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ORIGINAL ARTICLE

Impact of the COVID-19 outbreak on hospitalizations and outcomes in patients with acute myocardial infarction in a Japanese Single Center

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Abstract

There are a few Japanese data regarding the incidence and outcomes of acute myocardial infarction (AMI) after the coronavirus disease 2019 (COVID-19) outbreak. We retrospectively reviewed the data of AMI patients admitted to the Nihon University Itabashi Hospital after a COVID-19 outbreak in 2020 (COVID-19 period) and the same period from 2017 to 2019 (control period). The patients' characteristics, time course of admission, diagnosis, and treatment of AMI, and 30-day mortality were compared between the two period-groups for both ST-segment elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI), respectively. The AMI inpatients decreased by 5.7% after the COVID-19 outbreak. There were no differences among most patient backgrounds between the two-period groups. For NSTEMI, the time from the symptom onset to admission was significantly longer, and that from the AMI diagnosis to the catheter examination tended to be longer during the COVID-19 period than the control period, but not for STEMI. The 30-day mortality was significantly higher during the COVID-19 period for NSTEMI (23.1% vs. 1.9%, $P=0.004$), but not for STEMI (9.4% vs. 8.3%, $P=0.77$). In conclusion, hospitalizations for AMI decreased after the COVID-19 outbreak. Acute cardiac care for STEMI and the associated outcome did not change, but NSTEMI outcome worsened after the COVID-19 outbreak, which may have been associated with delayed medical treatment due to the indirect impact of the COVID-19 pandemic.

Keywords COVID-19 outbreak · Acute myocardial infarction · Time from the symptom onset to admission

Abbreviations

AMI	Acute myocardial infarction
CABG	Coronary artery bypass graft
CAG	Coronary angiography
CK	Creatine kinase
COVID-19	Coronavirus disease 2019
CVIT	Cardiovascular Intervention and Therapeutics
ECG	Electrocardiography
IABP	Intra-aortic balloon pump
JCS	Japanese Circulation Society
MI	Myocardial infarction
NSTEMI	Non-ST elevation myocardial infarction
OHCA	Out of hospital cardiac arrest
PCI	Percutaneous coronary intervention
PHEIC	Public Health Emergency of International Concern emergency
POBA	Plain old balloon angioplasty
PPE	Personal protective equipment
STEMI	ST elevation myocardial infarction
TIMI	Thrombolysis in myocardial infarction
VA-ECMO	Veno-arterial extracorporeal membrane oxygenation
WHO	World health organization

Introduction

In December 2019, a novel coronavirus causing pneumonia was first reported in Wuhan City, Hubei, China [1]. Shortly thereafter, it spread not only within China but throughout the

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world. In Japan, the first coronavirus disease 2019 (COVID-19) case was reported on January 16, 2020. Since then, the preparations for a medical treatment system assuming a COVID-19 spread were started at each hospital in Japan.

Several studies from outside of Japan have reported a significantly decreased incidence of acute myocardial infarctions (AMIs), increased AMIs detected in out-of-hospital cardiac arrests (OHCAs) and increased mortality from AMIs after the COVID-19 outbreak as compared to the same period in the past [2–6]. In Japan, after the world health organization (WHO) pandemic declaration on March 11, 2020, both the Cardiovascular Intervention and Therapeutics (CVIT) [7] and Japanese Circulation Society (JCS) academic societies [8], dealing with the AMI medical care, have proposed an AMI treatment strategy, which has been aimed to prevent infections in health care workers and maintain the treatment in critical and urgent patients even during the COVID-19 spread. Nonetheless, because of the little available data in Japan, it remains unclear whether the reported data throughout the world would be applicable to those Japanese patients. We, therefore, investigated the incidence and outcome of AMIs after the ongoing COVID-19 outbreak in Japan, in comparison to the same days between 2017 and 2019.

Methods

Study patients

Because WHO declared a state of Public Health Emergency of International Concern emergency (PHEIC) on January 30, 2020, and Nihon University Itabashi Hospital, Tokyo, Japan, officially started responding to the COVID-19 from that same day, we defined AMI patients from January 30, 2020 to September 30, 2020 as the patients during the COVID-19 period. To evaluate the temporal differences in the patient characteristics and outcomes, we defined AMI patients on the same days between 2017 and 2019 as controls. We included AMI patients that had been admitted to Nihon University Itabashi Hospital, Tokyo, Japan, between January 30 and September 30, 2020 (COVID-19 period, $n=66$) and AMIs on the same days during the years 2017–2019 as the reference (control period, $n=210$), and the characteristics and outcomes of the AMIs between the two period-groups were compared for both ST-elevation myocardial infarctions (STEMIs) and non-STEMIs (NSTEMIs), separately. All patients included in the study had been admitted within 30 days of the AMI symptom onset. The patients included were identified through a review of the records of consecutive patients admitted for AMIs, and all had consented, by the opt-out method, to the use of their data for study purposes.

The study protocol was approved by the Ethics Committee of Nihon University Itabashi Hospital (RK-201121-01) and was in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Data collection and definitions

Information from the patients' clinical records had been entered anonymously into an Excel spreadsheet by physicians or the clinical research coordinator at Nihon University Itabashi Hospital. For the purpose of the study, we obtained the following data: number of hospitalizations for AMIs, clinical characteristics, and treatment outcomes in the patients.

AMIs had been diagnosed on the basis of the patients' symptoms and a serum troponin-I concentration of >0.014 ng/mL with or without ST-segment elevation of >2 mm in the precordial leads or >1 mm in the limb leads on electrocardiography (ECG). The infarction was classified as a STEMI or NSTEMI, depending on the presence or absence of ST-segment elevation [9]. Echocardiography was performed at the time of admission.

The following cardiovascular risk factors were assessed: hypertension (defined as the use of an antihypertensive agent, systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg), diabetes mellitus (defined as the use of an oral hypoglycemic agent or insulin or a glycosylated hemoglobin level of $\geq 6.5\%$), dyslipidemia (defined as the use of a statin or triglyceride-lowering drug, a low-density lipoprotein concentration of ≥ 140 mg/dL, a high-density lipoprotein concentration of <40 mg/dL, or a triglyceride concentration of ≥ 150 mg/dL) [10]. Heart failure, if present at the time of the initial presentation, was classified by the severity according to the Killip system [11].

