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Pre-Hospital Delay and Outcomes in Myocardial Infarction With Nonobstructive Coronary Arteries

Seok Oh, MD[1], Kyung Hoon Cho, MD, PhD[1,2], Min Chul Kim, MD, PhD[1,2], Doo Sun Sim, MD, PhD[1,2], Young Joon Hong, MD, PhD[1,2], Ju Han Kim, MD, PhD[1,2], Youngkeun Ahn, MD, PhD, FACC, FSCAI[1,2], and Myung Ho Jeong, MD, PhD, FACC, FAHA, FESC, FSCAI, FAPSIC[1,2,3]

[1]Department of Cardiology, Chonnam National University Hospital, Gwangju, Korea
[2]Department of Cardiology, Chonnam National University Medical School, Gwangju, Korea
[3]Department of Cardiology, Gwangju Veterans Hospital, Gwangju, Korea

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Correspondence to
Myung Ho Jeong, MD, PhD, FACC, FAHA, FESC, FSCAI, FAPSIC
Department of Cardiology, Chonnam National University Hospital, Chonnam National University Medical School, 42, Jebong-ro, Dong-gu, Gwangju 61469, Korea
Email: myungho@chollian.net

ORCID iDs
Seok Oh
https://orcid.org/0000-0002-6193-2982
Kyung Hoon Cho
https://orcid.org/0000-0002-0377-6352
Min Chul Kim
https://orcid.org/0000-0001-6026-1702
Doo Sun Sim
https://orcid.org/0000-0003-4162-7902
Young Joon Hong
https://orcid.org/0000-0003-0192-8161
Ju Han Kim
https://orcid.org/0000-0002-3186-0770
Youngkeun Ahn
https://orcid.org/0000-0003-2022-9366

AUTHOR'S SUMMARY

Since real-world evidence on the relationship between delayed hospitalization and outcomes in myocardial infarction with nonobstructive coronary arteries (MINOCA) is lacking, we evaluated the clinical characteristics and mortality outcomes among patients with MINOCA, according to the symptom-to-door time. This is the first systematic comparative analysis investigating this relationship, showing that delayed hospitalization in patients with MINOCA is associated with high mortality over the next 2 years. Despite these selected patients do not require timely revascularization, multidisciplinary efforts are warranted to reduce the delay in hospitalization then improve their clinical outcomes.

ABSTRACT

Background and Objectives: Real-world evidence on the relationship between delayed hospitalization and outcomes in myocardial infarction with nonobstructive coronary arteries (MINOCA) is lacking. Hence, we aimed to evaluate the clinical characteristics of patients with MINOCA and the 2-year mortality outcomes in this patient population according to the symptom-to-door time (SDT).
Methods: Overall, 861 patients with MINOCA from 2 Korean nationwide observational registries (2011–2020) were included and categorized as early or late presenters. Late presentation was defined as SDT ≥12 hours in patients with ST-segment elevation myocardial infarction (STEMI) and SDT ≥24 hours in patients with non-STEMI. The primary outcome was 2-year all-cause mortality. Propensity score matching (PSM) and age-sex adjusted analysis were used to determine whether late presentation independently affected mortality. Multivariate logistic regression analysis was used to examine the independent factors correlated with late presentation.
Results: In unadjusted data, late presenters had a notably higher risk of 2-year all-cause mortality than early presenters (hazard ratio [HR], 2.44; 95% confidence interval [CI], 1.47–4.08). This trend persisted in age-sex adjusted analysis (adjusted HR, 2.29; 95% CI, 1.36–3.84) and PSM-adjusted analysis (adjusted HR, 2.18; 95% CI, 1.05–4.53). The positive independent factors for late presentation included female sex, no emergency medical service use and high creatinine level, whereas the negative independent factor was a dyslipidemia.

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Myung Ho Jeong
https://orcid.org/0000-0003-2424-810X

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Conflict of Interest
The authors have no financial conflicts of interest.

Data Sharing Statement
The data generated in this study is available from the corresponding author upon reasonable request.

Author Contributions
Conceptualization: Oh S; Data curation: Oh S; Formal analysis: Oh S; Investigation: Oh S; Methodology: Oh S; Resources: Oh S, Jeong MH; Supervision: Jeong MH; Writing - original draft: Oh S; Writing - review & editing: Cho KH, Kim MC, Sim DS, Hong YJ, Kim JH, Ahn Y, Jeong MH.

Conclusions: Late presentation is associated with higher mortality in patients with MINOCA. Multidisciplinary efforts are needed to reduce pre-hospital delay, thereby improving the clinical outcomes in these patients.

Keywords: Adverse effects; Cardiovascular disease; Myocardial infarction; Time-to-treatment; Treatment outcome

INTRODUCTION

Myocardial infarction with nonobstructive coronary arteries (MINOCA), a working diagnosis of acute myocardial infarction (AMI) with normal or minimally obstructive (<50% stenosis) coronary arteries on coronary angiography,[1)2)] accounts for approximately 5–15% of all AMI cases[3)] and encompasses a heterogeneous group of conditions with different etiologies.[2)] Therefore, MINOCA has become a research focus topic in cardiology.[4)] Although many patients with MINOCA do not require percutaneous coronary intervention (PCI), timely medical management is important because the clinical outcomes for patients with MINOCA are comparable with those for patients with type 1 AMI.[5)]

Time-to-presentation, often defined as the symptom-to-door time (SDT), is considered a predictor of poor AMI prognosis. Given that SDT indicates the time interval during which a patient's myocardial tissue is uncontrollably damaged,[6)] pre-hospital delay, manifested as prolonged SDT, has been shown to worsen the clinical outcomes of AMI.[7)8)] However, most related studies have been conducted in large cohorts, with the majority of patients having type 1 AMI, and not MINOCA. To date, the relationship between delayed hospitalization and outcomes in patients with MINOCA is controversial. Thus, the present study aimed to evaluate the characteristics of patients with MINOCA and investigate their 2-year mortality outcomes according to SDT.

