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ORIGINAL ARTICLE
Ischemic Heart Disease

Impact of the Coronavirus Disease 2019 (COVID-19) Pandemic on the Severity and the Mortality of Acute Myocardial Infarction in Japan

— Analysis From the JROAD-DPC Database —

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Background: Coronavirus disease 2019 (COVID-19) has impacted on cardiovascular disease. However, it remains unclear whether the COVID-19 pandemic has impacted on disease severity and patients' prognosis of acute myocardial infarction (AMI) in Japan.

Methods and Results: We retrospectively accumulated data from the Japanese Registry of All Cardiac and Vascular Diseases–Diagnosis Procedure Combination (JROAD-DPC) study (April 2019 to March 2021). Patients were divided into a before COVID-19 pandemic group or a during COVID-19 pandemic group. The proportion of patients who presented with cardiogenic shock (Killip class Ⅳ) was compared between groups, in association with 30-day mortality as the primary outcome. Killip class Ⅳ AMI significantly increased in the during COVID-19 pandemic group (15.7% vs. 14.5% in the before pandemic group, P<0.0001). The 30-day mortality was higher in the during COVID-19 pandemic group (9.6% vs. 9.2% in the before COVID-19 pandemic group, P=0.049). However, there was no significant difference in the adjusted 30-day mortality in each Killip class between the before and during COVID-19 pandemic groups.

Conclusions: During the early stage of the COVID-19 pandemic in Japan, 30-day mortality of AMI increased, mainly because of the increase of Killip class Ⅳ AMI patients. However, irrespective of the COVID-19 pandemic, the adjusted 30-day mortality of each Killip classification group was unchanged.

Key Words: Acute coronary syndrome; Acute myocardial infarction; Cardiovascular disease

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread around the world since December 2019, because of its characteristic high transmission, and has resulted in a pandemic.[1] The virus is known to cause cardiovascular injury, such as heart failure, arrhythmia, venous thromboembolism, myocarditis, and acute coronary syndrome (ACS) including acute myocardial infarction (AMI). The mechanisms of cardiovascular injury from coronavirus disease 2019 (COVID-19) have not been fully understood and are likely multifactorial. One potential mechanism is direct myocardial involvement mediated by angiotensin-converting enzyme 2.[2] Some reports have shown that mechanisms of COVID-19-related cardiac involvement include a cytokine storm mediated by an imbalanced response among subtypes of T helper cells, and hypoxia-induced excessive intracellular calcium leading to cardiac myocyte apoptosis.[3,4] Recent reports have also suggested that COVID-19 infection affects the severity of AMI patients by increasing their predisposition to thrombotic burden.[5]

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In contrast, during the COVID-19 pandemic, AMI patients become more severe even if they were negative for COVID-19 testing. There are two main reasons for this. First, there might have been a delay in presentation among patients with coronary disease because of a fear of contracting COVID-19 in hospital. Second, the medical staff's initial treatment, including primary percutaneous coronary intervention (PCI), might have been delayed because of the need to prevent infection and the need to undergo COVID-19 testing before treatment. This increase in the number of severe AMI patients causes an increase in the mortality rate. In addition, during the COVID-19 pandemic, the mortality rate may also have increased because several cardiovascular procedures were restricted due to medical resources being consumed by the pandemic. Therefore, COVID-19 may directly and indirectly affect the severity and mortality of AMI patients. Furthermore, these indirect effects can be caused not only by COVID-19 but also other infectious diseases that might cause a pandemic in the future. Thus, we should know how the severity and mortality of AMI patients has been changed during the COVID-19 pandemic. The main aim of this study was to demonstrate the impact of the COVID-19 pandemic on the severity and mortality of AMI in Japan using the Japanese Registry of All Cardiac and Vascular Diseases–Diagnosis Procedure Combination (JROAD-DPC) database.

Methods

The JROAD-DPC Database

The JROAD-DPC is a nationwide claims database comprising data from hospitals in Japan collected between April 2012 and March 2021. We used International Classification of Diseases, Tenth Revision (ICD-10) codes to extract data for patients aged ≥20 years who were hospitalized for acute cardiovascular diseases (CVD; AMI, acute heart failure, venous thromboembolism, or ruptured aortic aneurysm) or had scheduled surgeries or procedures for CVD (ischemic heart disease, valvular heart disease, aortic aneurysm, atrial septal defect, venous thromboembolism, or peripheral arterial disease), scheduled catheter ablation, scheduled permanent pacemaker implantation and replacement, or scheduled left ventricular assist device implantation. The following data were collectable in the JROAD-DPC database: patient age and sex, height, body weight, body mass index (BMI), ICD-10 diagnosis codes, Killip classification, route of admission, Japan coma scale on admission, treatment procedures, discharge status, and medical costs. The JROAD institutional survey data were merged with the per-patient data in the JROAD-DPC database to assess the association of institutional factors with the prognosis of each patient. The ICD-10 codes, surgical codes and procedure combination codes are listed in **Supplementary Table 1**.

