Clinical Profile and 30-Day Mortality of Invasively Managed Patients with Suspected Acute Coronary Syndrome During the COVID-19 Outbreak

Pablo Salinas, MD, Alejandro Travieso, MD, Carlos Vergara-Uzcategui, MD, Gabriela Tirado-Conte, MD, Fernando Macaya, MD, Hernán Mejía-Rentería, MD, Luis Nombela-Franco, MD, Iván J Núñez-Gil, MD, Nieves Gonzalo, MD, Pilar Jiménez-Quevedo, MD, María-José Pérez-Vizcayno, MD, Javier Escaned, MD and Antonio Fernández-Ortiz, MD

Summary

The COVID-19 pandemic severely disrupted cardiovascular care during the spring of 2020 in Europe. Our study analyzed the clinical profile, COVID-19 impact, and 30-day prognosis of invasively managed patients with acute coronary syndrome (ACS) compared to a historical cohort.

All invasively managed ACS patients from March 1st to April 30th, 2020 were compared to a cohort from the same timeframe of 2019 (n = 316). COVID-19 confirmed cases were defined by a positive SARS-CoV-2 polymerase chain reaction (PCR) test (CoV+). The primary outcome was all-cause 30-day mortality and multivariable predictors of this outcome.

A 40.4% reduction in ACS patients was noted (198 cases in 2019 to 118 in 2020), and 11% of 2020 ACS patients were CoV+. Baseline characteristics were similar between groups. There were significantly more in-hospital patients with ACS (15.3% versus 6.1%, P = 0.007), and fewer patients were found to have a culprit lesion (58.5% versus 74.2%, P = 0.004) in 2020 compared to 2019. Thirty-day mortality in 2020 (7%) was not different from that in 2019 (4.2%), P = 0.294, but it was significantly higher in CoV+ patients (23.1%) compared to that in negative SARS-CoV-2 PCR test (CoV−) patients (5%), P = 0.047, in the 2020 group. In the multivariate analysis, CoV+ was an independent mortality predictor (OR = 9.8, 95% CI = 1.48-64.78), along with the left ventricular ejection fraction (LVEF) (OR = 0.91, 95% CI = 0.86-0.97), P = 0.0006.

This study found increased 30-day mortality of invasively managed CoV+ ACS patients compared to that of CoV− patients during the 2020 COVID-19 spring outbreak. In the multivariable analysis, a SARS-CoV-2 positive test was independently associated with 30-day mortality. Further investigations of the underlying physiopathological relations between COVID-19 and ACS are warranted.

Key words: Myocardial infarction, SARS-CoV-2 PCR, Percutaneous coronary intervention
fast-tracking PCR testing of all patients before catheterization, and implementation of full personal protective equipment if the patient had an undetermined Covid status or if emergent catheterization is necessary.

Although some preliminary data suggest increased ACS-related mortality during the COVID-19 pandemic, patient-level data are currently lacking. Our study aimed to analyze patient characteristics, in-hospital management and 30-day prognosis of invasively managed ACS patients during the COVID-19 pandemic compared to a historical cohort from the same timeframe in 2019.

**Methods**

Our Interventional Cardiology database gathers prospective data on all patients undergoing cardiac catheterization until hospital discharge. It comprises a network of three referral hospitals and one tertiary hospital (two of them are primary percutaneous coronary intervention [PCI] hubs) and six cathlabs, sharing the same team of interventional cardiologists and providing healthcare to a population of over 1 million people in Madrid, Spain. We included all ACS and cardiac arrest patients undergoing cardiac catheterization from March 1st, 2020 (24 hours after the first COVID-19 admission in the area) to April 30th, 2020 as the study group. As a control group, we explored the same period (March-April) in 2019 and January-February in 2020 (Figure 1). To control for seasonal changes and potential under-reporting of COVID-19 cases during January or February 2020 due to reduced awareness, we chose March 1st to April 30th, 2019 as the control group.

