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**Occam’s razor or Hickam’s dictum-COVID-19 is not a textbook aetiology of acute pancreatitis: A modified Naranjo Score appraisal**

Teng TZJ *et al*. COVID-19 and acute pancreatitis

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**Abstract**

BACKGROUND

Acute pancreatitis (AP) is a disease spectrum ranging from mild to severe disease. During the coronavirus disease 2019 (COVID-19) pandemic, numerous reports of AP have been published, with most authors concluding a causal relationship between COVID-19 and AP. Retrospective case reports or small case series are unable to accurately determine the cause-effect relationship between COVID-19 and AP.

AIM

To establish whether COVID-19 is a cause of AP using the modified Naranjo scoring system.

METHODS

A systematic review was conducted on PubMed, World of Science and Embase for articles reporting COVID-19 and AP from inception to August 2021. Exclusion criteria were cases of AP which were not reported to be due to COVID-19 infection, age < 18 years old, review articles and retrospective cohort studies. The original 10-item Naranjo scoring system (total score 13) was devised to approximate the likelihood of a clinical presentation to be secondary to an adverse drug reaction. We modified the original scoring system into a 8-item modified Naranjo scoring system (total score 9) to determine the cause-effect relationship between COVID-19 and AP. A cumulative score was decided for each case presented in the included articles. Interpretation of the modified Naranjo scoring system is as follows: ≤ 3: Doubtful, 4-6: Possible, ≥ 7: Probable cause.

RESULTS

The initial search resulted in 909 articles, with 740 articles after removal of duplicates. A total of 67 articles were included in the final analysis, with 76 patients which had AP reported to be due to COVID-19. The mean age was 47.8 (range 18-94) years. Majority of patients (73.3%) had ≤ 7 d between onset of COVID-19 infection and diagnosis of AP. There were only 45 (59.2%) patients who had adequate investigations to rule out common aetiologies (gallstones, choledocholithiasis, alcohol, hypertriglyceridemia, hypercalcemia and trauma) of AP. Immunoglobulin G4 testing was conducted in 9 (13.5%) patients to rule out autoimmune AP. Only 5 (6.6%) patients underwent endoscopic ultrasound and/or magnetic resonance cholangiopancreatogram to rule out occult microlithiasis, pancreatic malignancy and pancreas divisum. None of the patients had other recently diagnosed viral infections apart from COVID-19 infection, or underwent genetic testing to rule out hereditary AP. There were 32 (42.1%), 39 (51.3%) and 5 (6.6%) patients with doubtful, possible, and probable cause-effect relationship respectively between COVID-19 and AP.

CONCLUSION

Current evidence is weak to establish a strong link between COVID-19 and AP. Investigations should be performed to rule out other causes of AP before establishing COVID-19 as an aetiology.

**Key Words:** COVID-19; Infections; Pancreatic diseases; Pancreatitis; Post-acute COVID-19 syndrome

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**Core Tip:** Numerous reports of acute pancreatitis (AP) have been published during the coronavirus disease 2019 (COVID-19) pandemic, citing COVID-19 as an aetiology of AP. However, COVID-19 has not been well-established to be a cause of AP. A total of 76 patients were included in our systematic review and were assessed using the modified Naranjo score; there were 32 (42.1%), 39 (51.3%) and 5 (6.6%) patients with doubtful, possible, and probable cause-effect relationship respectively between COVID-19 and AP. The link between COVID-19 and AP is weak based on current literature; COVID-19 should still remain a diagnosis of exclusion for AP until further evidence.

**INTRODUCTION**

Acute pancreatitis (AP) is a disease spectrum ranging from mild to severe, with an incidence of 50-80 per 100000 population[1]. Gallstone disorders and alcohol abuse remain the two commonest global causes of AP[2]. In rare circumstances, AP may be triggered by viral or parasitic infections[3,4]. Recently, there have been reports of AP caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of the time of this article, the coronavirus disease-2019 (COVID-19) pandemic is responsible for over 642 million infections and 6.6 million deaths worldwide[5]. While COVID-19 is primarily a respiratory disease, patients with COVID-19 infection may experience extra-pulmonary symptoms[6]. There has been an increase in reports of autoimmune and inflammatory conditions attributed to SARS-CoV-2[7], one example of which is AP. While there have been sporadic case reports and attempts at literature reviews on the potential cases of COVID-19-induced AP, the significant increase in cases reported raises concerns regarding COVID-19 as a definitive causal etiology for AP rather than an epiphenomenon[8].

The distinction between “association” *vs* “causation” can only be derived by prospective longitudinal studies involving a large population or by rigorous statistical analysis of large datasets and registries. It remains unproven if published reports of AP (effect) are beyond doubt due to COVID-19 infection (causal etiology). This is similar to determining whether symptoms experienced following ingestion of a new medication may be coined as an “adverse drug reaction” and attributed to that drug. Naranjo *et al*[9] designed a questionnaire to determine the likelihood of an adverse drug reaction (effect) due to a drug (causal etiology) rather than associated confounding factors[9]. Recently, we have reported the utility of modified Naranjo score to diagnose AP in patients prescribed with sulphasalazine[10]. This is a novel study which aims to systematically review case series and/or reports on COVID-19-induced AP and assess them using the modified Naranjo score to determine whether there is a cause-effect relationship.

