Is the Prognosis Favourable in Patients without Cardiogenic Shock on Admission Following Acute Myocardial Infarction in the Left Main Trunk?

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Background: Acute myocardial infarction in the left main trunk (LM-AMI) is a rare but serious condition. The purpose of the present study was to clarify differences in prognosis and factors associated with in-hospital death for patients with LM-AMI with or without CS on admission. **Methods:** The present retrospective observational study cohort consisted of 183 patients with LM-AMI in the registry of the Cardiovascular Research Consortium-8 Universities in eastern Japan between 1997 and 2016. The patients with LM-AMI were divided into two groups: those with CS on admission and those who did not have CS on admission. **Results:** In-hospital mortality in the CS and the non-CS group was 70.8% and 22.3%, respectively. In the non-CS group, the in-hospital mortality significantly increased along with increased Killip class (p = 0.028). Multivariate analysis showed a significantly elevated HR of 5.59 (95% CI, 1.24 to 25.26; p = 0.025) for in-hospital death among patients in the non-CS group categorized into Killip classification III. In contrast, in the CS group, the HR of coronary slow-flow after percutaneous coronary intervention for in-hospital death was 3.08 (95% CI, 1.52 to 6.25; p = 0.002). **Conclusions:** The prognosis of the non-CS group among patients with LM-AMI was also worse. The risk factors for in-hospital death between the CS and non-CS groups were different. Even for the non-CS group, the severity of heart failure was correlated with in-hospital death.
KEY WORDS: acute myocardial infarction, cardiogenic shock, in-hospital death, left main trunk

I. Objective

Acute myocardial infarction in the left main trunk (LM-AMI) is a serious clinical condition with a mortality of at least 20 to 40%[1–3]. Although more rapid reperfusion therapy is very import-ant especially in LM-AMI, most in-hospital deaths in patients with LM-AMI are caused by pump failure with extensive myocardial damage in a short period of time. Factors associated with in-hospital death in patients with LM-AMI include cardiogenic shock (CS)[1, 2, 4, 5], cardiopulmonary resuscitation (CPR)[5] and low glomerular filtration rate (GFR)[2]. Among these factors, CS in particular has a large impact on the prognosis of patients[1, 2 4–6]. However, no reports have compared patients with or without CS because LM-AMI is relatively rare (2.2% of AMI cases)[7]. Especially, it is also unclear what factors in patients without CS are associated with in-hospital death.

The authors considered that it is important to clarify differences between the two groups of clinical characteristics on admission to help determine optimal management of medical treatment, including revascularization and assisted circulation devices.

The purpose of the present study was to clarify differences in prognosis and factors associated with in-hospital death for patients with LM-AMI with or without CS on admission.

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II. Patients or materials

A total of 183 patients who met the MONICA criteria[7] for LM-AMI were enrolled in this study. These patients had been admitted from May 1997 through December 2016 to any of 10 medical facilities in the Cardiovascular Research Consortium-8 Universities (CIRC-8U: Iwate Medical University, Kitasato University Hospital, Tokai University Hospital, Dokkyo Medical University Hospital, Dokkyo Medical University Koshigaya Hospital, Dokkyo Medical University Nikko Medical Center, Saitama Medical University International Medical Center, St. Marianna University Hospital, Teikyo University Hospital, and Kyorin University Hospital). This study was conducted in accordance with the code of ethics stated in the Declaration of Helsinki after receiving approval from the ethics committee in each institute.

Clinical information including patient characteristics was obtained from the medical records. Study patients were divided into two groups for comparison based on the presence or absence of CS (Killip class IV on admission; systolic blood pressure < 90 mmHg and peripheral circulatory failure) at the time of hospital admission. The patients who underwent defibrillation for ventricular fibrillation during transport and improved their vitals at admission were included in the non-CS group. Patients with systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg on admission, or patients taking antihypertensive drug(s) were defined as having hypertension. Patients with HbA1c ≥ 6.5% (NGSP), fasting blood glucose level ≥ 126 mg/dL, casual blood glucose level ≥ 200 mg/dL, or blood glucose level at 2 hours after 75 g of oral glucose tolerance test (OGTT) ≥ 200 mg/dL found on examination during their hospital stay, or patients under any antidiabetic treatments (diet regimen, oral medication, insulin therapy) were defined as having diabetes. Patients with total cholesterol level ≥ 220 mg/dL, low-density lipoprotein (LDL) cholesterol level ≥ 140 mg/dL, high-density lipoprotein (HDL) cholesterol < 40 mg/dL or triglyceride level ≥ 150 mg/dL in the examination on admission, or patients being administered hypolipidaemic drug(s) were defined as having dyslipidaemia. In accordance with the MONICA criteria, patients having 2 times or more higher CK or CK-MB (creatine kinase-muscle/brain) levels than the reference level who met at least one of the following criteria were diagnosed as having AMI[8]: 1) symptoms associated with ischaemic cardiac diseases; 2) newly developed Q waves on electrocardiography; and 3) significant ischaemic changes in ST segment. Bleeding complications were classified as Type 3 or higher according to the Bleeding Academic Research Consortium (BARC)[9] as follows: Type 3a, overt bleeding with haemoglobin drop of 3–5 g/dL or any transfusion; Type 3b, overt bleeding with haemoglobin drop of ≥ 5 g/dL, bleeding requiring pressors or surgical intervention, or cardiac tamponade; Type 3c, intraocular or intracranial bleed; Type 4, CABG-related bleeding; transfusion of ≥ 5 units blood, repeat sternotomy and chest tube output ≥ 2 litres within 24 hours; Type 5, fatal bleeding.

