A case-control, multicentre study of consecutive patients with COVID-19 and acute (myo)pericarditis: incidence, risk factors, clinical characteristics and outcomes

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ABSTRACT
Objective To estimate incidence, risk factors, clinical characteristics and outcomes of acute (myo)pericarditis (AMP) in patients with COVID-19.
Methods Case-control, retrospective review, consecutive case inclusion performed in 62 Spanish EDs. All COVID-19 patients with AMP (cases) were compared in clinical characteristics and outcomes with COVID-19 without AMP (control group A) and non-COVID patients with AMP (control group B). We estimated unadjusted standardised incidence (SI, not adjusted by population’s age/sex) of AMP in COVID-19 and non-COVID populations (per 100 000/year).
Results We identified 67 AMP in COVID-19 patients (SI=56.5, OR with respect to non-COVID patients=4.43, 95% CI=3.98 to 4.94). Remarkably, COVID-19 cases presented with chest pain less frequently than non-COVID patients and had less typical ECG changes, higher NT-proBNP (N-terminal prohormone of brain natriuretic peptide), more left and right ventricular dysfunction in echocardiography and more need of inotropic/vasopressor drugs. Admission to intensive care was higher than control group A (OR=3.22, 95% CI=1.43 to 7.23), and in-hospital mortality was higher than control group B (OR=7.75, 95% CI=2.77 to 21.7).
Conclusion AMP is unusual as a form of COVID-19 presentation (about 1% cases), but SI is more than fourfold higher than non-COVID population, and it is less symptomatic, more severe and has higher in-hospital mortality; therefore, rapid recognition, echocardiographic assessment of myopericardial inflammation/dysfunction and treatment with vasoactive drugs when needed are recommended in AMP in patients with COVID-19.

INTRODUCTION
Infection by SARS-CoV-2 is mainly characterised by fever and respiratory symptoms, with dyspnoea and lung infiltrates being present in more than 50% of hospitalised cases.1 A significant number of other signs and symptoms can be present, involving the gastrointestinal tract, liver, skeletal muscle or the coagulation cascade, biochemically detected by increased D-dimers, which is related to complications and worse prognosis.1–4 Acute (myo)pericarditis (AMP) is a potential manifestation of some viral infections, including parvovirus B19, human herpes virus, Epstein-Barr virus, enterovirus, cytomegalovirus, adenovirus, HIV and hepatitis C virus. Isolated case reports have been recently published in patients with COVID-19;5–12 however, as large case series are lacking, the actual frequency of AMP in patients with COVID-19 is currently unknown. Additionally, in some reported cases, the clinical course of AMP appeared after the patient had been admitted10 and this could, to some extent, represent the expression of the increased number of complications that can be found in patients who...
METHODS

Study design and setting

This case-control study is part of the multicentre Unusual Manifestations of COVID-19 (UMC-19) project, designed to investigate the potential relationship between COVID-19 and 10 different entities that could be influenced by SARS-CoV-2 infection itself.13 14 This study, labelled UMC-19 Study 5 (UMC-19-S5) is a retrospective, case-control, ED-based, multicentre study designed to describe the incidence, risk factors, clinical characteristics and outcomes for AMP in patients with COVID-19.

The UMC-19-S5 was carried out in 62 EDs (roughly, the 20% of Spanish EDs of the Public Health System; figure 1). Altogether these 62 hospitals provide health coverage to 15 094 000 citizens (32% of the population of 46.9 million of Spain) and make up a balanced representation of the Spanish territory, type of hospital and involvement in the pandemic.11

Participants

Cases

Cases were patients who attended the ED between 1 March and 30 April 2020 and had a diagnosis of SARS-CoV-2 and AMP. The diagnosis of AMP was based on the presence of at least two of the following four manifestations or findings according to the European Society of Cardiology guidelines criteria:15 (1) chest pain, (2) pericardial friction rub, (3) characteristic ECG changes (new widespread ST elevation or PR depression) and (4) pericardial effusion. As supportive findings, we also considered inflammatory marker elevation of white cell count (WCC), the erythrocyte sedimentation rate, C reactive protein (CRP) and evidence of inflammation by imaging modalities. Diagnostic adjudication was made locally by the principal investigator of each centre, without external review. Mild cases that were entirely managed in the ED and directly discharged home without hospitalisation were included. Diagnosis of COVID-19 for this study was based on SARS-CoV-2 RNA detection in a nasopharyngeal swab by reverse transcriptase PCR (RT-PCR) and/or based on a clinically compatible clinical picture (including at least malaise, fever and cough) or the presence of typical lung parenchymal infiltrates in chest X-rays (bilateral interstitial lung infiltrates and ground-glass infiltrates) in patients with some clinical symptoms attributable to COVID-19. The initial COVID-19 clinical suspicion in patients without RT-PCR confirmation (due to shortage of tests at some time points of the first pandemic wave) was reviewed and finally adjudicated by the principal investigator of each centre, without external review.