Coronary angiography (CAG) was performed in consenting patients during their hospitalization for an AMI. The definition of the TIMI flow was graded as TIMI 0 = no perfusion, TIMI 1 = penetration without perfusion, TIMI 2 = partial perfusion, or TIMI 3 = complete perfusion, as described for the Phase I TIMI Trial [12]. If percutaneous coronary intervention (PCI) was performed during the same session as the index CAG, it was defined as an ad hoc PCI, and especially for STEMIs, an ad-hoc PCI as the primary reperfusion strategy for AMIs without previous or concomitant thrombolytic therapy was defined as a primary PCI [13].

Evaluations and study endpoint

We first divided the total 276 AMI patients into 2 groups: those who had been admitted between January 30 and September 30, 2020 (COVID-19 period, $n=66$) and those

during those same days between 2017 and 2019 (control period, $n=210$), and investigated the number of total AMI, STEMI, and NSTEMI inpatients between those same days (January 30 and September 30) during the COVID-19 and control periods. Next, we investigated the STEMI and NSTEMI patients separately, and compared the patient characteristics between the two groups, respectively, for both STEMIs (COVID-19 period; $n=53$, control period; $n=156$) and NSTEMIs (COVID-19 period; $n=13$, control period; $n=54$), respectively.

The main study endpoint was the 30-day mortality, defined as in-hospital deaths from any cause within 30 days after admission, which was ascertained through our review of the patient data. Thus, we compared the 30-day mortality between the patients in the COVID-19 period and those in the control period, for both STEMIs and NSTEMIs, separately.

Statistical analysis

Continuous variables are shown as the mean ± SD values, and differences between groups were analysed by a Student's *t*-test or Mann–Whitney *U* test. Categorical variables are shown as the number and percentage of patients, and the between-group differences in these variables were analysed by chi-square or Fisher's exact test. The 30-day mortality among the patients during the COVID-19 and control periods was estimated by the Kaplan–Meier method, and the between-group differences were assessed by a log-rank test. All analyses were performed with SPSS Statistics 19.0 software (SPSS Inc., Chicago, IL, USA), and a $P<0.05$ was considered significant.

Results

Comparison of the AMI inpatients between the COVID-19 and control periods

During the COVID-19 period, there was a 5.7% reduction in AMI inpatients, 1.9% increase in STEMIs, and 27.8% reduction in NSTEMIs as compared to that during the control period, respectively (Fig. 1). During this period, none of the AMI patients had COVID-19.

Characteristics of the patients during the COVID-19 and control periods for both the STEMI and NSTEMI patients

For both the STEMIs and NSTEMIs, clinical characteristics, CAG findings, time trend of admissions, AMI diagnosis, and catheter examinations, and therapeutic interventions between the COVID-19 and control periods are summarized

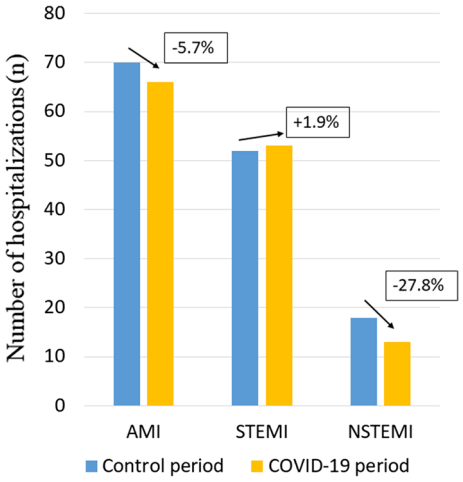


Fig. 1 Number of AMI, STEMI, and NSTEMI inpatients between the COVID-19 and control groups. During the COVID-19 period, there was a 5.7% reduction in AMI inpatients, 1.9% increase in STEMIs, and 27.8% reduction in NSTEMIs compared to that during the control period, respectively

in Table 1. There were no significant differences in the age and sex between the two groups for both STEMIs and NSTEMIs. For STEMI patients, those during the COVID-19 period had a significantly higher BMI (25.5 ± 4.3 kg/m^2 vs. 23.3 ± 4.0 kg/m^2, $P=0.001$) and higher incidence of diabetes mellitus (46.2% vs. 29.7%, $P=0.030$) than those during the control period, whereas, NSTEMI patients during the COVID-19 period had a numerically (but not significantly) higher incidence of diabetes mellitus (61.5% vs. 38.9%, $P=0.14$) than those during the control period. In STEMIs, OHCAs were observed in 12.2% during the COVID-19 period and in only 5.9% during the control period ($P=0.21$). In NSTEMIs, the patients during the COVID-19 period had a higher heart rate on admission than those during the control period (102.1 ± 22.9% vs. 85.3 ± 27.9, $P=0.049$). In STEMIs, the serum CK level and peak CK level were numerically lower during the COVID-19 period (454.5 ± 586.2 mg/dL vs. 637.6 ± 1672.2 mg/dL in the control period, $P=0.44$, and 2510.2 ± 2600.9 mg/dL vs. 3032.3 ± 5276.7 mg/dL, $P=0.49$, respectively), but those values were conversely higher in NSTEMIs (665.8 ± 1139.7 mg/dL vs. 367.9 ± 463.9 mg/dL, $P=0.14$, and 4509.4 ± 11,177.3 mg/dL vs. 1281.2 ± 1606.5 mg/dL, $P=0.32$, respectively). In NSTEMIs, the time from the symptom onset to admission was significantly longer during the COVID-19 period than the control period (426.2 ± 374.2 min vs. 197.7 ± 254.2 min, $P=0.011$), and the time from the diagnosis of an AMI to the CAG tended to be longer (463.3 ± 670.1 min vs. 136.2 ± 213.4 min, $P=0.11$), whereas there was no significant tendency regarding the time trend of admissions, diagnoses, and treatment in the STEMIs.

