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ORIGINAL ARTICLE

A case-control emergency department-based analysis of acute pancreatitis in Covid-19: Results of the UMC-19-S_6

Òscar Miró[1] | Pere Llorens[2] | Sònia Jiménez[1] | Pascual Piñera[3] | Guillermo Burillo-Putze[4] | Alfonso Martín[5] | Francisco J Martín-Sánchez[6] | Jorge Lamberechts[6] | Aitor Alquézar-Arbé[7] | Javier Jacob[8] | José Noceda[9] | María J Cano Cano[10] | María J Fortuny Bayarri[11] | Juan M Marín Porrino[12] | Napoleón Meléndez[13] | Carles Pérez García[14] | José V Brasó Aznar[15] | María C Ponce[16] | Elena Díaz Fernández[17] | Laura Ejarque Martínez[18] | Ana Peiró Gómez[19] | Josep Tost[20] | María J Domínguez[21] | Francisco J Teigell Muñoz[22] | Juan González del Castillo[6] | the Spanish Investigators on Emergency Situations TeAm (SIESTA) network*

[1]Emergency Department, Hospital Clínic, IDIBAPS, University of Barcelona, Barcelona, Spain

[2]Emergency Department, Hospital General de Alicante, University Miguel Hernández, Elche, Spain

[3]Emergency Department, Hospital Reina Sofía, Murcia, Spain

[4]Emergency Department, Hospital Universitario de Canarias, Tenerife, Spain

[5]Emergency Department, Hospital Severo Ochoa, Leganés, Spain

[6]Emergency Department, Hospital Clínico San Carlos, IDISSC, UnivesdadComplutense, Madrid, Spain

[7]Emergency Department, Hospital de la Santa Creu I Sant Pau, Barcelona, Spain

[8]Emergency Department, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain

[9]Emergency Department, Hospital Clínico Universitario de Valencia, Valencia, Spain

[10]Emergency Department, Hospital Arnau de Vilanova de Valencia, Valencia, Spain

[11]Emergency Department, Hospital Francesc de Borja de Gandia, Valencia, Spain

[12]Emergency Department, Hospital Marina

Abstract

Background/Purpose: We investigated the incidence, risk factors, clinical characteristics and outcomes of acute pancreatitis (AP) in patients with COVID-19 attending the emergency department (ED), before hospitalization.

Methods: We retrospectively reviewed all COVID patients diagnosed with AP in 62 Spanish EDs (20% of Spanish EDs, COVID-AP) during the COVID outbreak. We formed two control groups: COVID patients without AP (COVID-non-AP) and non-COVID patients with AP (non-COVID-AP). Unadjusted comparisons between cases and controls were performed regarding 59 baseline and clinical characteristics and four outcomes.

Results: We identified 54 AP in 74 814 patients with COVID-19 attending the ED (frequency = 0.72‰, 95% CI = 0.54-0.94‰). This frequency was lower than in non-COVID patients (2231/1 388 879, 1.61‰, 95% CI = 1.54-1.67; OR = 0.44, 95% CI = 0.34-0.58). Etiology of AP was similar in both groups, being biliary origin in about 50%. Twenty-six clinical characteristics of COVID patients were associated with a higher risk of developing AP: abdominal pain (OR = 59.4, 95% CI = 23.7-149), raised blood amylase (OR = 31.8; 95% CI = 1.60-632) and vomiting (OR = 15.8, 95% CI = 6.69-37.2) being the strongest, and some inflammatory markers (C-reactive protein, procalcitonin, platelets, D-dimer) were more increased. Compared to non-COVID-AP, COVID-AP patients differed in 23 variables; the strongest ones related to COVID symptoms, but less abdominal pain was reported, pancreatic enzymes raise was lower, and severity (estimated by BISAP and SOFA score at ED arrival)

*Spanish Investigators on Emergency Situations TeAm (SIESTA) network details present in Appendix 1.

Baixa de Villajoyosa, Alicante, Spain
[13]Emergency Department, Hospital Virgen de los Lirios, Alcoi, Spain
[14]Emergency Department, Hospital LluísAlcanys de Xàtiva, Valencia, Spain
[15]Emergency Department, Hospital Universtario de La Ribera, Valencia, Spain
[16]Emergency Department, Hospital de la Vega Baja, Orihuela, Spain
[17]Emergency Department, Hospital UniversitarioSant Joan, Alicante, Spain
[18]Emergency Department, Hospital General de Requena, Valencia, Spain
[19]Emergency Department, Hospital de Lliria, Valencia, Spain
[20]Emergency Department, Hospital de Terrassa, Barcelona, Spain
[21]Emergency Department, Hospital Universitario de Fuenlabrada, Madrid, Spain
[22]Emergency Department, Hospital Universitario Infanta Cristina de Parla, Madrid, Spain

Correspondence
Òscar Miró, Emergency Department, Hospital Clínic, Villarroel 170, 08036 Barcelona, Catalonia, Spain
Email: omiro@clinic.cat

was higher. The in-hospital mortality (adjusted for age and sex) of COVID-AP did not differ from COVID-non-AP (OR = 1.12, 95% CI = 0.45-245) but was higher than non-COVID-AP (OR = 2.46, 95% CI = 1.35-4.48).

Conclusions: Acute pancreatitis as presenting form of COVID-19 in the ED is unusual (<1‰ cases). Some clinically distinctive characteristics are present compared to the remaining COVID patients and can help to identify this unusual manifestation. In-hospital mortality of COVID-AP does not differ from COVID-non-AP but is higher than non-COVID-AP, and the higher severity of AP in COVID patients could partially contribute to this increment.

KEYWORDS
acute pancreatitis, clinical characteristics, COVID-19, incidence, risk factors, SARS-Cov-2

1 | INTRODUCTION

Infection by SARS-Cov-2 is mainly characterized by fever and respiratory symptoms, with dyspnea and lung infiltrates being present in more than 50% of hospitalized cases.[1] A significant number of other signs and symptoms can also be present, involving the gastrointestinal tract, hepatic inflammation, myalgia and rhabdomyolysis, or a pro-coagulant state, biochemically detected by increased D-dimers, which is related to complications and a worse prognosis.[1–4] In addition, isolated case reports and short case series have described unusual clinical manifestations in patients with COVID-19. However, in some patients, some of these entities appear after the patient has been admitted – while the patient is hospitalized and, to some extent, represents the expression of the increased number of complications that may have developed in patients who are bedridden, multidrug-treated and/or in very poor condition. In this scenario, it is difficult to quantify the real association of a certain manifestation with the pathogenesis of the disease caused by SARS-Cov-2 infection.

Acute pancreatitis is a potential manifestation of viral infections and has been reported in connection with mumps, coxsackievirus, hepatitis B, cytomegalovirus, varicella-zoster, herpes simplex and human immunodeficiency virus (HIV).[5,6] Some isolated cases of acute pancreatitis have been reported during SARS-CoV-2 infection,[7–10] although the real frequency in patients with COVID-19 is currently unknown. Indeed, there is no case series of acute pancreatitis in COVID patients allowing estimation of its frequency. In the present study, we aimed to investigate the incidence of acute pancreatitis in patients attending the emergency department (ED), before hospitalization and treatment with specific drugs for SARS-Cov-2 infection. The specific objectives were: (a) to determine the frequency of acute pancreatitis in patients with COVID-19; (b to uncover the risk factors associated with the development of acute pancreatitis in patients with COVID-19; (c) to describe whether there are any distinctive clinical characteristics in these patients in comparison with acute pancreatitis observed in non-COVID patients; and (d) to investigate the outcomes of COVID patients presenting acute pancreatitis.

