Capítulo 93

Pancreatic repercussions among patients with COVID-19: Integrative Literature Review

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ABSTRACT
Despite the important findings related to the tropism of the virus by the pancreas and the severity of these repercussions among patients, it is still unclear in the literature which are the main changes and diagnoses commonly found in patients with COVID-19 with pancreatic symptoms. METHODOLOGY: This is an integrative literature review, conducted according to the PRISMA guidelines. The review was conducted in the Pubmed, VHL, and Elsevier databases. Studies conducted with adults of both sexes were included and reviews, research editorials, letters to the reader, or editorial comments were excluded. The search and selection process was conducted by peers. RESULTS: Of 131 studies identified only 07 were included. There was a predominance of descriptive studies with non-probability sample variability. The main gastrointestinal symptoms reported were abdominal pain (localized in the right iliac fossa and/or diffuse), nausea, vomiting (of non-biliary nature), and/or diarrhea. From the pancreatic repercussions, it was noticed the presence of acute pancreatitis was in about 24% of the studies included in the review, and it was seen that these patients needed oxygen, through mechanical ventilation or nasal catheter. CONCLUSION patients infected with the SARS-CoV-2 virus, showed changes at the pancreatic level, had elevated serum lipase and the minority cited increased amylase, and some had the outcome of pancreatitis. However, research is still inconclusive and lacking in information on the subject, which makes further studies in the area necessary.

Keywords: Pancreatitis, Pancreas, COVID-19.

1 INTRODUCTION

In December 2019, in the province of Wuhan, China, the first case of infection with the SARS-CoV-2 virus that causes severe acute respiratory syndrome, widely known as Coronavirus-19 (COVID-19) (CHMIELIK, 2021; TURCO, 2020; SRAN, 2021). In a short time, the virus spread to more than 100 countries, becoming a serious public health problem worldwide, since in a short period, the infection had already reached more than 186 million people, leading to approximately more than 4 million deaths from December 2019 to July 12, 2021 (WHO, 2021).

Among the classic clinical manifestations, characterized by cough, dyspnea, and fever (FANG, 2021), several studies have pointed to the presence of extrapulmonary symptoms, such as fatigue, myalgia, and headache (ALSHARIF, 2021; WEST, 2021; MESQUITA, 2021; CHUNG, 2021).

Particularly other outcomes considered serious have been attributed to COVID-19 infection, as an example a substantial body of evidence that reported outcomes related to cardiovascular diseases, such as myocarditis, myocardial infarction, microvascular thrombosis; neurological, such as neuroinflammation, neurodegeneration, depression and ischemic stroke; renal diseases, such as acute kidney injury, chronic kidney disease, renal and liver failure, such as liver damage with transaminitis and cholangiocellular injury (GARG, 2021; TAJBAKHSH, 2021; MAHALAKSHMI, 2021; BITENCOURT, 2021; MAGRO, 2021; NARDO, 2021).

In this context, reports also show gastrointestinal manifestations including the presence of abdominal pain, nausea, vomiting, and diarrhea (JEELANI, 2021). In addition, it is possible to emphasize that COVID-19, in addition to causing changes in the organs already mentioned above, also had studies that showed changes at the pancreatic level, in addition to other organs that suffer from the consequences of this infection (PATEL, 2020).

Although pancreatic lesions have well-known etiologies, the SARS-CoV-2 virus is an emerging pathogen that complicates pancreatic lesions (WIFI, 2021), even though most reported cases have so far been of symptom presentation. mild pancreatic disorders (WIFI, 2021).

Regarding possible correlations, studies show that the SARS-CoV-2 virus seems to have a tropism with ACE2 receptors, present in the cells of the islets of the pancreas, which can cause pancreatic damage (PANDANABOYANA, 2021). In addition, these enzymatic alterations also point to a possible picture of acute pancreatitis which, according to the Atlanta classification, can be diagnosed when two of the three established criteria are met: 1- abdominal pain characteristic of pancreatitis; 2- elevated levels of pancreatic enzymes (lipase or amylase) at least three times above the reference value; 3- radiological findings (RAMSEY, 2021).

Despite the important findings related to the tropism of the virus for the pancreas and the severity of these repercussions among patients, it is still unclear in the literature which are the main alterations and diagnoses commonly found in patients who present COVID-19 with pancreatic symptoms.

2 METHODOLOGY

This is an integrative literature review, carried out following the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analyses- PRISMA (BRASIL, 2014). The research question included the PICO strategy (AROMATARIS et al., 2017), whose acronym represents: Patient (P), Intervention (I), Context (Co) and was defined by: "What are the pancreatic repercussions associated with COVID-19? 19? The review was conducted in the Pubmed, BVS and Elsevier databases. The descriptors registered in Imesh, COVID-19", "pancreas" and "pancreatitis" were used, combined from the logical operator "AND".

The inclusion criteria for the studies involved: 1- Case report studies, case series, and also observational studies; 2- Studies carried out with adults of both sexes; 3-Studies published in the year 2021; 4- Evidencing the RT-PCR diagnostic method for SARS-CoV-2; 5- Published in English, Spanish or Portuguese. The following were excluded: 1- Repeated studies in the database; 2-Samples with patients with pre-existing pancreatic diseases; 3-Systematic review, research editorials, letters to the reader, or editorial comments.

The search and selection process was conducted by peers and consensus meetings were conducted with a third senior researcher to reduce discrepancies and include studies, reducing the risk of methodological bias in the entry of articles.

In the initial stage of the analysis, titles and abstracts were read, followed by a critical reading of the full text of those studies considered possibly eligible.

For the construction of the tables of results, the following information was extracted: Country where the study was carried out, sample size, age group, inclusion and exclusion criteria, length of stay, respiratory symptoms on admission, gastrointestinal symptoms, clinical evolution, and pancreatic repercussions.

3 RESULTS

Of a total of 131 studies, in the end, only 11 were included because they met all the inclusion criteria (FIGURE 1).

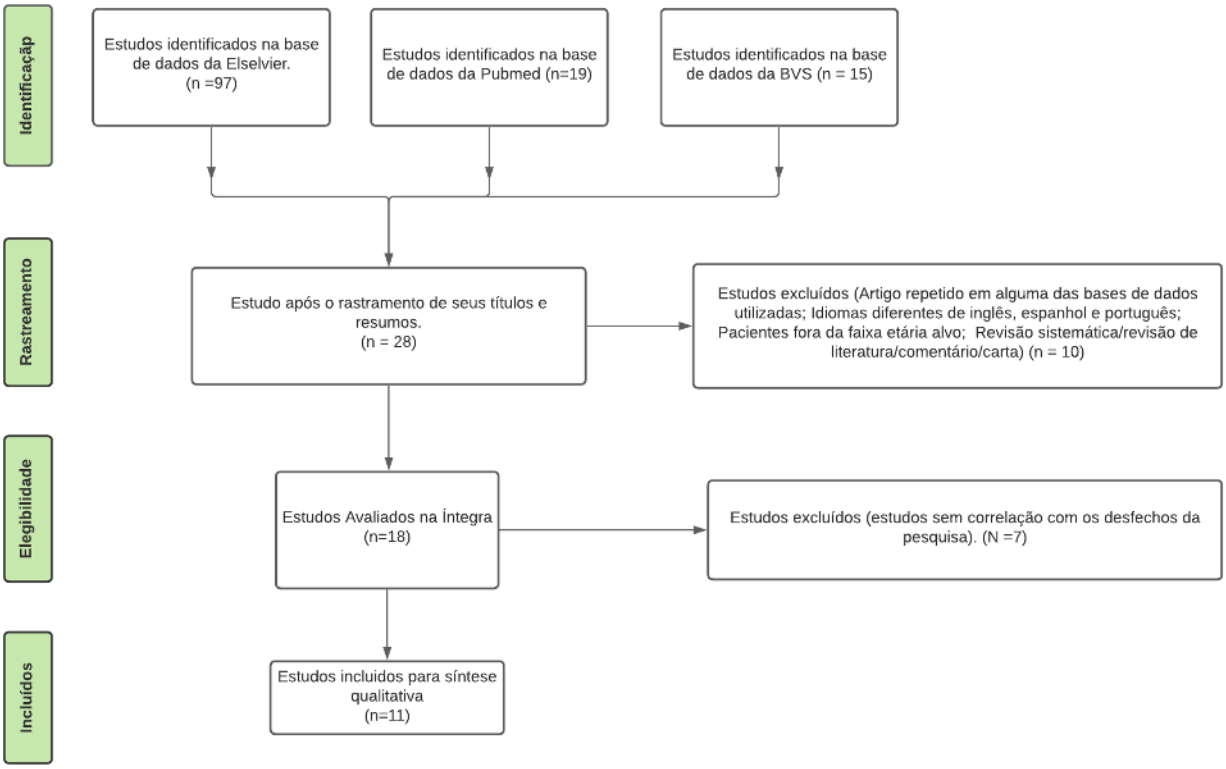

Figura 1: Fluxograma de sistematização dos estudos incluídos nessa revisão

Identification
Tracking
Eligibility
Included
Studies identified in the Elsevier database (n=97)
Studies identified in the PubMed database (n=19)
Studies identified in the VHL database (n=15)
Studies after tracking their titles and abstracts (n=28)
Excluded studies (Article repeated in any of the databases used; languages other than English, Spanish and Portuguese; patients outside the target age range; systematic review/literature review/comment/letter) (n=10)
Studies Evaluated in Integra (n=18)
Excluded studies (studies without correlation with research outcomes) (n=07)
Studies included for qualitative synthesis (n=11)

Thus, it was noticed that the vast majority (7) were performed in the USA, followed by Italy and Germany. There was great variation in sample size between studies ranging from 13 to 1896 patients followed up, except for three case reports that were included. Among the study designs, it was observed that there was a large number of studies, such as cohort, case-control, retrospective, and also case reports (Chart 1).

Table 1 - Overview of the articles included in the review, according to authors, country, type of study, sample number, and target age group.

Nª	Authors and year of publication	Country	Study Type	Sample Number	Age Group
1.	Ivan Tomasi, Luca Scott, Jack Cullen	USA	Case Report	1	Male 31 years
2.	Awais Ahmed, Jason	USA	Control Case Study	992	18+

	C.Fisher, Mark B.Pochapin				
3.	Suresh Kumar Nayudu, Jasbir Makker, Haozhe Sun, Dongmin Shin, Sharon Renner, Syeda H. Salman, Nikhitha Mantri, Maleeha Zahid, Sudharshan Reddy Gongati, Sridhar Chilimuri,	EUA	Retrospective Study	900	18+
4.	Ankur Patel, Troy Sanders, Sujay Alvencar, Alyssa Y. Choi, Jade Law, Janaki Shah, Karishma Patel, Michelle Nguyen, Taliha Yasin, Daniel M. Kim, Preeti Prakash, Tahnee K. Sidhu, