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ORIGINAL ARTICLE

Clinical characteristics and prognostic factors in acute coronary syndrome patients complicated with cardiogenic shock in Japan: analysis from the Japanese Circulation Society Cardiovascular Shock Registry

Kazuo Sakamoto[1,2] · Tetsuya Matoba[1,2] · Masahiro Mohri[1,3] · Yasushi Ueki[1,4] · Yasuyuki Tsujita[1,5] · Masao Yamasaki[1,6] · Nobuhiro Tanaka[1,7] · Yohei Hokama[1,7] · Motoki Fukutomi[1,8] · Katsutaka Hashiba[1,9] · Rei Fukuhara[1,10] · Satoru Suwa[1,11] · Hirohide Matsuura[1,12] · Eizo Tachibana[1,13] · Naohiro Yonemoto[1,14] · Ken Nagao[1,15]

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Abstract
Cardiogenic shock frequently leads to death even with intensive treatment. Although the leading cause of cardiogenic shock is acute coronary syndrome (ACS), the clinical characteristics and the prognosis of ACS with cardiogenic shock in the present era still remain to be elucidated. We analyzed clinical characteristics and predictors of 30-day mortality in ACS with cardiogenic shock in Japan. The Japanese Circulation Society Cardiovascular Shock registry was a prospective, observational, multicenter, cohort study. Between May 2012 and June 2014, 495 ACS patients with cardiogenic shock were analyzed. The primary endpoint was 30-day all-cause mortality. The median [interquartile range; IQR] age was 71.0 [63.0, 80.0] years. The median [IQR] value of systolic blood pressure (SBP) and heart rate were 75.0 [50.0, 86.5] mm Hg and 65.0 [38.0, 98.0] bpm, respectively. Multivariable analysis showed an odds ratio (OR) of 4.76 (confidence intervals; CI 1.97–11.5, $p<0.001$) in the lowest SBP category (<50 mm Hg) for SBP ≥ 90 mm Hg. Moreover, age per 10 years increase (OR 1.38, CI 1.18–1.61, $p=0.002$), deep coma (OR 3.49, CI 1.94–6.34, $p<0.001$), congestive heart failure (OR 3.81, CI 2.04–7.59, $p<0.001$) and left main trunk disease (LMTD) (OR 2.81, CI 1.55–5.10, $p<0.001$) were independent predictors. Severe hypotension, older age, deep coma, congestive heart failure, and LMTD were independent unfavorable factors in ACS complicated by cardiogenic shock in Japan. A prompt assessment of high-risk patients referring to those predictors in emergency room could lead to appropriate treatment without delay.

Keywords Acute coronary syndrome · Cardiogenic shock · Mortality · Prognostic factors

✉ Tetsuya Matoba
matoba@cardiol.med.kyushu-u.ac.jp

1 JCS Shock Registry Scientific Committee, Tokyo, Japan

2 Department of Cardiovascular Medicine, Kyushu University Hospital, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan

3 Department of Cardiology, Japan Community Healthcare Organization Kyushu Hospital, Kitakyushu, Japan

4 Emergency and Critical Care Center, Shinshu University School of Medicine, Matsumoto, Japan

5 Department of Critical and Intensive Care Medicine, Shiga University of Medical Science, Otsu, Japan

6 Department of Cardiovascular Medicine, NTT Medical Center, Tokyo, Japan

7 Department of Cardiology, Tokyo Medical University Hachioji Medical Center, Hachioji, Japan

8 Division of Cardiovascular Medicine, Jichi Medical University School of Medicine, Shimotsuke, Japan

9 Division of Cardiology, Yokohama City University Medical Center, Yokohama, Japan

10 Department of Cardiology, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, Japan

11 Department of Cardiovascular Medicine, Juntendo University Shizuoka Hospital, Izunokuni, Japan

12 Department of Cardiology, Miyazaki Medical Association Hospital, Miyazaki, Japan

13 Department of Cardiology, Kawaguchi Municipal Medical Center, Kawaguchi, Japan

14 Department of Biostatistics, Kyoto University School of Public Health, Kyoto, Japan

15 Cardiovascular Center, Nihon University Hospital, Tokyo, Japan

Introduction

Cardiogenic shock is caused by severe cardiac dysfunction and frequently leads to death even with intensive treatment [1–3]. The leading cause of cardiogenic shock is acute coronary syndrome (ACS) including ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA), and the incidence rates of cardiogenic shock among ACS have ranged from 2 to 5% [4–6]. Previous studies revealed the clinical characteristics and several prognostic factors of ACS complicated with cardiogenic shock for each era [5–9]. On the other hand, early coronary angiography (CAG) and coronary intervention have been reported to reduce the risk of recurrent ischemia and shorten the hospital stay in ACS [10]. Emergent CAG and subsequent coronary revascularization for ACS have been standardized all over the world including Japan. Recently, the safety of percutaneous coronary intervention (PCI) for elderly ACS patients has been shown in Japan that is one of aging nations [11]. In addition, Inoue et al. reported that the PCI rate for acute myocardial infarction (AMI) all over Japan did not vary so much [12]. However, the clinical characteristics and the prognosis of ACS with cardiogenic shock in the present era when therapeutic strategy has been less affected by the universal risk of age and regional disparities remain to be elucidated. The purpose of this study was to describe clinical characteristics and predictors of 30-day mortality in ACS with cardiogenic shock from the Japanese Circulation Society Cardiovascular Shock Registry (JCS Shock Registry) [13].