Table 1 Baseline and clinical characteristics of AMI patients between the COVID-19 and control periods

	STEMI ($n=209$)			NSTEMI ($n=67$)		
	COVID-19 period ($n=53$)	Control period ($n=156$)	*P* value	COVID-19 period ($n=13$)	Control period ($n=54$)	*P* value
Age (year)	67.4 ± 12.4	68.2 ± 13.5	0.72	70.2 ± 12.3	68.5 ± 13.1	0.67
Male, sex	41 (77.4%)	128 (82.1%)	0.45	12 (92.3%)	48 (88.9%)	1.00
Body mass index (kg/m^2)	25.5 ± 4.3	23.3 ± 4.0	0.001	23.2 ± 3.5	24.7 ± 4.5	0.27
Coronary risk factor						
Hypertension	40 (76.9%)	101 (65.2%)	0.12	11 (84.6%)	42 (77.8%)	0.72
Diabetes mellitus	24 (46.2%)	46 (29.7%)	0.030	8 (61.5%)	21 (38.9%)	0.14
Dyslipidemia	36 (69.2%)	85 (54.8%)	0.068	11 (84.6%)	31 (57.4%)	0.11
Current smoking	35 (68.6%)	104 (67.1%)	1.00	11 (84.6%)	38 (71.7%)	0.49
History of stroke	7 (13.7%)	14 (9.0%)	0.34	3 (23.1%)	5 (9.3%)	0.18
History of PCI	8 (15.7%)	28 (18.1%)	0.70	2 (15.4%)	13 (24.1%)	0.72
History of CABG	0	4 (2.6%)	0.57	1 (7.7%)	1 (1.9%)	0.35
Clinical presentation						
OHCA	6 (12.2%)	9 (5.9%)	0.21	0 (0.0%)	2 (3.8%)	1.00
Systolic blood pressure (mmHg)	138.3 ± 28.1	138.9 ± 32.2	0.91	160.0 ± 26.9	147.6 ± 24.7	0.12
Diastolic blood pressure (mmHg)	86.0 ± 21.0	86.6 ± 20.4	0.87	96.4 ± 13.6	91.0 ± 20.3	0.39
Heart rate (bpm)	79.8 ± 24.1	83.9 ± 23.9	0.30	102.1 ± 22.9	85.3 ± 27.9	0.049
Body temperature (°C)	36.1 ± 0.8	36.0 ± 0.8	0.59	36.3 ± 0.4	36.2 ± 0.7	0.60
Respiratory rate (breaths/min)	21.2 ± 11.3	20.1 ± 6.5	0.44	21.8 ± 5.5	20.7 ± 7.1	0.62
Killip classification						
Killip I	38 (71.7%)	107 (68.6%)	0.77	8 (61.5%)	33 (61.1%)	0.52
Killip II	5 (9.4%)	22 (14.1%)		1 (7.7%)	12 (22.2%)	
Killip III	2 (3.8%)	8 (5.1%)		2 (15.4%)	4 (7.4%)	
Killip IV	8 (15.1%)	19 (12.2%)		2 (15.4%)	5 (9.3%)	
Left ventricular ejection fraction (%)	48.1 ± 14.2	47.7 ± 14.8	0.89	40.6 ± 23.1	48.5 ± 13.0	0.26
Lactate (mmol/L)	2.9 ± 3.6	3.1 ± 3.5	0.73	2.2 ± 1.7	2.1 ± 1.5	0.94
Hemoglobin (g/dL)	136 ± 2.3	13.5 ± 2.5	0.71	14.4 ± 1.9	13.4 ± 2.3	0.15
CK	454.5 ± 586.2	637.6 ± 1672.2	0.44	665.8 ± 1139.7	367.9 ± 463.9	0.14
peak CK	2510.2 ± 2600.9	3032.3 ± 5276.7	0.49	4509.4 ± 11,177.3	1281.2 ± 1606.5	0.32
Undergoing CAG	53 (100.0%)	152 (97.4%)	0.57	12 (92.3%)	54 (100.0%)	0.19
Culprit vessel of MI						
Left main trunk	2 (3.8%)	11 (7.2%)	0.52	1 (9.1%)	1 (1.9%)	0.21
Left anterior descending coronary artery	23 (43.4%)	67 (44.1%)	0.93	5 (45.5%)	27 (50.0%)	0.783
Left circumflex coronary artery	4 (7.5%)	18 (11.8%)	0.38	4 (36.4%)	16 (29.6%)	0.73
Right coronary artery	24 (45.3%)	55 (36.2%)	0.24	0	10 (18.5%)	0.19
Graft	0	1 (0.7%)	1.00	1 (9.1%)	0	0.17
Pre TIMI flow						0.52
0	37 (69.8%)	91 (59.9%)		3 (27.3%)	24 (44.4%)	
1	11 (20.8%)	28 (18.4%)		5 (45.5%)	14 (25.9%)	
2	0	1 (0.7%)		0	2 (3.7%)	
3	5 (9.4%)	32 (21.1%)		3 (27.3%)	14 (25.9%)	
Number of diseased vessels						
1 vessel disease	24 (46.2%)	82 (54.3%)	0.15	5 (45.5%)	22 (40.7%)	0.82
2 vessel disease	12 (23.1%)	42 (27.8%)		3 (27.3%)	20 (37.0%)	
3 vessel disease	16 (30.8%)	27 (17.9%)		3 (27.3%)	12 (22.2%)	
Multi vessel disease	28 (53.8%)	69 (45.7%)	0.31	6 (54.5%)	32 (59.3%)	1.00
Time from the symptom onset to admission (min)	265.8 ± 357.7	205.0 ± 272.7	0.20	426.2 ± 374.2	197.7 ± 254.2	0.011

Table 1 (continued)

	STEMI ($n=209$)			NSTEMI ($n=67$)		
	COVID-19 period ($n=53$)	Control period ($n=156$)	*P* value	COVID-19 period ($n=13$)	Control period ($n=54$)	*P* value
Time from admission to the diagnosis of the AMI (min)	37.0 ± 83.6	46.8 ± 63.4	0.38	92.2 ± 109.4	83.9 ± 90.7	0.78
Time from the diagnosis of the AMI to the CAG (min)	74.5 ± 59.4	82.4 ± 198.2	0.78	463.3 ± 670.1	136.2 ± 213.4	0.11
Door to balloon time (min)	103.1 ± 62.5	127.6 ± 145.2	0.11			
Therapeutic intervention						
Undergoing ad-hoc PCI	51 (96.2%)	145 (92.9%)	0.52	11 (91.7%)	48 (88.9%)	1.00
Undergoing primary PCI	51 (96.2%)	145 (92.9%)	0.52	–	–	–
POBA only	3 (6.0%)	17 (11.7%)	0.25	0	8 (17.4%)	0.33
Any mare-metal stent	0	3 (2.1%)	0.57	0	0	–
Any drug-eluting stent	47 (94.0%)	125 (86.2%)	0.14	11 (100.0%)	38 (82.6%)	0.33
Mechanical circulatory support						
IABP	25 (47.2%)	67 (42.9%)	0.59	6 (46.2%)	20 (37.0%)	0.55
VA-ECMO	5 (9.4%)	10 (6.4%)	0.54	1 (7.7%)	4 (7.4%)	1.00
IMPELLA	0	7 (4.5%)	0.120	0	2 (3.7%)	1.00
Mechanical ventilation	12 (22.6%)	26 (16.7%)	0.33	3 (23.1%)	8 (14.8%)	0.44
Non invasive positive pressure ventilation	4 (7.5%)	22 (14.1%)	0.21	2 (15.4%)	13 (24.1%)	0.72