**MATERIALS AND METHODS**

***Study selection and search strategy***

A systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines[11]. A literature search was performed on PubMed, World of Science and Embase for articles on COVID-19 and AP from inception till August 8, 2021. The following search terms were used: ((“COVID-19” OR “Coronavirus 19” OR “SARS-CoV-2”) AND (“Pancreatitis” OR “Acute Pancreatitis” OR “Acute Edematous Pancreatitis” OR “Pancreatic Inflammation”)); MeSH terms were used where available. Inclusion criteria were case series and/or case reports on AP, where the aetiology was thought to be COVID-19 infection. Exclusion criteria were (1) reports on AP but aetiology was not attributed to COVID-19 infection; (2) cases with patients < 18 years old; and (3) based on article type (non-English language, review articles and retrospective cohort and/or case-control studies). After removing of duplicates, three authors (Tang ZJT, Chua BQY, and Lim PK) independently screened the articles for potential inclusion by title and abstract. Subsequently, the full texts of screened studies were obtained and reviewed for eligibility. As some case reports may not have abstracts published, full texts were reviewed if abstracts were not available. Conflicts were resolved by appeal to the senior author.

***The modified Naranjo score***

The original Naranjo score was described by Naranjo *et al*[9] in 1981 as a means of approximating the likelihood of attributing a patient’s presentation to a medication and labelling it as an adverse drug reaction[9]. It consists of ten closed-ended questions with the options for “Yes”, “No,” and “Do not know”, each with varying points allocated from “- 1” to “+ 2”. The total score is 13 and may be interpreted as such: ≤ 0: Doubtful, 1-4: Possible; 5-8: Probably and ≥ 9: Definite. Existing studies have modified the Naranjo score to determine the cause-effect relationship in various pathologies[10]. In this review, we propose a modification to the Naranjo score to determine the likelihood of COVID-19-induced AP (Table 1). This is a 8-item scoring system with a total of 9 points; a cumulative score was calculated for each case, and a probability classification was assigned based on their score: ≤ 3: Doubtful, 4-6: Possible, ≥ 7: Probable.

Our modified version of the Naranjo score retained some of the questions used in the original study: Whether reports suggest a causal relationship, if the resolution of COVID-19 led to the resolution of AP, and ruling out alternative causes of AP. Common causes of AP were defined as gallstones, choledocholithiasis, alcohol, hypertriglyceridaemia, hypercalcaemia or trauma. Investigations for these included history and physical examination (for alcohol and trauma), biochemical investigations (for hypertriglyceridaemia and hypercalcemia), imaging studies (ultrasonography and/or computed tomography of the abdomen and pelvis) (for gallstones or choledocholiathisis) and endoscopic retrograde cholangiopancreatogram for choledocholithiasis in the presence of abnormal liver function test and/or biliary dilation. The original Naranjo score included the need for drug challenge test or placebo, but this was not appropriate for this study, as a “drug challenge” would imply re-introduction of COVID-19 infection and identifying if the patient had recurrence of AP. Instead, whether the resolution of infection led to the resolution of acute pancreatitis was included as a criterion.

We additionally included questions on whether there is a cause-effect temporal relationship and a more in-depth approach in ruling out the other aetiologies of AP. This included ruling out autoimmune pancreatitis with testing for serum Immunoglobulin G4 (IgG4)[12], or whether an endoscopic ultrasound (EUS) or magnetic resonance cholangiopancreatography (MRCP) was performed to rule out occult microlithiasis, pancreatic malignancy or pancreatic divisum[13]. While genetic testing to rule out hereditary pancreatitis is a consideration[14], this was omitted in our modified Naranjo score as none of the included articles performed genetic tests for confirming/excluding hereditary pancreatitis. Additionally, there are no strict recommendations on the exact indications for genetic counselling and/or testing in AP, limiting its utility for inclusion in our proposed scoring system[15].

***Data extraction***

Three authors (Tang ZJT, Chua BQY, and Lim PK) performed all data extraction independently using the systematic review management tool Covidence (https://www.covidence.org). The following data were extracted: Year of study, age, and gender of the patient, and features relevant to the modified Naranjo score, as shown in Table 1.

**RESULTS**

The initial search resulted in 909 articles, with 740 articles after removal of duplicates. A total of 67 articles were included in the final analysis (Figure 1). There was a total of 76 patients which had AP reported to be due to COVID-19. Data extracted from all cases were reported in Table 2[16-82]. Seventy-six patients with a mean age of 47.8 years (range 18-94) were reported. There were 32 (42.1%), 39 (51.3%) and 5 (6.6%) patients with doubtful, possible, and probable cause-effect relationship respectively between COVID-19 and AP (Figure 2A). Majority of patients (73.7%, *n* = 56/76) had a short duration of latency (≤ 7 d) between the onset of infection and AP. Most reports did not explore the temporal relation between COVID-19 and AP; only 20 (26.3%) patients were described to have a temporal relationship between COVID-19 and AP. Common aetiologies of AP were ruled out in 45 (59.2%) patients. Serum IgG4 Levels were tested to rule out autoimmune pancreatitis in 9 (13.6%) patients. None of the patients were recently diagnosed with an infection known to cause AP, *e.g.*, Coxsackie virus, cytomegalovirus, or herpes simplex virus. Only a minority (6.6%, *n* = 5/76) underwent either EUS or ERCP. None of the patients underwent genetic testing, *e.g.*, *SPINK-1*, to rule out hereditary AP.

