Advance Publication

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ORIGINAL ARTICLE

Clinical Characteristics and Outcomes of Patients Presenting With Acute Myocardial Infarction Without Cardiogenic Shock

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Background: Most patients with acute myocardial infarction (AMI) present in the emergency department in a hemodynamically stable condition (i.e., non-cardiogenic shock) (AMI-NCS). However, few studies specifically focused on the clinical characteristics and outcomes of AMI-NCS patients. Temporal trends in clinical characteristics, in-hospital occurrence of in-hospital adverse outcomes, and the effect of primary percutaneous coronary intervention (PPCI) were examined.

Methods and Results: Between April 2012 and March 2018, 176,275 AMI-NCS patients (67.7% of the total AMI population; 25.4% female; mean age 68.6±13.1 years) were identified in a nationwide Japanese administrative database. During the 6-year study period, AMI-NCS patients have been getting older and had an increasing burden of comorbidities. The rates of 30-day all-cause mortality and in-hospital complications were 2.6% and 30.5%, respectively. Thirty-day all-cause mortality did not change significantly over time, whereas in-hospital complications, especially major non-cardiac events, increased progressively. On multivariable analyses, higher age, higher Killip class, atrial fibrillation, chronic renal failure, and malignancy were independently associated with both increased 30-day mortality and in-hospital complications. PPCI was independently associated with lower mortality and in-hospital complications.

Conclusions: The clinical background of AMI-NCS patients has been becoming more complex with increasing age and the burden of comorbidities, with increased in-hospital complications. More active and appropriate application of PPCI may further decrease adverse events and improve survival of AMI-NCS patients.

Key Words: Acute myocardial infarction; Comorbidities; In-hospital adverse outcome; Non-cardiogenic shock; Primary percutaneous coronary intervention

The majority of patients with acute myocardial infarction (AMI) are admitted to hospitals in a hemodynamically stable condition (i.e., without cardiogenic shock [CS]). Such patients with non-cardiogenic shock AMI (AMI-NCS) have relatively lower mortality than patients with AMI complicated by cardiogenic shock (AMI-CS).[1–3] However, AMI-NCS remains a potentially life-threatening condition because hemodynamic deterioration can occur during the hospital course. Cardiac and non-cardiac adverse events, if non-fatal, can also occur. These adverse outcomes can impair patient functional capacity and quality of life. Of note, the population is continuously aging worldwide; therefore, an increasing number of elderly patients with multiple comorbidities are expected to present with AMI, which may worsen clinical outcomes even in patients with

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Table 1. Trends in Baseline Characteristics of AMI-NCS Patients

	Total	2012	2013	2014
Number of patients	176,275	24,057	25,672	28,432
Female, n (%)	44,687 (25.4)	6,130 (25.5)	6,535 (25.5)	7,295 (25.7)
Age, years, mean±SD	68.6±13.1	68.1±13.0	68.3±13.1	68.4±13.1
Age category, years, n (%)				
<60	42,365 (24.0)	5,916 (24.6)	6,184 (24.1)	6,890 (24.3)
60–70	46,940 (26.6)	6,639 (27.6)	6,953 (27.1)	7,485 (26.3)
70–80	47,441 (26.9)	6,463 (26.9)	6,947 (27.1)	7,831 (27.5)
80–90	33,102 (18.8)	4,277 (17.8)	4,715 (18.4)	5,299 (18.6)
≥90	6,427 (3.6)	762 (3.2)	873 (3.4)	927 (3.3)
BMI, kg/m², mean±SD	23.8±4.6	23.7±4.1	23.7±4.4	23.8±4.9
Clinical characteristic, n (%)				
Ambulance transport	112,703 (64.0)	14,172 (58.9)	15,882 (61.9)	18,135 (63.8)
Full-score BI at admission	52,027 (29.5)	7,222 (30.0)	7,539 (29.4)	8,189 (28.8)
Killip class I	113,282 (64.3)	14,570 (60.6)	16,256 (63.3)	17,986 (63.3)
Killip class II	62,993 (35.7)	9,487 (39.4)	9,416 (36.7)	10,446 (36.7)
Previous IHD	8,087 (4.6)	1,082 (4.5)	1,001 (3.9)	1,278 (4.5)
Hypertension	119,942 (68.0)	16,308 (67.8)	17,253 (67.2)	19,185 (67.5)
Diabetes mellitus	52,966 (30.0)	7,011 (29.1)	7,648 (29.8)	8,380 (29.5)
Hyperlipidemia	115,862 (65.7)	15,018 (62.4)	16,023 (62.4)	18,500 (65.1)
Atrial fibrillation	4,246 (2.4)	463 (1.9)	527 (2.1)	625 (2.2)
Chronic pulmonary disease	4,704 (2.7)	574 (2.4)	590 (2.3)	718 (2.5)
Chronic renal failure	8,076 (4.6)	894 (3.7)	1,030 (4.0)	1,100 (3.9)
Peripheral vascular disease	6,993 (4.0)	1,312 (5.5)	1,038 (4.0)	1,016 (3.6)
Cerebrovascular disease	8,076 (4.6)	1,270 (5.3)	1,199 (4.7)	1,222 (4.3)
Dementia	3,937 (2.2)	360 (1.5)	428 (1.7)	582 (2.0)
Malignancy	5,294 (3.0)	673 (2.8)	672 (2.6)	788 (2.8)
Procedure, n (%)				
Overall CAG	167,499 (95.0)	22,722 (94.5)	24,324 (94.7)	27,019 (95.0)
PCI	153,758 (87.2)	20,577 (85.5)	22,254 (86.7)	24,829 (87.3)
Primary PCI	144,539 (82.0)	19,129 (79.5)	20,729 (80.7)	23,384 (82.2)
CABG	2,647 (1.5)	408 (1.7)	394 (1.5)	433 (1.5)

AMI-NCS, acute myocardial infarction with non-cardiogenic shock; BI, Barthel index; BMI, body mass index; CABG, coronary artery bypass graft; CAG, coronary angiography; IHD, ischemic heart disease; PCI, percutaneous coronary intervention.

(**Table 1** continued the next page.)

AMI-NCS. To date, few studies have specifically focused on the clinical characteristics and outcomes of patients with AMI-NCS.

In this study, the aim was to investigate the AMI-NCS population in the contemporary era of primary percutaneous coronary intervention (PPCI) to examine: (1) temporal trends in clinical characteristics; (2) in-hospital occurrence of cardiac and non-cardiac complications; (3) baseline factors associated with in-hospital adverse outcomes; and (4) the effect of PPCI on clinical outcomes, using the database of a Japanese nationwide registry.

