Heart and Vessels (2019) 34:1140–1147
https://doi.org/10.1007/s00380-019-01350-z

ORIGINAL ARTICLE

Higher non-cardiac mortality and lesser impact of early revascularization in patients with type 2 compared to type 1 acute myocardial infarction: results from the Tokyo CCU Network registry

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Received: 26 September 2018 / Accepted: 18 January 2019 / Published online: 25 January 2019

Abstract
As the definition of type 2 acute myocardial infarction (AMI) is obscure, the characteristics of this disease vary among studies. The clinical significance of type 2 AMI is unclear. We surveyed the Tokyo Cardiovascular Care Unit (CCU) Network registry between 2010 and 2014. The difference in clinical characteristics and the impact of revascularization in patients with type 1 and type 2 AMI were evaluated. The cohort study included 12514 patients admitted to CCU (type 1 AMI, 12023; type 2 AMI, 491; mean age, 68 ± 15 years; 75% male). Coronary angiography was performed in 11402 patients (95%) with type 1 AMI and 427 (87%) with type 2 AMI ($p < 0.001$). Type 2 AMI was associated with higher in-hospital mortality (type 1 AMI, 769 (6.4%); type 2 AMI, 54 (11.0%); adjusted odds ratio (OR) 1.64; 95% confidence interval (CI) 1.12–2.41; $p = 0.011$) and higher non-cardiac mortality (adjusted OR 2.19; 95% CI 1.33–3.62; $p = 0.002$), but similar cardiac mortality rate compared to type 1 AMI (adjusted OR 1.17; 95% CI 0.71–1.91; $p = 0.539$). Percutaneous coronary intervention (PCI) within 24 h after the onset was associated with lower in-hospital mortality in those with type 1 AMI (OR 0.47; 95% CI 0.40–0.55; $p < 0.001$), but not in those with type 2 AMI (OR 1.09; 95% CI 0.62–1.94; $p = 0.763$). The results persisted after adjustment for multivariate logistic regression analysis and inverted probability weighting. In conclusion, patients with type 2 AMI had higher in-hospital mortality owing to higher non-cardiac death. More refined definitions focusing on the treatment of comorbidities may be required, as the treatment strategy for type 2 AMI can be different from that for type 1 AMI.

Keywords Type 2 AMI · Acute myocardial infarction · Universal definition of myocardial infarction · Non-cardiac mortality · Percutaneous coronary intervention

Introduction

The measurement of cardiac troponins resulted in a paradigm shift in the diagnosis of acute myocardial infarction (AMI). The use of cardiac troponin improves sensitivity but reduces specificity. Therefore, type 2 AMI, which is due to myocardial ischemia resulting from either increased oxygen demand or decreased oxygen supply, was introduced into the universal definition [1] to distinguish it from classic AMI, called as type 1 AMI. Patients with type 2 AMI may or may not have atherosclerotic coronary artery disease (CAD). There is an ongoing controversy regarding whether the presence of CAD should be introduced as a criterion for type 2 AMI [2]. The varied incidence of type 2 AMI, from 1.6 to 29.6% [3–5], reflects vague definitions and various reporting practices. Overall, type 2 AMI may be underdiagnosed. Collinson et al. criticized type 2 AMI, expressed it as a chimera, and believed that type 2 AMI was confusing and not evidence-based [6]. Whether the clinical course and the treatment strategy of the farraginous group vary from those of type 1 AMI has not been investigated sufficiently. The present study aimed to clarify the clinical characteristics and the clinical impact of coronary revascularization in Japanese patients with type 2 AMI.

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Materials and methods

Study population

The Tokyo Cardiovascular Care Unit (CCU) Network Database is an ongoing, multicenter, and prospective population-based registry. The Tokyo CCU Network consists of 72 institutes and provides acute cardiac medical care for 13 million residents in Tokyo. The present study included those with ST-segment elevation myocardial infarction (STEMI) between 2010 and 2014. All data were analyzed retrospectively.

