

# COVID-19 and Acute Pancreatitis: A Systematic Review of Case Reports and Case Series

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**BACKGROUND:** Coronavirus disease 2019 (COVID-19) presents mainly with mild symptoms and involvement of the respiratory system. Acute pancreatitis has also been reported during the course of COVID-19.

**OBJECTIVE:** Our aim is to review and analyze all reported cases of COVID-19 associated acute pancreatitis, reporting the demographics, clinical characteristics, laboratory and imaging findings, comorbidities and outcomes.

**DATA SOURCES:** We conducted a systematic search of Pubmed/MEDLINE, SciELO and Google Scholar to identify case reports and case series, reporting COVID-19 associated acute pancreatitis in adults.

**STUDY SELECTION:** There were no ethnicity, gender or language restrictions. The following terms were searched in combination: "COVID-19" OR "SARS-CoV-2" OR "Coronavirus 19" AND "Pancreatic Inflammation" OR "Pancreatitis" OR "Pancreatic Injury" OR "Pancreatic Disease" OR "Pancreatic Damage". Case reports and case series describing COVID-19 associated acute pancreatitis in adults were included. COVID-19 infection was established with testing of nasal and throat swabs using reverse transcription polymerase chain reaction. The diagnosis of acute pancreatitis was confirmed in accordance to the revised criteria of Atlanta classification of the Acute Pancreatitis Classification Working Group. Exclusion of other causes of acute pancreatitis was also required for the selection of the cases.

**DATA EXTRACTION:** The following data were extracted from each report: the first author, year of publication, age of the patient, gender, gastrointestinal symptoms due to acute pancreatitis, respiratory-general symptoms, COVID-19 severity, underlying diseases, laboratory findings, imaging features and outcome.

**DATA SYNTHESIS:** Finally, we identified and analyzed 31 articles (30 case reports and 1 case series of 2 cases), which included 32 cases of COVID-19 induced acute pancreatitis.

**CONCLUSION:** COVID-19 associated acute pancreatitis affected mostly females. The median age of the patients was 53.5 years. Concerning laboratory findings, lipase and amylase were greater than three times the ULN while WBC counts and CRP were elevated in the most of the cases. The most frequent gastrointestinal, respiratory and general symptom was abdominal pain, dyspnea and fever, respectively.

The most common imaging feature was acute interstitial edematous pancreatitis and the most frequent comorbidity was arterial hypertension while several patients had no medical history. The outcome was favorable despite the fact that most of the patients experienced severe and critical illness.

**LIMITATIONS:** Our results are limited by the quality and extent of the data in the reports. More specifically, case series and case reports are unchecked, and while they can recommend hypotheses they are not able to confirm robust associations.

**CONFLICT OF INTEREST:** None

Acute pancreatitis is the leading cause of hospital admission for disorders of the gastrointestinal tract in several countries.<sup>1</sup> Gallstones and alcohol overconsumption are well-established risk factors. Other factors, possibly genetic, probably have a role. Drugs are an additional causative factor of acute pancreatitis. Moreover, smoking and diabetes type II increase the probability of acute pancreatitis development.

Mild cases are generally successfully managed with a conservative approach. Severe cases frequently need admission to an intensive care unit for monitoring and managing complications of the disease, which are related to high rates of mortality, even when the treatment is optimal.<sup>2</sup>

Approximately 10% of cases of acute pancreatitis are considered to have infectious microorganisms as an underlying cause.<sup>3</sup> These microorganisms include viruses (like Coxsackie B and hepatitis), bacteria (like *Mycoplasma pneumonia* and *Leptospira*), and parasites (like *Ascaris lumbricoides* and *Fasciola hepatica*). Each microorganism leads to acute pancreatitis through various mechanisms.<sup>3</sup> Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly worldwide and is characterized by the World Health Organization as an international public health emergency. Besides typical symptoms and signs from respiratory system, acute pancreatitis has been reported during the course of the disease.<sup>4</sup>

COVID-19 associated pancreatic inflammation results from the expression of angiotensin converting enzyme 2 (ACE2) receptors in pancreatic tissue. The structural protein glycosylated-spike (S) protein, encoded by SARS-CoV-2 genome, primarily induces the immune response of the host. The S protein binds to ACE2 receptor sites on the cell surface membrane mediating the cell invasion. ACE2 receptors are not only expressed

in lung alveolar type-2 cells. ACE2 receptors are expressed in the pancreas, in both exocrine glands and islets, in a higher grade than in the lungs.<sup>5,6</sup> This expression of ACE2 receptors can lead to pancreatic cell damage during COVID-19 infection. Direct cytotoxic action of SARS-CoV-2 or indirect, immune-mediated, systemic inflammation could be the mechanism of pathogenesis for pancreatic injury.<sup>5,6</sup>

Globally, the incidence of acute pancreatitis ranges between 5 and 80 per 100000 population, with the highest incidence observed in the United States and Finland.<sup>7</sup> The incidence of SARS-CoV-2 infection varies among regions. Cyprus has the highest incidence of COVID-19 cases among its population in Europe at 55424 per 100000 people, followed by a rate of 52738 per 100000 in Iceland.<sup>8</sup> In United States the incidence ranges between 2698 cases per 100000 population in Hawaii and 14541 cases per 100000 population in North Dakota.<sup>8</sup> In this study, we aimed to review and analyze all reported cases of COVID-19 associated acute pancreatitis, reporting the demographics, clinical characteristics, laboratory and imaging findings, comorbidities and outcomes.