Controls

We defined two different control groups. Control group A was formed by COVID-19 patients without AMP who presented to the ED during the same time period as the cases. This group was constituted by selecting five COVID-19 patients for every case with AMP detected by each centre. Selection (case:control ratio of 1:5) was performed by the inclusion of patients with COVID-19 seen immediately before or after each case.

Control group B was made up of patients with non-COVID diagnosed with AMP attending the ED during the same period as the cases (1 March to 30 April 2020) as well as patients with AMP diagnosed in the ED from 1 March to 30 April 2019.

Independent variables

We extracted 55 independent variables in cases and controls which included demographics, comorbidities, symptoms, vitals at ED arrival, blood parameters and radiological findings in CXRs. In patients with AMP (cases and control group B), we also recorded troponin and NT-proBNP blood concentrations, serological studies and the main ECG and echocardiographic findings if these tests were performed. Final aetiological diagnostic was recorded; of note, cases of AMP in patients with COVID-19 were not classified into the ‘viral aetiology’ group and they were computed into the ‘idiopathic’ group (unless they could be classified in any other specific category). We recorded the presence in the medical reports of each one of the four main diagnostic criteria of AMP, as well as of the additional supporting diagnostic findings. When the criteria were not described in the medical report, we assumed they were not present. Finally, we recorded the specific treatment provided to treat AMP, as well as the use of vasoactive drugs (either inotropes or vasopressors).

Outcomes

We defined four different outcomes for cases and controls which consisted of: (1) hospitalisation; (2) admission to intensive care unit (ICU); (3) prolonged hospitalisation (defined as a length of stay >7 days, which is the median length of stay of hospitalised patients in Spain), and (4) in-hospital all-cause mortality. We specified causes of death in patients with AMP, as into...
### Table 1  Baseline, clinical, analytical and radiological characteristics, and outcomes of patients with COVID-19 with acute (myo)pericarditis and comparison with patients with COVID-19 without acute (myo)pericarditis (control group A) and with patients without COVID-19 with acute (myo)pericarditis (control group B)