Methods

Study Protocol and Population

The present study was a retrospective observational study based on a nationwide Japanese administrative case-mix Diagnostic Procedure Combination (DPC) database, the Japanese Registry Of All cardiac and vascular Disease (JROAD)-DPC.[4–6] In brief, the JROAD-DPC database is DPC-based payment health insurance claim data about hospitalization due to cardiovascular diseases collected from the 1,085 Japanese Circulation Society (JCS)-certified hospitals between April 2012 and March 2018. Using the International Classification of Disease, Tenth Revision (ICD-10), codes of I21.0, I21.1, I21.2, I21.3, I21.4, and I21.9 for AMI hospitalization recorded as "the main diagnosis", "the admission-precipitating diagnosis", or "the most resource-consuming diagnosis" in the DPC claim data, 260,543 AMI patients aged ≥20 years were identified. The ICD-10 code for AMI was validated in the JROAD-DPC database, as previously described.[4] Of these patients, 28,350 patients were excluded for missing values of the Killip classification. The remaining participants were divided into AMI-CS and AMI-NCS groups based on their condition at admission.[5] The AMI-CS, equivalent to the SCAI C/D/E group, was defined as Killip classification 3 or 4 that met at least one of the following criteria: (1) mechanical circulatory support use; or (2) intravenous administration of catecholamines on admission. Patients with Killip classification 3 (n=9,598) and 4 (n=6,691), or out-of-hospital cardiac arrest (n=484) were also excluded for the possibility of CS. The remaining patients were enrolled in this study as having AMI-NCS.

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	2015	2016	2017	P for trend
Number of patients	30,455	33,606	34,053	–
Female, n (%)	7,697 (25.3)	8,525 (25.4)	8,505 (25.0)	<0.001
Age, years, mean±SD	68.5±13.1	68.7±13.2	69.2±13.1	<0.001
Age category, years, n (%)				<0.001
<60	7,323 (24.0)	8,110 (24.1)	7,942 (23.3)	
60–70	8,142 (26.7)	8,949 (26.6)	8,772 (25.8)	
70–80	8,185 (26.9)	8,808 (26.2)	9,207 (27.0)	
80–90	5,714 (18.8)	6,421 (19.1)	6,676 (19.6)	
≥90	1,091 (3.6)	1,318 (3.9)	1,456 (4.3)	
BMI, kg/m², mean±SD	23.9±4.2	23.8±5.2	23.9±4.4	<0.001
Clinical characteristic, n (%)				
Ambulance transport	19,572 (64.4)	22,417 (66.8)	22,525 (66.2)	<0.001
Full-score BI at admission	8,685 (28.5)	9,669 (28.8)	10,723 (31.5)	0.001
Killip class I	19,464 (63.9)	22,181 (66.0)	22,825 (67.0)	<0.001
Killip class II	10,991 (36.1)	11,425 (34.0)	11,228 (33.0)	
Previous IHD	1,551 (5.1)	1,639 (4.9)	1,536 (4.5)	0.001
Hypertension	20,450 (67.1)	23,287 (69.3)	23,459 (68.9)	<0.001
Diabetes mellitus	8,944 (29.4)	10,431 (31.0)	10,552 (31.0)	<0.001
Hyperlipidemia	19,663 (64.6)	23,053 (68.6)	23,605 (69.3)	<0.001
Atrial fibrillation	768 (2.5)	880 (2.6)	983 (2.9)	<0.001
Chronic pulmonary disease	762 (2.5)	992 (3.0)	1,068 (3.1)	<0.001
Chronic renal failure	1,299 (4.3)	1,533 (4.6)	1,684 (4.9)	<0.001
Peripheral vascular disease	1,019 (3.3)	1,336 (4.0)	1,272 (3.7)	<0.001
Cerebrovascular disease	1,243 (4.1)	1,561 (4.6)	1,581 (4.6)	0.003
Dementia	684 (2.2)	867 (2.6)	1,016 (3.0)	<0.001
Malignancy	839 (2.8)	1,114 (3.3)	1,208 (3.5)	<0.001
Procedure, n (%)				
Overall CAG	29,027 (95.3)	32,035 (95.3)	32,372 (95.1)	<0.001
PCI	26,767 (87.9)	29,543 (87.9)	29,788 (87.5)	<0.001
Primary PCI	25,256 (82.9)	27,890 (83.0)	28,151 (82.7)	<0.001
CABG	475 (1.6)	467 (1.4)	470 (1.4)	0.001

Variables

The following variables were extracted from the JROAD-DPC database as baseline clinical characteristics: age, sex, body mass index, duration of hospital stay, emergency admission, ambulance transport, Killip classification, activities of daily living (ADL) score (Barthel index: 100 or <100), comorbidities on admission (previous ischemic heart disease, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, chronic pulmonary disease, chronic renal disease, peripheral vascular disease, cerebrovascular disease, dementia, and malignancy). PPCI was defined as PCI performed on the day of, or day after admission. In regard to the regional differences in the medical system for emergency cardiac care, JCS-certified hospital density by the prefecture where the institution was located was used. JCS-certified hospital density (hospitals/km^2) was calculated by dividing the number of hospitals by inhabitable area where the institution was located. Data for the inhabitable area in 2015 were obtained from the Japanese Government Statistics. The JCS-certified hospital density was divided into quartiles.[7]

Outcomes

The primary outcome was 30-day all-cause mortality, and the secondary outcomes were newly developed in-hospital complications. The in-hospital complications were defined as a composite of cardiac events and major non-cardiac events. The cardiac events were defined as a composite of heart failure after admission, life-threatening arrhythmia (defibrillator use), use of an intra-aortic balloon pump (IABP), extracorporeal membrane oxygenation (ECMO), respirator, or extra pacing, and mechanical complications of AMI. The major non-cardiac events were defined as a composite of pneumonia, sepsis, hemodialysis, major bleeding (intracranial hemorrhage, gastrointestinal bleeding, other bleeding needing red blood cell transfusion[8]), and ischemic stroke.

Ethics Statement

This study protocol was approved by the ethics committees of Kawasaki Medical School (No. 3928), Miyazaki Prefectural Nobeoka Hospital (No. 20200721-1), and Kumamoto University Hospital (No. 2095). Each hospital anonymized patient IDs using the code-change equations made by each hospital in the original DPC data, which were sent to the Ministry of Health, Labour and Welfare. Patients were notified through homepages or posters in each hospital that their information was collected by this study. Patients could opt-out of the collection of their information from the database if they wished to be excluded.

