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COVID-19 pandemic is associated with mechanical complications in patients with ST-elevation myocardial infarction

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ABSTRACT

Objective Although there are regional reports that the COVID-19 pandemic is associated with a reduction in acute myocardial infarction presentations and primary percutaneous coronary intervention (PCI) procedures, little is known about the impact of the COVID-19 pandemic on mechanical complications resulting from ST-segment elevation myocardial infarction (STEMI) and mortality.

Methods This single-centre retrospective cohort study analysed presentations, incidence of mechanical complications, and mortality in patients with STEMI before and after a state of emergency was declared due to the COVID-19 pandemic by the Japanese government on 7 April 2020.

Results We analysed 359 patients with STEMI hospitalised before the declaration and 63 patients hospitalised after the declaration. The proportion of patients with late presentation was significantly higher after the declaration than before (25.4% vs 14.2%, p=0.03). The incidence of late presentation was significantly higher during the COVID-19 pandemic than before (incidence rate ratio (IRR), 2.41; 95% CI, 1.37 to 4.05; p=0.001, even after adjusting for month (IRR, 2.61; 95% CI, 1.33 to 5.13; p<0.01). Primary PCI was performed significantly less often after the declaration than before (68.3% vs 82.5%, p=0.009). The mechanical complication resulting from STEMI occurred in 13 of 359 (3.6%) patients before the declaration and 9 of 63 (14.3%) patients after the declaration (p<0.001). However, the incidence of in-hospital death (before, 6.2% vs after, 6.4%, p=0.95) was comparable.

Conclusions Following the COVID-19 pandemic, an increased incidence of mechanical complications resulting from STEMI was observed. Instructing people to stay at home, without effectively educating them to immediately seek medical attention when suffering symptoms of a heart attack, may worsen outcomes in patients with STEMI.

INTRODUCTION

Osaka prefecture is the second epicentre of the COVID-19 pandemic in Japan. The WHO declared a COVID-19 pandemic on 11 March 2020. In response to this statement, Japan

Key questions

What is already known about this subject?
► Little is known about the impact of the COVID-19 pandemic on mechanical complications resulting from ST-segment elevation myocardial infarction (STEMI) and mortality.

What does this study add?
► Our analysis of 422 consecutive patients with STEMI showed that the incidence of mechanical complications increased fourfold after a state of emergency was declared for the COVID-19 pandemic when compared with historical controls.
► However, in-hospital mortality did not increase (before, 6.2% vs after, 6.4%, p=0.95).

How might this impact on clinical practice?
► In the case of diseases such as STEMI, where the time course affects prognosis, emergency medical services (EMS) activation at the right time is necessary and individuals need to be educated to call EMS appropriately.

declared a state of emergency on 7 April 2020 and instructed people to stay at home.

Although there are regional reports that the COVID-19 pandemic is associated with a reduction in both acute myocardial infarction (AMI) presentations and primary percutaneous coronary intervention (PCI) procedures,[1–7] little is known about the impact of the COVID-19 pandemic on mechanical complications resulting from ST-segment elevation myocardial infarction (STEMI) and mortality. If patients with STEMI stay home, there may be a delay in presentation, leading to worsening symptoms or a higher incidence of mechanical complications.

Therefore, we hypothesised that patients with STEMI during the COVID-19 pandemic have been delayed hospital arrival and subsequently poorer prognosis than a historical cohort of patients with STEMI. To address this

question, we compared mortality, prevalence of delayed hospital arrival and incidence of mechanical complications resulting from STEMI before versus after a state of emergency was declared for the COVID-19 pandemic in Japan.

METHODS

Study design, population and outcomes

The study population was extracted from an observational single-centre registry of patients with AMI admitted to the National Cerebral and Cardiovascular Center of Japan. This registry has enrolled consecutive patients with AMI since 2001 and its findings have been previously published.[8–10]

We conducted a retrospective cohort study of patients with STEMI between 7 April 2020, the day that a state of emergency was declared for the COVID-19 pandemic, and 14 August 2020. Patients with STEMI between 1 January 2018 and 6 April 2020 were included in the historical cohort. AMI was defined according to the fourth universal definition of myocardial infarction.[11] Briefly, patients with AMI should have ischaemic changes based on cardiac troponin values with at least 1 value above the 99th percentile upper reference limit and present with ischaemic symptoms such as chest pain lasting longer than 30 min or new ischaemic electrocardiographic signs. ST elevation should be a new finding at the J-point in two contiguous leads with a cut-point of ≥1 mm in all leads other than leads V2–V3, where the following cut-points apply: ≥2 mm in men aged ≥40 years, ≥2.5 mm in men aged <40 years or ≥1.5 mm in women regardless of age. This study included patients who were admitted within 2 weeks after the onset of AMI and type 1 or type 2 myocardial infarction. Late presentation was defined as onset-to-door time longer than 24 hours because the indication for primary PCI was limited to onset-to-door time longer than 24 hours.[12–14] The allocation of emergency coronary angiography, coronary intervention and surgical treatment was determined by the attending physician or heart team according to guidelines.[12–14] The definition of primary PCI was urgent balloon angioplasty (with or without stenting) without the use of fibrinolytic therapy to open the infarct-related artery during acute STEMI.[15]