|               | Cases (COVID-19 and AMP) N=67 | Control group A (COVID-19 and non-AMP) N=335 | Control group B (non-COVID and AMP) N=335 |
|---------------|-------------------------------|---------------------------------------------|------------------------------------------|
| **Demographics** |                               |                                             |                                          |
| Age (years) (median (IQR) | 51 (39–71)                     | 65 (52–77) *                              | 45 (30–66)†                             |
| Sex (male)     | 41 (61.2)                      | 176 (52.5)                                 | 237 (70.7)                               |
| **Comorbidities** |                               |                                             |                                          |
| Hypertension   | 22 (33.8)                      | 153 (45.7)                                 | 89 (26.6)                                |
| Dyslipidaemia  | 13 (19.4)                      | 112 (33.4) *                               | 72 (21.5)                                |
| Diabetes mellitus | 10 (14.9)                     | 60 (17.9)                                   | 36 (10.7)                                |
| Coronary artery disease | 7 (10.4)                  | 25 (7.5)                                   | 18 (5.4)                                 |
| Chronic kidney disease | 6 (9.0)                      | 22 (6.6)                                   | 25 (7.5)                                 |
| Active cancer   | 6 (9.0)                        | 31 (9.3)                                   | 42 (12.5)                                |
| Obesity (clinically estimated) | 5 (7.5)                  | 52 (15.5)                                  | 32 (9.6)                                 |
| Asthma          | 5 (7.5)                        | 24 (7.2)                                   | 17 (5.1)                                 |
| Chronic obstructive pulmonary disease | 4 (6.0)                  | 28 (8.4)                                   | 18 (5.4)                                 |
| Active smoker   | 4 (6.0)                        | 22 (6.6)                                   | 75 (22.4)†                               |
| Peripheral artery disease | 4 (6.0)                  | 15 (4.5)                                   | 15 (4.5)                                 |
| Chronic liver disease | 4 (6.0)                      | 12 (3.6)                                   | 12 (3.6)                                 |
| Chronic heart disease | 3 (4.5)                      | 28 (8.4)                                   | 22 (6.6)                                 |
| Cerebrovascular disease | 3 (4.5)                      | 24 (7.2)                                   | 6 (1.8)                                  |
| Dementia        | 1 (1.5)                        | 30 (9.0) *                                 | 4 (1.2)                                  |
| **Symptoms at ED arrival** |                               |                                             |                                          |
| Length of symptoms (days) (median (IQR)) | 5 (1–8)                  | 7 (3–10)                                   | 2 (1–5)†                                 |
| Chest pain      | 54 (80.6)                      | 42 (12.5) *                                | 307 (91.6)†                              |
| Dyspnoea        | 37 (55.2)                      | 185 (5.2)                                  | 97 (29.0)†                               |
| Cough           | 26 (39.8)                      | 196 (58.5) *                               | 35 (10.4)†                               |
| Fever >38°C     | 20 (29.9)                      | 198 (59.1) *                               | 52 (15.5)†                               |
| Abdominal pain  | 9 (13.4)                       | 17 (5.1) *                                 | 13 (3.9)†                                |
| Vomiting        | 9 (13.4)                       | 24 (7.2)                                   | 13 (3.9)†                                |
| Diarrhoea       | 7 (10.4)                       | 54 (16.1)                                  | 16 (4.8)                                 |
| Expectoration   | 7 (10.4)                       | 49 (14.6)                                  | 10 (3.0)†                                |
| Rhinorrhea      | 5 (7.5)                        | 23 (6.9)                                   | 10 (3.0)                                 |
| Dysgeusia       | 3 (4.5)                        | 26 (7.8)                                    | 1 (0.3)†                                 |
| Anosmia         | 2 (3.0)                        | 22 (6.6)                                   | 1 (0.3)†                                 |
| Syncope         | 2 (3.0)                        | 14 (4.2)                                   | 5 (1.5)                                  |
| **Signs at ED arrival (median (IQR))** |                               |                                             |                                          |
| Temperature (°C) | 36.4 (36.0–37.0)               | 36.6 (36.0–37.3)                           | 36.2 (36.0–36.8)                         |
| SBP (mm Hg)     | 130 (115–146)                  | 125 (114–140)                              | 128 (117–140)                            |
| HR (bpm)        | 92 (80–106)                    | 88 (78–100)                                | 85 (75–99)†                              |
| RR (bpm)        | 19 (16–24)                     | 18 (16–23)                                 | 16 (14–20)†                              |
| Room air pulse oximetry (%) | 97 (94–99)                   | 96 (92–98) *                               | 98 (96–99)                               |
| **Laboratory findings (median (IQR))** |                               |                                             |                                          |
| Creatinine (mg/dL) | 0.88 (0.73–1.19)              | 0.87 (0.72–1.10)                           | 0.87 (0.75–1.05)                         |
| Sodium (mmol/L) | 139 (135–141)                 | 138 (136–140)                              | 139 (137–141)                            |
| Potassium (mmol/L) | 4.1 (3.7–4.4)                | 4.0 (3.7–4.4)                              | 4.1 (3.9–4.4)                            |
| Aspartate aminotransferase (U/L) | 31 (20–51)                  | 30 (22–48)                                 | 23 (18–37)                               |
| Bilirubin (mg/dL) | 0.72 (0.48–1.43)              | 0.50 (0.36–0.70) *                         | 0.64 (0.40–0.97)                         |
| Alkaline phosphatase (U/L) | 71 (54–94)                  | 71 (57–95)                                 | 87 (61–107)                              |
| Lactate dehydrogenase (U/L) | 262 (187–447)               | 278 (211–359)                              | 205 (163–255)†                           |
| Haemoglobin (g/L) | 135 (119–150)                | 139 (127–148)                              | 140 (128–151)                            |
| Leucocyte (x10^9 cells/L) | 8.2 (6.6–10.8)              | 6.7 (4.9–9.1)                              | 9.3 (6.8–12.6)                           |
| Lymphocyte count (x10^9 cells/L) | 1.4 (0.8–1.7)               | 1.1 (0.8–1.6)                              | 1.7 (1.1–2.3)†                           |
| Platelets (x10^9 cells/L) | 236 (191–304)                | 206 (161–259)                              | 241 (199–292)                            |
| D-dimer (ng/mL) | 944 (302–2164)                | 640 (370–1280)                             | 500 (285–1530)                           |
| C-reactive protein (mg/dL) | 3.2 (0.3–10.4)              | 5.9 (1.9–12.2) *                          | 2.0 (0.5–8.1)                            |
| Ferritin (ng/mL) | 429 (44–870)                  | 495 (270–1183)                             | 184 (134–317)                            |