Baseline characteristics, clinical presentation, procedural findings, and in-hospital outcomes were prospectively collected during our usual workflow. The 30-day follow-up information on vital status and major adverse cardiovascular events (death, myocardial infarction or new revascularization) were recovered from electronic records and telephone calls (physical clinical visits were cancelled during the COVID-19 pandemic). Nine (4.5%) patients from 2019 and 4 (3.4%) from 2020 were considered lost to follow-up (information missing or follow-up < 30 days). In the 2020 cohort, COVID-19 confirmed cases were defined as those with a positive SARS-CoV-2 PCR test (CoV+) during admission and/or 7 days after admission. Day zero for the 30-day follow-up began on index catheterization because there was high dispersion in 2020 hospital stay (Table 1). To account for the differences in troponin testing assays from different hospitals, we reported multiples (times) of the upper reference limit (MURL = absolute peak troponin value divided by the upper reference limit). Stent thrombosis was defined following the Academic Research Consortium criteria. Recurrent myocardial infarction (MI) corresponds to spontaneous MI. Further definitions are detailed in the Supplemental Text of this study. The primary outcome was all-cause, 30-day mortality as a binary variable. The secondary combined endpoint of a major adverse cardiovascular event was defined as all-cause mortality, spontaneous MI, or new revascularization.

Categorical variables are presented as counts and percentages. Continuous variables are presented as medians.
and interquartile ranges. To compare categorical variables, we used the chi-squared test or Fisher’s F, as appropriate, and to compare continuous variables, we used the Mann-Whitney test. To compare the number of cases in different periods (Figure 1), we used the chi-squared goodness of fit test. To obtain predictors of 30-day mortality, we used binary logistic regression, and a multivariable model was built for testing those univariable predictors with \( P < 0.3 \) with regression of all possible subsets, and a model with lower Akaiake Information Criteria was selected (Supplemental Tables I and II). A two-tailed \( P \) value of 0.05 was considered to be significant. SPSS 21 (IBM) and STATATA 14 (StataCorp) were used to perform these analyses.

**Results**

Regular hospital care changed abruptly on March 10th, 2020, when hospitals in Madrid were instructed to cancel all elective procedures and minimize admission time. The Spanish government issued a lockdown decree on March 15th, which was followed by a dramatic drop in invasively managed ACS incident cases after the second week of March (Figure 2). We previously reported a significant decrease in ACS cases during the study period compared to March-April 2019 and January-February 2020 (Figure 1). In our cardiology network of four hospitals, an invasive or early invasive strategy is pursued in nearly all ACS cases, except low-risk ACS, and this protocol remained unchanged during the COVID-19 pandemic. Separate pathways for CoV+ and CoV− patients were created from March 10th. Patients with undetermined CoV status were managed as CoV+ until PCR testing was performed.

Local protocols during March and April 2020 recommended PCR testing only to symptomatic patients and those with epidemiological close-contact criteria. Nevertheless, the frequency of PCR testing on ACS cases increased in time, from 25.9% of ACS cases in week 0%–89.5% in week 8 (linear trend, \( P < 0.001 \)). Overall, 61/118 of 2020 patients had no PCR testing during admission. During the following 30 days, only one out of those 61 untested patients had a COVID-19 confirmed infection (18 days after discharge). From the remaining 57 patients, 13 had a positive CoV+ PCR testing (22.8% of tested patients, 11% of the overall 2020 cohort). Six out of the 13 CoV+ patients had ACS during primary COVID-19 admission, whereas the other 7 were admitted primarily with ACS and showed positive PCR testing outcomes during admission.