## CASES AND METHODS

### *Search strategy and article selection*

We conducted a systematic search of Pubmed/MEDLINE, SciELO and Google Scholar to identify case reports and case series, reporting COVID-19 associated acute pancreatitis in adults, using the Patient, Intervention, Comparison and Outcome (PICO) Model.<sup>9</sup> There were no ethnicity or gender restrictions. In addition, there were no language restrictions. We assessed all articles published from 01 January 2020 to 20 April 2021. A protocol of the study, including details of the methods used in the systematic review has been deposited in the PROSPERO database (<https://www.crd>).

york.ac.uk/PROSPERO/) with the registration number CRD42021266917.

The following terms were searched in combination: "COVID-19" OR "SARS-CoV-2" OR "Coronavirus 19" AND "Pancreatic Inflammation" OR "Pancreatitis" OR "Pancreatic Injury" OR "Pancreatic Disease" OR "Pancreatic Damage". The search was conducted by two reviewers (VEG, CD). Articles were first screened for relevance by title. Then they were evaluated by abstract. The relevant case reports were enrolled for full-text review. Moreover, a manual search of the lists of the references of these texts was performed for identifying additional relevant case reports and case series.

Case reports and case series describing COVID-19 associated acute pancreatitis in adults were included. COVID-19 infection was established with testing of nasal and throat swabs using reverse transcription polymerase chain reaction. The diagnosis of acute pancreatitis was confirmed in accordance to the revised criteria of the Atlanta Acute Pancreatitis Classification Working Group.<sup>10</sup> At least two of the following three criteria had to be present for a diagnosis of acute pancreatitis: a) typical pain of acute pancreatitis (acute onset of a severe and persistent epigastric pain often with radiation to the back) b) serum lipase or amylase elevated at least three times the upper limit of normal; c) compatible imaging findings of acute pancreatitis on abdominal computed tomography (CT), on magnetic resonance imaging (MRI) or abdominal ultrasonography (U/S).<sup>10</sup> Exclusion of other causes of acute pancreatitis was also required for the selection of the cases.

#### Data extraction

The following data were extracted from each report: the first author, year of publication, age of the patient, gender, gastrointestinal symptoms due to acute pancreatitis, respiratory-general symptoms, COVID-19 severity, underlying diseases, laboratory findings, imaging features and outcome. The tool suggested by Murad et al to assess the methodological quality and synthesis of the case series and case reports was utilized.<sup>11</sup> The possible best score was 6 for a case report or a case series of good quality. The patients represented the whole experience of the researchers, the diagnosis of SARS-CoV-2 and the outcomes were adequately ascertained; other causes of pancreatitis were excluded. The follow-up was long enough for outcomes to occur and the described cases had sufficient details to allow other researchers to replicate the findings. **Table 1** shows the use of the tool suggested by Murad et al in our review. In addition, we followed the PRISMA (Preferred

Reporting Items For Systematic Reviews And Meta-Analyses) guidelines for writing this review.<sup>12</sup>

The statistical analysis of data was performed with IBM SPSS for Windows, Version 13.0 (Armonk, New York, United States: IBM Corp). Continuous variables were tested for normality of distribution by the Kolmogorov-Smirnov test. For normally distributed values, descriptive results are presented as mean (standard deviation) and median while categorical variables are mentioned as numbers and percentages. The meta-regression analysis was performed using a random-effects model and stepwise selection of variables.<sup>13</sup> To determine if the findings affected the severity of COVID-19, we used a meta-regression analysis using the following equations:  $Severity1 = \beta_0 + \beta_1 * \log_1(lipase)$  and  $Severity2 = \beta_0 + \beta_1 * \log_2(amylase)$ .

## RESULTS

The systematic search identified 71 possibly relevant records after review of the title, abstract or full text screening, and after exclusion of duplicates (**Figure 1**). Forty records were excluded after careful screening of the titles and abstracts, since they did not mention COVID-19 associated with acute pancreatitis presented as case reports or case series. Finally, we identified 31 articles (30 case reports and 1 case series of 2 cases), which included 32 cases of COVID-19 induced acute pancreatitis (**Tables 2, 3, 4**).<sup>14-44</sup> Nineteen patients were females (59.4%) and 13 patients were males (40.6%). The median age was 53.5 years (range 20-76 years). The median age of the females was 52 years (range 20-76 years) (median 52) years and the median age of the males was 48 (24-68) years.