1. Statistical analysis

A retrospective observational study was conducted to compare the clinical data such as clinical characteristics, in-hospital mortality and therapeutic regimen between the CS and non-CS groups. Actual measured values were expressed as the mean ± standard deviation (SD), and analyses for comparison were performed by using Mann-Whitney U test and chi-square test. The end point of the present study was hospital discharge or all-cause death. The cumulative survival rate in the period was estimated by Kaplan-Meier method. Cox proportional hazard models were used to obtain hazard ratios for in-hospital death. Multivariate analysis was performed on covariates, including age, gender, Killip classification, and some factors according to the univariate analysis of all patients. Statistical analyses were conducted with SPSS 25.0 for Windows (IBM, Chicago, IL, USA).

The peak CK level in predicting in-hospital death was analysed with an area under the receiver-operating characteristic (ROC) curve (AUC). In all analyses, p < 0.05 was considered to be statistically significant.

III. Results

Clinical characteristics of the patients in the CS and non-CS groups are summarized in (Table 1). The mean age of all patients was 71.2 years old. About 80% in patients with LM-AMI were male. Overall in-hospital mortality in the entire population of patients with LM-AMI was 45.4%. CS was found in 89 (48.6%) of the 183 patients with LM-AMI. In-hospital mortality in the CS and the non-CS group was 70.8% and 22.3%, respectively. There were no significant differences in prevalence of coronary risk factors or history of myocardial infarction between the two groups. Mean eGFR was significantly lower in the CS group than in the non-CS group. Intra-aortic balloon pumping (IABP) and venoarterial extracorporeal membrane oxygenation (VA-ECMO) were introduced in 84.2% and 25.7%, respectively. VA-ECMO was introduced in 38.2% of patients in the CS group and 13.8% of those who had not presented with CS on admission. Three out of the four patients who developed mechanical complications (four cases of myocardial rupture) underwent primary PCI, and two of them developed coronary slow flow (not shown in a table).

The in-hospital mortality significantly increased along with increased Killip class (Supplemental Fig. 1). Characteristics of the survival group (n=100) and death group (n=83) are summarized in (Table 2). Overall, in the patients with LM-AMI, the