Regarding cathlab personnel, none of the nine senior interventional cardiologists were infected during the study period, and 1/8 of the fellows were infected during a short exposure time (only the first 2 weeks since the fellow pro-
gram was halted during lockdown). Regarding cardiology residents and nurses, we can only provide limited data because most of them were re-commissioned to COVID-19 care in ICU units. In the tertiary center after lockdown (6 weeks), a stable team of eight nurses remained in cathlab activity only, and three of them became infected from SARS-CoV-2 with a mild clinical course.

A total of 316 patients (198 from 2019 and 118 from 2020) were included. Baseline characteristics are presented in Table I, and they were similar between the 2019 and 2020 cohorts and between CoV+ and CoV− patients. The clinical presentation was also similar; roughly 50% of them were non-ST elevation myocardial infarction MI (NSTEMI); 30%, ST elevation myocardial infarction MI (STEMI); and 20%, unstable angina. However, there were significantly more in-hospital patients with ACS in the 2020 cohort than in 2019 (15.3% versus 6.1%, \( P = 0.007 \)). Notably, during March-April 2020, almost half (46.2%) of the patients with CoV+ had the ACS as a secondary event during hospital admission (all of these were primary COVID-19 admissions), which was significantly higher than the 11.4% of those with in-hospital ACS and CoV−\( P = 0.001 \). The CoV+ group had numerically higher (3x) D Dimer levels and numerically lower (9x) troponin levels than CoV− patients, although it did not reach statistical significance.

Procedural findings and discharge data are presented in Table II. There were no differences in the extent of coronary artery disease. However, a smaller number of patients were found to have a culprit lesion in coronary angiography in the 2020 cohort, particularly in those who were CoV+. The hospital stay was shorter in 2020 (median 4 days) compared to that in 2019 (median 6 days), \( P = 0.004 \), but longer in CoV+ (median 14 days) compared to CoV− (median 4 days) patients, because of the primary COVID-19 admissions. The categorized discharge diagnoses were significantly different with less confirmed ACS diagnoses and more non-cardiac diagnoses in the 2020 cohort compared to those in 2019 (Table II). The CoV+ and CoV− patients had a similar pattern with non-statistically

