ABSTRACT

Background: It has been known that the fear of contagion during the coronavirus disease 2019 (COVID-19) creates time delays with subsequent impact on mortality in patients with acute myocardial infarction (AMI). However, difference of time delay and clinical outcome in patients with ST-segment elevation myocardial infarction (STEMI) or non-STEMI between the COVID-19 pandemic and pre-pandemic era has not been fully investigated yet in Korea. The aim of this study was to investigate the impact of COVID-19 pandemic on time delays and clinical outcome in patients with STEMI or non-STEMI compared to the same period years prior.

Methods: A total of 598 patients with STEMI (n = 195) or non-STEMI (n = 403) who underwent coronary angiography during the COVID-19 pandemic (February 1 to April 30, 2020) and pre-pandemic era (February 1 to April 30, 2017, 2018, and 2019) were analyzed in this study. Main outcomes were the incidence of time delay, cardiac arrest, and in-hospital death.

Results: There was 13.5% reduction in the number of patients hospitalized with AMI during the pandemic compared to pre-pandemic era. In patients with STEMI, door to balloon time tended to be longer during the pandemic compared to pre-pandemic era (55.7 ± 12.6 minutes vs. 60.8 ± 13.0 minutes, \(P = 0.08\)). There were no significant differences in cardiac arrest (15.6% vs. 10.4%, \(P = 0.397\)) and in-hospital mortality (15.6% vs. 10.4%, \(P = 0.397\)) between pre-pandemic and the pandemic era. In patients with non-STEMI, symptom to door time was significantly longer (310.0 ± 346.2 minutes vs. 511.5 ± 635.7 minutes, \(P = 0.038\)) and the incidence of cardiac arrest (0.9% vs. 3.5%, \(P = 0.017\)) and in-hospital mortality (0.3% vs. 2.3%, \(P = 0.045\)) was significantly greater during the pandemic compared to pre-pandemic era. Among medications, angiotensin converting enzyme inhibitors/angiotensin type 2 receptor blockers (ACE-I/ARBs) were underused in STEMI (64.6% vs. 45.8%, \(P = 0.021\)) and non-STEMI (67.8% vs. 57.0%, \(P = 0.061\)) during the pandemic.

Conclusion: During the COVID-19 pandemic, there has been a considerable reduction in hospital admissions for AMI, time delay, and underuse of ACE-I/ARBs for the management of AMI, and this might be closely associated with the excess death in Korea.

Keywords: Coronavirus; SARS-CoV-2; COVID-19; Time Delay; Cardiac Arrest; Acute Myocardial Infarction; Prognosis
INTRODUCTION

As the coronavirus disease 2019 (COVID-19) infection spreads around the world, each country was reporting many excess deaths. Excess deaths were defined as any death that exceeds the expected number of deaths based on the number of deaths over the past several years. During the COVID-19 pandemic, there are several reports regarding excess death that does not directly associate with COVID-19 infection because of lockdown and stay-at-home campaign. It has been known that the fear of contagion during the COVID-19 pandemic creates time delays with subsequent impact on mortality in patients with acute myocardial infarction (AMI). However, difference of time delay and clinical outcome in patients with ST-segment elevation myocardial infarction (STEMI) or non-STEMI between pre-pandemic and pandemic era has not been fully investigated yet in Korea. Therefore, the aim of this study was to investigate the impact of COVID-19 pandemic on time delay and clinical outcome in patients with STEMI or non-STEMI.

METHODS

Study design and patient population

This observational study included 721 consecutive patients who were diagnosed with AMI at admission during pre-pandemic era (February, March, April 2017, 2018, and 2019) and COVID-19 pandemic era (February, March, April 2020). Patients who were registered in the Kyungpook National University Hospital—AMI registry within the study period were enrolled in this study. AMI was diagnosed based on the presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischemia. STEMI and non-STEMI were defined according to fourth universal definition of myocardial infarction. Study flow diagram was shown in Fig. 1. Of these, patients who did not receive coronary angiography (n = 71) or were diagnosed with variant angina (n = 23), stress induced cardiomyopathy (n = 2), or other diagnoses (n = 27) were excluded. Baseline characteristics of the patients who did not receive coronary angiography are shown in Supplementary Table 1. Finally, 598 patients who underwent coronary angiography in the pre-pandemic and pandemic era with same diagnosis during the same period were analyzed in this study. Among them, 195 patients were diagnosed as STEMI at pre-pandemic (n = 147) and pandemic era (n = 48), whereas 403 patients were diagnosed as non-STEMI at pre-pandemic (n = 317) and pandemic era (n = 86), respectively.