2 | METHODS

2.1 | Study design and setting

The present study forms part of the Unusual Manifestations of Covid-19 (UMC-19) project, which was designed to

investigate the potential relationship between COVID-19 and 10 different entities that could be influenced by SARS-Cov-2 infection itself: acute pancreatitis, meningoencephalitis, Guillain-Barre syndrome, (myo)pericarditis, spontaneous pneumothorax, acute coronary syndrome, deep venous thrombosis, pulmonary embolism, ictus and gastrointestinal bleeding. The main objectives of the UMC-19 project were common for all entities and consisted in the description of the incidence, risk factors, clinical characteristics, and outcomes for each particular entity, including COVID patients who did not develop these entities as well as non-COVID patients that presented these entities as comparators.

In Spain, the first case of SARS-Cov-2 infection was detected on January 31 2020. The definition of the COVID period for the inclusion of cases in the present UMC-19 project study was set from March 1 to April 30 2020. During this 61-day period, 213 435 cases of COVID-19 were confirmed in Spain by the Ministry of Health.[11] For the recruitment of controls, the UMC-19 project selected patients from two different periods: one corresponding to the same dates as the cases (from March 1 to April 30 2020) and one corresponding to the same period of the previous year (from March 1 to April 30 2019).

The investigators forming the steering committee of the UMC-19 project initially contacted 152 Spanish EDs, which roughly constituted half of the 312 hospital EDs of the Spanish public health network. Of these, 81 considered participation and analyzed the protocol, and finally 62 (20% of Spanish EDs) consented to participate and duly sent all the data required (Figure 1). Altogether these 62 hospitals provide health coverage to 15.5 million citizens (33% of the population of 46.9 million of Spain) and make up a balanced representation of the Spanish territory (representing 12 of the 17 Spanish autonomous communities), type of hospital (community, reference and high-technology university hospitals were included) and involvement in the pandemic (with EDs attending from 1% to 47% of the ED census during the COVID outbreak period corresponding to COVID patients).[12]

The investigation of acute pancreatitis in COVID patients, one of the entities included in the UMC-19 project, was labeled as the UMC-19 Study 6 (UMC-19-S_6) and consisted of a retrospective, case-control, ED-based, multicenter study that reviewed the medical reports of COVID patients who were diagnosed with acute pancreatitis during ED assessment and were managed in Spanish EDs before hospitalization.

2.2 | Cases of the UMC-19-S_6

The case group was formed by COVID patients with the diagnosis of acute pancreatitis made at ED presentation based on the presence of at least two of the following three

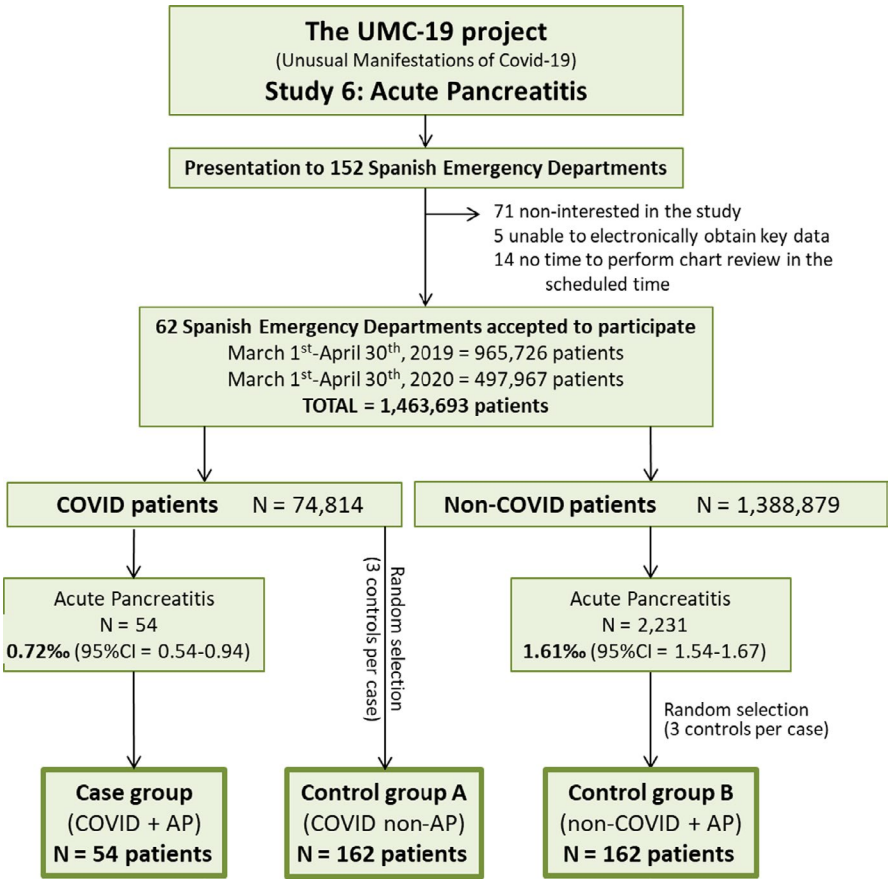

FIGURE 1 Study design and Inclusion flow chart. AP, acute pancreatitis

manifestations: (a) acute abdominal pain and tenderness in the upper abdomen; (b) elevated pancreatic enzyme levels (amylase or lipase elevated > 3 times the upper limit of normal) in the blood, urine, or ascitic fluid; and (c) abnormal imaging findings in the pancreas associated with acute pancreatitis.[13,14] Diagnostic adjudication was locally made by the principal investigator of each center, without external review. On the other hand, diagnosis of COVID-19 was accepted based on SARS-CoV-2 antigen detection in a nasopharyngeal swab by reverse transcriptase polymerase chain reaction (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.

2.3 | Controls of the UMC-19-S_6

We defined two different control groups. One group was formed by COVID patients (without acute pancreatitis) attending the ED during the same COVID outbreak period used for case inclusion (March 1 to April 30 2020). This group was constituted by selecting three COVID patients for every case detected by each center. Selection was randomly performed by the inclusion of the three COVID patients seen immediately before or after each case. Controls were not matched with cases for any variable at this point. This group, named control group A, was specifically designed to uncover the risk factors associated with the development of acute pancreatitis in COVID patients.

The second control group was made up of all non-COVID patients diagnosed with acute pancreatitis attending the ED during the same period as the cases (March 1 to April 30 2020), which was defined in the same terms as the cases. In order to avoid the possibility that some of these control cases could eventually have an inadvertent infection by SARS-Cov-2, and could have a different clinical profile from those usually attending the ED due to the population lockdown during the outbreak, we also included all patients with acute pancreatitis diagnosed in the ED from March 1 to April 30 2019, just one year before the COVID pandemic. To select controls, every center made an alphabetically-ordered list of non-COVID patients with acute pancreatitis and selected the needed number of controls (three by each case) according to such a list, irrespective of whether patients were seen in the ED during 2019 or 2020. Controls were not matched with cases for any variable at this point. This group was denominated control group B and was specifically designed to uncover the particular distinctive clinical characteristics of acute pancreatitis in COVID patients with respect to acute pancreatitis developed in the general population.