Data collection

The Tokyo CCU Network Database includes age, gender, vital signs, Killip classification, history of hypertension, dyslipidemia, diabetes mellitus, comorbidities such as sepsis and renal failure, myocardial infarction, and percutaneous coronary intervention (PCI), blood examination and drugs during hospitalization, findings on cardiac angiogram, the devices used for PCI, and in-hospital mortality. Estimated glomerular filtration rate (eGFR) was calculated from the formula for Japanese patients as below: eGFR (mL/min/1.73 m^2) = 194 × serum $Cr^{-1.094}$ × $age^{-0.287}$ × (0.739 if female) [7].

Definition

Type 1 AMI is defined as spontaneous AMI. The category relates to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries, leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis [8]. Type 2 AMI is defined as AMI secondary to an ischemic imbalance because of increased oxygen demands (e.g., sustained tachyarrhythmia, ventricular hypertrophy, or hyperthyroidism) or decreased supply (e.g., severe anemia, hypotension, hypoxia, vasospasm, or coronary embolism). Type 2 AMI includes atherosclerosis and oxygen supply/demand imbalance, vasospasm or microvascular dysfunction, non-atherosclerotic coronary dissection, and oxygen supply/demand imbalance alone [8]. The categorization was judged by cardiologists certificated by the Japanese Circulation Society in each of the 72 institutes. Exclusive auditing by an investigator (M.T.) ensured proper registration of each patient.

Early coronary angiography (CAG) and PCI were defined as the procedures performed within 24 h after onset.

Peripheral artery disease (PAD) was diagnosed if an ankle-brachial systolic blood pressure index ≤ 0.9 and/or narrowing/occluded arteries of the lower extremity were confirmed by imaging such as computed tomography, magnetic resonance angiography, and angiography.

Inclusion and exclusion criteria

Patients with either type 1 or type 2 AMI were included. Those with an absence of data regarding the classification based on the Third Universal Definition of Myocardial Infarction were excluded.

Endpoint

The primary endpoint was in-hospital mortality. The secondary endpoints were cardiac and non-cardiac death. The cause of death was confirmed by cardiologists in charge at each institute based on either autopsy or clinical data.

Ethical principles

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, in line with the Ethical Guidelines for Epidemiological Research by the Japanese government. The study was approved by the institutional review board of Tokyo CCU Network Scientific Committee. According to the guidelines, the study satisfied the conditions for waiving the requirement for informed consent from individual participants.

Statistical analysis

Numerical data were presented as mean ± standard deviation if the data followed normal distribution. Otherwise, the data were presented as median and interquartile range (Q1–Q3) values. Categorical variables were expressed as absolute numbers or percentages. Continuous variables were analyzed using the unpaired Student t test and Mann–Whitney U test. The Fisher's exact test and the χ^2 test were used for categorical variables. The in-hospital mortality was assessed using uni- and multivariate logistic regression analyses and expressed as odds ratio (OR), 95% confidence interval (CI), and p values. Variables with p values < 0.10 in the univariate regression analysis were entered in the multivariate logistic regression analysis. In an adjusted model, age, gender, Killip classification, hemoglobin level, serum creatinine level, hypertension, dyslipidemia, and diabetes mellitus were included. Propensity score-matching was used for comparing both treatment and control groups regarding potential confounding factors and to evaluate the clinical impact of early PCI. Variables used for propensity score-matching were decided using the logit model. Inverse probability weights (IPW) was an effective way to minimize selection bias. The clinical variables used to generate IPW were age,

gender, hypertension, dyslipidemia, diabetes mellitus, PAD [9], history of stroke and PCI, Killip classification, a value of serum creatinine, hemoglobin, C-reactive protein (CRP), and brain natriuretic peptide (BNP). Age, serum creatinine, hemoglobin, CRP, and BNP divided into tertile levels. Balance between both groups was assessed based on standardized difference, variance ratio, and propensity score distribution. Statistical significance was set at $p < 0.05$. All statistical analyses were carried out using Stata software, version 14 (StataCorp, College Station, TX).