The majority of the patients had abdominal pain as clinical manifestation (28/32, 87.5%). Other gastrointestinal symptoms were nausea, vomiting, diarrhea, constipation, anorexia and lack of flatus, while 2 (6.3%) of the patients presented with no gastrointestinal symptoms. Twenty (62.5%) patients presented with dyspnea and 14 (43.8%) presented with cough. A majority of patients had fever (59.4%). Four (12.5%) patients had no respiratory or general symptoms, while 2 (6.3%) patients had no respiratory symptoms. According to classification into severity of illness categories by National Institutes of Health (NIH),<sup>45</sup> 8 (25%) patients had mild SARS-CoV-2 illness, 4 (12.5%) patients had moderate SARS-CoV-2 illness, 10 (31.2%) patients had severe SARS-CoV-2 illness and 10 (31.2%) patients had critical SARS-CoV-2 illness (**Table 4**).

The data on serum amylase levels in 27 patients was over three times the upper limit of normal (ULN), while the rest had amylase levels less than three times of ULN.

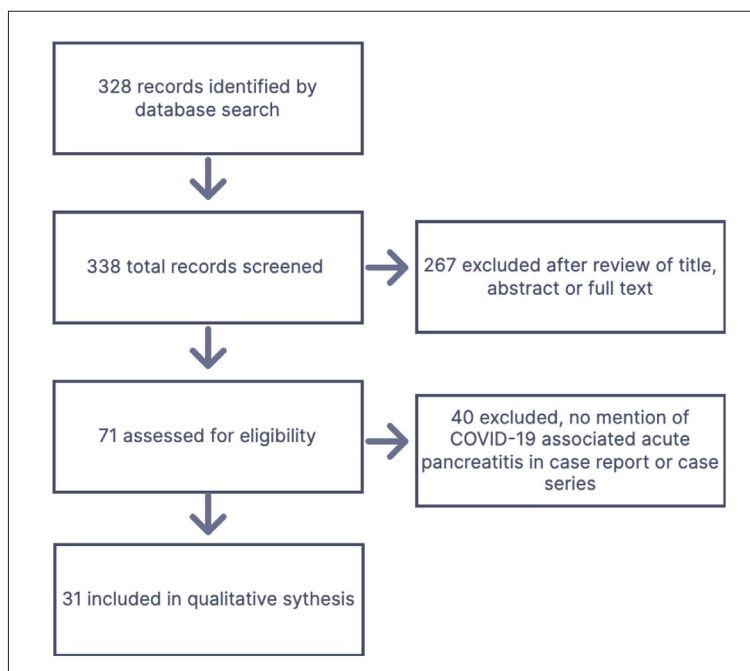
**Table 1.** Tool for evaluating the methodological quality of case reports and case series of the current review suggested by Murad et al.<sup>11</sup>

Domains	Leading explanatory questions	Cases and cases series included in the current review	Score
Selection	1. Does the patient(s) represent(s) the whole experience of the investigator (center) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?	Yes	1
Ascertainment	2. Was the exposure adequately ascertained?	Yes	1
	3. Was the outcome adequately ascertained?	Yes	1
Causality	4. Were other alternative causes that may explain the observation ruled out?	Yes	1
	5. Was there a challenge/rechallenge phenomenon?	No	0
	6. Was there a dose–response effect?	No	0
Reporting	7. Was follow-up long enough for outcomes to occur?	Yes	1
	8. Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?	Yes	1
<b>Total Score</b>			<b>6</b>

Data about lipase levels were available in 22 patients. The majority of these patients (21/22, 95.5%) had lipase levels over three times of ULN while only 1 patient (1/22, 0.5%) had lipase levels less than three times of ULN. Data about white blood cells (WBC) count were available in 26 patients. Twelve patients (12/26, 46.2%) had elevated WBC count, 12 (46.2%) had WBC count with normal limits while 2 (7.6%) had decreased WBC count. Data on C-reactive protein were available in 20 patients. Eighteen patients (90%) had elevated levels of CRP while 2 (10%) had CRP levels within normal limits. Imaging data were available in 31 patients (**Table 4**). Twenty-one (67.8%) of the patients had abdominal CT or MRI features compatible with acute interstitial edematous pancreatitis. Medical history data were available in 31 patients. Arterial hypertension was most common, followed by diabetes mellitus, obesity, cholecystectomy and others. Two female patients were pregnant while 12 patients (38.5%) had no medical history.

Data on outcome were available in 30 cases. All these patients recovered (30/30, 100%). In two cases, the outcome was unknown because the article was published while patients were still hospitalized.

The meta-regression analysis included the 30 articles that presented full laboratory findings following development of acute pancreatitis (**Table 5**). The R value of



**Figure 1.** Flow diagram for study selection.

**Table 2.** Demographic and clinical characteristics including COVID-19 severity and outcome of patients with COVID-19-induced acute pancreatitis.

