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ORIGINAL ARTICLE

Characteristics and In-Hospital Outcomes of Patients With Myocardial Infarction With Non-Obstructive Coronary Arteries
— Insights From the Real-World JAMIR Database —

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Background: Few studies have investigated the clinical characteristics and in-hospital outcomes of patients with myocardial infarction with non-obstructive coronary arteries (MINOCA) using real-world databases in the coronary intervention era.

Methods and Results: We conducted a retrospective analysis of 22,236 patients (mean [±SD] age 68±13 years, 23.4% female) enrolled in the Japan Acute Myocardial Infarction Registry (JAMIR) between 2011 and 2016. Based on urgent coronary angiography findings, 286 (1.3%) patients were diagnosed as MINOCA, and the remaining 21,950 (98.7%) as MI with obstructive coronary artery disease (MI-CAD). MINOCA patients were characterized by younger age, fewer coronary risk factors, lower rate of ST-elevation myocardial infarction, lower Killip classification, and lower peak creatinine phosphokinase levels than MI-CAD patients. In-hospital all-cause mortality did not differ between the MINOCA and MI-CAD groups (5.2% vs. 5.7%, respectively; P=0.82). Comparing cause-specific mortality, non-cardiac mortality was higher in the MINOCA than MI-CAD group (4.2% vs. 1.6%; P<0.01). Importantly, non-cardiac death was more prevalent among elderly (≥65 years) than younger (<65 years) patients in the MI-CAD group, whereas this trend was not observed in the MINOCA group.

Conclusions: Analysis of the real-world JAMIR database revealed a relatively high prevalence of non-cardiac death among MINOCA patients, underscoring the need for comprehensive management to improve disease prognosis, particularly in younger patients.

Key Words: In-hospital mortality; Myocardial infarction with non-obstructive coronary arteries (MINOCA); Non-cardiac mortality; Pathophysiology

Acute myocardial infarction (AMI) remains one of cardiology's most severe conditions, primarily driven by plaque disruption and subsequent thrombus formation, leading to acute coronary obstruction and myocardial ischemia. This pathophysiology predominantly manifests as AMI, known as "myocardial infarction with obstructive coronary artery disease" (MI-CAD).

In recent years, another entity, termed "myocardial infarction with non-obstructive coronary arteries" (MINOCA), has gained recognition. Diagnostic criteria for MINOCA, outlined in guidelines from the US, Europe, and Japan, include AMI defined by the fourth universal definition of

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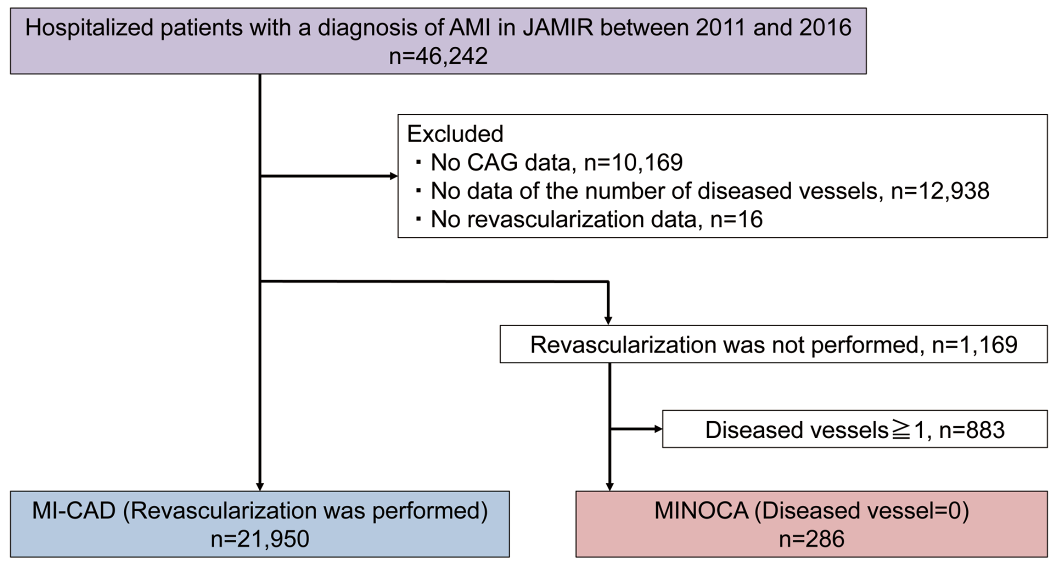