Results

Patient characteristics

The cohort study included 16274 patients with AMI. Of them, 3546 (22%) were excluded due to lack of data regarding the third universal definition of myocardial infarction. AMI was classified into six subtypes as shown in Fig. 1. Seventy-three patients with type 3 AMI, 53 with type 4a AMI, 77 with type 4b AMI, and 11 with type 5 AMI were excluded. Eventually, 12514 patients (type 1 AMI, 12023; type 2 AMI, 491; mean age, 68 ± 15 years; 75% male) were evaluated. The patients with type 2 AMI were older, more likely to be female, and had a lower body mass index as compared to those with type 1 AMI. There was no significant difference in vital signs and ejection fraction between the groups. Patients with type 2 AMI demonstrated lower values of hemoglobin, peak creatinine kinase, and cholesterol, and higher values of CRP, serum creatinine, BNP, and D-dimer. The detailed characteristics are shown in Table 1. Possible provoking conditions in patients with type 2 AMI were as follows: congestive heart failure (101, 21%); anemia (58, 12%); tachyarrhythmia (54, 11%); infection/sepsis (45, 9%); multiple organ failure/shock (41, 8%); digestive disease (25, 5%); and coronary vasospasm (4, 1%). CAG was performed in 11402 patients (95%) with type 1 AMI and 427 (87%) with type 2 AMI ($p < 0.001$). The angiographic characteristics are shown in Table 2. Notably, almost 90% of patients with type 2 AMI demonstrated > 75% of stenosis. There was no significant difference in the prevalence of the culprit lesions between the groups. Patients with type 1 AMI were more likely to take antiplatelet therapy, renin-angiotensin system inhibitors, ß blockers, and statins in comparison to those with type 2 AMI ($p < 0.001$), while those with type 2 AMI took calcium channel blockers (CCB) more frequently (16% vs. 29%, $p < 0.001$) (Table 3).

In-hospital mortality

In-hospital death occurred in 823 patients and the mortality rate was 6.6%. Of them, 769 patients with type 1 AMI (6.4%) and 54 patients with type 2 AMI (11.0%) died. Patients with type 2 AMI had a higher mortality than those with type 1 AMI (odds ratio (OR), 1.80; 95%