#	Author, Year	Age/ Gender	Medical history	Gastrointestinal manifestations	Respiratory- general symptoms	Severity of COVID-19	Outcome
1	Meyers, 2020 <sup>14</sup>	67/M	Arterial hypertension Cholecystectomy Alcohol use	Abdominal pain	Dyspnea Fever	Severe	Recovered
2	Karimzadeh, 2020 <sup>15</sup>	65/F	Arterial hypertension Asthma	Abdominal pain Nausea	Dyspnea Chills Myalgia	Severe	Recovered
3	Shinohara, 2020 <sup>16</sup>	58/M	Arterial hypertension	Abdominal pain	Dyspnea Fever	Critical	Recovered
4	Rabice, 2020 <sup>17</sup>	36/F	Pregnancy Diabetes mellitus Asthma Obesity	Abdominal pain Nausea Vomiting	Dry cough Fever Myalgia	Severe	Recovered
5	Meireles, 2020 <sup>18</sup>	36/F	Post-HELLP syndrome Stage V chronic kidney disease Arterial hypertension	Abdominal pain Nausea Vomiting	Dry cough Dyspnea Fever	Moderate	Recovered
6	Fernandes, 2020 <sup>19</sup>	36/F	No medical history	Abdominal pain	Dyspnea Fever Headache	Moderate	Recovered
7	Alwaeli, 2020 <sup>20</sup>	30/M	No medical history	Abdominal pain Nausea Vomiting Diarrhea	Dry cough Dyspnea Fever	Critical	Recovered
8	Narang, 2020 <sup>21</sup>	20/F	Pregnancy Obesity Cholecystectomy	Abdominal pain Nausea Vomiting	Dyspnea	Critical	Recovered
9	Kandasamy, 2020 <sup>22</sup>	45/F	No medical history	Abdominal pain Nausea Vomiting	Dyspnea	Severe	Recovered
10	Kumaran, 2020 <sup>23</sup>	67/F	Laparotomy and small bowel resection and anastomosis of superior mesenteric artery stenosis Arterial hypertension	Abdominal pain Diarrhea Vomiting	Dyspnea	Severe	Recovered
11	Acherjya, 2020 <sup>24</sup>	57/F	Arterial hypertension Diabetes mellitus Active malignancy of breast and larynx	Abdominal pain Vomiting	No respiratory symptoms Fever Generalized body ache Loss of smell Fatigue Arthralgia	Severe	Recovered
12	Bokhari, 2020 <sup>25</sup>	32/M	No medical history	Abdominal pain Vomiting	Productive cough Fever Myalgia	Mild	Recovered
13	Mazrouei, 2020 <sup>26</sup>	24/M	N/A	Abdominal pain Nausea Vomiting	No respiratory- other symptoms	Mild	Recovered
14	Patnaik, 2020 <sup>27</sup>	29/M	No medical history	Abdominal pain	Dyspnea Fever	Moderate	Recovered

**Table 2 (cont.).** Demographic and clinical characteristics including COVID-19 severity and outcome of patients with COVID-19-induced acute pancreatitis.

#	Author, Year	Age/ Gender	Medical history	Gastrointestinal manifestations	Respiratory- general symptoms	Severity of COVID-19	Outcome
15	Schepis, 2020 <sup>28</sup>	67/F	Recent hospitalization for Interstitial Edematous acute pancreatitis of unknown origin	Abdominal pain Vomiting	No respiratory- other symptoms	Mild	Recovered
16	Aloysius, 2020 <sup>29</sup>	36/F	Chronic anxiety Obesity	Abdominal pain Nausea Vomiting Diarrhea	Dry cough Dyspnea Fever	Critical	Recovered
17	Gonzalo-Voltas, 2020 <sup>30</sup>	76/F	Hypercholesterolemia Gastroesophageal reflux	Abdominal pain Vomiting	No respiratory- other symptoms	Mild	Recovered
18	Alves, 2020 <sup>31</sup>	56/F	Arterial hypertension	Abdominal pain	Dry cough Dyspnea Fatigue	Critical	Recovered
19	Ghosh, 2020 <sup>32</sup>	63/M	Diabetes mellitus	No Gastrointestinal Symptoms	Dyspnea Dry cough Fever	Severe	Recovered
20	Kataria, 2020 <sup>33</sup>	49/F	No medical history	Abdominal pain Nausea Vomiting	Dyspnea Dry cough Lethargy Fever	Critical	Recovered
21	Hadi, 2020 <sup>34</sup>	47/F	No medical history	Anorexia	Dyspnea Fever Headache Neck Pain Sore Throat	Critical	N/A
22	Hadi, 2020 <sup>34</sup>	68/F	Arterial hypertension Hypothyroidism Osteoporosis	Abdominal pain Vomiting Diarrhea	Fever Fatigue Polydipsia	Critical	N/A
23	Brikman, 2020 <sup>35</sup>	61/M	No medical history	Abdominal pain	Dyspnea Cough Fever	Critical	Recovered
24	Lakshmanan, 2020 <sup>36</sup>	68/M	Nursing home resident Diabetes mellitus Arterial hypertension Stage IV chronic kidney disease	Anorexia Nausea Vomiting	No respiratory- other symptoms	Mild	Recovered
25	Miao, 2020 <sup>37</sup>	26/F	No medical history	Abdominal pain Vomiting	No respiratory symptoms Fever	Mild	Recovered
26	Pinte, 2020 <sup>38</sup>	47/M	No medical history	Abdominal pain Nausea Constipation Lack of flatus	Dry cough	Mild	Recovered
27	Anand, 2020 <sup>39</sup>	59/F	Cholecystectomy Thrombophilia	Abdominal pain Constipation	Cough Fever Sore Throat Myalgia	Mild	Recovered