METHODS

Ethical statement

This study was ratified by the Institutional Review Board (IRB) of Chonnam National University Hospital (IRB No. CNUH-2024-065). The requirement for informed consent was waived owing to the retrospective nature of the study.

Study design and data source

This study conducted a post-hoc analysis of the subgroup of patients with MINOCA included in 2 Korean nationwide AMI cohorts, namely the Korea Acute Myocardial Infarction Registry-National Institutes of Health (KAMIR-NIH) cohort (from November 1, 2011, to December 31, 2015) and the Korea Acute Myocardial Infarction Registry-V (KAMIR-V) cohort (from January 1, 2016, to June 30, 2020). The 2 cohorts involved the participation of 20 and 33 medical institutions capable of performing PCI and coronary artery bypass graft surgery, respectively. The protocols for these 2 registry studies were approved by the Ethics Committee or IRB of each participating center.[9)] All the data were derived from these 2 registries.

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Study population

We merged the 2 datasets to increase the statistical power of the study. From the pooled KAMIR-NIH/KAMIR-V database, 28,949 patients were initially screened. Patients who did not have AMI as a final diagnosis, had any significant obstructive coronary artery disease (CAD), had invalid SDT data, or underwent thrombolysis were excluded. Finally, 861 patients were included and categorized as early or late presenters according to the time of presentation (**Figure 1**).

Definition of myocardial infarction with nonobstructive coronary arteries

The diagnosis of AMI was based on the diagnostic criteria provided in current guidelines[10] and published studies.[1)9)] AMI was defined as myocardial injury evidenced by the elevation of cardiac biomarkers and at least one of the following: clinical symptoms suggestive of myocardial ischemia; abnormalities indicative of myocardial ischemia in 12-lead electrocardiography; loss of myocardial viability or regional wall motion abnormalities in cardiovascular imaging. Among AMI cases, ST-segment elevation myocardial infarction (STEMI) was defined as new-onset ST-segment elevation in ≥2 continuous leads with other key elements of AMI definition.[10] As mentioned above, MINOCA was defined as AMI without any significant obstructive CAD (≥50% diameter stenosis of any major epicardial coronary artery).

Definition of pre-hospital delay

Presentation time was defined based on SDT, which was the time interval from recent symptoms to hospital admission. The time of symptom onset was determined after interviewing the patient. Based on previous studies,[7)8)] late presentation was defined as an SDT ≥12 hours in patients with STEMI and ≥24 hours in patients with non-STEMI (NSTEMI).

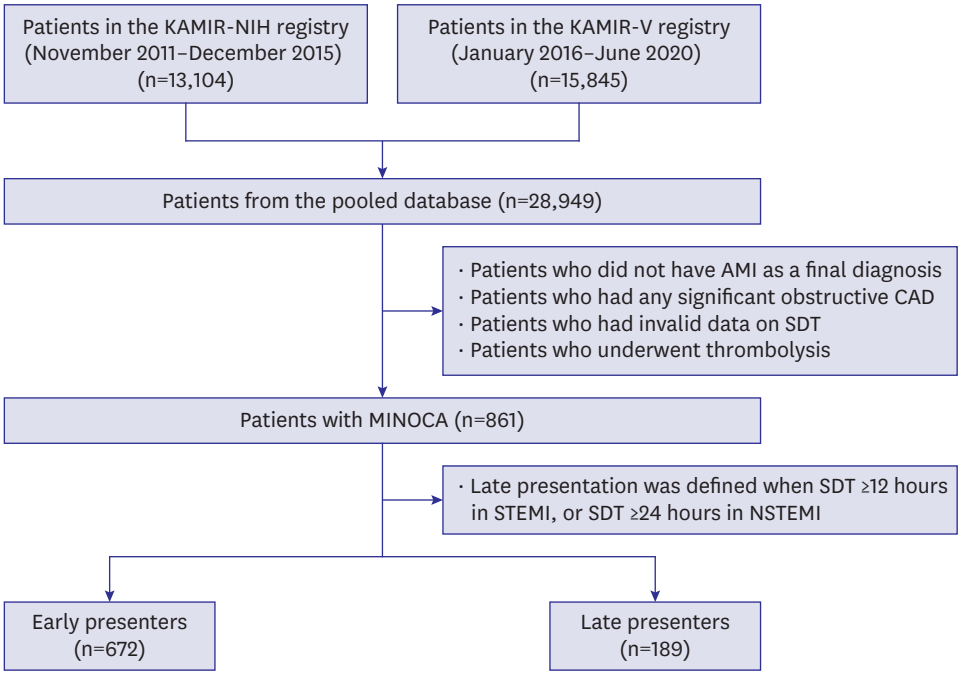

Figure 1. Study flowchart.
AMI = acute myocardial infarction; CAD = coronary artery disease; KAMIR-NIH = Korea Acute Myocardial Infarction Registry-National Institutes of Health; KAMIR-V = Korea Acute Myocardial Infarction Registry-V; MINOCA = myocardial infarction without obstructive coronary arteries; NSTEMI = non-ST-segment elevation myocardial infarction; SDT = symptom-to-door time; STEMI = ST-segment elevation myocardial infarction.

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Clinical data assessment and baseline covariates

The clinicodemographic characteristics of patients were assessed. All collected covariates were defined using standardized definitions provided by the committee boards of the KAMIR-NIH and KAMIR-V registries.[5)9)]

Study outcomes and follow-up

Differences in outcomes between the early and late presenters were assessed. The primary outcome was all-cause death, defined as a composite of cardiac and non-cardiac deaths. The exploratory outcomes included major adverse cardiac events (MACEs), cardiac death, noncardiac death, nonfatal myocardial infarction (NFMI), revascularization, and admission for angina. MACEs were defined as a composite of cardiac death, NFMI, revascularization, and admission for angina. Revascularization was defined as any PCI or coronary artery bypass graft surgery. Admission for angina referred to first-time readmission attributable to myocardial ischemia-related clinical symptoms as the chief complaint.

All patients were recommended to complete a clinical follow-up duration of approximately 24 months. Follow-up was censored on the date of the study outcome, date of death, or the end of the study period.

Statistical methods

Patients were categorized into early and late presenters based on SDT, and the differences in clinical outcomes between the 2 groups were analyzed. Continuous variables were expressed as mean±standard deviation and analyzed using Student's t-test and analysis of variance. Meanwhile, categorical variables were presented as numbers and percentages and analyzed using Pearson's chi-squared test, Fisher's exact test, or the Mantel–Haenszel linear-by-linear association.

Given that disparities in background covariates could affect study outcomes, sensitivity analyses, including both propensity score matching (PSM) and age-sex adjusted analysis, were conducted to reduce the effects of treatment selection bias or confounders and then balance covariates, which is summarized in **Supplementary Data 1**. The cumulative incidence of each study outcome was illustrated as time-to-event survival curves using the Kaplan–Meier method and compared between groups using the log-rank test.

Furthermore, a multivariate logistic regression analysis was conducted to verify the independent factors correlated with delayed hospitalization in patients with MINOCA, which is summarized in **Supplementary Data 2**.

Data manipulation and analyses were performed using STATA version 15.0 (StataCorp., College Station, TX, USA) and SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Statistical significance was defined as $p<0.05$.

RESULTS

Baseline patient characteristics

Among the 861 patients included in the study, 672 (78.0%) and 189 (22.0%) were early and late presenters, respectively. **Table 1** lists the baseline characteristics of the early and late presenters. Early presenters (n=672) exhibited shorter SDT and significantly higher levels of creatine kinase-MB (CK-MB) than late presenters (n=189). Late presenters were older and

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Table 1. Baseline characteristics

Characteristics	Before covariate adjustment				After covariate adjustment (PSM)			
	Early presenters (n=672)	Late presenters (n=189)	p value	SMD	Early presenters (n=330)	Late presenters (n=110)	p value	SMD
SDT (hour)	0.22±0.21	21.22±144.09	**<0.001**		0.21±0.20	23.39±174.07	**<0.001**	
CK-MB (mg/dL)	30.34±64.45	18.71±42.38	**<0.001**		32.24±63.57	15.66±24.91	**0.001**	
Troponin-I (mg/dL)	10.21±26.04	9.81±59.04	**<0.001**		9.66±21.10	4.38±8.95	**0.001**	
Age	62.78±12.68	66.80±12.77	**<0.001**		63.25±12.90	63.92±10.86	0.594	
Age ≥75 years	131 (19.5)	56 (29.6)	**0.003**	0.193	70 (21.2)	20 (18.2)	0.495	−0.051
Male sex	428 (63.7)	99 (52.4)	**0.005**	−0.352	200 (60.6)	63 (57.3)	0.537	0.016
Smoking history	318 (48.4)	71 (38.8)	**0.021**	−0.189	153 (46.4)	51 (46.4)	1.000	0.053
Use of EMS	108 (16.1)	12 (6.3)	**0.001**	−0.325	28 (8.5)	9 (8.2)	0.921	0.182
Killip class III–IV	53 (7.9)	16 (8.5)	0.800	0.128	22 (6.7)	7 (6.4)	0.912	0.101
BMI ≥25 kg/m^2	206 (34.6)	54 (34.0)	0.876	−0.047	108 (32.7)	40 (36.4)	0.485	−0.052
Hypertension	343 (51.0)	106 (56.1)	0.220	0.122	175 (53.0)	61 (55.5)	0.659	0.010
Diabetes mellitus	152 (22.6)	55 (29.1)	0.065	0.161	77 (23.3)	25 (22.7)	0.896	0.094
Dyslipidemia	84 (12.5)	13 (6.9)	**0.031**	−0.168	27 (8.2)	8 (7.3)	0.760	−0.081
Prior CAD	195 (29.0)	48 (25.4)	0.329	−0.031	83 (25.1)	30 (27.3)	0.659	0.077
Prior CVA	35 (5.2)	16 (8.5)	0.096	0.075	18 (5.4)	6 (5.4)	1.000	−0.217
Family history of CAD	33 (5.0)	2 (1.1)	**0.012**	−0.279	5 (1.5)	2 (1.8)	1.000	0.000
eGFR <60 mL/min/1.73 m^2	102 (15.2)	53 (28.0)	**<0.001**	0.317	54 (16.4)	15 (13.6)	0.496	0.066
LVEF <40%	49 (7.9)	17 (9.6)	0.480	0.022	24 (7.3)	7 (6.4)	0.747	0.095
STEMI as a final diagnosis	80 (11.9)	25 (13.2)	0.623	0.029	42 (12.7)	16 (14.5)	0.625	0.095
In-hospital death	17 (2.5)	3 (1.6)	0.590		3 (0.9)	0 (0.0)	0.577	
Aspirin	620 (92.3)	181 (95.8)	0.095		309 (93.6)	108 (98.2)	0.082	
P2Y12 inhibitors	606 (90.2)	177 (93.7)	0.142		303 (91.8)	106 (96.4)	0.133	
Beta-blockers	242 (36.0)	89 (47.1)	**0.006**		125 (37.9)	53 (48.2)	0.057	
RAAS inhibitors	334 (49.7)	99 (52.4)	0.515		184 (55.8)	58 (52.7)	0.580	
Statins	511 (76.0)	148 (78.3)	0.516		261 (79.1)	92 (83.6)	0.300	
Calcium channel blockers	338 (50.3)	76 (40.2)	**0.014**		175 (53.0)	52 (47.3)	0.295	