Table 1 Clinical characteristics of patients with LM-AMI

	All (n=183)	Non-CS (n=94)	CS (n=89)	p value
Age (years)	71.2 ± 11.0	72.0 ± 10.5	70.3 ± 11.5	0.319
Gender (Male)	79.8 %	74.5 %	85.4 %	0.067
Body mass index (kg/m²)	23.3 ± 3.8	23.2 ± 3.7	23.5 ± 3.9	0.635
Cardiopulmonary resuscitation	16.4 %	5.3 %	28.1 %	＜0.001
Past history of percutaneous coronary intervention	13.1%	16.0%	10.1%	0.221
Past history of coronary artery bypass grafting	2.7 %	5.3 %	0	0.026
Past history of cerebral infarction	11.5 %	11.7 %	11.2 %	0.924
Current smoking	48.6 %	54.3 %	44.9 %	0.480
Hypertension	41.0 %	52.6 %	39.3 %	0.545
Diabetes mellitus	61.7 %	63.8 %	60.1 %	0.907
Dyslipidemia	47.5 %	53.2 %	41.6 %	0.175
Heart rate(/minute)	85.7 ± 30.0	86.5 ± 19.5	84.8 ± 38.0	0.547
Systolic blood preassure	117.4 ± 35.2	131.3 ± 30.4	100.3 ± 33.3	＜0.001
Killip classification	I =38, II =21, III =23, IV =89, ?=12	I =38, II =21, III =23, IV =0, ?=12	I =0, II =0, III =0, IV =89, ?=0	＜0.001
Sinus rhythm on admission	72.1 %	84.0 %	75.3 %	＜0.001
ST- elevation acute myocardial infarction	57.3 %	50.0 %	65.1 %	0.001
Left ventricular dysfunction (ejection fraction < 40%)	41.5 %	34.0 %	50.1 %	＜0.001
Median of serum creatinine on admission (mg/dL)	1.05	0.94	1.10	0.037
Estimated glomerular filtration rate (eGFR) (mL/min/1.73m²)	52.0 ± 24.8	55.3 ± 28.3	48.4 ± 20.1	0.018
Hemoglobin A1c (%)	6.2 ± 2.6	6.3 ± 3.1	6.1 ± 1.3	0.245
Number of patients with vessel disease	SVD=47, DVD=59, TVD=33, LM only=32, ?=11	SVD=24, DVD=27, TVD=20, LM only=17, ?=6	SVD=23, DVD=32, TVD=13, LM only=16, ?=5	0.667
Lesions at ostium or at the body of left main trunk	63.3 %	61.4 %	64.9 %	0.922
Collaterals	13.7 %	12.8 %	14.6 %	0.904
Coronary artery dominant	Left=19, Right=41, Balance=97	Left=9, Right=17, Balance=50	Left=10, Right=25, Balance=47	0.092
Emergency percutaneous coronary intervention (PCI)	76.0 %	61.7 %	91.0 %	＜0.001
Door to balloon time (median) (minutes)	66.4	69.2	63.7	0.924
Coronary slow flow after PCI (final TIMI flow grade < 3)	12.0 %	2.1 %	22.5 %	＜0.001
Intra-aortic balloon pumping	84.2 %	77.7 %	91.0 %	0.057
Venoarterial extracorporeal membrane oxygenation	25.7 %	13.8 %	38.2 %	＜0.001
Emergency coronary artery bypass grafting	20.2 %	27.7 %	12.4 %	0.010
Major bleeding	6.0 %	3.2 %	9.0 %	0.013
Peak creatine kinase (median) (IU/L)	4054.0	1660.5	9819.0	＜0.001
Peak creatine kinase >= 6195.5 (IU/L)*	43.2 %	24.5 %	61.8 %	＜0.001
Peak creatine kinase >= 6218.5 (IU/L)**	43.2 %	24.5 %	61.8 %	＜0.001
Peak creatine kinase >=10184.5 (IU/L)***	32.8 %	20.2 %	46.1 %	＜0.001
Hospitalization (days) (median)	19.5 ± 30.4	23.5 ± 26.9	11.5 ± 34.0	0.023
In-hospital death	45.4 %	22.3 %	70.8 %	＜0.001

*Cutoff value in all patients
**Cutoff value in the non-CS group
***Cutoff value in the CS group
CS: cardiogenic shock, DVD: double vessel disease , LM: left main, SVD: single vessel disease, TVD: triple vessel disease

Killip classification on admission, low cardiac function (left ventricular ejection fraction [LVEF] < 40%) on admission, maximum CK level, rate of PCI, and rate of VA-ECMO were significantly higher in the death group. All five patients with a history of coronary artery bypass grafting (CABG) were in the non-CS group and alive during the hospitalization. Among the non-CS group (n=94), the Killip classification and maximum CK level were significantly higher in the death group. In both the non-CS and CS groups, VA-ECMO was introduced in equal to or more than half of the death group. Among these 47 patients in whom

Table 2 Comparison of characteristics between the groups with or without cardiogenic shock on admission

	All of LM-AMI (n=183)			Non-CS (n=94)			CS (n=89)		
	Survival (n=100)	Death (n=83)	p value	Survival (n=73)	Death (n=21)	p value	Survival (n=27)	Death (n=62)	p value
Age (years)	70.7±12.0	71.8±9.7	0.992	71.4±12.0	73.9±8.7	0.510	68.6±14.3	71.1±10.0	0.851
Gender (Male)	81.0%	78.3%	0.653	78.1%	61.9%	0.136	88.9%	83.9%	0.540
Body mass index (kg/m²)	23.0±3.2	23.9±4.5	0.309	23.0±3.3	24.1±5.0	0.599	22.9±3.0	23.8±4.3	0.480
Cardiopulmonary resuscitation	9.0%	25.3%	0.003	5.5%	4.8%	0.898	18.5%	32.2%	0.187
Past history of percutaneous coronary intervention	15.0%	10.8%	0.414	15.0%	19.0%	0.633	14.8%	8.1%	0.347
Past history of coronary artery bypass grafting	5.0%	0	0.040	6.8%	0%	0.225	0	0	—
Past history of cerebral infarction	12.0%	10.8%	0.857	13.7%	4.8%	0.281	7.4%	12.9%	0.435
Current smoking	54.0%	45.8%	0.088	42.5%	95.2%	0.840	48.1%	43.5%	0.017
Hypertension	40.0%	42.2%	0.784	43.8%	85.7%	0.641	29.6%	43.5%	0.218
Diabetes melitus	67.0%	55.4%	0.164	68.5%	47.6%	0.027	63.0%	59.7%	0.889
Dyslipidemia	53.0%	41.0%	0.124	53.4%	52.4%	0.933	51.9%	37.1%	0.186
Heart rate (/minute)	86.6±23.4	84.7±36.3	0.370	86.0±19.7	88.1±19.2	0.902	87.9±31.4	83.4±40.9	0.716
Systolic blood pressure	126.6±21.5	104.9±36.4	<0.001	133.1±29.1	125.3±34.5	0.375	108.7±31.3	96.0±33.8	0.064
Killip classification	I =34, II =17, III =14, IV =27, ?=8	I =4, II =4, III =9, IV =62, ?=4	<0.001	I =34, II =17, III =14, IV =0, ?=8	I =4, II =4, III =9, IV =0, ?=4	0.011	I =0, II =0, III =0, IV =27, ?=0	I =0, II =0, III =0, IV =62, ?=0	—
Sinus rhythm on admission	82.0%	60.2%	0.002	86.3%	76.2%	0.267	70.4%	56.5%	0.198
ST- elevation acute myocardial infarction	50.0%	66.2%	0.001	45.2%	66.7%	0.095	63.0%	66.1%	0.202
Left ventricular dysfunction (ejection fraction <40%)	34.0%	50.6%	<0.001	30.1%	42.9%	0.281	44.4%	53.2%	0.006
Median of serum creatinine on admission (mg/dL)	0.97	1.10	0.037	0.94	0.96	0.616	1.00	1.17	0.048
Estimated glomerular filtration rate (eGFR) (mL/min/1.73m²)	55.13±28.63	48.40±20.08	0.018	55.1±30.0	55.4±23.8	0.776	56.0±24.4	45.1±17.1	0.034
Renal dysfunction (eGFR < 60mL/min/1.73m²)	55.0%	75.9%	0.002	52.0%	57.1%	0.333	63.0%	80.6%	0.094
High density lipoprotein cholesterol (mg/dL)	49.3±15.8	38.5±14.9	<0.001	49.1±17.1	38.5±17.0	0.092	49.7±9.9	38.5±14.4	0.002
Hemoglobin A1c (%)	6.0±1.5	6.6±3.7	0.358	6.0±1.4	7.6±7.1	0.771	6.1±1.7	6.2±1.1	0.358
Number of patients with vessel disease	SVD=31, DVD=29, TVD=15, LM only=17, ?=8	SVD=16, DVD=30, TVD=18, LM only=16, ?=3	0.235	SVD=19, DVD=22, TVD=13, LM only=13, ?=6	SVD=5, DVD=5, TVD=7, LM only=4, ?=0	0.456	SVD=12, DVD=7, TVD=2, LM only=4, ?=2	SVD=11, DVD=25, TVD=11, LM only=12, ?=3	0.130
Lesions at ostium or at the body of left main trunk	62.9%	63.6%	0.922	62.0%	60.0%	0.877	65.0%	64.9%	0.994
Collaterals	10.0%	18.0%	0.171	11.0%	19.0%	0.421	7.4%	17.7%	0.208
Coronary artery dominant	Left=7, Right=19, Balance=54	Left=12, Right=23, Balance=43	0.092	Left=5, Right=12, Balance=39	Left=4, Right=5, Balance=11	0.188	Left=2, Right=7, Balance=15	Left=8, Right=18, Balance=32	0.482
Emergency percutaneous coronary intervention (PCI)	67.0%	90.4%	<0.001	57.5%	76.2%	0.178	81.5%	95.2%	0.039
Door to balloon time (median) (minutes)	64.6	67.9	0.924	69.9	67.9	0.905	54.1	68.0	0.571
Coronary slow flow after PCI (final TIMI grade < 3)	3.0%	19.3%	0.001	2.7%	0%	0.409	3.7%	30.6%	0.023
Intra-aortic balloon pumping	77.0%	92.8%	0.016	74.0%	90.5%	0.213	85.2%	100.0%	0.207
Venoarterial extracorporeal membrane oxygenation	5.0%	50.6%	<0.001	2.7%	52.4%	<0.001	11.1%	50.0%	0.001
Emergency coronary artery bypass grafting	29.0%	9.6%	0.001	30.1%	19.0%	0.319	25.9%	6.5%	0.011
Major bleeding	4.0%	8.4%	0.220	2.7%	4.8%	0.617	7.4%	9.7%	0.732
Peak creatine kinase (median) (IU/L)	1965.5	11695.0	<0.001	1035.0	12345.0	<0.001	6824.0	11578.0	0.158
Peak creatine kinase >= 6195.5 (IU/L)*	23.0%	67.5%	<0.001	12.3%	66.7%	<0.001	48.1%	67.7%	0.052
Peak creatine kinase >= 6218.5 (IU/L)**	23.0%	67.5%	<0.001	12.3%	66.7%	<0.001	48.1%	67.7%	0.052
Peak creatine kinase >= 10184.5 (IU/L)***	13.0%	56.6%	<0.001	8.2%	61.9%	<0.001	25.9%	54.8%	0.008
Hospitalization (days) (median)	27.0±33.4	5.0±21.4	<0.001	25.0±28.7	7.0±10.8	<0.001	46.5±41.1	4.5±24.0	<0.001

*Cutoff value in all patients
**Cutoff value in the non-CS group
***Cutoff value in the CS group
CS: cardiogenic shock, DVD: double vessel disease , LM: left main, SVD: single vessel disease, TVD: triple vessel disease

VA-ECMO was performed, 3 patients experienced bleeding complications of Type 3 or higher according to the BARC criteria[9].