**Table 2 (cont.).** Demographic and clinical characteristics including COVID-19 severity and outcome of patients with COVID-19-induced acute pancreatitis.

#	Author, Year	Age/ Gender	Medical history	Gastrointestinal manifestations	Respiratory- general symptoms	Severity of COVID-19	Outcome
28	Wifi, 2021 <sup>40</sup>	72/F	Obesity Arterial hypertension Ischemic heart disease	Abdominal pain Nausea Vomiting	Cough Nasal Sneezing	Severe	Recovered
29	Mohammadi Arbati, 2021 <sup>41</sup>	28/M	No medical history	Abdominal pain Nausea Vomiting	Dyspnea Dry cough Fever Myalgia	Critical	Recovered
30	Maalouf, 2021 <sup>42</sup>	62/M	Arterial hypertension Diabetes mellitus End-stage renal disease status Post Kidney Transplant	Abdominal pain Diarrhea Vomiting Anorexia	Dyspnea	Moderate	Recovered
31	AlHarm, 2021 <sup>43</sup>	52/F	Diabetes mellitus Arterial hypertension Hypothyroidism Obesity	Abdominal pain Nausea Vomiting	Dry cough Dyspnea Fever	Severe	Recovered
32	Chivato Martín- Falquina, 2021 <sup>44</sup>	55/M	No medical history	No Gastrointestinal Symptoms	Dyspnea	Severe	Recovered

HELLP: Hemolysis, Elevated Liver Enzymes, Low Platelet Count.

**Table 3.** Laboratory and Imaging findings among the 32 cases following development of acute pancreatitis.

#	Author, Year	Lipase (U/L)	Amylase (U/L)	WBC/CRP	Abdominal imaging features
1	Meyers, 2020 <sup>14</sup>	>3 times of UNL	N/A	N/A / N/A	Abdominal CT: acute interstitial edematous pancreatitis.
2	Karimzadeh, 2020 <sup>15</sup>	>3 times of UNL	<3 times of ULN	Normal/ N/A	Abdominal CT: no abnormal findings.
3	Shinohara, 2020 <sup>16</sup>	N/A	>3 times of UNL	Normal/ Elevated	Abdominal CT: acute interstitial edematous pancreatitis.
4	Rabice, 2020 <sup>17</sup>	>3 times of UNL	<3 times of ULN	Normal/ N/A	Abdominal CT was not recommended as it would not change clinical management.
5	Meireles, 2020 <sup>18</sup>	>3 times of UNL	>3 times of UNL	N/A/ Elevated	Angio-abdominal CT: exclusion of ischemic changes
6	Fernandes, 2020 <sup>19</sup>	>3 times of UNL	>3 times of UNL	N/A/ N/A	Abdominal CT: acute interstitial edematous pancreatitis.
7	Alwaeli, 2020 <sup>20</sup>	>3 times of UNL	<3 times of ULN	Normal/ N/A	Abdominal CT: acute interstitial edematous pancreatitis.
8	Narang, 2020 <sup>21</sup>	>3 times of UNL	>3 times of UNL	Elevated/ N/A	Abdominal MRI: acute interstitial edematous pancreatitis.
9	Kandasamy, 2020 <sup>22</sup>	>3 times of UNL	>3 times of UNL	Elevated/ N/A	Abdominal CT: acute interstitial edematous pancreatitis.
10	Kumaran, 2020 <sup>23</sup>	N/A	>3 times of UNL	Elevated/ Elevated	Abdominal CT: necrotizing pancreatitis
11	Acherjya, 2020 <sup>24</sup>	>3 times of UNL	<3 times of UNL	Decreased/ Elevated	Abdominal CT: acute interstitial edematous pancreatitis.
12	Bokhari, 2020 <sup>25</sup>	>3 times of UNL	>3 times of UNL	Elevated/ Elevated	Abdominal CT: acute interstitial edematous pancreatitis.