Methods

Study design of JCS Shock Registry

The JCS Cardiovascular Shock Registry was a prospective, observational, multicenter cohort study. Each hospital's ethics committee approved the registry, which was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000008441; http://www.umin.ac.jp/ctr/index/htm/). Patients diagnosed with cardiovascular shock were enrolled from 82 centers in Japan between May 2012 and June 2014 [13]. Cardiovascular shock included ACS, non-ischemic arrhythmia, aortic disease, myocarditis, cardiomyopathy, pulmonary thromboembolism, valvular heart disease, infective endocarditis, cardiac tamponade and others. Eligible patients had out-of-hospital onset of cardiovascular shock which met 1 major criterion and ≥ 1 minor criteria. Major criteria of shock were (1) systolic blood pressure (SBP) ≤ 100 mm Hg and heart rate < 60 beats/min or > 100 beats/min, and (2) decrease in SBP > 30 mm Hg from the usual values. Minor criteria were the presence of cold sweat, pallor of the skin, cyanosis, a capillary refill time ≥ 2 s, consciousness disturbance, or vital organ hypoperfusion. Patients who had out-of-hospital cardiac arrest (OHCA) were eligible if they were in a state of shock on arrival, after return of spontaneous circulation (ROSC). Patients younger than 16 years or those without ROSC were prospectively excluded.

Definitions

ACS included STEMI, NSTEMI, and UA. Non-ST-segment elevation ACS (NSTE-ACS) was defined in conjunction with NSTEMI and UA following *2014 guideline for the management of patients with non-ST-elevation acute coronary syndromes* [14]. The primary endpoint was all-cause mortality (death from any cause) at 30 days after hospital arrival. Congestive heart failure was diagnosed according to the Framingham criteria at the time of hospital presentation [15]. A history of hypertension and diabetes mellitus was defined as follows (referring to the patients' past history and reports): hypertension was defined as SBP ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or ongoing medical therapy for hypertension; diabetes mellitus was defined as HbA1c ≥ 6.5%, casual plasma glucose level ≥ 200 mg/dl, or treatment with oral hypoglycemic agents or an insulin injection. Consciousness levels were recorded in the Japan Coma Scale. A deep coma status, Japan Coma Scale 300 that corresponds to Glasgow Coma Scale 3, was assessed as a potential predictive factor.

Statistical analysis

Continuous variables were shown as medians and interquartile ranges or means and standard deviations depending on the distributions, and binary and categorical variables were calculated as frequencies (percentages). The univariate logistic regression analysis was carried out with variables listed in the baseline characteristics. Furthermore, multivariable logistic regression analysis was performed with a combination of variables that were significant in the univariate analysis and previously reported variables (age, SBP, heart rate, hypertension, diabetes mellitus, deep coma, congestive heart failure, serum creatinine and emergent CAG) to clarify prognostic factors of 30-day mortality in this study [5–9]. Hemodynamic parameters were reclassified by categories (SBP < 50 mm Hg, 50–69 mm Hg, 70–89 mm Hg, ≥ 90 mm Hg; heart rate < 40 bpm, 40–79 bpm, 80–119 bpm, ≥ 120 bpm). Emergent CAG was adopted as a therapeutic variable because emergent CAG represented the intention to treat patients more clearly than revascularization. The all-cause mortality curve in overall ACS patients was constructed using the Kaplan–Meier method. We defined the statistical significance as $p < 0.05$. The JMP software version 12 (SAS institute Inc., NC, USA) was used in statistical analyses.

Results

Patient population

A total of 1004 patients (from 1 to 71 patients from each facility) were enrolled in the JCS Shock Registry; however, 25 were excluded because they had OHCA without ROSC ($n = 23$) or non-shock states at the presentation ($n = 2$). Of the remaining 979 patients, 499 patients (51.0%) had cardiogenic shock due to ACS. Therefore, 495 patients, excluding 4 patients whose classification of ACS was not recorded, were analyzed (Fig. 1).