The primary outcome was the incidence of mechanical complications during hospitalisation in patients with STEMI before and after the declaration in Japan. Secondary outcomes were onset-to-door time, treatment management (revascularisation and circulatory assist device use) and in-hospital outcomes (death and length of hospitalisation). Mechanical complications consisted of acute free wall rupture, contained rupture, ventricular septal rupture and papillary muscle rupture. Definitions of mechanical complications were previously reported.[16] In brief, acute free wall rupture was defined as an abrupt transmural tear of the infarcted area causing hemopericardium, cardiac tamponade and death in <30 min without emergent surgical treatment. Contained rupture

was defined as a gradual or incomplete tear or erosion of the infarcted area with slow bleeding into the pericardial sac causing progressive or recurrent cardiac tamponade. Ventricular septal rupture was diagnosed with colour Doppler echocardiography showing abnormal shunting via the interventricular septum or a significant increase in oxygen saturation in the right ventricle. Papillary muscle rupture was diagnosed based on echocardiographic findings of tears in the papillary muscle or chordae tendineae causing acute mitral regurgitation.

Data were abstracted from medical records. Age; sex; comorbidities such as hypertension, diabetes and dyslipidaemia; smoking status; history of myocardial infarction; prior revascularisation; onset-to-door time and Killip classification were recorded on admission. Chronic kidney disease was defined as an estimated glomerular filtration rate ≤60 mL/min/1.73 m^2 in this study.

Statistical analysis

Non-normally distributed continuous data were summarised as medians (IQR) and compared using the Wilcoxon rank sum test. Categorical variables were compared using the χ^2 test or Fisher's exact test as appropriate. To investigate the association between the declaration and late presentation, we used Poisson regression with the number of late presentations per 2 weeks as a dependent variable, timing relative to the declaration (before or after) as an independent variable of interest, month as an independent variable (covariate) and logarithm of the population size of Osaka prefecture in August 2019 as an offset term. We exponentiated regression coefficients obtained from the Poisson regression analysis to show incidence rate ratios (IRRs) for late presentation by timing relative to the declaration. Logistic regression analysis was used to obtain ORs and 95% CIs for primary and secondary outcomes. We performed multivariate analysis to adjust for baseline variables, including established risk factors for mechanical complications (age, female sex, anterior myocardial infarction, de novo myocardial infarction and single-vessel disease)[16–19] and timing relative to the declaration (model 1). Model 2 included factors that were significant in the univariate analysis and established risk factors for mechanical complications. For sensitivity analysis, any variable with p<0.05 during univariate analysis was included in a multivariate model to identify independent predictors of the primary outcome. Late presentation was not included in the multivariate analysis of the primary outcome to avoid overfitting. Late presentation was considered an intermediate variable in the relationship between the declaration and mechanical complications. Intermediate variables should not be adjusted because it will lead to overadjustment.[20] P values of <0.05 were considered statistically significant. Statistical analysis was performed using JMP (V.11.0, SAS Institute) except for the analysis of IRR, which was performed using R statistical software (V.4.0.2, The R Foundation).
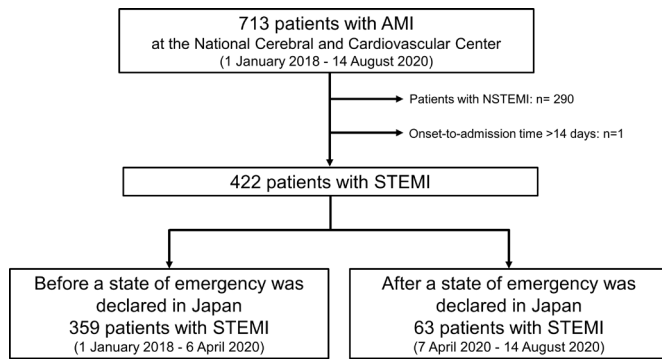
Figure 1 Study flow chart. AMI, acute myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

RESULTS

This study included 713 patients with AMI. We excluded patients with non-STEMI (n=290) and patients with STEMI who presented more than 2 weeks (n=1) after onset. Ultimately, we analysed 422 patients with STEMI (figure 1). After a state of emergency was declared for Osaka, 63 patients with STEMI were admitted to our hospital. In this cohort, COVID-19 PCR testing was performed in 56 patients; all PCR tests were negative. Table 1 shows the baseline characteristics of patients before and after the declaration. Compared with before the declaration, a significantly lower proportion of patients after the declaration had hypertension (p=0.04), but there were no significant differences in age, sex, smoking status, chronic kidney disease or previous coronary revascularisation between the groups.