**DISCUSSION**

AP is a common cause of acute abdominal pain and hospital admissions and present as a disease spectrum[83]. In view of the COVID-19 pandemic, many retrospective case reports suggesting COVID-19 as a cause of AP have been published. It is an obligation to critically appraise these reports to define the strength of the association and evaluate if the co-occurrence is a mere association or actual causation. This novel study adopted the modified Naranjo scale and concluded the cause-effect relationship between COVID-19 and AP in most reports as doubtful (42.1%) or possible (51.3%).

While gallstones and alcohol consumption remain the most common aetiologies, in rare situations, viral infections have been reported to cause AP[3,4]. However, this should be a diagnosis of exclusion after ruling out of common aetiologies for AP. In our review, the reason why strong conclusions could not be drawn for most cases was the absence of serum IgG4 Levels (86.4%) to rule out autoimmune AP (score of + 1) and EUS or MRCP (93.4%) to rule out structural causes (*e.g.* occult microlithiasis or pancreatic divisum) (score of +1). Authors reporting further cases of AP where COVID-19 is suggested as an aetiology should perform these tests to rule out other aetiologies of AP prior to conclusion of COVID-19-induced AP. While the results do not confirm AP as a possible aetiology of COVID-19, it is still prudent to consider COVID-19 when patients present with AP, especially if there are concurrent clinical features of COVID-19 with temporal relation of symptoms and if other common causes are ruled out.

The current literature is torn on the idea that the SARS-CoV2 virus could have induced the recent cases of AP, where some propose a direct causal relationship and others claim the SARS-CoV2 virus as a bystander in the instances of idiopathic AP[84-86]. For the former, two possible mechanisms have been described: The direct effect of the SARS-CoV2 RNA on pancreatic tissue due to viral tropism and the indirect effect due to microthrombi formation. Regarding the direct mechanism, the expression of the angiotensin converting enzyme 2 (ACE2) protein on the SARS-CoV2 virus primes its entry into the pancreas. This expression of the ACE2 protein was similarly found in the islet and exocrine tissue microvasculature and in a subset of pancreatic ducts, as well as the TMPRSS2 proteins found in the ductal cells[84]; this suggests entry of SARS-CoV2 into pancreatic tissue resulting in AP. Regarding the indirect mechanism, SARS-CoV2 causes microthrombi formation due to its ability to invade endothelial cells *via* the ACE2 protein. This phenomenon is also observed in other virus infections, such as viral hepatitis[85]. Microthrombus in vasculature triggers hypoperfusion of the pancreas, resulting in ischemic pancreatitis. However, the above theories are merely conjectures made from parallel existing conditions superimposed on an under-researched virus. The possibility of COVID-19 being a pure bystander in the formation of AP also exists. This may be a situation of Occam’s razor– where we look to connect the dots between a relatively new disease and the patients’ manifestations– *vs* a pure case of Hickam’s dictum– where a patient happens to present with two mutually exclusive conditions. After all, it must be noted that idiopathic AP is a function of diagnostic workup efforts[86]. The lack of serological tests for IgG4, MRCP scan, and EUS imaging could inflate the association between COVID-19 and AP. As randomized studies cannot be conducted to establish COVID-19 as an aetiology for AP, critical appraisal of retrospective data is essential to discern association from causation.

The temporal relation of events is one of the important determinants of distinguishing causation from the association. Many authors did not explicitly mention a temporal relation of onset or resolution of COVID-19 and AP. While COVID-19 infections primarily involve the respiratory system, multi-systemic involvement have been reported. Since COVID-19 is a prerequisite for COVID-19 associated AP, we shall discuss the respiratory and imaging features first. COVID-19-induced AP may manifest in the absence of any respiratory symptoms or radiological evidence of lung involvement. Purayil *et al*[67] reported a 58-year-old male presenting with abdominal pain; a polymerase chain reaction (PCR) for COVID-19 was only done in response to his chest x-ray, which revealed bilateral infiltrates in the absence of respiratory symptoms[67]. A chest x-ray is routinely performed in patients with acute abdomen to rule out free air under the diaphragm secondary to hollow viscus perforation, which also can cause hyperamylasaemia and remain an important differential diagnosis of AP[87]. Additionally, chest x-ray findings form a part of scoring systems to predict severity and clinical outcomes in AP patients[88,89]. In the patient reported by Purayil *et al*[67], the chest x-ray was sensitive to detect COVID-19 changes and complemented the diagnostic work-up for epigastric pain. As most patients with AP will have a chest x-ray performed and due to the widespread prevalence of COVID-19 in the community, it is not possible to ascertain if COVID-19 resulted in AP or if the two diseases merely occurred simultaneously yet independently of each other.

The prevalence of gastrointestinal symptoms in COVID-19 infected patients ranges from 3.0%-79%, of which only 2.2%-6.0% of patients present with abdominal pain[90-92]. Abdominal pain is the most common symptom of AP and acute epigastric pain is one of the key diagnostic criteria of AP. Thus it remains unclear if gastrointestinal manifestations of COVID-19 are secondary to AP. Though resuscitation and early management of AP patients are not determined by aetiology, definite management for prevention of future occurences is determined by aetiology. Thus, knowledge of COVID-19 as an aetiology of AP is important as it stops the pursuit of aetiology identification, guides physician on the counselling of their patients, and impacts management decision for cholecystectomy. In patients with mild biliary pancreatitis, index admission laparoscopic cholecystectomy is considered good clinical practice while surgery should be delayed in patients with COVID-19 infection to minimize risk to healthcare workers and reduce patient morbidity[93,94]. Shao *et al*[95] analysed 589 patients with COVID-19 infection prior to surgery and concluded that postoperative mortality was nearly 6 times higher for patients infected with COVID-19 within 2 wk before surgery when adjusting for patient and procedure level factors[95]. Furthermore, delaying cholecystectomy in patients with biliary pancreatitis could increase the risk of future biliary events[88]. Thus, determining the aetiology of AP is essential as it impacts clinical decisions.

In addition to abdominal pain and imaging features, it is important to discuss the role of serum enzymes. While both amylase and lipase are usually measured in patients presenting with acute abdomen suggesting AP, the timing at which they rise can be cross-referenced to the time at which COVID-19 infection was diagnosed, which may shed some light on whether COVID-19 is a cause of AP, or merely coincidental. Amylase tends to rise within 3 to 6 h of AP and persists for up to 5 d. However, serum amylase has a relatively short half-life of 12 h and may return to normal limits within a day. Serum lipase rises similarly within 3 to 6 h, peaks at 24 h, and persists for 8 to 14 d. Hence, a patient with raised amylase or lipase alongside a concomitant COVID-19 infection before this time span of 12-24 h may still have AP caused by COVID-19. This clarity blurs if we consider the virus's incubation period and heterogeneity in the clinical presentation of both COVID-19 and AP. Stephens *et al*[96] reported 234 COVID-19 positive patients in the critical care unit, of which 52 (22.2%) patients had peak amylase three times the upper limit of normal, of which only 4 (1.7%) met the revised Atlanta criteria for diagnosis of AP[96]. Furthermore, some authors report COVID-19 associated hyperamylasemia secondary to pancreatic injury which does not amount to clinical AP[97,98]. This could be attributed to amylase release from other viscera like the gastrointestinal tract or elevated serum levels due to reduced renal excretion as a result of critical illness-related kidney injury[96]. A contrast-enhanced imaging remains an essential tool to diagnose AP, but it would not establish COVID-19 as a causative aetiology.

As the temporal occurrence of events (*e.g.* onset of abdominal pain, chest x-ray imaging, serum enzymes, and abdominal imaging) do not aid the distinction of causation or association, a different approach is essential. This situation is similar to the dilemma of attributing a clinical presentation towards an adverse drug reaction. The Naranjo score is a useful tool that aids clinical judgment in differentiating the cause-effect relationship between a drug and its possible adverse drug reaction[9]. While useful in determining the causality, it should be noted that the scale does not offer prognostic information. In addition, the Naranjo score includes isolating toxic concentrations of drugs in body fluids, clinical response to placebo administration, and a drug rechallenge to assess symptoms occurrence. While most authors report positive COVID-19 rapid antigen test and PCR, the response to placebo and re-infection are not reported. It is not possible to assess if the patients were re-infected with COVID-19 (after reporting of the case) with repeat AP and unethical to do this experimentally. Thus, no comment can be made on whether a ‘re-challenge’ would bring about similar symptoms. If these parameters are scored negative, many cases would be disadvantaged from the strength of causation, and thus, a modification of the Naranjo score that excludes placebo administration and re-infection was considered essential to determine COVID-19 as a cause of AP fairly. This approach has been reported in the past for sulphasalazine-induced AP and prednisolone induced pneumatosis coli[10,99]. Using this strategy, we determined the strength of association and possible causation as doubtful, possible or probable. Other established methods of determining a causal relationship between various aetiological agents and AP include the Badalov categorisation[100]. The Badalov categorisation was similarly designed to investigate association between drugs and adverse drug reactions; this involves assigning drugs into 5 categories (Class Ia, Ib, II, III and IV) based on the number of case reports published, drug rechallenge, latency and whether alternative causes were excluded. However, we have chosen to adopt the Naranjo score as it allows for a case-by-case evaluation of each report as opposed to a blanket categorization of COVID-19 as a possible aetiological agent of AP. Secondly, the Naranjo score also provides a better idea on the degree of association by generating data on a numerical scale which allows for in-depth analysis. Centers should continue reporting such occurrences of COVID-19-induced pancreatitis and consider incorporating our modified Naranjo score; artificial intelligence methods may subsequently be used to diagnose COVID-19-induced pancreatitis[101,102].

