Journal of the American Heart Association

ORIGINAL RESEARCH

Clinical Characteristics and Outcome of Patients With Myocardial Infarction With Nonobstructive Coronary Arteries in Japan: Insights From the Miyagi Acute Myocardial Infarction Registry Study

Kiyotaka Hao, MD, PhD; Jun Takahashi, MD, PhD; Koichi Sato, MD, PhD; Kento Fukui, MD, PhD; Tomohiko Shindo, MD, PhD; Kazuma Oyama, MD, PhD; Kensuke Nishimiya, MD, PhD; Shigeo Godo, MD, PhD; Takashi Shiroto, MD, PhD; Hiroaki Shimokawa, MD, PhD; Satoshi Yasuda, MD, PhD

BACKGROUND: Clinical characteristics and outcomes of patients with myocardial infarction (MI) with nonobstructive coronary arteries (MINOCA) are not fully understood, particularly in Japan.

METHODS AND RESULTS: We enrolled a total of 8881 patients with acute MI from the Miyagi Acute Myocardial Infarction Registry Study (2012–2020), with a median age of 69 years. Among them, 239 patients (2.7%) were diagnosed with MINOCA. Compared with those with MI with obstructive coronary artery disease (MI-CAD), patients with MINOCA were more often women, had a higher incidence of non–ST-segment–elevation MI and a lower prevalence of dyslipidemia. Compared with patients with MI-CAD, patients with MINOCA in all age groups (<59, 60–69, 70–79, >80 years of age) had a higher incidence of non–ST-segment–elevation MI. Additionally, those ≤59 years of age were more often women and had a lower prevalence of diabetes and dyslipidemia. In-hospital mortality increased with age in patients with MI-CAD (3.9% for <59 years of age, 5.6% for 60–69 years of age, 8.3% for 70–79 years of age, and 15.2% for >80 years of age; P<0.01), but not in patients with MINOCA (4.5%, 7.4%, 6.0%, and 9.6%, respectively; P=0.36). Compared with patients with MI-CAD, patients with MINOCA had lower in-hospital mortality for Killip class IV (40.7% versus 20.0%; adjusted odds ratio [OR], 0.31 [95% CI, 0.10–0.94]; P=0.04) and renal dysfunction (20.0% versus 7.1%; adjusted OR, 0.29 [95% CI, 0.09–0.96]; P=0.04).

CONCLUSIONS: Patients with MINOCA exhibit distinct clinical characteristics and outcomes compared with those with MI-CAD, particularly in terms of age, sex, prevalence of comorbidities, and in-hospital mortality. These findings underscore the importance of tailored clinical approaches for patients with MINOCA.

Key Words: acute myocardial infarction ■ nonobstructive coronary artery ■ prognosis

With the widespread use of coronary angiography (CAG) in the early clinical management of acute myocardial infarction (AMI), it has been revealed that some patients with AMI have no evidence of obstructive coronary artery disease (CAD).[1–3] These patients are labeled as having myocardial infarction (MI) with nonobstructive coronary arteries (MINOCA).[4] The underlying pathophysiological mechanisms of

Correspondence to: Satoshi Yasuda, MD, PhD, Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1, Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan. Email: syasuda@cardio.med.tohoku.ac.jp

This article was sent to Rushi V. Parikh, MD, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.124.036802

For Sources of Funding and Disclosures, see page 8.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Patients with myocardial infarction with nonobstructive coronary arteries in all age groups (<59, 60–69, 70–79, >80 years of age) had a higher incidence of non–ST-segment–elevation myocardial infarction compared with those with myocardial infarction with obstructive coronary artery disease, whereas patients with myocardial infarction with nonobstructive coronary arteries ≤59 years of age were more often women and had a lower prevalence of diabetes and dyslipidemia compared with patients with myocardial infarction with obstructive coronary artery disease.
- Compared with patients with myocardial infarction with obstructive coronary artery disease, patients with myocardial infarction with nonobstructive coronary arteries had lower in-hospital mortality for Killip class IV and renal dysfunction.

What Are the Clinical Implications?

- Patients with myocardial infarction with nonobstructive coronary arteries exhibit distinct clinical characteristics and outcomes compared with those with myocardial infarction with obstructive coronary artery disease, particularly in terms of age, sex, prevalence of comorbidities, and in-hospital mortality.

Nonstandard Abbreviations and Acronyms

CAG	coronary angiography
MI-CAD	myocardial infarction with obstructive coronary artery disease
MINOCA	myocardial infarction with nonobstructive coronary arteries

MINOCA are not fully understood. Guidelines indicate that MINOCA encompasses a group of heterogeneous diseases with different pathological mechanisms, including plaque disruption, spasm, thromboembolism, dissection, microvascular dysfunction, ischemic myocardial injury due to supply/demand mismatch, and clinically undetected myocarditis or takotsubo cardiomyopathy.[5] This diversity in mechanisms contributes to the complexity in diagnosing and managing MINOCA.

Several studies, including a large systematic review, have shown that patients with MINOCA generally have lower in-hospital mortality than those with MI with obstructive CAD (MI-CAD).[4,6–10] However, these findings are not entirely consistent across all reports, indicating the need for further research to fully understand the outcomes associated with MINOCA.

The optimal treatment strategy for patients with MINOCA remains uncertain, which complicates their prognosis and identification of predictors. Recent studies have documented a strong relationship between age and in-hospital mortality in patients with MINOCA compared with patients with MI-CAD.[6] Interestingly, the lower in-hospital mortality in patients with MINOCA compared with patients with MI-CAD was more evident among older patients.[6] This suggests that age might play a significant role in the prognosis of patients with MINOCA.

The Miyagi AMI Registry Study[11,12] is a prospective, multicenter, observational study for >40 years since 1979 in Japan, a country with a high proportion of older patients.[13] Therefore, in the present study, we examined the clinical characteristics and in-hospital outcomes of patients with MINOCA, compared with those with MI-CAD in Japan.