Continued
Table 1  Continued

|                | Cases (COVID-19 and AMP) | Control group A (COVID-19 and non-AMP) | Control group B (non-COVID and AMP) |
|----------------|--------------------------|----------------------------------------|-------------------------------------|
|                | N=67 N (%)               | N=335 N (%)                            | N=335 N (%)                         |
| Procalcitonin (ng/mL) | 0.06 (0.02–0.28) | 0.10 (0.06–0.22) | 0.08 (0.04–0.43) |
| CXR            | N=65                     | N=325                                  | N=316                               |
| Cardiomegaly   | 18 (27.7)                | 34 (10.5)*                             | 73 (23.0)                           |
| Pleural effusion| 8 (12.3)                 | 14 (4.3)*                              | 40 (12.6)                           |
| Intersitial lung infiltrates | 21 (32.3) | 143 (44.0) | 9 (2.8)* |
| Ground-glass lung opacities | 16 (24.6) | 187 (57.5)* | 8 (2.5)* |

Outcomes

|                | N=65                     | N=325                                  | N=316                               |
|----------------|--------------------------|----------------------------------------|-------------------------------------|
| Hospitalisation| 43 (64.2)                | 253 (75.5)                             | 174 (51.9)                          |
| Admission to ICU| 11 (16.4)                | 22 (6.6)*                              | 35 (10.4)                           |
| Prolonged hospitalisation | 21 (34.4) | 133 (39.9) | 76 (22.8) |
| In-hospital mortality | 11 (16.4) | 55 (16.4) | 8 (2.4)* |

Procalcitonin (ng/mL) 0.06 (0.02–0.28) 0.10 (0.06–0.22) 0.08 (0.04–0.43)

Comparison of baseline, clinical, analytical and radiological characteristics of COVID-19 patients developing acute (myopericarditis) with respect to COVID-19 patients not developing acute (myopericarditis)

|                | OR  | 95% CI |
|----------------|-----|--------|
| Chest pain     | 13.346 | 7.331 to 24.30 |
| Bilirubin >1 mg/dL | 4.455 | 2.045 to 9.701 |
| Cardiomegaly in CXR | 3.280 | 1.710 to 6.270 |
| Pleural effusion in CXR | 3.120 | 1.250 to 7.770 |
| Age <40 years | 3.049 | 1.647 to 5.650 |
| Abdominal pain | 2.903 | 1.234 to 6.826 |
| Leucocyte count >10^9 cells/L | 2.187 | 1.205 to 3.969 |
| Platelet count >300×10^9 elements/L | 2.181 | 1.149 to 4.138 |
| Pulse oximetry at ED arrival <96% | 0.573 | 0.329 to 0.996 |
| C-reactive protein >5 mg/dL | 0.549 | 0.311 to 0.969 |
| Dyslipidaemia | 0.479 | 0.251 to 0.915 |
| Cough | 0.450 | 0.263 to 0.770 |
| Fever >38°C | 0.294 | 0.167 to 0.519 |
| Ground-glass lung opacities in CXR | 0.241 | 0.131 to 0.442 |
| Dementia | 0.154 | 0.021 to 1.150 |