2.4 | Independent variables

We collected 59 independent variables in cases and controls, which included two demographic data (age, sex), 14 comorbidities (hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, chronic heart failure, obesity [clinically estimated], chronic liver disease, chronic obstructive pulmonary disease, asthma, active smoker, cerebrovascular disease, chronic kidney disease [creatinine > 2 mg/dL], dementia, active cancer), 12 symptoms (time elapsed from symptom onset to ED attendance, fever, rhinorrhea, cough, expectoration, dyspnea, chest pain, abdominal pain, vomiting, diarrhea, anosmia, dysgeusia), five vitals at ED arrival (temperature, systolic blood pressure, heart rate, respiratory rate, room air pulsioxymetry), 22 blood parameters (amylase, lipase, aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin, alkaline phosphatase, lactate dehydrogenase [LDH], C-reactive protein [CRP], procalcitonin, creatinine, sodium, potassium, calcium, magnesium, hemoglobin, leucocytes, lymphocytes, platelets, activated partial thromboplastin time, prothrombin time, fibrinogen, D-dimer) and four radiological findings in chest X-rays (cardiomegaly, pleural effusion, interstitial lung infiltrates and ground-glass opacities).

In patients with acute pancreatitis (cases and control group B), we also recorded specific risk factors for acute pancreatitis (chronic alcoholism, and previous antecedent of alcohol abuse and episodes of acute pancreatitis), severity of the current episode of acute pancreatitis at ED arrival assessed by two different scores, one specifically developed for acute pancreatitis (BISAP score[15]) and one developed of critical patients with sepsis (SOFA score[16]), the type of imaging (ultrasonography and/or computerized tomography) and the main results and endoscopic interventions recorded or performed during ED patient management, and the final etiological diagnosis of the current episode.

2.5 | Outcomes

We defined four different outcomes for cases and controls which consisted in: (a) the need for hospitalization; (b) the need for admission to intensive care; (c) prolonged hospitalization (defined as a length of stay > 7 days, which is the median length of stay of hospitalized patients in Spain); and (d) in-hospital all-cause mortality.

2.6 | Statistical analysis

Discrete variables were expressed as absolute values and percentages, and continuous variables as median and interquartile range (IQR). Frequencies were expressed per thousand

(‰) cases or controls, with 95% confidence interval (CI). Differences between the case and the control groups were assessed by the chi-square test (or Fisher exact test if needed) for qualitative variables and by the Mann–Whitney non-parametric test for quantitative variables. The magnitude of associations was expressed as unadjusted odds ratio (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 acute pancreatitis 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. As an exception, outcomes were adjusted for age and sex.

In addition to the main planned outcome analysis, we run two sensitivity analyses in order to ascertain the consistency of our results. The sensibility analysis A consisted of selecting only COVID patients (in case and control A groups) with SARS-CoV-2 infection confirmed by RT-PCR and disregarding those in whom COVID-19 diagnosis was exclusively based on clinical criteria. The sensitivity analysis B consisted of creating pairs of cases and control A patients and pairs of cases and control B patients matched by propensity score. To obtain propensity score, we used linear regression modeling provided by SPSS using as covariates/factors age, sex and baseline comorbidities with unequally ($P < 0.05$) distributed between groups. For case and control B groups matching, BISAP score was added to the model. A relative difference of less than 10% in propensity score was required for matching.

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 (v.24) statistical software package (IBM, Armonk, New York, USA).

2.7 | 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 acted as the central ethical committee. Under the exceptional circumstances generated by the COVID-19 pandemic, the urgent need to obtain feasible data related to this new disease, and the non-interventional and retrospective nature of the project, the requirement of obtaining written patient consent to be included in the study was waived. All patients were codified by investigators of the participating centers before entering their data into the general database, thereby ensuring patient anonymity to investigators analyzing the database. The UMC-19-S_6 was carried out in strict compliance with the principles of the Declaration of Helsinki. The authors designed the study, gathered and analyzed the data, vouched for the data and analysis, wrote the paper, and decided to publish.

3 | RESULTS

A total of 74 814 patients with COVID-19 were attended in the 62 Spanish EDs participating in the UMC-19-S_6 (Figure 1) during the 61-day study period. Fifty-four of these patients presented acute pancreatitis (frequency = 0.72‰, 95% CI = 0.54-0.94‰) and constituted the case group. Control group A was formed by 162 randomly selected COVID patients without acute pancreatitis during the same period. COVID infection was confirmed by PCR in 40 cases and 120 control A patients (74.1% in both groups). On the other hand, 1 388 879 non-COVID patients were seen during the 122-day period (61 days in the 2020 COVID period and 61 in the 2019 pre-COVID period), and 2,231 diagnoses of acute pancreatitis were made (frequency = 1.61‰, 95% CI = 1.54-1.67). These patients constituted control group B. The relative frequency of acute pancreatitis in COVID compared to non-COVID patients coming to the ED resulted in an OR of 0.44 (95% CI = 0.34-0.581.93).

The mean age of COVID patients with acute pancreatitis (cases) was 68 years; 72% were males, and the most frequent comorbidities were hypertension (65%), dyslipidemia (50%), diabetes mellitus (28%), and active cancer and obesity (24% each). The most frequent symptomatology was abdominal pain (80%), vomiting (48%), fever (43%) and dyspnea (29%), and the median time from symptom onset to ED consultation (whichever was first) was 3 days. The remaining clinical characteristics, as well as the vitals at ED arrival, laboratory findings and chest X-ray alterations are presented in Table 1.

In patients with acute pancreatitis, chronic alcoholism was less frequently present in cases than in control group B patients, and severity of the current episode of pancreatitis assessed when patient arrived to ED was higher in cases, either assessed by BISAP or by SOFA score (Table 2). Imaging studies to assess acute pancreatitis were ordered in the ED in 74% of COVID patients and in 85% of non-COVID patients ($P = 0.10$; Table 2). Ultrasonography and dual imaging studies (by ultrasonography and computerized tomography) were more frequently performed in non-COVID patients. The main findings did not differ between the two groups, and a similar percentage of patients were treated with endoscopic retrograde cholangiopancreatography and sphincterotomy during ED stay (5.6% and 6.8%, respectively). Final etiologic diagnosis of the current episode of pancreatitis did not differ among COVID and non-COVID patients: about 50% were biliary, about 10% alcoholic and in about 25% the origin was unknown or unreported (Table 2).

When cases were compared with controls, some statistically significant differences were found (Table 1), and the magnitudes of these associations are shown in Table 3. In COVID patients, complaints of abdominal pain and vomiting and a rise in blood amylase levels were the most indicative of the presence of a concomitant acute pancreatitis, all with ORs

TABLE 1 Baseline characteristics of patients with COVID-19 with acute pancreatitis and comparison with patients with COVID-19 without acute pancreatitis (control A group) and with patients without COVID-19 with acute pancreatitis (control B group)