METHODS

The present study was approved by the institutional review board of Tohoku University Graduate School of Medicine (2017-1-284), under the condition that personal data are protected at all times. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Miyagi AMI Registry Study and Study Population

In the Miyagi AMI Registry Study, all 45 hospitals with a cardiac care unit or cardiac catheterization facility in the Miyagi prefecture, located in northeastern Japan with a population of approximately 2.35 million, have been participating (Data S1); thus, almost all patients with AMI in the Miyagi prefecture have been prospectively enrolled.[11,12] Because the Miyagi AMI Registry Study is an observational study, informed consent was obtained in the form of opt out. In this registry, AMI was diagnosed based on the WHO-MONICA (World Health Organization-Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) criteria, including typical severe chest pain accompanied by ischemic ECG changes and elevated serum levels of creatine kinase (CK).[14] In 2000, the European Society of Cardiology and American College of Cardiology proposed new criteria for the diagnosis of AMI as a universal definition, in which cardiac troponin was a preferred biomarker of cardiac injury.[15] Since then, cardiac troponin has been widely applied for the diagnosis of AMI in Japan.[16,17] Therefore, we applied both CK and troponin as cardiac markers for diagnosis of AMI in the present study.

In the Miyagi AMI Registry Study, we excluded patients with nonischemic myocardial disorders such as takotsubo cardiomyopathy and myocarditis.[11,12] The treatment strategies, including medication and selection of reperfusion therapies, were left to the discretion of the individual cardiologist in charge. The information collected in the Miyagi AMI Registry Study included age, sex, date and time of symptom onset, prehospital management (eg, use of ambulance, time interval from symptom onset to admission), infarction site, coronary risk factors (hypertension, diabetes, dyslipidemia, and smoking), reperfusion therapies (eg, thrombolysis and/or percutaneous coronary intervention), peak CK levels, and in-hospital mortality.[11,12] Our registration form was revised occasionally during the 45 years as required, and angiographic data were available for patients enrolled after 2012.

Therefore, in the present study, we enrolled a total of 8881 patients with AMI who had coronary angiographic data in the Miyagi AMI Registry between 2012 and 2020 and examined the clinical characteristics and outcome of patients with MINOCA. MINOCA was defined as patients with AMI without obstructive lesions in the emergent CAG.[5] In the Miyagi AMI Registry Study, no data were available for long-term outcomes of patients with AMI after discharge. Thus, if the same case developed an MI again and was readmitted to the hospital within the research period above, that event was counted as a new, independent event.

Statistical Analysis

Continuous variables were expressed as median with interquartile range (IQR) and compared using the Mann-Whitney *U* test. Categorical variables were expressed as number with percentage and compared using the Fisher exact test or the χ^2 test, as appropriate. To examine differences between the MINOCA and MI-CAD groups by age, patients were divided into 4 age groups (<59, 60–69, 70–79, >80 years), and the Cochran-Armitage test for trend was used. To identify factors associated with MINOCA, univariable and multivariable logistic regression models were applied. Covariates included age, sex, ST-segment–elevation MI, coronary risk factors, renal dysfunction (serum creatinine >1.2 mg/dL), heart failure with Killip class on admission, and cardiac arrest on admission. Odds ratio (OR) and 95% CI were calculated using a stepwise variable selection procedure. The impact of MINOCA on in-hospital mortality was examined in subgroups stratified by age, sex, Killip class on admission, presence of ST-segment–elevation MI, and renal dysfunction. A multivariable logistic regression model was used to adjust for covariates including age and sex. The interaction between MINOCA and predefined clinical subgroups on in-hospital mortality was assessed using a logistic regression model with interaction terms. A *P* value of <0.05 and a *P* value for interaction of <0.10 were considered as statistically significant. All statistical analyses were performed using IBM SPSS Statistics 25.0 (IBM, Armonk, NY) and R software (version 3.0.3, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Prevalence of Patients With MINOCA

Among the 8881 patients with AMI, 239 (2.7%) were diagnosed with MINOCA, whereas 8642 (97.3%) were diagnosed with MI-CAD. When divided into 4 age groups (<59, 60–69, 70–79, >80 years of age), female patients ≤59 years of age had a higher prevalence of MINOCA compared with male patients (8.5% versus 2.4%, *P*<0.01) (Figure 1). The prevalence of MINOCA in female patients decreased with age (<59 years of age: 8.5%, 60–69 years of age: 3.7%, 70–79 years of age: 3.6%, >80 years of age: 2.6%; *P*<0.05 for trend), which was not observed in male patients (<59 years of age: 2.4%, 60–69 years of age: 2.1%, 70–79 years of

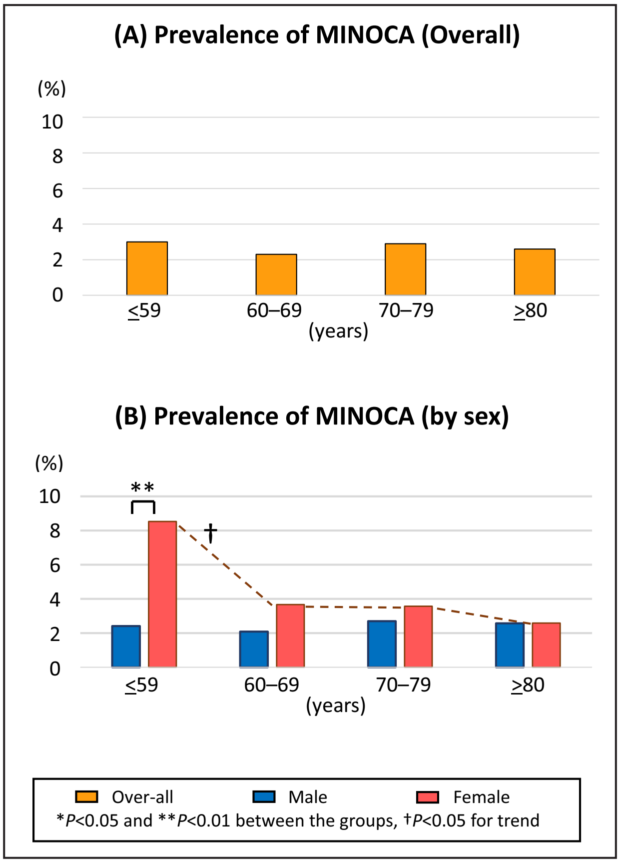

Figure 1. Prevalence of MINOCA by age.
A, Overall population. **B**, Male and female patients. MINOCA indicates myocardial infarction with nonobstructive coronary arteries.