Baseline characteristics

Patients' baseline clinical characteristics with the number of missing data were shown in Table 1. Regarding overall ACS cohort (495 patients) in the left column, the median age was 71.0 years and male occupied 73.9%. As for hemodynamic parameters, the median value of SBP and heart rate were 75 mm Hg and 65 bpm, respectively. Deep coma was seen in 28.1%. In addition, 82.4% of patients developed STEMI and 74.7% complicated with congestive heart failure. Furthermore, emergent CAG was performed in 90.5% and left main trunk disease (LMTD) and three-vessel disease (3VD) was found in 15.3% and 25.7% each. In the right column showing the number of missing data, SpO_2 was not measured in 21.2% and left ventricular ejection fraction (LVEF) was not reported in 181 patients (36.6%). Concerning past history of cardiovascular events (previous myocardial infarction and prior coronary artery bypass graft), as many as 80% could not be noted.

Table 1 Baseline characteristics

Factors	Overall ($n = 495$)	Missing data, *n*
Age (years)		
Median [IQR]	71.0 [63.0, 80.0]	0
Mean ± SD	70.6 ± 12.4	
Male, *n* (%)	366 (73.9)	0
OHCA, *n* (%)	142 (28.7)	0
Time from symptom onset to hospital arrival (min)		
Median [IQR]	70.0 [40.0, 265.0]	66
SBP (mm Hg)		
Median [IQR]	75.0 [50.0, 86.5]	10
Mean ± SD	61.6 ± 34.5	
Heart rate (beats/min)		
Median [IQR]	65.0 [38.0, 98.0]	7
Mean ± SD	65.4 ± 43.4	
SpO_2 (%) Median [IQR]	98.0 [92.8, 100]	105
Deep coma, *n* (%)	139 (28.1)	2
Body mass index (kg/m^2)		
Mean ± SD	23.1 ± 3.9	84
Dyslipidemia, *n* (%)	175 (35.3)	0
Diabetes mellitus, *n* (%)	171 (34.5)	0
Hypertension, *n* (%)	293 (59.2)	0
Previous myocardial infarction, *n* (%)	34 (34.3)	396
Prior CABG, *n* (%)	10 (10.1)	396
STEMI, *n* (%)	408 (82.4)	0
Congestive heart failure, *n* (%)	370 (74.7)	0
LVEF (%)		
Mean ± SD	41.4 ± 17.4	181
Serum creatinine (mg/dl)		
Median [IQR]	1.20 [0.93, 1.48]	12
Troponin T positive, *n* (%)	354 (71.5)	13
Emergent CAG, *n* (%)	448 (90.5)	2
Left main trunk disease, *n* (%)	76 (15.3)	0
Three-vessel disease, *n* (%)	127 (25.7)	10

OHCA Out-of-hospital cardiac arrest; *SBP* systolic blood pressure; *CABG* coronary artery bypass graft; *STEMI* ST-segment elevation myocardial infarction; *LVEF* left ventricular ejection fraction; *CAG* coronary angiography; *SD* standard deviation; *IQR* interquartile range

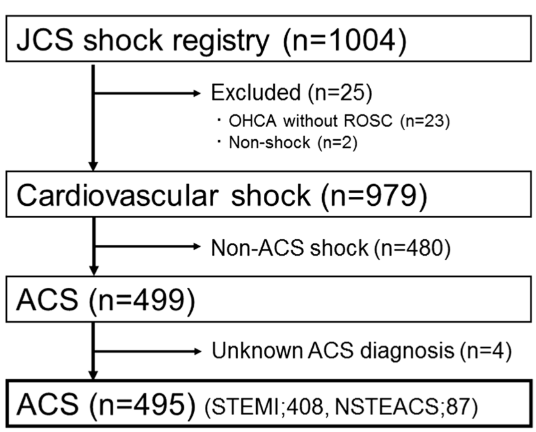

Fig. 1 Flow diagram of acute coronary syndrome (ACS) patients from Japanese Circulation Society (JCS) Shock Registry. OHCA: out-of-hospital cardiac arrest; ROSC: return of spontaneous circulation; STEMI: ST-segment elevation myocardial infarction; NSTEACS: non-ST-segment elevation ACS

Univariate analysis to predict 30-day mortality

165 patients (33.3%) were dead in 495 ACS patients. The clinical parameters to predict 30-day mortality by univariate