**Table 3 (cont.).** Laboratory and Imaging findings among the 32 cases following development of acute pancreatitis.

#	Author, Year	Lipase (U/L)	Amylase (U/L)	WBC/CRP	Abdominal imaging features
13	Mazrouei, 2020 <sup>26</sup>	>3 times of UNL	>3 times of UNL	N/A N/A	Abdominal CT: acute interstitial edematous pancreatitis.
14	Patnaik, 2020 <sup>27</sup>	>3 times of UNL	>3 times of UNL	Elevated/ Elevated	Abdominal CT, Abdominal U/S : acute interstitial edematous pancreatitis and no evidence of common bile duct calculi.
15	Schepis, 2020 <sup>28</sup>	N/A	>3 times of UNL	Normal/ N/A	Abdominal CT: large pancreatic pseudocyst causing a partial stomach outlet obstruction
16	Aloysius, 2020 <sup>29</sup>	>3 times of UNL	>3 times of UNL	Normal/ Elevated	Abdominal CT: normal gall bladder, biliary tract, with unremarkable pancreas.
17	Gonzalo-Voltas, 2020 <sup>30</sup>	N/A	>3 times of UNL	Elevated/ Elevated	Abdominal CT: acute interstitial edematous pancreatitis.
18	Alves, 2020 <sup>31</sup>	>3 times of UNL	>3 times of UNL	N/A/ N/A	Abdominal CT: acute interstitial edematous pancreatitis.
19	Ghosh, 2020 <sup>32</sup>	<3 times of UNL	<3 times of UNL	Normal/ Elevated	Abdominal CT: necrotizing pancreatitis
20	Kataria, 2020 <sup>33</sup>	>3 times of UNL	>3 times of UNL	Normal/ Elevated	Abdominal CT: acute interstitial edematous pancreatitis.
21	Hadi, 2020 <sup>34</sup>	N/A	>3 times of UNL	Normal/ Elevated	Abdominal U/S: acute interstitial edematous pancreatitis.
22	Hadi, 2020 <sup>34</sup>	N/A	>3 times of UNL	Normal/ Elevated	N/A
23	Brikman, 2020 <sup>35</sup>	>3 times of UNL	<3 times of UNL	Elevated/ N/A	Abdominal CT: acute interstitial edematous pancreatitis.
24	Lakshmanan, 2020 <sup>36</sup>	>3 times of UNL	>3 times of UNL	Normal/ Elevated	Abdominal CT: acute interstitial edematous pancreatitis (peripancreatic fat stranding, greatest around the tail, with mild duodenal wall thickening and adjacent fat stranding)
25	Miao, 2020 <sup>37</sup>	>3 times of UNL	N/A	Normal/ Elevated	Abdominal CT, abdominal U/S: acute interstitial edematous pancreatitis.
26	Pinte, 2020 <sup>38</sup>	N/A	N/A	Elevated/ Elevated	Abdominal CT: acute interstitial edematous pancreatitis.
27	Anand, 2020 <sup>39</sup>	N/A	N/A	Elevated/ Elevated	Abdominal CT: acute interstitial edematous pancreatitis.
28	Wifi, 2021 <sup>40</sup>	>3 times of UNL	>3 times of UNL	Elevated/ Elevated	Abdominal CT: without abnormal findings
29	Mohammadi Arbati, 2021 <sup>41</sup>	>3 times of UNL	>3 times of UNL	Elevated/ Normal	Abdominal CT: necrotizing pancreatitis
30	Maalouf, 2021 <sup>42</sup>	>3 times of UNL	N/A	Decreased/ Elevated	Abdominal MRI: necrotizing pancreatitis
31	AlHarm, 2021 <sup>43</sup>	N/A	<3 times of UNL	Elevated/ Normal	Abdominal CT: acute interstitial edematous pancreatitis.
32	Chivato Martin-Falquina, 2021 <sup>44</sup>	N/A	>3 times of UNL	N/A N/A	Abdominal CT: acute interstitial edematous pancreatitis.

CRP: C-reactive protein; CT: Computerized tomography; MRI: Magnetic resonance imaging, U/S: Ultrasonography, UNL: Upper limit of normal, WBC: White blood cells.



**Table 4.** Demographic and clinical data from the 32 cases.

Demographics	
Gender	
Males	13/32 (59.4)
Females	19/32 (40.6)
Gastrointestinal symptoms	
Abdominal pain	28/32 (87.5)
Nausea	14/32 (43.8)
Vomiting	20/32 (62.5)
Diarrhea	5/32 (15.6)
Constipation	2/32 (6.3)
Anorexia	3/32 (9.3)
Lack of flatus	1/32 (3.1)
No gastrointestinal symptoms	2/32 (6.3)
Respiratory/General symptoms	
Dyspnea	20/32 (62.5)
Cough	14/32 (43.8)
Fever	19/32 (59.4)
Myalgia	4/32 (12.5)
Fatigue	3/32 (9.3)
Headache	2/32 (6.3)
No respiratory or general symptoms	4/32 (12.5)
No respiratory symptoms	2/32 (6.3)
COVID-19 Severity	
Mild SARS-CoV-2 illness	8/32 (25)
Moderate SARS-CoV-2 illness	4/32 (12.5)
Severe SARS-CoV-2 illness	10/32 (31.2)
Critical SARS-CoV-2 illness/ Need for admission to ICU	10/32 (31.2)
Laboratory findings following development of acute pancreatitis	
Amylase levels over three times of ULN	20/27 (74.1)
Amylase levels less than three times of ULN	7/27 (25.9)
Lipase levels over three times of ULN	21/22 (95.5)
Lipase levels less than three times of ULN	1/22 (0.5)
Elevated white blood cell count	12/26 (46.2)

