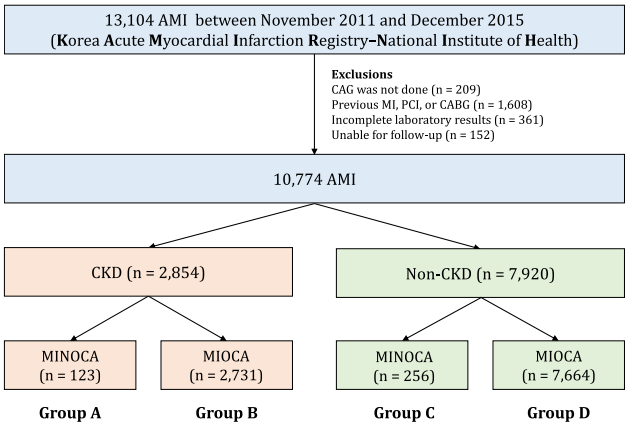
2.2. PERCUTANEOUS CORONARY INTERVENTION AND MEDICAL TREATMENT. Well-established guidelines were followed to determine the need for CAG and PCI.[10] Before PCI, patients were administered loading doses of aspirin (200-300 mg) combined with clopidogrel (300-600 mg), ticagrelor (180 mg), or prasugrel (60 mg). Subsequently, all patients were prescribed a daily dose of 100 mg aspirin and, as dual antiplatelet therapy, either 75 mg clopidogrel or 90 mg ticagrelor twice daily, or 5–10 mg prasugrel for a minimum duration of 1 year post-PCI. If MINOCA is suspected, a vasospasm test is recommended as a standard of care. Vasospasm can be identified by the occurrence of a spontaneous coronary spasm with ST-segment elevation (STE, ≥0.1 mV) on a coronary

angiogram and/or a documented coronary spasm during an ergonovine provocation test. A positive result for epicardial coronary spasm was determined when there was a focal or diffuse reduction in the epicardial coronary diameter by ≥ 90% compared to the relaxed state when followed by intracoronary nitroglycerin administration. This reduction should be accompanied by the reproduction of the patient's symptoms and ischemic electrocardiographic shifts.[11] The operators had the liberty to decide the access site, revascularization strategy, and stent option.

2.3. STUDY DEFINITIONS AND CLINICAL OUTCOMES. The guidelines presented in the fourth universal definition of MI[12] served as the basis for the diagnostic criteria for AMI. Atypical chest pain was defined as chest pain that does not have the typical features of angina.[12] In this study, we employed the Chronic Kidney Disease Epidemiology Collaboration equation[13] to calculate glomerular function, and CKD was defined as an eGFR lower than 60 ml/min/1.73 m^2.[14] The primary outcome of the present study was the rate of all-cause death during a 3-year follow-up period. The secondary outcomes were cardiac death (CD), non-CD (NCD), recurrent MI, and any revascularization during the same 3-year period. Unless there was an indisputable non-cardiac cause, all deaths were categorized as CD.[15] In this study, periprocedural MI was not considered as a clinical outcome. Clinically indicated revascularization procedures performed after the patient's discharge from index hospitalization were categorized as any revascularization events according to the definitions established by the Academic Research Consortium.[16] In our study, we defined MINOCA according to the fourth universal definition of MI,[12] stating that the combination of symptoms and a positive cardiac biomarker in the appropriate clinical scenario is diagnostic of AMI, while having nonobstructive CAD (<50% diameter stenosis in a major epicardial vessel) as observed in coronary angiography. We conducted our research by excluding patients who met the exclusion criteria shown in **Fig. 1**.

2.4. STATISTICAL ANALYSES. Unpaired t-tests were used for continuous variables. The findings are presented as either mean ± standard deviation or median (interquartile range). Categorical variables were analyzed using either the chi-square test or Fisher's exact test. The results are expressed as counts and percentages. Univariate analyses were conducted for all variables in both the MINOCA and MIOCA groups with a significance threshold of $P < 0.05$. Multicollinearity tests were performed to ensure the absence of collinearity among the significant variables[17] (Supplementary Table 1). Additionally, the results of the collinearity test for all-cause death between the CKD and non-CKD groups were included in Supplementary Table 2. Variance inflation factor values were computed to assess the extent of multicollinearity among the variables. When the variance inflation factor values were higher than 5, we considered it indicative of a significant level of multicollinearity.[18] Other indicators to define the presence of multicollinearity were a tolerance value falling below 0.1 or a condition index exceeding 10.[18] All variables in **Table 1** were included in the propensity score (PS)-matched analysis. The concordance statistic (C-statistic) for propensity score-matched analysis was 0.612. Matching patients in the MINOCA group to those in the MIOCA group was performed in a 1:1 fashion using the nearest available pair-matching method, and matching was conducted with a caliper width of 0.1. Supplementary Table 3 shows the baseline characteristics of the MINOCA and MIOCA groups before and after the PS-matched analysis. Kaplan-Meier curve analysis was used to estimate the clinical outcomes, and the log-rank test was used to compare the variances between groups. To account for potential confounding variables, a PS-adjusted analysis was conducted using a logistic regression model. To determine statistical significance, the threshold was set at $P < 0.05$. Statistical analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) software version 20 (IBM, Armonk, NY, USA).