Comparison of clinical, analytical and radiological characteristics of COVID-19 patients developing acute (myopericarditis) with respect to non-COVID patients developing acute (myopericarditis)

|                | OR  | 95% CI |
|----------------|-----|--------|
| Lung interstitial infiltrates in CXR | 16.33  | 7.035 to 37.92  |
| Dyspnoea | 15.66 | 1.603 to 152.9  |
| Ground-glass lung opacities in CXR | 12.61  | 5.125 to 31.04  |
| Anoxia | 10.28 | 0.918 to 115.0  |
| Cough | 5.436 | 2.973 to 9.937  |
| Lactate dehydrogenase >300 U/L | 4.442 | 1.928 to 10.24 |
| Abdominal pain | 3.844 | 1.571 to 9.404  |
| Vomiting | 3.844 | 1.571 to 9.404  |
| Expectoration | 3.792 | 1.389 to 10.35 |
| Tachypnoea >20 bpm | 3.379 | 1.844 to 6.192  |
| Dysuria | 3.026 | 1.770 to 5.174  |
| Length of symptoms >7 days | 2.890 | 1.565 to 5.348  |
| Lymphocyte count <1 (×10^3 cells/L) | 2.878 | 1.603 to 5.165  |
| Aspartate aminotransferase >40 U/L | 2.559 | 1.242 to 5.374 |
| Fever >38°C | 2.316 | 1.270 to 4.224 |
| Tachycardia >100 bpm | 1.819 | 1.017 to 3.254 |
| Age <40 years | 0.600 | 0.340 to 1.057 |
| Chest pain | 0.379 | 0.185 to 0.777  |
| Active smoker | 0.220 | 0.078 to 0.624 |

p values denote statistically significant differences (p<0.05). *P values refer to comparison between cases and control group A. **P values refer to comparison between cases and control group B. AMP, acute (myo)pericarditis; ICU, intensive care unit.

Table 2  Magnitude of statistically significant associations found in the unadjusted analysis

Differences between the case and the control groups were assessed by the χ² test (or Fisher’s exact test as appropriate) for categorical variables and by the Mann-Whitney non-parametric test for continuous variables. The magnitude of associations was expressed as unadjusted OR with 95% CI. Continuous variables were dichotomized using clinically meaningful cut-offs or around the median of the distribution. As the number of patients with AMP we expected to identify was not large, we did not plan to go further in the investigation of the significant relationships identified in the unadjusted analysis using adjusted models, with the exception of outcomes, which were adjusted for age and sex.

In all comparisons, statistical significance was accepted if the p-value was <0.05 or if the 95% CI of the risk estimations excluded the value 1. The analyses were performed with the SPSS (V24) statistical software package (IBM, Armonk, New York, USA).

Ethics

The UMC-19 project was approved by the Ethics Committee of the Hospital Clínic of Barcelona (Spain), with the reference number HCB/2020/0534, and it was carried out in strict compliance with the principles of the Declaration of Helsinki.

cardiovascular, non-cardiovascular or unknown, according to the Academic Research Consortium-2 consensus.¹⁶

Statistical analysis

Discrete variables were expressed as absolute values and percentages, and continuous variables as median and IQR. The incidence of AMP in COVID-19 and non-COVID patients were expressed per thousand (%) and standardised incidence (not adjusted by population’s age/sex) as cases per 100 000 per year, both with 95% CI. For non-COVID patients, partial calculations were made for the COVID-19 (2020) and non-COVID (2019) periods of patient inclusion. To estimate COVID-19 prevalence in each ED catchment area during COVID-19 period, we used the seroprevalence of SARS-CoV-2 in the province of that ED as determined in a wide Spanish study performed between 27 April and 11 May 2020.¹⁷ We also used OR with 95% CI to compare the incidence of AMP in COVID-19 patients with respect to non-COVID patients globally, and for COVID-19 and non-COVID periods individually.

The magnitude of statistically significant associations found in the unadjusted analysis using adjusted models, with the exception of outcomes, which were adjusted for age and sex.
Patient and public involvement

Patients were not involved in the recruitment and conduct of the study. The authors are unable to disseminate the findings to study participants directly.

RESULTS

A total of 74,814 patients with COVID-19 attended the 62 Spanish EDs participating in the UMC-19-S (figure 1) during the 61-day study period. In 67 of these patients, AMP diagnosis was adjudicated (incidence=0.90‰, 95% CI=0.69‰ to 1.14‰) and constituted the case group. Control group A included 335 COVID-19 patients without AMP during the same period. COVID-19 infection was confirmed by RT-PCR in 45 cases and 246 control group A patients (67.2% and 73.4%, respectively, p=0.30), while in the remaining patients, COVID-19 diagnosis was based on epidemiological context and clinical data.