### Table II. Procedural Findings and Discharge Data

| Clinical presentation | Total (n = 316) | 2019 (n = 198) | 2020 (n = 118) | \( P \) | 2020 CoV− (n = 105) | 2020 CoV+ (n = 13) | \( P \) |
|-----------------------|----------------|---------------|---------------|------|---------------------|------------------|------|
| ACS type              |                |               |               |      |                     |                  |      |
| Unstable Angina       | 75 (23.7%)     | 40 (20.2%)    | 35 (29.7%)    | 0.124| 31 (29.5%)          | 4 (30.8%)        |      |
| NSTEMI                | 147 (46.5%)    | 99 (50%)      | 48 (40.7%)    |      | 42 (40%)            | 6 (46.2%)        |      |
| STEMI                 | 94 (29.8%)     | 59 (29.8%)    | 35 (29.7%)    |      | 32 (30.5%)          | 3 (23.1%)        |      |
| Peak Troponin (MURL)  | 44.8 (4.3–432) | 52.4 (5.4–359.5) | 26.4 (3.6–530.5) | 0.519| 27.6 (4.8–590)     | 3.6 (0.6–117.9) | 0.105|
| Peak D-Dimer          | 568 (297.5–2009)| NA            | 568 (297.5–2009)|      | 483.5 (344.3–1201.8)| 1410 (223.3–12907.3) | 0.664|
| Primary/facilitated PCI| 70 (22.2%)    | 45 (22.7%)    | 25 (21.2%)    |      | 75 (23.7%)          | 23 (19.9%)       | 0.587|
| In-hospital ACS       | 30 (9.5%)      | 12 (6.1%)     | 18 (15.3%)    |      | 12 (11.4%)          | 6 (46.2%)        | 0.001|
| Cardiogenic shock     | 16 (5.1%)      | 11 (5.6%)     | 5 (4.2%)      |      | 4 (3.8%)            | 1 (7.7%)         | 0.518|
| Procedural findings   |               |               |               |      |                     |                  |      |
| N° of vessels > 70% DS| 66 (20.9%)     | 42 (21.2%)    | 24 (20.3%)    | 0.853| 21 (20%)            | 3 (23.1%)        | 0.795|
| No CAD                | 1 (0–2)        | 1 (0–1–25)    | 1 (0–2)       | 0.305| 1 (0–2)             | 1 (0–2.5)        | 0.844|
| Culprit lesion        | 216 (68.4%)    | 147 (74.2%)   | 69 (58.5%)    | 0.004| 65 (61.9%)          | 4 (30.8%)        | 0.032|
| Revascularization     | 189 (59.8%)    | 117 (59.1%)   | 72 (61%)      | 0.176| 67 (63.8%)          | 5 (35.8%)        | 0.077|
| No. of treated vessels| 1 (0–1)        | 1 (0–1)       | 1 (0–1)       | 0.949| 1 (0–1)             | 0 (0–1)          | 0.107|
| Total stent number    | 1 (0–1)        | 1 (0–1)       | 0 (0–1)       | 0.765| 1 (0–1)             | 0 (0–1)          | 0.256|
| Complete revascularization | 104 (32.9%) | 54 (27.3%) | 50 (42.4%) | 0.392 | 48 (47.5%) | 2 (16.7%) | 0.042 |
| Discharge             |               |               |               |      |                     |                  |      |
| Discharge LVEF        | 52 (45–60)     | 52 (45.8–58)  | 57 (44.3–60)  | 0.116| 56 (45–60)          | 60 (37–61)       | 0.177|
| Hospital Stay         | 5 (3–10)       | 6 (4–10)      | 4 (2–9.3)     | 0.004| 4 (2–7)             | 14 (5.5–20)      | 0.005|
| Discharge diagnosis   |               |               |               | 0.018|                     |                  | 0.637|
| Confirmed ACS         | 256 (81%)      | 167 (84.3%)   | 89 (75.4%)    | 0.018| 80 (76.2%)          | 9 (69.2%)        |      |
| TS, MC, or MINOCA     | 46 (14.6%)     | 27 (13.6%)    | 19 (16.1%)    | 0.853| 17 (16.2%)          | 2 (15.4%)        |      |
| Others§               | 14 (4.4%)      | 4 (2%)        | 10 (8.5%)     | 0.853| 8 (7.6%)            | 2 (15.4%)        |      |
| Discharge DAPT        |               |               |               | 0.507|                     |                  | 0.177|
| None or SAPT          | 79 (26.2%)     | 46 (24%)      | 29 (29%)      | 0.788| 33 (30%)            | 4 (40%)          |      |
| DAPT                  | 175 (57.9%)    | 114 (59.4%)   | 61 (55.5%)    | 0.788| 58 (58%)            | 3 (30%)          |      |
| Anticoagulation + SAPT or DAPT | 48 (15.9%) | 32 (16.7%) | 16 (14.5%) | 0.788 | 13 (13%) | 3 (30%) |      |

ACS indicates acute coronary syndrome; MI, myocardial infarction; MURL, multiples of upper reference limit; PCI, percutaneous coronary intervention; CAD, coronary artery disease; DS, diameter stenosis; LVEF, left ventricular ejection fraction; TS, Tako-Tsubo syndrome; MC, myocarditis; MINOCA, MI with normal coronary arteries with no specific diagnosis such as MC or TS; DAPT, dual antiplatelet therapy; and SAPT, single antiplatelet therapy. See detailed description in Supplemental Table III.
and 5.9% of CoV− patients, COVID-19 during admission. Major adverse cardiac events at 30 days were found in 4.8% of 2019 patients in 2019 and 5.1% in 2020 (P = 0.294), but with a significant difference.