Values are presented as number (%) for categorical values and as means±standard deviations for continuous values.
Statistically significant data are in boldface.
BMI = body mass index; CAD = coronary artery disease; CK-MB = creatine kinase-MB; CVA = cerebrovascular accident; eGFR = estimated glomerular filtration; EMS = emergency medical service; LVEF = left ventricular ejection fraction; PSM = propensity score matching; RAAS = renin-angiotensin-aldosterone system; SDT = symptom-to-door time; SMD = standard mean difference; STEMI = ST-segment elevation myocardial infarction.

less likely to use emergency medical service (EMS) and had a lower proportion of males and smokers than early presenters. Late presenters also had a lower prevalence of dyslipidemia and family history of CAD but had worse kidney function with a higher proportion of patients with estimated glomerular filtration (eGFR) <60 mL/min/1.73 m^2. Among post-discharge medications, beta-blocker use was high in late presenters, whereas calcium channel blocker (CCBs) use was high in early presenters. Successful balancing of background covariates between the 2 groups was achieved after PSM (**Supplementary Figure 1**).

Study outcomes

Among the 861 patients, 20 died during the index hospitalization, 33 were lost to follow up, then a total of 808 patients were successfully managed, discharged, followed up, and analyzed for clinical outcomes. The incidence of all study outcomes, including all-cause death, is summarized in **Table 2**. The median follow-up period was 727 days. The 2-year all-cause mortality rate was 7.7% in the overall population, 13.6% in late presenters, and 6.0% in early presenters. Compared with early presenters, late presenters had a significantly higher risk of all-cause death in all 3 different analyses. In the unadjusted analysis, the risks of cardiac and non-cardiac death increased by 136% and 150%, respectively, in late presenters. In the age-sex adjusted analysis, the risk of non-cardiac death increased by 141% in late presenters. In the PSM-adjusted analysis, the risk of cardiac death increased by 187% in late presenters. Compared with early presenters, late presenters had a significantly higher risk

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Table 2. HRs and 95% CI showing associations between late presentation and the incidence of study outcomes with respect to unadjusted, age-sex adjusted, PSM-adjusted, IPTW-adjusted, and full-adjusted models

Outcomes	Total participants (n=808)	Events		Unadjusted HR (95% CI)	Age-sex adjusted HR (95% CI)	PSM-adjusted HR (95% CI)
		Late presenters	Early presenters			
All-cause death	62 (7.7)	24 (13.6)	38 (6.0)	2.44 (1.47–4.08)	2.29 (1.36–3.84)	2.18 (1.05–4.53)
Cardiac death	26 (3.2)	10 (5.7)	16 (2.5)	2.36 (1.07–5.21)	2.13 (0.96–4.74)	2.87 (1.04–7.92)
Non-cardiac death	36 (4.5)	14 (7.9)	22 (3.5)	2.50 (1.28–4.90)	2.41 (1.22–4.74)	1.63 (0.56–4.78)
NFMI	27 (3.3)	10 (5.7)	17 (2.7)	2.24 (1.02–4.89)	2.38 (1.09–5.22)	4.10 (1.10–15.27)
Any revascularization	14 (1.7)	5 (2.8)	9 (1.4)	2.07 (0.69–6.18)	2.39 (0.80–7.15)	4.26 (0.95–19.03)
Admission for angina	28 (3.5)	3 (1.7)	25 (4.0)	0.45 (0.13–1.48)	0.35 (0.11–1.18)	0.26 (0.03–2.02)
MACE	76 (9.4)	21 (11.9)	55 (8.7)	1.43 (0.86–2.36)	1.36 (0.82–2.26)	1.69 (0.84–3.39)

Values are presented as number (%).
CI = confidence interval; HR = hazard ratio; IPTW = inverse probability of treatment weighting; MACE = major adverse cardiac event; NFMI = non-fatal myocardial infarction; PSM = propensity score matching.

of NFMI in all 3 different analyses. The incidence of other study outcomes was comparable between the 2 groups.

The cumulative incidences of the study outcomes are shown in **Figure 2**. In the unadjusted analysis, the incidences of all-cause death and cardiac and non-cardiac deaths were significantly higher in late presenters than in early presenters. In the PSM-adjusted