The authors divided the patients into three groups according to the period of occurrences (not shown in a table): 1997–2005 (n = 29), 2006–2010 (n = 42), and 2011–2016 (n = 112). A rate of IABP was no change (89.7%, 90.5% and 83.3%: p = 0.436). However, rates of emergency PCI (46.4%, 75.6% and 85.6%: p < 0.001) and VA-ECMO (6.9%, 23.8% and 32.4%: p = 0.02) were increased. Conversely, a rate of emergency CABG was decreased in trend (55.2%, 21.4% and 10.7%: p < 0.001). Meanwhile, in-hospital mortality was increased in trend (24.1%, 45.2% and 50.9%: p = 0.036).

This study evaluated in-hospital death and the relations of the peak CK level using ROC curves (Supplemental Fig. 2 A, B, C). The AUC was 0.740, and the cutoff value of this ROC curve was 6195.5 IU/L in the entire population of LM-AMI patients. On the other hand, in the non-CS group, the AUC was 0.781, and the cutoff value of this ROC curve was 6218.5 IU/L. In the CS group, the AUC was 0.595, and the cutoff value of this ROC curve was 10184.5 IU/L.

Fig. 1 shows the results of univariate analysis, conducted based on the abovementioned results, regarding risk factors associated with in-hospital mortality in relation to the presence or absence of CS. In the non-CS group, hazard ratios for in-hospital mortality were significantly higher in patients with a high peak CK level. In the CS group, hazard ratios for in-hospital mortality were significantly higher in patients with coronary slow flow after PCI. The cumulative survival rates of each factors in all patients were as shown Supplemental Fig. 3.

Fig. 2 shows the results of multivariate analysis on hazard ratios for in-hospital mortality in the entire population of the study patients, the non-CS group, and the CS group. Patients with LM-AMI tended to have a higher risk ratio for in-hospital death in the higher Killip classification (P value for trend = 0.047). In the non-CS group, the hazard ratio increased almost 5 times in patients categorized in Killip classification III. In the CS group, the hazard ratio was high in patients with coronary slow flow (Thrombolysis in Myocardial Infarction ; TIMI flow grade < 3) after PCI, which was most strongly associated with in-hospital outcomes in this group.
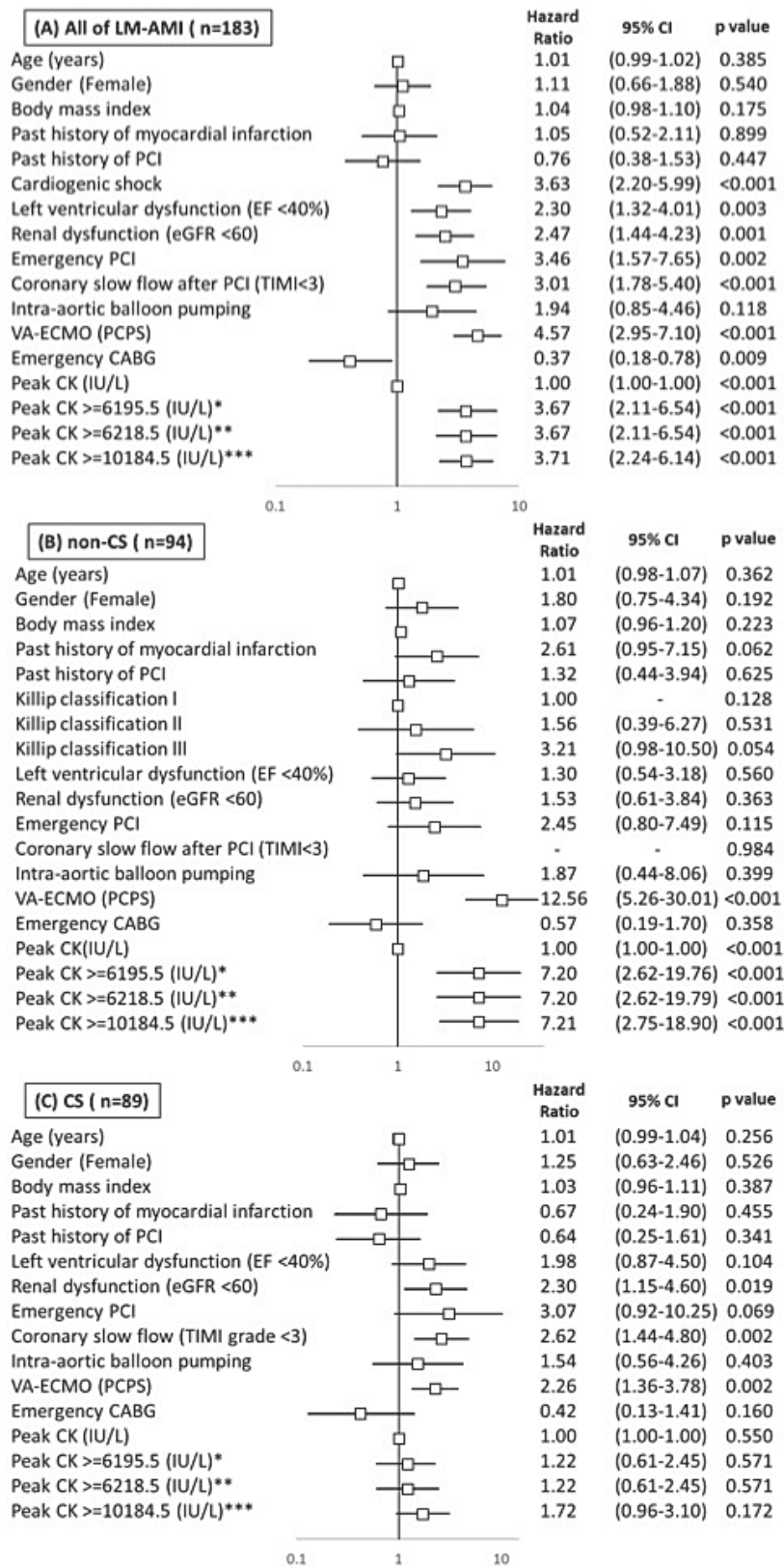
(A) All of LM-AMI (n=183)