Mean ± SD values or number (%) of patients are shown. *by Student's *t* test, Mann–Whitney *U* test, chi-square test, or Fisher's exact test

AMI acute myocardial infarction, *CABG* coronary artery bypass graft, *CAG* coronary angiography, *CK* creatine kinase, *COVID-19* coronavirus disease 2019, *IABP* intra-aortic balloon pump, *MI* myocardial infarction, *NSTEMI* non-ST elevation myocardial infarction, *OHCA* out of hospital cardiac arrest, *PCI* percutaneous coronary intervention, *POBA* plain old balloon angioplasty, *STEMI* ST elevation myocardial infarction, *TIMI* thrombolysis in myocardial infarction, *VA-ECMO* veno-arterial extracorporeal membrane oxygenation

Association between time-year and 30-day mortality

The follow-up time was 28.0 ± 6.9 days in the patients with STEMIs and 29.1 ± 4.1 in those with NSTEMIs, respectively. Overall, the 30-day mortality was 8.6% (18/209) for STEMIs and 6.0 (4/67) % for NSTEMIs. For STEMIs, the 30-day mortality rate during the COVID-19 period was 9.4% and it was not significantly different from that during the control period (vs. 8.3%, $P=0.772$ by log-rank test) (Fig. 2), whereas, for NSTEMIs, the 30-day mortality rate during the COVID-19 period was significantly higher than that during the control period (23.1% vs. 1.9%, $P=0.004$ by log-rank test) (Fig. 3).

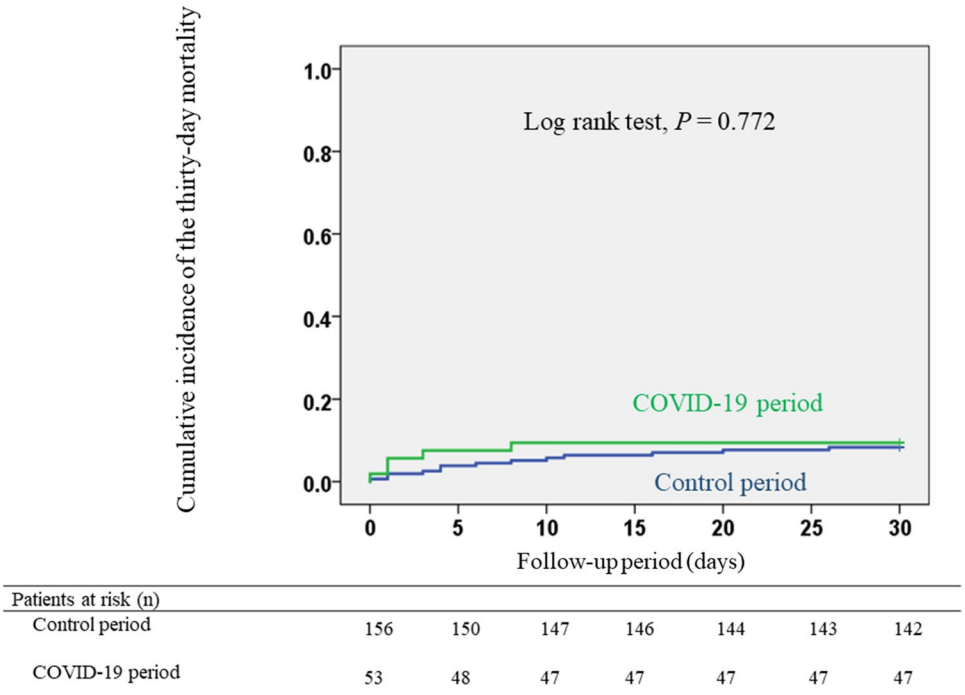
Discussion

Major findings

The major findings in the present study were as follows: (1) there was a 5.7% reduction in hospitalizations of AMI patients during the COVID-19 period than during the control period in Japan, (2) the 30-day mortality in the STEMI patients was not significantly different between the COVID-19 and control periods, and (3) in the NSTEMI patients, the time from the symptom onset to admission was significantly longer during the COVID-19 period than control period, and the 30-day mortality was significantly higher during the COVID-19 period. This study disclosed the impact of the COVID-19 outbreak on the hospitalizations and outcomes of patients with AMIs in Japan, where medical institutions have recommended active treatment for AMIs, such as a PCI, under infection prevention measures during the COVID19 pandemic.

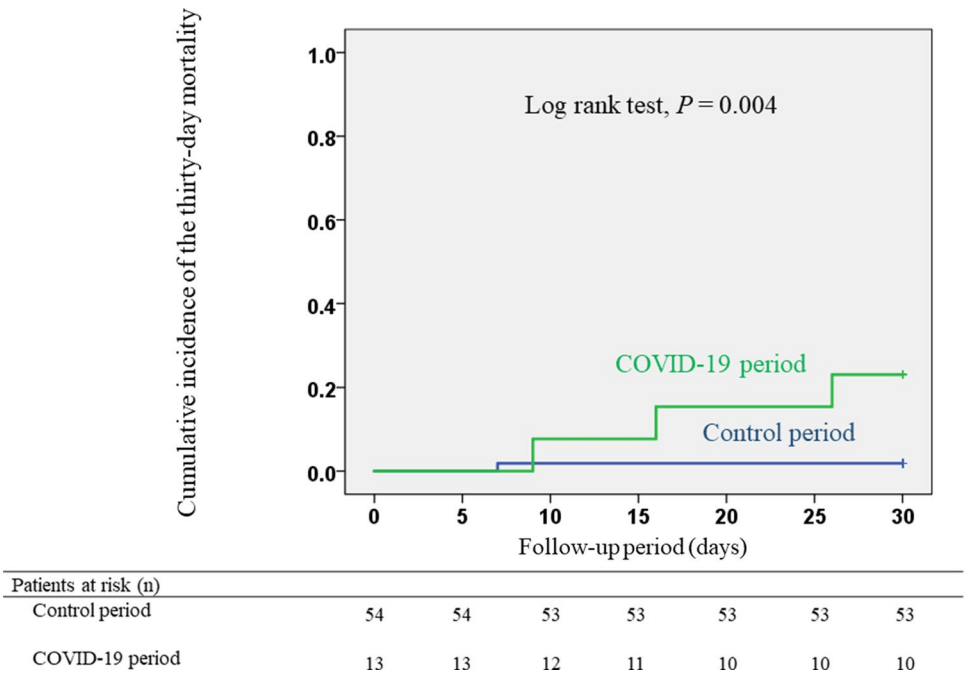
Impact of COVID-19 on hospitalizations for AMIs