Table 2. In-Hospital Outcome by Year for AMI-NCS Patients

	Total (n=176,275)	2012	2013	2014
30-day all-cause mortality, n (%)	4,506 (2.6)	597 (2.5)	674 (2.6)	723 (2.5)
Full-score BI at discharge, n (%)	139,076 (78.9)	18,941 (78.7)	20,111 (78.3)	22,502 (79.1)
In-hospital complications, n (%)	53,714 (30.5)	7,282 (30.3)	7,713 (30.0)	8,353 (29.4)
Cardiac events, n (%)	44,052 (25.0)	6,108 (25.4)	6,568 (25.6)	7,049 (24.8)
Heart failure after admission	18,803 (10.7)	2,453 (10.2)	2,540 (9.9)	2,960 (10.4)
Life-threatening arrhythmia (Defibrillator use)	6,421 (3.6)	905 (3.8)	1,052 (4.1)	1,044 (3.7)
IABP	14,313 (8.1)	2,153 (8.9)	2,254 (8.8)	2,330 (8.2)
ECMO	915 (0.5)	103 (0.4)	107 (0.4)	152 (0.5)
Respirator	13,778 (7.8)	1,727 (7.2)	2,039 (7.9)	2,163 (7.6)
Extra pacing	6,381 (3.6)	993 (4.1)	1,115 (4.3)	1,098 (3.9)
Mechanical complications	610 (0.3)	89 (0.4)	82 (0.3)	86 (0.3)
Major non-cardiac events, n (%)	16,897 (9.6)	2,080 (8.6)	2,158 (8.4)	2,412 (8.5)
Sepsis	1,196 (0.7)	99 (0.4)	118 (0.5)	200 (0.7)
Pneumonia	7,415 (4.2)	742 (3.1)	818 (3.2)	944 (3.3)
Hemodialysis	4,167 (2.4)	512 (2.1)	585 (2.3)	638 (2.2)
Major bleeding	4,221 (2.4)	656 (2.7)	571 (2.2)	628 (2.2)
Ischemic stroke	1,577 (0.9)	236 (1.0)	271 (1.1)	228 (0.8)

	2015	2016	2017	P for trend
30-day all-cause mortality, n (%)	762 (2.5)	873 (2.6)	877 (2.6)	0.824
Full-score BI at discharge, n (%)	24,189 (79.4)	26,575 (79.1)	26,758 (78.6)	0.549
In-hospital complications, n (%)	8,951 (29.4)	10,547 (31.4)	10,868 (31.9)	<0.001
Cardiac events, n (%)	7,505 (24.6)	8,397 (25.0)	8,425 (24.7)	0.015
Heart failure after admission	3,277 (10.8)	3,847 (11.4)	3,726 (10.9)	<0.001
Life-threatening arrhythmia (Defibrillator use)	1,049 (3.4)	1,185 (3.5)	1,186 (3.5)	<0.001
IABP	2,411 (7.9)	2,574 (7.7)	2,591 (7.6)	<0.001
ECMO	156 (0.5)	198 (0.6)	199 (0.6)	0.001
Respirator	2,313 (7.6)	2,697 (8.0)	2,839 (8.3)	<0.001
Extra pacing	1,015 (3.3)	1,123 (3.3)	1,037 (3.0)	<0.001
Mechanical complications	111 (0.4)	121 (0.4)	121 (0.4)	0.998
Major non-cardiac events, n (%)	2,594 (8.5)	3,614 (10.8)	4,039 (11.9)	<0.001
Sepsis	238 (0.8)	280 (0.8)	261 (0.8)	<0.001
Pneumonia	949 (3.1)	1,809 (5.4)	2,153 (6.3)	<0.001
Hemodialysis	723 (2.4)	784 (2.3)	925 (2.7)	<0.001
Major bleeding	682 (2.2)	817 (2.4)	867 (2.5)	0.999
Ischemic stroke	259 (0.9)	290 (0.9)	293 (0.9)	0.009

AMI-NCS, acute myocardial infarction with non-cardiogenic shock; BI, Barthel index; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump.

Statistical Analysis

Continuous variables are summarized as means±standard deviation and categorical variables as frequencies or percentages. For continuous variables, comparisons between groups were made using the unpaired t-test. Categorical variables were compared using the chi-squared test. The Cochran-Armitage test was used to assess trend across time. Univariable and multivariable mixed-effects logistic regression analyses, with the institution as a random intercept, were performed to identify clinical factors on admission for predicting 30-day all-cause mortality and in-hospital complications. Multivariable mixed-effects logistic regression analyses and propensity score matching (PSM) were performed to evaluate whether major non-cardiac events after admission were independently associated with 30-day all-cause mortality.

Variables showing a value of $P<0.05$ on univariable analysis were entered into the multivariable model. The results are summarized as odds ratios (OR) and 95% confidence intervals (CIs). PSM using the nearest-neighbor matching method was constructed by logistic regression modeling, adjusting for the variables listed in **Supplementary Tables 1**–**3**. Standard mean differences were calculated. A P value <0.05 was considered significant. All statistical analyses were conducted using STATA version 17 statistical software (Stata Corp, College Station, TX, USA).

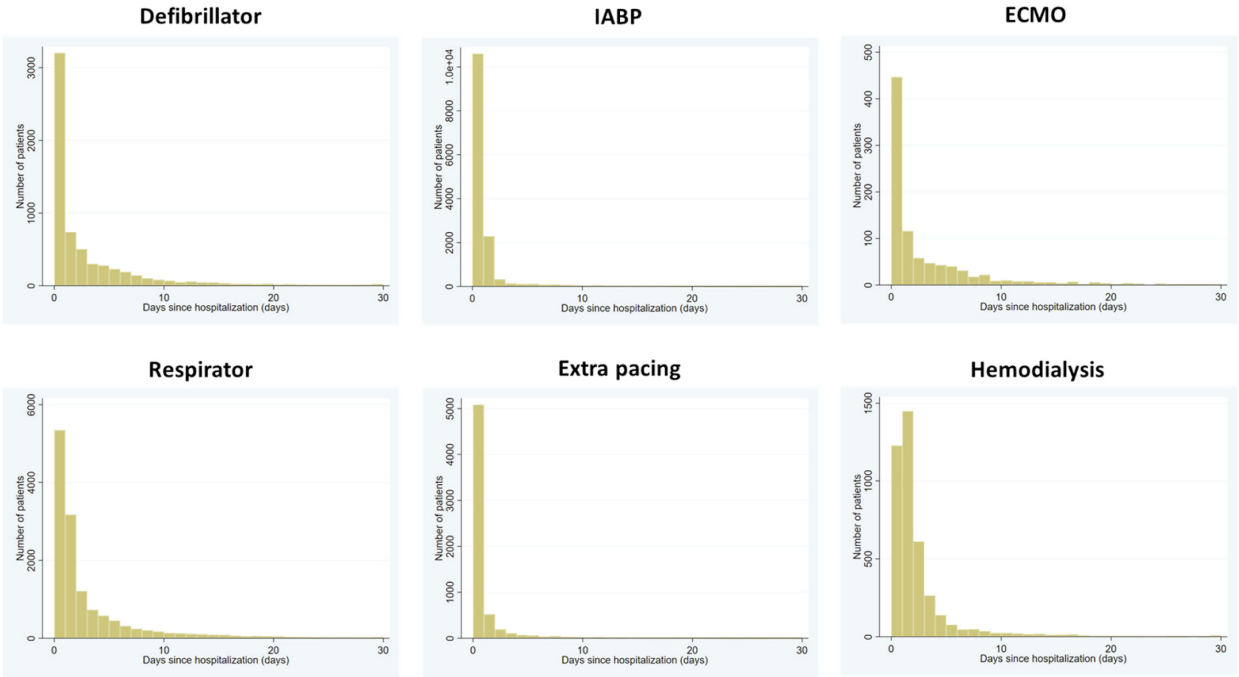

Figure 1. Number of clinical events by date of onset in AMI-NCS patients. These figures show the number of events for each clinical event from the day of admission. AMI-NCS, acute myocardial infarction with non-cardiogenic shock; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation.