Within the 2020 cohort, in-hospital mortality was higher in CoV+ patients (23.1%) compared to that in CoV− patients (2.9%), P = 0.017. At 30 days, mortality remained significantly higher in CoV+ patients, 23.1% versus 5.0%, P = 0.047. Figure 3B illustrates 2020 mortality across ACS types and PCR testing. The cause of death was cardiac in 7/8 and 6/8 patients in 2019 and 2020, respectively. Major adverse cardiac events at 30 days were found in 4.8% of 2019 patients and 7.9% of 2020 patients, P = 0.365 (individual components of the combined endpoint are listed in Table III).

Within the 2020 cohort, across ACS types. The cause of death was cardiac in 4/5 CoV− patients (the other patient died from COVID-19 21 days after discharge [he was not tested but had no symptoms during the ACS admission]) and in 2/3 CoV+ patients (the other patient died from COVID-19 during admission). Major adverse cardiac events at 30 days were found in 23.1% of CoV+ patients and 5.9% of CoV− patients, P = 0.066 (individual components of the combined endpoint are listed in Table III).

The univariate predictors of 30-day mortality in the 2020 cohort were LVEF (with a protective effect: OR = 0.92 [0.87-0.97] per 1% increment in LVEF, P = 0.004) and CoV+ (OR = 5.75 [1.19-27.78], P = 0.029). In the multivariable model, both variables remained as independent predictors of 30-day mortality: LVEF (OR = 0.91 [0.86-0.97]) and CoV+ (OR = 9.8 [1.48-64.78]), multivariate model P = 0.0006.

**Discussion**

This study reports patient-level data from invasively managed ACS during the spring of the 2020 COVID-19 pandemic in a network of four hospitals in Madrid, Spain, compared to a historical cohort of the same timeframe in 2019. The main results are as follows: (1) A significant decrease in ACS cases (40.4%) was found in 2020 compared to those in 2019, with similar baseline clinical characteristics and clinical presentation; (2) a higher rate of in-hospital ACS and a lower rate of culprit lesion found in 2020 was driven by the CoV+ patients; and (3) 30-day mortality increased non-significantly from 4.2% in 2019 to 7% in 2020 (P = 0.294), but with a significant difference between CoV+ (23.1%) and CoV− (5%) in the 2020 group.

The decrease in cases from 2019 to 2020 is similar to that observed in other European countries, as demonstrated by several surveys. The reasons explaining this decline are all speculative and have been discussed mostly in scientific correspondence. They include a lower hospital attendance rate due to fear of contagion or of taxing a collapsed healthcare system, limited physical activity, lower air pollution, and fewer out-of-hospital cardiac arrests or deaths.

Notably, the rate of CoV+ present in our ACS cohort
(11%) is similar to the estimated prevalence in the general population in our area, 11.3% (95% CI = 9.8-13.0). Because we did not test all of our patients, we cannot estimate true prevalence. Despite this limitation, the data suggest that patients at risk for ACS have a similar risk for COVID-19 as the general population. However, the in-hospital ACS rate was significantly higher in 2020 (15.3%) compared to that in 2019 (6.1%), and this is mainly driven by 6/13 CoV+ (46.2%) patients who presented with ACS during their COVID-19 admission. The cathlab staff data are limited and are not the main purpose of this study, but we believe they are relevant. There may be a higher risk of infection in nurses during interventional cardiology activity. Likely, the more distant position of the interventional cardiologist from the patient’s head might be less risky than the position of a circulating cathlab’s nurse when the nurse administers medication.

The risk of infection-related MI is known and is caused by three leading causes: increased oxygen demand, hypoxemia, and inflammation.

The risk of MI during respiratory bacterial pneumonia is 7%-8%, and during laboratory-confirmed influenza infection, it is 6%, but it is unknown for COVID-19. However, infection-related troponin leaks are difficult to distinguish from definite ACS, and the coronary angiography often remains essential to differential diagnosis. Moreover, although preliminary data linking COVID-19 and thrombosis pointed toward coagulation disorders, a study from intensive care COVID-19 patients found mainly extracorporeal circuits and venous thromboembolic events, with very few arterial athrombolic events such as MI and stroke.

