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ABOUT COVER

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Insufficient etiological workup of COVID-19-associated acute pancreatitis: A systematic review

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Abstract

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, mostly causing respiratory symptoms, is also known to affect the gastrointestinal tract. Several case reports hypothesize that SARS-CoV-2 could be an etiological factor in acute pancreatitis (AP).

AIM

To assess all the available evidence in the literature relating to coronavirus disease 2019 (COVID-19) and AP.

METHODS

We performed a systematic review of the available literature on the topic. The systematic search was conducted on 15 May 2020 on MEDLINE, EMBASE, CENTRAL, Web of Science and Scopus with a search key using the terms "amylase," "lipase," "pancr*," "COVID-19" and synonyms. Due to the low quality and poor comparability of the studies, a meta-analysis was not performed.

RESULTS

Six case reports and two retrospective cohorts were included, containing data on eleven COVID-19 patients with AP. Five patients had AP according to the Atlanta classification. Other publications did not provide sufficient information on the diagnostic criteria. Most cases were considered SARS-CoV-2-induced, while

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several established etiological factors were not investigated. We were able to identify other possible causes in most of them.

CONCLUSION

We strongly highlight the need for adherence to the guidelines during a diagnostic and etiological workup, which could alter therapy.

Key Words: Pancreas; COVID-19; Pancreatic involvement; Pancreatitis; Amylase; Lipase

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Core Tip: As the severe acute respiratory syndrome coronavirus 2 pandemic spreads, numerous coronavirus disease 2019 patients will be diagnosed with acute pancreatitis (AP). Viral infections are known etiological factors of AP, but taking a look at the available literature several shortcomings of the diagnostic end etiological workups were uncovered, therefore the causative relationship between coronavirus disease 2019 and AP cannot be established. We highlight the fundamental role of guideline adherence in the diagnosis and etiological workup of AP since etiology-specific therapeutic options are available. Identifying underlying etiological factors is the foundation of high-quality patient care in AP.

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INTRODUCTION

In 2019, a novel coronavirus emerged in Wuhan, China, causing multiple cases of severe pneumonia and launching the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. The clinical syndrome seen in SARS-CoV-2 infection is called coronavirus disease 2019 (COVID-19). The main clinical symptoms of COVID-19 are fever, cough, myalgia, and fatigue^[1]. Pulmonary involvement is the most frequent^[2], but systemic dissociation is seen in severe cases. Furthermore, a significant proportion of patients exhibit gastrointestinal symptoms such as diarrhea, vomiting, and abdominal pain. SARS-CoV-2 was also detected in stool specimens^[3] and in the cytoplasm of gastric, duodenal, and rectal glandular epithelial cells^[4].

Viral infections such as mumps, Coxsackie, hepatitis, and herpes viruses are known causes of pancreatitis^[5]. There is a strong possibility that, like other, less common causes of acute pancreatitis (AP), infectious etiology is underdiagnosed on account of the insufficient workup of idiopathic cases and cases where an apparent cause (*e.g.*, alcohol consumption) is already established^[6-8].

On the other hand, during a pandemic of such proportions, polymerase chain reaction testing is made widely available. This will of course lead to a proportion of patients with a variety of diseases, including AP, being diagnosed with SARS-CoV-2 infection. Given the right temporal association, even a more experienced practitioner could be led to ponder a cause-effect relationship between COVID-19 and AP. Even more so, taking into account the often-neglected etiological workup of idiopathic cases and the opportunity to aid the scientific and medical communities by providing information on presumed complications of the infection.

This systematic review aims to assess all publications containing COVID-19 AP cases and to determine the plausibility of an association between the two.

MATERIALS AND METHODS

Protocol and registration

This systematic review was registered with PROSPERO as “Pancreas involvement in COVID-19: A systematic review” under registration number CRD42020186426. After completing the systematic search, we decided to deviate from the protocol for the eligibility of studies: We narrowed our focus to AP from the original plan of any pancreatic involvement. We did so because slight pancreatic enzyme elevation in COVID-19 patients, reported by two studies^[9,10], has already been discussed by de-Madaria *et al*^[11] and information on pancreatic cancer patients, reported by three studies^[12-14] is at this point far too scarce to even discuss its relation with COVID-19 and effect on outcomes. There were no other deviations from the protocol.

Eligibility criteria

Any study, regardless of design, was considered eligible if it contained the original data on at least 1 SARS-CoV-2-infected individual diagnosed with AP. Only human studies were eligible; studies containing solely animal or *in vitro* data were excluded.

Systematic search and selection; data extraction

Using the same search key as detailed in the supplementary material (Supplemental 1), the systematic search was conducted in five databases: EMBASE, MEDLINE (via PubMed), CENTRAL, Web of Science, and Scopus. The last systematic search was carried out on May 14, 2020. The search was restricted to 2020, and no other filters were applied. Citations were exported to a reference management program (EndNote X9, Clarivate Analytics). Two independent review authors (Ocskay K and Juhász MF) conducted the selection by title, abstract and full text based on the previously disclosed, predetermined set of rules. After each selection step, Cohen’s kappa coefficient (κ)^[15] was calculated. An independent third party (SK) settled any disagreements. Citing articles and references in the studies assessed for eligibility in the full-text phase were reviewed to identify any additional eligible records. Data were extracted from all eligible studies into a standardized Excel sheet designed on the basis of recommendations from the Cochrane Collaboration^[16] (for details on data extraction, see Supplemental 2).

Risk of bias assessment and determination of the quality of evidence

The Joanna Briggs Institute Critical Appraisal Checklist for Case Reports^[17] was used to assess the risk of bias in case reports, and the Newcastle–Ottawa Scale^[18] was used for cohorts (results in Supplemental 3). Due to the design and quality of the included studies, the Grading of Recommendations, Assessment, Development, and Evaluations approach was not used and a very low grade of evidence was automatically established.

Statistical analysis

Only qualitative synthesis was performed; no statistical analysis was carried out.

RESULTS

Systematic search and selection

The details of the systematic search and selection are presented in Figure 1.

Characteristics of included studies

In total, six case reports and two retrospective cohort studies were included in this systematic review (Table 1). Information on the diagnostic criteria and etiological factors of AP was collected from the appropriate case reports in Table 2. Of the six cases, five fulfilled the diagnostic criteria for acute pancreatitis^[19], and in one case^[20] enzyme elevation reached the threshold. However, abdominal pain could not be reported on account of the patient being ventilated and sedated, and no imaging findings were disclosed. A case report by Gou *et al*^[21] was not included in this table, as biliary etiology was determined and COVID-19 symptoms first emerged on day 18 of the patient’s hospital stay; thus, the infection was not assumed as an etiological factor^[21].

In a retrospective cohort of COVID-19 mortality cases by Li *et al*^[22], AP is listed as an underlying disease in a single patient without further clarification as to whether it is a

Table 1 Characteristics of included studies

Ref.	Study design	Study population	AP, n (%)	Description
Aloysius <i>et al</i> ^[29] , United States	Case report	One AP patient with COVID-19	1 (100)	36-year-old obese female presenting with AP. No sign of biliary pathology, denies alcoholism, TG unremarkable
Anand <i>et al</i> ^[44] , United Kingdom	Case report	One AP patient with COVID-19	1 (100)	A 59-year-old cholecystectomized woman with minimal alcohol consumption, readmitted with abdominal symptoms five days after discharge with doxycycline for co-infection. CT showed signs of AP on a formerly atrophic pancreas
Gou <i>et al</i> ^[21] , China	Case report	Four “pancreatic disease” patients with COVID-19 pneumonia	1 (25)	One female with AP (51), biliary etiology confirmed, showed initial COVID-19 symptoms 18 d after admission
Hadi <i>et al</i> ^[45] , Denmark	Case report	Three family members with COVID-19	2 (67)	Idiopathic AP in mother (68) and daughter (47), both requiring intensive care and ventilation
Hossain <i>et al</i> ^[23] , United States	Retrospective cohort	119 COVID-19 patients presenting at ER with non-respiratory symptoms	3/32 (9.4)	Out of the 101 instances where abdominal/pelvic CT was obtained, 32 had acute/significant findings, including three cases of pancreatitis. No more information available on these patients
Li <i>et al</i> ^[22] , China	Retrospective cohort	25 death cases with COVID-19	1 (4)	A 56-year-old male patient had AP as an “underlying disease”—it is not clear whether this is from his medical history or was present concomitantly
Meireles <i>et al</i> ^[46] , Portugal	Case report	One AP patient with COVID-19	1 (100)	36-year-old female, AP symptoms started on day 11 of disease, US and CT showed no signs of biliary pathology/ischemia. No information on alcohol consumption. Negatively screened for multiple viruses
Morrison <i>et al</i> ^[20] , United States	Case report	Two cases of acute hypertriglyceridemia in COVID-19 patients	1 (50)	Acute hypertriglyceridemia-induced AP after treatment with tocilizumab, ritonavir, lopinavir, ribavirin, hydroxychloroquine, and propofol

AP n (%) is the number (percentage) of patients with acute pancreatitis. COVID-19: Coronavirus disease 2019; AP: Acute pancreatitis; US: Ultrasonography; CT: Computed tomography.

past event from the patient’s medical history or it occurred during COVID-19-related hospitalization^[22]. Hossain *et al*^[23] noted three cases of AP among 119 patients presenting to the ER with non-respiratory symptoms who turned out to have concomitant SARS-CoV-2 infection^[23].

DISCUSSION

The multiple-hit theory can be implemented in the pathogenesis of AP^[24]; therefore, information on possible contributing factors was collected for each case (Table 2). Multiple etiological factors are often responsible for AP^[24], but the lack of proper workup often leads to cases being deemed idiopathic or an important factor not being discovered due to the presence of a more convenient diagnosis^[6]. In addition to the established etiological factors, various mechanisms have been postulated as the cause of pancreatic damage in COVID-19.

SARS-CoV-2 enters epithelia through the angiotensin-converting enzyme 2^[25], which is abundantly expressed in the pancreas^[26,27]. SARS-CoV-2 RNA and protein were also shown by *in situ* hybridization and immunohistochemistry from autopsy samples of infected patients’ pancreas^[28]. Aloysius proposed that virus replication may have a direct cytopathic effect or elicit pancreatic cell death as a consequence of the immune response^[29]. Furthermore, microvascular injury and thrombosis have been described as a consequence of COVID-19^[30,31], which, complicated with shock and gastrointestinal hypoperfusion^[32], could also cause pancreatic damage^[33].

However, a cause-effect relationship has not been investigated directly so far. Also, before entertaining the possibility of a new virus as a causative agent in cases where no apparent etiological factors are present, other, less frequent causes of AP must be considered. In such cases, the International Association of Pancreatology/American Pancreatic Association (IAP/APA) recommendations should be followed^[6,7,19].

For instance, drugs used in treating COVID-19 may cause pancreatic damage directly or indirectly. A patient whose case was presented as idiopathic AP was on a course of doxycycline, which is a drug with a documented probable association with pancreatitis^[34]. Several drugs currently used or being considered for COVID-19 might play a role in the pathogenesis of pancreatitis, such as enalapril, asparaginase,

Table 2 Diagnostic and etiological workup and quality assessment of the studies

Ref.	Diagnostic workup			COVID-19 (PCR)	Etiological workup									Quality of case reports	
	Abdominal pain	Enzyme elevation (3x)	Imaging		Biliary	Alcohol	HTG (> 11.5 mmol/L)	Drug	Hypercalcemia	Ischemia	Auto-immunity	Viral (except nCoV)	Anatomy	JBI Overall rating (/8)	Written according to CARE
Aloysius <i>et al</i> ^[29] , United States	+	+	-	+	?	-	-	-	?	?	?	?	-	3	No
Anand <i>et al</i> ^[44] , United Kingdom	+	?	+	+	?	-	?	+	?	?	?	?	-	0	No
Hadi <i>et al</i> ^[45] , Denmark	?	+	+	+	?	-	-	?	-	+	?	?	?	4	No
	+	+	?	+	?	?	?	+	-	+	?	?	?	2	
Meireles <i>et al</i> ^[46] , Portugal	+	+	-	+	?	-	-	-	-	-	-	-	-	1	No
Morrison <i>et al</i> ^[20] , United States	?	+	?	+	?	?	+	+	?	+	?	?	?	1	No