FIGURE 1 Flowchart



3. RESULTS

3.1. BASELINE CHARACTERISTICS. Table 1, Supplementary Table 3, and Supplementary Table 4

TABLE 1 Baseline characteristics

Variables	CKD (n = 2,854)			Non-CKD (n = 7,920)		
	MINOCA (n = 123, group A)	MIOCA (n = 2,731, group B)	P value	MINOCA (n = 256, group C)	MIOCA (n = 7,664, group D)	P value
Male, n (%)	50 (40.7)	1,537 (56.3)	0.001	172 (67.2)	6,266 (81.8)	<0.001
Age, years	66.5 ± 12.5	67.4 ± 12.3	0.422	59.7 ± 12.6	61.8 ± 12.4	0.010
LVEF, %	60.4 ± 10.1	51.8 ± 11.2	<0.001	60.4 ± 9.1	52.3 ± 10.7	<0.001
BMI, kg/m^2	23.8 ± 3.6	23.6 ± 3.3	0.735	24.1 ± 3.4	24.2 ± 3.3	0.478
SBP, mmHg	132.9 ± 28.9	131.0 ± 27.8	0.466	134.5 ± 25.9	132.4 ± 27.1	0.199
DBP, mmHg	79.8 ± 16.4	79.1 ± 16.5	0.632	80.8 ± 14.4	80.5 ± 16.4	0.721
Cardiogenic shock, n (%)	3 (2.4)	132 (4.8)	0.280	5 (2.0)	298 (3.9)	0.134
CPR on admission, n (%)	8 (6.5)	172 (6.3)	0.850	6 (2.3)	374 (4.9)	0.072
Atypical chest pain, n (%)	31 (25.2)	388 (14.2)	0.002	40 (15.6)	919 (12.0)	0.080
Dyspnea, n (%)	25 (20.3)	665 (24.4)	0.334	47 (18.4)	1,688 (22.0)	0.191
EKG on admission						
ST-segment elevation, n (%)	21 (17.1)	1,356 (49.7)	<0.001	31 (12.1)	4,057 (52.9)	<0.001
ST-segment depression, n (%)	17 (13.8)	343 (12.6)	0.677	23 (9.0)	886 (11.6)	0.232
No ST-segment change, n (%)	58 (47.2)	540 (19.8)	<0.001	138 (53.9)	1,519 (19.8)	<0.001
T-wave inversion, n (%)	21 (17.1)	433 (15.9)	0.706	48 (18.8)	1,017 (13.3)	0.011
Atrial fibrillation, n (%)	11 (8.9)	155 (5.7)	0.163	14 (5.5)	373 (4.9)	0.660
Killip class 1I/III, n (%)	22 (17.9)	508 (18.6)	0.906	30 (11.7)	1,064 (13.9)	0.358
Hypertension, n (%)	60 (48.8)	1,491 (54.6)	0.229	123 (48.0)	3,573 (46.6)	0.653
Diabetes mellitus, n (%)	35 (28.5)	762 (27.9)	0.894	53 (20.7)	1,961 (25.6)	0.080
Dyslipidemia, n (%)	13 (10.6)	264 (9.7)	0.741	18 (7.0)	811 (10.6)	0.077
Previous HF, n (%)	2 (1.6)	36 (1.3)	0.771	8 (3.1)	66 (0.9)	0.003
Previous stroke, n (%)	8 (6.5)	166 (6.1)	0.847	9 (3.5)	387 (5.0)	0.309
Current smokers, n (%)	27 (22.0)	818 (30.0)	0.069	91 (35.5)	3,522 (46.0)	0.001
Peak CK-MB, ng/mL	9.4 (4.4-25.4)	51.7 (10.3-167.9)	<0.001	10.2 (3.4-31.0)	59.7 (11.2-189.6)	<0.001
Peak troponin-I, ng/mL	1.6 (0.5-6.4) (n = 119)	18.9 (3.3-50.0) (n = 2,400)	<0.001	2.0 (0.4-7.7) (n = 234)	20.4 (3.51-51.2) (n = 6,551)	<0.001
Peak troponin-T, ng/mL	0.6 (0.4-1.1) (n = 4)	1.3 (0.3-4.4) (n = 331)	0.002	0.6 (0.1-1.0) (n = 22)	1.3 (0.3-4.6) (n = 1,113)	0.245
Serum creatinine, mg/dL	0.94 ± 0.90	1.05 ± 1.00	0.207	0.96 ± 1.02	1.08 ± 1.12	0.060
Total cholesterol, mg/dL	170.7 ± 45.5	181.6 ± 43.9	0.009	171.3 ± 59.1	183.1 ± 45.3	0.002
Triglyceride, mg/dL	113.0 ± 80.6	123.7 ± 97.2	0.203	136.6 ± 143.9	141.0 ± 125.6	0.798
HDL cholesterol, mg/dL	47.4 ± 14.0	43.5 ± 12.5	0.014	47.5 ± 14.3	42.6 ± 11.7	<0.001
LDL cholesterol, mg/dL	105.5 ± 41.7	116.4 ± 42.0	0.006	100.1 ± 33.6	115.9 ± 39.4	<0.001
Hs-CRP, mg/dL	2.79 ± 9.03 (n = 58)	1.76 ± 7.48 (n = 1,677)	0.392	1.45 ± 3.41 (n = 113)	1.43 ± 6.09 (n = 4,747)	0.937
Discharge medications						
Aspirin, n (%)	94 (76.4)	2,717 (99.5)	<0.001	195 (76.2)	7,633 (99.6)	<0.001
Clopidogrel, n (%)	48 (39.0)	1,994 (73.0)	<0.001	91 (35.5)	5,315 (69.4)	<0.001
Ticagrelor, n (%)	3 (2.4)	476 (17.4)	<0.001	8 (3.1)	1,540 (20.1)	<0.001
Prasugrel, n (%)	2 (1.6)	261 (9.6)	0.001	6 (2.3)	809 (10.6)	<0.001
Beta-blockers, n (%)	53 (43.1)	2,292 (83.9)	<0.001	78 (30.5)	6,543 (85.4)	<0.001
ACEIs or ARBs, n (%)	67 (54.5)	2,166 (79.3)	<0.001	117 (45.7)	6,127 (79.9)	<0.001
Calcium channel blockers, n (%)	54 (43.9)	144 (5.3)	<0.001	144 (56.3)	429 (5.6)	<0.001
Statin, n (%)	96 (78.0)	2,513 (92.0)	<0.001	194 (75.8)	7,187 (93.8)	<0.001
Anticoagulant, n (%)	6 (4.9)	95 (3.5)	0.411	9 (3.5)	210 (2.7)	0.457
Vasospasm (+), n (%)	22 (17.9)			78 (30.5)		
Infarct-related artery						
Left main, n (%)		42 (1.5)			150 (2.0)	
LAD, n (%)		1,247 (45.7)			3,455 (45.1)	
LCx, n (%)		531 (19.4)			1,566 (20.4)	
RCA, n (%)		911 (33.4)			2,493 (32.5)	
Treated vessel						
Left main, n (%)		70 (2.6)			226 (2.9)	
LAD, n (%)		1,577 (57.7)			4,270 (55.7)	
LCx, n (%)		753 (27.6)			1,988 (25.9)	
RCA, n (%)		1,033 (37.8)			2,964 (38.7)	
Multivessel disease, n (%)		1,337 (49.0)			3,645 (47.6)	
Pre-PCI TIMI flow grade 0/1 (IRA), n (%)		1,511 (55.3)			4,293 (56.0)	

Continued on the next page

TABLE 1 Continued

Variables	CKD (n = 2,854)			Non-CKD (n = 7,920)		
	MINOCA (n = 123, group A)	MIOCA (n = 2,731, group B)	P value	MINOCA (n = 256, group C)	MIOCA (n = 7,664, group D)	P value
ACC/AHA type B2/C lesions, n (%)		2,256 (82.6)			6,378 (83.2)	
IVUS/OCT, n (%)		456 (16.7)			1,566 (20.4)	
FFR, n (%)		30 (1.1)			106 (1.4)	
PCI						
Plain old balloon angioplasty, n (%)		108 (4.0)			313 (4.1)	
Bare-metal stent, n (%)		86 (3.1)			195 (2.5)	
First-generation DES, n (%)		93 (3.4)			248 (3.2)	
Second-generation DES, n (%)		2,489 (91.1)			7,015 (91.5)	
Successful PCI, n (%)		2,507 (91.8)			7,126 (93.0)	
Stent diameter (mm)		3.08 ± 0.41			3.15 ± 0.44	
Stent length (mm)		29.2 ± 13.0			29.1 ± 13.1	
Number of stents		1.09 ± 0.54			1.08 ± 0.52	
CABG, n (%)		11 (0.4)			35 (0.5)	

Values are mean ± standard deviation or median (interquartile range) or numbers and percentages. The P values for continuous data were obtained from the unpaired t-test. The P values for categorical data were obtained from the chi-square or Fisher's exact test. Abbreviations: MINOCA, myocardial infarction with nonobstructive coronary arteries; MIOCA, myocardial infarction with obstructive coronary arteries; LVEF, left ventricular ejection fraction; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CPR, cardiopulmonary resuscitation; EKG, electrocardiogram; HF, heart failure; CK-MB, creatine kinase myocardial band; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Hs-CRP, high-sensitivity C-reactive protein; ACEIs, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction; ACC/AHA, American College of Cardiology/American Heart Association; IVUS/OCT, intravascular ultrasound/optical coherence tomography; FFR, fractional flow reserve; DES, drug-eluting stent; CABG, coronary artery bypass graft.

provide an overview of the baseline characteristics of the participants. In both the CKD and non-CKD groups, the MINOCA group exhibited significantly higher mean values of left ventricular ejection fraction (LVEF), a greater number of patients with no ST-segment changes, a higher average value of high-density lipoprotein (HDL)-cholesterol, and a higher number of patients taking calcium channel blockers at discharge than the MIOCA group. However, the number of male patients; number of patients showing STE; peak creatine kinase myocardial band (CK-MB) and peak troponin-I levels; mean values of total cholesterol and low-density lipoprotein cholesterol; and number of patients prescribed aspirin, clopidogrel, ticagrelor, prasugrel, beta-blockers, angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB), and statins at discharge were significantly higher in the MIOCA group than in the MINOCA group (**Table 1**). In both the MINOCA and MIOCA groups, the non-CKD group had a significantly higher number of male patients, a higher number of current smokers, and a higher average peak CK-MB value than the CKD group (Supplementary Table 4). The variables included in the multivariable analysis were selected as follows: male sex, age, LVEF, cardiogenic shock, cardiopulmonary resuscitation (CPR) upon admission, atypical chest pain, STE, ST-segment depression, no ST-segment change, and T-wave inversion on the electrocardiogram; hypertension and diabetes mellitus; previous heart failure, current smoker; levels of peak CK-MB and troponin-I; and total cholesterol and HDL cholesterol (Supplementary Table 1).