However, our study has its limitations. Firstly, given the nature of our study, prospective studies and systematic reviews were not analysed as they lack individual patient data. Additionally, interpretation of this study is limited by the small sample size of 76 patients. Secondly, a majority of included case reports date after the introduction of the COVID-19 vaccine. Many reports did not mention the vaccination status of the patient; COVID-19 vaccination has also been reported as a potential cause of AP which adds on to the dilemma[24,103]. Thirdly, with the advent of novel drugs used in COVID-19 treatment, the possibility of drug-induced AP needs to be considered as a differential diagnosis. Remdesivir is an antiviral drug widely used in the management of COVID-19 and it is increasingly reported to cause pancreatic injury with associated hyperamylasaemia as well as AP[104,105]. Fourthly, authors may not have reported cases where patients were reinfected by COVID-19. This is a potential limitation in the calculation of the modified Naranjo score. Fifthly, the determination of the criteria for “doubtful”, “possible” and “probable” is arbitrary. If we subtract one point from the minimum of each category (*i.e.* ≤ 2 for doubtful, 3-5 for possible and ≥ 6 for probable) to increase the causation strength, this would result in 8 (compared to 32) patients, 49 patients (compared to 39), and 19 patients (compared to 5) respectively (Figure 2A and B). As the median score was 4, if we use it as the cut-off, 32 patients (score < 4) will be categorized as “less likely” and 44 patients (score ≥ 4) as “more likely” to have COVID-19-induced AP. Thus, the assignment of scores, though partly arbitrary, the fact still prevails that existing reports have doubt about COVID-19 infection causing AP. Lastly, while some of the screened cases reported fatalities[13], our study did not assess the severity and mortality of COVID-19 induced AP.

**CONCLUSION**

The use of our proposed modified Naranjo score may help to determine whether COVID-19 is a likely aetiology of AP and may assist clinicians in making useful clinical decisions. The current evidence is weak to establish a strong causal link between COVID-19 and AP, and more evidence is necessary before COVID-19 should be incorporated as a “textbook aetiology” of AP.

**ARTICLE HIGHLIGHTS**

***Research background***

Acute pancreatitis (AP) is a disease spectrum ranging from mild to severe disease. During the Coronavirus Disease-2019 (COVID-19) pandemic, numerous reports of AP have been published, with most authors concluding a causal relationship between COVID-19 and AP.

***Research motivation***

Published reports or case series of COVID-19-induced AP are retrospective in nature and are unable to accurately determine the cause-effect relationship between COVID-19 and AP.

***Research objectives***

This study aims to establish whether COVID-19 is a cause of AP by proposing a scoring system *i.e.* the modified Naranjo scoring system.

***Research methods***

A systematic review was conducted on PubMed, World of Science and Embase for articles reporting COVID-19 and AP from inception to August 2021. Exclusion criteria were cases of AP which were not reported to be due to COVID-19 infection, age < 18 years old, review articles and retrospective cohort studies. The original 10-item Naranjo scoring system (total score 13) was devised to approximate the likelihood of a clinical presentation to be secondary to an adverse drug reaction. We modified the original scoring system into a 8-item modified Naranjo scoring system (total score 9) to determine the cause-effect relationship between COVID-19 and AP. A cumulative score was decided for each case presented in the included articles. Interpretation of the modified Naranjo scoring system is as follows: ≤ 3: Doubtful, 4-6: Possible, ≥ 7: Probable cause.

***Research results***

The initial search resulted in 909 articles, with 740 articles after removal of duplicates. A total of 67 articles were included in the final analysis, with 76 patients which had AP reported to be due to COVID-19. The mean age was 47.8 (range 18-94) years. Majority of patients (73.3%) had ≤ 7 d between onset of COVID-19 infection and diagnosis of AP. There were only 45 (59.2%) patients who had adequate investigations to rule out common aetiologies (gallstones, choledocholithiasis, alcohol, hypertriglyceridemia, hypercalcemia and trauma) of AP. Immunoglobulin G4 testing was conducted in 9 (13.5%) patients to rule out autoimmune AP. Only 5 (6.6%) patients underwent endoscopic ultrasound and/or magnetic resonance cholangiopancreatogram to rule out occult microlithiasis, pancreatic malignancy and pancreas divisum. None of the patients had other recently diagnosed viral infections apart from COVID-19 infection, or underwent genetic testing to rule out hereditary AP. There were 32 (42.1%), 39 (51.3%) and 5 (6.6%) patients with doubtful, possible, and probable cause-effect relationship respectively between COVID-19 and AP.

***Research conclusions***

Current evidence is weak to establish a strong link between COVID-19 and AP. Investigations should be performed to rule out other causes of AP before establishing COVID-19 as an aetiology.

***Research perspectives***

The use of our proposed modified Naranjo score may help to determine whether COVID-19 is a likely etiology of AP and may assist clinicians in making useful clinical decisions.

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Grade B (Very good): 0

Grade C (Good): C, C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Ait Addi R, Morocco; Jamshidi MB, Czech Republic **S-Editor:** Li L **L-Editor:** A **P-Editor:** Li L

**Figure Legends**



**Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses figure showing the study selection process.**



**Figure 2 Graphical representation of the probability of Coronavirus Disease-2019 as an aetiology of acute pancreatitis.** A: Using the modified Naranjo score proposed; B: Using the modified Naranjo score, if a score of 1 was subtracted from the minimum cut-off for each category, where ≤ 2 is for doubtful, 3-5 is for possible and ≥ 6 is for probable significance. COVID-19: Coronavirus Disease-2019.

**Table 1 Modified Naranjo Score used to grade the included studies with respective points allocated to each criterion**

|  |  |  |  |
| --- | --- | --- | --- |
| **Criteria** | **Yes** | **No** | **Unsure** |
| Are there published reports of the COVID-19 causing acute pancreatitis? | + 1 | 0 | 0 |
| Was there short latency (≤ 7 d) between the onset of infection and the diagnosis of acute pancreatitis? | + 2 | - 1 | 0 |
| Was there a temporal relationship (≤ 1 mo) between onset of infection and onset of acute pancreatitis symptoms? | + 1 | - 1 | 0 |
| Did the acute pancreatitis resolve following resolution of the infection? | + 1 | - 1 | 0 |
| Were all commonly known causes of acute pancreatitis ruled out? (*e.g.*, gallstones/choledocholithiasis, alcohol, hypertriglyceridaemia, hypercalcaemia, ERCP, trauma) | + 1 | - 1 | 0 |
| Was a serum IgG4 level checked? (To rule out autoimmune pancreatitis) | + 1 | 0 | 0 |
| Does the patient have or was the patient recently diagnosed with an infection (other than COVID-19) which could cause pancreatitis? | - 1 | + 1 | 0 |
| Was an EUS and/or MRCP performed? (*e.g.*, to rule out occult microlithiasis, pancreatic malignancy and pancreas divisum) | + 1 | - 1 | 0 |

COVID-19: Corona Virus Infectious Disease-2019; IgG4: Immunoglobulin G4; ERCP: Endoscopic retrograde cholangiopancreatography; EUS: Endoscopic ultrasound; MRCP: Magnetic resonance cholangiopancreatography.