The Atlanta criteria were used for diagnosis. Biliary microlithiasis was included in the “biliary” etiology, so endoscopic ultrasonography or magnetic resonance cholangiopancreatography was needed to rule out this factor. Ischemia was considered in the case of shock and vasopressor therapy and was ruled out by computed tomography angiogram. Anatomical malformations were ruled out by computed tomography. The two columns on the right demonstrate the quality of included case reports based on the risk of bias according to the overall Joanna Briggs Institute Critical Appraisal score and adherence to Case Report guidelines on reporting cases. CARE: Case Report Guidelines; JBI: Joanna Briggs Institute; PCR: Polymerase chain reaction.

estrogens, and steroids^[34]. Hypertriglyceridemia, another established etiological factor frequently neglected, can also occur as a consequence of therapy, as in the case described by Morrison *et al*^[20]. Not only tocilizumab^[35] but propofol and ritonavir could also have been responsible for the elevation of serum triglyceride levels in this case^[36]. Hypertriglyceridemia-associated drug-induced AP was observed^[37,38] in association with the following drugs being tested for COVID-19 according to our search on clinicaltrials.gov: lisinopril, asparaginase, estrogens, isotretinoin, steroids, propofol, and ruxolitinib.

In a case reported by Aloysius *et al*^[29], there are no apparent etiological factors present in the description. Even so, the report does not describe any further efforts to identify the seemingly idiopathic etiology, such as performing an endoscopic ultrasonogram. While thoroughly ruled out AP-associated viruses and even screened for antinuclear antibodies, they also did not utilize endoscopic ultrasonogram during the etiology search.