	Hazard Ratio	95% CI	p value
Age (years)	1.01	(0.99-1.02)	0.385
Gender (Female)	1.11	(0.66-1.88)	0.540
Body mass index	1.04	(0.98-1.10)	0.175
Past history of myocardial infarction	1.05	(0.52-2.11)	0.899
Past history of PCI	0.76	(0.38-1.53)	0.447
Cardiogenic shock	3.63	(2.20-5.99)	<0.001
Left ventricular dysfunction (EF <40%)	2.30	(1.32-4.01)	0.003
Renal dysfunction (eGFR <60)	2.47	(1.44-4.23)	0.001
Emergency PCI	3.46	(1.57-7.65)	0.002
Coronary slow flow after PCI (TIMI<3)	3.01	(1.78-5.40)	<0.001
Intra-aortic balloon pumping	1.94	(0.85-4.46)	0.118
VA-ECMO (PCPS)	4.57	(2.95-7.10)	<0.001
Emergency CABG	0.37	(0.18-0.78)	0.009
Peak CK (IU/L)	1.00	(1.00-1.00)	<0.001
Peak CK >=6195.5 (IU/L)*	3.67	(2.11-6.54)	<0.001
Peak CK >=6218.5 (IU/L)**	3.67	(2.11-6.54)	<0.001
Peak CK >=10184.5 (IU/L)***	3.71	(2.24-6.14)	<0.001

(B) non-CS (n=94)

	Hazard Ratio	95% CI	p value
Age (years)	1.01	(0.98-1.07)	0.362
Gender (Female)	1.80	(0.75-4.34)	0.192
Body mass index	1.07	(0.96-1.20)	0.223
Past history of myocardial infarction	2.61	(0.95-7.15)	0.062
Past history of PCI	1.32	(0.44-3.94)	0.625
Killip classification I	1.00	-	0.128
Killip classification II	1.56	(0.39-6.27)	0.531
Killip classification III	3.21	(0.98-10.50)	0.054
Left ventricular dysfunction (EF <40%)	1.30	(0.54-3.18)	0.560
Renal dysfunction (eGFR <60)	1.53	(0.61-3.84)	0.363
Emergency PCI	2.45	(0.80-7.49)	0.115
Coronary slow flow after PCI (TIMI<3)	-	-	0.984
Intra-aortic balloon pumping	1.87	(0.44-8.06)	0.399
VA-ECMO (PCPS)	12.56	(5.26-30.01)	<0.001
Emergency CABG	0.57	(0.19-1.70)	0.358
Peak CK(IU/L)	1.00	(1.00-1.00)	<0.001
Peak CK >=6195.5 (IU/L)*	7.20	(2.62-19.76)	<0.001
Peak CK >=6218.5 (IU/L)**	7.20	(2.62-19.79)	<0.001
Peak CK >=10184.5 (IU/L)***	7.21	(2.75-18.90)	<0.001

(C) CS (n=89)