Figure 1. Flowchart showing selection of the study population. Patients with acute myocardial infarction (AMI) were divided into 2 groups, namely the myocardial infarction with obstructive coronary artery disease (MI-CAD) and myocardial infarction with non-obstructive coronary arteries (MINOCA) groups according to the presence or absence of revascularization and diseased vessels. CAG, coronary angiography; JAMIR, Japan Acute Myocardial Infarction Registry.

myocardial infarction (MI) criteria, non-obstructive coronary arteries on angiography (no stenotic legion angiographically ≥50% in major coronary arteries), and the absence of specific alternative diagnoses (e.g., sepsis, pulmonary embolism, myocarditis, and Takotsubo syndrome).[1–3]

Over past decades, AMI patients have been increasingly aging and presenting with more coronary risk factors. The greater use of reperfusion therapies, such as primary percutaneous coronary intervention and antithrombotic therapy, has improved in-hospital outcomes.[4,5] These findings underscore the importance of the underlying atherothrombotic process in AMI patients, leading to the establishment of MI-CAD management practices summarized in guidelines for the treatment of AMI.[6] However, MINOCA patients have remained largely uninformed due to a lack of recognition and relevant objective evidence.

MINOCA is a heterogeneous syndrome with various pathophysiological mechanisms, making it difficult to diagnose and manage.[7] Indeed, the reported prevalence of MINOCA ranges from 1% to 14%, with varied prognoses, across studies.[8–12]

The aim of this study was to investigate the clinical characteristics and in-hospital outcomes of MINOCA in Japan using the real-world Japan Acute Myocardial Infarction Registry (JAMIR) database. Elucidating the clinical profiles of MINOCA patients in the era of coronary intervention will help establish guidance for the management of acute ischemic heart disease, which has a different disease concept from MI-CAD, and improve the prognosis of AMI patients overall.

Methods

JAMIR is a nationwide multicenter real-world large-scale integrated registry consisting of 10 representative regional AMI registries in Japan (**Supplementary Figure**). In the JAMIR, patients with type 1 MI as proposed by the third universal definition of MI were included.[13] Detailed protocols of the JAMIR have been published previously.[14] The present study was conducted in accordance with the ethical principles in the Declaration of Helsinki and was approved by the institutional review board of each participating hospital. Given that this study was a non-invasive observational investigation and appropriately anonymized personal information, written informed consent was not required (No. 2023-1-793).

Study Subjects

The patient flow diagram for this study is shown in **Figure 1**. Study subjects were derived from the JAMIR database, in which a total of 46,242 AMI patients within 24 h of onset were enrolled consecutively between January 2011 and December 2016. From those, we excluded patients with a complete lack of findings on urgent coronary angiography (n=10,169). Furthermore, patients who had no informa-

The JAMIR Investigators are listed in the **Appendix**.
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Table 1. Patient Characteristics at Baseline

	Overall (n=22,236)	MINOCA (n=286)	MI-CAD (n=21,950)	P value
Age (years)	67.8±13.1	63.2±15.0	67.9±13.1	<0.01
Female (%)	23.4	27.3	23.4	0.13
Hypertension (%)	64.5	51.2	64.6	<0.01
Diabetes (%)	32.5	16.0	32.7	<0.01
Dyslipidemia (%)	47.0	29.8	47.2	<0.01
Smoking (%)	45.1	45.5	45.1	0.91
Ambulance transport (%)	78.2	73.7	78.3	0.07
In-hospital onset (%)	3.6	3.6	3.6	0.97
Onset-to-door time (min)	136 (61–337)	119 (60–372)	136 (61–336)	0.10
STEMI (%)	79.8	54.5	80.2	<0.01
MCS (%)	16.6	7.3	16.7	<0.01
Peak CK level (μ/L)	1,682 (699–3,373)	619 (246–1,360)	1,705 (714–3,391)	<0.01
Killip classification (%)				<0.01
I	74.8	85.3	74.7	
II	11.2	6.1	11.3	
III	5.0	2.5	5.0	
IV	9.0	6.1	9.0	

Unless indicated otherwise, data are given as the mean ± SD, median (interquartile range), or %. CK, creatine kinase; MCS, mechanical circulatory support; MI-CAD, myocardial infarction with obstructive coronary artery disease; MINOCA, myocardial infarction with non-obstructive coronary arteries; STEMI, ST-elevation myocardial infarction.