Table 1. Clinical Characteristics of the Study Population

Characteristic	MINOCA, n=239 (2.7%)	MI-CAD, n=8642 (97.3%)	*P* value
Age, y, median	69 (59–78)	69 (60–78)	0.40
Age >70 y	49.8% (119/239)	48.6% (4203/8642)	0.72
Women	29.7% (71/239)	21.4% (1859/8642)	<0.01
Hypertension	65.7% (157/239)	70.1% (6088/8642)	0.14
Diabetes	31.0% (74/239)	36.0% (3123/8642)	0.11
Dyslipidemia	30.1% (72/239)	40.0% (3471/8642)	<0.01
Smoking	42.7% (102/239)	42.5% (3692/8642)	0.96
Renal dysfunction	19.3% (42/218)	17.3% (1291/7479)	0.44
STEMI	51.1% (115/225)	76.1% (6369/8642)	<0.01
NSTEMI	48.9% (110/225)	23.9% (1998/8642)	
Killip class on admission			0.04
I	77.0% (184/239)	81.6% (7051/8642)	
II	4.6% (11/239)	6.1% (523/8642)	
III	5.9% (14/239)	3.7% (324/8642)	
IV	12.6% (30/239)	8.6% (744/8642)	
Cardiac arrest on admission	5.4% (13/239)	3.7% (317/8642)	0.15
Peak CK (U/L)	667 (353–1170)	1505 (642–3131)	<0.01

Values are expressed as median with interquartile range or n (%). CK indicates creatine kinase; MI-CAD, myocardial infarction with obstructive coronary artery disease; MINOCA, myocardial infarction with nonobstructive coronary arteries; NSTEMI, non–ST-segment–elevation myocardial infarction; and STEMI, ST-segment–elevation myocardial infarction.

age: 2.7%, >80 years of age: 2.6%; *P*=0.52 for trend) (Figure 1).

Clinical Characteristics of Patients With MINOCA

The clinical characteristics of patients with MI-CAD and MINOCA are summarized in Table 1. The median age was 69 years in both the MI-CAD and MINOCA cohorts. Patients with MINOCA exhibited a higher prevalence of women and non–ST-segment–elevation MI (NSTEMI), along with a lower prevalence of dyslipidemia. Moreover, patients with MINOCA presented with a higher Killip class on admission, despite the lower peak CK levels compared with patients with MI-CAD (median, 667 IU [IQR, 353–1170] versus 1505 IU [IQR, 642–3131], *P*<0.01). Multivariable logistic regression analysis revealed that female sex (OR, 1.76 [95% CI, 1.26–2.46]; *P*<0.01), NSTEMI presentation (OR, 2.97 [95% CI, 2.24–3.93]; *P*<0.01), absence of dyslipidemia (OR, 0.63 [95% CI, 0.47–0.86]; *P*<0.01), and higher Killip class on admission (OR, 1.18 [95% CI, 1.00–1.38]; *P*=0.49) were significantly associated with the diagnosis of MINOCA (Table 2).

Upon stratification by age, the MINOCA group demonstrated a higher prevalence of NSTEMI across all age categories compared with the MI-CAD group (Figure 2). Among patients <59 years of age, the MINOCA group exhibited a lower prevalence of dyslipidemia (16.7% versus 47.2%, *P*<0.01) and diabetes (21.2% versus 33.6%, *P*<0.05) in contrast with the MI-CAD group, although these differences were not observed in the remaining age groups (≥60 years of age).

In-Hospital Mortality in Patients With MINOCA

The overall in-hospital mortality did not significantly differ between the MINOCA and MI-CAD groups (6.7% versus 8.0%, *P*=0.55). When stratified by age, in-hospital mortality showed an increasing trend with age in the MI-CAD group (<59/60–69/70–79/>80 years of age, 3.9%/5.6%/8.3%/15.2%, respectively, *P*<0.05 for trend), whereas such a trend was not observed in the MINOCA group (4.5%/7.4%/6.0%/9.6%, respectively, *P*=0.36 for trend) (Figure 3). Age, sex, and NSTEMI did not significantly influence the difference in in-hospital mortality between the MINOCA and MI-CAD groups (Figure 4).In both the MINOCA and

Table 2. Factors Associated With Myocardial Infarction With Nonobstructive Coronary Arteries

Factor	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age per 10 y	0.95 (0.86–1.04)	0.25		
Women	1.55 (1.17–2.06)	<0.01	1.76 (1.26–2.46)	<0.01
NSTEMI	3.05 (2.34–3.99)	<0.01	2.97 (2.24–3.93)	<0.01
Hypertension	0.82 (0.62–1.07)	0.14		
Diabetes	0.80 (0.61–1.06)	0.17		
Dyslipidemia	0.65 (0.49–0.85)	<0.01	0.63 (0.47–0.86)	<0.01
Current smoking	1.00 (0.78–1.30)	0.97		
Renal dysfunction	1.00 (0.97–1.03)	0.85		
Killip class on admission	1.16 (1.03–1.32)	0.02	1.18 (1.00–1.38)	0.49
Cardiac arrest on admission	1.52 (0.86–2.69)	0.15		

NSTEMI indicates non–ST-segment–elevation myocardial infarction; and OR, odds ratio.