	Hazard Ratio	95% CI	p value
Age (years)	1.01	(0.99-1.04)	0.256
Gender (Female)	1.25	(0.63-2.46)	0.526
Body mass index	1.03	(0.96-1.11)	0.387
Past history of myocardial infarction	0.67	(0.24-1.90)	0.455
Past history of PCI	0.64	(0.25-1.61)	0.341
Left ventricular dysfunction (EF <40%)	1.98	(0.87-4.50)	0.104
Renal dysfunction (eGFR <60)	2.30	(1.15-4.60)	0.019
Emergency PCI	3.07	(0.92-10.25)	0.069
Coronary slow flow (TIMI grade <3)	2.62	(1.44-4.80)	0.002
Intra-aortic balloon pumping	1.54	(0.56-4.26)	0.403
VA-ECMO (PCPS)	2.26	(1.36-3.78)	0.002
Emergency CABG	0.42	(0.13-1.41)	0.160
Peak CK (IU/L)	1.00	(1.00-1.00)	0.550
Peak CK >=6195.5 (IU/L)*	1.22	(0.61-2.45)	0.571
Peak CK >=6218.5 (IU/L)**	1.22	(0.61-2.45)	0.571
Peak CK >=10184.5 (IU/L)***	1.72	(0.96-3.10)	0.172

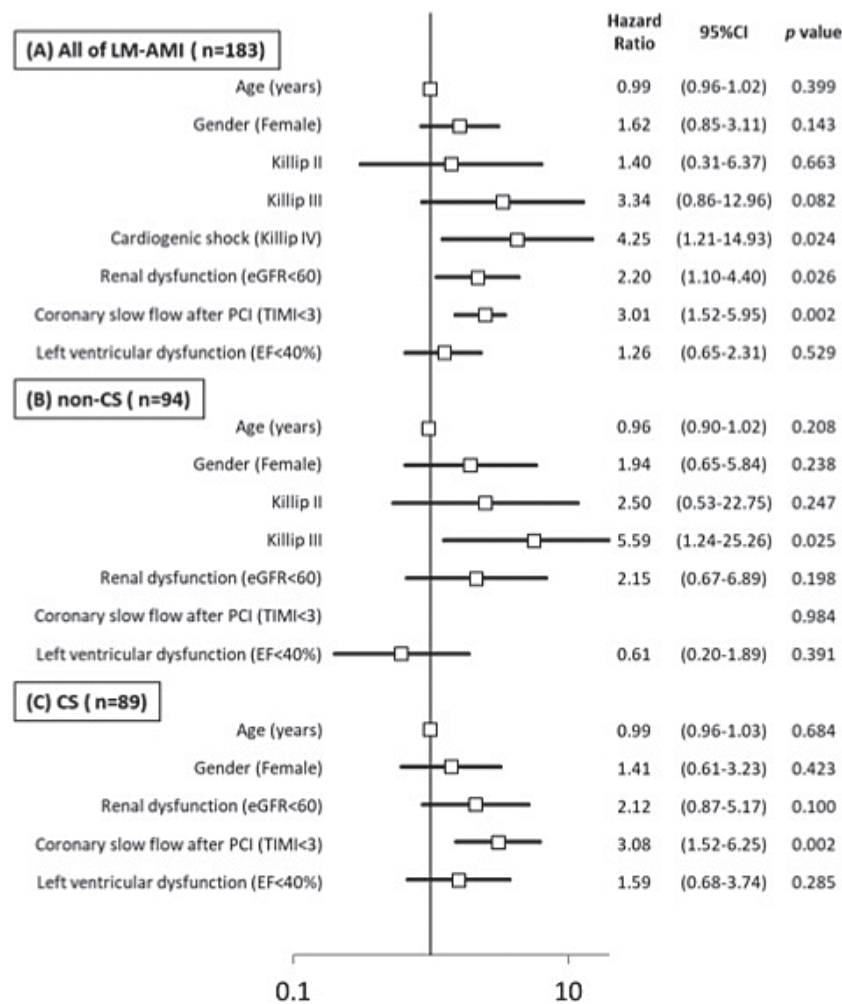**Fig. 1** Hazard ratios of in-hospital death according to univariate analysis.

Fig. 2 Hazard ratios of in-hospital death according to multivariate analysis.

IV. Discussion

The present study revealed that the risk factors and cutoff value of peak serum CK for in-hospital death between the CS and non-CS groups were different. The major risk factor of in-hospital death in the former was coronary slow-flow / no-reflow after PCI and in the latter was severity of heart failure.

In-hospital mortality in patients with LM-AMI in this study was 45.4%, which was similar to that reported in a previous study[1]. Furthermore, in this cohort, in-hospital mortality in the non-CS group was 22.3%, which was higher than the previously reported in-hospital mortality in patients with AMI (8–10%)[10].