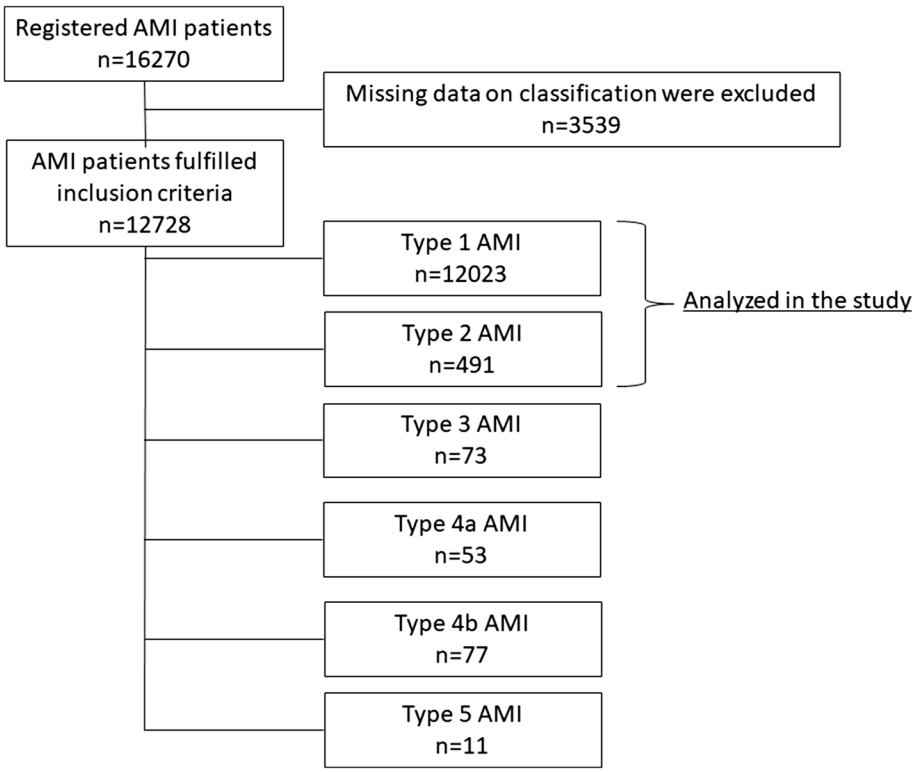

Fig. 1 Study population. Out of a total of 16270 AMI patients, 12023 type 1 AMI and 491 type 2 AMI patients were included. *AMI* acute myocardial infarction

Table 1 Patient characteristics

	All ($n=12514$)	Type 1 AMI ($n=12023$)	Type 2 AMI ($n=491$)	p value
Patient background				
Age (years)	68 ± 15	68 ± 15	70 ± 13	0.003
Male [*n* (%)]	9422 (75)	9072 (75)	350 (71)	0.036
Height (cm)	162 ± 10	162 ± 10	161 ± 10	0.003
Body weight (kg)	63 ± 14	63 ± 14	61 ± 13	< 0.001
BMI (kg/m^2)	24 ± 4	24 ± 4	23 ± 4	0.022
Systolic BP (mmHg)	131 ± 37	131 ± 32	128 ± 36	NS
Diastolic BP (mmHg)	78 ± 19	78 ± 19	77 ± 20	NS
Heart rata (bpm)	78 ± 23	78 ± 23	80 ± 26	NS
Respiratory rate (min^{-1})	20 ± 5	20 ± 5	21 ± 5	NS
Body temperature (°)	36.3 ± 0.6	36.3 ± 0.6	36.3 ± 0.7	NS
Hypertension [*n* (%)]	7375 (60)	7064 (59)	311 (63)	NS
Dyslipidemia [*n* (%)]	5312 (42)	5044 (42)	174 (35)	0.004
Diabetes mellitus [*n* (%)]	3893 (31)	3745 (31)	148 (30)	NS
PAD [*n* (%)]	190 (2)	182 (2)	8 (2)	NS
Past history of stroke [*n* (%)]	796 (6)	748 (6)	35 (7)	NS
Past history of PCI [*n* (%)]	1282 (10)	1120 (9)	65 (13)	0.004
Killip 1 [*n* (%)]	9021 (72)	8685 (72)	336 (68)	NS
Killip 2 [*n* (%)]	1489 (12)	1429 (12)	60 (12)	NS
Killip 3 [*n* (%)]	714 (6)	673 (6)	41 (8)	0.010
Killip 4 [*n* (%)]	928 (7)	889 (7)	39 (8)	NS
Unknown of Killip [*n* (%)]	362 (3)	347 (3)	15 (3)	NS
Electrocardiogram				
STEMI [*n* (%)]	9205 (74)	8917 (74)	288 (59)	< 0.001
Echocardiogram				
Ejection fraction (%)	51 ± 12	51 ± 12	52 ± 13	NS
Laboratory data				
Hemoglobin (mg/dl)	13.7 ± 2.2	13.7 ± 2.2	13.0 ± 2.6	< 0.001
C-reactive protein (mg/dl)	0.3 (0.1–1.0)	0.3 (0.1–0.9)	0.3 (0.1–1.8)	< 0.001
Creatinine (mg/dl)	1.0 ± 0.8	1.0 ± 0.8	1.2 ± 0.9	0.031
eGFR (ml/min/1.73^2)	64 (47–81)	64 (48–81)	60 (41–78)	0.001
Peak creatinine kinase (IU/L)	1488 (606–3049)	1513 (613–3089)	1038 (445–2048)	< 0.001
HbA1c (%)	6.2 ± 1.0	6.2 ± 1.0	6.1 ± 0.9	NS
BNP (pg/ml)	103 (32–329)	102 (32–326)	143 (41–445)	0.002
Total cholesterol (mg/dl)	189 ± 46	190 ± 46	174 ± 42	< 0.001
LDL (mg/dl)	118 ± 40	118 ± 40	104 ± 40	< 0.001
HDL (mg/dl)	47 ± 14	47 ± 14	47 ± 15	NS
D-dimer (μg/ml)	0.9 (0.6–1.7)	0.9 (0.6–1.7)	1.0 (0.7–1.9)	0.003
Procedure				
Early CAG [*n* (%)]	11833 (95)	11406 (95)	427 (87)	< 0.001
Early PCI [*n* (%)]	9464 (77)	9206 (77)	258 (53)	< 0.001
TIMI flow				
TIMI3 prior to PCI (%)	16	14	21	< 0.001
TIMI3 post PCI (%)	93	93	89	0.014