This study showed 75.7% of STEMI, and 24.3% of NSTEMI, which were well in line with the previous Japanese data (68.9% STEMI and 31.1%NSTEMI), [14] while our STEMI rate was larger than that (22% STEMI) in Western countries [15]. This single-center study indicated a 5.7% reduction in AMI inpatients during the COVID-19 period as compared to that during the pre-COVID-19 period, which seemed lower than that in the previous reports from other countries showing that AMI inpatients had decreased significantly by 48.4% in Italy [2] and 35.6% in Southern India [16]. Important to note, this study showed the number of hospitalizations in the NSTEMI decreased but it did not in the STEMI. Data



Patients at risk (n)							
Control period	156	150	147	146	144	143	142
COVID-19 period	53	48	47	47	47	47	47

Fig. 2 Kaplan–Meyer curves of the 30-day mortality among the patients during the COVID-19 period and that during the control period in patients with an ST-segment elevation myocardial infarction (STEMI). The incidence of the 30-day mortality was not statistically significant between the COVID-19 and control periods (9.4% vs. 8.3%, $P = 0.772$ by log-rank test)



Patients at risk (n)							
Control period	54	54	53	53	53	53	53
COVID-19 period	13	13	12	11	10	10	10

Fig. 3 Kaplan–Meyer curves of the 30-day mortality among the patients during the COVID-19 period and control period in patients with a non-ST segment elevation myocardial infarction (NSTEMI). The 30-day mortality was significantly higher in the patients during the COVID-19 period than control period (23.1% vs. 1.9%, $P = 0.004$ by log-rank test)

including Japan in acute aortic disease reported that the number of hospitalized patients did not change regardless of the COVID-19 period, because the patients had typical and catastrophic symptoms to seek acute aortic care [17]. This data together with ours might suggest that when complaining of typical and catastrophic symptoms, such patients as aortic disease and STEMI seek an emergency request and the number of hospitalizations is maintained regardless of the COVID-19 period. In the present study, the age and prevalence of diabetes mellitus in the NSTEMI patients during the COVID-19 period were highest (but not statistically significance) (age: 70.2 ± 12.3, and diabetes mellitus: 61.5%). It is well-known that atypical symptoms are often seen, especially in the elderly and patients with diabetes mellitus [18]. The NSTEMI patients might tend to have atypical symptoms, and thus they may have afraid to seek an emergency request or hospital visit, which could lead to decrease in the number of hospitalizations.

The effect of COVID-19 on AMIs was explained not only by the direct effect of developing an AMI by a thrombosis associated with COVID-19 [19], but also an indirect effect, which could lead to a change in the incidence, hospitalizations, and outcomes of AMI patients without COVID-19. The indirect effect of COVID-19 might be multifactorial. Fear of contracting COVID-19 could have made patients with AMI afraid to seek acute cardiac treatment. Patients misinterpreting AMI symptoms such as atypical chest pain and shortness of breath as symptoms of COVID-19 might have interfered with an early diagnosis of an AMI by choosing home recuperation [20]. Furthermore, even after visiting a hospital, the time required to exclude COVID-19 may have prolonged the time required for a conventional detailed examination and treatment, which could have delayed the detection and treatment. An early diagnosis and early treatment are important for improving the prognosis of AMIs [21, 22], and it is considered that the prognosis deteriorates due to those indirect effects during the COVID-19 period. On the other hand, stay-at-home orders and movement restrictions within the public space affected the everyday life of patients and may have heightened the level of the stress during the COVID-19 pandemic [23], which may increase the incidence of stress-induced AMIs [24]. These indirect factors might have influenced each other and affected the number of AMI hospitalizations during the COVID-19 period.

Characteristics and outcomes of STEMIs during the COVID-19 period in Japan as compared to Outside Japan

In the present study, the 30-day mortality of STEMIs did not differ and was rather numerically higher during the COVID-19 period than the control period. On the other hand, the results outside of Japan showed an increase in mortality from AMIs during the COVID-19 pandemic [2, 5, 25]. The reason could be considered to be that the time from the symptom onset to the diagnosis of the AMI and the time from the diagnosis to the primary PCI, and the primary PCI enforcement rates differed between our study and the other countries [25, 26]. Xin-yan Fu et al. suggested that the prehospital and in-hospital treatment times for STEMIs after the COVID-19 outbreak were significantly longer than those before, which resulted in a mortality increase in Hangzhou, China [25]. Mahmoud SED et al. suggested that the volume of primary PCI was decreased in 80% of centers in Egypt [26]. Furthermore, in the STEMI patients in Milan, there were an increase in the time interval between symptom onset to hospitalization [27]. On the other hands, regarding acute aortic disease in the data including Japan, the time between symptom onset and referral showed no difference between COVID-19 period (2020) and controlled period (2019) [17]. It has been considered that typical aortic syndrome is a catastrophic clinical event that patients will be more likely to complain accurately as symptoms and seek medical advice and that the provision of acute aortic care and emergency operations is independent of any COVID-19 outbreak. This data suggests that if the patients suffering AMI could complain of typical and catastrophic chest pain, it can be performed according to the conventional guidelines from the symptom onset to hospitalization regardless of the COVID-19 outbreak in Japan. In Japan, in April 2020, two major organizations associated with AMI treatment, including the CVIT and JCS, recommended the strategy for AMIs during the COVID-19 era, and a primary PCI for a STEMI should be actively performed under infection prevention measures to save the lives of patients even when COVID-19 cannot be ruled out. In our hospital, the same medical treatment system for AMIs had already been started from January 30, 2020. The flowchart of the AMI treatment during the COVID-19 era has been updated day by day and the latest one in our hospital is shown in Fig. 4. As a result of our effort based on the AMI treatment flowchart and paramedics, in the STEMI patients in our cohort, the time from the symptom onset to admission, to the diagnosis of the AMI, and to the CAG during the COVID-19 period was the same as that during the control period. Furthermore, the primary PCI during the COVID-19 period was performed to the same extent as that during the control group. These might have lessened the increase in the mortality during the COVID-19 period. This might also be supported by our finding that the peak CK and CKMB levels were not higher and were rather lower during the COVID-19 period than the control period.

Characteristics and outcomes of NSTEMIs during the COVID-19 period in Japan

We found that the 30-day mortality of NSTEMIs was significantly higher during the COVID-19 period than control period. In NSTEMIs, it has been reported that early revascularization improves the prognosis [[21, 22]. In the present study, the time from the onset of the NSTEMI to admission was significantly longer during the COVID-19 period, and it was considered that myocardial damage may have already progressed by the initial examination. Furthermore, the time from the diagnosis to the CAG tended to be longer during the COVID-19 period, which may also have resulted in an increase in the 30-day mortality. In our hospital, until August 2020, catheter examination was not performed until COVID-19 was denied even with non-ST elevation acute coronary syndrome (NSTE-ACS) high risk, but after that, if the patients have NSTE-ACS high risk, emergent catheter examination has been performed under maximum personal protective equipment (PPE). The latest flowchart, updated on August 15, 2020, shown in Fig. 4 is designed to enable an early diagnosis and early treatment, and we will strive to

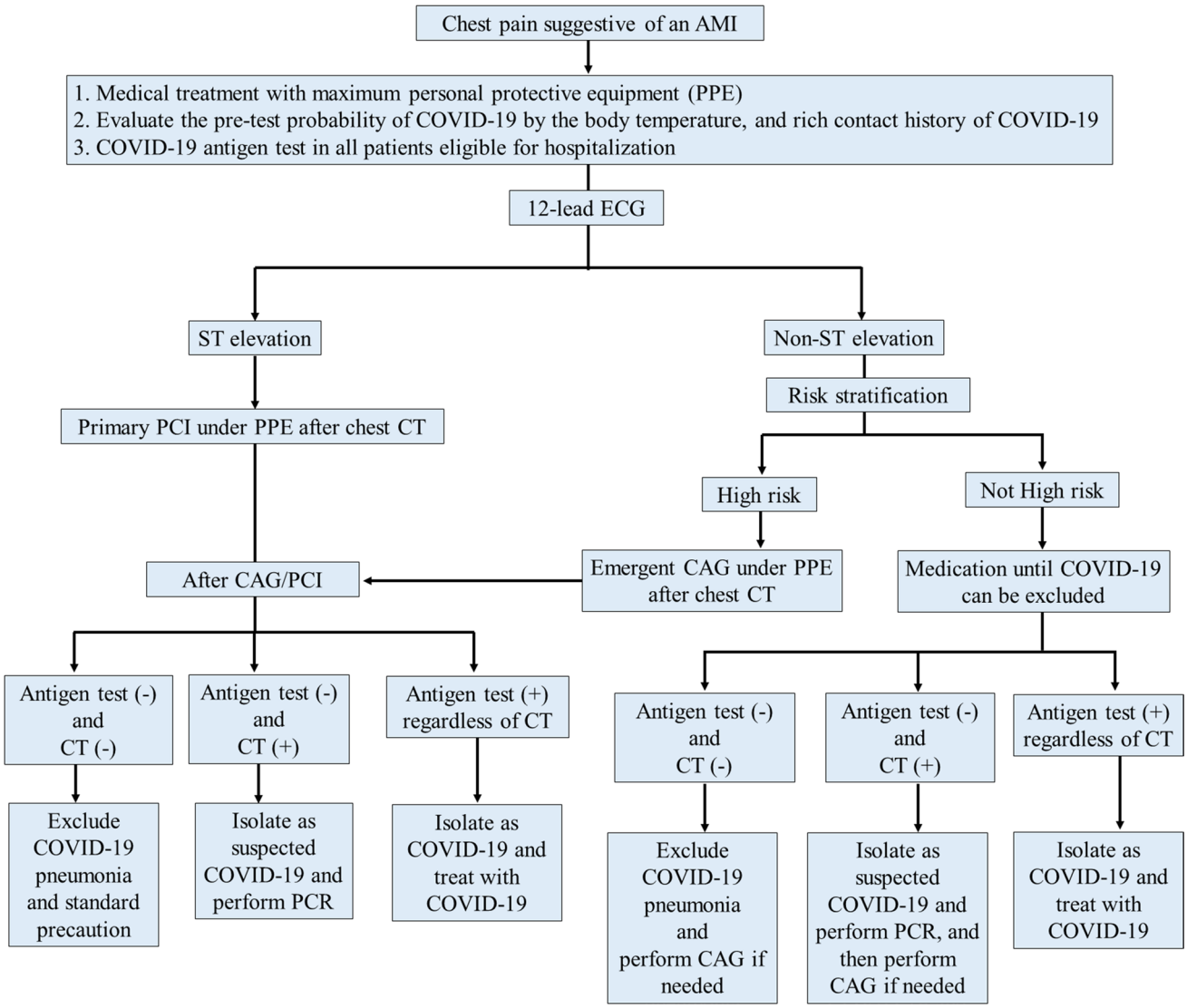


Fig. 4 The flowchart of the medical treatment of the patients suspected of an acute myocardial infarction (AMI), whose COVID-19 could not be excluded at Nihon University Itabashi hospital. The latest version was updated on August 15, 2020. *AMI* acute myocardial infarction, *CAG* coronary angiography, *COVID-19* coronavirus disease 2019, *CT* computed tomography, *ECG* electrocardiogram, *PCI* percutaneous coronary intervention, *PCR* polymerase chain reaction

improve the mortality from AMIs even during the COVID-19 period. Also, we have provided patient education including the importance of early detection among patients who are visiting our hospital, especially those who are at risk of ACS, to decrease the time between the symptom onset to admission.

Clinical implications

The present study suggested that the patients with STEMIs could achieve the same outcome as those before the COVID-19 outbreak by always performing infection prevention measures with maximum personal protective equipment (PPE) assuming a COVID-19 spread when performing an acute cardiac treatment. The latest flowchart of the AMI treatment at Nihon University Itabashi hospital is shown in Fig. 4, and it will be updated day by day with the advancements in the COVID-19 knowledge. It is considered to be effective to continue to work on an early diagnosis and early treatment with the above protocol, which could demonstrate that the 30-day mortality of STEMIs did not increase even during the COVID-19 period. Also, it is necessary to educate patients to shorten the time from the symptom onset to the hospitalization.

Study limitations

Our study data should be interpreted in light of our study limitations. First, it was carried out as a single-center retrospective observational study, and the number of AMIs was small. Second, because it was the result of 8 months from January 30 to September 30 after the COVID-19 outbreak and within one year, the hospitalizations and outcomes of AMIs throughout the year, including the seasonal characteristics, could not be compared. Third, for both STEMIs and NSTEMIs, the patient background was not exactly same between the two COVID-19 period and control period groups, so other factors beyond the COVID-19 outbreak could have affected the 30-day mortality. For example, as described above, the age and prevalence of diabetes mellitus were highest (but not statistically significant) in the NSTEMI patients during the COVID 19 period among the four groups. Those patient factors might have prolonged the time between the symptom onset and hospital visits in this study. Finally, the observation period was as short as 1 month, and thus the long-term outcomes were not evaluated.

Conclusion

This study demonstrated the effects of the COVID-19 outbreak on AMI treatment in Japan for both STEMIs and NSTEMIs, as compared to the same period in the past. In the STEMIs, we could obtain the same outcomes as usual by performing an acute treatment mainly with a primary PCI under infection countermeasures assuming COVID-19. On the other hand, the 30-day mortality from NSTEMIs during the COVID-19 period was higher than that in the control period, which might have been caused by the delay in the time from the AMI onset to admission and the time from the diagnosis to catheterization, due to the indirect effect of COVID-19. These findings suggested that, while keeping in mind the direct and indirect effects of COVID-19, in the initial visit where COVID-19 cannot be excluded, it is important to work on an early detection and early treatment as usual under infection preventive measures for COVID-19 with maximum PPE, in order not to increase the mortality rate of AMIs.

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Declarations

Conflict of interests The authors declare that they have no competing interests.

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References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395:497–506
2. De Rosa S, Spaccarotella C, Basso C, Calabrò MP, Curcio A, Filardi PP, Mancone M, Mercuro G, Muscoli S, Nodari S, Pedrinelli R, Sinagra G, Indolfi C (2020) Reduction of hospitalizations for myocardial infarction in Italy in the COVID-19 era. Eur Heart J 41:2083–2088
3. Metzler B, Siostrzonek P, Binder RK, Bauer A, Reinstadler SJ (2020) Decline of acute coronary syndrome admissions in Austria since the outbreak of COVID-19: the pandemic response causes cardiac collateral damage. Eur Heart J 41:1852–1853
4. Garcia S, Albaghdadi MS, Meraj PM, Schmidt C, Garberich R, Jaffer FA, Dixon S, Rade JJ, Tannenbaum M, Chambers J, Huang PP, Henry TD (2020) Reduction in ST-segment elevation cardiac catheterization laboratory activations in the United States during COVID-19 Pandemic. J Am Coll Cardiol 75:2871–2872
5. Song C, Liu S, Yin D, Wang Y, Zhao Y, Yang W, Qiao S, Dou K, Xu B (2020) Impact of public health emergency response to COVID-19 on management and outcome for STEMI patients in Beijing—a Single-Center Historic Control Study. Curr Probl Cardiol. https://doi.org/10.1016/j.cpcardiol.2020.100693
6. Rashid M, Gale CP, Curzen N, Ludman P, De Belder M, Timmis A, Mohamed MO, Lüscher TF, Hains J, Wu J, Shoaib A, Kontopantelis E, Roebuck C, Denwood T, Deanfield J, Mamas MA (2020) Impact of COVID19 pandemic on the incidence and management of out of hospital cardiac arrest in patients presenting with acute myocardial infarction in England. J Am Heart Assoc. https://doi.org/10.1161/JAHA.120.018379
7. The Japanese Association of Cardiovascular Intervention and Therapeutics (CVIT) (2020) Recommendations for cardiac catheterization and treatment under the spread of coronavirus infection. http://www.cvit.jp/files/news/2020/0413.pdf **(accessed Dec 3rd, 2020)**
8. The Japanese Circulation Society (JCS) (2020) COVID-19 Recommendations for maintaining the cardiovascular medical system during the epidemic. URL: https://www.j-circ.or.jp/cms/wp-content/uploads/2020/04/COVID-19 **(accessed Dec 3rd, 2020)**
9. Kimura K, Kimura T, Ishihara M, Nakagawa Y, Nakao K, Miyauchi K, Sakamoto T, Tsujita K, Hagiwara N, Miyazaki S, Ako J, Arai H, Ishii H, Origuchi H, Shimizu W, Takemura H, Tahara Y, Morino Y, Iino K, Itoh T, Iwanaga Y, Uchida K, Endo H, Kongoji K, Sakamoto K, Shiomi H, Shimohama T, Suzuki A, Takahashi J, Takeuchi I, Tanaka A, Tamura T, Nakashima T, Noguchi T, Fukamachi D, Mizuno T, Yamaguchi J, Yodogawa K, Kosuge M, Kohsaka S, Yoshino H, Yasuda S, Shimokawa H, Hirayama A, Akasaka T, Haze K, Ogawa H, Tsutsui H, Yamazaki T (2019) JCS 2018 guideline on diagnosis and treatment of acute coronary syndrome. Circ J 83:1085–1196
10. Arai R, Suzuki S, Semba H, Arita T, Yagi N, Otsuka T, Sagara K, Sasaki K, Kano H, Matsuno S, Kato Y, Uejima T, Oikawa Y, Kunihara T, Yajima J, Yamashita T (2018) The predictive role of *E*/*e*' on ischemic stroke and atrial fibrillation in Japanese patients without atrial fibrillation. J Cardiol 72:33–41