	Cases (COVID and AP) N = 54 n (%)	Control group A (COVID and non-AP) N = 162 n (%)	Control group B (non-COVID and AP) N = 162 n (%)	P-value*	P-value**
Demographics					
Age (years) [median (IQR)]	68 (53-79)	62 (46-77)	61 (49-77)	0.26	0.34
Sex (male)	39 (72.2)	85 (52.5)	91 (56.2)	**0.01**	**0.04**
Comorbidities					
Hypertension	35 (64.8)	69 (42.6)	86 (53.1)	**0.007**	0.16
Dyslipidemia	27 (50.0)	47 (29.0)	65 (40.1)	**0.008**	0.21
Diabetes mellitus	15 (27.8)	23 (14.2)	37 (22.8)	**0.04**	0.47
Active cancer	13 (24.1)	15 (9.3)	16 (9.9)	**0.009**	**0.01**
Obesity (clinically estimated)	13 (24.1)	21 (13.0)	37 (22.8)	0.08	0.85
Chronic obstructive pulmonary disease	11 (20.4)	18 (11.1)	144 (88.9)	0.11	**0.001**
Chronic kidney disease	11 (20.4)	5 (3.1)	14 (8.6)	**<0.001**	**0.03**
Coronary artery disease	5 (9.3)	9 (5.6)	12 (7.4)	0.35	0.77
Cerebrovascular disease	5 (9.3)	11 (6.8)	6 (3.7)	0.55	0.15
Chronic liver disease	5 (9.3)	5 (3.1)	19 (11.7)	0.13	0.80
Asthma	4 (7.4)	8 (4.9)	6 (3.7)	0.50	0.27
Chronic heart failure	4 (7.4)	12 (7.4)	9 (5.6)	1.00	0.74
Peripheral artery disease	4 (7.4)	8 (4.9)	8 (4.9)	0.50	0.55
Dementia	3 (5.6)	13 (8.0)	1 (0.6)	0.77	**0.04**
Symptoms at ED arrival					
Length of symptoms (days) [median (IQR)]	3 (1-6)	7 (4-10)	1 (1-3)	**<0.001**	**0.001**
Fever (>38°C)	23 (42.6)	93 (57.4)	13 (8.0)	0.08	**<0.001**
Rhinorrhea	5 (9.3)	8 (4.9)	0 (0)	0.32	**<0.001**
Cough	9 (16.7)	100 (61.7)	1 (0.6)	**<0.001**	**<0.001**
Expectoration	4 (7.4)	16 (9.9)	1 (0.6)	0.79	**0.02**
Dyspnea	11 (20.4)	89 (54.9)	2 (1.2)	**<0.001**	**<0.001**
Anosmia	3 (5.6)	11 (6.8)	0 (0)	1.00	**0.02**
Dysgeusia	3 (4.9)	8 (4.9)	0 (0)	1.00	**0.02**
Chest pain	4 (7.4)	20 (12.3)	4 (2.5)	0.45	0.11
Abdominal pain	43 (79.6)	10 (6.2)	157 (96.9)	**<0.001**	**<0.001**
Vomiting	26 (48.1)	9 (5.6)	98 (60.5)	**<0.001**	0.12
Diarrhea	6 (11.1)	32 (19.8)	16 (9.9)	0.22	0.80
Signs at ED arrival [median (IQR)]					
Temperature (°C)	36.5 (36.0-37.5)	36.6 (36.0-37.3)	36.1 (36.0-36.5)	0.64	**0.004**
Systolic blood pressure (mmHg)	132 (108-150)	126 (115-140)	135 (118-151)	0.61	0.22
Heart rate (bpm)	87 (77-94)	89 (79-98)	79 (70-92)	0.30	**0.03**
Respiratory rate (bpm)	18 (15-20)	18 (16-22)	16 (14-19)	0.05	0.27
Room air pulsioxymetry (%)	96 (95-98)	96 (93-98)	97 (96-98)	0.22	**0.04**

(Continues)

TABLE 1 (Continued)

	Cases (COVID and AP) N = 54 n (%)	Control group A (COVID and non-AP) N = 162 n (%)	Control group B (non-COVID and AP) N = 162 n (%)	P-value*	P-value**
Laboratory findings [median (IQR)]					
Hemoglobin (g/L)	137 (119-146)	139 (130-148)	146 (132-157)	0.27	**0.002**
Leucocyte count (cells/μL)	9,200 (6700-14900)	6,700 (4500-8800)	10,800 (7700-14100)	**<0.001**	0.19
Lymphocyte count (cells/μL)	900 (600-1385)	1,140 (800-1715)	1,300 (900-1860)	**0.008**	**0.001**
Platelets (10^3cells/μL)	239 (181-317)	206 (158-269)	227 (183-271)	**0.02**	0.30
Protrombin time (seconds)	12.7 (12.1-14.7)	12.5 (11.7-13.7)	12.4 (11.2-14.2)	0.39	0.15
APTT (seconds)	30.3 (25.1-34.4)	29.3 (25.7-34.4)	28.3 (25.0-31.7)	0.99	0.13
Fibrinogen (mg/dL)	575 (500-660)	500 (422-664)	451 (372-543)	0.08	**<0.001**
D-dimer (ng/mL)	1,134 (520-3800)	629 (343-1270)	644 (343-1270)	**0.01**	0.26
C-reactive protein (mg/dL)	9.5 (2.5-17.8)	5.7 (1.7-10.9)	1.5 (0.4-8.4)	**0.02**	**<0.001**
Procalcitonin (ng/mL)	0.19 (0.06-3.00)	0.10 (0.06-0.15)	0.12 (0.05-0.76)	**0.03**	0.55
Lactate dehydrogenase (IU/L)	282 (198-435)	267 (201-357)	257 (192-396)	0.54	0.54
Creatinine (mg/dL)	1.0 (0.8-1.6)	0.8 (0.7-1.1)	0.9 (0.7-1.0)	**0.005**	**0.003**
Sodium (mmol/L)	138 (135-140)	139 (136-140)	139 (138-140)	0.23	0.18
Potassium (mmol/L)	4.0 (3.7-4.5)	4.1 (3.8-4.4)	4.0 (3.7-4.3)	0.41	0.69
Calcium (mg/dL)	8.8 (7.8-9.3)	8.7 (8.2-9.1)	8.7 (8.2-9.3)	0.68	0.51
Magnesium (mg/dL)	2.0 (1.7-2.2)	1.9 (1.8-2.0)	2.0 (1.8-2.1)	0.68	0.56
Aspartate animotransferase (IU/L)	57 (27-147)	31 (21-48)	96 (25-247)	**<0.001**	0.19
Alanine aminotransferase (IU/L)	64 (25-193)	25 (17-35)	66 (25-261)	**<0.001**	0.73
Bilirubin (mg/dL)	1.0 (0.5-4.1)	0.5 (0.4-0.7)	1.1 (0.5-2.4)	**<0.001**	0.75
Alkaline phosphatase (IU/L)	132 (73-270)	69 (54-110)	111 (82-151)	**<0.001**	0.30
Amylase (IU/L)	363 (134-1144)	62 (48-65)	959 (265-2467)	**0.003**	**0.006**
Lipase (IU/L)	945 (149-2466)	-	1811 (290-6845)	-	**0.008**
Chest X-ray	N = 51	N = 157	N = 113		
Cardiomegaly	5 (10.4)	11 (7.1)	9 (8.5)	0.54	0.77
Interstitial lung infiltrates	13 (25.5)	71 (45.2)	2 (1.8)	**0.01**	**<0.001**
Ground-glass lung opacities	20 (39.2)	89 (56.7)	3 (2.7)	**0.04**	**<0.001**
Pleura effusion	8 (16.7)	6 (3.8)	2 (1.8)	**0.005**	**0.001**

Note: Abbreviations: AP, acute pancreatitis; APTT, activated partial thromboplastin time; ED, emergency department.

Bold *P* values denote statistical significance ($P < 0.05$).