AMI acute myocardial infarction, *BMI* body mass index, *BP* blood pressure, *eGFR* estimated glomerular filtration rate, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *NS* not significant, *PAD* peripheral artery disease, *PCI* percutaneous coronary intervention, *STEMI* ST-segment elevation myocardial infarction, *TIMI* Thrombolysis in Myocardial Infarction

Table 2 Angiographical characteristics

	All	Type 1 AMI	Type 2 AMI	*p* value
Organic lesion				
LMT (%)	6.4	6.4	6.3	NS
LAD (%)	70.0	70.1	66.4	0.001
LCx (%)	40.1	40.1	40.3	NS
RCA (%)	52.1	52.1	52.2	NS
No lesion (%)	0.1	0.0	0.3	NS
Stenosis of < 75%	2.5	2.2	10.8	< 0.001
TIMI flow				
TIMI3 prior to PCI (%)	16.0	15.6	28.6	< 0.001
TIMI3 post PCI (%)	92.8	92.9	89.0	0.014

AMI acute myocardial infarction, *CAG* coronary angiography, *LAD* left anterior descending artery, *LCx* left circumflex artery, *LMT* left main trunk, *NS* not significant, *RCA* right coronary artery, *TIMI* Thrombolysis in Myocardial Infarction

CI, 1.35–2.41; $p < 0.001$). Multivariate logistic regression analysis showed similar results (OR, 1.64; 95% CI, 1.12–2.41; $p = 0.011$).

Cause of death

Cardiac, non-cardiac, and unidentified death occurred in 503, 316, and 4 patients, respectively. The type 2 AMI group showed a higher non-cardiac mortality rate as compared with the type 1 AMI group, while the cardiac mortality rate was similar between the groups. The results persisted even after adjustment (Fig. 2a–c). Considering cardiac death in patients with type 1 and type 2 AMI, 97 patients died from congestive heart failure; re-infarction, 17; cardiogenic shock, 234; cardiac rupture, 84; and lethal arrhythmia, 73 (2 cases with cardiogenic shock overlapped with lethal arrhythmia). Only the prevalence of heart failure as the cause of death was higher in those with type 2 AMI than in those with type 1 AMI (type 1 AMI, 89 [0.7%]; type 2 AMI, 8 [1.6%], $p = 0.028$), regardless of the similar EF.