3.2. CLINICAL OUTCOMES. In-hospital mortality and the main results at the 3-year follow-up are presented in **Tables 2 and 3**. **Fig. 2**A-E provide the relevant information on these outcomes. In-hospital adjusted mortality did not show significant differences between the MINOCA and MIOCA groups in either the CKD or non-CKD groups (**Table 2**). In the CKD group, all-cause death occurred in 13.8% of patients at 3 years in the MINOCA group and in 10.9% of patients at 3 years in the MIOCA group (adjusted hazard ratio [aHR], 1.821; 95% CI, 0.943-3.517; P = 0.074, **Fig. 2**A). Moreover, the adjusted CD (**Fig. 2**B) and recurrent MI (**Fig. 2**D) rates were similar between the MINOCA and MIOCA groups. However, the NCD rate (**Fig. 2**C) was significantly higher in the MINOCA group than in the MIOCA group (aHR, 2.605; 95% CI, 1.085-6.265; P = 0.032). In the non-CKD group, the adjusted all-cause death, CD, NCD, and recurrent MI rates were similar between the MINOCA and MIOCA groups. In both the CKD and non-CKD groups, the adjusted any revascularization rates (**Fig. 2**E) were significantly higher in the MIOCA group than in the MINOCA group (P = 0.035 and P = 0.034, respectively) (**Table 2**). These results were verified using a PS-adjusted analysis. As shown in **Table 3**, the in-hospital adjusted mortality rates in the MINOCA group were similar between the CKD and non-CKD groups. In the MIOCA group, the in-hospital adjusted all-cause death rate was significantly

TABLE 2 Clinical outcomes between the MINOCA and MIOCA groups in patients with or without CKD

	In-hospital outcomes								
	CKD, n = 2,854								
				Unadjusted		Multivariable-adjusted		Propensity score-adjusted	
Outcomes	MINOCA (n = 123, group A)	MIOCA (n = 2,731, group B)	Log-rank	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
All-cause death	3 (2.5)	69 (2.5)	0.955	1.034 (0.326 3.286)	0.955	1.436 (0.405 5.094)	0.575	1.467 (0.421 5.161)	0.542
Cardiac death	1 (0.8)	51 (1.9)	0.398	0.436 (0.060 3.157)	0.411	4.627 (0.593 36.11)	0.144	4.391 (0.566 34.04)	0.157
Non-cardiac death	2 (1.7)	18 (0.6)	0.210	2.468 (0.573 10.64)	0.225	6.774 (0.966 47.10)	0.054	5.778 (0.819 40.76)	0.078
	Non-CKD, n = 7,920								
				Unadjusted		Multivariable-adjusted		Propensity score-adjusted	
Outcomes	MINOCA (n = 256, group C)	MIOCA (n = 7,664, group D)	Log-rank	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
All-cause death	3 (1.2)	124 (1.6)	0.576	0.722 (0.230 2.271)	0.578	1.301 (0.383 4.413)	0.673	1.372 (0.408 4.608)	0.609
Cardiac death	1 (0.4)	96 (1.3)	0.219	0.311 (0.043 2.232)	0.246	3.212 (0.424 24.36)	0.259	3.367 (0.451 28.21)	0.228
Non-cardiac death	2 (0.8)	28 (0.3)	0.290	2.129 (0.507 8.939)	0.302	3.143 (0.566 17.44)	0.190	2.362 (0.456 12.22)	0.305
	3-year outcomes								
	CKD, n = 2,854								
				Unadjusted		Multivariable-adjusted		Propensity score-adjusted	
Outcomes	MINOCA (n = 123, group A)	MIOCA (n = 2,731, group B)	Log-rank	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
All-cause death	17 (13.8)	297 (10.9)	0.329	1.274 (0.782 2.078)	0.331	1.821 (0.943 3.517)	0.074	1.355 (0.756 2.427)	0.308
Cardiac death	7 (5.7)	182 (6.7)	0.686	0.856 (0.402 1.821)	0.686	1.238 (0.451 3.398)	0.679	1.369 (0.551 3.401)	0.499
Non-cardiac death	10 (8.1)	115 (4.2)	0.041	1.938 (1.015 3.697)	0.045	2.605 (1.085 6.256)	0.032	2.705 (1.133 7.019)	0.021
Recurrent MI	4 (3.5)	87 (3.4)	0.965	1.022 (0.375 2.786)	0.965	2.766 (0.532 14.38)	0.226	1.534 (0.444 6.299)	0.498
Any revascularization	1 (0.8)	219 (8.6)	0.004	0.097 (0.014 0.694)	0.020	8.376 (1.163 60.33)	0.035	9.857 (1.396 98.52)	0.022
	Non-CKD, n = 7,920								
				Unadjusted		Multivariable-adjusted		Propensity score-adjusted	
Outcomes	MINOCA (n = 256, group C)	MIOCA (n = 7,664, group D)	Log-rank	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
All-cause death	17 (6.6)	595 (7.8)	0.495	0.846 (0.522 1.370)	0.496	1.397 (0.704 2.774)	0.339	1.231 (0.683 2.148)	0.465
Cardiac death	10 (3.9)	374 (4.9)	0.467	0.792 (0.423 1.485)	0.468	1.037 (0.458 2.346)	0.930	1.008 (0.497 2.041)	0.983
Non-cardiac death	7 (2.7)	221 (2.9)	0.862	0.931 (0.441 1.986)	0.862	2.670 (0.768 9.278)	0.122	1.764 (0.711 4.375)	0.220
Recurrent MI	7 (2.8)	201 (2.6)	0.928	1.035 (0.487 2.200)	0.928	1.516 (0.653 3.519)	0.332	1.352 (0.600 3.048)	0.467
Any revascularization	5 (2.0)	654 (8.9)	<0.001	0.220 (0.091 0.529)	0.001	2.626 (1.077 6.400)	0.034	2.543 (1.045 6.189)	0.040
		Total, n = 10,774							
				Unadjusted		Multivariable-adjusted		Propensity score-adjusted	
Outcomes	MINOCA (n = 380, group A + C)	MIOCA (n = 10,395, group B + D)	Log-rank	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
All-cause death	34 (8.8)	892 (8.6)	0.838	1.036 (0.736 1.460)	0.838	1.068 (0.667 1.710)	0.785	1.018 (0.542 1.488)	0.981
Cardiac death	17 (4.4)	556 (5.4)	0.454	0.832 (0.513 1.348)	0.455	1.117 (0.597 2.091)	0.730	1.110 (0.558 1.922)	0.796
Non-cardiac death	17 (4.4)	336 (3.2)	0.199	1.374 (0.844 2.237)	0.201	1.019 (0.496 2.093)	0.958	1.116 (0.618 2.108)	0.716
Recurrent MI	11 (3.0)	288 (2.9)	0.895	1.041 (0.570 1.901)	0.895	1.011 (0.478 2.137)	0.977	1.031 (0.524 2.280)	0.894
Any revascularization	6 (1.6)	873 (8.8)	<0.001	0.181 (0.081 0.403)	<0.001	3.640 (1.618 8.189)	0.002	3.720 (1.624 8.522)	0.002

Abbreviations: CKD, chronic kidney disease; MINOCA, myocardial infarction with nonobstructive coronary arteries; MIOCA, myocardial infarction with obstructive coronary arteries; HR, hazard ratio; CI, confidence interval; LVEF, left ventricular ejection fraction; CPR, cardiopulmonary resuscitation; CK-MB, creatine kinase myocardial band; HDL, high-density lipoprotein. Adjusted by male sex, age, LVEF, cardiogenic shock, CPR on admission, atypical chest pain, dyspnea, ST-segment elevation, ST-segment depression, No ST-segment change, T-wave inversion, hypertension; diabetes mellitus; previous heart failure; current smoker; peak CK-MB, peak troponin-I, total cholesterol, and HDL cholesterol (Supplementary Table 1).