**Table 2 Summary of all the included case reports (*n* = 76 patients) with respective patient demographics, modified Naranjo Score and interpretation**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **No** | **First author** | **Year** | **Patient Age/Sex** | **Scoring** | **Summed Score** | **Result1** |
| 1 | Acherjya *et al*[16] | 2020 | 57/F | 1 | 2 | 1 | 1 | 1 | 0 | 1 | - 1 | 6 | Possible |
| 2 | Al-Douri *et al*[17] | 2020 | 45/F | 1 | 2 | 1 | 0 | 1 | 0 | 1 | - 1 | 5 | Possible |
| 3 | Al-Harmi *et al*[18] | 2021 | 52/F | 1 | 0 | 1 | 0 | 1 | 0 | 1 | - 1 | 3 | Doubtful |
| 4 | Ali *et al*[19] | 2021 | 53/M | 1 | 0 | 1 | 0 | - 1 | 0 | 1 | - 1 | 1 | Doubtful |
| 5 | Aloysius *et al*[20] | 2020 | 36/F | 1 | 2 | 1 | 1 | 1 | 0 | 1 | - 1 | 6 | Possible |
| 6 | Alves *et al*[21] | 2020 | 56/F | 1 | 2 | 1 | 1 | 1 | 0 | 1 | 1 | 8 | Probable |
| 7 | Alwaeli *et al*[22] | 2020 | 30/M | 1 | 2 | 1 | 0 | 1 | 0 | 1 | - 1 | 5 | Possible |
| 8 | Amé and Balderramo[23] | 2022 | 42/F | 1 | 2 | 1 | 0 | 1 | 0 | 1 | - 1 | 5 | Possible |
| 9 |  | 65/F | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 6 | Possible |
| 10 | Anand *et al*[24] | 2020 | 59/F | 1 | 0 | 1 | 0 | 1 | 0 | 1 | - 1 | 3 | Doubtful |
| 11 | Arjun *et al*[25] | 2020 | 34/M | 1 | 2 | 1 | 1 | 1 | 1 | 1 | - 1 | 7 | Probable |
| 12 | Bains *et al*[26] | 2020 | 68/M | 1 | 2 | 1 | 0 | - 1 | 0 | 1 | 1 | 5 | Possible |
| 13 | Bokhari and Mahmood[27] | 2020 | 32/M | 1 | 2 | 1 | 0 | 1 | 0 | 1 | - 1 | 5 | Possible |
| 14 | Bouali *et al*[28] | 2021 | 60/F | 1 | 2 | 1 | 0 | - 1 | 0 | 1 | - 1 | 3 | Doubtful |
| 15 | Brikman *et al*[29] | 2020 | 61/M | 1 | 0 | 1 | 0 | 1 | 0 | 1 | - 1 | 3 | Doubtful |
| 16 | Canastar *et al*[30] | 2020 | 64/M | 1 | 2 | 1 | 0 | - 1 | 0 | 1 | - 1 | 3 | Doubtful |
| 17 | Chandra *et al*[31] | 2021 | 53/M | 1 | 2 | 1 | 0 | - 1 | 0 | 1 | - 1 | 3 | Doubtful |
| 18 | Cheung *et al*[32] | 2020 | 38/M | 1 | 2 | 1 | 0 | 1 | 1 | 1 | 1 | 8 | Probable |
| 19 | Chivato *et al*[33] | 2021 | 55/M | 1 | 2 | 1 | 1 | 1 | 0 | 1 | 1 | 8 | Probable |
| 20 | Dufani *et al*[34] | 2020 | 27/F | 1 | 2 | 1 | 0 | 1 | 0 | 1 | - 1 | 5 | Possible |
| 21 | Elhence *et al*[35] | 2020 | 31/F | 1 | 0 | 1 | 0 | - 1 | 0 | 1 | - 1 | 1 | Doubtful |
| 22 |  | 40/M | 1 | 0 | 1 | 0 | - 1 | 0 | 1 | - 1 | 1 | Doubtful |
| 23 |  | 42/M | 1 | 0 | 1 | 0 | - 1 | 0 | 1 | - 1 | 1 | Doubtful |
| 24 | Fernandes *et al*[36] | 2020 | 36/F | 1 | 2 | 1 | 1 | 1 | 0 | 1 | - 1 | 6 | Possible |
| 25 | Fiore *et al*[37] | 2021 | 42/M | 1 | 2 | 1 | 0 | 1 | 0 | 1 | - 1 | 5 | Possible |
| 26 |  | 70/M | 1 | 0 | 1 | 0 | 1 | 0 | 1 | - 1 | 3 | Doubtful |
| 27 | Gadiparthi *et al*[38] | 2020 | 40/M | 1 | 2 | 1 | 1 | - 1 | 0 | 1 | - 1 | 4 | Possible |
| 28 | Gadiparthi *et al*[39] | 2021 | 74/F | 1 | 2 | 1 | 0 | 1 | 0 | 1 | - 1 | 5 | Possible |
| 29 | Gonzalo-Voltas *et al*[40] | 2020 | 76/F | 1 | 2 | 1 | 1 | 1 | 0 | 1 | - 1 | 6 | Possible |
| 30 | Gupta *et al*[41] | 2021 | 25/F | 1 | 2 | 1 | 1 | 1 | 0 | 1 | -1 | 6 | Possible |
| 31 | Hadi *et al*[42] | 2020 | 47/F | 1 | 2 | 1 | 0 | - 1 | 0 | 1 | - 1 | 3 | Doubtful |
| 32 |  | 68/F | 1 | 2 | 1 | 0 | - 1 | 0 | 1 | - 1 | 3 | Doubtful |
| 33 | Hanif *et al*[43] | 2021 | 30/F | 1 | 2 | 1 | 0 | - 1 | 0 | 1 | - 1 | 3 | Doubtful |
| 34 | Hassani *et al*[44] | 2020 | 78/F | 1 | 2 | 1 | 0 | 1 | 0 | 1 | - 1 | 5 | Possible |
| 35 | Ibrahim *et al*[45] | 2020 | 33/M | 1 | 2 | 1 | 0 | - 1 | 0 | 1 | - 1 | 3 | Doubtful |
| 36 | Jespersen Nizamic *et al*[46] | 2020 | 49/W | 1 | 0 | 1 | 0 | 1 | 0 | 1 | - 1 | 3 | Doubtful |
| 37 | Kandasamy[47] | 2020 | 45/F | 1 | 2 | 1 | 1 | 1 | 0 | 1 | - 1 | 6 | Possible |