**P* values refer to comparison between cases and control A group.

***P* values refer to comparison between cases and control B group.

10-fold greater with respect to COVID patients without acute pancreatitis (ORs of 59, 16 and 32, respectively). Similarly, chest X-ray findings such as lung interstitial infiltrates, parenchymal glass-ground opacities and pleural effusion were extremely increased (ORs of 24, 19 and 11, respectively). As expected, abnormalities in hepatic and biliary blood tests were also more frequently present among cases than in patients in control group B. Remarkably, some inflammatory markers (CRP, procalcitonine, platelets, D-dimer) as well as pleural effusion (OR of 5) were also more frequently seen in cases than in control A patients. Conversely, cases less frequently presented cough and dyspnea. Finally, acute pancreatitis was also found to be associated with male sex and hypertension, dyslipidemia, diabetes mellitus and active cancer as comorbidities.

On the other hand, compared to non-COVID patients with acute pancreatitis (control group B patients), the most

TABLE 2 Specific clinical data, imaging and endoscopic findings, and final etiologic diagnosis in patients with acute pancreatitis, comparing those with (cases) and without (control group B) COVID-19

	Cases (COVID and AP) N = 54 n (%)	Control group B (non-COVID and AP) N = 162 n (%)	P-value
Risk factors			
Chronic alcoholism	4 (7.4)	33 (20.4)	**0.03**
Ex-alcoholism	5 (9.3)	10 (6.2)	0.44
Previous episodes of acute pancreatitis	11 (20.4)	51 (31.5)	0.12
Severity of the episode of acute pancreatitis			
BISAP score (points) [median (IQR)]	2 (2-3)	2 (1-3)	**0.008**
0 points	6 (11.1)	23 (14.2)	
1 point	12 (22.2)	55 (34.0)	
2 points	17 (31.5)	60 (37.0)	
>2 points	19 (35.2)	24 (14.8)	
SOFA score (points) [median (IQR)]	3 (1-4)	1 (1-3)	**0.005**
0 points	7 (13.0)	27 (16.7)	
1 point	9 (16.7)	61 (37.7)	
2 points	10 (18.5)	15 (9.3)	
>3 points	28 (51.9)	59 (34.6)	
Imaging technique used in the emergency department			
Ultrasonography	12 (22.2)	106 (65.4)	**<0.001**
Computerized tomography	33 (61.1)	75 (46.3)	0.08
Both	5 (9.3)	44 (27.2)	**0.008**
Any of them	40 (74.1)	137 (84.6)	0.10
Main imaging findings in gastroscopy	N = 40	N = 137	
Gallstones	5 (12.5)	35 (25.5)	0.09
Common bile duct enlargement and/or choledocholithiasis	4 (10.0)	12 (8.8)	0.76
Pancreatic edema, inflammation, collections or Wirsung duct dilatation supporting diagnosis of acute pancreatitis on imaging	24 (60.0)	76 (55.5)	0.72
Endoscopic retrograde cholangiopancreatography (plus sphincterotomy)	3 (5.6)	11 (6.8)	1.00
Final etiological diagnosis of the episode of acute pancreatitis			
Biliary	26 (48.1)	90 (55.6)	0.35
Alcoholic	2 (3.7)	19 (11.7)	0.11
Neoplassia	4 (7.4)	3 (1.9)	0.07
Chronic pancreatitis (acute exacerbation)	1 (1.9)	5 (3.1)	0.59
Pharmacological	2 (3.7)	3 (1.9)	0.60
Infectious	3 (5.6)	1 (0.6)	0.05
Hypertriglyceridemia	1 (1.9)	2 (1.2)	1.00
Iatrogenic	0 (0)	2 (1.2)	0.41
Anatomic abnormalities	0 (0)	1 (0.6)	0.56
Unknown/Unreported	15 (27.8)	36 (22.2)	0.52

Abbreviations: AP, acute pancreatitis.

Bold *P* values denote statistical significance ($P < 0.05$).

distinctive findings in COVID patients with acute pancreatitis were the presence of the symptoms of COVID infection: fever, cough, expectoration, dyspnea, dysgeusia and anosmia, with ORs over 10-fold higher (ORs of 14, 32, 13, 21, 22 and 22, respectively, Table 3). They were also more frequently male and, remarkably, the complaint

TABLE 3 Magnitude of statistically significant associations found in the unadjusted analysis

	Odds ratio (95% confidence interval)
Risk factors for the development of acute pancreatitis in COVID patients (compared to COVID patients not developing acute pancreatitis)	
Abdominal pain	59.4 (23.7-149)
Amylase > 140 IU/L	31.8 (1.60-632)
Vomiting	15.8 (6.69-37.2)
Chronic kidney disease	8.03 (2.65-24.4)
Alkaline phosphatase > 150 IU/L	7.61 (2.57-22.5)
Bilirubin > 1 mg/dL	6.27 (2.77-14.2)
Alanine aminotransferase > 40 IU/L	6.22 (3.06-12.7)
Leucocytes > 10 000 cells/μL	5.56 (2.65-11.7)
Pleural effusion in chest X-ray	5.00 (1.64-15.2)
Creatinine > 1.3 mg/dL	3.85 (1.78-8.33)
Aspartate aminotransferase > 40 IU/L	3.21 (1.57-5.56)
Active cancer	3.11 (1.37-7.05)
Hypertension	2.48 (1.31-4.71)
Dyslipidemia	2.45 (1.30-4.60)
Male sex	2.36 (1.21-4.61)
Diabetes mellitus	2.32 (1.11-4.88)
Lymphocytes < 1,000 cells/ μL	2.07 (1.07-3.99)
Platelets > 300 000 elements/μL	2.07 (0.95-4.52)
Procalcitonin > 0.1 ng/mL	1.99 (0.82-4.80)
D-dimer > 1,000 ng/mL	1.98 (0.93-4.20)
C-reactive protein > 5 mg/dL	1.85 (0.94-3.64)
Lung parenchymal glass-ground opacities in chest X-ray	0.49 (0.26-0.94)
Lung interstitial infiltrates in chest X-ray	0.41 (0.21-0.84)
Symptoms lasting > 7 days	0.32 (0.15-0.71)
Dyspnea	0.21 (0.10-0.44)
Cough	0.12 (0.06-0.27)
Distinctive clinical characteristics of acute pancreatitis in COVID patients (respect to acute pancreatitis in non-COVID patients)	
Cough	32.1 (3.97-261)
Lung interstitial infiltrates in chest X-ray	23.7 (6.60-84.5)
Dysgeusia	22.1 (1.12-435)
Anosmia	22.1 (1.12-435)
Dyspnea	20.5 (4.37-95.8)
Lung parenchymal glass-ground opacities in chest X-ray	19.0 (4.10-88.0)
Fever (>38ºC)	14.3 (5.85-34.9)
Expectoration	12.9 (1.41-118)
Pleural effusion in chest X-ray	10.7 (2.18-52.5)
Dementia	9.47 (0.96-93.1)
Chronic obstructive pulmonary disease	5.66 (2.07-15.5)
C-reactive protein > 5 mg/dL	4.87 (2.44-9.72)
Fibrinogen > 500 mg/dL	4.70 (1.73-12.8)
Creatinine > 1.3 mg/dL	4.41 (2.02-9.60)
Active cancer	2.89 (1.29-6.50)
Symptoms lasting > 7 days	2.75 (1.07-7.04)
Chronic kidney disease	2.70 (1.15-6.39)
Hemoglobin < 120 g/L	2.44 (1.13-5.24)
Lymphocytes < 1,000 cells/ μL	2.43 (1.26-4.69)
Male sex	2.02 (1.04-3.97)
Lipase > 1,000 IU/L	0.62 (0.27-1.44)
Amylase > 1,000 IU/L	0.34 (0.15-0.78)
Abdominal pain	0.12 (0.04-0.38)

of abdominal pain was not as frequent in COVID patients with acute pancreatitis as in non-COVID patients (OR of 0.12) and neither were blood amylase concentrations over 1,000 IU/L (ORs of 0.34).

COVID patients with acute pancreatitis were hospitalized in 96% of cases; 9% were admitted to the ICU at some point during hospital stay, 53% experienced prolonged hospitalization (>7 days) and 17% died during hospital stay. With respect to COVID patients without acute pancreatitis, and after adjustment for age and sex, the only outcome that was statistically different was hospitalization (OR = 7.94, 95% CI = 1.72-36.7), while in-hospital mortality was very similar (OR = 1.12, 95% CI = 0.45-2.79) (Figure 2). Similar findings were found in sensitivity analysis A comparing 40 cases and 120 control A patients; as well as in sensitivity analysis B comparing 48 pairs of matched individuals (Figure 3). On the other hand, compared to non-COVID patients with acute pancreatitis, cases more frequently had prolonged hospitalization (OR = 1.71, 95% CI = 1.21-2.42) and a higher risk of in-hospital mortality (OR = 2.46, 95% CI = 1.35-4.48) (Figure 2). Sensitivity analysis A comparing 40 cases with 162 control B patients reported significant differences in the same outcomes (prolonged hospitalization and mortality), while sensitivity analysis B comparing 45 pairs of matched individuals, despite providing outcome estimations similar to those found in the main analysis, such differences did not reach statistical significance due to a wider 95% confidence interval (Figure 3).

4 | DISCUSSION

We found that around 0.75‰ of COVID patients coming to the ED were concomitantly diagnosed with acute pancreatitis. This frequency, found during a 2-month period of the COVID outbreak in Spain, should be considered as low compared with both the frequency observed in non-COVID patients coming to the ED found in the present study (around 1.5‰) and the annual incidence reported in the general population in the United States (up to 0.35‰)[17]. Remarkably, our study did not include cases of acute pancreatitis appearing after the initiation of antibiotics or antiviral drugs, a circumstance that could increase the risk due to drug-related adverse events. Therefore, the decreased OR of 0.44 for COVID patients found in the UMC-19-S_6 suggests that pancreas may not be a target for direct SARS-CoV-2 tropism or indirect viral-induced damage due to inflammatory or for immunological response generated by the virus. Interestingly, our results are in agreement with a very recent study performed in patients hospitalized in 12 New York hospitals during the COVID pandemic also found a decreased OR of 0.62 (95% CI = 0.42-0.91) for acute pancreatitis in COVID patients (32 acute pancreatitis among 11 883 hospitalizations) respect to non-COVID patients (157 acute pancreatitis among 36 129 hospitalizations).[18]

Some predisposing factors were found in previous cases of acute pancreatitis reported in COVID patients.[7–10] Two of three first-line family members admitted to an ICU in Denmark developed severe acute pancreatitis, suggesting a genetic predisposition to pancreatic involvement in COVID patients.[7] Morrison *et al*. reported two cases of hypertriglyceridemia secondary to tocilizumab used to treat SARS-CoV-2 infection in the US; one case had elevated biomarkers consistent with pancreatitis.[10] In another two cases of acute pancreatitis reported separately, the temporal relationship with COVID-19 and the lack of other etiologies suggest coronavirus-induced pancreatitis.[8,9] The presence of angiotensin-converting enzyme-2 (ACE-2) receptors in pancreatic islet cells has been suggested as a potential link, since part of the pathogenesis of COVID-19 is thought to be mediated by such receptors.[9,19] According to this hypothesis, acute pancreatitis in COVID-19 could be directly due to the cytopathic effect of local SARS-CoV-2 replication or indirectly due to harmful immune response induced by the virus. Nevertheless, if this mechanism really exists, one would expect the frequency of acute pancreatitis to be increased in COVID patients compared to the general population, and in the present study this increased incidence was not found.

COVID patients developing acute pancreatitis differed from the remaining COVID patients in that the differences in their data were more related to acute pancreatitis than to COVID infection. Abdominal pain and vomiting are two signatures of acute pancreatitis, but these manifestations can be present in up to 17% of COVID patients.[16] This could lead to the misdiagnosis of acute pancreatitis in patients with a mild rise in enzyme levels and digestive symptoms derived from the COVID infection itself. Our patients fulfilled at least two out of the three criteria internationally accepted for the diagnosis of acute pancreatitis.[13,14] Remarkably, our COVID patients with acute pancreatitis had a higher increase in inflammatory markers (CRP, procalcitonin, platelets, D-dimer) than those without acute pancreatitis. The significance of these findings is unknown and merits further studies to elucidate if they imply any connection between inflammatory activity in COVID patients and pancreas involvement. The presence of pleural effusion in chest X-ray, barely seen in COVID-19, could be an additional red flag when abdominal pain is present in these patients.

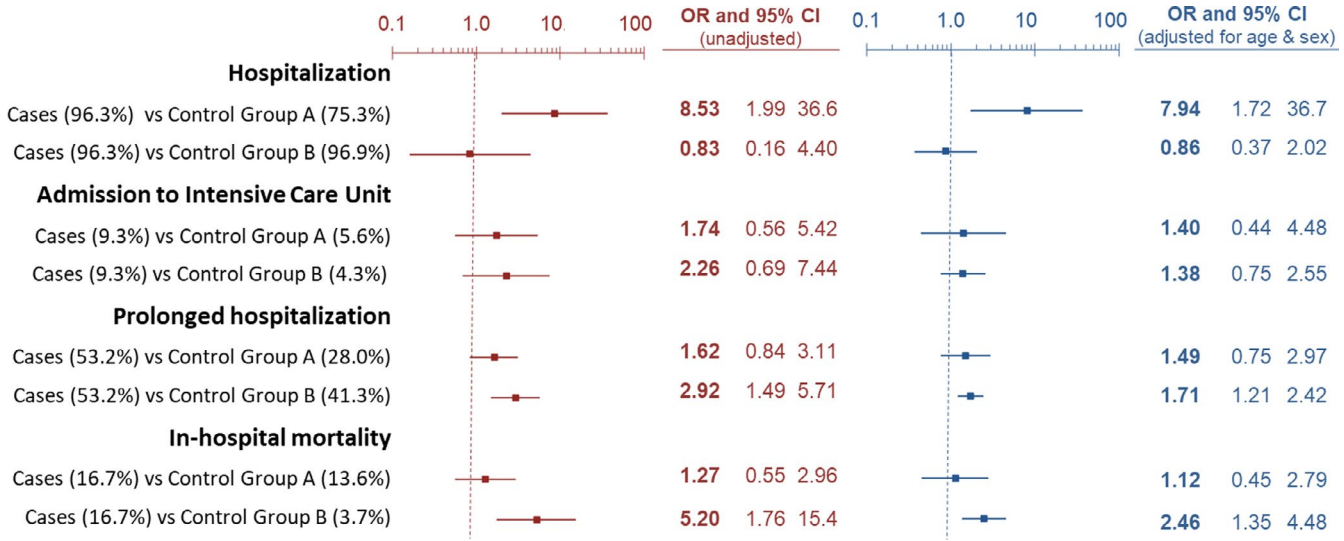

FIGURE 2 Outcomes of patients with COVID-19 and acute pancreatitis compared with controls