TABLE 3 Clinical outcomes between the CKD and non-CKD groups in patients with MINOCA or MIOCA

	In-hospital outcomes						
	MINOCA, n = 379						
				Unadjusted		Multivariable-adjusted*	
Outcomes	CKD (n = 123, group A)	Non-CKD (n = 256, group C)	Log-rank	HR (95% CI)	P	HR (95% CI)	P
All-cause death	3 (2.5)	3 (1.2)	0.353	2.099 (0.424–10.40)	0.364	1.248 (0.197–7.924)	0.814
Cardiac death	1 (0.8)	1 (0.4)	0.592	2.001 (0.131–33.55)	0.600	-	-
Non-cardiac death	2 (1.7)	2 (0.8)	0.448	2.120 (0.296–14.90)	0.458	1.605 (0.175–14.73)	0.676
	MIOCA, n = 10,395						
				Unadjusted		Multivariable-adjusted*	
	CKD (n = 2,731, group B)	Non-CKD (n = 7,664, group D)	Log-rank	HR (95% CI)	P	HR (95% CI)	P
All-cause death	69 (2.5)	124 (1.6)	0.002	1.569 (1.169–2.106)	0.003	1.415 (1.038–1.928)	0.028
Cardiac death	51 (1.9)	96 (1.3)	0.019	1.497 (1.066–2.102)	0.020	1.361 (0.950–1.951)	0.093
Non-cardiac death	18 (0.6)	28 (0.3)	0.045	1.816 (1.005–3.283)	0.048	1.567 (0.859–2.895)	0.142
	3-year outcomes						
	MINOCA, n = 379						
				Unadjusted		Multivariable-adjusted*	
Outcomes	CKD (n = 123, group A)	Non-CKD (n = 256, group C)	Log-rank	HR (95% CI)	P	HR (95% CI)	P
All-cause death	17 (13.8)	17 (6.6)	0.021	2.160 (1.103–4.231)	0.025	2.261 (1.120–4.563)	0.023
Cardiac death	7 (5.7)	10 (3.9)	0.394	1.517 (0.577–3.986)	0.398	1.469 (0.545–3.961)	0.447
Non-cardiac death	10 (8.1)	7 (2.7)	0.016	3.075 (1.170–8.078)	0.023	3.421 (1.207–9.698)	0.021
Recurrent MI	4 (3.5)	7 (2.8)	0.748	1.223 (0.358–4.179)	0.748	1.016 (0.317–3.863)	0.875
Any revascularization	1 (0.8)	5 (2.0)	0.414	0.420 (0.049–3.593)	0.428	2.349 (0.263–20.97)	0.444
	MIOCA, n = 10,395						
				Unadjusted		Multivariable-adjusted*	
	CKD (n = 2,731, group B)	Non-CKD (n = 7,664, group D)	Log-rank	HR (95% CI)	P	HR (95% CI)	P
All-cause death	297 (10.9)	595 (7.8)	<0.001	1.425 (1.240–1.638)	<0.001	1.306 (1.133–1.505)	<0.001
Cardiac death	182 (6.7)	374 (4.9)	<0.001	1.387 (1.162–1.656)	<0.001	1.271 (1.061–1.523)	0.009
Non-cardiac death	115 (4.2)	221 (2.9)	0.001	1.490 (1.189–1.866)	0.001	1.363 (1.084–1.715)	0.008
Recurrent MI	87 (3.4)	201 (2.6)	0.088	1.244 (0.967–1.600)	0.089	1.183 (0.918–1.524)	0.195
Any revascularization	219 (8.6)	654 (8.9)	0.585	0.958 (0.822–1.117)	0.586	1.078 (0.923–1.260)	0.344
	Total, n = 10,774						
				Unadjusted		Multivariable-adjusted*	
Outcomes	CKD (n = 2,854, group A + B)	Non-CKD (n = 7,920, group C + D)	Log-rank	HR (95% CI)	P	HR (95% CI)	P
All-cause death	314 (11.0)	612 (7.7)	<0.001	1.449 (1.265–1.660)	<0.001	1.338 (1.165–1.537)	<0.001
Cardiac death	189 (6.6)	384 (4.8)	<0.001	1.388 (1.166–1.652)	<0.001	1.281 (1.072–1.530)	0.006
Non-cardiac death	125 (4.4)	228 (2.9)	<0.001	1.553 (1.248–1.931)	<0.001	1.431 (1.147–1.787)	0.002
Recurrent MI	91 (3.4)	208 (2.9)	0.082	1.244 (0.972–1.591)	0.083	1.184 (0.924–1.518)	0.182
Any revascularization	220 (8.2)	659 (8.7)	0.461	0.944 (0.811–1.100)	0.461	1.091 (0.934–1.275)	0.270

Abbreviations: MINOCA, myocardial infarction with nonobstructive coronary arteries; MIOCA, myocardial infarction with obstructive coronary arteries; HR, hazard ratio; CI, confidence interval; LVEF, left ventricular ejection fraction; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CPR, cardiopulmonary resuscitation; CK-MB, creatine kinase myocardial band. *Adjusted by male sex, age, LVEF, BMI, SBP, DBP, cardiogenic shock, CPR on admission, atypical chest pain, dyspnea, ST-segment elevation, T-wave inversion, Killip class II/III, hypertension, diabetes mellitus, previous heart failure, previous stroke, current smoker, peak CK-MB, and peak troponin-I. (Supplementary Table 2).

higher in the CKD group than in the non-CKD group (aHR, 1.415; 95% CI, 1.038-1.928; P = 0.028). During the 3-year follow-up period in both the MINOCA and MIOCA groups, all-cause death (aHR, 2.261; P = 0.023 and aHR, 1.306; P < 0.001, respectively) and NCD (aHR, 3.421; P = 0.021 and aHR, 1.633; P = 0.008, respectively) were significantly higher in the CKD group than in the non-CKD group. Additionally, in the MIOCA group, the CD rate was higher in the CKD group than in the non-CKD group (aHR, 1.271; P = 0.009). The independent predictors of all-cause mortality at 3-year follow-up in patients with MINOCA or MIOCA were identified using multivariate Cox proportional hazards models, as presented in **Table 4**. In both the MINOCA and MIOCA groups, several factors were found to be common significant independent predictors of all-cause mortality. These included advanced age (≥65 years old, P < 0.002 and

FIGURE 2 Kaplan-Meier analysis for all-cause death (A), CD (B), non-CD (C), recurrent MI (D), and any revascularization (E) during a 3-year follow-up period