Implementation rate and clinical impact of early PCI

In the present study, early CAG was performed in 11833 (95%) of all the patients; early PCI was performed in 9464 patients (76%). There were more patients who underwent early CAG and PCI in the type 1 AMI group compared to the type 2 AMI group [early CAG: 11406 (95%) in type 1 AMI and 427 (87%) in type 2 AMI, $p < 0.001$; early PCI: 9206 (77%) in type 1 AMI and 258 (53%) in type 2 AMI, $p < 0.001$]. Multivariate logistic regression analysis and IPW revealed that early PCI performed within 24 h after onset was associated with lower in-hospital mortality in patients with type 1 AMI. However, similar results were not observed in patients with type 2 AMI (Table 4).

Discussion

The present study revealed that in-hospital mortality rate in patients with type 2 AMI was higher than that in those with type 1 AMI, and these results were due to higher non-cardiac mortality. Furthermore, the association between early PCI and reduced in-hospital mortality was unclear in those with type 2 AMI. The result may reflect higher non-cardiac death in the subgroup. These data indicate that not only cardiologists, but also other specialists should participate in the clinical management in the setting of type 2 AMI to overcome high mortality.

Since the definition of type 2 AMI is obscure, we should verify whether the characteristics of type 2 AMI in the present study are different from those in past studies. The previous studies [10–12] reported that patients with type 2 AMI were older, more likely to be female, and less often referred for PCI than those with type 1 AMI. Moreover, short-term mortality was higher in the type 2 AMI group than in the type 1 AMI group. The similarities of patients' background would guarantee the accuracy in the diagnosis of type 2 AMI in our study.

On the other hand, some findings such as the prevalence of type 2 AMI and implemental rate of CAG and PCI varied among the present study and other studies. A meta-analysis

Table 3 Medication

	All ($n = 12514$)	Type1 AMI ($n = 12023$)	Type 2 AMI ($n = 491$)	*p* value
Antiplatelet therapy [*n* (%)]	12138 (97)	11662 (97)	442 (90)	< 0.001
ACE-I and/or ARB [*n* (%)]	7785 (62)	7531 (63)	254 (52)	< 0.001
β Blocker [*n* (%)]	7022 (56)	6786 (56)	236 (48)	< 0.001
Statin [*n* (%)]	9536 (76)	9238 (77)	298 (61)	< 0.001
CCB [*n* (%)]	2101 (17)	1961 (16)	140 (29)	< 0.001

ACE-I angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *CCB* calcium channel blocker