Further studies are required to assess whether the COVID-19-related MI rate is similar to that of other respiratory infections.

The finding of a culprit lesion was significantly lower in the 2020 cohort compared to that in 2019 (58.5% versus 74.2%, P = 0.004) and even lower in CoV+ compared to CoV− patients (30.8% versus 61.9%, P = 0.032). We propose two plausible explanations. First, type 2 MI (discrepancy between oxygen supply and demand) is a more likely underlying cause in the setting of a respiratory infection (tachycardia, fever, hypoxia, and changes in vessel tone) than type 1 MI (thrombosis due to rupture and/or plaque ulceration, culprit lesion). There is, to the best of our knowledge, no study comparing type 1 and type 2 MIs in the setting of respiratory infections. However, a propensity-score-matching study by Vejpongsa et al. demonstrated a higher proportion of NSTEMI (90.3%) over STEMI presentation in MI with coexisting influenza infection compared to MI without viral respiratory infection (74.6%). This finding indicates that respiratory infections might affect the type of MI presentation. Moreover, our finding agrees with other studies, such as the one by Stefanini et al., who reported on a cohort of STEMI patients in the setting of an acute COVID-19 infection, finding only 60.7% of patients with a culprit lesion requiring revascularization. Second, SARS-CoV-2-related disorders (endothelial dysfunction, cytokine storm) and other non-related disorders (pulmonary embolism and Takotsubo syndrome) might mimic ACS directing patients toward an urgent coronary angiogram without culprit lesion or even coronary artery disease findings. The proportion of patients with a final diagnosis other than ACS was significantly higher in 2020 compared to that in 2019 and numerically higher in CoV− compared to CoV+ patients (Table II and Supplemental Table III). Despite this, coronary angiography is still encouraged to avoid overlooking a true coronary occlusion in patients with COVID-19 and suspected ACS.

The data on ACS-related mortality during the COVID-19 pandemic is, to date, minimal. In a 1-week multicenter survey across Italian coronary care units, the overall case-fatality rate (in-hospital) for AMI was 9.7% compared to 2.8% in a control group of 2019 (P < 0.001). The case-fatality rate of CoV+ patients was 28.6% for STEMI and 0% for NSTEMI. This indicates a very different pattern to our series, which had higher mortality in NSTEMI than in STEMI (Figure 3B). However, the Italian study had no patient-level data, so comparisons should be made with caution. Moreover, we believe that 30-day mortality is a more accurate measure given the lengthy hospital stays that CoV+ patients often have (our interquartile range of CoV+ patients was 5-20 days). Finally, the rate of CoV+ in that series can be calculated from the breakdown data reported by the authors, namely 33 CoV+ patients from a total of 319 AMI, 10.34%; which is very similar to that in our study.

The 30-day mortality was higher in CoV+ patients (Figure 3B), and CoV+ was an independent 30-day mortality prognostic factor. However, further studies with larger datasets are required to elucidate the mechanisms of this association. To fulfill this objective, there are collaborative ongoing research initiatives such as Long-term Effects of Coronavirus Disease 2019 on the Cardiovascular System (CV-COVID-19, NCT04359927), Acute Cardiovascular Events Triggered by COVID-19-Related Stress (JoCORE, NCT04368637), International COVID19 Clinical Evaluation Registry (HOPE COVID 19, NCT 04334291), and Impact of COVID19 Outbreak in Cardiac Acute Care (CCU-COVID19, NCT04344912). The results of these studies are eagerly awaited. Regarding causes of death, in our study, 6/8 patients of the 2020 cohort had cardiac death, suggesting that ACS complicating a COVID-19 admission (or vice versa) facilitates fatal cardiac complications.