Table 2 Univariate analysis to predict 30-day mortality

Factors	Odds ratio	95% CI	*p* value
Age, per 10 years increase	1.11	0.95–1.30	0.177
Male	0.83	0.39–0.55	0.387
OHCA	2.76	1.84–4.13	<0.001
Time from symptom onset to hospital arrival, per 10 min increase	1.00	0.95–1.06	0.937
SBP			
≥ 90 mm Hg	1.0 (reference)		
70–89 mm Hg	1.35	0.76–2.48	0.314
50–69 mm Hg	3.18	1.66–6.22	<0.001
< 50 mm Hg	5.21	2.87–9.76	<0.001
Heart rate			
≥ 120 bpm	1.90	0.98–3.64	0.059
80–119 bpm	1.54	0.94–2.56	0.090
40–79 bpm	1.0 (reference)		
< 40 bpm	2.66	1.62–4.41	<0.001
SpO_2, per 1.0% decrease	1.05	1.05–1.06	<0.001
Deep coma	4.43	2.92–6.72	<0.001
Body mass index	1.03	0.98–1.08	0.304
Dyslipidemia	0.55	0.37–0.83	0.005
Diabetes mellitus	1.13	0.76–1.67	0.548
Hypertension	0.87	0.60–1.27	0.477
Previous myocardial infarction	1.06	0.45–2.49	0.898
Prior CABG	0.69	0.17–2.86	0.606
STEMI	0.62	0.38–0.99	0.048
Congestive heart failure	4.59	2.61–8.08	<0.001
LVEF, per 1.0% increase	0.93	0.91–0.95	<0.001
Serum creatinine, per 1.0 mg/dl increase	1.11	1.00–1.24	0.047
Troponin T positive	0.98	0.64–1.50	0.911
Emergent CAG	0.36	0.19–0.67	0.001
Left main trunk disease	2.79	1.69–4.58	<0.001
Three-vessel disease	1.49	0.96–2.30	0.076

CI confidence interval; *OHCA* out-of-hospital cardiac arrest; *SBP* systolic blood pressure; *CABG* coronary artery bypass graft; *STEMI* ST-segment elevation myocardial infarction; *LVEF* left ventricular ejection fraction; *CAG* coronary angiography

analysis was shown in Table 2. According to this analysis, odds ratios (ORs) for 70–89 mm Hg, 50–69 mm Hg and SBP < 50 mm Hg (vs. ≥ 90 mm Hg) were 1.35 (95% confidence interval [CI] 0.76–2.48, $p = 0.314$), 3.18 (CI 1.66–6.22, $p < 0.001$) and 5.21 (CI 2.87–9.76, $p < 0.001$), respectively. Regarding the impact of heart rate, the second lowest category (heart rate 40–79 bpm) was the reference, because the lowest category (heart rate < 40 bpm) had significant greater risk compared to the second lowest category and a nonsignificant trend toward a greater risk at heart rate ≥ 80 bpm. Furthermore, other significant prognostic indicators are as follows: OHCA (OR 2.76, CI 1.84–4.13, $p < 0.001$), SpO_2 per 1.0% decrease (OR 1.05, CI 1.05–1.06, $p < 0.001$), deep coma (OR 4.43, CI 2.92–6.72, $p < 0.001$), Dyslipidemia (OR 0.55, CI 0.37–0.83, $p = 0.005$), STEMI (OR 0.62, CI 0.38–0.99, $p = 0.048$), congestive heart failure (OR 4.59, CI 2.61–8.08, $p < 0.001$), LVEF per 1.0% increase (OR 0.93, CI 0.91–0.95, $p < 0.001$), serum creatinine per 1.0 mg/dl increase (OR 1.11, CI 1.00–1.24, $p = 0.047$), emergent CAG (OR 0.36, CI 0.19–0.67, $p = 0.001$) and LMTD (OR 2.79, CI 1.69–4.58, $p < 0.001$).

Multivariable analysis for 30-day mortality

Multivariable analysis for 30-day mortality was performed with 13 variables to adjust possible confounders (Table 3). The lower SBP showed a trend of poor prognosis as same as in univariate analysis, that is, 30-day mortality was significantly greater in the second lowest (50–69 mm Hg) and the lowest SBP category (< 50 mm Hg) for SBP ≥ 90 mm Hg with an OR of 3.89 (CI 1.73–8.74, $p = 0.001$) and 4.76 (CI 1.97–11.5, $p < 0.001$), respectively. In contrast,

Table 3 Multivariable analysis for 30-day mortality

Factors ($n=474$)	Odds ratio	95% CI	p value
Age, per 10 years increase	1.37	1.11–1.69	0.003
OHCA	0.73	0.32–1.67	0.458
SBP			
≥ 90 mm Hg	1.0 (reference)		
70–89 mm Hg	1.77	0.77–4.08	0.182
50–69 mm Hg	3.89	1.73–8.74	0.001
< 50 mm Hg	4.76	1.97–11.5	<0.001
Heart rate			
≥ 120 bpm	1.57	0.74–3.34	0.245
80–119 bpm	1.27	0.70–2.30	0.433
40–79 bpm	1.0 (reference)		
< 40 bpm	0.68	0.30–1.57	0.369
Deep coma	4.56	2.03–10.3	<0.001
Dyslipidemia	0.64	0.39–1.06	0.081
Hypertension	0.98	0.60–1.58	0.924
Diabetes mellitus	1.05	0.65–1.70	0.848
STEMI	1.10	0.61–1.98	0.758
Congestive heart failure	3.35	1.70–6.61	<0.001
Serum creatinine, per 1.0 mg/dl increase	1.06	0.94–1.19	0.343
Emergent CAG	0.48	0.22–1.06	0.069
Left main trunk disease	2.81	1.55–5.10	<0.001