Clinical assessment

Baseline demographic and clinical characteristics including age, sex, cardiovascular risk factors such as hypertension, diabetes mellitus, hyperlipidemia, and current smoking, and presenting characteristics were collected at the time of admission. Electrocardiogram was recorded and analyzed by attending cardiologists. Left ventricular ejection fraction was assessed by two-D echocardiography prior to hospital discharge. Venous blood samples were obtained at the time of admission. All patients’ data and procedural details were collected at the time of admission. All patients’ medications were collected during hospitalization.

Definition of time variables

Transfer time in hospital was defined as transfer time from emergency room (ER) to catheterization laboratory. Symptom-to-door time was defined as the time from symptom onset to ER arrival in our hospital. Door-to-balloon time was defined as the time of ER arrival to the first passage of an intracoronary device.

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Clinical outcomes

The primary outcomes were the incidence of time delay, cardiac arrest, and in-hospital mortality. During the follow-up period, clinical outcome data were obtained by reviewing medical records and interviewing patients by telephone.

Statistical analyses

Data were expressed as mean ± standard deviation for continuous variables and as percentages for categorical variables. Comparisons between baseline variables were assessed using Student’s t-test for continuous variables and Pearson’s χ² test for categorical variables. Normality test was performed for all continuous variables. Analyses were conducted to compare eras (pre-pandemic versus pandemic) and were stratified based on presentation (non-STEMI or STEMI). The cumulative incidence rates of cardiac arrest and in-hospital death between pre-pandemic and pandemic eras were estimated by Kaplan-Meier curve using the log-rank test. For all analyses, a 2-sided P-value < 0.05 was considered statistically significant. Statistical analysis was performed using the Statistical Package for the Social Sciences, version 20.0 (IBM Corp., Armonk, NY, USA).

Ethics statement

The protocol was approved by the ethics committee of Kyungpook National University Hospital (KNUH 2021-09-026) as minimal-risk research using data collected for routine clinical practice and waived the requirement for informed consent.
RESULTS

During the pandemic era, there was 13.5% reduction in the number of patients hospitalized with AMI compared with pre-pandemic era, which was mainly driven by 18.8% reduction in non-STEMI (Fig. 2).

Baseline characteristics are presented in Table 1. There were no significant differences in demographic characteristic including age, sex, body mass index between pre-pandemic and pandemic era both STEMI and non-STEMI. In initial presentation, systolic ($P=0.002$) and diastolic blood pressure ($P=0.003$) was significantly lower in the pre-pandemic era compared with those of pandemic era in STEMI, but not in non-STEMI. Among cardiovascular risk factors, dyslipidemia ($P=0.008$) was significantly higher during pandemic era compared with pre-pandemic era in non-STEMI. There were no significant differences of prevalence of other cardiovascular risk factors hypertension, diabetes mellitus, previous ischemic heart disease, chronic kidney disease, and current smoking between pre-pandemic and pandemic era both STEMI and non-STEMI.8 Left ventricular ejection fraction ($P=0.069$) was lower during pandemic era in non-STEMI, but not in STEMI. Among laboratory findings, low-density lipoprotein cholesterol level was significantly lower during pandemic era compared with pre-pandemic era in STEMI. There were no significant differences in the serum levels of hemoglobin, glucose, hemoglobin A1c, lipid profiles, and creatinine between two eras in both STEMI and non-STEMI. Among medications, the use of P2Y12 inhibitors were lower in the pre-pandemic era, whereas the use of angiotensin converting enzyme inhibitors/angiotensin type 2 receptor blockers (ACE-I/ARBs) were lower during pandemic era in both STEMI and non-STEMI.

Angiographic and procedural characteristics are presented in Table 2. In patients with STEMI, there were no significant differences in diseases vessel, multivessel disease, treated vessel, pre thrombolysis in myocardial infarction flow, fluoroscopy time procedure time, frequency of angioplasty, and the number of stents between pre-pandemic and pandemic era. The amount of contrast was significantly higher during pandemic era compared to that of pre-pandemic era ($P=0.002$). In patients with non-STEMI, left main coronary artery diseases was significantly higher during the pandemic era compared with pre-pandemic era ($P=0.037$). Accordingly, percutaneous coronary intervention of left main coronary artery disease was performed more frequently during pandemic era compared with pre-pandemic era ($P=0.032$).