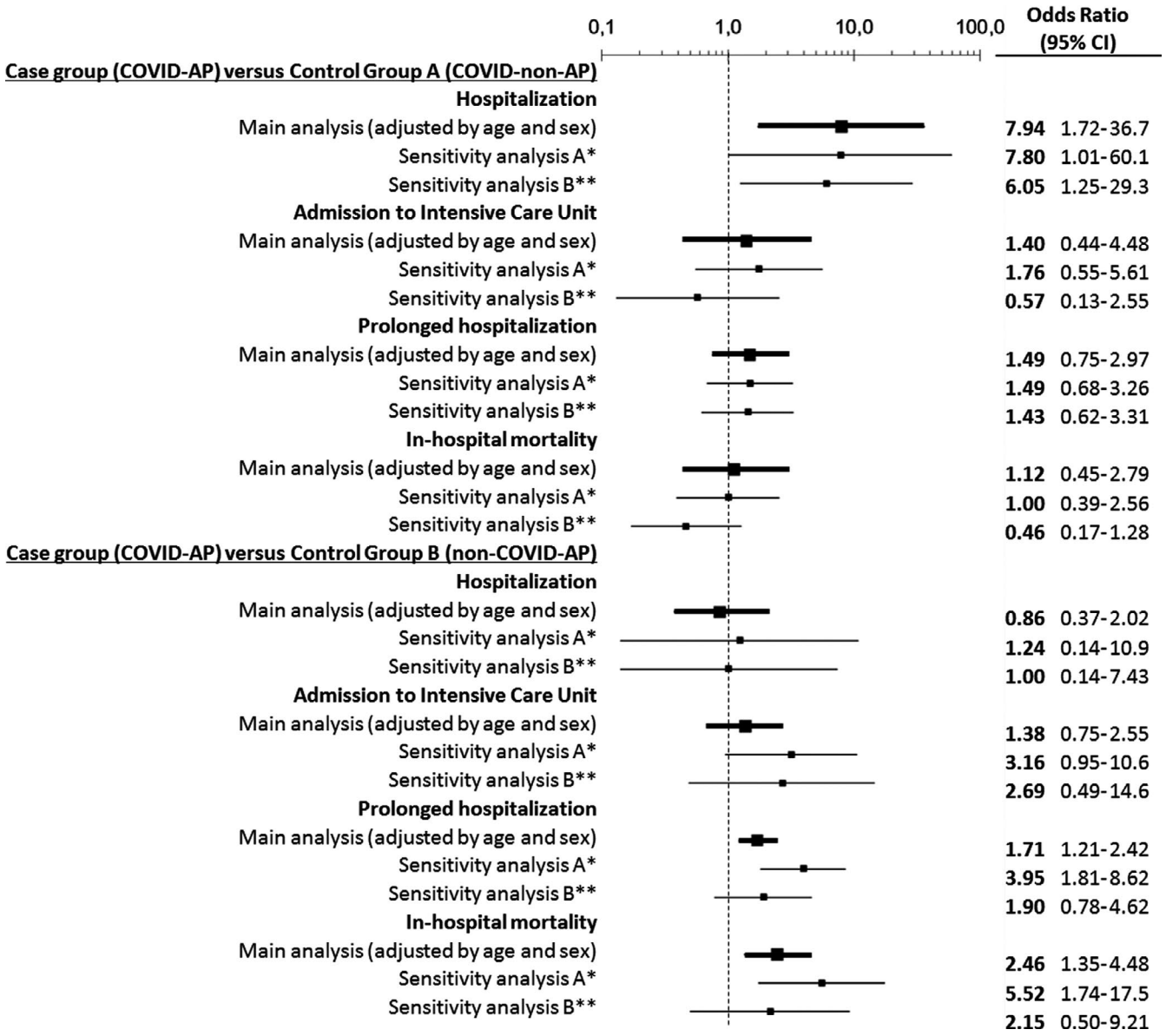

FIGURE 3 Outcomes of patients with COVID-19 and acute pancreatitis compared with controls estimated in the main analysis (adjusted by age and sex) and in the sensitivity analysis A and B. *Sensitivity analysis A consisted of only using COVID patients (in case and control A groups) with COVID diagnosis confirmed by reverse transcriptase polymerase chain reaction to detect SARS-CoV-2 RNA. **Sensitivity analysis B consisted of comparing pairs of cases and controls matched by propensity score. Propensity score for cases and control A patients matching was obtained using age as covariate and sex, hypertension, dyslipemia, diabetes mellitus, active cancer and chronic kidney disease as factors and rendered 48 pairs of matched cases:control A patients. Propensity score for cases and control B patients matching was obtained using age and BISAP score as covariates and sex, active cancer, chronic kidney disease, chronic obstructive pulmonary disease and dementia as factors and rendered 45 pairs of matched cases:control B patients. AP, acute pancreatitis

The clinical characteristics of acute pancreatitis in COVID patients differed from those of acute pancreatitis in non-COVID patients in relation to many baseline, clinical and analytical data, with most of these characteristics depending on the presence of SARS-CoV-2 infection. Of note, increases in amylase and lipase levels were more moderate and abdominal pain was less frequent in COVID patients with acute pancreatitis which may make it more difficult to diagnose acute pancreatitis in these patients than in the general population. Thus, a high degree of suspicion is recommended in EDs. On the other hand, although we did not explore the potential effect of patient race, results from the Inamdar et al. study suggest that Black and Hispanic races are more represented in acute pancreatitis developed in COVID patients than in acute pancreatitis developed in non-COVID patients.[18]

COVID patients with acute pancreatitis showed similar outcomes to those of the rest of COVID patients, with the exception that the former more frequently need hospitalization. However, in-hospital mortality did not significantly differ.

On the other hand, there was a clear increment of mortality in these patients with respect to acute pancreatitis in non-COVID patients. Probably, part of this increment in in-hospital mortality is in relation to the severity of the viral infection because, as a general rule, mortality rates between 10% and 20% have been reported in hospitalized COVID patients.[20–22] Nonetheless, we have identified that severity of the current episode of acute pancreatitis, assessed by two different scores when a patient arrived at ED, seems to be higher in COVID patients, and therefore, acute pancreatitis itself could be contributing, to some extent, to the worse prognosis observed in acute pancreatitis developed by COVID patients in respect to non-COVID patients.

4.1 | Limitations

This study has several limitations. First, as abdominal pain and vomiting can be seen as constitutive symptoms of COVID-19, some cases of mild, paucisymptomatic acute pancreatitis could have remained undiagnosed if pancreatic enzyme determination was not ordered. Second, we did not adjust the incidence of acute pancreatitis in COVID for all relevant patient-related or disease-related factors influencing the relative frequency of acute pancreatitis presentation and outcomes, and this could somewhat alter the estimations presented in the current study. Third, in around one quarter of COVID-19 patients the diagnosis was based exclusively on clinical and/or radiological findings, with no microbiological confirmation. This was due to a shortage of diagnostic tests during the first pandemic surge in Spain.[23] We have tried to cover this gap by repeating the outcome analysis using only cases and control A patients with SARS-CoV-2 infection confirmed by RT-PCR, and such analysis (the sensitivity analysis A) rendered the same significant associations as the main analysis. Fourth, as a retrospective study, although the case record form was standardized, there was no monitoring of data collection methods, and diagnosis and outcome adjudication were done locally. Fifth, the UMC-19-S_6 was designed to randomly select patients for control groups A and B no planned matching for any patient characteristic. Therefore, as we did not balance any potential confounder in the study design, our study design produced groups that diverged in many baseline characteristics. Although the sensitivity analysis B tried to overcome this limitation and obtained similar estimations as those found in the main analysis, we cannot rule out that a different design could modify, to some extent, our findings. Finally, in depth analysis of the severity of acute pancreatitis in patients with COVID was not performed and we were not able to identify the real role of acute pancreatitis in the increment of in-hospital mortality observed when it is developed by COVID patients respect to non-COVID patients.