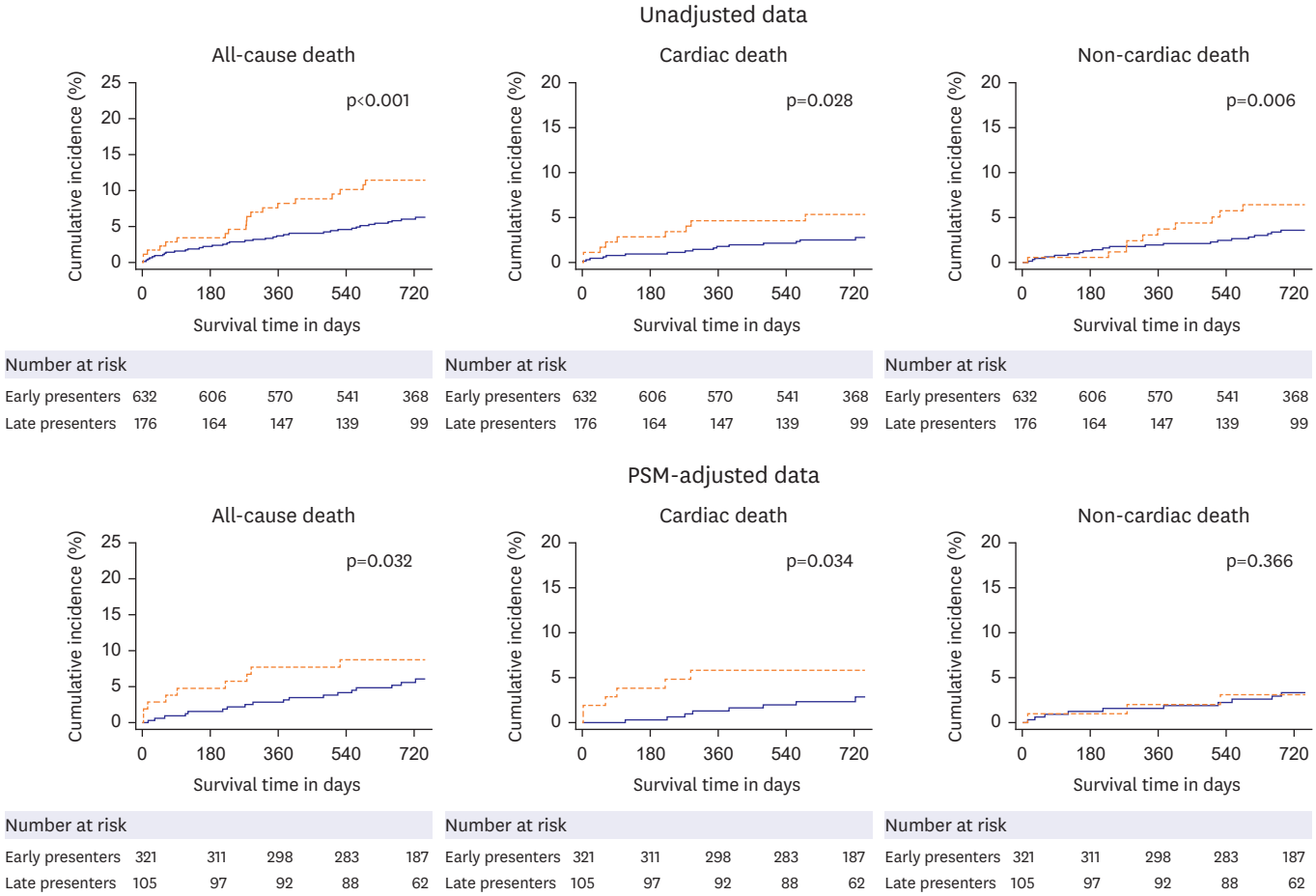

Figure 2. Kaplan–Meier survival curves in unadjusted and PSM-adjusted analyses. Late presenters had a higher incidence rate of all-cause death in unadjusted, sex-age population-adjusted, and PSM-adjusted analyses.
PSM = propensity score matching.

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analysis, the incidences of all-cause death and cardiac death were significantly higher in late presenters than in their counterparts.

Independent factors associated with late presentation

Multivariable logistic regression analysis of the correlates of late presentation showed that female sex (adjusted odds ratio [aOR], 1.79; 95% confidence interval [CI], 1.06–3.01), no use of EMS (aOR, 2.67; 95% CI, 1.29–5.55) and eGFR <60 mL/min/1.73 m^2 (aOR, 1.85; 95% CI, 1.11–3.08) were positively related to late presentation, whereas dyslipidemia (aOR, 0.48; 95% CI, 0.24–0.99) was negatively associated to late presentation (**Table 3**).

Subgroup-specific analysis of all-cause death

The results of all-cause death analysis in pre-specified subgroups demonstrated that the trends in treatment effect for the primary endpoint were broadly consistent across the subgroups of interest, except for left ventricular ejection fraction (LVEF) (**Table 4**). In other words, there was a notable interaction between the comparison groups and LVEF. Among patients with LVEF ≥40%, the incidence of all-cause death was significantly higher in late presenters than early presenters (4.2% vs. 13.5%; adjusted HR, 3.45; 95% CI, 1.90–6.29). Among patients with LVEF <40%, however, there were no significant differences between early and late presenters.

DISCUSSION

To date, the relationship between delayed hospitalization and outcomes in patients with MINOCA has not been established. In 2 large-scale, nationwide, Korean AMI observational cohorts, late presentation was found to be associated with poorer mortality outcomes in patients with MINOCA. These trends persisted consistently in other statistical models, including the multivariable Cox model and PSM-adjusted analysis. Female sex, no use of EMS, worse kidney function and dyslipidemia were independently associated with late presentation in patients with MINOCA.