Definitions

The diagnosis of AMI was determined by the physician and identified according to the ICD-10 codes for AMI (I21.0, I21.1, I21.2, I21.3, I21.4, and I21.9) as the main diagnosis, the admission-precipitating diagnosis, or the most resource-consuming diagnosis for the hospitalization, as recorded in the DPC/PDPS claim data. The Killip classification on admission was determined by the attending physician: class I patients are free of rales and a third heart sound (S3); class II patients have rales, but only to a mild to moderate degree (<50% of lung fields); class III patients have rales in more than half of each lung field; class IV patients have cardiogenic shock.[6] Deep coma was determined by the conscious levels of the Japan coma scale 300 (300, 300A, 300I, 300 IA, 300R, 300RA, 300 RI, and 300RIA in the DPC data). The Japan coma scale comprises 4 main categories: 0 and 1-, 2-, and 3-digit codes corresponding to alert, awake without stimuli, arousable with some stimuli, and unarousable by a forceful stimulus, respectively. Each code is further divided into 3 subcategories: 1, 2 and 3 in the 1-digit code, 10, 20, and 30 in the 2-digit code, and 100, 200, and 300 in the 3-digit code. The Japan coma scale of 0 is equal to the Glasgow coma scale of 15 (E4V5M6), while a Japan coma scale of 300 corresponds to the Glasgow coma scale of 3 (E1V1M1).[7] Cardiac arrest was determined by the ICD-10 diagnosis code I46.0 (Cardiac arrest with successful resuscitation). COVID-19-positive patients and those who performed COVID-19 testing were extracted based on the main and secondary diagnosis, the admission-precipitating diagnosis, or the most resource-consuming diagnosis for the hospitalization, and diagnoses of comorbidities or complications. There were no data on the time from the hospital arrival to reperfusion (door-to-balloon [DTB] time). However, in Killip I–III AMI patients, surgical codes (K5461, K5491) means achieving revascularization within 90 min from the hospital arrival. Therefore, we used these data to determine the achievement rate of DTB time <90 min. Achievement rates of DTB time <90 min were calculated as patients who underwent PCI within 90 min from the hospital arrival/patients who underwent PCI.

Outcomes

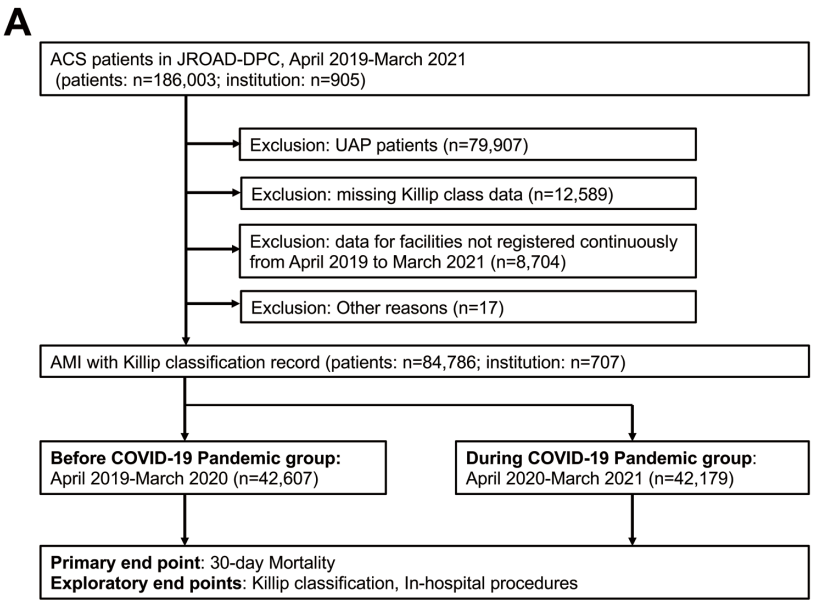
We defined death within day 30 from admission as the primary outcome of this study, which was identified from the JROAD-DPC database. We also investigated AMI severity as Killip classification, and in-hospital procedures between the before and during COVID-19 pandemic groups.

Statistical Analysis

Data are presented as mean±SD for normally distributed data, and as median interquartile range (IQR) for asymmetrically distributed data, or absolute number (proportion) for categorical data. The differences among quartiles were compared using analysis of variance for continuous variables and chi-square test for non-continuous and categorical variables. The main outcome measure was 30-day mortality. The adjusted odds ratio of 30-day mortality was assessed using univariate analysis and some multivariate logistic regression models. We defined statistical significance as $P<0.05$. JMP pro version 16.0.0 was used for statistical analyses.

Ethics Statement

The JROAD-DPC study was planned in accordance with the World Medical Association Declaration of Helsinki and approved by the institutional review board of the National Cerebral and Cardiovascular Center (NCVC), Osaka, Japan, which waived the requirement for individual informed consent according to the "opt-out" principle. Each participating hospital anonymized each patient's identity in the DPC/PDPS claim data by a code change equation and submitted the DPC/PDPS claim data to the NCVC. The specific study plan of this study was reviewed and approved by the Ethics Committee of the Kyushu



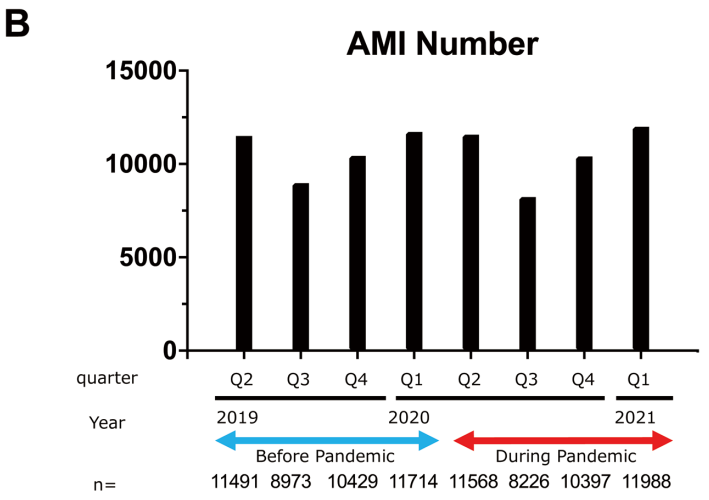


Figure 1. (**A**) Study flowchart of patient enrollment. (**B**) Trends in the number of acute myocardial infarction (AMI) patients in this study. Q1, April–June; Q2, July–September; Q3, October–December; Q4, January–March. ACS, acute coronary syndrome; DPC, diagnosis procedure combination; JROAD, Japanese Registry of All Cardiac and Vascular Diseases; UAP, unstable angina pectoris.