![Fig. 2. Frequency of hospital admission of overall AMI, STEMI, and non-STEMI from February to April in 2017, 2018, 2019, and 2020. AMI = acute myocardial infarction, STEMI = ST-segment elevation myocardial infarction.](https://doi.org/10.3346/jkms.2022.37.e167)
Time variables related to logistics of care of AMI are presented in Table 3. Time distribution of symptom to ER time, ER to catheterization lab arrival time, and door to balloon time between pre-pandemic and pandemic era in both STEMI and non-STEMI are shown in Supplementary Fig. 1. In patients with STEMI, there was no significant difference in symptom to ER time, symptom to catheterization lab arrival time, symptom to balloon time, and ER to catheterization lab time between pre-pandemic and pandemic era. Door to balloon time was shorter in the pre-pandemic era compared with pandemic era \((P = 0.080)\). In patients with non-STEMI, symptom to ER time was significantly longer during the pandemic compared with pre-pandemic era \((P = 0.038)\). Patients who arrived ER within 360 minutes \((72.7\% \text{ vs. } 57.1\%, \ P = 0.040)\) and within 720 minutes \((87.6\% \text{ vs. } 75.5\%, \ P = 0.040)\) were significantly higher in the pre-pandemic era compared with pandemic era in non-STEMI, but not in STEMI (Fig. 3).

In patients with STEMI, there were no significant differences in in-hospital death \((8.8\% \text{ vs. } 4.2\%, \ P = 0.345)\) and cardiac arrest \((15.6\% \text{ vs. } 10.4\%, \ P = 0.397)\) between pre-pandemic
and pandemic era (Fig. 4). In patients with non-STEMI, in-hospital death (2.3% vs. 0.3%, \( P = 0.045 \)) and cardiac arrest (3.5% vs. 0.9%, \( P = 0.017 \)) were significantly higher during pandemic era compared with pre-pandemic era.

**DISCUSSION**

The main findings of this observational study are as follows. First, the number of patients who were admitted with a suspicion of AMI were decreased during the pandemic. Second, there were considerable time delays including system delay in STEMI and patient delay in non-STEMI during the pandemic. Third, the incidence of in-hospital death and cardiac arrest was significantly higher during the pandemic in non-STEMI, but not in STEMI.

There are three intriguing findings in our study. First, there has been a reduction in hospital admissions for AMI,\(^9\) and this might be closely related to the excess death in Korea during