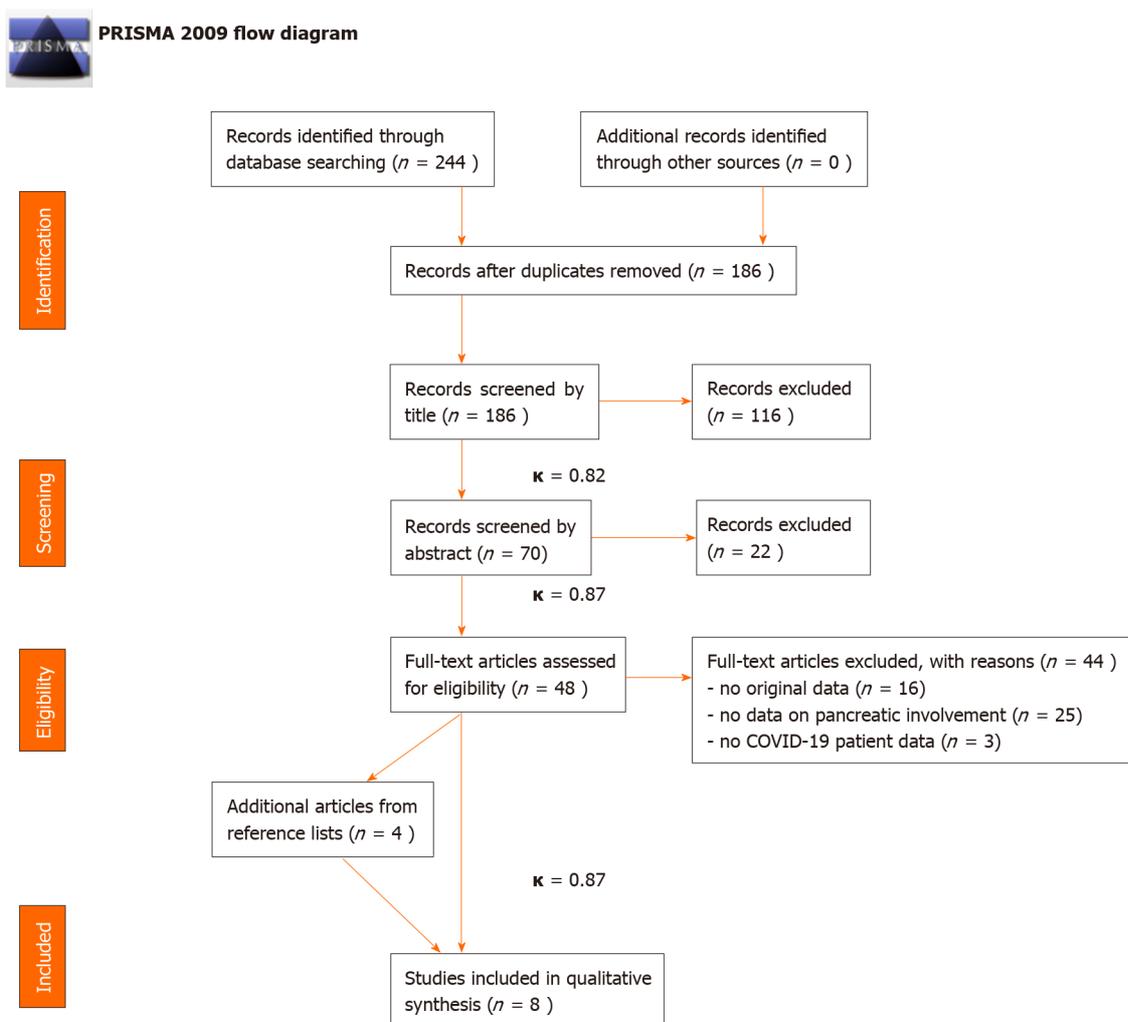


Figure 1 PRISMA flow diagram demonstrating the selection of studies to be included in the review. κ represents Cohen's Kappa values indicating the rate of agreement between selection coordinators. COVID-19: Coronavirus disease 2019.

Other than the highlighted problems tied to the etiological workup, we would like to briefly address an issue with the diagnosis. Two studies not included in this review^[9,10] labeled patients with serum amylase and/or lipase values higher than the upper limit of normal to possess “pancreatic injury”. As de-Madaria *et al*^[11] pointed out in reflecting on Wang *et al*^[9], the elevation of pancreatic enzyme levels in the blood is not necessarily a consequence of an insult to the pancreas. Possible reasons are the high prevalence of renal impairment and diabetes mellitus, gastroenteritis, and metabolic changes, such as acidosis, or even salivary glandular entry by SARS CoV-2^[39-42]. More importantly, a slight elevation in serum amylase and/or lipase levels alone is not established as an indicator of pancreatic damage. The Atlanta diagnostic criteria should be applied when determining the presence of AP^[19].

The case reports in our review carry considerable risk of bias and their deviation from the Case Report guideline^[43] on reporting methods. As demonstrated, the etiological workup of patients was incomplete, and often COVID-19 was named as the causative agent of AP, while other established factors were also present.

Considering limitations, incomplete reporting of the included studies encompasses a high risk of bias in our analysis^[44-46].

CONCLUSION

To conclude, we strongly emphasize the need for guideline adherence when diagnosing and uncovering the underlying etiological factors of AP, even during a pandemic. As specific therapeutic options^[19] are available depending on etiology, neglecting these steps can hinder direct therapy and lower the chances of recovery,

while increasing the probability of complications and recurrent episodes.

ARTICLE HIGHLIGHTS

Research background

Since the rapid progression of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, numerous publications postulated pancreatic involvement. Furthermore, angiotensin-converting enzyme 2 expression -the cellular entry point of the virus- was described in the pancreas.

Research motivation

Multiple etiological factors can be uncovered in a large proportion of acute pancreatitis cases. Therefore, the characterization of SARS-CoV-2 infection as a potential contributing factor was necessary.

Research objectives

Our aim was to review all available clinical evidence on acute pancreatitis cases in coronavirus disease 2019 (COVID-19) patients and to analyze the role of COVID-19 as an etiological factor.

Research methods

A systematic search was conducted in five databases on 14 May 2020 (registration number CRD42020186426). Record selection and data extraction were carried out by two independent review authors. Studies containing the original data of at least 1 SARS-CoV-2-infected individual diagnosed with acute pancreatitis were considered eligible. The Joanna Briggs Institute Critical Appraisal Checklist for Case Reports and the Newcastle–Ottawa Scale were used for risk of bias assessment.

Research results

Eight studies (six case reports and two retrospective cohort studies) were included in this systematic review. All acute pancreatitis cases lacked proper etiological workup, but SARS-CoV-2 infection was confirmed by polymerase chain reaction in all cases. High risk of bias and non-compliance with the Case Report guideline was noted in all case reports.

Research conclusions

Guideline adherence is a quality indicator of patient care. We advise all clinicians to conduct proper etiological workup before entertaining the possibility of SARS-CoV-2 as a causative agent of acute pancreatitis.

Research perspectives

The potential mechanisms of pancreatic damage in COVID-19 should be investigated utilizing basic research methods and animal models to evaluate a possible causative association between SARS-CoV-2 and AP.

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