During the 2020 study period, 423,153 non-COVID patients were seen, and 965,726 during the 61-day period in 2019 for a total of 1,388,879 non-COVID patients. Of these, 626 were diagnosed with AMP (230 in COVID-19 period and 396 in the pre-COVID period). Control group B was formed by 368 selected patients from these 626 non-COVID patients with AMP. Overall incidence of AMP in the study was 0.45‰ (95% CI=0.42‰ to 0.49‰), with a COVID-19 period incidence of 0.54‰ (95% CI=0.48‰ to 0.62‰) and a pre-COVID period incidence of 0.41‰ (95% CI=0.37‰ to 0.45‰).

The median age of COVID-19 patients with AMP (cases) was 51 years; 61% were men, and the most frequent comorbidities were hypertension (34%), dyslipidaemia (19%), diabetes mellitus (15%) and coronary artery disease (10%) (table 1 and online supplemental table 1). The most frequent symptomatology was chest pain (66%), dyspnoea (55%), cough (39%) and fever (30%), and the median time from symptom onset to ED consultation (whichever was first) was 5 days.

There was a higher frequency of AMP in COVID-19 compared with non-COVID ED patients (control groups A and B) (OR of 1.99 (95% CI=1.55 to 2.56)). AMP was more frequent in COVID-19 patients than in non-COVID patients during the 2020 study period (OR 1.94 (95% CI=1.48 to 2.55)) and in patients in the pre-COVID period (OR 2.19 (95% CI=1.69 to 2.83)). The unadjusted standardised incidences of AMP were 5.65 per 100 000 COVID-19 individuals per year (95% CI=5.27 to 60.1) and 12.7 per 100 000 non-COVID individuals per year (95% CI=12.2 to 13.3, with partial unadjusted standard incidences of 9.6 in 2020–COVID-19 period and 15.7 in 2019 pre-COVID period). Consequently, the OR of AMP for COVID-19 with respect to non-COVID patients was of 4.43 (95% CI=3.98 to 4.94), with partial OR of 5.89, 95% CI=5.27 to 6.58, when compared with non-COVID patients from the COVID-19 period, and partial OR of 3.59, 95% CI=3.23 to 3.99, when compared with non-COVID patients from the pre-COVID period.

COVID-19 patients with acute (myo)pericarditis versus COVID-19 patients without acute (myo)pericarditis

COVID-19 patients with AMP were significantly different to COVID-19 patients without AMP (control group A) with regard to age, presence of chest pain, cardiomegaly, pleural effusion and elevated bilirubin, all with ORs over threefold greater (table 2) Although some biomarkers of inflammatory activity were significantly higher (WCC and platelet count), CRP was significantly lower. Compared with non-COVID patients with AMP (control group B patients), dysgeusia, anosmia and cough were more common in COVID-19 patients with AMP as were findings of COVID-19 infection on chest X-ray (lung interstitial infiltrates or ground-glass lung opacities), all with ORs over fivefold higher (table 3). Chest pain was not as frequent in COVID-19 patients with AMP as in non-COVID patients with AMP (OR of 0.38; 95% CI 0.19 to 0.78).

COVID-19 acute (myo)pericarditis versus non-COVID acute (myo)pericarditis

COVID-19 patients with AMP were similar to non-COVID patients with AMP (control group B) with regard to elevated troponin I and ECG findings; the most frequent finding was diffuse ST elevation (48% vs 60%, p=0.06). However a NT-proBNP over 1000ng/mL was more common in COVID-19 cases in 69% and 31% (p=0.01).
Echocardiography was performed in 54 COVID-19 and 251 non-
COVID patients with AMP (81% and 75%, p=0.35), and the most frequent finding was pericardial effusion (48% and 49%, p=0.87). COVID-19 patients more frequently had right (20% vs 10%, p=0.03) and left (32% vs 14%) ventricular dysfunction.