11. Qian G, Jin RJ, Fu ZH, Yang YQ, Su HL, Dong W, Guo J, Jing J, Guo YL, Chen YD (2017) Development and validation of clinical risk score to predict the cardiac rupture in patients with STEMI. Am J Emerg Med 35:589–593
12. Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, Dodge HT, Francis CK, Hillis D, Ludbrook P et al (1987) Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clin Findings Through Hosp Discharge Circul 76:142–154
13. Keeley EC, Boura JA, Grines CL (2003) Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 361:13–20
14. Ishihara M, Fujino M, Ogawa H, Yasuda S, Noguchi T, Nakao K, Ozaki Y, Kimura K, Suwa S, Fujimoto K, Nakama Y, Morita T, Shimizu W, Saito Y, Tsujita K, Nishimura K, Miyamoto Y (2015) Clinical presentation, management and outcome of Japanese patients with acute myocardial infarction in the Troponin Era—Japanese Registry of Acute Myocardial Infarction Diagnosed by Universal Definition (J-MINUET). Circ J 79:1255–1262
15. Roger VL, Weston SA, Gerber Y, Killian JM, Dunlay SM, Jaffe AS, Bell MR, Kors J, Yawn BP, Jacobsen SJ (2010) Trends in incidence, severity, and outcome of hospitalized myocardial infarction. Circulation 121:863–869
16. Meenakshisundaram R, Senthilkumaran S, Thirumalaikolundusubramanian P, Joy M, Jena NN, Vadivelu R, Ayyasamy S, Chandrasekaran VP (2020) Status of acute myocardial infarction in Southern India During COVID-19 lockdown: a multicentric study. Mayo Clin Proc Innov Qual Outcomes 4:506–510
17. Czerny M, Gottardi R, Puiu P, Bernecker OY, Citro R, Della Corte A, di Marco L, Fink M, Gosslau Y, Haldenwang PL, Heijmen RH, Hugas-Mallorqui M, Iesu S, Jacobsen O, Jassar AS, Juraszek A, Kolowca M, Lepidi S, Marrocco-Trischitta MM, Matsuda H, Meisenbacher K, Micari A, Minatoya K, Park KH, Peterss S, Petrich M, Piffaretti G, Probst C, Reutersberg B, Rosati F, Schachner B, Schachner T, Sorokin VA, Szeberin Z, Szopinski P, Di Tommaso L, Trimarchi S, Verhoeven ELG, Vogt F, Voetsch A, Walter T, Weiss G, Yuan X, Benedetto F, De Bellis A, Do M, Discher P, Zierer A, Rylski B, van den Berg JC, Wyss TR, Bossone E, Schmidli J, Nienaber C, Accarino G, Baldascino F, Böckler D, Corazzari C, Da I, de Beaufort H, De Troia C, Dumfarth J, Galbiati D, Gorgatti F, Hagl C, Hamiko M, Huber F, Hyhlik-Duerr A, Ianelli G, Iesu I, Jung JC, Kainz FM, Katsargyris A, Koter S, Kusmierczyk M, Kolsut P, Lengyel B, Lomazzi C, Muneretto C, Nava G, Nolte T, Pacini D, Pleban E, Rychla M, Sakamoto K, Shijo T, Yokawa K, Siepe M, Sirch J, Strauch J, Sule JA, Tobler EL, Walter C, Weigang E (2021) Impact of the coronavirus disease 2019 (COVID-19) pandemic on the care of patients with acute and chronic aortic conditions. Eur J Cardiothorac Surg. https://doi.org/10.1093/ejcts/ezaa452
18. Kosuge M, Kimura K, Kojima S, Sakamoto T, Ishihara M, Asada Y, Tei C, Miyazaki S, Sonoda M, Tsuchihashi K, Yamagishi M, Ikeda Y, Shirai M, Hiraoka H, Inoue T, Saito F, Ogawa H (2006) Sex differences in early mortality of patients undergoing primary stenting for acute myocardial infarction. Circ J 70:217–221
19. Gąsecka A, Borovac JA, Guerreiro RA, Giustozzi M, Parker W, Caldeira D, Chiva-Blanch G (2020) Thrombotic complications in patients with COVID-19: pathophysiological mechanisms, diagnosis, and treatment. Cardiovasc Drugs Ther. https://doi.org/10.1007/s10557-020-07084-9
20. Mohammad MA, Koul S, Olivecrona GK, Götberg M, Tydén P, Rydberg E, Scherstén F, Alfredsson J, Vasko P, Omerovic E, Angerås O, Fröbert O, Calais F, Völz S, Ulvenstam A, Venetsanos D, Yndigegn T, Oldgren J, Sarno G, Grimfjärd P, Persson J, Witt N, Ostenfeld E, Lindahl B, James SK, Erlinge D (2020) Incidence and outcome of myocardial infarction treated with percutaneous coronary intervention during COVID-19 pandemic. Heart. https://doi.org/10.1136/heartjnl-2020-317685
21. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, Neumann FJ, Robertson DH, DeLucca PT, DiBattiste PM, Gibson CM, Braunwald E (2001) Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 344:1879–1887
22. Mathew V, Farkouh M, Grill DE, Urban LH, Cusma JT, Reeder GS, Holmes DR Jr, Gersh BJ (2001) Clinical risk stratification correlates with the angiographic extent of coronary artery disease in unstable angina. J Am Coll Cardiol 37:2053–2058
23. Limbers CA, McCollum C, Greenwood E (2020) Physical activity moderates the association between parenting stress and quality of life in working mothers during the COVID-19 pandemic. Ment Health Phys Act 19:100358
24. Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M, Almahmeed WA, Blackett KN, Sitthi-amorn C, Sato H, Yusuf S (2004) Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. Lancet 364:953–962
25. Fu XY, Shen XF, Cheng YR, Zhou MY, Ye L, Feng ZH, Xu Z, Chen J, Wang MW, Zhang XW (2020) Effect of COVID-19 outbreak on the treatment time of patients with acute ST-segment elevation myocardial infarction. Am J Emerg Med. https://doi.org/10.1016/j.ajem.2020.09.038
26. Mahmoud SED, Etriby SE, Etriby AE, Ghalib A (2020) Management trends in the Cath Lab during the COVID-19 period, an Egyptian survey. Curr Probl Cardiol 46(3):100715
27. Gramegna M, Baldetti L, Beneduce A, Pannone L, Falasconi G, Calvo F, Pazzanese V, Sacchi S, Pagnesi M, Moroni F, Ajello S, Melisurgo G, Agricola E, Camici PG, Scandroglio AM, Landoni G, Ciceri F, Zangrillo A, Cappelletti AM (2020) ST-segment-elevation myocardial infarction during COVID-19 Pandemic: insights from a Regional Public Service Healthcare Hub. Circ Cardiovasc Interv 13:e009413