**Table 4 (cont.).** Demographic and clinical data from the 32 cases.

Demographics	
White blood cell count with normal limits	12/26 (46.2)
Decreased WBC count	2/26 (7.6)
Elevated levels of CRP	18/20 (90)
C-reactive protein levels within normal limits	2/20 (10)
Imaging features	
Acute interstitial edematous pancreatitis	21/31 (67.8)
Necrotizing pancreatitis	4/31 (12.9)
No abnormal imaging findings	3/31 (9.7)
Abdominal CT was not performed due to pregnancy	1/31 (3.2)
Angio-abdominal CT was conducted in order to exclude ischemic changes	1/31 (3.2)
Large pancreatic pseudocyst causing a partial stomach outlet obstruction on abdominal CT	1/31 (3.2)
Medical history	
Arterial hypertension	11/31 (35.5)
Diabetes mellitus	6/31 (19.4)
Obesity	5/31 (16.1)
Cholecystectomy	3/31 (9.7)
Asthma	2/31 (6.5)
Chronic kidney disease	3/31 (9.7)
Osteoporosis	1/31 (3.2)
Hypothyroidism	2/31 (6.5)
Gastroesophageal reflux	1/31 (3.2)
Hypercholesterolemia	1/31 (3.2)
Active cancer of larynx and breast	1/31 (3.2)
Thrombophilia	1/31 (3.2)
Pregnancy	2/31 (6.5)
No medical history	12/31 (38.5)
Outcomes	
Recovery	30/30 (100)
Death	0

Data are n (%); ULN: Upper limit of normal.

**Table 5.** Data for the meta-regression meta-analysis.

#	Author, Year	Age/ Gender	Severity of COVID-19	Lipase (U/L)	Amylase (U/L)
1	Meyers, 2020 <sup>14</sup>	67/M	Severe	>3 times of UNL	N/A
2	Karimzadeh, 2020 <sup>15</sup>	65/F	Severe	>3 times of UNL	<3 times of UNL
3	Shinohara, 2020 <sup>16</sup>	58/M	Critical	N/A	>3 times of UNL
4	Rabice, 2020 <sup>17</sup>	36/F	Severe	>3 times of UNL	<3 times of UNL
5	Meireles, 2020 <sup>18</sup>	36/F	Moderate	>3 times of UNL	>3 times of UNL
6	Fernandes, 2020 <sup>19</sup>	36/F	Moderate	>3 times of UNL	>3 times of UNL
7	Alwaeli, 2020 <sup>20</sup>	30/M	Critical	>3 times of UNL	<3 times of UNL
8	Narang, 2020 <sup>21</sup>	20/F	Critical	>3 times of UNL	>3 times of UNL
9	Kandasamy, 2020 <sup>22</sup>	45/F	Severe	>3 times of UNL	>3 times of UNL
10	Kumaran, 2020 <sup>23</sup>	67/F	Severe	N/A	>3 times of UNL
11	Acherjya, 2020 <sup>24</sup>	57/F	Severe	>3 times of UNL	<3 times of UNL
12	Bokhari, 2020 <sup>25</sup>	32/M	Mild	>3 times of UNL	>3 times of UNL
13	Mazrouei, 2020 <sup>26</sup>	24/M	Mild	>3 times of UNL	>3 times of UNL
14	Patnaik, 2020 <sup>27</sup>	29/M	Moderate	>3 times of UNL	>3 times of UNL
15	Schepis, 2020 <sup>28</sup>	67/F	Mild	N/A	>3 times of UNL
16	Aloysius, 2020 <sup>29</sup>	36/F	Critical	>3 times of UNL	>3 times of UNL
17	Gonzalo-Voltas, 2020 <sup>30</sup>	76/F	Mild	N/A	>3 times of UNL
18	Alves, 2020 <sup>31</sup>	56/F	Critical	>3 times of UNL	>3 times of UNL
19	Ghosh, 2020 <sup>32</sup>	63/M	Severe	<3 times of UNL	<3 times of UNL
20	Kataria, 2020 <sup>33</sup>	49/F	Critical	>3 times of UNL	>3 times of UNL
21	Hadi, 2020 <sup>34</sup>	47/F	Critical	N/A	>3 times of UNL
22	Hadi, 2020 <sup>34</sup>	68/F	Critical	N/A	>3 times of UNL
23	Brikman, 2020 <sup>35</sup>	61/M	Critical	>3 times of UNL	<3 times of UNL
24	Lakshmanan, 2020 <sup>36</sup>	68/M	Mild	>3 times of UNL	>3 times of UNL
25	Miao, 2020 <sup>37</sup>	26/F	Mild	>3 times of UNL	N/A
26	Pinte, 2020 <sup>38</sup>	47/M	Mild	N/A	N/A
27	Anand, 2020 <sup>39</sup>	59/F	Mild	N/A	N/A
28	Wifi, 2021 <sup>40</sup>	72/F	Severe	>3 times of UNL	>3 times of UNL
29	Mohammadi Arbaty, 2021 <sup>41</sup>	28/M	Critical	>3 times of UNL	>3 times of UNL
30	Maalouf, 2021 <sup>42</sup>	62/M	Moderate	>3 times of UNL	N/A
31	AlHarm, 2021 <sup>43</sup>	52/F	Severe	N/A	<3 times of UNL
32	Chivato Martín-Falquina, 2021 <sup>44</sup>	55/M	Severe	N/A	>3 times of UNL

ULN: Upper limit of normal

0.461 represents the simple correlation, which indicates a moderate degree of correlation. The  $R^2$  value indicates how much of the total variation in severity, the dependent variable, was explained by the independent variables. In this case,  $R^2$  indicated that only 21.3% could be explained by the independent variables. The association of the regression model was statistically significant (i.e., a good fit for the data) ( $P < .05$ ) (Tables 6 and 7).

## DISCUSSION

There are very few case reports and case series describing COVID-19 induced acute pancreatitis. To our knowledge, we present the largest and most comprehensive systematic review of case reports and case series on SARS-CoV-2 infection causing acute pancreatitis. The ages of the patients were uniformly distributed with a median age of 53.5 years. The majority of the patients were females. Lipase and amylase were greater than three times the ULN while WBC counts and CRP were elevated in the most of the cases. The majority of the patients mentioned abdominal pain while other frequent symptoms were nausea and vomiting. The most common respiratory symptoms were dyspnea and cough. Fever was the most frequent general symptom and in some cases neither respiratory nor general symptoms were present. Most of the patients experienced severe and critical SARS-CoV-2 illness. The imaging features of abdominal CT were mostly compatible with acute interstitial edematous pancreatitis. The most frequent comorbidity was arterial hypertension and 38.5% of the patients had no medical history. In addition, where data were available, all the patients recovered.

The results of meta-regression analysis showed a low heterogeneity between the studies regarding the sever-

ity of COVID-19 disease and that serum levels of lipase and amylase had a moderate positive correlation with the severity of COVID-19 disease.

Data from studies about COVID-19 patients presenting with acute pancreatitis are limited. Szatmary et al in a study of hospitalized patients for acute pancreatitis found only 5 patients with SARS-CoV-2 infection in whom other causes of acute pancreatitis were excluded. All the patients were young adult males with a median age of 42 years and all were obese with no history of cardiovascular disease. There were no data about serum lipase levels; serum amylase levels were increased. Abdominal CT was used to establish the final diagnosis. The finding of pancreatic inflammation on CT was mild pancreatic edema without pancreatic or peripancreatic necrosis, compatible with acute interstitial edematous pancreatitis. In this study, all patients with COVID-19 associated acute pancreatitis recovered.<sup>46</sup>

Our systematic review was written after a comprehensive search of the literature with specific criteria for inclusion and quality assessment. However, our results are limited by the quality and extent of the data in the reports. More specifically, case series and case reports are unchecked, and while they can recommend hypotheses they are not able to confirm robust associations. Clinicians should be aware of the few cases reported in the literature, suggesting that acute pancreatitis can result from COVID-19. While case reports can provide signals, they are not strong enough for statistical inference. Thus, the evidence provided is insufficient to suggest systematic screening in patients with COVID-19 for pancreatic involvement, but should alert physicians of possible pancreatic involvement by SARS-CoV-2.

In conclusion, COVID-19 associated acute pancreatitis affected mostly females with a median age of 53.5 years. Concerning laboratory findings, lipase and amylase were greater than three times the ULN while WBC counts and CRP were elevated in the most of the cases. The most frequent gastrointestinal, respiratory and general symptom was abdominal pain, dyspnea and fever, respectively. The most common imaging feature was acute interstitial edematous pancreatitis and the most frequent comorbidity was arterial hypertension while several patients had no medical history. The outcome was favorable despite the fact that most of the patients experienced severe and critical illness. Our results warrant the need for larger controlled research to detect acute pancreatitis during COVID-19 course and to provide data on patient characteristics and outcomes.

**Table 6.** Results of the regression analysis for lipase (n=24).

Parameter	Beta estimate	z	P
$\beta_0$	-.484	-.780	.442
$\beta_1$	.753	2.072	.124

$$\text{Severity}_1 = -.484 + 753 \cdot \log_1(\text{lipase})$$

**Table 7.** Results of the regression analysis for amylase lipase (n=27).

Parameter	Beta estimate	z	P
$\beta_0$	-.484	-.780	.442
$\beta_1$	1.223	1.586	.042

$$\text{Severity}_2 = -.484 + 1,223 \cdot \log_2(\text{amylase})$$

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