Table 2. Univariable and Multivariable Analyses for In-Hospital Outcomes of MINOCA and MI-CAD

	MINOCA (%)	MI-CAD (%)	Univariable analysis			Multivariable analysis		
			OR	95% CI	P value	OR	95% CI	P value
In-hospital mortality	5.2	5.7	0.90	0.54–1.53	0.72	1.06	0.63–1.80	0.82
Cardiac mortality	1.1	4.1	0.25	0.08–0.77	<0.01	0.28	0.09–0.89	0.03
Non-cardiac mortality	4.2	1.6	2.66	1.48–4.79	<0.01	3.14	1.74–5.68	<0.01

Multivariable analyses were adjusted for age and sex. CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

tion on either the number of diseased coronary vessels that showed luminal narrowing ≥50% on angiography in any of coronary arteries (n=12,938) or the implementation of revascularization therapies (n=16) were excluded. Finally, 286 patients who did not undergo coronary revascularization and had no coronary artery with ≥50% organic stenosis were categorized as having MINOCA. The remaining 21,950 patients who received myocardial revascularization procedures or had diseased coronary arteries were classified as MI-CAD.

Definitions and Clinical Outcomes

Detailed definitions of cardiovascular disease risk factors, including hypertension, dyslipidemia, diabetes, and smoking, as well as ST-segment elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI), have been provided elsewhere.[15] The major outcomes assessed in the present study were in-hospital all-cause death, in-hospital cardiac death, and in-hospital non-cardiac death. All deaths were initially considered cardiac unless a clear non-cardiac cause was identified. Cardiac death was defined as death resulting from cardiogenic shock, heart failure, arrhythmia, reinfarction, or septal or free wall rupture. Non-cardiac death was diagnosed when patients died without any cardiac complications aside from stable AMI. Specifically, non-cardiac death included fatalities attributed to cerebral, vascular, or other non-cardiac factors such as bleeding, cancer, respiratory failure, infections, renal failure, liver failure, and gastrointestinal disease. When a patient died of multiple organ failure with concurrent heart failure, cardiogenic shock, or other cardiac complications, the death was categorized as cardiac, even if non-cardiac complications were present.[16–19]

Statistical Analysis

Continuous variables are presented as the mean ± SD or as the median with interquartile range (IQR), whereas categorical variables are expressed as percentages. Group comparisons were conducted using the Mann-Whitney U test for continuous variables and the Chi-squared test for categorical variables. A multivariable logistic regression model, adjusted for age and sex, was used to compare the incidence of in-hospital outcomes between the MINOCA and MI-CAD groups. In addition, both univariable and multivariable analyses were performed to identify factors associated with in-hospital all-cause mortality within each MI group. Clinically important factors (e.g., age, sex, and coronary risk factors) and known prognostic predictors for AMI patients (e.g., ST changes, peak creatine kinase [CK], and Killip classification) were selected as variables for the univariable analysis. Then, clinically relevant factors and variables showing significant differences between the 2