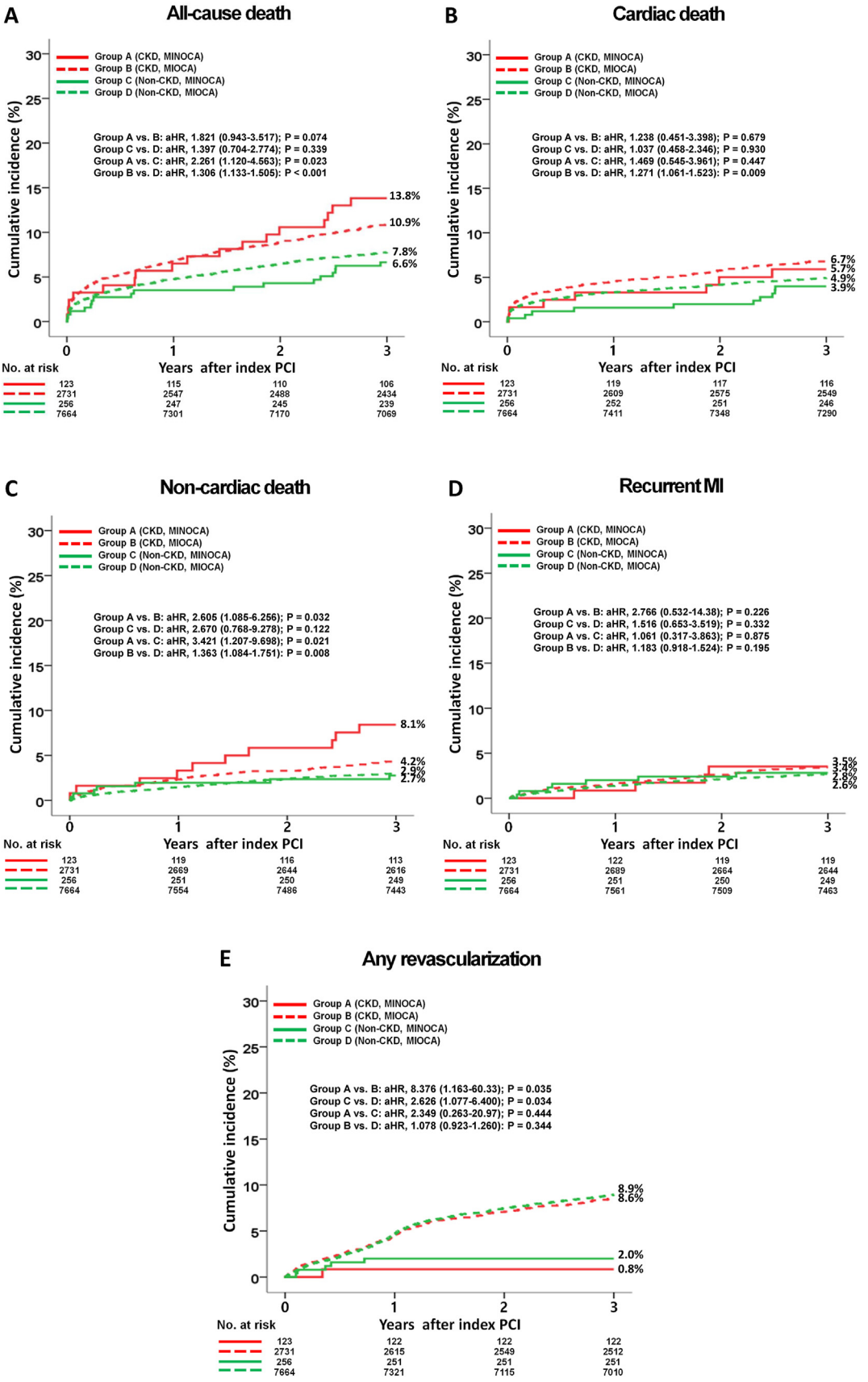


TABLE 4 Independent predictors for all-cause death

	MINOCA				MIOCA			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
Variables	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Male	2.091 (1.056–4.140)	0.034	1.402 (0.801–3.018)	0.313	1.910 (1.668–2.186)	<0.001	1.003 (0.808–1.247)	0.875
Age, ≥65 years	4.293 (1.943–9.483)	<0.001	2.351 (1.203–4.982)	0.002	5.689 (4.785–6.765)	<0.001	3.712 (2.984–4.131)	<0.001
LVEF, <50%	3.094 (1.508–6.347)	0.002	1.010 (0.241–2.941)	0.591	2.856 (2.496–3.269)	<0.001	1.972 (1.713–2.391)	<0.001
Cardiogenic shock	1.507 (0.206–11.02)	0.686	3.675 (0.312–41.02)	0.482	2.567 (2.046–3.222)	<0.001	1.351 (1.052–1.915)	0.024
CPR on admission	8.001 (3.310–19.34)	<0.001	7.707 (2.175–21.45)	0.002	8.506 (7.311–9.895)	<0.001	2.826 (2.178–3.665)	<0.001
Atypical chest pain	3.225 (1.679–6.585)	0.001	2.741 (1.217–4.872)	0.046	3.732 (3.246–4.292)	<0.001	1.687 (1.339–2.089)	<0.001
ST-segment elevation	1.394 (0.557–3.365)	0.461	1.452 (0.784–3.954)	0.202	1.263 (1.107–1.441)	0.001	1.208 (1.097–1.401)	0.019
Hypertension	1.553 (0.785–3.075)	0.206	1.093 (0.314–3.809)	0.889	1.829 (1.597–2.095)	<0.001	1.280 (1.031–1.588)	0.025
Diabetes mellitus	3.198 (1.630–6.272)	0.001	2.271 (1.041–4.352)	0.039	1.985 (1.736–2.269)	<0.001	1.325 (1.124–1.635)	0.001
CK-MB	1.001 (0.995–1.007)	0.759	1.003 (0.988–1.018)	0.719	1.000 (0.999–1.001)	0.527	1.000 (0.999–1.001)	0.994
Troponin-I	1.004 (0.996–1.012)	0.339	0.990 (0.944–1.039)	0.683	0.998 (0.997–1.002)	<0.001	1.001 (1.000–1.002)	0.014
Nonuse of Beta-blocker	1.903 (0.972–3.728)	0.061	1.189 (0.293–2.813)	0.709	3.622 (3.160–4.152)	<0.001	2.250 (1.793–2.521)	<0.001
Nonuse of ACEI/ARB	1.175 (0.599–2.304)	0.639	2.184 (2.001–5.102)	0.036	2.785 (2.435–3.186)	<0.001	1.215 (1.108–1.327)	<0.001
Nonuse of statin	2.806 (1.426–5.523)	0.003	4.012 (2.140–9.415)	<0.001	6.870 (5.928–7.962)	<0.001	3.084 (2.484–3.963)	<0.001
Nonuse of CCB	3.755 (1.700–8.294)	0.001	3.584 (0.987–6.804)	0.090	1.274 (0.984–1.649)	0.066	1.031 (0.732–1.473)	0.866
Hs-CRP	1.046 (1.019–1.075)	0.001	1.039 (1.003–1.043)	0.002	1.017 (1.013–1.021)	<0.001	1.007 (1.001–1.012)	0.012

Abbreviations: MINOCA, myocardial infarction with nonobstructive coronary arteries; MIOCA, myocardial infarction with obstructive coronary arteries; HR, hazard ratio; CI, confidence interval; LVEF, left ventricular ejection fraction; CPR, cardiopulmonary resuscitation; CK-MB, creatine kinase myocardial band; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blocker; Hs-CRP, high-sensitivity c-reactive protein.

$P < 0.001$, respectively), CPR on admission ($P = 0.002$ and $P < 0.001$, respectively), atypical chest pain ($P = 0.046$ and $P < 0.001$, respectively), diabetes mellitus ($P = 0.039$ and $P = 0.001$, respectively), the nonuse of ACEI/ARB ($P = 0.036$ and $P < 0.001$, respectively), the nonuse of statin ($P < 0.001$ and $P < 0.001$, respectively), and serum level of high-sensitivity C-reactive protein (hs-CRP, $P < 0.001$ and $P < 0.012$, respectively).

4. DISCUSSION

The main findings of this prospective observational study were as follows: (1) regardless of renal function, in-hospital adjusted all-cause death, CD, and NCD rates were similar between the MINOCA and MIOCA groups; (2) during a 3-year follow-up period, in both CKD and non-CKD groups, although the adjusted all-cause death, CD, and recurrent MI rates were not significantly different between the MINOCA and MIOCA groups, the adjusted any revascularization rate was significantly higher in the MIOCA than in the MINOCA group; (3) in the CKD group, the MINOCA group showed a significantly higher rate of NCD than the MIOCA group; (4) in the MIOCA group, in-hospital all-cause death rates and 3-year CD rates were significantly higher in the CKD group than in the non-CKD group; (5) in both the MINOCA and MIOCA groups, the CKD group showed significantly higher rates of all-cause death and NCD than the non-CKD group.