Results

Temporal Trends in Clinical Characteristics and Outcomes in Patients With AMI-NCS

Of the 260,543 patients with AMI registered in the JROAD-DPC database from April 2012 to March 2018, 176,275 (67.7%) patients were diagnosed with AMI-NCS at the time of hospital admission (**Supplementary Figure**). Their clinical characteristics and temporal changes are shown in **Table 1**. The AMI-NCS patients included 44,687 females (25.4%), and the mean age was 68.6±13.1 years; 113,282 patients (64.3%) presented in Killip class 1 on admission. The prevalence of comorbidities was: hypertension (68.0%), diabetes mellitus (30.0%), hyperlipidemia (65.7%), chronic renal failure (4.6%), dementia (2.2%), and malignancy (3.0%). When looking at the temporal trends in patient characteristics by fiscal year (2012–2017), patients presenting with AMI-NCS were getting older (P for trend <0.001). In particular, the prevalence of nonagenarian patients increased significantly from 3.6% to 4.3% during the study period. Patients became more likely to use an ambulance and less likely to present with heart failure on admission (i.e., Killip class 1). As to the clinical background characteristics of AMI-NCS patients, the prevalence of comorbidities such as hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, chronic pulmonary disease, and chronic renal failure increased over time. Furthermore, the prevalence of dementia increased significantly from 1.5% to 3.0% (p for trend <0.001), as did the prevalence of malignancy, from 2.8% to 3.5% (p for trend <0.001), during the study period.

All-cause mortality and in-hospital complication rates are shown in **Table 2** and **Figure 1**. The 30-day all-cause mortality was 2.6% and was unchanged during the study period. In-hospital complications occurred in 30.5% of patients, and their incidence increased significantly during the study period. Cardiac events occurred in 25.0% of AMI-NCS patients during hospitalization, which consisted of heart failure after admission (10.7%), life-threatening arrhythmia (3.6%), the use of IABP (8.1%), ECMO (0.5%), respirator (7.8%), and extra pacing (3.6%), and mechanical complications of AMI (0.3%). Most cardiac events occurred on the first or second day of admission (**Figure 1**). Overall, the incidence of cardiac events did not change significantly; specifically, the usage rate of IABP and extra pacing decreased gradually, whereas the usage rate of ECMO and respirator increased. Major non-cardiac events occurred in 9.6% of AMI-NCS patients (sepsis, 0.7%; pneumonia, 4.2%; hemodialysis, 2.4%; major bleeding 2.4%; stroke 0.9%). The incidence of major non-cardiac events, in particular, sepsis, pneumonia, and hemodialysis, increased significantly during the study period (8.6% in the year 2012 to 11.9% in the year 2017, P for trend <0.001).

Clinical Factors Associated With 30-Day All-Cause Mortality and In-Hospital Complications

Tables 3 and **4** show the results of univariable and multivariable analyses of clinical characteristics associated with 30-day all-cause mortality and in-hospital adverse events.

On univariable analysis, both patients who died within 30 days and patients who had in-hospital complications had in common the following clinical characteristics: older age, lower BMI, lower rate of full-score Barthel Index, and

Table 3. Univariable and Multivariable Logistic Regression Analyses to Identify Clinical Background Characteristics for Predicting 30-Day All-Cause Mortality

	30-day all-cause mortality (–)	30-day all-cause mortality (+)		Univariable		Multivariable	
	171,769 (91.4)	4,506 (2.6)		OR (95% CI)	P value	OR (95% CI)	P value
Age category, years, n (%)			Age (reference, <60 years)	2.52 (2.45–2.60)	<0.001	1.85 (1.78–1.92)	<0.001
<60	42,177 (24.6)	188 (4.2)					
60–70	46,469 (27.1)	471 (10.5)					
70–80	46,395 (27.0)	1,046 (23.2)					
80–90	31,201 (18.2)	1,901 (42.2)					
≥90	5,527 (3.2)	900 (20.0)					
Female, n (%)	42,638 (24.8)	2,049 (45.5)	Female	2.52 (2.37–2.68)	<0.001	1.18 (1.10–1.28)	<0.001
BMI category, kg/m², n (%)			BMI (reference, <18.5 kg/m²)	0.46 (0.43–0.48)	<0.001	0.88 (0.83–0.94)	<0.001
<18.5	10,050 (6.3)	736 (21.3)					
18.5–25	95,140 (59.4)	2,042 (59.1)					
25–30	44,914 (28.1)	561 (16.2)					
≥30	9,959 (6.2)	114 (3.3)					
Clinical characteristic, n (%)							
Ambulance transport	109,440 (63.8)	3,263 (72.4)		1.53 (1.43–1.64)	<0.001	1.40 (1.29–1.51)	<0.001
Full-score BI at admission	51,397 (29.9)	630 (14.0)		0.33 (0.30–0.36)	<0.001	0.56 (0.50–0.62)	<0.001
Killip class I	111,283 (64.8)	1,999 (44.4)	Killip II (reference, I)	2.50 (2.35–2.66)	<0.001	1.80 (1.67–1.94)	<0.001
Killip class II	60,486 (35.2)	2,507 (55.6)					
Previous IHD	8,027 (4.7)	60 (1.3)		0.27 (0.21–0.35)	<0.001	0.32 (0.24–0.43)	<0.001
Hypertension	118,472 (69.0)	1,470 (32.6)		0.20 (0.19–0.21)	<0.001	0.40 (0.37–0.43)	<0.001
Diabetes mellitus	52,000 (30.3)	966 (21.4)		0.63 (0.58–0.67)	<0.001	0.86 (0.79–0.94)	0.001
Hyperlipidemia	114,927 (66.9)	935 (20.8)		0.12 (0.11–0.13)	<0.001	0.31 (0.28–0.33)	<0.001
Atrial fibrillation	4,078 (2.4)	168 (3.7)		1.59 (1.36–1.86)	<0.001	1.31 (1.09–1.57)	0.004
Chronic pulmonary disease	4,541 (2.6)	163 (3.6)		1.39 (1.19–1.63)	<0.001	0.91 (0.76–1.10)	0.337
Chronic renal failure	7,073 (4.1)	467 (10.4)		2.77 (2.50–3.06)	<0.001	1.65 (1.46–1.85)	<0.001
Peripheral vascular disease	6,768 (3.9)	225 (5.0)		1.26 (1.09–1.45)	<0.001	1.11 (0.94–1.31)	0.233
Cerebrovascular disease	7,685 (4.5)	391 (8.7)		2.02 (1.81–2.25)	<0.001	1.09 (0.96–1.25)	0.176
Dementia	3,626 (2.1)	311 (6.9)		3.43 (3.04–3.87)	<0.001	0.90 (0.77–1.05)	0.178
Malignancy	5,025 (2.9)	269 (6.0)		2.12 (1.87–2.42)	<0.001	1.23 (1.06–1.43)	0.008
Primary PCI, n (%)	142,271 (82.8)	2,268 (50.3)		0.20 (0.19–0.22)	<0.001	0.45 (0.42–0.49)	<0.001
JCS-certified hospital density, n (%)			JCS-certified hospital density (reference, Q1)	0.93 (0.90–0.97)	<0.001	0.93 (0.89–0.98)	0.006
Q1	40,988 (23.9)	1,163 (25.8)					
Q2	44,044 (25.6)	1,182 (26.2)					
Q3	45,897 (26.7)	1,241 (27.5)					
Q4	40,840 (23.8)	920 (20.4)					