CI confidence interval; *OHCA* out-of-hospital cardiac arrest; *SBP* systolic blood pressure; *STEMI* ST-segment elevation myocardial infarction; *CAG* coronary angiography

heart rate was not significantly associated with 30-day mortality for every category comparison in multivariable analysis. Moreover, age per 10 years increase (OR 1.37, CI 1.11–1.69, $p=0.003$), deep coma (OR 4.56, CI 2.03–10.3, $p<0.001$), congestive heart failure (OR 3.35, CI 1.70–6.61, $p<0.001$) and LMTD (OR 2.81, CI 1.55–5.10, $p<0.001$) were independent predictors.

Discussion

This study revealed the characteristics and the prognostic factors of ACS with cardiogenic shock in nation-wide observational cohort study in Japan (the JCS Shock Registry). 30-day mortality and prognostic factors of ACS patients complicated with shock in the contemporary era were similar to previous reports from overseas, which raised a clinical issue in emergency cardiovascular care. A prompt assessment of high-risk patients referring to clinical predictors in emergency room (ER) could lead to appropriate treatment without delay and help us avoid missing the potentially ill patients.

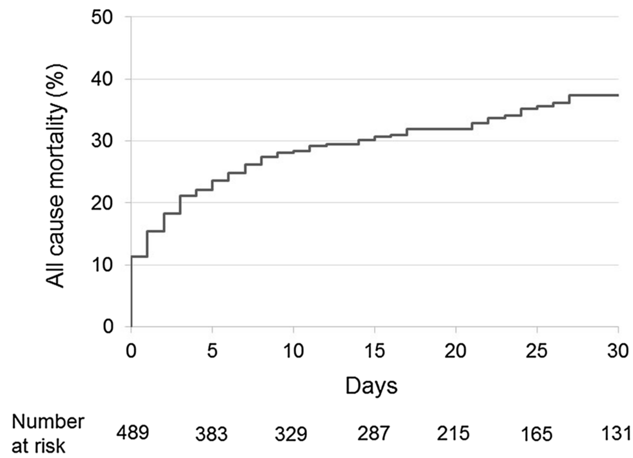

Fig. 2 Kaplan–Meier analysis of all-cause mortality in overall acute coronary syndrome patients from Japanese Circulation Society Shock Registry

The impact of shock state on 30-day mortality

This study showed that 30-day mortality of ACS with cardiogenic shock was still high as one-third (Fig. 2.). In the 1960s, when percutaneous coronary intervention was not introduced in ACS patients, the mortality rates were more than 50% [16]. Even though the mortality rates have declined with advances in coronary care unit and coronary catheterization, cardiogenic shock has been the most frequent cause of in-hospital death among ACS patients [17–19]. In this study, despite emergency CAG was performed in about 90% patients and subsequent revascularization was undergone in as high as 80%, the prognosis was comparable to previous reports with a smaller proportion of patients who underwent revascularization [5, 6]. This indicated that the impact of shock was still critical in ACS, even with the appropriate intervention and the contemporary therapies. In addition, the mortality rate of 33.3% in ACS patients was close to 34.3% in the whole analysis of JCS Shock Registry, that is, shock state could considerably affect the mortality regardless of the cause of shock [13].

Prognostic predictors in ACS patients with shock

In univariate analysis, OHCA, declined SBP, lethal bradycardia, decreased SpO_2, deep coma, the presence of congestive heart failure, increased serum creatinine and LMTD were unfavorable predictors, while dyslipidemia, STEMI, preserved LVEF and emergent CAG were favorable factors. According to multivariable analysis, older age, declined SBP, deep coma, congestive heart failure and LMTD were independently associated with 30-day mortality.