Despite MINOCA being characterized by clinical evidence of MI with normal or near-normal coronary arteries on angiography (stenosis severity <50%), the prognosis of MINOCA is not as favorable as reported by early cohort studies.[4,5] Furthermore, the available literature comparing the long-term prognosis of MINOCA and MIOCA according to renal function is notably limited.[8] As kidney function deteriorates, the composition of atherosclerotic plaques undergo changes, including increased lipid and necrotic cores, enhanced neovascularization, and decreased fibrous content.[19] These changes in the composition of atherosclerotic plaques can potentially enhance the vulnerability to intraplaque hemorrhage and rupture.[19] In the Zalewska-Adamiec et al. study,[8] the 3-year mortality rates were similar between patients with MINOCA and CKD and those with MIOCA and CKD. However, it should be noted that the number of MINOCA cases in that study (n = 178)[8] was limited, and there was a lack of comprehensive data on the baseline characteristics and 3-year clinical outcomes of the MIOCA patient cohort. Moreover, their study[8] was a single-center study. Therefore, we aimed to assess the long-term clinical outcomes of the MINOCA and MIOCA groups in both the CKD and non-CKD populations, specifically focusing on renal function outcomes in the MINOCA group. Our goal was to provide insights that could help improve the prognosis of patients with MINOCA in clinical practice.

Patients with MINOCA, in contrast to those with MIOCA, are typically younger, have a lower smoking prevalence, and display lower total cholesterol and low-density lipoprotein cholesterol levels.[20] In Supplementary Table 3, the MINOCA group demonstrates significantly younger mean age (P = 0.044), a lower number of current smokers (P < 0.001), and lower mean values of total cholesterol (P < 0.001) and low-density lipoprotein cholesterol levels (P < 0.001) than the MIOCA group. Non-STEMI (NSTEMI) was the predominant presentation in approximately two-thirds of patients with MINOCA.[21] In both the CKD and non-CKD groups, the number of patients showing STE was significantly lower in the MINOCA group than in the MIOCA group (**Table 1**). The fourth universal definition of MI[12] estimates that the prevalence of MI with MINOCA ranges from 6% to 8% in patients diagnosed with MI. However, the MINOCA incidence in our registry is relatively low (379/10774 = 3.5%). Considering that there were 209 patients (1.6%) who did not undergo coronary angiography and 361 patients (2.8%) who were excluded because of incomplete laboratory results in this study (**Fig. 1**), it is anticipated that some of the patients with MINOCA were included. Although, taking this into account, it is believed that the number of MINOCA patients in the study population is not very small; it is also a limitation of this study that the number of patients with MINOCA is relatively small.

Planer et al.[4] demonstrated that the 1-year unplanned revascularization rate was significantly higher in patients who underwent MIOCA than in those who underwent MINOCA (log-rank test, P = 0.002). In our study, regardless of renal function, the adjusted 3-year any revascularization rate was significantly higher in the MIOCA group than that in the MINOCA group (P = 0.035 and P = 0.034, respectively; **Table 2** and **Fig. 2**E). These findings can be attributed to the characteristics of the MIOCA group, in which PCI was performed, compared to the MINOCA group, which underwent medical treatment.[22] Additionally, in the Planer et al. study,[4] in the matched cohort, the overall 1-year mortality rate was significantly higher in patients with MINOCA (P = 0.04), driven by greater NCD. In our study, in the CKD group (**Table 2**), although all-cause death (**Fig. 2**A) and CD (**Fig. 2**B) were not significantly different between the MINOCA and MIOCA groups, the 3-year NCD rate (**Fig. 2**C) was significantly higher in the MINOCA group than in the MIOCA group after multivariate and PS-adjusted analyses (P = 0.032 and P = 0.021, respectively, **Table 2**). Recently, a study[23] revealed that NCD rates were significantly higher in the NSTEMI group than in the STEMI group in both the CKD and non-CKD groups (P = 0.004 and P = 0.006, respectively) among 18,875 patients with AMI. Considering the finding that NSTEMI was more common in the MINOCA group,[21] we can speculate that their results[23] are similar to ours. As shown in **Table 3**, in both the MINOCA and MIOCA groups, the adjusted 3-year NCD rates (P = 0.021 and P = 0.001, respectively) were significantly higher in the CKD group than in the non-CKD group. The causes of NCD are outlined in Supplementary Table 5. The presence of CKD substantially increases the susceptibility of patients to sepsis, leading to a higher likelihood of morbidity and mortality.[24] Furthermore, despite an incomplete understanding of the exact pathophysiological pathways responsible for both progressive CKD and its multisystem manifestations, it is well established that CKD is a systemic disorder characterized by hypertension, accelerated vascular disease, chronic cardiac dysfunction, compromised bone integrity, and an increased risk of certain malignancies.[25] In our study, in the MINOCA group, the rate of sepsis (3.3% vs. 0.4%; P = 0.040) was significantly higher in the CKD group. In the MIOCA group, the rates of multiple organ failure (1.5% vs. 0.8%; P = 0.004) and stroke (1.2% vs. 0.7%; P = 0.006) were significantly higher than those in the CKD group (Supplementary Table 5). MINOCA can cause sudden cardiac death (SCD).[26] It is also meaningful to investigate the rate of SCD among the MINOCA group in this study. However, in the KAMIR-NIH dataset, the variable for SCD was not mandatory. Therefore, despite our efforts to obtain information on SCD, it was not possible, and unfortunately, we could not provide this information.

The decline in GFR is accompanied by an escalation in vascular calcification, particularly in the intima and media of large vessels, which is closely correlated with all-cause death in CKD.[27] In our study, in both the MINOCA and MIOCA groups, the CKD group showed significantly higher rates of all-cause death and NCD than the non-CKD group. Additionally, in the MIOCA group, the in-hospital all-cause death and 3-year CD rates were significantly higher in the CKD group than in the non-CKD group (**Table 3**).

The prognostic implications of MINOCA remain unclear and have not been fully investigated. There is a pressing need to ascertain the risk factors associated with poorer long-term prognosis in patients with MINOCA, as this information can assist in identifying individuals who would benefit from closer surveillance and thorough medical assessment. Advanced age, diabetes mellitus, nonuse of ACEI/ARB and statin, and hs-CRP serum levels were significant independent predictors of all-cause death in the

MINOCA group (Table 4). In a previous study, increased CRP levels on hospital admission in patients with MINOCA were also found to be a marker of worse clinical outcomes during a median follow-up period of 7.1 years.[28] Those in the MINOCA group were generally younger than those in the MIOCA group. However, advanced age among patients with MINOCA is associated with increased risk of major adverse events (aHR/year 1.05; $P < 0.001$).[29] A meta-analysis of the patients with MINOCA revealed that women had more adverse clinical outcomes than men (10.1% vs. 9.1%; odds ratio 1.3) over a mean follow-up of 2 years.[30] Another study also emphasized that older age (aHR, 1.05) and diabetes mellitus (aHR, 1.44) were independent predictors for adverse cardiac events.[31] Lindahl et al.[32] found that the HRs for adverse events were low after patients were treated with ACEI/ARB and statin (0.82 and 0.77, respectively) in patients with MINOCA during a mean follow-up of 4.1 years. Furthermore, Stepien et al.[33] showed that statin prescription upon discharge was less common in patients with AMI who were diagnosed with active cancer. However, irrespective of the cancer diagnosis, the absence of statin use was independently correlated with an increased risk of long-term mortality (HR 2.13, 95% CI, 1.61–2.78; $P < 0.001$). In addition, from another perspective, CKD can also affect the prescription of pharmacological therapy since some medications can be contraindicated if severe CKD is present. Despite the beneficial effects of beta-blockers and ACEI/ARB in patients with MINOCA,[34] in our study, the number of patients in the CKD group who received these drugs as discharge medications was significantly lower than those in patients with MIOCA (Table 1)

Although the presence of CKD was a reason not to perform spasm-provocative testing due to concerns of complications,[35] we performed CAG with pharmacologic intracoronary provocation testing to investigate unexplained chest pain in patients whose coronary arteries appear normal or without obstruction, in accordance with international guidelines.[36]

In this study, there was no significant difference in all-cause mortality rates between the MINOCA and MIOCA groups regardless of renal function. This indicates that MINOCA is as clinically important as MIOCA.[4,8] Specifically, in the CKD group, the MINOCA group had a higher rate of NCD, with sepsis[24] being the leading cause. Additionally, even in the MIOCA group, the CKD group had a higher rate of NCD than the non-CKD group, with multiple organ failures and strokes being the primary causes (Supplementary Table 5).[25,27] Patients with NSTEMI accounted for a higher proportion of MINOCA cases than patients with STEMI. This study is unique in demonstrating that NSTEMI has a higher rate of NCD than STEMI and that the CKD group had a higher rate of NCD than the non-CKD group.[23] Although this study was conducted in a single country, it was a multicenter and prospective study involving 20 tertiary hospitals. Therefore, the results of this 3-year outcome study based on renal function in MINOCA highlight the importance of MINOCA among interventional cardiologists and the need for more intensive follow-ups and aggressive treatments to reduce NCD.