### Table 2. Angiographic and procedural characteristics in study subjects

| Variables               | STEMI          |          | P value | Non-STEMI          |          | P value |
|-------------------------|----------------|----------|---------|-------------------|----------|---------|
|                         | Pre-pandemic era (n = 147) | Pandemic era (n = 48) |         | Pre-pandemic era (n = 317) | Pandemic era (n = 86) |         |
| Disease vessels         |                |          |         |                   |          |         |
| Left main trunk         | 4 (2.7)        | 2 (4.2)  | 0.615   | 36 (11.5)         | 17 (20.2) | 0.037   |
| Left anterior descending artery | 109 (74.1) | 33 (68.8) | 0.465   | 223 (71.2)        | 63 (75.0) | 0.496   |
| Left circumflex artery  | 73 (49.7)      | 21 (43.8)| 0.477   | 169 (54.0)        | 48 (57.1) | 0.607   |
| Right coronary artery   | 89 (60.5)      | 34 (70.8)| 0.200   | 181 (57.8)        | 39 (46.4) | 0.062   |
| Multivessel disease     | 124 (84.4)     | 37 (77.1)| 0.249   | 254 (81.2)        | 71 (84.5) | 0.476   |
| Treated vessels         |                |          |         |                   |          |         |
| Left main trunk         | 2 (1.4)        | 2 (4.2)  | 0.234   | 27 (8.6)          | 14 (16.7) | 0.032   |
| Left anterior descending artery | 79 (53.7) | 25 (52.1) | 0.842   | 161 (51.4)        | 42 (50.0) | 0.815   |
| Left circumflex artery  | 36 (24.7)      | 15 (31.3)| 0.368   | 94 (30.0)         | 28 (33.3) | 0.560   |
| Right coronary artery   | 68 (46.3)      | 23 (47.9)| 0.842   | 119 (38.0)        | 24 (28.6) | 0.109   |
| Pre TIMI flow 0         | 17 (11.6)      | 8 (16.7) | 0.359   | 98 (30.3)         | 32 (37.2) | 0.221   |
| Fluoroscopy time, sec   | 202.0 ± 244.8  | 444.4 ± 1,302.9 | 0.288 | 1,006.9 ± 959.7 | 1,053.9 ± 703.1 | 0.675   |
| Procedure time, min     | 57.6 ± 30.0    | 53.1 ± 20.0| 0.332 | 68.5 ± 39.2 | 69.4 ± 34.3 | 0.838   |
| Contrast amount, mL     | 99.9 ± 37.4    | 118.1 ± 23.3| 0.002 | 107.6 ± 54.1 | 119.1 ± 48.0 | 0.074   |
| Angioplasty             |                |          |         |                   |          |         |
| None                    | 7 (4.8)        | 2 (4.2)  | 0.796   | 37 (11.8)         | 12 (14.3) | 0.742   |
| Balloon angioplasty     | 6 (4.1)        | 1 (2.1)  | 0.796   | 22 (7.0)          | 7 (8.3)  | 0.796   |
| Stent implantation      | 134 (91.9)     | 45 (91.8)| 0.796   | 254 (81.2)        | 65 (77.4) | 0.796   |
| No. of stent            | 1.2 ± 0.6      | 1.3 ± 0.6| 0.796   | 1.1 ± 0.8         | 1.1 ± 0.8 | 0.796   |

Data are expressed as mean ± standard deviation or number (percent).

STEMI = ST-segment elevation myocardial infarction, TIMI = thrombolysis in myocardial infarction.

### Table 3. Time variables in study subjects

| Variables               | STEMI          |          | P value | Non-STEMI          |          | P value |
|-------------------------|----------------|----------|---------|-------------------|----------|---------|
|                         | Pre-pandemic era (n = 147) | Pandemic era (n = 48) |         | Pre-pandemic era (n = 317) | Pandemic era (n = 86) |         |
| Symptom to ER time, min | 202.0 ± 244.8  | 444.4 ± 1,302.9 | 0.364   | 310.0 ± 346.2 | 511.5 ± 635.7 | 0.038   |
| Symptom to cath lab time, min | 241.3 ± 244.8 | 487.0 ± 1,304.2 | 0.119   | 2,773.3 ± 2,812.1 | 3,042.0 ± 2,855.6 | 0.561   |
| Symptom to balloon time, min | 258.2 ± 244.5 | 505.3 ± 1,304.6 | 0.356   | 2,614.8 ± 2,694.3 | 3,139.6 ± 3,047.1 | 0.194   |
| ER to cath lab time, min | 38.8 ± 12.5   | 42.6 ± 10.2| 0.175   | 2,666.9 ± 2,999.5 | 2,635.8 ± 2,990.1 | 0.941   |
| Door to balloon time, min | 55.7 ± 12.6   | 60.8 ± 13.2| 0.080   | 2,619.0 ± 3,014.7 | 2,665.2 ± 3,114.4 | 0.921   |
| Length of stay, days    | 6.82 ± 4.39   | 5.20 ± 1.44| 0.074   | 6.48 ± 5.82  | 6.07 ± 5.41  | 0.555   |

Data are expressed as mean ± standard deviation or number (percent).

STEMI = ST-segment elevation myocardial infarction, ER = emergency room, cath = catheterization, lab = laboratory.

*Non-parametric test.*
Little is known about the associations between patient delay and clinical outcomes during the COVID-19 pandemic in Korea. The COVID-19 pandemic is spreading rapidly around the world, causing hundreds of thousands of excess deaths in

### Fig. 3. Comparison of patient delay in (A) ST-segment elevation myocardial infarction and (B) non-ST-segment elevation myocardial infarction between pre-pandemic and pandemic era.

**ER** = emergency room.

### Fig. 4. The incidence of in-hospital death and cardiac arrest in (A) STEMI and (B) non-STEMI between pre-pandemic and pandemic era.  