| 38 | [Karimzadeh](https://www.ncbi.nlm.nih.gov/pubmed/?term=Karimzadeh%20S%5BAuthor%5D&cauthor=true&cauthor_uid=32576441) *et al*[48] | 2020 | 65/F | 1 | 2 | 1 | 0 | - 1 | 0 | 1 | - 1 | 3 | Doubtful |
| 39 | Kataria and Sharif[49] | 2020 | 49/F | 1 | 2 | 1 | 1 | 1 | 0 | 1 | - 1 | 6 | Possible |
| 40 | Kolhe *et al*[50] | 2020 | 19/F | 1 | 2 | 1 | 1 | 1 | 0 | 1 | - 1 | 6 | Possible |
| 41 | Kumaran *et al*[51] | 2020 | 67/F | 1 | 2 | 1 | 1 | 1 | 1 | 1 | - 1 | 7 | Probable |
| 42 | Kurihara *et al*[52] | 2020 | 55/M | 1 | 0 | 1 | 0 | 1 | 0 | 1 | - 1 | 3 | Doubtful |
| 43 | Lakshmanan and Malik[53] | 2020 | 68/M | 1 | 2 | 1 | 0 | 1 | 0 | 1 | - 1 | 5 | Possible |
| 44 | Maalouf *et al*[54] | 2021 | 62/M | 1 | 2 | 1 | 0 | 1 | 0 | 1 | - 1 | 6 | Possible |
| 45 | Mazrouei *et al*[55] | 2020 | 24/M | 1 | 2 | 1 | 0 | - 1 | 0 | 1 | - 1 | 3 | Doubtful |
| 46 | Meireles *et al*[56] | 2020 | 36/F | 1 | 0 | 1 | 1 | 1 | 1 | 1 | - 1 | 5 | Possible |
| 47 | Merza *et al*[57] | 2020 | 57/M | 1 | 2 | 1 | 0 | - 1 | 0 | 1 | - 1 | 3 | Doubtful |
| 48 |  | 70/M | 1 | 0 | 1 | 0 | - 1 | 0 | 1 | - 1 | 1 | Doubtful |
| 49 | Meyers *et al*[58] | 2020 | 67/M | 1 | 2 | 1 | 0 | - 1 | 1 | 1 | - 1 | 4 | Possible |
| 50 | Miao *et al*[59] | 2020 | 26/F | 1 | 2 | 1 | 0 | - 1 | 0 | 1 | - 1 | 3 | Doubtful |
| 51 | Mobin *et al*[60] | 2020 | 18/M | 1 | 2 | 1 | 0 | 1 | 0 | 1 | - 1 | 5 | Possible |
| 52 |  | 66/M | 1 | 2 | 1 | 1 | - 1 | 0 | 1 | - 1 | 4 | Possible |
| 53 | Mohammadi Arbati and Molseghi[61] | 2021 | 28/M | 1 | 2 | 1 | 0 | - 1 | 0 | 1 | - 1 | 3 | Doubtful |
| 54 | Muhammad Abrar Jeelani *et al*[62] | 2021 | 24/M | 1 | 0 | 1 | 1 | 1 | 0 | 1 | - 1 | 4 | Possible |
| 55 | Naqvi *et al*[63] | 2020 | 69/F | 1 | 2 | 1 | 0 | 1 | 0 | 1 | - 1 | 5 | Possible |
| 56 | Narang *et al*[64] | 2021 | 20/F | 1 | 2 | 1 | 0 | 1 | 1 | 1 | - 1 | 6 | Possible |
| 57 | Patnaik *et al*[65] | 2020 | 29/M | 1 | 2 | 1 | 0 | 1 | 0 | 1 | - 1 | 5 | Possible |
| 58 | Pinte and Baicus[66] | 2020 | 47/M | 1 | 0 | 1 | 0 | 1 | 0 | 1 | - 1 | 4 | Possible |
| 59 | Purayil *et al*[67] | 2020 | 58/M | 1 | 2 | 1 | 0 | - 1 | 0 | 1 | - 1 | 3 | Doubtful |
| 60 | Rabice *et al*[68] | 2020 | 36/F | 1 | 2 | 1 | 1 | 1 | 0 | 1 | - 1 | 6 | Possible |
| 61 | Rotar *et al*[69] | 2020 | 39/M | 1 | 2 | 1 | 0 | - 1 | 0 | 1 | - 1 | 3 | Doubtful |
| 62 | Sandhu *et al*[70] | 2021 | 25/F | 1 | 2 | 1 | 0 | 1 | 0 | 1 | - 1 | 5 | Possible |
| 63 | Shinohara *et al*[71] | 2020 | 58/M | 1 | 0 | 1 | 1 | - 1 | 0 | 1 | - 1 | 2 | Doubtful |
| 64 | Simou *et al*[72] | 2020 | 67/NM | 1 | 0 | 1 | 0 | - 1 | 0 | 1 | - 1 | 1 | Doubtful |
| 65 | Singh and Kharoud[73] | 2020 | 94/F | 1 | 2 | 1 | 0 | 1 | 1 | 1 | - 1 | 6 | Possible |
| 66 |  | 58/F | 1 | 0 | 1 | 0 | 1 | 1 | 1 | - 1 | 4 | Possible |
| 67 | Srinivasan *et al*[74] | 2021 | 52/F | 1 | 2 | 1 | 0 | - 1 | 0 | 1 | - 1 | 3 | Doubtful |
| 68 | Tollard *et al*[75] | 2021 | 32/F | 1 | 2 | 1 | 0 | 1 | 0 | 1 | - 1 | 5 | Possible |
| 69 | Tomasi *et al*[76] | 2021 | 31/M | 1 | 2 | 1 | 0 | 1 | 0 | 1 | - 1 | 5 | Possible |
| 70 | Truscello *et al*[77] | 2020 | 71/M | 1 | 2 | 1 | 0 | - 1 | 0 | 1 | - 1 | 3 | Doubtful |
| 71 | Wang *et al*[78] | 2020 | 42/M | 1 | 2 | 1 | 0 | 1 | 0 | 1 | - 1 | 5 | Possible |
| 72 |  | 35/M | 1 | 2 | 1 | 1 | 1 | 0 | 1 | - 1 | 6 | Possible |
| 73 | Wifi *et al*[79] | 2021 | 72/F | 1 | 2 | 1 | 0 | - 1 | 0 | 1 | - 1 | 3 | Doubtful |
| 74 | Yamamoto *et al*[80] | 2021 | 70/F | 1 | 0 | 1 | 0 | - 1 | 0 | 1 | - 1 | 1 | Doubtful |
| 75 | Zeng *et al*[81] | 2020 | 36/M | 1 | 2 | 1 | 0 | 0 | 0 | 1 | - 1 | 4 | Possible |
| 76 | Zielecki *et al*[82] | 2020 | 38/M | 1 | 0 | 1 | 1 | - 1 | 0 | 1 | 0 | 3 | Doubtful |

**1**Interpretation of the modified Naranjo score is as follows: ≤ 3: Doubtful, 4-6: Possible, ≥ 7: Probable.

F: Female; M: Male; NM: Not mentioned.