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Results

Database

In the JROAD-DPC database, 186,003 ACS patients were identified according to the ICD-10 codes from 905 facilities. First, we excluded unstable angina pectoris patients by reference to ICD-10 codes as the main diagnosis, the admission-precipitating diagnosis, or the most resource-consuming diagnosis for the hospitalization, as recorded in the DPC/PDPS claim data. We also excluded cases without Killip classification.

We defined the COVID-19 pandemic according to the state of emergency by the Japanese government and divided patients into two groups: before COVID-19 pandemic, April 2019 to March 2020; and during COVID-19 pandemic, April 2020 to March 2021. To match facility factors between the two groups, we used data for institutions that registered in two consecutive years from April 2019 to March 2021. Finally, 84,786 patients from 707 individual institutions were enrolled: the before COVID-19 pandemic group included 42,607 patients, and the during COVID-19 pandemic group included 42,179 patients (**Figure 1A**). **Figure 1B** shows the trends in the number of AMI patients over the period. The trends were generally similar between the two groups.

Patient Characteristics

The baseline characteristics of the two patient groups are shown in **Table 1**. The median age was 71 years in the before COVID-19 pandemic group and 72 in the during COVID-19 pandemic group. There was no significant difference between the before and the during COVID-19 groups in percentage of female sex, admission by ambu-

Table 1. Baseline Characteristics of the Study

Patient factors	Overall (n=84,786)	Before the COVID-19 pandemic (n=42,607)	During the COVID-19 pandemic (n=42,179)	P value (Before vs. During)
Age, median [IQR]	72 [62, 81]	71 [62, 80]	72 [62, 81]	0.0004
Female sex	22,633 (26.7)	11,268 (26.5)	11,365 (26.9)	0.10
Admission by ambulance	60,288 (71.1)	30,222 (70.9)	30,066 (71.3)	0.26
Deep coma	3,742 (4.4)	1,833 (4.3)	1,909 (4.5)	0.11
Cardiac arrest on admission	1,258 (1.5)	665 (1.6)	593 (1.4)	0.062
Height	162.11±9.78	162.09±9.77	162.13±9.79	0.64
Body weight	63.28±14.22	63.16±14.14	63.39±14.30	0.023
BMI (kg/m^2)	23.92±3.97	23.89±3.96	23.96±3.98	0.0067
High BMI	5,275 (6.87)	2,573 (6.67)	2,702 (7.07)	0.028
Low BMI	5,055 (6.58)	2,583 (6.69)	2,472 (6.47)	0.21
Hypertension	53,319 (62.9)	26,877 (63.1)	26,442 (62.7)	0.24
Diabetes	26,073 (30.8)	12,922 (30.3)	13,151 (31.2)	0.0073
Dyslipidemia	55,009 (64.9)	27,695 (65.0)	27,314 (64.8)	0.46
Renal disease without HD	6,465 (7.6)	3,133 (7.4)	3,332 (7.9)	0.0027
Renal disease with HD	2,904 (3.4)	1,383 (3.2)	1,521 (3.6)	0.0035
Peripheral vascular disease	2,458 (2.9)	1,256 (3.0)	1,202 (2.9)	0.39
Cerebrovascular disease	3,811 (4.5)	1,912 (4.5)	1,899 (4.5)	0.92
Chronic pulmonary disease	2,552 (3.0)	1,240 (2.9)	1,312 (3.1)	0.088

Unless otherwise indicated, data are presented as mean±SD or n (%). BMI, body mass index; COVID-19, coronavirus disease 2019; HD, hemodialysis.

lance, deep coma (Japan coma scale 300/Glasgow coma scale E1V1M1), and resuscitated cardiac arrest (ICD-10 I46.0), although these factors were known to be associated with the severity of the AMI patients.[8] Patients who were diagnosed with diabetes, renal disease and underwent dialysis were more frequently observed in the during COVID-19 pandemic group. BMI was significantly higher in the during COVID-19 pandemic group.

Severity and Mortality of AMI During the COVID-19 Pandemic

Figure 2A shows the Killip classification before and during the COVID-19 pandemic. In this study, Killip IV rates of AMI significantly increased in the during COVID-19 pandemic group (14.5% in the before COVID-19 pandemic group vs. 15.7% in the during COVID-19 pandemic group, P<0.0001). The primary outcome, 30-day mortality of patients with AMI, is shown in **Figure 2B**. In this study, the 30-day mortality was higher in the during COVID-19 pandemic group (9.6% vs. 9.2% in the before COVID-19 pandemic group, P=0.049). However, the 30-day mortality stratified by Killip class was not different (**Figure 2C**); Killip class I (2.0% vs. 2.1% in the before and during COVID-19 pandemic groups), Killip class II (4.3% vs. 4.5%), Killip class III (12.2% vs. 12.1%), and Killip class IV (42.3% vs. 42.0%).