Table 3. Independent factors for late presentation

Characteristics	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Demographics				
Age ≥75 years	1.74 (1.21–2.51)	0.003	1.43 (0.89–2.27)	0.137
Female sex	1.59 (1.15–2.21)	0.005	1.79 (1.06–3.01)	**0.029**
Smoking history	0.68 (0.48–0.94)	0.022	1.13 (0.67–1.91)	0.637
No use of EMS	2.82 (1.52–5.25)	0.001	2.67 (1.29–5.55)	**0.008**
Killip functional class III–IV	1.08 (0.60–1.93)	0.800	1.03 (0.52–2.07)	0.925
BMI ≥25 kg/m^2	0.97 (0.67–1.40)	0.876	0.96 (0.64–1.45)	0.856
Past medical history				
Hypertension	1.22 (0.89–1.69)	0.221	1.03 (0.69–1.54)	0.886
Diabetes mellitus	1.40 (0.98–2.02)	0.066	1.28 (0.81–2.04)	0.288
Dyslipidemia	0.52 (0.28–0.95)	0.033	0.48 (0.24–0.99)	**0.048**
Prior CAD	0.83 (0.58–1.20)	0.329	0.87 (0.56–1.35)	0.522
Prior CVA	1.68 (0.91–3.10)	0.099	1.18 (0.56–2.52)	0.660
Family history of CAD	0.21 (0.05–0.86)	0.031	0.36 (0.08–1.56)	0.170
eGFR <60 mL/min/1.73 m^2	2.17 (1.48–3.17)	<0.001	1.85 (1.11–3.08)	**0.018**
LVEF <40%	1.23 (0.69–2.20)	0.481	0.75 (0.36–1.56)	0.447
STEMI as a final diagnosis	1.13 (0.70–1.83)	0.624	1.49 (0.85–2.62)	0.164

Statistically significant data are in boldface.
BMI = body mass index; CAD = coronary artery disease; CI = confidence interval; CVA = cerebrovascular accident; eGFR = estimated glomerular filtration rate; EMS = emergency medical service; LVEF = left ventricular ejection fraction; OR = odds ratio; STEMI = ST-segment elevation myocardial infarction.

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Table 4. Exploratory subgroup analysis comparing HRs for all-cause death according to the time of presentation

Characteristics	Number of participants with an event		Adjusted HR (95% CI)	Interaction p value
	Early presenters	Late presenters		
Total	38/632 (6.0)	24/176 (13.6)		
Age (years)				0.432
≥75	12/121 (9.9)	7/47 (14.9)	1.74 (0.68–4.45)	
<75	26/511 (5.1)	17/129 (13.2)	2.72 (1.48–5.02)	
Sex				0.666
Male	20/401 (5.0)	11/91 (12.1)	2.62 (1.26–5.48)	
Female	18/231 (7.8)	13/85 (15.3)	2.09 (1.02–4.28)	
Killip class				0.704
III–IV	6/39 (15.4)	4/15 (26.7)	1.89 (0.53–6.75)	
I–II	32/592 (5.4)	20/161 (12.4)	2.47 (1.41–4.33)	
BMI (kg/m^2)				0.639
≥25	7/193 (3.6)	5/51 (9.8)	2.97 (0.94–9.37)	
<25	28/371 (7.5)	15/97 (15.5)	2.16 (1.15–4.06)	
Hypertension				0.653
Yes	21/324 (6.5)	16/101 (15.8)	2.64 (1.38–5.06)	
No	17/308 (5.5)	8/75 (10.7)	2.07 (0.89–4.80)	
Diabetes mellitus				0.988
Yes	17/137 (12.4)	13/51 (25.5)	2.24 (1.08–4.61)	
No	21/495 (4.2)	11/125 (8.8)	2.22 (1.07–4.60)	
Dyslipidemia				0.71
Yes	4/80 (5.0)	1/13 (7.7)	1.64 (0.18–14.68)	
No	34/552 (6.2)	23/163 (14.1)	2.48 (1.46–4.21)	
Prior CAD				0.208
Yes	11/186 (5.9)	10/46 (21.7)	3.88 (1.64–9.18)	
No	27/446 (6.0)	14/130 (10.8)	1.93 (1.01–3.70)	
Prior CVA				0.946
Yes	1/32 (3.1)	1/14 (7.1)	2.71 (0.17–43.37)	
No	37/598 (6.2)	23/162 (14.2)	2.46 (1.46–4.13)	
eGFR (mL/min/1.73 m^2)				0.644
<60	16/89 (18.0)	14/48 (29.2)	1.68 (0.82–3.45)	
≥60	21/540 (3.9)	10/128 (7.8)	2.15 (1.01–4.57)	
LVEF (%)				**0.006**
<40	9/41 (21.9)	1/16 (6.2)	0.31 (0.04–2.48)	
≥40	23/545 (4.2)	20/148 (13.5)	3.45 (1.90–6.29)	
Final diagnosis				0.734
STEMI	5/67 (7.5)	3/22 (13.6)	1.94 (0.46–8.12)	
NSTEMI	33/565 (5.8)	21/154 (13.6)	2.52 (1.46–4.36)	

Values are presented as number (%). All HRs are for late presenters as compared with early presenters. Multivariable Cox proportional-hazards model was used to estimated HRs. Statistically significant data are in boldface.
BMI = body mass index; CAD = coronary artery disease; CI = confidence interval; CVA = cerebrovascular accident; eGFR = estimated glomerular filtration rate; HR = hazard ratio; LVEF = left ventricular ejection fraction; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

Some notable findings regarding demographic characteristics were identified. Compared to late presenters, early presenters had exhibited significantly higher levels of CK-MB. At least, this observation aligns with the relatively short median time to detection of CK-MB, suggesting a reasonable association with early presentation. Late presenters were older, included more females, and used EMS less frequently. Female and older patients often do not recognize prodromal chest symptoms,[1)11)12)] and this may explain the later-recognized AMI with pre-hospital delay.[1)11)] Thus, the distributions of both age and sex in our study were predictable. In addition, considering that EMS use is beneficial for shortening SDT,[12)] the lower EMS use among late presenters seems to provide sufficient explanation for our findings. According to our further analysis (**Table 3**), no use of EMS was independently associated with late presentation in this population. Meanwhile, the proportion of smokers was lower in late presenters than in early presenters, consistent with previous evidence