4.1. LIMITATIONS. This study has several limitations. First, although we employed PS-adjusted analysis to mitigate the potential impact of residual confounders, they cannot be completely eliminated. Second, in a quality registry, there may have been underreported and/or missing data, and the study population was small. Third, the 3-year follow-up period in this study may be considered relatively short for estimating long-term clinical outcomes. Fourth, patients with MINOCA represent a diverse cohort, and it would have been preferable to exclude patients with magnetic resonance imaging (MRI)-proven myocarditis.[3] The lack of patients who have undergone cardiac magnetic resonance (CMR) is a main limitation because more than 50% of patients suspected with MINOCA who receive CMR are often reclassified as having non-MINOCA conditions.[37] However, the KAMIR-NIH registry does not provide data on whether MRI was performed to identify clinically unrecognized myocarditis. Real-world practice is often characterized by low rates of MRI use due to the cost implications associated with performing MRI. However, we believe that our study population is appropriate because it comprises patients commonly encountered by clinicians during routine real-world practice, for whom necessary secondary prevention treatments are provided. Additionally, we are aware that MINOCA is a complex and heterogeneous condition with various underlying causes, including microvascular dysfunction, plaque disruption without significant blockage, and other non-coronary factors that can lead to MI, which need to be excluded.[3,12] Nevertheless, in the context of the Korean healthcare (Medical Assurance) system, it should be noted that intravascular ultrasound, optical coherent tomography, and fractional flow reserve tests for patients with nonobstructive CAD are not

covered by insurance and patients are responsible for the costs. Considering the high cost of these examinations, it becomes challenging to include these tests along with coronary angiography, leading to a limitation in our study where we could not completely exclude alternative causes in patients with MINOCA due to the unavailability of these tests.

5. CONCLUSION

In this prospective observational study, during a 3-year follow-up period, patients with MINOCA exhibited a mortality rate similar to that of patients with MIOCA, suggesting poor prognosis. Moreover, there was a high prevalence of NCD in patients with MINOCA and CKD, indicating the importance of closely monitoring renal function, implementing individualized interventions to mitigate non-CD, and enhance survival rates in this patient population. However, our findings require further validation in additional studies.

CONFLICTS OF INTEREST

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

DISCLOSURES

None

FUNDING

This research was supported by a fund (2016-ER6304-02) by Research of Korea Centers for Disease Control and Prevention.

DATA AVAILABILITY STATEMENT

Data is contained within the article or supplementary material.

AUTHOR CONTRIBUTIONS

Conceptualization, Yong Hoon Kim, Ae-Young Her, Seung-Woon Rha, Cheol Ung Choi, Byoung Geol Choi, Soohyung Park, Dong Oh Kang, Jung Rae Cho, Ji Young Park, Sang-Ho Park and Myung Ho Jeong; **Data curation,** Yong Hoon Kim, Ae-Young Her, Byoung Geol Choi, Soohyung Park and Dong Oh Kang; Formal analysis, Yong Hoon Kim, Ae-Young Her, Byoung Geol Choi, Soohyung Park and Dong Oh Kang; **Funding acquisition,** Myung Ho Jeong; **Investigation,** Yong Hoon Kim, Ae-Young Her, Seung-Woon Rha, Cheol Ung Choi, Byoung Geol Choi, Soohyung Park, Dong Oh Kang, Jung Rae Cho, Ji Young Park, Sang-Ho Park and Myung Ho Jeong; **Methodology,** Yong Hoon Kim, Ae-Young Her, Seung-Woon Rha, Byoung Geol Choi, Soohyung Park, Dong Oh Kang, Jung Rae Cho, Ji Young Park, Sang-Ho Park and Myung Ho Jeong; **Project administration,** Yong Hoon Kim, Ae-Young Her, Seung-Woon Rha, Cheol Ung Choi, Jung Rae Cho, Ji Young Park, Sang-Ho Park and Myung Ho Jeong; **Resources,** Seung-Woon Rha, Cheol Ung Choi, Soohyung Park, Dong Oh Kang and Myung Ho Jeong; **Software,** Yong Hoon Kim, Ae-Young Her, Byoung Geol Choi, Soohyung Park and Dong Oh Kang; **Supervision,** Yong Hoon Kim, Seung-Woon Rha and Myung Ho Jeong; **Validation,** Yong Hoon Kim, Ae-Young Her, Seung-Woon Rha, Cheol Ung Choi, Byoung Geol Choi, Soohyung Park, Dong Oh Kang, Jung Rae Cho, Ji Young Park, Sang-Ho Park and Myung Ho Jeong; **Visualization,** Yong Hoon Kim, Ae-Young Her, Seung-Woon Rha, Cheol Ung Choi, Byoung Geol Choi, Soohyung Park, Dong Oh Kang, Jung Rae Cho, Ji Young Park, Sang-Ho Park and Myung Ho Jeong; **Writing – original draft,** Yong Hoon Kim and Ae-Young Her; **Writing – review & editing,** Yong Hoon Kim, Ae-Young Her, Seung-Woon Rha, Cheol Ung Choi, Byoung Geol Choi, Soohyung Park, Dong Oh Kang, Jung Rae Cho, Ji Young Park, Sang-Ho Park and Myung Ho Jeong.

INSTITUTIONAL REVIEW BOARD STATEMENT

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Chonnam National University Hospital Institutional Review Board (IRB) Ethics Committee (protocol code CNUH-2011-172 and March 1, 2011)

ACKNOWLEDGEMENTS Investigators of KAMIR-NIH (Korea Acute Myocardial Infarction Registry-National Institutes of Health) Myung Ho Jeong, Chonnam National University Hospital, Gwangju, Korea, Young Jo Kim, Yeungnam University Medical Center, Daegu, Korea, Chong Jin Kim, Kyunghee University Hospital at Gangdong, Seoul, Korea, Myeong Chan Cho, Chungbuk National University Hospital, Cheongju, Korea, Hyo-Soo Kim, Seoul National University Hospital, Seoul, Korea, Hyeon-Cheol Gwon, Samsung Medical Center, Seoul, Korea, Ki Bae Seung, Seoul St. Mary's Hospital, Seoul, Korea, Dong Joo Oh, Korea University Guro Hospital, Seoul, Korea, Shung Chull Chae, Kyungpook National University Hospital, Daegu, Korea, Kwang Soo Cha, Pusan National University Hospital, Busan, Korea, Junghan Yoon, Wonju Severance Christian Hospital, Wonju, Korea, Jei-Keon Chae, Chonbuk National University

Hospital, Jeonju, Korea, Seung Jae Joo, Jeju National University Hospital, Jeju, Korea, Dong-Ju Choi, Seoul National University Bundang Hospital, Bundang, Korea, Seung-Ho Hur, Keimyung University Dongsan Medical Center, Daegu, Korea, In Whan Seong, Chungnam National University Hospital, Daejeon, Korea, Doo Il Kim, Inje University Haeundae Paik Hospital, Busan, Korea, Seok Kyu Oh, Wonkwang University Hospital, Iksan, Korea, Tae Hoon Ahn, Gachon University Gil Medical Center, Incheon, Korea, Jin-Yong Hwang, Gyeongsang National University Hospital, Jinju, Korea.