Adjusted 30-Day Mortality for During/Before the COVID-19 Pandemic

Because there are differences in the background factors that may contribute to the 30-day mortality between the two groups, we analyzed the 30-day mortality in several models, as shown in **Table 2**. **Table 2** presents the multiple logistic regression-derived adjusted odds ratio of 30-day mortality for the during COVID-19 pandemic group compared with the before COVID-19 pandemic group. Although non-adjusted 30-day mortality was higher in the during COVID-19 pandemic group, the adjusted odds ratio of 30-day mortality was not significant for the during/before COVID-19 pandemic groups in all models. Interestingly, in model 4, the 30-day mortality by adjusting age, gender, admission by ambulance, deep coma, cardiac arrest on admission, BMI, comorbidities and Killip classification of AMI patients showed a lowest median odds ratio (OR 0.96, CI [0.90–1.03]). Odds ratios of 30-day mortality of each factor are shown in **Supplementary Table 2**.

In-Hospital Procedures During the COVID-19 Pandemic

We exploratorily analyzed in-hospital procedures for overall (**Table 3**) and Killip IV (**Figure 3**) AMI patients. The proportion of patients who underwent revascularization was not different between the before and after COVID-19 pandemic groups in overall AMI patients (PCI: 85.6% vs. 85.4% in the before and during COVID-19 pandemic groups; coronary artery bypass graft [CABG]: 1.83% vs. 1.88%), as well as in Killip IV patients (PCI: 73.9% vs. 74.2% in the before and during COVID-19 pandemic groups; CABG: 3.82% vs. 3.24%). Among Killip I–III AMI patients, the achievement rate of DTB time <90 min was low in the during COVID-19 pandemic group (53.4% vs. 54.4% in the before COVID-19 pandemic group, P=0.014). In only Killip III AMI patients, the achievement rate was significantly decreased in the during COVID-19 pandemic group (50.1% vs. 54.3% in the before COVID-19 pandemic group, P=0.039; **Supplementary Figure 1**).

The proportion of patients who underwent intubation and respirator use in the during COVD-19 pandemic group was higher than that in the before COVID-19 pandemic group (intubation: 7.2% vs. 7.9% in the before and during COVID-19 pandemic groups, P=0.0001; respirator

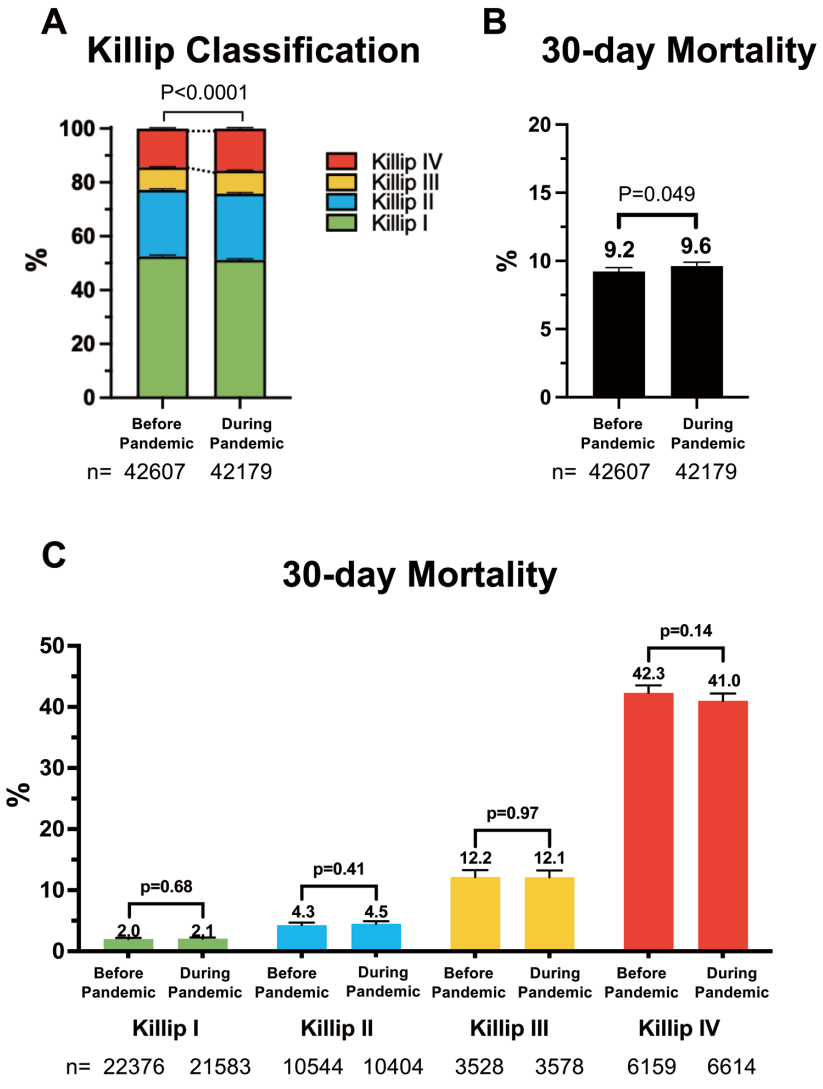

Figure 2. (**A**) Killip classification between the two groups. Data reported in percentage. The rate of Killip IV acute myocardial infarction (AMI) patients was compared. Statistical analysis was performed using Chi-squared tests. Statistical significance was reached with P<0.05. (**B**) Thirty-day mortality of AMI patients overall. We compared the 30-day mortality among the two groups. Statistical analysis was performed using Chi-squared tests. Statistical significance was reached with P<0.05. (**C**) Thirty-day mortality of AMI patients per Killip classification in Japan (April 2019–March 2021). Thirty-day mortality by Killip class was compared. Statistical analysis was performed using Chi-squared tests. Statistical significance was reached with P<0.05.

use: 17.6% vs. 18.2% in the before and during COVID-19 pandemic groups, P=0.012). The proportions are higher in the Killip IV patients, but not different between the before and during COVID-19 pandemic groups (**Figure 3B**).