Finally, the 30-day mortality in CoV− patients during the pandemic was reasonably good (5%), considering the burden held by Madrid’s healthcare system. We believe this was the result of great efforts to keep the structures supporting Primary-PCI networks, COVID-19-free acute cardiovascular care units, and invasive management when appropriate during the peak of the pandemic. These efforts, together with public advice on seeking emergency attention if an acute MI or stroke is suspected, should be kept in mind if the second wave of COVID-19 eventually arises.

There are some limitations to this study. First, although representative of a population of 1 million people, the number of patients included during these 2 months is limited. During the beginning of April, in all four hospitals, regular cardiology care was severely disrupted by, for example, temporary closures in referral cathlabs (patients were referred to the tertiary center) and the derivation of
most coronary care beds as respiratory intensive care beds. We peaked from 1980 COVID-19 patients (more than 100% of nominal hospital beds) admitted in all four hospitals from our network by April 3rd, 2020. Therefore, we cannot rule out that some ACS patients were not diagnosed adequately as ACS or referred to cardiac catheterization. Also, PCR was not performed to all 2020 patients, so some patients could have subclinical COVID-19 during the ACS admission. Despite that, only one developed clinical COVID-19 during follow-up, so the clinical impact is likely small. Other limitations are the inherent potential biases of the observational nature of this study and the differences in rules of confinement and healthcare system demands in other European countries that may limit generalization to other nations.

Conclusion

This study found increased 30-day mortality of invasively managed ACS with CoV+ compared to CoV− during the 2020 COVID-19 spring outbreak. However, overall 30-day mortality in 2020 was not different from a historical cohort of the same timeframe in 2019. A SARS-CoV-2 positive PCR test was independently associated with 30-day mortality: OR = 9.8; 95% CI = 1.48-64.78, P = 0.018. Further studies investigating the underlying physiopathological relations between COVID-19 and ACS are warranted.

Acknowledgment

We would like to thank Christian Bengoa for proofreading the article. We are indebted to a large number of health professionals who took care of patients during the difficult times of the COVID-19 pandemic.

Disclosure

Conflicts of interest: None.

References

1. Informe n° 27. Situación de COVID-19 en España a 30 de abril de 2020. Available at: https://www.isciii.es/quehacemos/servicios/vigilanciasaludpublica/renave/enfermedades/transmISIBLES documentos/informes/informes%20covid-19/informe%20n%2c2ba%2027.%20situacion%20covid-19%2c%20en%20espa%C3%81a%20a%2020%20abr%2020%2020.pdf. Accessed June 9, 2020.
2. Madjid M, Safavi-Naeini P, Solomon SD, et al. Potential Effects of Coronavirus on the Cardiovascular System: A Review. JAMA Cardiol 2020 (in press).
3. ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic. Available at: https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance. Accessed June 9, 2020.
4. De Rosa S, Spaccarotella C, Basso C, et al. Reduction of hospitalizations for myocardial infarction in Italy in the COVID-19 era. Eur Heart J 2020; 41: 2083-8.
5. Metzler B, Siostrozonc P, Binder RK, et al. 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: 1852-3.
6. Rodríguez-Leor O, Cid-Alvarez B, Ojeda S, et al. Impact of the COVID-19 pandemic on interventional cardiology activity in Spain. Rec Interv Cardiol 2020; 2: 82-9.
7. De Filippo O, D’Ascenzo F, Angelini F, et al. Reduced Rate of Hospital Admissions for ACS during Covid-19 Outbreak in Northern Italy. N Engl J Med 2020; 383: 88-9.
8. Salinas P, Travieso A, Vergara C, et al. Relación temporal entre ingresos por síndrome coronario agudo con tratamiento invasivo y confinamiento durante la pandemia de COVID-19. RECIC 2020 (in press).
9. Chieffo A, Stefanini GG, Price S, et al. EAPCI Position Statement on Invasive Management of Acute Coronary Syndromes during the COVID-19 pandemic. Eur Heart J 2020; 41: 1839-51.
10. Romaguera R, Cruz-González I, Jurado-Román A, et al. Consideraciones sobre el abordaje invasivo de la cardiopatía isquémica y estructural durante el brote de coronavirus COVID-19. RECIC 2020; 2: 112-7.
11. Stefanini GG, Montorlano M, Trabattoni D, et al. ST-Elevation Myocardial Infarction in Patients with COVID-19: Clinical and Angiographic Outcomes. Circulation 2020; 141: 2113-6.
12. Pinto Slottow TL, Waksman R. Overview of the 2006 Food and Drug Administration Circulatory System Devices Panel meeting on drug-eluting stent thrombosis. Catheter Cardiovasc Interv 2007; 69: 1064-74.
13. Furnival GM, Wilson RW. Regressions by Leaps and Bounds. Technometrics 1974; 16: 499-511.
14. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016; 37: 267-315.
15. Baldi E, Sechi GM, Mare C, et al. Out-of-Hospital Cardiac Arrest during the Covid-19 Outbreak in Italy. N Engl J Med 2020; 383: 496-8.
16. Rangé G, Hakim R, Mottreff P. Where have the STEMI’s gone during COVID-19 lockdown? Eur Heart J Qual Care Clin Outcomes 2020; 6: 223-4.
17. Ashraf S, Ilyas S, Alraies MC. Acute coronary syndrome in the time of the COVID-19 pandemic. Eur Heart J 2020; 41: 2089-91.
18. New York City Department of Health and Mental Hygiene (DOHMH) COVID-19 Response Team. Preliminary Estimate of Excess Mortality during the COVID-19 Outbreak—New York City, March 11-May 2, 2020. MMWR Morb Mortal Wkly Rep 2020; 69: 603-5.
19. Ministerio de Sanidad, Consumo y Bienestar Social-Ciudadanos-Estudio Nacional de sero-Epidemiología de la Infección por SARS-CoV-2 en España (ENE-Covid). Available at: https://www.mscbs.gob.es/ciudadanos/ene-covid/home.htm. Accessed May 23, 2020.
20. Mushker DM, Abers MS, Corrales-Medina VF. Acute Infection and Myocardial Infarction. N Engl J Med 2019; 380: 171-6.
21. Helms J, Tacquard C, Severac F, et al. COVID-19-Guidance. Accessed June 9, 2020.
22. Thuygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol 2018; 72: 2231-64.
23. Muscente F, De Caterina R. Causal relationship between influenza infection and risk of acute myocardial infarction: pathophysiological hypothesis and clinical implications. Eur Heart J 2020; 22: E68-72.
24. Vejpongsa P, Kitkungvan D, Madjid M, et al. Outcomes of Acute Myocardial Infarction in Patients with Influenza and Other Viral Respiratory Infections. Am J Med 2019; 132: 1173-
25. Nijjer SS, Petraco R, Sen S. Optimal management of acute coronary syndromes in the era of COVID-19. Heart 2020; 106: 1609-16.

26. Yousefzai R, Bhimaraj A. Misdiagnosis in the COVID-19 Era: When Zebras Are Everywhere, Don’t Forget the Horses. JACC: Case Reports 2020; 2: 1614-9.

27. Fear of COVID-19 keeping more than half of heart attack patients away from hospitals. Available at: https://www.escardio.org/The-ESC/Press-Office/Press-releases/Fear-of-COVID-19-keeping-more-than-half-of-heart-attack-patients-away-from-hospitals. Accessed June 16, 2020.

28. Xu S, Li Y. Beware of the second wave of COVID-19. Lancet 2020; 395: 1321-2.

**Supplemental Files**

- Supplemental Text
- Supplemental Tables I-III
- Please see supplemental files; https://doi.org/10.1536/ihj.20-574.