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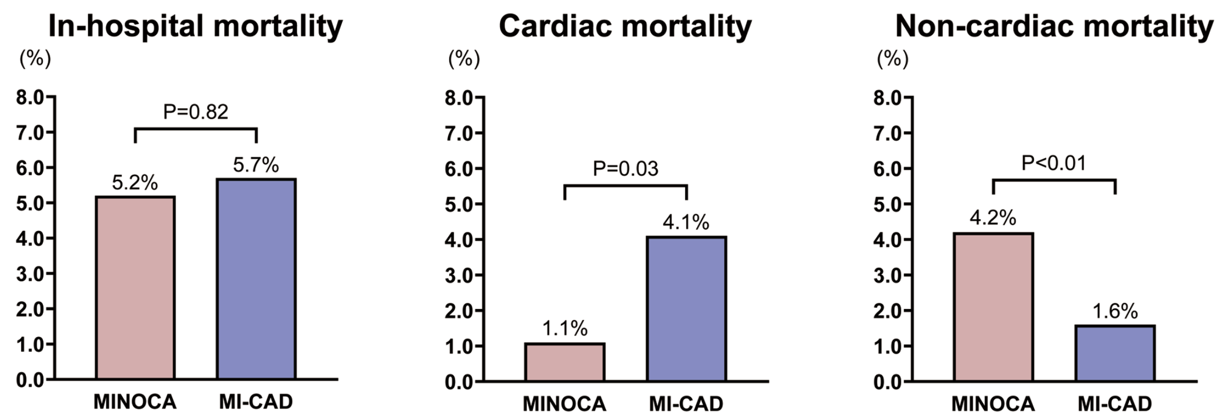

Figure 2. Comparison of in-hospital outcomes between the myocardial infarction with obstructive coronary artery disease (MI-CAD) and myocardial infarction with non-obstructive coronary arteries (MINOCA) groups.

Table 3. Factors Associated With In-Hospital Mortality in MINOCA and MI-CAD Patients

	MINOCA					
	Univariable analysis			Multivariable analysis		
	OR	95% CI	P value	OR	95% CI	P value
Age	1.02	0.98–1.05	0.43			
Female sex	0.40	0.09–1.79	0.23			
Hypertension	0.70	0.15–3.27	0.65			
Diabetes	0.87	0.10–7.59	0.90			
Dyslipidemia	0.94	0.18–5.07	0.94			
Smoking	0.31	0.08–1.14	0.08			
STEMI	2.76	0.56–13.58	0.21			
Peak CK (/1,000 units/L)	2.34	1.38–3.97	<0.01	2.51	1.21–5.20	0.01
Killip classification	3.75	2.31–6.10	<0.01	3.77	1.72–8.23	<0.01
	MI-CAD					
	Univariable analysis			**Multivariable analysis**		
	OR	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Age	1.04	1.04–1.05	<0.01	1.03	1.01–1.05	<0.01
Female sex	1.52	1.34–1.72	<0.01	1.49	0.99–2.24	0.06
Hypertension	0.97	0.82–1.14	0.67			
Diabetes	1.32	1.13–1.55	<0.01	1.71	1.17–2.51	0.01
Dyslipidemia	0.43	0.36–0.51	<0.01	0.45	0.31–0.66	<0.01
Smoking	0.51	0.45–0.58	<0.01	0.60	0.36–1.00*	0.049
STEMI	1.33	1.13–1.58	<0.01			
Peak CK (/1,000 units/L)	1.23	1.21–1.26	<0.01	1.21	1.15–1.27	<0.01
Killip classification	2.93	2.80–3.08	<0.01	2.33	2.02–2.70	<0.01

Variables with P<0.10 in univariable analysis were assigned to the stepwise regression model. Multivariable analysis was performed with the variables selected by this stepwise regression model. *The value 0.997 was rounded up to 1.00. Abbreviations as in Tables 1,2.

groups in the univariable analysis (P<0.1) were selected as covariates for the multivariable logistic regression model, using a stepwise backward elimination procedure. Two-tailed P<0.05 was considered statistically significant. All data analyses were performed using JMP Pro version 16.0.0 (SAS Institute, Inc., Cary, NC, USA).

Results

Clinical Characteristics of MINOCA Patients

In this study, MINOCA patients (n=286) comprised 1.3% of the overall subjects from the JAMIR database (n=22,236). Their clinical features are summarized in **Table 1**. Compared with MI-CAD patients, MINOCA patients were

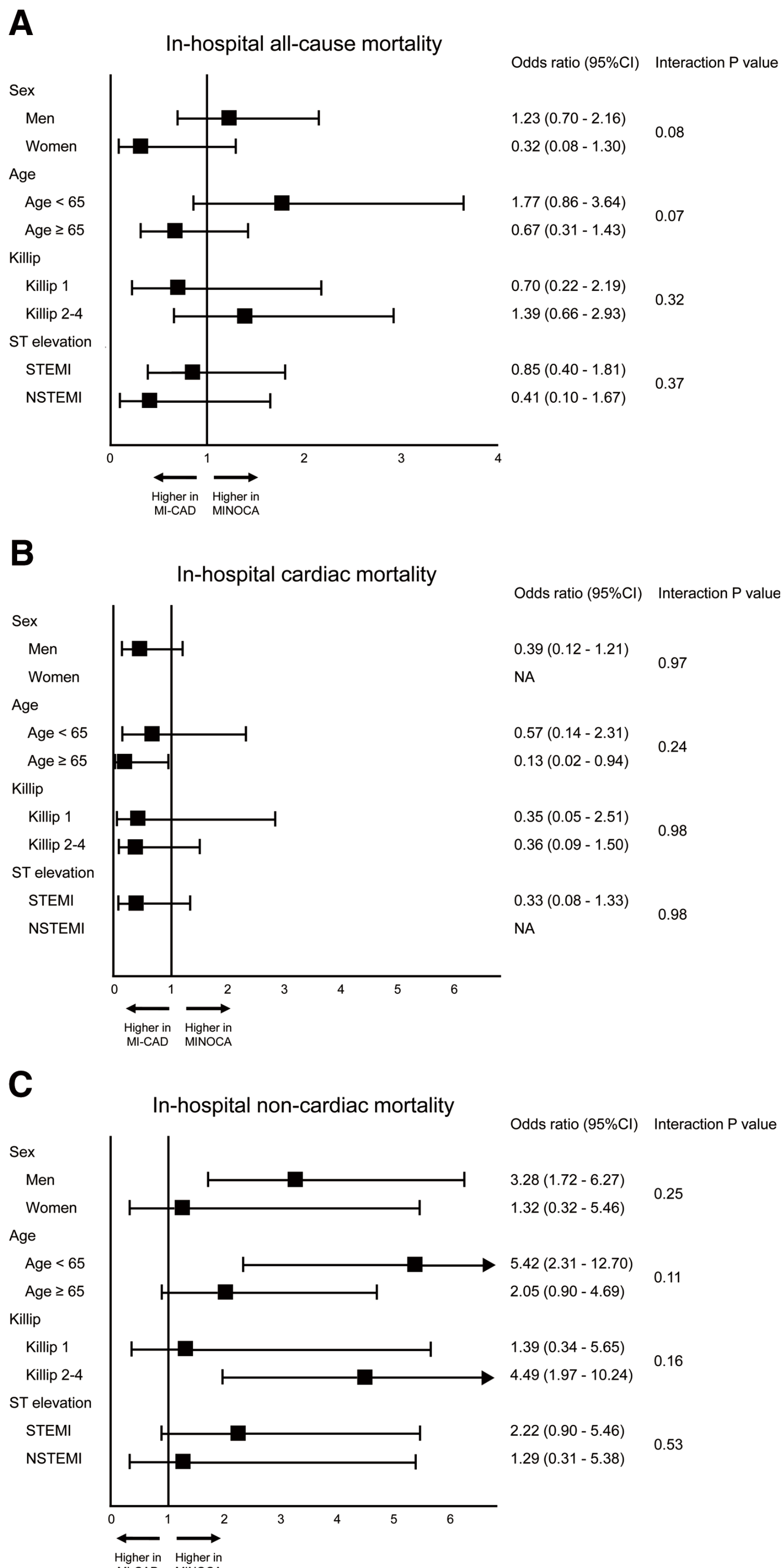

Figure 3. Forest plots showing in-hospital (**A**) all-cause mortality, (**B**) cardiac mortality, and (**C**) non-cardiac mortality outcomes in subgroup analyses. CI, confidence interval; MI-CAD, myocardial infarction with obstructive coronary artery disease; MINOCA, myocardial infarction with non-obstructive coronary arteries; NA, not available; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

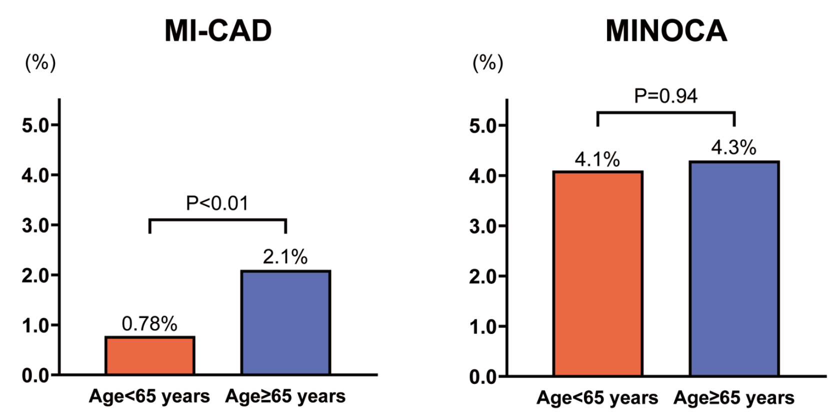

Figure 4. Generation differences in non-cardiac mortality among myocardial infarction with non-obstructive coronary arteries (MINOCA) and myocardial infarction with obstructive coronary artery disease (MI-CAD) patients.

typically younger, had fewer coronary risk factors, a lower prevalence of STEMI, lower Killip classification grades upon presentation, and lower peak CK levels. Although the proportion of female patients appeared to be higher in the MINOCA than MI-CAD group, this difference did not achieve statistical significance. Similarly, there were no significant differences between the 2 groups in the utilization rate of ambulance transport, the percentage of patients with in-hospital onset, the need for mechanical circulatory support devices, or onset-to-door time.

In-Hospital Outcomes of MINOCA

The in-hospital outcomes are summarized in **Table 2** and **Figure 2**. There was no significant difference in in-hospital all-cause mortality between the MINOCA and MI-CAD groups (5.2% vs. 5.7% [P=0.72]; odds ratio [OR] 0.90; 95% confidence interval [CI] 0.54–1.53). However, compared with the MI-CAD group, the MINOCA group exhibited a significantly higher rate of in-hospital non-cardiac mortality (4.2% vs. 1.6% [P<0.01]; OR 2.66; 95% CI 1.48–4.79) and a lower incidence of in-hospital cardiac death (1.1% vs. 4.1% [P<0.01]; OR 0.25; 95% CI 0.08–0.77). These trends persisted even after adjusting for age and sex in a binomial logistic regression model (in-hospital mortality: adjusted OR 1.06 [95% CI 0.63–1.80]; non-cardiac mortality: adjusted OR 3.14 [95% CI 1.74–5.68]; cardiac mortality: adjusted OR 0.28 [95% CI 0.09–0.89]; **Table 2**). Factors associated with in-hospital all-cause death in each group are presented in **Table 3**. In the multivariable logistic regression model, higher age, female sex, diabetes, higher peak CK levels, and higher Killip classification grades were identified as predictors of in-hospital all-cause death in MI-CAD patients. In the MINOCA group, higher peak CK levels and higher Killip classification grades were consistently identified as predictors for fatal events during hospitalization.

Generation Differences in Non-Cardiac Mortality Among MINOCA and MI-CAD Patients

Subgroup analyses, stratified by age, sex, Killip classification grade, and MI type, for in-hospital all-cause mortality, cardiac mortality, and non-cardiac mortality are shown in **Figure 3**. Across all subgroups, in-hospital all-cause mortality did not differ significantly between the MINOCA and MI-CAD groups (**Figure 3A**). Among elderly (age ≥65 years) patients, cardiac mortality was significantly higher in the MI-CAD than MINOCA group (OR 0.13; 95% CI 0.02–0.94]; **Figure 3B**). Conversely, among non-elderly (age <65 years) patients, non-cardiac death occurred significantly more frequently in the MINOCA than MI-CAD group (OR 5.42; 95% CI 2.31–12.7; **Figure 3C**). Interestingly, in the MI-CAD group, non-cardiac death was more common among elderly (≥65 years) than non-elderly (<65 years) patients (2.1% vs. 0.78% [P<0.01]; OR 2.76; 95% CI 2.11–3.61), whereas this pattern was not observed in the MINOCA group (4.3% vs. 4.1% for elderly and non-elderly patients, respectively [P=0.94]; OR 1.04; 95% CI 0.33–3.32; **Figure 4**).

Discussion

The major findings of the present study are as follows: (1) MINOCA patients represented 1.3% of all subjects in the JAMIR database; (2) MINOCA patients exhibited distinct characteristics, including younger age, fewer coronary risk factors, a lower incidence of STEMI, lower Killip classification grades, and lower peak CK levels, compared with MI-CAD patients; (3) there was no significant difference in in-hospital all-cause mortality between the MINOCA and MI-CAD groups; (4) however, non-cardiac mortality was notably higher in the MINOCA group; and (5) of particular note, there was a disparity in non-cardiac mortality between elderly and non-elderly patients in the MI-CAD group, but not in the MINOCA group.

Patient Characteristics and Incidence of MINOCA

Recent systematic reviews have reported a wide range in the prevalence of MINOCA, from 1% to 14%, with an overall calculated incidence of 6% (95% CI 5–7%).[8] The prevalence of MINOCA in the JAMIR appears slightly lower than that reported in previous studies.

Prior investigations have consistently identified MINOCA patients as typically younger[8,9] and more frequently female,[8,20,21] with lower rates of smoking,[9,20,21] hypertension,[9] hyperlipidemia,[8,9,20] and diabetes[9,20] compared with MI-CAD patients. Although some patient characteristics of MINOCA in the JAMIR align with these findings, such as younger age and fewer coronary risk factors, the prevalence of MINOCA and the proportion of female patients were comparatively lower. Several factors may account for these discrepancies. First, patients included in the JAMIR were generally older (mean age 67.8±13.1 years) compared with other registries (mean age 64.1 years in Korean Acute

Myocardial Infarction-National Institutes of Health [KAMIR-NIH] [SD not available] and median age 61 years [IQR 52–71 years] in Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With the Guidelines [ACTION-GWTG]).[9,21] Elderly patients, often characterized by advanced atherosclerosis, may present with angiographic coronary artery stenosis (≥50%), which could be unrelated to the culprit lesion but still result in a diagnosis of MI-CAD rather than MINOCA. Second, the utilization of intravascular imaging techniques in Japan, such as intravascular ultrasound imaging (IVUS), is notably higher than in other countries. Although precise data on the rate of imaging device use from the JAMIR was not available, real-world evidence from Japan indicates that IVUS is used in 84.8% of patients undergoing PCI.[22] This contrasts with usage rates reported in Korea (43–55%)[23–25] and the US (42.2%).[26] The widespread use of IVUS in Japan enhances the detection of minor plaque rupture or thrombus, which may contribute to an increased diagnosis of AMI as MI-CAD and subsequent stenting. Third, some cases may not have been diagnosed as AMI due to the absence of coronary artery occlusion on coronary angiography and so were not registered in the JAMIR. There may have been cases among the 10,169 patients excluded from the present study due to the lack of coronary angiography data where emergency coronary angiography was not performed if coronary computed tomography angiography did not identify any significant abnormalities.

In-Hospital Mortality of MINOCA Patients

Previous studies have shown varying rates of in-hospital mortality for MINOCA, ranging from approximately 1% to 3%, and findings regarding its comparison to MI-CAD have been inconsistent, with some studies reporting lower,[8,20] higher,[12] or non-significantly different rates.[21] However, in the JAMIR, in-hospital mortality did not show a significant difference between MINOCA and MI-CAD patients, and the in-hospital mortality rate for MINOCA appeared to be higher than that reported in previous studies. This disparity could be attributed to 2 potential factors. First, the JAMIR population was older than that of other registries, as mentioned above. Second, although some studies excluded patients with cardiac arrest or cardiogenic shock,[9,20] JAMIR did not exclude such severe cases. Given that older and severely ill patients are more likely to experience poorer outcomes, it is plausible that MINOCA patients in the JAMIR had a higher rate of in-hospital mortality compared with those in previous studies.

Clinical Outcomes and Related Factors Among MINOCA Patients

In the JAMIR, we identified higher peak CK and higher Killip classification as independent predictors for in-hospital all-cause mortality among MINOCA patients. These predictors also applied to MI-CAD patients, but the remaining predictors in MI-CAD, such as higher age, female sex, diabetes, dyslipidemia, and smoking, did not apply to MINOCA. According to this, the short-term outcome of MI-CAD may be affected by coronary risk factors, but this does not apply to MINOCA patients.

In this study we observed that non-cardiac mortality among elderly patients was significantly higher in the MI-CAD group, whereas in the MINOCA group non-cardiac mortality rates were similar between elderly and younger patients. This finding underscores the importance of the precise diagnosis and treatment of non-cardiac conditions, which could contribute to non-cardiac mortality, particularly in younger patients, to improve short-term prognosis of MINOCA. Previous studies have highlighted increased rates of non-cardiac mortality among MINOCA patients,[27–30] with some indicating lower cardiovascular mortality rates, higher respiratory mortality rates, and similar cancer mortality rates compared with MI-CAD patients.[27] Our findings in the JAMIR align with these studies, suggesting that MINOCA represents a heterogeneous entity with diverse etiologies, as acknowledged in recent expert statements from Japan, America, and Europe.[1–3] Indeed, a recent study demonstrated that the primary etiologies responsible for in-hospital non-cardiac death in AMI patients overall were infection (49%), bleeding (14%), respiratory failure (9%), and cerebral infarction (7%).[31] These findings may help explain the pathogenesis of non-cardiac death in MINOCA patients.

MI-CAD causes severe damage to the heart and is characterized as a life-threatening disease, but the treatment for MI-CAD in recent years is relatively well established. Conversely, MINOCA causes less damage to the heart than MI-CAD, but the various etiologies and differences in background could make the management of MINOCA complex. More comprehensive evaluations of the underlying mechanisms should be undertaken to determine the appropriate treatment for MINOCA.[7] Recent guidelines recommend both invasive approaches (e.g., IVUS, optical coherence tomography, and comprehensive coronary functional testing) and non-invasive approaches (e.g., cardiac magnetic resonance imaging, coronary computed tomography, echocardiography, and blood sample data) for MINOCA.[1–3] Specifically, in the Women's Heart Attack Research Program (HARP) study, the combined use of optical coherence tomography and cardiac magnetic resonance imaging identified a cause of MINOCA in 85% of cases.[32] In addition, coronary vasospasm is known to be a common cause of MINOCA.[33,34] A recent study involving 80 MINOCA patients undergoing pharmacological spasm provocation testing during the acute phase of MI demonstrated that approximately half the subjects had a positive result and were at high risk of future cardiovascular events.[35] These findings suggest that a multimodal approach, combining techniques such as optical coherence tomography, cardiac magnetic resonance imaging, and pharmacological spasm provocation testing, is essential for identifying the underlying mechanisms in patients presenting with MINOCA.

Study Limitations

Our study has several limitations. First, being a non-randomized retrospective observational study, it may have been susceptible to residual confounding or selection bias, which could not be ruled out entirely. Second, the absence of data concerning coronary angiography, intravascular imaging, and other modalities for elucidating the etiologies of MINOCA limited our ability to comprehensively understand the underlying causes of this condition. Third, our study only obtained in-hospital outcomes, precluding an evaluation of the long-term prognosis of MINOCA. Fourth, the JAMIR had only an either/or choice (cardiac or non-cardiac) regarding the kind of in-hospital death. Thus, further information on details of the cause of in-hospital deaths was unavailable. In addition, our database did not include information on non-cardiac conditions, such as cancer status, malnutrition, and other exacerbating factors that may be associated with non-cardiac mortality. Therefore, future research should comprehensively evaluate both the causes of death and the overall condition of MINOCA patients.

Conclusions

The present nationwide real-world registry study, JAMIR, revealed a higher incidence of non-cardiac mortality in the MINOCA group compared with the MI-CAD group. This finding underscores the clinical significance of conducting more comprehensive evaluations to understand the underlying pathophysiological mechanisms.

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Disclosures

Y.S., K.K., and S.Y. are members of *Circulation Journal*'s Editorial Team. The remaining authors have no conflicts of interest to declare.

IRB Information

This study was approved by the Ethics Committee of Tohoku University Graduate School of Medicine (Reference no. 2023-1-793).

Data Availability

The data underlying this article cannot be shared publicly due to ethical reasons.

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Appendix

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Supplementary Files

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