**STEMI** = ST-segment elevation myocardial infarction.

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**Table:**

| Time (min) | Pre-pandemic | Pandemic | P-value |
|------------|--------------|----------|---------|
| < 180      | 59.2%        | 63.8%    | 0.579   |
| < 360      | 80.8%        | 87.2%    | 0.325   |
| < 720      | 92.5%        | 93.6%    | 0.802   |

| Time (min) | Pre-pandemic | Pandemic | P-value |
|------------|--------------|----------|---------|
| < 180      | 49.7%        | 36.7%    | 0.111   |
| < 360      | 72.7%        | 57.1%    | 0.040   |
| < 720      | 87.6%        | 75.5%    | 0.040   |

**Fig. 3.** Comparison of patient delay in (A) ST-segment elevation myocardial infarction and (B) non-ST-segment elevation myocardial infarction between pre-pandemic and pandemic era.
many countries. However, some of excess death might not be directly related to COVID-19 infection. In the United States, mortality increased by 20% during the COVID-19 pandemic from March to July 2020. However, COVID-19 was a documented cause of only 67% of these excess deaths. In Daegu city, Korea, crude death rate increased during the COVID-19 pandemic from February to April 2020 (Supplementary Fig. 2). However, COVID-19 was a documented cause of about 40% of these excess deaths. Interestingly, Western countries reported a decrease in hospitalization for acute cardiovascular disease (CVD) such as AMI and stroke during the COVID-19 pandemic. It might be explained by true population-level reduction of acute CVD because of shifts in dietary pattern (i.e., decreased consumption of high-sodium, fast food intake), reduced exposure to ambient air pollution, telemedicine, decline in ambulatory CVD clinic visits, outpatient testing, deferral of elective procedures, stay-at-home messaging from government and media, and seasonal variation. However, one of the possible explanations is that many patients were reluctant to visit the hospital due to the fear of contacting COVID-19. Recently, Google Trends meta-data showed that search volume for chest pain is strongly correlated with COVID-19 case numbers in the United States. This indicates that the fear of contacting COVID-19 may be leading patients to self-triage using internet searches instead of hospital admission. In our study, there has been a considerable decrease in hospital admission for AMI. In addition, AMI patients visited the hospital later than usual. Although our study excluded suspected AMI patients with cardiac enzyme elevation, cardiac arrest, cardiogenic shock, or ventricular tachycardia/fibrillation who did not receive coronary angiography, the number of these patients were numerically lower in the pandemic era (Supplementary Fig. 3). Therefore, it seems to be evident that acute care of CVD may be delayed, deferred, or abbreviated during the COVID-19 pandemic. Considering the high mortality of CVD, this late presentation may increase ‘collateral COVID-19 mortality’ and contribute to these excess deaths during the COVID-19 pandemic. Therefore, patients suffering from non-COVID-19 related acute CVD continue to receive timely, evidence based and high-quality care.

Second, logistics of AMI care were delayed during the COVID-19 pandemic. However, the pattern of time delay and the effect on in-hospital death and cardiac arrest were different between STEMI and non-STEMI. In the present study, patients with STEMI have a trend for longer door to balloon time during the pandemic. This system delay might be because it took time to put on personal protective equipment and to transfer patients due to uncertainty about COVID-19 infection. Interestingly, the incidence of in-hospital death and cardiac arrest was lower during the pandemic. Patients with STEMI may have died while staying at home without coming to the hospital despite symptoms. In addition, symptom to ER time was significantly longer and the incidence of in-hospital death and cardiac arrest was significantly higher in non-STEMI during the pandemic. Patients delay in non-STEMI due to the fear of possibility contacting patients with COVID-19 at ER is thought to have led to greater in-hospital death and cardiac arrest during the pandemic. Therefore, it seems that the system delay of STEMI and the patient delay of non-STEMI differently contributed to worsening the prognosis of patients with AMI during the pandemic.

Third, ACE-I/ARBs were significantly underused for the management of AMI during the COVID-19 pandemic. In Korea, this information is interesting and valuable because there have been few real-world data regarding usage of ACE-I/ARBs for AMI in the early period of COVID-19 pandemic. Previous studies showed that COVID-19 patients with diabetes mellitus and hypertension appear to have worse prognosis due to overexpression of ACE2 receptor in airway alveolar epithelial cells because SARS-CoV-2 uses the ACE2 receptor to enter the
lungs in a mechanism.\textsuperscript{35-40} Therefore, there has been some concerns regarding the negative effect of ACE-I/ARBs by upregulation of ACE2 receptors that patients receiving ACE-I/ARBs may be more susceptible to COVID-19 infection and have poorer outcomes. Major cardiology scientific associations have rejected these correlation hypotheses for now.\textsuperscript{41-43} However, in the present study, it has been documented that ACE-Is/ARBs were significantly underused for the management of AMI in the early period of the pandemic although there is no significant evidence to support an association between COVID-19 and ACE-I/ARBs. The suboptimal use of ACE-I/ARBs during the pandemic may affect the clinical outcome in this study.

This study has certain limitations that should be noted. First, because this study was a single center and observational study, we could not completely exclude the possibility of residual confounding factors that were not available in our registry. Second, we collected symptom onset time based on the patient's memory. Therefore, we could not completely exclude the possibility of recall bias. Third, the reason for late presentation was not collected in our registry. Therefore, our results should only be regarded as hypothesis generating. However, the limitations of the study should not undermine the strength of this study, namely that it includes patients encountered in day-to-day clinical practice before and during the pandemic. Despite these limitations, we believe that our data could provide the clinical insight necessary to understand contemporary management and prognosis for AMI during the pandemic.

In conclusion, during the COVID-19 pandemic, there has been a considerable reduction in hospital admissions for AMI, time delay, and underuse of ACE-I/ARBs for the management of AMI, and this might be closely associated with the excess death in Korea.

**SUPPLEMENTARY MATERIALS**

**Supplementary Table 1**
Baseline characteristics of patients who did not receive coronary angiography

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**Supplementary Fig. 1**
Time distribution of study subjects. (A) Symptom to ER time, (B) ER to cath lab time, and (C) door to balloon time in STEMI. (D) Symptom to ER time, (E) ER to cath lab time, and (F) door to balloon time in non-STEMI.

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**Supplementary Fig. 2**
The crude death rates (A) and the number of death and excess death (B) in Daegu city, Korea from 2017 to 2020. The 2020 Daegu non-COVID-19 indicates the number of people who died from non-COVID-19 related illness. The 2020 Daegu COVID-19 indicates the number of people who died from COVID-19 infection.

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Supplementary Fig. 3
Frequency of hospital admission of overall suspected acute MI patients with cardiac enzyme elevation, cardiac arrest, cardiogenic shock, or ventricular tachycardia/fibrillation who were not perform coronary angiography from February to April in 2017, 2018, 2019, and 2020.