Regarding mechanical circulatory support (MCS), the proportion of patients who underwent intra-aortic balloon pumping was not different between the before and during COVID-19 pandemic groups in overall and Killip IV AMI (**Table 3**, **Figure 3C**). An interesting finding was that the proportion of patients who underwent venoarterial extracorporeal membrane oxygenation (VA-ECMO) decreased, and that of Impella® increased during the COVID-19 pandemic, which was remarkable in Killip IV AMI patients (VA-ECMO: 16.1% vs. 13.2% in the before and during COVID-19 pandemic groups, P <0.0001; Impella®: 3.7% vs. 5.3%, P<0.0001; **Table 3**, **Figure 3C**).

COVID-19 Test Results in AMI Patients During the COVID-19 Pandemic

We divided the during COVID-19 pandemic group into three subgroups, which included the COVID-19 not-tested

Table 2. Multiple Logistic Regression-Derived Adjusted OR of 30-Day Mortality for the Before and During COVID-19 Pandemic Groups

Variable: Before and during COVID-19	OR [95% CI]	P value
Model 1	1.03 [0.98, 1.08]	0.20
Model 2	1.02 [0.97, 1.08]	0.46
Model 3	1.00 [0.94, 1.07]	0.89
Model 4	0.96 [0.90, 1.03]	0.31

Model 1: Age, Sex. Model 2: Model 1+Admission by ambulance, Deep coma, Cardiac arrest on admission. Model 3: Model 2+High BMI+Low BMI+Comorbidities (Hypertension, Diabetes, Dyslipidemia, Renal disease without HD, Renal disease with HD, Peripheral vascular disease, Cerebrovascular disease, Chronic pulmonary disease). Model 4: Model 3+Killip classification. OR, odds ratio. Other abbreviations as in Table 1.

Table 3. In-Hospital Procedures

Patient factors	Overall (n=84,786)	Before the COVID-19 pandemic (n=42,607)	During the COVID-19 pandemic (n=42,179)	P value (Before vs. During)
PCI	72,465 (85.5)	36,463 (85.6)	36,002 (85.4)	0.35
CABG	1,573 (1.86)	779 (1.83)	794 (1.88)	0.56
Intubation	6,413 (7.6)	3,075 (7.2)	3,338 (7.9)	0.0001
Respirator	15,185 (17.9)	7,490 (17.6)	7,695 (18.2)	0.012
IABP	60,288 (71.1)	5,576 (13.1)	5,508 (13.1)	0.90
VA-ECMO	2,465 (2.9)	1,310 (3.1)	1,155 (2.7)	0.0036
Impella	781 (0.9)	327 (0.8)	454 (1.1)	<0.0001

Data are presented as n (%). CABG, coronary artery bypass graft; COVID-19, coronavirus disease 2019; IABP, intra-aortic balloon pumping; PCI, percutaneous coronary intervention; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