COVID-19 patients with AMP were less frequently treated with non-steroidal anti-inflammatory drugs (72% vs 83%, p=0.03) and colchicine (34% vs 53%, p=0.002) and more frequently with corticosteroids (33% vs 20%, p=0.02) and inotropes/vaspressors (21% vs 2%, p<0.001) compared with non-COVID AMP patients. The most frequent aetiological diagnostic in both groups was idiopathic AMP (76% and 78%, p=0.75), and the only significant difference was found in metabolic AMP, which was more frequently seen in COVID-19 patients (5.1% vs 0.3%, p=0.02). Nine cases of AMP had a viral aetiology confirmed by serological studies, three in COVID-19 patients (all corresponding to cytomegalovirus) and six in non-
COVID patients (three Epstein-Barr virus, two cytomegalovirus, one parvovirus). The number and distribution of the main diagnostic and supporting findings of AMP in COVID-19 and non-COVID patients are presented in figure 2.

Outcomes of COVID-19 patients with acute (myo)pericarditis

COVID-19 patients with AMP were hospitalised in 64% of cases, 16% were admitted to the ICU at some point during hospital stay, 34% experienced prolonged hospitalisation (>7 days) and 16% died during hospital stay (11 patients, 3 due to cardiovascular causes, 3 due to non-cardiovascular causes and 5 unknown; table 3). After adjustment, COVID-19 patients with AMP were more likely to have an ICU admission compared with COVID-19 patients without AMP (OR=3.22, 95% CI=1.43 to 7.26), but there was no difference in mortality. COVID-19 patients with AMP were more likely than non-COVID-19 patients with AMP who had higher in-hospital mortality (OR=7.75, 95% CI=2.77 to 21.7) (figure 3). However, significantly higher rates of all-cause mortality (with increased rates of cardiovascular mortality and mortality of unknown origin, but not of non-cardiovascular

Figure 2  Main and additional supporting diagnostic findings in COVID patients with acute (myo)pericarditis (case group) and non-COVID patients with acute (myo)pericarditis (control group B). CRP, C-reactive protein; WBC, white blood cell

Figure 3  Outcomes of patients with COVID-19 and acute (myo)pericarditis compared with COVID-19 patients without acute (myo)pericarditis (control group A) and non-COVID patients with acute (myo)pericarditis (control group B), unadjusted (in red) and adjusted for age and sex (in blue).
origin) were observed in COVID-19 patients with AMP than in non-COVID patients (table 3).

DISCUSSION
To our knowledge, the UMC-19-S₅ is the largest series of consecutive AMP reported in COVID-19 patients, and there are four main findings that merit highlighting. First, the incidence of AMP in COVID-19 patients is double than the incidence of AMP in the general population (non-COVID patients) coming to ED, and unadjusted standardised incidence is over fourfold of that found in the non-COVID population. Second, young age is the main risk factor associated with the development of AMP in patients infected by SARS-CoV-2. Third, AMP in COVID-19 patients could be more difficult to diagnose than those without COVID-19, as chest pain and ECG typical signatures (key findings to suspect AMP) could be absent in up to one-fifth of cases. And fourth, based on clinical findings, including NT-BNP, echocardiogram and the use of vasopressors, the severity of AMP in COVID-19 patients seems to be greater.

We found that AMP is diagnosed in around 0.5‰ of the general population (non-COVID patients) entering EDs, with very similar incidences in the pre-COVID and COVID-19 periods (0.41‰ and 0.54‰, respectively). These figures are within the relative frequencies reported in previous ED-based studies (0.15‰–0.81‰). Therefore, our finding of around 1‰ AMP in COVID-19 patients coming to the ED during the COVID-19 outbreak is double than that observed in non-COVID patients. Similarly, the unadjusted standardised incidence of AMP for general (non-COVID) population found in the UMC-19-S₀ of 12.7 per 100,000 per year (9.6 and 15.7 for the COVID-19 and pre-COVID periods, respectively) is within the range of previously reported general incidences: 27.7 in a prospective, observational cohort study involving two general Italian hospitals, 18.0 in a Swedish registry of the general population and 7.4 in retired US military personnel. Therefore, the unadjusted standardised incidence of 51.9 AMP cases per 100,000 COVID-19 patients per year, which is more than fourfold higher than in non-COVID population, is also remarkably high. Additionally, 76% of AMP in COVID-19 patients were diagnosed as idiopathic in the present study, in agreement with the figure of 80%–90% labelled idiopathic in Western Europe and North America. Two-thirds of the idiopathic cases of AMP in our study had a positive RT-PCR, and thus our findings strongly suggest a pathogenic role of SARS-CoV-2, and the need to add this pathogen to the list of viral causes of AMP.