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supporting a predominance of smoking in males.[13] These distributions were consistent with those of previous studies in the general AMI population.[1][14]

Regarding comorbidities, late presenters had a lower prevalence of dyslipidemia and family history of CAD than early presenters, and the rates in early presenters were comparable with those in the general AMI population.[1][15] Dyslipidemia promotes lipid accumulation and inflammation within the arterial wall, leading to foam cell formation.[16] Population-based cohort studies have shown that a family history of CAD is associated with increased carotid intima-media thickness.[15][17] Despite the relatively lower burden of coronary atherosclerosis in MINOCA,[18] these 2 predisposing factors may partly contribute to MINOCA progression and cause mild luminal narrowing of the coronary arteries. Given their contribution to atherosclerosis, the higher prevalence of these variables could explain the earlier onset of the symptoms and signs of myocardial ischemia. In particular, the presence of dyslipidemia seems to be independently associated with early hospitalization (**Table 3**). Considering that dyslipidemia is one of the well-established independent risk factors for CAD, including AMI, it is theoretically possible that these patients are well aware of their predisposing factors and thereby present to the hospital sooner following symptom development (**Table 3**). However, since evidence regarding the association between these variables and SDT is still lacking, further studies should be conducted to elucidate it.

Meanwhile, late presenters had a higher proportion of patients with eGFR <60 mL/min/1.73 m^2 than early presenters, indicating that the former had worse kidney function. A retrospective analysis showed that impaired kidney function was associated with painless AMI.[19] That is, patients with worse kidney function are more likely to develop late-onset AMI. This finding may align with our results that worse kidney function is independently correlated with late presentation in patients with MINOCA.

The importance of rapid reperfusion for AMI in the clinical setting is established based on the traditional belief that coronary artery thromboembolic obstruction results in irreversible myocardial damage in a time-dependent manner.[20] In an animal study, coronary occlusion contributed to the development of myocardial necrosis, which was complete approximately 6 hours after the onset of occlusion.[20] In the Gruppo Italiano per lo Studio della Streptochinasi nell' Infarto Miocardico trial, early reperfusion with streptokinase within the first hour of symptom onset reduced mortality by 50% among patients with AMI; however, this benefit was reduced to 26% if streptokinase was administered 3 h after symptom onset.[21] The time-dependent efficacy of reperfusion strategy has been further demonstrated in other clinical studies.[22]

Meanwhile, since primary PCI is more effective than thrombolysis for reducing MACEs in most patients, PCI has become the mainstay of treatment for AMI,[1] and its optimal timing has become a major focus of attention. Therefore, with the growing interest in SDT as an important determinant of ischemic time, there has been a surge in the number of published comparative studies on early versus late presentation of AMI.[7][8] Many clinical studies have evaluated the clinical benefits of timely treatment in early presenters with AMI (<12 hours of symptoms onset in STEMI and <24 hours of symptom onset in NSTEMI).[7][8] However, in most of these studies, most participants had type 1 AMI. To date, real-world data on the association between SDT and clinical outcomes following MINOCA are still lacking. Considering that most patients with MINOCA do not have obvious coronary obstruction, these patients generally do not require timely PCI, and the lack of scientific research in this field is predictable. However, MINOCA accounts for a sizable minority of all AMI cases,

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occurring in roughly 5–15% of patients.[3] Moreover, these patients tend to have more non-negligible adverse events than their counterparts.[5] Therefore, it is clinically necessary to examine the association in this population.

Although it is well established that ischemic time, such as SDT, is an important influencing factor for the clinical prognosis of patients with AMI,[7][8] a consensus regarding its clinical impact in patients with MINOCA is lacking. To the best of our knowledge, this is the first study to evaluate the mortality rate of early and late presenters in this population. Our study provides novel insights into this under-researched topic, suggesting that the late presenters of MINOCA have worse outcomes than the early presenters. Thus, our analysis provides insight into whether missing the "golden" treatment window is also crucial in these patients even though most of them do not require PCI. Moreover, our study demonstrates that the time of initiation of therapeutic medications in such patients may also lead to significantly different outcomes.

Additionally, we further analyzed patients with either STEMI or NSTEMI separately. Among patients with STEMI (**Supplementary Table 1**), all HRs for the primary outcome were numerically higher in late presenters than in early presenters in the 3 different analyses. However, all HRs had relatively large 95% CIs, thereby failing to demonstrate statistical significance. Moreover, the HRs with 95% CIs for some treatment estimates were not calculated. Among patients with NSTEMI (**Supplementary Table 2**), all HRs for the primary outcome were consistently higher in late presenters than in the 3 different analyses. Compared with the results in the overall population, those in the STEMI population were generally statistically attenuated. One possible explanation is the relatively small sample size of these datasets. Given that the CI tends to be large by default, and the treatment effect needs to be large enough to reach statistical significance in studies with small sample sizes, the assertive claim of non-significance would disregard the huge uncertainty in the effect estimate. Hence, further large-scale clinical studies are required to confirm clinical relevance in the future.