Clinical outcomes are shown in table 2. Onset-to-door time was significantly longer during COVID-19 pandemic than before the declaration (2.4 (1.0–8.1) vs 4.1 (1.3–24.5) hours, p=0.02); furthermore, 16 (25.4%)

patients after the declaration had a late presentation; this proportion was significantly higher than the proportion observed before the declaration (n=51, 14.2%; p=0.03). Primary PCI was performed significantly less often in patients after the declaration compared with before (n=43, 68.3% vs n=296, 82.5%, p=0.009). There were twelve and four patients not treated with primary PCI before and after the declaration, respectively. Before the declaration, the reasons for not undergoing primary PCI were vasospastic angina (n=3), coronary artery bypass grafting (n=2) surgery for the mechanical complications (n=2),patient condition (n=2), distal culprit lesion (n=1), operator's decision (n=1) and not obtained consent for PCI (n=1). After the declaration, the reasons were vasospastic angina (n=1), spontaneous coronary artery dissection (n=1), distal culprit lesion (n=1) and coronary artery bypass grafting (n=1). There were no patients treated with fibrinolysis in all study patients. The primary outcome of mechanical complications occurred in 22 of 422 patients (5.2%). It occurred in 13 of 359 patients before the declaration (3.6%) and 9 of 63 patients after the declaration (14.3%; p<0.001). Acute free wall rupture, contained rupture, ventricular septal rupture and papillary muscle rupture occurred in one (0.3%), six (1.7%), four (1.1%) and two (0.6%) patients before the declaration, and three (4.8%), three (4.8%), three (4.8%) and zero patients after the declaration, respectively. In-hospital mortality (before, 6.2% vs after, 6.4%; p=0.95) and cause of death were comparable among patients before and after the declaration.

Among 22 patients who reached the primary outcome (online supplemental table 1), 3 of 13 patients (patients 4, 7 and 12) before the declaration and 1 of 9 patients (patient 19) after the declaration did not receive surgical treatment due to his or her medical condition or the heart

Table 1 Baseline characteristics and clinical presentation

	Before a state of emergency declaration (n=359)		After a state of emergency declaration (n=63)		P value
Age, median (IQR), years	72	(61–80)	70	(59–79)	0.19
Male sex, n (%)	259	(72.1)	42	(66.7)	0.38
Body mass index, median (IQR), kg/m^2	23.2	(21.0–25.8)	23.2	(21.4–25.2)	0.85
Current smoker, n (%)	122	(34.0)	23	(36.5)	0.69
Hypertension, n (%)	253	(70.5)	36	(57.1)	0.04
Dyslipidaemia, n (%)	253	(70.5)	46	(73.0)	0.68
Diabetes mellitus, n (%)	136	(37.9)	16	(25.4)	0.06
Chronic kidney disease, n (%)	171	(47.6)	31	(49.2)	0.82
De novo myocardial infarction, n (%)	330	(91.9)	55	(87.3)	0.23
Prior PCI, n (%)	33	(9.2)	6	(9.5)	0.93
Prior CABG, n (%)	7	(2.0)	1	(1.6)	0.85
Anterior myocardial infarction, n (%)	180	(50.1)	25	(39.7)	0.13
Single vessel disease, n (%)	162	(45.4)	21	(33.3)	0.08

P values refer to the comparisons between the two groups.
CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