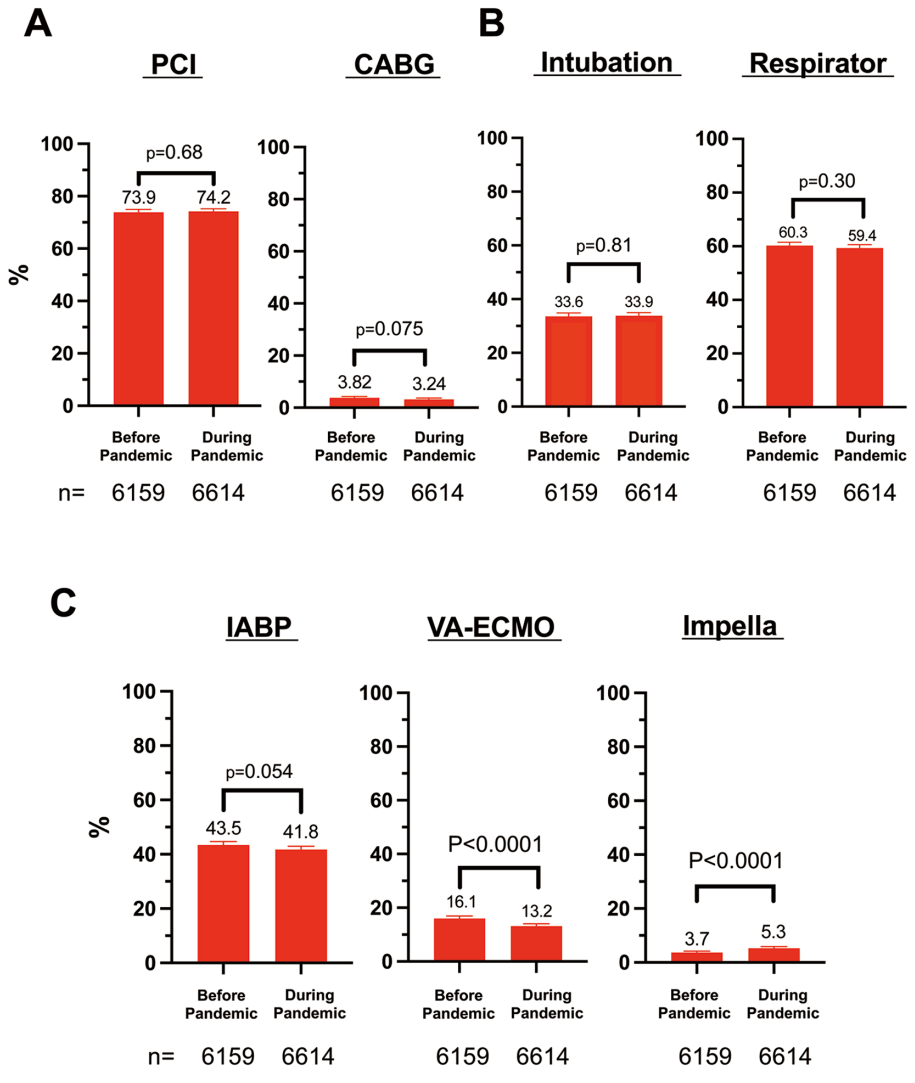

Figure 3. In-hospital procedures in Killip IV acute myocardial infarction (AMI) patients between the two groups. (**A**) Rates of patients who received percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG). (**B**) Rates of use of intubation and respirator. (**C**) Rates of use of mechanical care supports for intra-aortic balloon pumping (IABP), venoarterial extracorporeal membrane oxygenation (VA-ECMO) and Impella®. Statistical analysis was performed using Chi-squared tests. Statistical significance was reached with P<0.05.

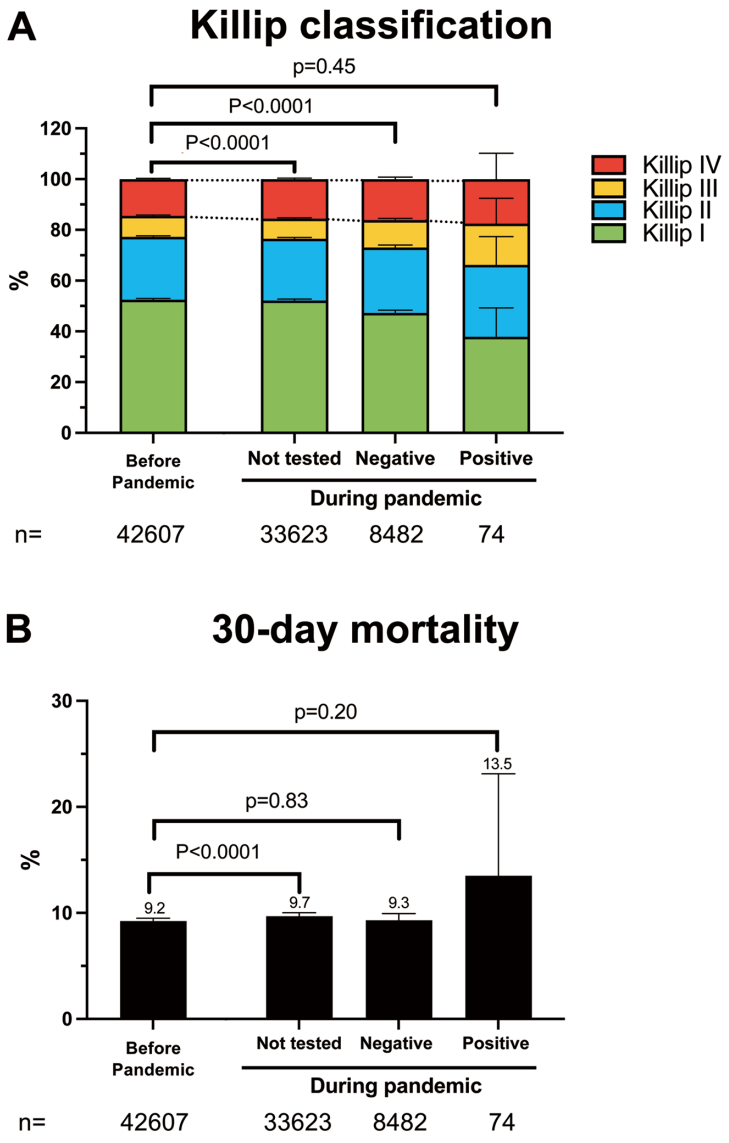

Figure 4. The during COVID-19 pandemic group was divided into three groups: the not-tested group, the COVID-19-negative group, and the COVID-19-positive group. Each group was compared with the before COVID-19 pandemic group. Statistical analysis was performed using Chi-squared tests. Statistical significance was reached with P<0.05. (**A**) Killip classification among the four groups. The rate of Killip IV AMI patients was compared. (**B**) Thirty-day mortality in each group.

group (n=33,623), the COVID-19-negative group (n=8,482) and the COVID-19-positive group (n=74; **Supplementary Figure 2**). We investigated the relationship between COVID-19 tests results and AMI severity and prognosis in the during COVID-19 pandemic group (**Figure 4**). During the COVID-19 pandemic in 2020, 20% of AMI patients were tested for COVID-19, with a 0.2% positive result. The percentage of Killip IV AMI patients tended to be higher not only in the COVID-19-positive group (17.6%) but also in the COVID-19 not-tested group (15.6%) and the COVID-19-negative group (16.1%) compared with the before COVID-19 pandemic group (14.5%; **Figure 4A**). The 30-day mortality of the COVID-19 positive group was 13.5% and it was higher than that of the before COVID-19 pandemic group (9.2%). Furthermore, the 30-day mortality of the not-tested group (9.7%) was also higher than the before COVID-19 pandemic group (**Figure 4B**). In overall patients, the rate of patients who underwent PCI was unchanged in both the COVID-19 not-tested group (85.2%) and the COVID-19-negative group (86.1%) compared with the before COVID-19 pandemic group (85.6%). However, in the COVID-19-positive group, the rate of patients who underwent PCI tended to be decreased (81.1%; **Supplementary Figure 3**). In Killip I–III AMI patients, the achievement rates of DTB time <90 was decreased in the COVID-19-negative (44.8%) and COVID-19-positive (42.6%) groups compared with the before COVID-19 pandemic group (47.6%; **Supplementary Figure 4**). The rate in the COVID-19 not-tested group (47.2%) was unchanged.