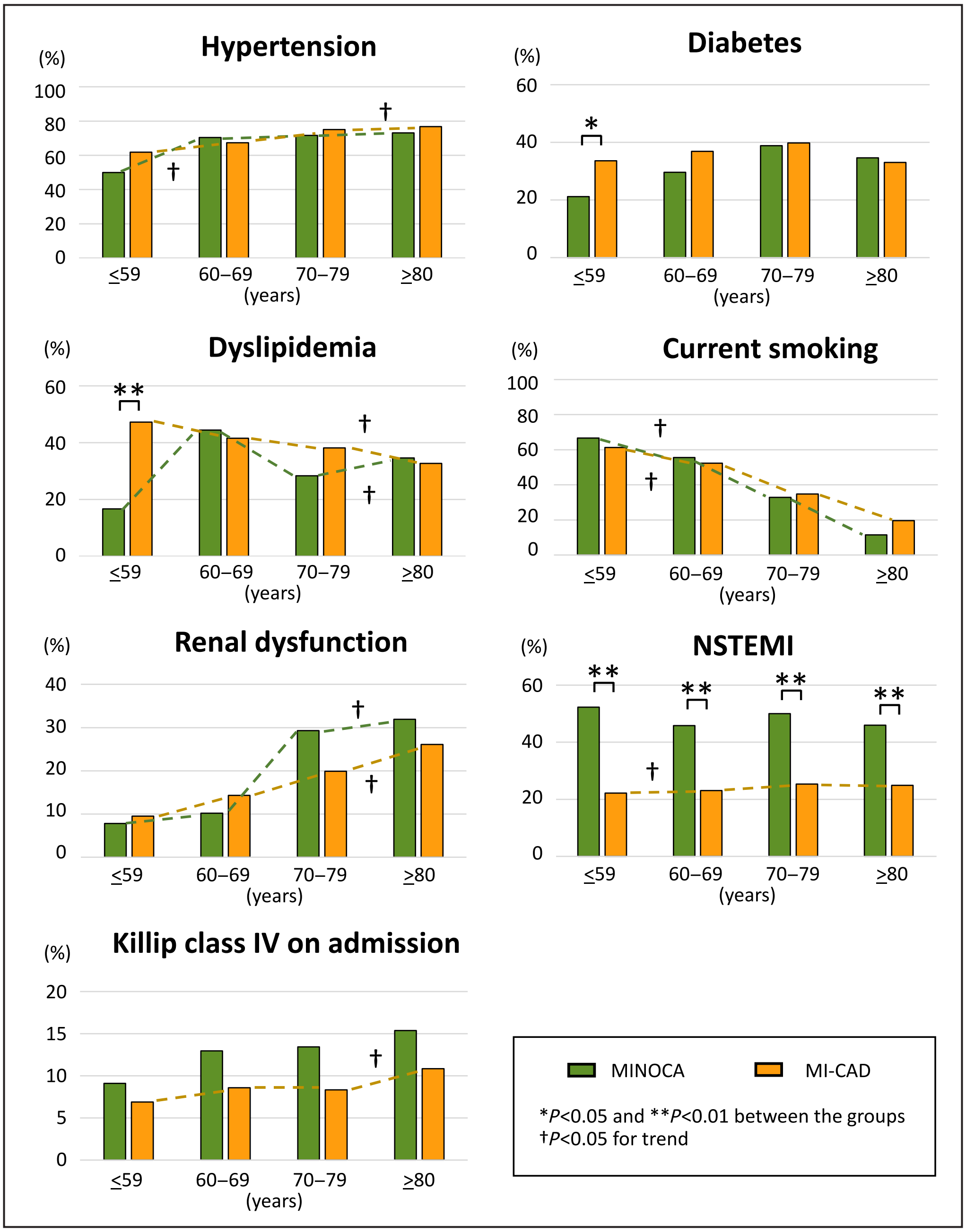

Figure 2. Clinical characteristics of patients with MINOCA and MI-CAD by age.
The difference between patients with MINOCA and MI-CAD in the prevalence of hypertension, diabetes, dyslipidemia, current smoking, renal failure, NSTEMI, and Killip class IV on admission is shown. MI-CAD indicates myocardial infarction with obstructive coronary artery disease; MINOCA, myocardial infarction with nonobstructive coronary arteries; and NSTEMI, non–ST-segment–elevation myocardial infarction.

MI-CAD cohorts, in-hospital mortality increased with higher Killip class on admission (MINOCA: Killip I/II/III/IV, 3.8%/0%/21.4%/20.0%, respectively, P<0.05 for trend; MI-CAD: 3.8%/10.1%/21.3%/40.7%, respectively, P<0.01) (Figure 3). Additionally, among patients with Killip class IV on admission, the MINOCA group exhibited a better in-hospital outcome compared with the MI-CAD group (20.0% versus 40.7%, adjusted OR, 0.31 [95% CI, 0.10–0.94]; P=0.04), whereas no significant difference was observed in those with Killip class I to III (3.8% versus 3.8%, P=0.99) (Figures 3 and 4). Similarly, among those with renal dysfunction, the MINOCA group showed better in-hospital outcomes than the MI-CAD group (7.1% versus 20.0%, P=0.02; adjusted OR, 0.29 [95% CI, 0.09–0.96]; P=0.04), whereas there was no significant difference among those without renal dysfunction (5.1% versus 5.5%, P=0.83) (Figure 4).

	In-hospital mortality (%)			MINOCA vs. MI-CAD		
	MINOCA (n=239)	MI-CAD (n=8542)	*P* value	Adjusted OR (95%CI)	*P* value	P for interaction
Over-all	6.7% (16/239)	8.0% (695/8642)	0.55	0.84 (0.50–1.41)	0.50	
Aged<70 years	5.8% (7/120)	4.8% (211/4441)	0.58	1.35 (0.62–2.95)	0.45	0.17
Aged≥70 years	7.6% (9/119)	11.5% (484/4201)	0.18	0.64 (0.32–1.28)	0.21	
Male	6.5% (11/168)	7.0% (474/6791)	0.83	0.93 (0.50–1.73)	0.82	0.59
Female	7.0% (5/71)	11.9% (221/1851)	0.21	0.46 (0.70–1.78)	0.46	
Renal dysfunction	7.1% (3/42)	20.0% (258/1291)	0.02	0.29 (0.09–0.96)	0.04	0.08
No renal dysfunction	5.1% (9/176)	5.5% (339/6188)	0.83	1.00 (0.50–1.98)	1.00	
STEMI	8.7% (10/115)	8.1% (517/6346)	0.83	1.09 (0.56–2.12)	0.80	0.45
NSTEMI	5.5% (6/110)	7.7% (154/1988)	0.38	0.72 (0.31–1.68)	0.45	
Killip class I-III	3.8% (7/184)	3.8% (270/7051)	0.99	1.04 (0.57–1.89)	0.90	0.05
Killip class IV	20.0% (6/30)	40.7% (303/744)	0.02	0.31 (0.10–0.94)	0.04	

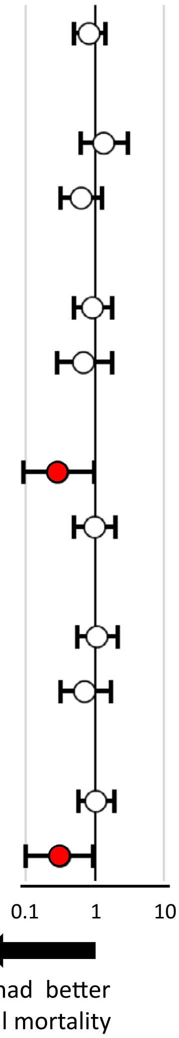

Figure 3. In-hospital mortality of patients with MINOCA and MI-CAD in subgroups.
Multivariable logistic regression analyses were performed to adjust for age and sex. MI-CAD indicates myocardial infarction with obstructive coronary artery disease; MINOCA, myocardial infarction with nonobstructive coronary arteries; NSTEMI, non–ST-segment–elevation myocardial infarction; OR, odds ratio; and STEMI, ST-segment–elevation myocardial infarction.