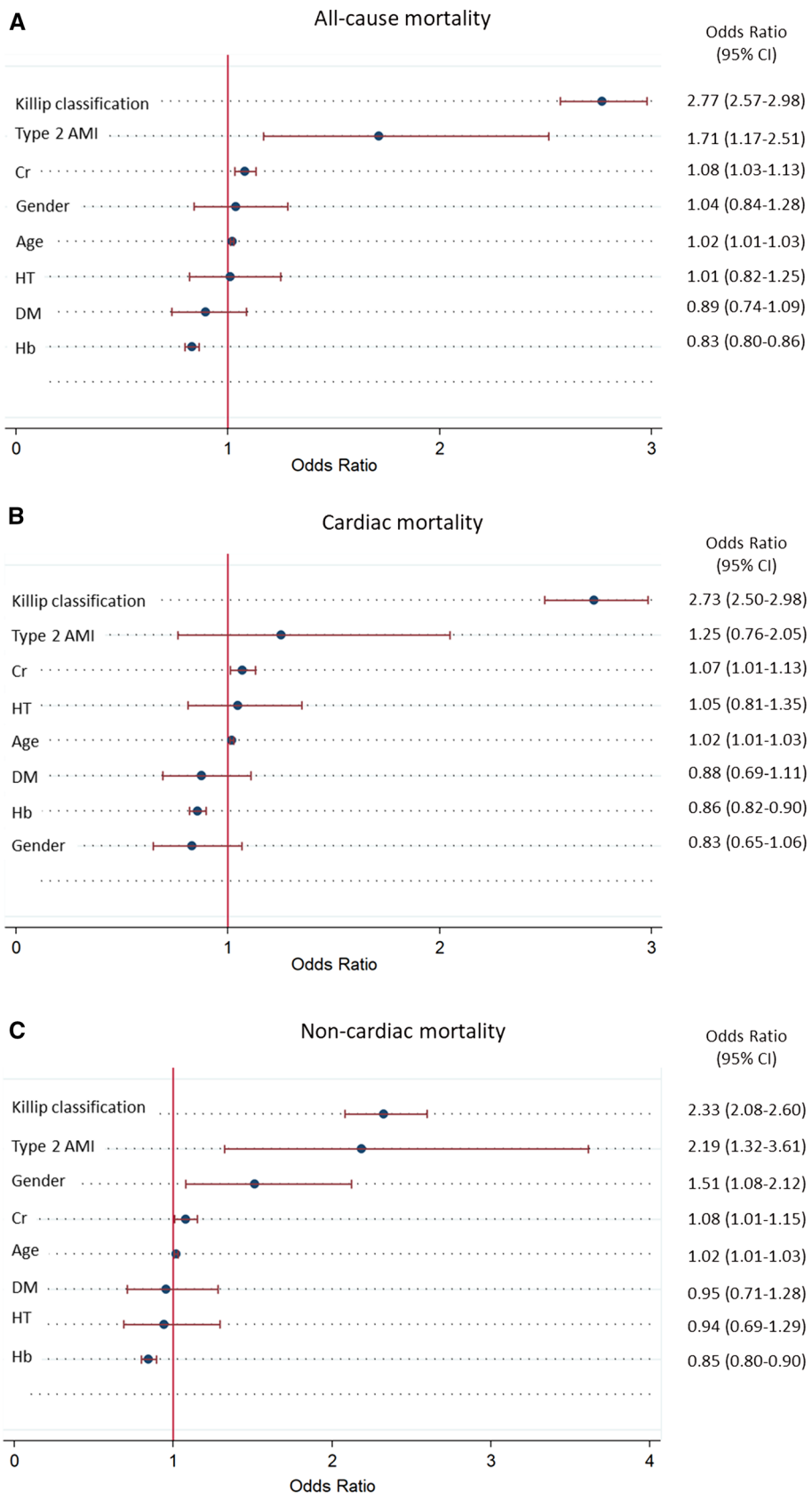

Fig. 2 **a** Multivariate logistic regression analysis for all-cause mortality. Patients with type 2 AMI had higher all-cause mortality as compared with those with type 1 AMI. Higher Killip classification, a higher value of creatinine, and older age were also related to poor outcome. A higher value of hemoglobin was associated with lower mortality. *AMI* acute myocardial infarction, *CI* confidence interval, *Cr* creatinine, *DM* diabetes mellitus, *Hb* hemoglobin, *HT* hypertension. **b** Multivariate logistic regression analysis for cardiac mortality. Prevalence of cardiac mortality was similar between type 1 and 2 AMI. **c** Multivariate logistic regression analysis for non-cardiac mortality. Type 2 AMI was related to a 2.19-fold increased risk for non-cardiac mortality

Table 4 The clinical impact of early intervention on in-hospital mortality

	Univariate			Multivariate			Inverse probability weighting		
	OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value
All	0.50	0.43–0.58	< 0.001	0.72	0.59–0.87	0.001	0.98	0.97–0.99	0.003
Type 1 AMI	0.47	0.40–0.55	< 0.001	0.67	0.55–0.83	< 0.001	0.98	0.97–0.99	0.002
Type 2 AMI	1.09	0.62–1.94	0.763	1.18	0.52–2.68	0.698	0.99	0.93–1.04	0.777