BI, Barthel index; BMI, body mass index; CI, confidence interval; IHD, ischemic heart disease; JCS, Japanese Circulation Society; OR, odds ratio; PCI, percutaneous coronary intervention.

higher Killip class compared with those who did not have in-hospital events. In addition, higher JCS-certified hospital density was associated with lower 30-day mortality.

On multivariable analysis, higher age, female sex, lower BMI, higher Killip class, no full-score Barthel Index, atrial fibrillation, chronic renal failure, malignancy, and lower JCS-certified hospital density were independently associated with increased 30-day all-cause mortality. Higher age, lower BMI, higher Killip class, no full-score Barthel Index, diabetes mellitus, atrial fibrillation, chronic pulmonary

Table 4. Univariable and Multivariable Logistic Regression Analyses to Identify Clinical Background Characteristics as Predictors of In-Hospital Complications

	In-hospital complication (–)	In-hospital complication (+)		Univariable		Multivariable	
	122,561 (69.5)	53,714 (30.5)		OR (95% CI)	P value	OR (95% CI)	P value
Age category, years, n (%)			Age (reference, <60 years)	1.20 (1.19–1.21)	<0.001	1.08 (1.07–1.10)	<0.001
<60	31,688 (25.9)	10,677 (19.9)					
60–70	33,615 (27.4)	13,325 (24.8)					
70–80	32,314 (26.4)	15,127 (28.2)					
80–90	20,969 (17.1)	12,133 (22.6)					
≥90	3,975 (3.2)	2,452 (4.6)					
Female, n (%)	30,264 (24.7)	14,423 (26.9)	Female	1.13 (1.10–1.16)	<0.001	0.97 (0.94–0.99)	0.020
BMI category, kg/m², n (%)			BMI (reference <18.5 kg/m²)	0.87 (0.86–0.88)	<0.001	0.98 (0.96–0.99)	0.010
<18.5	6,720 (5.9)	4,066 (8.2)					
18.5–25	67,290 (59.0)	29,892 (60.3)					
25–30	32,737 (28.7)	12,738 (25.7)					
≥30	7,214 (6.3)	2,859 (5.8)					
Clinical characteristic, n (%)							
Ambulance transport	76,021 (62.1)	36,682 (68.3)		1.32 (1.29–1.35)	<0.001	1.29 (1.26–1.33)	<0.001
Full-score BI at admission	38,267 (31.2)	13,760 (25.6)		0.69 (0.67–0.70)	<0.001	0.79 (0.77–0.82)	<0.001
Killip class I	84,804 (69.2)	28,478 (53.0)	Killip II (reference, I)	2.22 (2.17–2.27)	<0.001	2.03 (1.98–2.08)	<0.001
Killip class II	37,757 (30.8)	25,236 (47.0)					
Previous IHD	4,935 (4.0)	3,152 (5.9)		1.20 (1.15–1.27)	<0.001	1.24 (1.18–1.31)	<0.001
Hypertension	86,238 (70.4)	33,704 (62.7)		0.66 (0.64–0.67)	<0.001	0.78 (0.76–0.81)	<0.001
Diabetes mellitus	35,351 (28.8)	17,615 (32.8)		1.18 (1.16–1.21)	<0.001	1.18 (1.15–1.21)	<0.001
Hyperlipidemia	84,747 (69.1)	31,115 (57.9)		0.54 (0.53–0.56)	<0.001	0.73 (0.71–0.75)	<0.001
Atrial fibrillation	1,899 (1.5)	2,347 (4.4)		2.73 (2.57–2.92)	<0.001	2.52 (2.35–2.70)	<0.001
Chronic pulmonary disease	3,082 (2.5)	1,622 (3.0)		1.25 (1.18–1.34)	<0.001	1.12 (1.05–1.20)	0.001
Chronic renal failure	2,356 (1.9)	5,184 (9.7)		6.08 (5.77–6.40)	<0.001	5.25 (4.96–5.55)	<0.001
Peripheral vascular disease	4,219 (3.4)	2,774 (5.2)		1.29 (1.22–1.36)	<0.001	1.16 (1.09–1.23)	<0.001
Cerebrovascular disease	4,847 (4.0)	3,229 (6.0)		1.57 (1.50–1.65)	<0.001	1.31 (1.24–1.38)	<0.001
Dementia	2,528 (2.1)	1,409 (2.6)		1.43 (1.33–1.53)	<0.001	0.96 (0.89–1.04)	0.334
Malignancy	3,325 (2.7)	1,969 (3.7)		1.31 (1.23–1.39)	<0.001	1.11 (1.04–1.18)	0.002
Primary PCI, n (%)	101,721 (83.0)	42,818 (79.7)		0.77 (0.75–0.79)	<0.001	0.93 (0.90–0.96)	<0.001

Abbreviations as in Table 3.

disease, chronic renal failure, peripheral vascular disease, cerebrovascular disease, and malignancy were independently associated with increased in-hospital complications. Common independent predictors of cardiac and non-cardiac events were higher age, higher Killip, no full-score Barthel Index, diabetes mellitus, atrial fibrillation, chronic renal failure and cerebrovascular disease (**Supplementary Tables 4** and **5**). Higher BMI, previous ischemic heart disease, peripheral vascular disease, and dementia were independent factors associated with cardiac events, whereas female sex, lower BMI, chronic pulmonary disease, and malignancy were independent factors associated with non-cardiac events.

Relationship Between In-Hospital Complications and 30-Day All-Cause Mortality

PSM was performed to compare patients with in-hospital complications and those without, including 39,640 patients per group. There were no significant differences in clinical variables between the 2 groups (**Supplementary Table 1**). Patients with in-hospital complications had increased 30-day all-cause mortality (OR: 7.28, 95% CI: 6.44–8.23, P<0.001) (**Table 5**). Likewise, PSM comparisons between patients with cardiac events and those without (36,840 patients per group) and PSM comparisons between patients with major non-cardiac events and those without (1,2114 patients per group) were performed (**Supplementary**

Table 5. Propensity-Score Matched Relationship Between In-Hospital Complications and 30-Day All-Cause Mortality in AMI-NCS Patients

	30-day all-cause mortality			
	Univariable		Propensity-score matching	
	OR (95% CI)	P value	OR (95% CI)	P value
In-hospital complications	11.2 (10.40–12.12)	<0.001	7.28 (6.44–8.23)	<0.001
Cardiac events	10.6 (9.90–11.4)	<0.001	6.75 (6.01–7.58)	<0.001
Major non-cardiac events	4.04 (3.78–4.33)	<0.001	1.80 (1.58–2.05)	<0.001

AMI-NCS, acute myocardial infarction with non-cardiogenic shock; CI, confidence interval; OR, odds ratio.