Click here to view

REFERENCES

1. Our World in Data. Excess mortality during the coronavirus pandemic (COVID-19). https://ourworldindata.org/excess-mortality-covid. Updated 2021. Accessed October 4, 2021.
2. Korean Statistical Information Service (KOSIS). COVID-19-time excess death analysis. https://kosis.kr/covid/statistics_exceeddeath.do. Updated 2021. Accessed October 4, 2021.
3. Helal A, Shahin L, Abdelsalam M, Ibrahim M. Global effect of COVID-19 pandemic on the rate of acute coronary syndrome admissions: a comprehensive review of published literature. Open Heart 2021;8(1):e001645.
4. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). J Am Coll Cardiol 2018;72(18):2231-64.
5. Nathan AS, Raman S, Yang N, Painter I, Khatana SA, Dayoub EI, et al. Association between 90-minute door-to-balloon time, selective exclusion of myocardial infarction cases, and access site choice: insights from the cardiac care outcomes assessment program (COAP) in Washington State. Circ Cardiovasc Inter 2020;13(9):e009179.
6. Chandrasekhar J, Marley P, Allada C, McGill D, O’Connor S, Rahman M, et al. Symptom-to-balloon time is a strong predictor of adverse events following primary percutaneous coronary intervention: results from the Australian Capital Territory PCI Registry. Heart Lung Circ 2017;26(1):41-8.
7. Park J, Choi KH, Lee JM, Kim HK, Hwang D, Rhee TM, et al. Prognostic implications of door-to-balloon time and onset-to-door time on mortality in patients with ST-segment-elevation myocardial infarction treated with primary percutaneous coronary intervention. J Am Heart Assoc 2019;8(9):e012188.
8. Visseren FL, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021;42(34):3227-337.
9. Aldujeli A, Hamadeh A, Briedis K, Tecson KM, Rutland J, Krivickas Z, et al. Delays in presentation in patients with acute myocardial infarction during the COVID-19 pandemic. Cardiol Rev 2020;11(1):386-91.
10. Woolf SH, Chapman DA, Sabo RT, Weinberger DM, Hill L, Taylor DD. Excess deaths from COVID-19 and other causes, March-July 2020. JAMA 2020;324(15):1562-4.
11. Morelli N, Rota E, Terracciano C, Immovilli P, Spallazzi M, Colombi D, et al. The baffling case of ischemic stroke disappearance from the casualty department in the COVID-19 era. Eur Neurol 2020;83(2):213-5.
12. Aguiar de Sousa D, Sandset EC, Elkind MS. The curious case of the missing strokes during the COVID-19 pandemic. Stroke 2020;51(7):1921-3.
13. Ruiz-Roso MB, Knott-Torcal C, Matilla-Escalante DC, Garcimartín A, Sampedro-Nuñez MA, Dávalos A, et al. COVID-19 lockdown and changes of the dietary pattern and physical activity habits in a cohort of patients with type 2 diabetes mellitus. Nutrients 2020;12(8):2327.
14. Navarro-Cruz AR, Kammar-Garcia A, Mancilla-Galindo J, Quezada-Figuerola G, Talpa-Prisco M, Vera-López O, et al. Association of differences in dietary behaviours and lifestyle with self-reported weight gain during the COVID-19 lockdown in a university community from Chile: a cross-sectional study. Nutrients 2021;13(9):3213.
15. Sorić T, Brodić I, Mertens E, Sagastume D, Dolanc I, Jonjić A, et al. Evaluation of the food choice motives before and during the COVID-19 pandemic: a cross-sectional study of 1232 adults from Croatia. *Nutrients* 2021;13(9):3165. [PUBMED] [CROSSREF]

16. Venter ZS, Aunan K, Chowdhury S, Leelieveld J. COVID-19 lockdowns cause global air pollution declines. *Proc Natl Acad Sci U S A* 2020;117(32):18984-90. [PUBMED] [CROSSREF]

17. Tanzer-Gruener R, Li J, Eilenberg SR, Robinson AL, Presto AA. Impacts of modifiable factors on ambient air pollution: a case study of COVID-19 shutdowns. *Environ Sci Technol Lett* 2020;7(8):554-9. [CROSSREF]

18. Azuma K, Kagi N, Kim H, Hayashi M. Impact of climate and ambient air pollution on the epidemic growth during COVID-19 outbreak in Japan. *Environ Res* 2020;190:110042. [PUBMED] [CROSSREF]

19. Son JY, Fong KC, Heo S, Kim H, Lim CC, Bell ML. Reductions in mortality resulting from reduced air pollution levels due to COVID-19 mitigation measures. *Sci Total Environ* 2020;744:141012. [PUBMED] [CROSSREF]

20. Hollander JE, Carr BG. Virtually perfect? Telemedicine for COVID-19. *N Engl J Med* 2020;382(18):1679-81. [PUBMED] [CROSSREF]

21. Portnoy J, Waller M, Elliott T. Telemedicine in the era of COVID-19. *J Allergy Clin Immunol Pract* 2020;8(5):1489-91. [PUBMED] [CROSSREF]

22. Okuhara T, Okada H, Kiuchi T. Examining persuasive message type to encourage staying at home during the COVID-19 pandemic and social lockdown: a randomized controlled study in Japan. *Patient Educ Couns* 2020;103(12):2588-93. [PUBMED] [CROSSREF]

23. Knell G, Robertson MC, Dooley EE, Burford K, Mendez KS. Health behavior changes during COVID-19 pandemic and subsequent “Stay-at-Home” orders. *Int J Environ Res Public Health* 2020;17(17):6268. [PUBMED] [CROSSREF]

24. Limbers CA, McCollum C, Greenwood E. Physical activity moderates the association between parenting stress and quality of life in working mothers during the COVID-19 pandemic. *Ment Health Phys Act* 2020;19:100358. [PUBMED] [CROSSREF]