Many observational studies have shown the increased mortality with advanced age in ACS with shock and this study was no exception [5–9]. Age was not a predictor of death in univariate analysis but in multivariate analysis in this study. The disagreement may have been caused by the interactions among variances and the statistical significance in multivariate analysis was uncovered after the correction of confounders. Also, other possibilities were the following: (1) the effect of unbalanced sample size, (2) the influence of missing data, and (3) the large variation within a group compared to between groups. The blood pressure at the presentation has been an established predictor and lower SBP showed higher OR of 30-day mortality in this study as well [5, 7, 8]. Heart rate is one of the most important parameters along with blood pressure as used in shock index [20]. In univariate analysis of heart rate, the second lowest category (heart rate 40–79 bpm) showed the lowest risk as seen in another recent study [21]. Despite the Global Registry of Acute Coronary Events (GRACE) study showed that faster heart rate had poor prognosis, this analysis didn't show such a trend [7]. Conscious disturbance that indicates severe impairment of systemic circulation has been shown to correlate with higher risk of death in cardiogenic shock [5, 8]. Deep coma (Japan Coma Scale 300) was one of the strongest predictors in this study as the Glasgow Coma Scale of 3 was reported as a predictor of in-hospital mortality in patients with OHCA caused by ACS [22]. Moreover, congestive heart failure was another fatal predictor as same as in previous studies regarding ACS [7, 23]. Additionally, LVEF which closely involved with heart failure was a potential indicator of mortality, however, LVEF was not analyzed because of a large number of missing data [5]. The lack of sufficient data indicated that LVEF might not be always available in emergency settings though left ventricular systolic dysfunction is a central dogma in ACS with shock. The other prognostic factor was LMTD as reported in previous studies and the high mortality of ACS due to LMTD has been still a clinical challenge [6, 24]. LMTD causes circulatory collapse or lethal arrhythmia immediately after the onset, therefore, effective prehospital care as well as intensive care at hospital are needed. In the end, despite renal insufficiency could be associated with higher mortality, it is difficult to mention the definite impact of renal function on the mortality due to the variety of patients' background and cutoff values in previous studies [7–9].

As for the therapeutic intervention, emergent CAG was performed in 448 (90.5%) patients of all over 495 patients. Though the mortality of patients who underwent CAG was significantly lower (OR of 0.36) than that of patients without emergent CAG in univariate analysis, invasive tests or treatments would commonly be avoided in elderly and severely ill patients. According to additional analyses of this study, the patients without CAG were older ($p < 0.001$) and were accompanied by OHCA and deep coma more often ($p = 0.005$ and $p = 0.03$, respectively) compared to those who underwent CAG. In other words, avoiding CAG could have been a surrogate for the severity of patients. It was difficult to conclude that the evaluation of coronary arteries was essential to rescue ACS patients complicated with shock, however, carrying out CAG and subsequent revascularization would play a role in the series of treatment [25]. In terms of mechanical circulatory support, we had options of venoarterial extracorporeal membrane oxygenation, extracorporeal ventricular assist device and intra-aortic balloon pump, whereas percutaneous left ventricular assist device (pLVAD) that had shown the clinical benefit for cardiogenic shock was not available during the study period. The clinical impact of pLVAD on ACS with shock in Japan should be investigated in the future.

The severity of ACS in JCS Cardiovascular Shock Registry

From the viewpoint of pathophysiology, myocardial infarction compared to angina is more likely to become shock state because the contractility would be declined in myocardial infarction. In fact, as few as 3.0% of 495 patients were UA in this study and this result was comparable to the recent study [26]. Besides, the reason why only 72% had elevated troponin while 82% was diagnosed as STEMI was because not a few STEMI patients were diagnosed after admission despite they did not elevate troponin in ER. Furthermore, the characteristics of diseased vessels and the revascularization strategy could affect the outcome. The frequencies of LMTD and 3VD in the present study were 15% and 26% each. SHOCK trial reported that LMTD and 3VD in AMI with shock were 14% and 60%, respectively, and another report of 4700 STEMI with shock included less LMTD (2.4%) and 3VD (30%) [27, 28]. The difference of the severity of diseased vessels among studies may have been due to the differences of the patient characteristics and therapeutic trends. Finally, the optimal revascularization strategy for each patient was decided by each facility in this observational study, and the data of the number of revascularized branches other than culprit were not available. A previous meta-analysis showed that optional PCI for multivessel disease appeared to improve outcomes in patients with STEMI, while a recent study reported that the risk of death at 30 days was lower with culprit-lesion-only PCI [29, 30]. The impact of the different revascularization strategy on ACS in Japan remains to be investigated.

Limitations

First, data integrity, validity, and ascertainment bias are potential limitations. For instance, there is no criteria for the number of measurements of vital signs and the duration of shock state, that is, patients with similar vital signs could have had different severities. Whereas any clinical study has this kind of limitation, uniform data collection of ACS shock patients in this registry could have minimized these potential biases. Second, the JCS Shock Registry was organized in Japan, therefore, all the data may not simply be extrapolated to other countries where emergency medical system differs from Japan [31]. Third, a large amount of missing data was a limitation of this observational study in ER where we had a few constraints of information and time. Fourth, the different number of registered patients from every facility could have affected the outcome because the treatment strategy in every facility was not uniform. Fifth, risk stratification should be dynamic and needs iterative process depending on changes in the patient's clinical course ideally. Especially in the emergent care of cardiovascular shock patients, accurate and practical models are desirable to support clinicians' therapeutic decisions properly and promptly [32].

Conclusion

The results of this large observational study provided updated insights into the characteristics, management practices, and short-term mortality of patients with ACS complicated by cardiogenic shock in Japan. Severe hypotension, older age, deep coma, congestive heart failure and LMTD were independent unfavorable factors in this contemporary era. A prompt assessment of these severely ill patients referring to clinical predictors in ER could lead to appropriate treatment without delay.