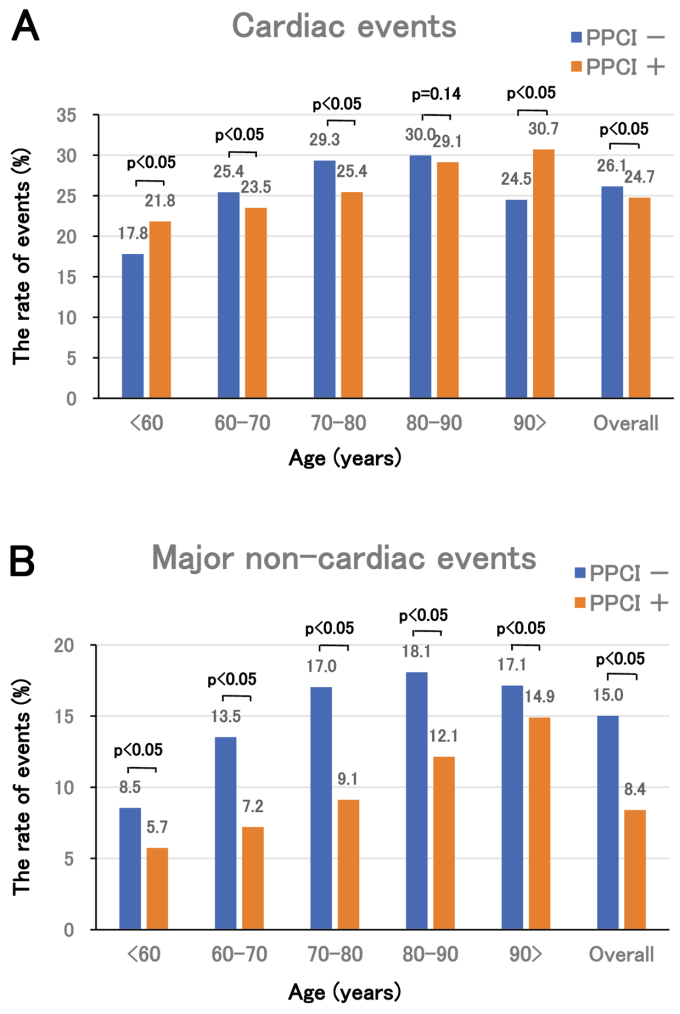

Figure 2. (**A**) Incidence of cardiac events by age with and without PPCI. (**B**) Incidence of major non-cardiac events by age with and without PPCI. Blue bar: patients did not receive PPCI. Orange bars: patients received PPCI. PPCI, primary percutaneous coronary intervention.

Tables 2 and **3**), showing that patients with cardiac events, as well as patients with major non-cardiac events, had increased 30-day all-cause mortality (OR: 6.75, 95% CI: 6.01 to 7.58; OR: 1.80, 95% CI: 1.58 to 2.05) (**Table 5**).

Effect of Primary PCI on Clinical Outcomes and ADL Based on Subgroups

During hospitalization, a total of 167,499 patients (95.0%) underwent coronary angiography, and PPCI was performed in 144,539 patients (82.0%) (**Table 1**). PPCI was independently associated with lower 30-day all-cause mortality and lower in-hospital complications (OR: 0.45, 95% CI: 0.42 to 0.49; OR: 0.93, 95% CI: 0.90 to 0.96) (**Tables 3** and **4**). When looking at the cardiac and major non-cardiac events separately, PPCI was associated with a lower incidence of major non-cardiac events, but not cardiac events (OR: 0.70, 95% CI: 0.67 to 0.73; OR: 0.99, 95% CI: 0.96 to 1.02) (**Supplementary Tables 4** and **5**). According to age subgroups (**Figure 2**), patients aged <90 years who underwent PPCI had a significantly lower number of cardiac events than those who did not, whereas patients aged ≥90 years who underwent PPCI had a significantly

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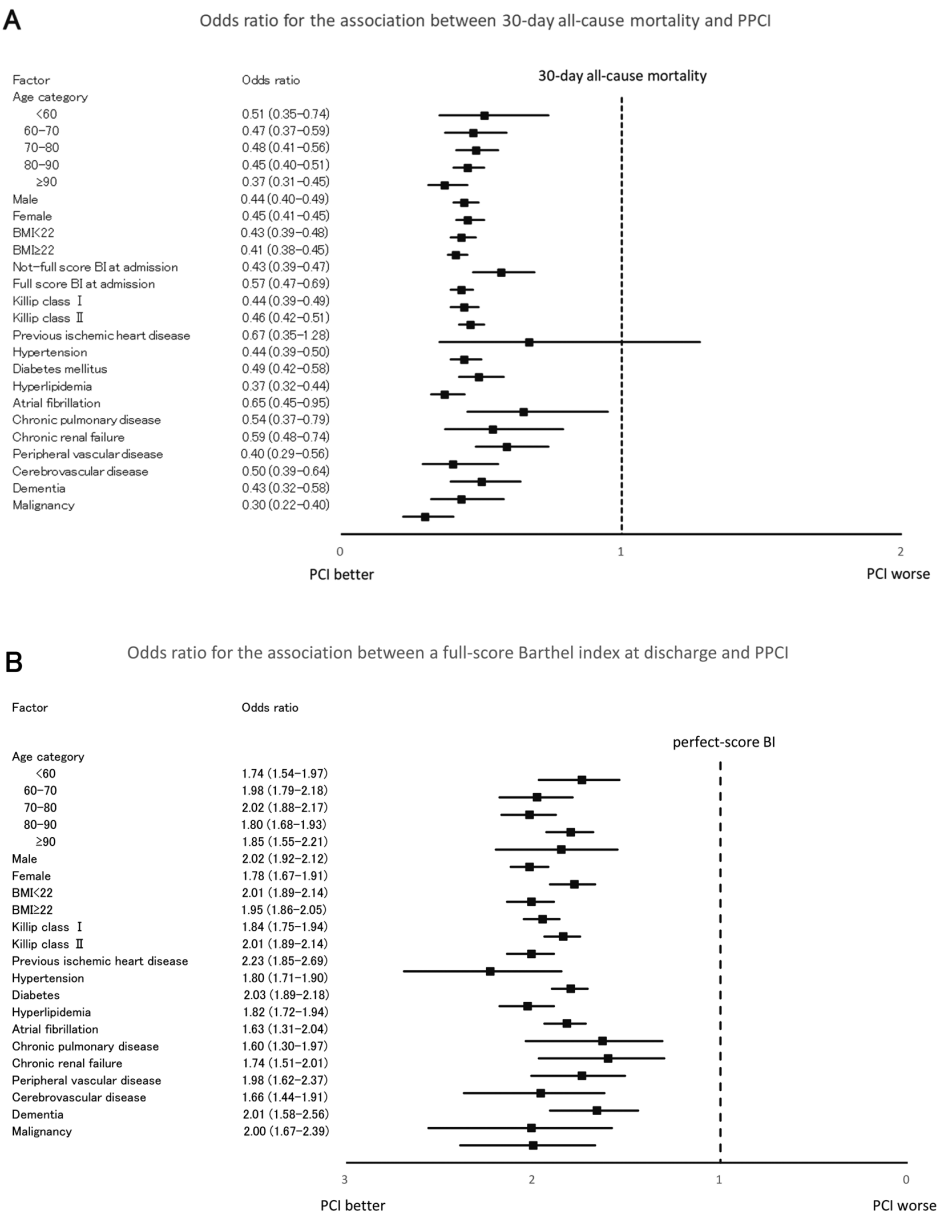