25. Gluckman TJ, Wilson MA, Chiu ST, Penny BW, Chepuri VB, Waggoner JW, et al. Case rates, treatment approaches, and outcomes in acute myocardial infarction during the coronavirus disease 2019 pandemic. *JAMA Cardiol* 2020;5(12):1419-24. [PUBMED] [CROSSREF]

26. Marotta M, Gorini F, Parlanti A, Chatzianagnostou K, Mazzone A, Berti S, et al. Fear of COVID-19 in patients with acute myocardial infarction. *Int J Environ Res Public Health* 2021;18(18):9847. [PUBMED] [CROSSREF]

27. Ciofani JL, Han D, Allahwala UK, Asrress KN, Bhindi R. Internet search volume for chest pain during the COVID-19 pandemic. *Am Heart J* 2021;231:157-9. [PUBMED] [CROSSREF]

28. Baldi E, Sechi GM, Mare C, Canevari F, Brancaglione A, Primi R, et al. Out-of-hospital cardiac arrest during the COVID-19 outbreak in Italy. *N Engl J Med* 2020;383(5):496-9. [PUBMED] [CROSSREF]

29. Bhatt AS, Moscone A, McElrath EE, Varshney AS, Claggett BL, Bhatt DL, et al. Fewer hospitalizations for acute cardiovascular conditions during the COVID-19 pandemic. *J Am Coll Cardiol* 2020;76(3):280-8. [PUBMED] [CROSSREF]

30. Mahmud E, Dauerman HL, Welt FG, Messenger JC, Rao SV, Grines C, et al. Management of acute myocardial infarction during the COVID-19 pandemic: a position statement from the Society for Cardiovascular Angiography and Interventions (SCAI), the American College of Cardiology (ACC), and the American College of Emergency Physicians (ACEP). *J Am Coll Cardiol* 2020;76(11):1375-84. [PUBMED] [CROSSREF]

31. Primessnig U, Pieske BM, Sherif M. Increased mortality and worse cardiac outcome of acute myocardial infarction during the early COVID-19 pandemic. *ESC Heart Fail* 2021;8(1):333-43. [PUBMED] [CROSSREF]

32. Park DW, Yang Y. Delay, death, and heterogeneity of primary PCI during the COVID-19 pandemic: an international perspective. *J Am Coll Cardiol* 2020;76(20):2331-3. [PUBMED] [CROSSREF]
33. Kitahara S, Fujino M, Honda S, Asaumi Y, Kataoka Y, Otsuka F, et al. COVID-19 pandemic is associated with mechanical complications in patients with ST-elevation myocardial infarction. *Open Heart* 2021;8(1):e001497.

34. Metzler B, Siostronzek P, Binder RK, Bauer A, Reinstadler SJ. Decline of acute coronary syndrome admissions in Austria since the outbreak of COVID-19: the pandemic response causes cardiac collateral damage. *Eur Heart J* 2020;41(19):1852-3.

35. Sparks MA, Crowley SD, Gurley SB, Mirotsou M, Coffman TM. Classical Renin-Angiotensin system in kidney physiology. *Compr Physiol* 2014;4(3):1201-28.

36. Li G, He X, Zhang L, Ran Q, Wang J, Xiong A, et al. Assessing ACE2 expression patterns in lung tissues in the pathogenesis of COVID-19. *J Autoimmun* 2020;112:102463.

37. Rico-Mesa JS, White A, Anderson AS. Outcomes in patients with COVID-19 infection taking ACEI/ARB. *Curr Cardiol Rep* 2020;22(5):31.

38. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020;8(5):475-81.

39. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382(18):1708-20.

40. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy* 2020;75(7):1730-41.

41. Hippisley-Cox J, Young D, Coupland C, Channon KM, Tan PS, Harrison DA, et al. Risk of severe COVID-19 disease with ACE inhibitors and angiotensin receptor blockers: cohort study including 8.3 million people. *Heart* 2020;106(19):1503-11.

42. Flacco ME, Acuti Martellucci C, Bravi F, Parruti G, Cappadona R, Mascitelli A, et al. Treatment with ACE inhibitors or ARBs and risk of severe/lethal COVID-19: a meta-analysis. *Heart* 2020;106(19):1519-24.

43. Rossi GP, Sanga V, Barton M. Potential harmful effects of discontinuing ACE-inhibitors and ARBs in COVID-19 patients. *Elife* 2020;9:e57278.