Mechanical assist devices (IABP or VA-ECMO) were frequently used in patients in both groups. The hazard ratio of in-hospital death was higher in patients using VA-ECMO in the non-CS group than in patients using VA-ECMO in the CS group. These patients did not have CS on admission, but CS occurred during the course of hospitalization. Some previous studies reported that clinical outcomes of cases requiring VA-ECMO among patients with LM-AMI were limited[1, 2, 5, 7]. In the present cohort, most of the patients who underwent VA-ECMO died. Aiba, et al.[11] also reported that VA-ECMO increased left ventricular afterload, which in turn resulted in a lack of recovery of myocardial function ; their results showed that all patients with a shock score of 9 or higher who underwent VA-ECMO or IABP died. Although IABP and VA-ECMO have been used for AMI with CS, the prognosis is still very poor[11, 12]. Recently, a new assisted circulation device IMPELLA® (ABIOMED. Inc., Danvers, U.S.A) is expected to be effective in patients with AMI who have CS[13]. In Japan, the device has been approved for treatment of only heart disease patients in CS[14]. Without CS, would the new device be unnecessary for patients with LM-AMI? Since the in-hospital mortality is extremely high in patients with LM-AMI, even in those without shock on admission, these patients may likely require prompt introduction of assisted circulation at the time of identification of findings suggestive of extensive infarc-

tion, such as complete occlusion of the LM[15].

1. Cutoff value of serum creatine kinase

The cutoff value of peak serum CK for in-hospital death according to the ROC curve was approximately 6,000 IU/L in the non-CS group and approximately 10,000 IU/L in the CS group. When the patients were divided into two groups at the cutoff value, in the non-CS group, the HR of in-hospital death in the high-CK group was significantly higher (seven times) compared with the low-CK group. In contrast, there was no significant difference between high and low CK in the CS group. The reason for this is that nearly half of patients in the CS group had 10,000 IU / L or higher of peak serum CK. Moreover, there is a possibility that some cases in the CS group died before reaching their peak CK level. There was no significant difference in hazard ratio at cutoff values of 6,000 IU / L and 10,000 IU / L (Fig. 1). The authors propose in the present report that 6,000 IU/L is a cutoff value of serum CK for in-hospital death in patients with LM-AMI.

2. Differences of the risk factors between the two groups

As a result of the multivariate analysis, risk factors related to in-hospital death in each group were different. The reasons are as follows. (1) In-hospital mortality increased with Killip class in patients with LM-AMI ; therefore, heart failure is a risk factor for in-hospital death in the non-CS (Killip class < 4) group. (2) The incidence of coronary slow-flow / no reflow after PCI in the non-CS group was very low (2.1% as shown in Table 1). (3) In contrast, the incidence of coronary slow-flow / no reflow after PCI in the CS group was significantly higher (22.5% as shown in Table 1), and most of them died. Even if there is no CS on admission, heart failure greatly influences the in-hospital prognosis in patients with LM-AMI (Table 2, Supplemental Fig. 1). In fact, a previous study reported that a complication of heart failure is a determinant of in-hospital and long-term prognoses in patients with LM-AMI[16].

3. Coronary slow-flow / no-reflow in the CS group

It has been shown that patients achieving a final TIMI 3 flow after primary PCI have a better prognosis than those showing coronary slow flow in patients with AMI[17]. Furthermore, achievement of TIMI 3 flow is an independent factor for survival in patients with Killip classification II or more, but not in patients with Killip classification I[18]. On multivariate analysis in our study, the proportion of patients with coronary slow flow was higher in the CS group than in the non-CS group. In addition, the hazard ratio of in-hospital death was significantly higher in patients with coronary slow flow (TIMI grade 0 to 2) after primary PCI than in patients with TIMI grade 3 in the CS group. The reasons for this may be as follows: 1) the demand of coronary flow by the myocardium has been reduced due to the extensive infarcted area and 2) the incidences of mechanical complications

(free wall rupture, ventricular septal rupture and papillary muscle rupture), serious arrhythmia and heart failure are high in patients with coronary slow flow[19]. In fact, in the present study, only one out of the four cases who developed mechanical complications achieved a TIMI 3 flow after primary PCI.

4. Study limitations

The present study has some limitations. First, the presence of some biases could not be excluded because this study is a retrospective observational study. In the present study, treatment strategy for LM-AMI within this time has changed greatly over time. However, there was no evidence that the spread of PCI and VA-ECMO improved the prognosis of LM-AMI in this cohort. The number of patients in the old data (especially before 2005) was small. At that time, there is a possibility that many cases died who had not undergone emergency coronary angiography. Older data may have been more affected by registration bias. However, since the present study is a multicentre collaborative research study, the measured bias may be less than that in single-facility studies.

Second, this study included patients who died before undergoing revascularization and patients who were transferred to one of our facilities to receive CABG after being diagnosed as having severe LM-AMI at another hospital. These facts probably influenced assessment of in-hospital outcomes and treatment method.

V. Conclusion

The present study found that coronary slow flow after primary PCI correlated with in-hospital death in the CS group among patients with LM-AMI. On the other hand, in the non-CS group, the presence of heart failure on admission and an abnormally high peak CK level correlated with in-hospital death. It is suggested that strict systemic management is necessary for patients with these risk factors, even in those without shock on admission.

Acknowledgements

Conflicts of interest

The authors have no conflicts of interest to declare.

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