Table 2 Procedural characteristics, clinical presentations and outcomes

	Before a state of emergency declaration (n=359)		After a state of emergency declaration (n=63)		P value
Onset-to-door time, median (IQR), hours	2.4	(1.0–8.1)	4.1	(1.3–24.5)	0.02
Late presentation, n (%)	51	(14.2)	16	(25.4)	0.03
Killip classification at admission					0.04
I, n (%)	290	(80.8)	43	(68.3)	
II, n (%)	8	(2.2)	4	(6.3)	
III, n (%)	11	(3.1)	1	(1.6)	
IV, n (%)	50	(13.9)	15	(23.8)	
Primary PCI, n (%)	296	(82.5)	43	(68.3)	0.009
Emergent CABG, n (%)	6	(1.7)	2	(3.2)	0.42
Mechanical complications, n (%)	13	(3.6)	9	(14.3)	<0.001
Free wall rupture, n (%)	1	(0.3)	3	(4.8)	
Contained rupture, n (%)	6	(1.7)	3	(4.8)	
Ventricular septal rupture, n (%)	4	(1.1)	3	(4.8)	
Papillary muscle rupture, n (%)	2	(0.6)	0	(0)	
Use of circulatory assist devices, n (%)	62	(17.3)	15	(23.8)	0.22
Surgical treatment for mechanical complications, n (%)	10/13	(76.9)	8/9	(88.9)	0.47
Cardiogenic embolism, n (%)	11	(3.1)	1	(1.6)	0.51
Left ventricular thrombus, n (%)	8	(2.2)	1	(1.6)	0.74
In-hospital death	22	(6.2)	4	(6.4)	0.95
Cause of death					0.74
Cardiac death	13	(59.1)	2	(50.0)	
Non-cardiac death	9	(40.9)	2	(50.0)	
Hospital stay, median (IQR), days	14	(11–20)	18	(14–33)	0.001

P values refer to the comparisons between the two groups.
CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

team's decision. All of these four patients died during hospitalisation. Among the 18 patients who received surgical treatment, 4 of 10 patients before the declaration and 1 of 8 patients after the declaration died. Hospital stay was significantly longer in patients after the declaration compared with before the declaration (14 (11–20) vs 18 (14–33) days; p=0.001). In Poisson regression analyses, the incidence of late STEMI presentation was higher during the COVID-19 pandemic period compared with the incidence before the declaration (IRR, 2.41; 95% CI, 1.37 to 4.05; p=0.001) and also higher than during the same time period in 2018–2019 for both periods (IRR, 3.20; 95% CI, 1.61 to 6.44; p=0.001). IRRs remained significant after adjusting for month (IRR, 2.61; 95% CI, 1.33 to 5.13; p<0.001 and IRR, 3.00; 95% CI, 1.48 to 6.26; p=0.003, respectively).

Compared with before the declaration, the pandemic period was associated with a twofold increase in the risk of late presentation (OR, 2.06; 95% CI, 1.08 to 3.90; p=0.03) and a fourfold increase in the risk of mechanical complications (OR, 4.44; 95% CI, 1.80 to 10.88; p=0.002). Table 3 shows univariate and multivariate results for the primary outcome. In the multivariate analysis, the

pandemic period was independently associated with the primary outcome (OR, 5.32; 95% CI, 2.01 to 14.03; p=0.001 in model 1 and OR, 5.78; 95% CI, 2.08 to 16.05; p=0.001 in model 2). In sensitivity analysis, when any variable with p<0.05 in the univariate analysis was included in a multivariate model, pandemic period was an independent predictor for the primary outcome (OR, 4.90; 95% CI, 1.84 to 13.05; p=0.001).

DISCUSSION

Our analysis of the impact of the COVID-19 pandemic on outcomes in patients with STEMI has several key findings. First, fewer primary PCI procedures, longer onset-to-door time and a larger proportion of late presentations among patients with STEMI were observed after the declaration of a state of emergency in Japan on 7 April 2020. Second, after adjusting for differences in baseline characteristics and established risk factors for mechanical complications due to STEMI, the incidence of mechanical complications of STEMI increased fivefold after the declaration, even though there were no significant differences with respect to in-hospital mortality. Our study is the first to

Table 3 Univariate and multivariate logistic analysis of risk factors for mechanical complications

	Univariate analysis			Multivariate analysis model 1*			Multivariate analysis model 2†		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Age	1.04	1.00 to 1.09	0.03	1.03	0.99 to 1.08	0.14	1.00	0.96 to 1.05	0.90
Female sex	3.90	1.62 to 9.40	0.002	3.41	1.29 to 9.04	0.01	3.54	1.29 to 9.73	0.01
Body mass index	0.97	0.87 to 1.09	0.65						
Current smoker	0.29	0.08 to 0.99	0.047				0.56	0.14 to 2.18	0.40
Hypertension	1.23	0.47 to 3.22	0.67	0.91	0.32 to 2.58	0.86	0.74	0.25 to 2.22	0.59
Diabetes mellitus	1.24	0.52 to 2.98	0.62						
Dyslipidaemia	0.58	0.24 to 1.38	0.22						
Chronic kidney disease	7.51	2.19 to 25.78	0.001				7.27	1.94 to 27.30	0.003
De novo myocardial infarction	2.08	0.27 to 15.89	0.48	1.90	0.22 to 15.88	0.55	2.49	0.28 to 22.26	0.41
Anterior myocardial infarction	2.37	0.95 to 5.93	0.07	3.23	1.21 to 8.57	0.02	3.49	1.26 to 9.64	0.02
Single-vessel disease	0.47	0.18 to 1.22	0.12	0.38	0.13 to 1.08	0.07	0.39	0.13 to 1.18	0.10
After a state of emergency declaration (vs before)	4.44	1.80 to 10.88	0.002	5.32	2.01 to 14.03	0.001	5.78	2.08 to 16.05	0.001