Discussion

In this study, we examined the impact of the COVID-19 pandemic on the severity and 30-day mortality of AMI in Japan using the JCS JROAD-DPC health insurance claim database. Major findings were: the proportion of Killip class IV AMI increased during the COVID-19 pandemic;

overall mortality of AMI increased during the COVID-19 pandemic; and there was no significant difference in the adjusted odds ratio of 30-day mortality before and during the COVID-19 pandemic.

Background of AMI Patients During the COVID-19 Pandemic

In this study, patients who were diagnosed with diabetes, renal disease and underwent dialysis were more frequent in the during COVID-19 pandemic group. These trends were observed in reports from Europe.[9] Some papers reported that the number of AMI patients decreased during the COVID-19 pandemic. Because of limited social and physical activity during the COVID-19 pandemic, people at low risk for AMI might be less likely to develop AMI.[10,11] This decrease in patients who were at low risk for AMI might result in a relative increase in the proportion of people with comorbidities.

In contrast, it was reported that diabetic patients had worsening HbA1c control during the COVID-19 pandemic.[12] This result might have caused an increase of the number of AMI patients among diabetic patients.

However, the comorbidity rate was lower in our cohort compared with previous reports.[9] This is because the DPC registry is based on the judgment of the attending physician and is limited in the number of patients that can be registered. Therefore, considering comorbidities in DPC database studies may be a limitation.

Severity of AMI During the COVID-19 Pandemic

Our hypothesis was that the number of severe AMI patients would increase, especially the number of patients with cardiogenic shock (i.e., Killip class IV patients). Previous studies from Europe reported that severe AMI patients increased during the COVID-19 pandemic compared with before the COVID-19 pandemic.[9,13] In a study from Italy, there was a 3-fold higher rate of cardiogenic shock patients during the COVID-19 pandemic compared with those before the COVID-19 pandemic (21% vs. 9%).[13] Although the difference is not as large, the findings in the present study are in line with those of previous studies. The proportion of Killip IV AMI patients in the during COVID-19 pandemic group was 15.7%, and it was 1.2 points higher than that of the before COVID-19 pandemic group in our study.

There are two possible reasons for the increase in the number of severe AMI patients, direct and indirect. One direct reason is that COVID-19 infection affects the severity of AMI, possibly through accelerating the thrombotic state.[3,5] One study from the UK showed the outcome of COVID-19-positive ACS patients; of the 12,958 patients hospitalized with ACS, 517 (4.0%) were COVID-19 positive, and the percentage of AMI patients presenting with cardiogenic shock was higher in COVID-19-positive patients (9.6%, n=45) compared with COVID-19-negative patients (3.9%, n=421).[14] In our study, during the COVID-19 pandemic in 2020, 20% of AMI patients were tested for COVID-19 (n=8,556), with 0.2% (n=74) positive, and the rate of AMI patients who presented with cardiogenic shock was 17.6% in COVID-19-positive patients (**Figure 4A**). The tendency for Killip IV to increase among COVID-19-infected patients was the same as in the UK study, but the number of infected patients in Japan was remarkably small in the early stages of the pandemic, so the contribution to the overall severity of AMI was thought to be small.

In contrast, indirect reasons include a delay of presentation to hospital. Patients who had symptoms such as chest pain were in fear of COVID-19 infection in hospital during the pandemic. A previous study in the US reported that the median pain-to-door time was significantly larger during the pandemic compared with before the pandemic (1,885 [880, 5,732] vs. 606 [388, 944] min, P<0.0001).[15] In Japan, the time required from emergency request to handover to doctor increased during the COVID-19 pandemic. It was approximately 39–40 min before the COVID-19 pandemic, but increased to approximately 42.8 min since the COVID-19 outbreak.[16]

There were no records of the pain-to-door time in the JROAD-DPC database. However, we could find a significant increase in the proportion of Killip IV AMI patients even in the COVID-19 not-tested group compared with that of the before COVID-19 pandemic group; this finding might be because of patients delaying presentation.

These findings suggest that the COVID-19 pandemic directly and indirectly impacted on the disease severity of AMI in the early stage of the COVID-19 pandemic in Japan.

Mortality of AMI During the COVID-19 Pandemic

In this study, we assessed 30-day mortality as the primary outcome, and it increased during the COVID-19 pandemic. This result was similar to the result in the US and Europe.[17] However, 30-day mortality during the COVID-19 pandemic in this study was lower than that of Japanese studies using data from the same period.[18] In this study, we only included hospitals that submitted the DPC claim data for 2 consecutive years before and during the COVID-19 pandemic; therefore, it is possible that this study did not include hospitals that cared for a large number of COVID-19 patients, compromising clinical research activities. As a result, this analysis may not reflect the full picture of care for AMI in Japan, and the mortality may be low.