Figure 3. Effect of primary percutaneous coronary intervention by each clinical factor. (**A**) Forest plots of odds ratios according to each subgroup for 30-days all-cause mortality in patients who had PPCI vs. those who did not. (**B**) Forest plots of odds ratios according to each subgroup for full-score Barthel index at discharge in patients who had PPCI vs. those who did not. BMI, body mass index; BI, Barthel index; PPCI, primary percutaneous coronary intervention.

higher number of cardiac events. PPCI was consistently and significantly associated with lower number major non-cardiac events in all age subgroups.

Figure 3 shows the forest plots of the OR according to each subgroup for 30-day all-cause mortality and full-score Barthel index at discharge in patients who had PPCI vs. those who did not. Patients who underwent PPCI had lower 30-day all-cause mortality in all subgroups, except for the subgroup who had previous ischemic heart disease, and had a significantly better Barthel index at discharge in all subgroups compared with those who did not undergo PPCI.

Discussion

In the present study, we investigated the temporal trends in clinical characteristics and clinical outcomes of patients presenting with AMI-NCS from 2012 to 2017. The main findings of this study can be summarized as follows: (1) the age and burden of baseline comorbidities of patients with AMI-NCS increased over time; (2) 30-day all-cause mortality was around 2.6% and did not change significantly during the study period, whereas in-hospital complications, especially major non-cardiac events, increased significantly over time; (3) higher age, female sex, higher Killip class,

and multiple baseline comorbidities were independently associated with increased 30-day all-cause mortality; (4) both cardiac and major non-cardiac events increased with increasing age; (5) the incidence of both cardiac and major non-cardiac events after admission was independently associated with increased 30-day all-cause mortality; and (6) PPCI was associated with improved in-hospital outcomes and better physical activity at hospital discharge in patients with AMI-NCS across various subgroups.

Temporal Trends in the Clinical Background Characteristics of Patients Presenting With AMI-NCS

The present study demonstrated that the age of onset of AMI-NCS patients in Japan has increased by about 1 year, and the burden of preexisting medical comorbidities has been increasing during the 6-year study period. According to the epidemiological changes in developed countries, the patient presenting with AMI has been getting older and having a more complicated baseline health condition. In the prospective, multicenter cohort study of ACS patients in Switzerland, the mean age of ACS patients increased from 78.6 years in 2001–2004 to 79.6 years in 2009–2012.[9] A report from the Danish nationwide registry showed an increasing proportion of older patients over time; in particular, patients aged ≥80 years accounted for 28.2% in 2004–2008 compared with 17.7% in 1984–1988 among patients at first-time hospitalization for myocardial infarction.[10] It is natural and has been demonstrated that older patients presenting with AMI have more comorbidities.[9,11] Specifically, in the present study, the prevalence of traditional atherosclerosis factors such as diabetes mellitus, hypertension, and dyslipidemia increased, which is in agreement with the previous Japanese prospective registry study[2] and other national registry studies from Switzerland,[9] France,[12] and the USA.[11]

The present data newly showed that the prevalence of dementia and malignancy has also increased. The SILVER-AMI study in the USA reported that 18% of AMI patients aged >75 years had comorbid dementia.[13] Comorbidity with dementia could prevent AMI patients from engaging in routine healthcare strategies through difficulty in their understanding and cooperation for diagnosis and treatment. The prevalence of malignancy is increasing as advances in oncology treatment have led to an increase in the number of malignancy survivors.[14] It is important to note that chemotherapy and radiation therapy for malignancy, as well as hypercoagulability of malignancy itself, are known risks for the incidence of AMI.[14] In addition, past treatment with anti-cancer drugs might impair basal organ function of the kidneys, bone marrow, and so on, which could cause non-cardiac complications during AMI treatment.[15] Another notable temporal trend of AMI-NCS observed in the present study was that the prevalence of patients presenting with Killip 1 on admission has increased, whereas that of those with Killip 2 has decreased. This observation was possibly due to the improved emergency transport systems and early diagnosis of AMI (e.g., high-sensitivity troponin).

In-Hospital Mortality in AMI-NCS Patients

The short-term mortality rate of AMI-NCS patients has been reported to be up to around 5%, which is much lower than that of AMI-CS patients whose mortality rate reaches over 20 to 70%.[3,5,16] The data from 2 French registries, which included STEMI patients without CS on admission who underwent PPCI (n=6,838 and 2,208), showed the in-hospital all-cause mortality of 3.3% and 5.4%.[17] A single-center, observational study from China reported that the all-cause mortality of 562 STEMI patients without CS on admission was 2.2% at 30 days after PPCI.[18] In line with the previous reports, the present study showed that 30-day all-cause mortality of AMI-NCS patients was around 2.6%, which did not change significantly during the study period despite including a broader population of AMI-NCS patients (i.e., ST-segment elevation and non-ST-segment-elevation MI, with and without PPCI). In addition, higher age, female sex, higher Killip class, and comorbidities of atrial fibrillation, chronic renal failure, and malignancy were independently associated with increased 30-day all-cause mortality, which is consistent with previous studies.[19,20] Notably, of these factors, malignancy, atrial fibrillation, and chronic renal failure were found to be increasing in prevalence in AMI-NCS patients in the present study. One of the possible mechanisms for the poor, even short-term, prognosis of patients with malignancy is thought to be that the success rate of PCI is reduced due to the enhancement of coagulation by tumor cells.[14,21] The increased mortality in patients with AMI and comorbid atrial fibrillation, and chronic renal failure might be attributable to the higher risks for heart failure, bleeding, and stroke in this population.[22–24] The optimal treatment strategy for these populations to improve their clinical outcomes should be established. Even though these factors that could increase 30-day all-cause mortality have increased, the 30-day all-cause mortality rate has not changed. This may be explained by the increase in the rate of PPCI, which may have counteracted the effects of a worsening patient background. Our study also revealed that higher JCS-certified hospital density was associated with lower mortality in AMI-NCS patients. Higher JCS-certified hospital density might lead to prompt transportation of AMI patients to the hospital capable of PPCI, likely resulting in earlier reperfusion and better clinical outcomes.