AMI acute myocardial infarction, *CI* confidence interval, *OR* odds ratio

conducted by Gupta et al. demonstrated that the prevalence of type 2 AMI was approximately 10% of all the AMI patients, whereas no more than 4% in our study. The difference in prevalence could be due to different subsets of the patients. The most common cause of type 2 AMI in the meta-analysis was operative stress with a prevalence of 20% [13]. The lower prevalence might be due to selection bias because our registry enrolled only emergency patients from the cardiovascular care unit (CCU), and did not include surgical patients. The implementation rate of CAG and PCI in the present study was much higher in those with type 2 AMI as compared with that in a previous study [12]. A high implementation rate of CAG may strengthen accurate diagnosis to distinguish type 2 AMI. A higher prevalence of STEMI in this cohort may also explain the high rate of CAG. The prevalence of significant stenosis in the present study was higher in comparison with that in the previous studies, which indicated 36–78% [5, 14–17]. This could be described by the characteristics of the registry that included only CCU patients. Patients with any comorbidities may be diagnosed as type 2 AMI regardless of stenosis/occlusion. Those with significant stenosis and no finding of plaque rapture may be also included in this category. Notably, the implementation rate of PCI (53%) was lesser than the prevalence of STEMI (59%) in those with type 2 AMI. This finding and the higher prescription rate of calcium channel blockers might suggest a contribution of vasospasm, which appears to be more frequent in the Japanese as compared with the Caucasian population [18].

The reasons why early PCI was not associated with reduced in-hospital mortality can be explained by higher non-cardiac death. Even if PCI could reduce the risk of cardiac death, failure of treatment of comorbidities or triggers of type 2 AMI would result in in-hospital mortality.

We should reconsider the significance of type 2 AMI. In some patients, the category may be only an adverse predictor of non-cardiac disease, rather than a subset of AMI [19, 20]. Non-cardiac disease with an elevated cardiac troponin may be regarded as a serious condition. Understanding the causes and/or comorbidities of type 2 AMI is important for proper treatment and improved prognosis. As McCarthy et al. pointed out, a more precise definition that does not cause misunderstanding among physicians is needed [21]. The significant differences regarding event-related mortality and treatment between the 2007 and 2012 universal definition [22] may indicate that the definition has been improvised. Further studies to investigate multidisciplinary treatment strategies depending on each cause of oxygen supply/demand mismatch may contribute to reducing the mortality in the setting of type 2 AMI.

There were some limitations in this study. First, although our registry included information regarding comorbidities, a definitive trigger for type 2 AMI was unknown, e.g., it was occasionally difficult to determine whether congestive heart failure was a trigger or a result of AMI. Second, the prevalence of STEMI was highly unusual for type 2 AMI. This would suggest that some patients with type 2 MI were not included in the present study because this was a series of patients admitted to the CCU. Some patients with Type 2 AMI are admitted to other departments such as medical intensive care unit (ICU), surgical ICU, or general medicine wards. Therefore, this series included more severe patients and might not be a representative sample of hospitalized patients with Type 2 AMI. Third, even though IPW adjusted confounding factors, the clinical impact of early PCI on in-hospital mortality in type 2 AMI patients was not determined because of possible unknown selection bias and the retrospective analysis. Finally, the dataset did not record long-term prognosis. Comorbidities would be important predictors for long-term clinical events such as death [23] and readmission [24]. Nevertheless, the present study emphasizes the importance of "type 2 AMI" for clinical management.

Conclusions

The patients with type 2 AMI had higher in-hospital mortality due to higher non-cardiac death. The association between early PCI and in-hospital mortality was not clear. The classification "type 2 AMI" seems to be essential because the treatment strategy may be radically different from that for type 1 AMI.

Acknowledgements Financial support for this study was provided by the Tokyo Metropolitan Government, and JSPS KAKENHI Grant

number 17K18085 [S.H.]. We thank all the cardiologists and staff participating in the Tokyo CCU Network and Ms. Nobuko Yoshida (Tokyo CCU Network office) for data acquisition.

Compliance withe ethical standards

Conflict of interest The authors report no conflicts of interest.

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