DISCUSSION

The major findings of the present study were as follows: (1) Patients with MINOCA, as compared with patients with MI-CAD, were more often women, with more NSTEMI cases, lower dyslipidemia rates, and higher Killip class on admission. (2) Patients with MINOCA, across all age groups, showed higher NSTEMI prevalence. Those ≤59 years of age were more often women and had lower diabetes/dyslipidemia rates. (3) In patients with MI-CAD, in-hospital mortality increased with age, unlike patients with MINOCA. (4) Patients with MINOCA, with Killip class IV or renal dysfunction, had better in-hospital outcomes than their counterpart patients with MI-CAD.

Prevalence of Patients With MINOCA

This systematic review comprising 176502 patients with AMI from 27 studies indicated an average MINOCA prevalence of 6% (95% CI, 5–7).[4] Large multicenter registry studies in the United States, Sweden, Canada, and Korea reported MINOCA rates of 5.9%, 8.0%, 5.8%, and 3.5%, respectively.[6,9,10,18] In our study with 8881 Japanese patients with AMI, the MINOCA incidence was notably lower at 2.7%, possibly attributable to 2 factors.

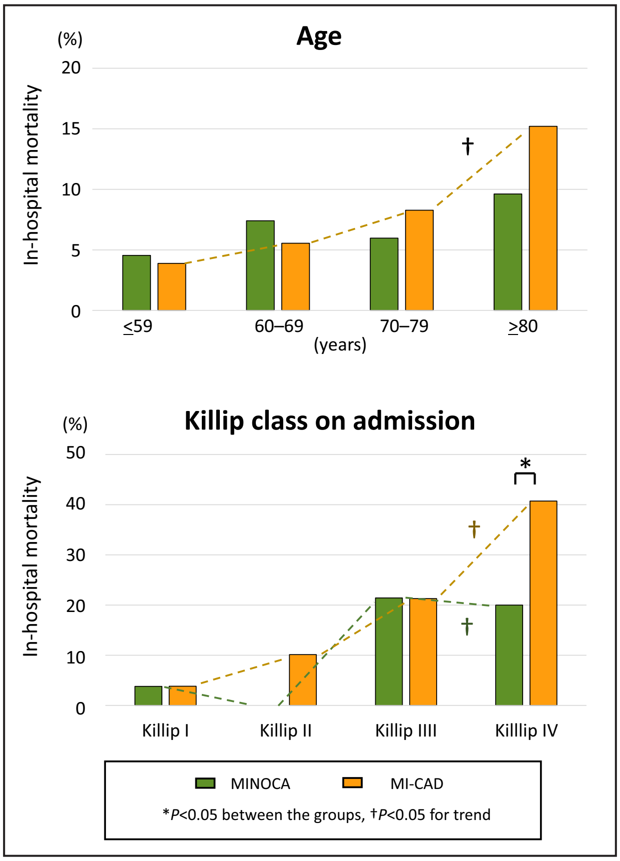

Figure 4. In-hospital mortality of patients with MINOCA and MI-CAD by age and Killip class on admission.
MI-CAD indicates myocardial infarction with obstructive coronary artery disease; and MINOCA indicates myocardial infarction with nonobstructive coronary arteries.

First, the age discrepancy within our study population may account for this variance. Unlike the systematic review and studies from Canada and Korea, where patients' mean ages were comparatively lower (ranging from 59 to 62 years of age), our study featured a notably older median age of 69 years, reflecting Japan's status as a super-aging society.[4,9,10,13] Additionally, Japan's inclination toward more frequent invasive strategies for AMI management, especially in older patients, might have contributed. Previous reports have highlighted Japan's higher usage rates of emergent CAG and primary percutaneous coronary intervention in patients with AMI, particularly among the older population.[19–23] Given that MINOCA diagnosis requires identifying nonobstructive coronary arteries via emergent CAG, our study population was naturally biased toward those undergoing this procedure, potentially skewing toward older patients and impacting MINOCA prevalence.

Second, discrepancies in MINOCA diagnostic criteria across studies may have influenced incidence rates. Initially, MINOCA was defined per the *Third Universal Definition of Myocardial Infarction*, encompassing ischemic and nonischemic myocardial injury causes like myocarditis and takotsubo cardiomyopathy.[24,25] However, the recent *Fourth Universal Definition of Myocardial Infarction* recommended excluding nonischemic and myocardial disorders from MINOCA diagnosis.[5,26–28] Our study adhered to this updated definition, excluding patients with nonischemic cardiac disorders, aligning with the *Fourth Universal Definition of Myocardial Infarction*.[5,26–28] Such differences in interpretation may have contributed to varying MINOCA incidence rates across studies.

Clinical Characteristics of Patients With MINOCA

Previous studies have consistently illustrated distinctive characteristics of patients with MINOCA, including younger age, higher female proportion, increased likelihood of NSTEMI, lower peak cardiac enzyme levels, and reduced incidence of heart failure on arrival.[4,6,9,29,30] However, the prevalence of traditional coronary risk factors, such as hypertension, diabetes, dyslipidemia, and smoking, varied across studies.[4,6,9,29,30] In line with these findings, our study also observed a higher female proportion and NSTEMI prevalence among patients with MINOCA, along with lower peak CK levels and reduced dyslipidemia prevalence. Intriguingly, patients with MINOCA in this study exhibited higher Killip classes on admission despite lower peak CK levels. This inconsistency might be attributed to the more frequent use of invasive strategies for AMI management in Japan, particularly among those characterized as high risk, including older age, heart failure, and cardiac shock.[19–23,31,32] Considering that a MINOCA diagnosis requires identifying nonobstructive coronary arteries via emergent angiography, our study might include patients with MINOCA with Killip class IV more frequently compared with other countries. Additionally, regional and racial disparities in MINOCA pathophysiology should be mentioned. An international registry study for patients with vasospastic angina, one of the main causes of MINOCA, demonstrated that Japanese patients with vasospastic angina had a higher prevalence of cardiac arrest compared with White patients.[33] However, our study lacked data on MINOCA mechanisms such as intracoronary imaging, spasm provocation test results, and cardiac magnetic resonance imaging,[27] representing a notable limitation.

In-Hospital Mortality of Patients With MINOCA

Our study revealed comparable in-hospital mortality rates between patients with MINOCA and MI-CAD (5.7% versus 6.9%), consistent with nationwide studies from Japan and Korea (6.4% versus 6.2% and 2.8% versus 3.5%, respectively).[9,34] Conversely, a systematic review reported better in-hospital mortality among patients with MINOCA compared with patients with MI-CAD (1.1% versus 3.2%), with similar findings in national registry studies from the United States and Canada (1.1% versus 2.9% and 0.8% versus 2.7%, respectively).[4,6,10] These disparities in MINOCA in-hospital mortality might derive from the higher age of our study population. However, among older patients ≥70 years of age, patients with MINOCA exhibited lower in-hospital mortality compared with patients with MI-CAD (7.6% versus 11.5%), contrasting with a reverse trend among younger patients <70 years of age (5.8% versus 4.8%), suggesting that age alone may not account for the mortality discrepancy. Correspondingly, the VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients) study found comparable 1-month mortality among younger patients 18 to 55 years of age (1.1% versus 0.6%), whereas the NCDR CathPCI Registry (National Cardiovascular Data Registry CathPCI Registry) showed better in-hospital mortality among older patients >65 years of age (2.1% versus 4.1%).[7,8] Additionally, the ACTION Registry-GWTG (Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With The Guidelines) demonstrated a significant association between older age and worse in-hospital mortality in patients with MINOCA compared with patients with MI-CAD.[6]

Moreover, our study revealed the differences in mortality between patients with MINOCA and MI-CAD for Killip class IV on admission or renal dysfunction, both of which are recognized as strong predictors of mortality in patients with AMI.[12,16,35] Patients with AMI with Killip class IV are known to have a higher frequency of multivessel disease or left-main lesions with poor prognosis, even after undergoing primary percutaneous coronary intervention.[12,16,36] Similarly, patients with renal dysfunction often present with multiple comorbidities such as hypertension and diabetes, alongside severe and diffuse coronary artery disease, contributing to an independent risk factor for cardiovascular events post-AMI.[35,37] Thus, the observed differences in the prognostic impact of Killip class IV or renal dysfunction between patients with MINOCA and MI-CAD might reflect underlying pathophysiological disparities.

Study Limitations

Several limitations warrant consideration in interpreting our study findings. First, despite the Miyagi AMI Registry Study's extensive duration spanning more than 40 years, angiographic data before 2012 were unavailable for our analysis. Consequently, patients enrolled before 2012 were excluded, potentially affecting the generalizability of our results. Second, the evolving diagnostic criteria for AMI over time, as well as variations in diagnostic approaches within the registry, may have influenced patient characteristics. Diagnosis relied on the WHO-MONICA criteria with CK initially and transitioned to the universal definition with troponin later, contributing to potential heterogeneity within the study population. Third, the absence of data including left ventricular function, underlying pathophysiological mechanisms of MINOCA, such as intracoronary imaging, spasm provocation tests, and cardiac magnetic resonance imaging, precluded a comprehensive exploration of this critical aspect. Fourth, our study's observational nature meant that treatment strategies, including CAG and interventions, were at the discretion of individual cardiologists, introducing potential bias into the results. Last, the lack of long-term outcome data for patients with AMI post-discharge in the Miyagi AMI Registry Study limited our ability to assess the extended impact of MINOCA and MI-CAD on patient prognosis.[16,17,27,38]

CONCLUSIONS

In this prospective, multicenter, observational study conducted in Japan's super-aging society, we demonstrated that patients with MINOCA exhibit distinct clinical characteristics and outcomes compared with those with MI-CAD, particularly in terms of age, sex, prevalence of comorbidities, and in-hospital mortality. These findings underscore the importance of tailored clinical approaches for patients with MINOCA.

ARTICLE INFORMATION

Received May 26, 2024; accepted December 5, 2024.

Affiliations

Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan (K.H., J.T., K.S., K.F., T.S., K.O., K.N., S.G., T.S., H.S., S.Y.); and International University of Health and Welfare, Narita, Japan (K.S., H.S.).

Acknowledgments

The authors thank all of the collaborators in the Miyagi AMI Registry Study. The authors also thank T. Kato for his assistance with the Miyagi AMI Registry Study.

Sources of Funding

This work was supported in part by grants-in-aid from Sendai City, the Miyagi Prefecture, the Miyagi Medical Association, Japan, and the Japan Society for the Promotion of Science KAKENHI (grant number JP22K08147).

Disclosures

Dr Shimokawa received lecture fees from Bayer Yakuhin (Osaka, Japan) and Daiichi Sankyo (Tokyo, Japan). Dr Yasuda received grant support from Takeda Pharmaceutical, Abbott, and Boston Scientific; and lecture fees from Daiichi Sankyo and Bristol Myers Squibb. The remaining authors have no disclosures to report.

Supplemental Material

Data S1

REFERENCES

1. Gehrie ER, Reynolds HR, Chen AY, Neelon BH, Roe MT, Gibler WB, Ohman EM, Newby LK, Peterson ED, Hochman JS. Characterization

and outcomes of women and men with non-ST-segment elevation myocardial infarction and nonobstructive coronary artery disease: results from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) quality improvement initiative. *Am Heart J*. 2009;158:688–694. doi: 10.1016/j.ahj.2009.08.004
2. Hochman JS, Tamis JE, Thompson TD, Weaver WD, White HD, van de Werf F, Aylward P, Topol EJ, Califf RM. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. *N Engl J Med*. 1999;341:226–232. doi: 10.1056/NEJM199907223410402
3. Baccouche H, Mahrholdt H, Meinhardt G, Merher R, Voehringer M, Hill S, Klingel K, Kandolf R, Sechtem U, Yilmaz A. Diagnostic synergy of non-invasive cardiovascular magnetic resonance and invasive endomyocardial biopsy in troponin-positive patients without coronary artery disease. *Eur Heart J*. 2009;30:2869–2879. doi: 10.1093/eurheartj/ehp328
4. 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;131:861–870. doi: 10.1161/CIRCULATIONAHA.114.011201
5. Hokimoto S, Kaikita K, Yasuda S, Tsujita K, Ishihara M, Matoba T, Matsuzawa Y, Mitsutake Y, Mitani Y, Murohara T, et al. JCS/CVIT/JCC 2023 guideline focused update on diagnosis and treatment of vasospastic angina (coronary spastic angina) and coronary microvascular dysfunction. *Circ J*. 2023;87:879–936. doi: 10.1253/circj.CJ-22-0779
6. Smilowitz NR, Mahajan AM, Roe MT, Hellkamp AS, Chiswell K, Gulati M, Reynolds HR. Mortality of myocardial infarction by sex, age, and obstructive coronary artery disease status in the ACTION Registry–GWTG (Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With the Guidelines). *Circ Cardiovas Qual Outcomes*. 2017;10:e003443. doi: 10.1161/CIRCOUTCOMES.116.003443
7. Safdar B, Spatz ES, Dreyer RP, Beltrame JF, Lichtman JH, Spertus JA, Reynolds HR, Geda M, Bueno H, Dziura JD, et al. Presentation, clinical profile, and prognosis of young patients with myocardial infarction with nonobstructive coronary arteries (MINOCA): results from the VIRGO study. *J Am Heart Assoc*. 2018;7:e009174. doi: 10.1161/JAHA.118.009174
8. Dreyer RP, Tavella R, Curtis JP, Wang Y, Pauspathy S, Messenger J, Rumsfeld JS, Maddox TM, Krumholz HM, Spertus JA, et al. Myocardial infarction with non-obstructive coronary arteries as compared with myocardial infarction and obstructive coronary disease: outcomes in a Medicare population. *Eur Heart J*. 2020;41:870–878. doi: 10.1093/eurheartj/ehz403
9. Choo EH, Chang K, Lee KY, Lee D, Kim JG, Ahn Y, Kim YJ, Chae SC, Cho MC, Kim CJ, et al. Prognosis and predictors of mortality in patients suffering myocardial infarction with non-obstructive coronary arteries. *J Am Heart Assoc*. 2019;8:e011990. doi: 10.1161/JAHA.119.011990
10. Bainey KR, Welsh RC, Alemayehu W, Westerhout CM, Traboulsi D, Anderson T, Brass N, Armstrong PW, Kaul P. Population-level incidence and outcomes of myocardial infarction with non-obstructive coronary arteries (MINOCA): insights from the Alberta contemporary acute coronary syndrome patients invasive treatment strategies (COAPT) study. *Int J Cardiol*. 2018;264:12–17. doi: 10.1016/j.ijcard.2018.04.004
11. Cui Y, Hao K, Takahashi J, Miyata S, Shindo T, Nishimiya K, Kikuchi Y, Tsuburaya R, Matsumoto Y, Ito K, et al. Age-specific trends in the incidence and in-hospital mortality of acute myocardial infarction over 30years in Japan—report from the Miyagi AMI registry study—. *Circ J*. 2017;81:520–528. doi: 10.1253/circj.CJ-16-0799
12. Sato K, Takahashi J, Hao K, Miyata S, Suda A, Shindo T, Ikeda S, Kikuchi Y, Shiroto T, Matsumoto Y, et al. Temporal trends in the prevalence and outcomes of geriatric patients with acute myocardial infarction in Japan-a report from the Miyagi AMI registry study. *J Cardiol*. 2020;75:465–472. doi: 10.1016/j.jjcc.2019.10.006
13. United Nations Department of Economic and Social Affairs Population Division. *World Population Prospects 2022: Summary of Results*. UN DESA/POP/2022/TR/NO. 3. Accessed November 20, 2024. https://www.un.org/development/desa/pd/sites/www.un.org.development.desa.pd/files/wpp2022_summary_of_results.pdf.
14. Palomaki P, Miettinen H, Mustaniemi H, Lehto S, Pyorala K, Mahonen M, Tuomilehto J. Diagnosis of acute myocardial infarction by MONICA and FINMONICA diagnostic criteria in comparison with hospital discharge diagnosis. *J Clin Epidemiol*. 1994;47:659–666. doi: 10.1016/0895-4356(94)90213-5
15. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined—consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol*. 2000;36:959–969. doi: 10.1016/S0735-1097(00)00804-4
16. Daida H, Miyauchi K, Ogawa H, Yokoi H, Matsumoto M, Kitakaze M, Kimura T, Matsubara T, Ikari Y, Kimura K, et al. Management and two-year long-term clinical outcome of acute coronary syndrome in Japan: prevention of atherothrombotic incidents following ischemic coronary attack (PACIFIC) registry. *Circ J*. 2013;77:934–943. doi: 10.1253/circj.CJ-13-0174
17. Ishihara M, Fujino M, Ogawa H, Yasuda S, Noguchi T, Nakao K, Ozaki Y, Kimura K, Suwa S, Fujimoto K, et al. Clinical presentation, management and outcome of Japanese patients with acute myocardial infarction in the troponin era—Japanese registry of acute myocardial infarction diagnosed by universal definition (J-MINUET). *Circ J*. 2015;79:1255–1262. doi: 10.1253/circj.CJ-15-0217
18. Lindahl B, Baron T, Erlinge D, Hadziosmanovic N, Nordenskjold A, Gard A, Jernberg T. Medical therapy for secondary prevention and long-term outcome in patients with myocardial infarction with nonobstructive coronary artery disease. *Circulation*. 2017;135:1481–1489. doi: 10.1161/CIRCULATIONAHA.116.026336
19. Kojima S, Nishihira K, Takegami M, Nakao YM, Honda S, Takahashi J, Takayama M, Shimokawa H, Sumiyoshi T, Ogawa H, et al. Nationwide real-world database of 20,462 patients enrolled in the Japanese acute myocardial infarction registry (JAMIR): impact of emergency coronary intervention in a super-aging population. *Int J Cardiol Heart Vasc*. 2018;20:1–6. doi: 10.1016/j.ijcha.2018.06.003
20. Ismayl M, Machanahalli Balakrishna A, Walters RW, Pajjuru VS, Goldsweig AM, Aboeata A. In-hospital mortality and readmission after ST-elevation myocardial infarction in nonagenarians: a nationwide analysis from the United States. *Catheter Cardiovasc Interv*. 2022;100:5–16. doi: 10.1002/ccd.30227
21. Kvakkestad KM, Abdelnoor M, Claussen PA, Eritsland J, Fossum E, Halvorsen S. Long-term survival in octogenarians and older patients with ST-elevation myocardial infarction in the era of primary angioplasty: a prospective cohort study. *Eur Heart J Acute Cardiovasc Care*. 2016;5:243–252. doi: 10.1177/2048872615574706
22. Lee KH, Ahn Y, Kim SS, Rhew SH, Jeong YW, Jang SY, Cho JY, Jeong HC, Park KH, Yoon NS, et al. Characteristics, in-hospital and long-term clinical outcomes of nonagenarian compared with octogenarian acute myocardial infarction patients. *J Korean Med Sci*. 2014;29:527–535. doi: 10.3346/jkms.2014.29.4.527
23. Zaman MJ, Stirling S, Shepstone L, Ryding A, Flather M, Bachmann M, Myint PK. The association between older age and receipt of care and outcomes in patients with acute coronary syndromes: a cohort study of the myocardial Ischaemia National Audit Project (MINAP). *Eur Heart J*. 2014;35:1551–1558. doi: 10.1093/eurheartj/ehu039
24. Agewall S, Beltrame JF, Reynolds HR, Niessner A, Rosano G, Caforio AL, de Caterina R, Zimarino M, Roffi M, Kjeldsen K, et al. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. *Eur Heart J*. 2017;38:143–153.
25. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, et al. Third universal definition of myocardial infarction. *Circulation*. 2012;126:2020–2035. doi: 10.1161/CIR.0b013e31826e1058
26. Pasupathy S, Tavella R, Beltrame JF. Myocardial infarction with nonobstructive coronary arteries (MINOCA): the past, present, and future management. *Circulation*. 2017;135:1490–1493. doi: 10.1161/CIRCULATIONAHA.117.027666
27. Tamis-Holland JE, Jneid H, Reynolds HR, Agewall S, Brilakis ES, Brown TM, Lerman A, Cushman M, Kumbhani DJ, Arslanian-Engoren C, et al. Contemporary diagnosis and management of patients with myocardial infarction in the absence of obstructive coronary artery disease: a scientific statement from the American Heart Association. *Circulation*. 2019;139:e891–e908. doi: 10.1161/CIR.0000000000000670
28. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD. Fourth universal definition of myocardial infarction (2018). *Circulation*. 2018;138:e618–e651. doi: 10.1161/CIR.0000000000000617
29. Daniel M, Agewall S, Caidahl K, Collste O, Ekenback C, Frick M, Henareh L, Jernberg T, Malmqvist K, et al. Effect of myocardial infarction with nonobstructive coronary arteries on physical capacity and quality-of-life. *Am J Cardiol*. 2017;120:341–346. doi: 10.1016/j.amjcard.2017.05.001
30. Barr PR, Harrison W, Smyth D, Flynn C, Lee M, Kerr AJ. Myocardial infarction without obstructive coronary artery disease is not a benign