*Multivariate logistic regression analysis with established risk factors for mechanical complications (age, female, anterior myocardial infarction, de novo myocardial infarction, single-vessel disease and after a state of declaration (vs before)).
†Multivariate logistic regression analysis with factors that were significant in the univariate analysis and established risk factors for mechanical complications.

show an increased incidence of mechanical complications in patients with STEMI due to late presentation during the COVID-19 pandemic. These findings suggest that behavioural changes in response to the crisis may lead to less healthcare utilisation, which may adversely influence STEMI outcomes.

The COVID-19 pandemic has led to radical transformation of social, economic and healthcare networks, which may have profound indirect consequences on clinical presentation and management of patients with STEMI. According to a report from Milan, Italy, the COVID-19 pandemic has significantly increased the proportion of patients with late presentation (50.0% vs 4.8%; p<0.01) and decreased the rate of primary PCI (80.8% vs 100%, p=0.06).[7] In another survey of 73 centres in Spain,[5] there was an estimated 40% reduction in procedures performed in the STEMI setting. There was an estimated 38% reduction in cardiac catheterisation laboratory STEMI activations in the USA.[2] Our study shows a 17% reduction in primary PCI procedures for STEMI after the declaration of the COVID-19 pandemic. Although a higher incidence of late presentation and a lower rate of primary PCI are associated with established risk factors for mechanical complications such as cardiac rupture and ventricular septum rupture,[15 16] there have been no previous reports of an increased rate of mechanical complications during the COVID-19 pandemic.

Our study focused on the incidence of mechanical complications in patients with STEMI after the declaration. Therefore, we adjusted for prognostic factors potentially associated with mechanical complications in patients with STEMI, including high age, female sex, single-vessel disease, de novo myocardial infarction and presence of hypertension. In the analysis, we did not include late presentation, which is an established risk factor for mechanical complications, to avoid overfitting. We considered late presentation to be an intermediate variable in the relationship between the declaration and mechanical complications. As shown in table 2, late presentation was significantly more common in patients after the declaration than in the 2 years prior. In addition, when we included the declaration as a variable in multivariate logistic regression models with mechanical complications as an outcome, the declaration was significantly associated with mechanical complications. These findings suggest that due to the stay-at-home request by the government in response to the COVID-19 pandemic, individuals may not be requesting emergency medical services (EMS) properly based on the fear of COVID-19. It has also been reported that stay-at-home orders influence mental health.[21] For diseases such as STEMI and stroke, in which the time course affects prognosis, EMS activation at the right time is necessary. Individuals need to be educated to call EMS appropriately to prevent delayed hospital presentation. Therefore, the global medical community needs to address public concerns and stress the importance of seeking prompt medical attention for symptoms of heart attack and stroke.

Our study has several limitations. First, this is an observational study in a single centre with a small number of patients examined. Therefore, there may be inherent flaws related to selection bias, spurious observations, unmeasured covariates and non-random allocation to treatment. Second, our institution is the only

government-designated advanced cardiovascular centre in Japan and one of the major hospitals able to perform PCI in the northern part of Osaka prefecture. Therefore, the population of this study did not reflect all patients residing in this area. Third, post-discharge follow-up data were not available. Finally, despite a significant increase in the number of mechanical complications, there were no significant differences observed in in-hospital mortality. These conflicting results might be explained by the low number of in-hospital mortality events and the small sample size of this study. A report from New York City showed a decline in the number of patients with myocardial infarction arriving at the hospital. Patients with cardiac rupture due to myocardial infarction who survived presented to the hospital, whereas patients with rupture who did not survive may have not reached the hospital and died at home. Further research is needed to evaluate mortality in patients with STEMI during the COVID-19 pandemic.

In conclusion, our analysis demonstrates that the incidence of mechanical complications was fourfold higher due to late presentation after a state of emergency was declared because of the COVID-19 pandemic in Japan. Although the rates of late presentation and mechanical complications due to STEMI increased after the declaration, we did not demonstrate any in-hospital mortality differences during the COVID-19 pandemic.

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