The increase in 30-day mortality was also caused directly and indirectly by the COVID-19 pandemic. In a previous study in England, the 30-day mortality of AMI patients was 30.8% (n=44) in COVID-19-positive patients compared with that in COVID-19-negative patients (4.1%, n=260).[14] In our study, the 30-day mortality of the COVID-19-positive patients tended to be higher than the before COVID-19 pandemic group (13.5% vs. 9.2%, P=0.20; **Figure 4B**). This might be because COVID-19 directly impacts on coronary circulation and/or myocardial injury causing an increase in mortality.[3] Additionally, in our study, although the proportion of patients treated with PCI in the before COVID-19 pandemic group was similar to those in previous reports that extracted data from the JROAD DPC,[19] the proportion in the COVID-19-positive group was low compared with the before COVID-19 pandemic group. Thus, the decrease in the proportion of patients treated with PCI might also be one of the reasons for the higher mortality in the COVID-19-positive group.

During the COVID-19 pandemic, suspected COVID-19 infection indirectly causes AMI mortality; the COVID-19 testing and triage in the emergency department and the application of infection-protective equipment might cause longer DTB time. Indeed, a previous report from the US showed that there was a significant prolongation in DTB time in non-ST-elevation MI during the pandemic with a

median time of 332 vs. 194 min (P=0.0371).[15] Although the exact DTB time cannot be determined in our study, among the Killip I, II and III AMI patients, the achievement rate of DTB time <90 min was decreased during the COVID-19 pandemic (**Supplementary Figure 3**). Furthermore, in our study, the achievement rate was changed not only in the COVID-19-positive group but also in the COVID-19-negative group during the COVID-19 pandemic, suggesting that the decrease in the achievement rate might be caused by in-hospital preparations including COVID-19 testing. However, the absolute difference of DTB <90 min achievement rate was minor. In Japan, AMI patients are treated in more than 1,000 PCI centers in a relatively decentralized manner,[8] which might limit the impact of the COVID-19 pandemic on the prolongation of DTB time.

In contrast, the 30-day mortality stratified by Killip class was unchanged (**Figure 2B**). Furthermore, multivariate analysis showed that the 30-day mortality adjusted by age, gender, BMI, admission by ambulance, deep coma, cardiac arrest on admission and comorbidities was also unchanged (**Table 2**).

Treatment procedures such as coronary revascularization, respirator or MCS for severe AMI patients during the COVID-19 pandemic was performed as well as that before the COVID-19 pandemic (**Figure 3**). The revascularization rate was low in the during COVID-19 pandemic group (PCI 85.4%, CABG 1.88%), but there was no difference between the before and during COVID-19 pandemic groups. Among MCS, we found that the use of VA-ECMO decreased during the pandemic. ECMO might be preserved for severe cardiopulmonary diseases other than AMI, including COVID-19 pneumonia.[20] In the study period, the use of Impella® was increasing after the introduction to Japan in 2017. Therefore, cardiologists could use Impella® for AMI cases with cardiogenic shock where they used VA-ECMO in the past.

These findings indicate that the increase in the number of Killip IV AMI itself might cause the increase of overall 30-day mortality during the COVID-19 pandemic in Japan.

Clinical Perspectives

As discussed above, the COVID-19 pandemic was associated with an increase of Killip IV AMI, possibly through direct effects including accelerating the thrombotic state, and indirect effects such as a delay of presentation to hospital. Although it can be said from our analysis that medical staff were able to manage Killip IV AMI patients well during the COVID-19 pandemic, to limit the severity of AMI in another pandemic in the future, a preventive use of anti-thrombotic therapy in COVID-19 patients to ameliorate the severity of AMI needs to be discussed and proven through clinical trials.[21] It may also be necessary to create a pre-hospital system in which AMI patients take less time to arrive at hospitals.

Study Limitations

This study has several limitations that need to be discussed. First, the JROAD-DPC database has a bias in the selection of the hospital, JCS affiliation and DPC/PDPS integration. Second, the primary endpoint, 30-day mortality, was defined as whether the patient had died by day 30 from admission, but it was not possible to follow up in cases where the patient was discharged from the hospital by day 30, especially in cases of Killip I. Therefore, the 30-day mortality may be underestimated. Third, this study was performed in the early stages of the COVID-19 pandemic in Japan, when there were few COVID-19-positive patients. Therefore, the impact of increasing numbers of COVID-19-positive patients during recent phases of the pandemic needs to be assessed using newer data. Last, we could not assess STEMI or non-STEMI separately, because the ICD-10 system does not always include the diagnosis of ST-segment elevation or non-ST-segment elevation for AMI. The inclusion of non-STEMI patients might affect the frequencies of revascularization and other procedures, and also the outcomes.

Conclusions

Our study evaluated the severity and 30-day mortality of patients with AMI in the early stages of the COVID-19 pandemic in Japan. We found that the COVID-19 pandemic had a substantial impact on the increase of severity and overall 30-day mortality of AMI patients. Despite of the increase of AMI severity, in-hospital procedures and adjusted 30-day mortality in the whole population was unchanged during the pandemic. The impact of increasing numbers of COVID-19-positive patients during recent phases of the pandemic needs to be assessed using newer data.

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Disclosure

T.M. is a member of *Circulation Reports*' Editorial Team. All other authors declare no conflicts of interest regarding this study.

IRB Information

The present study was approved by the Ethics Committee of the Kyushu University Hospital, Fukuoka, Japan. Reference number: 21072-00.

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Supplementary Files

Please find supplementary file(s);
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