condition (ANZACS-QI 10). *Heart Lung Circ*. 2018;27:165–174. doi: 10.1016/j.hlc.2017.02.023
31. Nishihira K, Honda S, Takegami M, Kojima S, Asaumi Y, Suzuki M, Kosuge M, Takahashi J, Sakata Y, Takayama M, et al. Impact of bleeding on mortality in patients with acute myocardial infarction complicated by cardiogenic shock. *Eur Heart J Acute Cardiovasc Care*. 2021;10:388–396. doi: 10.1093/ehjacc/zuab014
32. Kolte D, Khera S, Aronow WS, Mujib M, Palaniswamy C, Sule S, Jain D, Gotsis W, Ahmed A, Frishman WH, et al. Trends in incidence, management, and outcomes of cardiogenic shock complicating ST-elevation myocardial infarction in the United States. *J Am Heart Assoc*. 2014;3:e000590. doi: 10.1161/JAHA.113.000590
33. Sato K, Takahashi J, Odaka Y, Suda A, Sueda S, Teragawa H, Ishii K, Kiyooka T, Hirayama A, Sumiyoshi T, et al. Clinical characteristics and long-term prognosis of contemporary patients with vasospastic angina: ethnic differences detected in an international comparative study. *Int J Cardiol*. 2019;291:13–18. doi: 10.1016/j.ijcard.2019.02.038
34. Ishii M, Kaikita K, Sakamoto K, Seki T, Kawakami K, Nakai M, Sumita Y, Nishimura K, Miyamoto Y, Noguchi T, et al. Characteristics and in-hospital mortality of patients with myocardial infarction in the absence of obstructive coronary artery disease in super-aging society. *Int J Cardiol*. 2020;301:108–113. doi: 10.1016/j.ijcard.2019.09.037
35. Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, White HD, Nordlander R, Maggioni A, Dickstein K, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med*. 2004;351:1285–1295. doi: 10.1056/NEJMoa041365
36. Wong SC, Sanborn T, Sleeper LA, Webb JG, Pilchik R, Hart D, Mejnartowicz S, Antonelli TA, Lange R, French JK, et al. Angiographic findings and clinical correlates in patients with cardiogenic shock complicating acute myocardial infarction: a report from the SHOCK trial registry. *J Am Coll Cardiol* SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK? 2000;36:1077–1083. doi: 10.1016/S0735-1097(00)00873-1
37. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. *Hypertension*. 2003;42:1050–1065. doi: 10.1161/01.HYP.0000102971.85504.7c
38. Yasuda S, Shimokawa H. Acute myocardial infarction: the enduring challenge for cardiac protection and survival. *Circ J*. 2009;73:2000–2008. doi: 10.1253/circj.CJ-09-0655