In contrast, previous ischemic heart disease, hypertension, diabetes mellitus, and hyperlipidemia were associated with lower 30-day all-cause mortality in AMI-NCS patients. This paradoxical relationship between coronary risk factors and clinical outcomes was also reported in previous studies. An observational study from the US national registry of myocardial infarction examined the association between the number of coronary risk factors in 542,008 patients with first AMI and hospital mortality, and showed that in patients with AMI without prior cardiovascular disease, in-hospital mortality was inversely related to the number of coronary risk factors.[25] A previous large-scale study reported that high low-density lipoprotein (LDL)-C is inversely associated with mortality in people aged >60 years.[26] Similarly, some previous studies have reported that hypertension associated with cardiovascular disease is a J-shaped phenomenon due to decreased myocardial perfusion.[27] This discrepancy might reflect the real-world data of an aging society.

In-Hospital Complications in AMI-NCS Patients

The present study showed that, in addition to the factors identical to those associated with 30-day all-cause mortality (older age, higher Killip class, atrial fibrillation, chronic renal failure, and malignancy), other comorbidities such as previous ischemic heart disease, diabetes mellitus, chronic

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pulmonary disease, peripheral vascular disease, and cerebrovascular disease were independently associated with increased in-hospital complications. Interestingly, previous ischemic heart disease and diabetes mellitus were not directly associated with increased 30-day all-cause mortality, but they were associated with increased in-hospital complications. Specifically, previous ischemic heart disease was associated with an increase in cardiac events, whereas diabetes mellitus was associated with an increase in both cardiac and major non-cardiac events. Diabetes mellitus is thought to increase the risk of acute stent thrombosis more than hypertension and dyslipidemia, as well as pneumonia and sepsis, due to the increased susceptibility to infection. In patients with previous ischemic heart disease and diabetes mellitus, there might be unknown subclinical macroangiopathies such as peripheral arterial disease and cerebrovascular disease, on admission, which might also lead to higher in-hospital complications in those patients.

It is well known that various cardiac events, such as heart failure and mechanical complications, occur after myocardial infarction. The previous national registry reported that in-hospital complications in AMI patients decreased over 20 years since the improved performance of early perfusion therapy has reduced the risk of recurrent ischemic events.[28] Recent studies reported that cardiac event rates remain unchanged and plateaued during the last decade.[1,29] In contrast, some data suggest that the incidence of non-cardiac events has been increasing in recent years.[30] The present study showed that the incidence of in-hospital non-cardiac events has increased more than that of cardiac events. In particular, heart failure after admission, sepsis, and pneumonia increased significantly, which may explain the increased use of respirators. Hemodialysis also increased significantly in the present study. Considering that not only cardiac events, but also major non-cardiac events were independently associated with 30-day all-cause mortality, and that the incidence of both cardiac and major non-cardiac events was found to increase with older age in the present study, we should make efforts to reduce non-cardiac complications, as well as cardiac complications, to improve clinical outcomes of AMI-NCS patients.

Effects of Primary PCI on In-Hospital Outcomes in AMI-NCS Patients

PPCI has contributed to improving clinical outcomes of AMI patients, and has become the first-line, acute-phase treatment of AMI. Consistently, the present study showed that PPCI was associated with lower mortality and in-hospital complications in patients with AMI-NCS. In addition, the present study showed that PPCI was associated with a lower incidence of in-hospital non-cardiac events.[31] PPCI restores coronary blood flow, reduces infarct size, and therefore improves cardiac function, leading to early patient recovery in the acute phase of AMI. The positive hemodynamic effects may reduce the occurrence of congestion and hypoperfusion of various organs, and enable early ambulation and parenteral nutrition after AMI, reducing pneumonia and the risk of infection. These may explain the lower non-cardiac events, in addition to lower mortality, in patients who underwent PPCI in the present study. In addition, patients who underwent PPCI showed a significantly better Barthel index at discharge in all subgroups in the present study. These data support the active use of PPCI in AMI-NCS patients even in those with worse background characteristics. In contrast, AMI-NCS patients aged ≥90 years showed inconsistent findings for in-hospital mortality and cardiac complications after PPCI. It is not always easy to determine whether super-elderly patients with multiple comorbidities should undergo PPCI. The appropriate management of such cases requires further investigation.

Study Limitations

This study had several important limitations. First, the JROAD-DPC database was a retrospective, observational study based on medical claims. Some data may be underestimated because they are not reflected in claims. In particular, the prevalence of comorbidities might be underreported. Second, the Barthel index at admission might not accurately reflect the physical activity level of the patients before admission because it should have appeared worse at admission after the patients had suffered from AMI. In addition, the patients should have been instructed to have complete bedrest; this lack of instruction led to the underestimation of their Barthel index at admission compared to their actual functional capacity and resultant overestimation of the improvement of the Barthel index at discharge from admission. Therefore, it would be better to treat the Barthel index at admission as just reference data. Third, although adjustment for known confounders was performed, the data were observational in nature and inherently subject to residual confounding. For example, detailed hemodynamic, angiographic, echocardiographic data, and medications could not be extracted from the dataset. Forth, because we could not collect detailed information on medication such as dosage with accuracy, we did not assess the impact of advances in medical treatment on mortality, although it might also have contributed to the unchanged mortality despite worsening patient background during the study period. Fifth, it was not possible to distinguish between ST-segment elevation and non-ST-segment-elevation MI in this study; therefore, we were not able to examine the differences in in-hospital outcomes between the two patient groups. Sixth, the data lacked sufficient granularity to differentiate between cardiovascular and non-cardiovascular mortality. Finally, this registry includes mostly Japanese patients treated within the healthcare system in Japan. The results may be less generalizable to other populations in the healthcare systems of other countries.

Conclusions

The clinical background characteristics of AMI-NCS patients have been becoming more complex with increasing age and the burden of comorbidities, with increased in-hospital complications. Worse medical conditions before developing AMI correlate not only with a higher incidence of in-hospital complications, but also mortality. Ongoing efforts are needed to establish more effective management strategies to reduce both non-cardiac and cardiac complications. Appropriate and proactive use of PPCI could play an important role in achieving this goal.

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Disclosures

K.H., K.T., Y.K., Y. Ikari and S.U. are members of *Circulation Journal*'s Editorial Team.

IRB Information

This study protocol was approved by the ethics committees of Kawasaki Medical School (No. 3928), Miyazaki Prefectural Nobeoka Hospital (No. 20200721-1), and Kumamoto University Hospital (No. 2095).

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Supplementary Files

Please find supplementary file(s);
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