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Compliance with ethical standards

Conflict of interest We have no conflict of interest to declare.

References

1. Reynolds HR, Hochman JS (2008) Cardiogenic shock: current concepts and improving outcomes. Circulation 117:686–697
2. Jeger RV, Radovanovic D, Hunziker PR, Pfisterer ME, Stauffer JC, Erne P, Urban P, Plus Registry Investigators AMIS (2008) Ten-year trends in the incidence and treatment of cardiogenic shock. Ann Intern Med 149:618–626
3. Redfors B, Angerås O, Råmunddal T, Dworeck C, Haraldsson I, Ioanes D, Petursson P, Libungan B, Odenstedt J, Stewart J, Lodin E, Wahlin M, Albertsson P, Matejka G, Omerovic E (2015) 17-year trends in incidence and prognosis of cardiogenic shock in patients with acute myocardial infarction in western Sweden. Int J Cardiol 185:256–262
4. Awad HH, Anderson FA Jr, Gore JM, Goodman SG, Goldberg RJ (2012) Cardiogenic shock complicating acute coronary syndromes: insights from the Global Registry of Acute Coronary Events. Am Heart J 163:963–971
5. Harjola VP, Lassus J, Sionis A, Køber L, Tarvasmäki T, Spinar J, Parissis J, Banaszewski M, Silva-Cardoso J, Carubelli V, Di Somma S, Tolppanen H, Zeymer U, Thiele H, Nieminen MS, Mebazaa A, CardShock Study Investigators; GREAT Network (2015) Clinical picture and risk prediction of short-term mortality in cardiogenic shock. Eur J Heart Fail 17:501–509
6. Kunadian V, Qiu W, Ludman P, Redwood S, Curzen N, Stables R, Gunn J, Gershlick A, National Institute for Cardiovascular Outcomes Research (2014) Outcomes in patients with cardiogenic shock following percutaneous coronary intervention in the contemporary era: an analysis from the BCIS database (British Cardiovascular Intervention Society). JACC Cardiovasc Interv 7:1374–1385
7. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van De Werf F, Avezum A, Goodman SG, Flather MD, Fox KA, Global Registry of Acute Coronary Events Investigators (2003) Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med 163:2345–2353