5 | CONCLUSIONS

Despite these limitations, we conclude that the incidence of acute pancreatitis in COVID patients attending the ED is low and less than expected in the general population (non-COVID patients) attending the ED. A high degree of suspicion of acute pancreatitis must be considered in COVID patients, as they can present abdominal pain and vomiting as a mere consequence of viral infection while, on the other hand, these symptoms of pancreatic inflammation may not be as evident as in non-COVID patients. At the time of patient arrival to ED, severity of acute pancreatitis seems to be higher in COVID than in non-COVID patients, although the role of this finding in the increased mortality found in the former group in respect to the latter group is not determined by the present study. On the other hand, the development of acute pancreatitis in COVID patients is not associated with a higher mortality.

CONFLICT OF INTEREST

No author reports any conflict of interest directly or indirectly connected with this manuscript.

AUTHOR CONTRIBUTION

All the authors discussed the idea and design of study and provided patients. Data analysis and first draft writing was done by OM. All the authors have read this draft and provided insight for the final version. OM is the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to publication of the article.

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APPENDIX 1

The SIESTA network is formed by the following researchers and centers (all from Spain)

Steering Committee: Òscar Miró, Sònia Jiménez (Hospital Clínic, Barcelona), Juan González del Castillo, Francisco Javier Martín-Sánchez (Hospital Clínico San Carlos, Madrid), Pere Llorens (Hospital General de Alicante), Guillermo Burillo-Putze (Hospital Universitario de Canarias, Tenerife), Alfonso Martín (Hospital Universitario Severo Ochoa de Leganés, Madrid), Pascual Piñera Salmerón (Hospital General Universitario Reina Sofía, Murcia), E. Jorge García Lamberechts (Hospital Clínico San Carlos, Madrid), Javier Jacob (Hospital Universitario de Bellvitge, L'Hospitalet de Llobregat, Barcelona), Aitor Alquézar-Arbé (Hospital de la Santa Creu i Sant Pau, Barcelona).

Participating centers:

1. Hospital Universitario Doctor Peset Aleixandre de Valencia: María Luisa López Grima, Mª Ángeles Juan Gómez.

2. Hospital Universitario y Politécnico La Fe de Valencia: Javier Millán, Leticia Serrano Lázaro.

3. Hospital Universitario General de Alicante: Begoña Espinosa, Francisca Molina

4. Hospital Clínico Universitario de Valencia: José Noceda.

5. Hospital Arnau de Vilanova de Valencia: María José Cano Cano, Rosa Sorando Serra.

6. Hospital Francesc de Borja de Gandía, Valencia: María José FortunyBayarri, Francisco José Salvador Suárez.

7. Hospital General Universitario de Elche, Alicante: Matilde González Tejera.

8. Hospital Marina Baixa de Villajoyosa de Alicante: Andrea Estrada Herrera, Eduardo Lorenzo Garrido

9. Hospital Virgen de los Lirios, Alcoy Alicante: Patricia Borrás Albero.

10. Hospital Universitario Vinalopó de Elche (Alicante): Julio Armas Castro, Esther Ruescas Escolano

11. Hospital Universitario de Torrevieja de Alicante: Alexandra MilanMestre, Fernando Lajara Navarro

12. Hospital LluisAlcanys de Xativa: Carles Pérez García, Pilar Sánchez Amador.

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16. Hospital General de Requena de Valencia: Veronica de Los Santos, Carol Cuenca Valero.

17. Hospital de Lliria de Valencia: Ana Peiró Gómez, Elena Gonzalo Bellver.

18. Hospital de la Santa Creu i Sant Pau (Barcelona): Elena Avellana Pardina, Mar Soler Ferrer

19. Hospital Clinic (Barcelona): Carlos Cardozo.

20. Hospital Universitari de Bellvitge de Hospitalet de Llobregat (Barcelona): Alejandro Roset-Rigat, Irene Cabello-Zamora.

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25. Hospital Universitari de Girona Dr. Josep Trueta (Girona): MariaAdroher Muñoz, Ester Soy Ferrer.

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29. Hospital Clínico San Carlos (Madrid): Marcos Fragiel.

30. Hospital Universitario La Paz (Madrid): Elena Muñoz del Val, CharbelMarounEid

31. Hospital Universitario de la Princesa (Madrid): Carmen del Arco Galán, Guillermo Fernández Jiménez .

32. Hospital Universitario Severo Ochoa de Leganés (Madrid): Raquel Torres Gárate, Beatriz Valle Borrego

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38. Clínica Universidad Navarra de Madrid: Nieves López Laguna, María García-Uría.

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40. Complejo Asistencial Universitario de León: Begoña Carmona Ayuela, Mercedes Matias Flecha.

41. Hospital Universitario de Burgos: María Pilar López Díez.

42. Hospital Universitario Rio Hortega (Valladolid): Patricia Bustamante Marcos, Henar Bergaz Díez.

43. Complejo Asistencial de Soria: FadhBeddarChaib, Jorge Pablo Viscarra Gambarte.

44. Hospital Universitario Regional de Málaga: Manuel Salido, Miguel Moreno Fernández.

45. Hospital Universitario Juan Ramón Jiménez: María Ángeles Garrido López, Setefilla Borne Jérez.

46. Hospital Costa del Sol de Marbella: Carmen Agüera Urbano, Ana BelenGarcia Soto.

47. Hospital Valle de los Pedroches de Pozoblanco (Córdoba): Jorge Pedraza García.

48. Hospital Virgen del Rocío de Sevilla: Amparo Fernández de Simón Almela.

49. Complejo Hospitalario Universitario de A Coruña: Ricardo Calvo López.

50. Hospital Universitario LucusAugusti Lugo: Juan José López Díaz.

51. Complejo Hospitalario Universitario de Vigo. Hospital Álvaro Cunqueiro: María Teresa Maza Vera, Raquel Rodríguez Calveiro.

52. Hospital Universitario General de Albacete: Francisco Javier Lucas-Galan, María Ruiperez Moreno.

53. Hospital Virgen de la Luz (Cuenca): Félix González Martínez, Diana Moya Olmeda.

54. Hospital Nuestra Señora del Prado de Talavera de la Reina (Toledo): Ricardo Juárez.

55. Hospital Universitario de Canarias (Tenerife): Marcos ExpositoRodriguez, José Francisco Fernández Rodríguez.

56. Hospital Universitario de Gran Canaria Dr. Negrín: José Pavón Monzo, Nayra Cabrera González.

57. Hospital Universitario Central Asturias: Desire María Velarde Herrera, Beatriz María Martínez Bautista.

58. Hospital Universitario de Cabueñes (Gijón): Ana Patricia Niembro Valdés, Ana Murcia Olagüenaga.

59. Hospital Clínico Universitario Virgen de la Arrixaca: Eva Quero Motto, Nuria Tomas García.

60. Hospital General Universitario Reina Sofía de Murcia: Paula Lázaro Aragües, Pedro Alarcón Martínez.

61. Hospital San Pedro de Logroño: Noemí Ruiz de Lobera.

62. Hospital Clínico Universitario Lozano Blesa: José María Ferreras Amez, Belén Arribas Entrala.