The mechanism whereby early presentation confers mortality benefits for patients with MINOCA remains unclear. In principle, early presenters are more likely to receive earlier initiation of therapeutic medications for AMI. Since renin-angiotensin-aldosterone system inhibitors limit myocardial necrosis and/or attenuate left ventricular remodeling, earlier administration improves clinical outcomes.[23] Previous data also support the benefits of early initiation of statins.[24] Given that these medications have long-term beneficial effects on outcomes in patients with MINOCA,[25] early presenters may receive early medications and thereby have a better clinical outcome, even though there is no benefit from timely reperfusion in this population. Meanwhile, SDT may not only reflect the time until medical treatment.[26][27] That is, SDT may also reflect the socioeconomic status, marital status, or other inequalities, which seem to independently affect the cardiovascular outcomes in patients with established CAD.[26][27] However, since these factors were not considered in our analysis, further investigations are warranted.

Interestingly, our further analysis of angiographic findings in study participants showed early presenters had higher proportions of both vasospasm in coronary reactivity testing and spontaneous vasospasm than late presenters (**Supplementary Table 3**). Based on these results, early presenters seem to include more patients with coronary vasospasm, one of the major causes of MINOCA. It may be theoretically supported by the well-known common

knowledge that coronary vasospasm-induced angina can appear at rest and particularly between night and early morning, and can be accompanied by low exercise tolerance, especially in the morning. Also, these results may explain why CCBs were more prescribed, but beta-blockers were less prescribed in early presenters. Considering that CCBs are among the first-line therapeutic drugs, and beta-blockers are generally not prescribed in patients with coronary vasospasm, our "real-world" prescription patterns appear sufficiently accountable. Of course, these results may not fully account for different outcomes between the groups, given that mortality risk of MINOCA with coronary vasospasm did not differ from that of MINOCA without coronary vasospasm.[5] Despite our further analysis still does not fully explain the different other etiologies of MINOCA, however, these results are expected to be valuable in further understanding of MINOCA in the context of coronary vasospasm.

Meanwhile, only one association was observed between the time of presentation and LVEF status with respect to the primary endpoint. The time of presentation appeared to have no effect on the clinical outcomes among patients with LVEF <40%, whereas patients with LVEF ≥40% benefited from an early hospital visit, a finding that we found intriguing. According to a meta-analysis on comparative studies of patients with MINOCA and myocardial infarction with obstructive coronary arteries, reduced LVEF is one of the significant predictors of long-term prognosis in patients with MINOCA.[28] Moreover, since pharmacological agents such as beta-blockers and renin-angiotensin-aldosterone system inhibitors are well-established treatments for patients with reduced LVEF,[29][30] patients with LVEF <40% in this clinical context could potentially benefit from receiving such medications and other factors rather than from having a reduced SDT. Therefore, in our study, the clinical outcomes in the LVEF <40% subgroup might have been influenced by factors other than the time of presentation. Even though interesting, however, this association should be interpreted with caution, given the relatively small number of subjects.

Although the results of the present study offer novel insights into the clinical impact of pre-hospital delay in patients with MINOCA, it has several key limitations. First, despite our efforts to adjust for covariates using PSM, the potential for selection bias cannot be ruled out because of the probability of residual or immeasurable confounders or missing data. Especially, since the present study did not consider some immeasurable confounders such as cognitive function, access to healthcare services, health concerns or health behaviors, further evaluation of the relationship between these factors and SDT is needed. Second, in the present study, the definition of MINOCA was solely based on the absence of significant stenosis in the epicardial coronary artery. Given that the patients included in our study were enrolled in 2 registries between 2011 and 2020, MINOCA was not diagnosed at the time of referral during index hospitalization, but retrospectively on the basis of the available registry data. The retrospective identification of MINOCA based on registry data without prospective diagnostic confirmation could lead to misclassification. Third, data on several etiological factors that may influence clinical results were lacking. Owing to lack of detailed information on the imaging or functional assessment of coronary arteries, it is plausible that patients with other MINOCA-mimicking non-ischemic diseases, such as myocarditis or Takotsubo syndrome, might have been erroneously included in the study population, potentially skewing results. Therefore, we could not further investigate the different possible etiologies of MINOCA, a highly heterogenous disease constellation, such as coronary artery spasm, spontaneous coronary artery dissection, plaque disruption, or microvascular dysfunction.[5] Fourth, because this study was a post-hoc analysis of 2 Korean AMI cohorts, it did not take into account racial heterogeneity or international equivalents of this disease entity. Thus, the

results may not sufficiently reflect real-world outcomes in other countries. Fifth, we could not fully confirm a causal relationship between pre-hospital delay and study outcomes following MINOCA owing to the retrospective and non-randomized nature of this study. Owing to these methodologic limitations that may impact the scientific rigor of our study, the results should be interpreted with caution, and further clinical investigations are warranted.

In patients with MINOCA, late presentation is independently associated with female sex, no EMS use, worse kidney function and dyslipidemia. Importantly, late presentation is associated with higher mortality. Our real-world results emphasize the need for multidisciplinary efforts to improve the clinical outcomes of these patients.

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SUPPLEMENTARY MATERIALS

Supplementary Data 1
Detailed information of the method of propensity score matching and age-sex adjusted model

Supplementary Data 2
Detailed information of the multivariate logistic regression analysis for independent factors correlated with delayed hospitalization in patients with MINOCA

Supplementary Table 1
HRs and 95% CI showing associations between late presentation and incidence of study outcomes with respect to unadjusted, age-sex adjusted, PSM-adjusted models in participants with STEMI

Supplementary Table 2
HRs and 95% CI showing associations between late presentation and incidence of study outcomes with respect to unadjusted, age-sex adjusted, PSM-adjusted models in participants with NSTEMI

Supplementary Table 3
Angiographic findings in study participants

Supplementary Figure 1
Distributions of standardized mean differences before and after PSM.

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