8. Sleeper LA, Reynolds HR, White HD, Webb JG, Dzavík V, Hochman JS (2010) A severity scoring system for risk assessment of patients with cardiogenic shock: a report from the SHOCK Trial and Registry. Am Heart J 160:443–450
9. Poss J, Köster J, Fuernau G, Eitel I, de Waha S, Ouarrak T, Lassus J, Harjola VP, Zeymer U, Thiele H, Desch S (2017) Risk stratification for patients in cardiogenic shock after acute myocardial infarction. J Am Coll Cardiol 69:1913–1920
10. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A (2014) 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 35:2541–2619
11. Miura T, Miyashita Y, Motoki H, Shimada K, Kobayashi M, Nakajima H, Kimura H, Akanuma H, Mawatari E, Sato T, Hotta S, Kamiyoshi Y, Maruyama T, Watanabe N, Eisawa T, Aso S, Uchikawa S, Hashizume N, Sekimura N, Morita T, Ebisawa S, Izawa A, Tomita T, Koyama J, Ikeda U (2014) In-hospital clinical outcomes of elderly patients (≥ 80 years) undergoing percutaneous coronary intervention. Circ J 78:1097–1103
12. Inoue T, Kuwabara H, Fushimi K (2017) Regional variation in the use of percutaneous coronary intervention in Japan. Circ J 81:195–198
13. Ueki Y, Mohri M, Matoba T, Tsujita Y, Yamasaki M, Tachibana E, Yonemoto N, Nagao K (2016) Characteristics and predictors of mortality in patients with cardiovascular shock in Japan—results from the Japanese Circulation Society Cardiovascular Shock Registry. Circ J 80:852–859
14. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ (2014) 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 130:2354–2394
15. McKee PA, Castelli WP, McNamara PM, Kannel WB (1971) The natural history of congestive heart failure: the Framingham study. N Engl J Med 285:1441–1446
16. Killip T 3rd, Kimball JT (1967) Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. Am J Cardiol 20:457–464
17. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, Buller CE, Jacobs AK, Slater JN, Col J, McKinlay SM, LeJemtel TH (1999) Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. N Engl J Med 341:625–634
18. Hochman JS, Sleeper LA, White HD, Dzavik V, Wong SC, Menon V, Webb JG, Steingart R, Picard MH, Menegus MA, Boland J, Sanborn T, Buller CE, Modur S, Forman R, Desvigne-Nickens P, Jacobs AK, Slater JN, LeJemtel TH, Investigators SHOCK (2001) One-year survival following early revascularization for cardiogenic shock. JAMA 285:190–192
19. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW, American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines (2013) 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 127:362–425
20. Allgower M, Burri C (1967) Shock index. Dtsch Med Wochenschr 92:1947–1950
21. Jensen MT, Pereira M, Araujo C, Malmivaara A, Ferrieres J, Degano IR, Kirchberger I, Farmakis D, Garel P, Torre M, Marrugat J, Azevedo A (2018) Heart rate at admission is a predictor of in-hospital mortality in patients with acute coronary syndromes: results from 58 European hospitals: the European Hospital Benchmarking by outcomes in acute coronary syndrome processes study. Eur Heart J Acute Cardiovasc Care 7:149–157
22. Lettieri C, Savonitto S, De Servi S, Guagliumi G, Belli G, Repetto A, Piccaluga E, Politi A, Ettori F, Castiglioni B, Fabbiocchi F, De Cesare N, Sangiorgi G, Musumeci G, Onofri M, D'Urbano M, Pirelli S, Zanini R, Klugmann S, LombardIMA Study Group (2009) Emergency percutaneous coronary intervention in patients with ST-elevation myocardial infarction complicated by out-of-hospital cardiac arrest: early and medium-term outcome. Am Heart J 157:569–575
23. McNamara RL, Kennedy KF, Cohen DJ, Diercks DB, Moscucci M, Ramee S, Wang TY, Connolly T, Spertus JA (2016) Predicting in-hospital mortality in patients with acute myocardial infarction. J Am Coll Cardiol 68:626–635
24. Zeymer U, Vogt A, Zahn R, Weber MA, Tebbe U, Gottwik M, Bonzel T, Senges J, Neuhaus KL, Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte (ALKK) (2004) Predictors of in-hospital mortality in 1333 patients with acute myocardial infarction complicated by cardiogenic shock treated with primary percutaneous coronary intervention (PCI); Results of the primary PCI registry of the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte (ALKK). Eur Heart J 25:322–328
25. Geri G, Dumas F, Bougouin W, Varenne O, Daviaud F, Pène F, Lamhaut L, Chiche JD, Spaulding C, Mira JP, Empana JP, Cariou A (2015) Immediate percutaneous coronary intervention is associated with improved short- and long-term survival after out-of-hospital cardiac arrest. Circ Cardiovasc Interv. https://doi.org/10.1161/circinterventions.114.002303
26. D'Souza M, Sarkisian L, Saaby L, Poulsen TS, Gerke O, Larsen TB, Diederichsen AC, Jangaard N, Diederichsen SZ, Hosbond S, Hove J, Thygesen K, Mickley H (2015) Diagnosis of unstable angina pectoris has declined markedly with the advent of more sensitive troponin assays. Am J Med 128:852–860
27. Webb JG, Lowe AM, Sanborn TA, White HD, Sleeper LA, Carere RG, Buller CE, Wong SC, Boland J, Dzavik V, Porway M, Pate G, Bergman G, Hochman JS, Investigators SHOCK (2003) Percutaneous coronary intervention for cardiogenic shock in the SHOCK trial. J Am Coll Cardiol 42:1380–1386
28. Mehta RH, Ou F-S, Peterson ED, Shaw RE, Hillegass WB Jr, Rumsfeld JS, Roe MT, American College of Cardiology–National Cardiovascular Database Registry Investigators (2009) Clinical significance of post-procedural TIMI flow in patients with cardiogenic shock undergoing primary percutaneous coronary intervention. JACC Cardiovasc Interv 2:56–64
29. El-Hayek GE, Gershlick AH, Hong MK, Casso Dominguez A, Banning A, Afshar AE, Herzog E, Tamis-Holland JE (2015) Meta-analysis of randomized controlled trials comparing multivessel versus culprit-only revascularization for patients with ST-segment elevation myocardial infarction and multivessel disease undergoing primary percutaneous coronary intervention. Am J Cardiol 115:1481–1486

30. Thiele H, Akin I, Sandri M, de Waha-Thiele S, Meyer-Saraei R, Fuernau G, Eitel I, Nordbeck P, Geisler T, Landmesser U, Skurk C, Fach A, Jobs A, Lapp H, Piek JJ, Noc M, Goslar T, Felix SB, Maier LS, Stepinska J, Oldroyd K, Serpytis P, Montalescot G, Barthelemy O, Huber K, Windecker S, Hunziker L, Savonitto S, Torremante P, Vrints C, Schneider S, Zeymer U, Desch S (2018) CULPRIT-SHOCK investigators. N Engl J Med 379:1699–1710
31. Kitamura T, Iwami T, Kawamura T, Nagao K, Tanaka H, Hiraide A (2010) Nationwide public-access defibrillation in Japan. N Engl J Med 362:994–1004
32. Nakamura F, Nakai M (2017) Prediction models—why are they used or not used? Circ J 81:1766–1767