CORRESPONDING AUTHORS. Cardiovascular Center; Korea University Guro Hospital, 148, Gurodong-ro, Guro-gu, 08308, Seoul, Republic of Korea. Tel: +82 (2) 2626-3020, Fax: +82 (2) 864-3062. E-mail: swrha617@yahoo.co.kr OR Division of Cardiology, Department of Internal Medicine, Kangwon National University College of Medicine, Kangwon National University School of Medicine, 156 Baengnyeong Road, Chuncheon City, Gangwon Province, 24289, Republic of Korea. Tel: +82 (33) 258-9455, Fax: +82 (33) 258-2455. E-mail: yhkim02@kangwon.ac.kr.

REFERENCES

1. DeWood MA, Spores J, Notske R, et al. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. *N Engl J Med*. 1980;303(16):897-902.

2. DeWood MA, Stifter WF, Simpson CS, et al. Coronary arteriographic findings soon after non-Q-wave myocardial infarction. *N Engl J Med*. 1986;315(7):417-423.

3. Agewall S, Beltrame JF, Reynolds HR, et al. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. *Eur Heart J*. 2017;38(3):143-153.

4. Planer D, Mehran R, Ohman EM, et al. Prognosis of patients with non-ST-segment-elevation myocardial infarction and nonobstructive coronary artery disease: propensity-matched analysis from the Acute Catheterization and Urgent Intervention Triage Strategy trial. *Circ Cardiovasc Interv*. 2014;7(3):285-293.

5. Montone RA, Niccoli G, Fracassi F, et al. Patients with acute myocardial infarction and non-obstructive coronary arteries: safety and prognostic relevance of invasive coronary provocative tests. *Eur Heart J*. 2018;39(2):91-98.

6. Manjunath G, Tighiouart H, Ibrahim H, et al. Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. *J Am Coll Cardiol*. 2003;41(1):47-55.

7. Kim YH, Her AY, Jeong MH, et al. Comparison of two-year clinical outcomes according to glycemic status and renal function in patients with acute myocardial infarction following implantation of new-generation drug-eluting stents. *J Diabetes Complications*. 2021;35(11):108019.

8. Zalewska-Adamiec M, Malyszko J, Grodzka E, Kuzma L, Dobrzycki S, Bachorzewska-Gajewska H. The outcome of patients with myocardial infarction with non-obstructive coronary arteries (MINOCA) and impaired kidney function: a 3-year observational study. *Int Urol Nephrol*. 2021;53(12):2557-2566.

9. Kim JH, Chae SC, Oh DJ, et al. Multicenter cohort study of acute myocardial infarction in Korea - interim analysis of the Korea acute myocardial infarction registry-national institutes of health registry. *Circ J*. 2016;80(6):1427-1436.

10. Grech ED. ABC of interventional cardiology: percutaneous coronary intervention. II: the procedure. *BMJ*. 2003;326(7399):1137-1140.

11. Shin DI, Baek SH, Her SH, et al. The 24-month prognosis of patients with positive or intermediate results in the intracoronary ergonovine provocation test. *JACC Cardiovasc Interv*. 2015;8(7):914-923.

12. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol*. 2018;72(18):2231-2264.

13. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612.

14. Chu CD, McCulloch CE, Hsu RK, et al. Utility of the kidney failure risk equation and estimated GFR for estimating time to kidney failure in advanced CKD. *Am J Kidney Dis*. 2023;Jun 8;S0272-S6386(23):654-656. https://doi.org/10.1053/j.ajkd.2023.03.014

15. Lee JM, Rhee TM, Hahn JY, et al. Multivessel percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction with cardiogenic shock. *J Am Coll Cardiol*. 2018;71(8):844-856.

16. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115(17):2344-2351.

17. Vatcheva KP, Lee M, McCormick JB, Rahbar MH. Multicollinearity in regression analyses conducted in epidemiologic studies. *Epidemiology*. 2016;6(2):227.

18. Marcoulides KM, Raykov T. Evaluation of variance inflation factors in regression models using latent variable modeling methods. *Educ Psychol Meas*. 2019;79(5):874-882.

19. Kono K, Fujii H, Nakai K, et al. Composition and plaque patterns of coronary culprit lesions and clinical characteristics of patients with chronic kidney disease. *Kidney Int*. 2012;82(3):344-351.

20. Merlo AC, Troccolo A, Piredda E, Porto I, Gil Ad V. Myocardial infarction with non-obstructive coronary arteries: risk factors and associated comorbidities. *Front Cardiovasc Med*. 2022;9:895053.

21. Pasupathy S, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. *Circulation*. 2015;131(10):861-870.

22. Pijls NH, van Schaardenburgh P, Manoharan G, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. *J Am Coll Cardiol*. 2007;49(21):2105-2111.

23. Kim YH, Her AY, Jeong MH, et al. Two-year outcomes between ST-elevation and non-ST-elevation myocardial infarction in patients with chronic kidney disease undergoing newer-generation drug-eluting stent implantation. *Catheter Cardiovasc Interv*. 2022;99(4):1022-1037.

24. James MT, Laupland KB, Tonelli M, Manns BJ, Culleton BF, Hemmelgarn BR. Risk of bloodstream infection in patients with chronic kidney disease not treated with dialysis. *Arch Intern Med*. 2008;168(21):2333-2339.

25. Zoccali C, Vanholder R, Massy ZA, et al. The systemic nature of CKD. *Nat Rev Nephrol*. 2017;13(6):344-358.

26. Ciliberti G, Westaby J, Papadakis M, et al. Coronary artery dissection and myocardial infarction with nonobstructed coronary arteries: insights from a UK nationwide autopsy-based registry-brief report. *Arterioscler Thromb Vasc Biol*. 2023;43(5):787-792.

27. London GM, Guérin AP, Marchais SJ, Métivier F, Pannier B, Adda H. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant*. 2003;18(9):1731-1740.

28. Ciliberti G, Coiro S, Tritto I, et al. Predictors of poor clinical outcomes in patients with acute myocardial infarction and non-obstructed coronary arteries (MINOCA). *Int J Cardiol*. 2018;267:41-45.

29. Tsaban G, Peles I, Barrett O, et al. Non-obstructive coronary atherosclerosis is associated with adverse prognosis among patients diagnosed with myocardial infarction without obstructive coronary arteries. *Atherosclerosis*. 2023;366:8-13.

30. Chaudhary R, Bashline M, Novelli EM, et al. Sex-related differences in clinical outcomes among patients with myocardial infarction with nonobstructive coronary artery disease: a systematic review and meta-analysis. *Int J Cardiol*. 2022;369:1-4.

31. Nordenskjöld AM, Baron T, Eggers KM, Jernberg T, Lindahl B. Predictors of adverse outcome in patients with myocardial infarction with non-obstructive coronary artery (MINOCA) disease. *Int J Cardiol*. 2018;261:18-23.

32. Lindahl B, Baron T, Erlinge D, et al. Medical therapy for secondary prevention and long-term outcome in patients with myocardial infarction with nonobstructive coronary artery disease. *Circulation*. 2017;135(16):1481-1489.

33. Stepien K, Nowak K, Kachnic N, et al. Statin use in cancer patients with acute myocardial infarction and its impact on long-term mortality. *Pharmaceuticals*. 2022;15(8):919.

34. Ciliberti G, Verdoia M, Merlo M, et al. Pharmacological therapy for the prevention of cardiovascular events in patients with myocardial infarction with non-obstructed coronary arteries (MINOCA): insights from a multicentre national registry. *Int J Cardiol*. 2021;327:9-14.

35. Ciliberti G, Seshasai SRK, Ambrosio G, Kaski JC. Safety of intracoronary provocative testing for the diagnosis of coronary artery spasm. *Int J Cardiol*. 2017;244:77-83.

36. Task Force Members, Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013;34(38):2949-3003.

37. Pathik B, Raman B, Mohd Amin NH, et al. Troponin-positive chest pain with unobstructed coronary arteries: incremental diagnostic value of cardiovascular magnetic resonance imaging. *Eur Heart J Cardiovasc Imaging*. 2016;17(10):1146-1152.

KEYWORDS Myocardial infarction, MINOCA, Chronic kidney disease, Prognosis

APPENDIX A. SUPPLEMENTARY DATA Supplementary data to this article can be found online at https://doi.org/10.1016/j.hjc.2023.08.001.