COVID-19 patients developing AMP were younger than COVID-19 patients who did not develop AMP, and they less frequently had cough and fever and more frequently presented abdominal pain. Surprisingly, although leucocytes and platelets were increased compared with COVID-19 patients without AMP, lymphocytes, procalcitonin and ferritin were not significantly elevated, and CRP values were lower. Therefore, although AMP implies an inflammatory process, the presence of myopericarditis does not appear to be a marker of increased inflammation beyond that of SARS-CoV-2.

The clinical characteristics of AMP in COVID-19 patients differed from AMP in non-COVID patients. Remarkably, COVID-19 patients presented with chest pain less frequently (OR of 0.38). Imazio et al found that in idiopathic AMP 99% of patients presented with chest pain, 35% had pericardial rubs, ST-segment elevation was identified in 90% and pericardial effusion in 60%. Some of these findings (chest pain, typical ECG signatures) were less common in our COVID-19 patients, which could make AMP more difficult to diagnose in COVID-19 patients. On the other hand, although the percentage of patients with myocardial involvement detected by raised troponin levels was similar in COVID-19 and non-COVID patients with AMP (33% and 32%, respectively), the increments were higher in COVID-19 patients. COVID-19 patients with AMP more frequently had increased NT-proBNP, right and left ventricular dysfunction and need of inotropes/vasopressors than non-COVID AMP patients. All these data suggest a higher severity of AMP in COVID-19 patients. However, due to the observational nature of the UMC-19-S₅, it cannot be excluded that inotropic/vasoactive drugs were used because of the severity of other organ dysfunction linked to COVID-19 rather than to AMP itself. Nevertheless, our data support a high index of suspicion, and rapid echocardiography-based management with vasoactive treatment for AMP in COVID-19 patients.

With respect to the outcomes of cases, admission to the ICU was higher for COVID-19 patients with AMP than for COVID-19 patients without AMP (OR of 3.22), but hospitalisation, prolonged hospitalisation or in-hospital mortality rates did not differ. However, COVID-19 patients with AMP had a higher in-hospital mortality than AMP in the general population (OR of 7.75), even taking into account that in-hospital mortality found in our non-COVID population (2.3%) is higher than that reported in developed countries (around 1%). Although this increased mortality could be as its severity is greater in COVID-19 than in non-COVID patients. The increased rate of cardiovascular deaths in COVID-19 patients also supports this hypothesis.

Limitations
First, as this is a retrospective review, some cases of mild, paucisymptomatic AMP could have remained undiagnosed. Indeed, if ED visits tended to decrease during the COVID-19 period due to population lockdown and/or fears of COVID-19 contagion, some patients with AMP could have stayed home, and thus the real incidence of AMP could be underestimated. Second, we did not adjust the incidence of baseline and clinical AMP variables, and outcomes were only adjusted by age and sex. Therefore, other unexplored confounders could modify our findings in some extend. Third, in around one-third of patients with COVID-19 the diagnosis was based exclusively on clinical/radiological findings, with no microbiological confirmation, due to the shortage of RT-PCR tests. Fourth, although the case abstraction form was standardised, there was no monitoring of data collection methods, and diagnosis and outcome adjudication were done locally. Fifth, extensive aetiological study of all AMP cases was not carried out, and some cases classified as idiopathic could correspond to other categories.

CONCLUSIONS
The present data demonstrate an incidence of AMP in patients with COVID-19 higher than expected in the general population and support previous reports suggesting that SARS-CoV-2 should be added to the list of viruses able to cause AMP. In addition, other relevant findings of present study are that COVID-19 patients with AMP are more likely to be admitted in ICU than COVID-19 patients without AMP. They are also less likely to present with typical myopericarditis symptoms and more likely to die than patients with AMP without COVID-19. Therefore, special attention should be paid when patients with COVID-19 are evaluated in the ED. Although the size of our case series is limited and confounding cannot be effectively
excluded, we believe that rapid diagnosis, echocardiographic assessment of myopericardial inflammation and/or dysfunction and treatment with vasoactive drugs has to be recommended in AMP in patients with COVID-19.

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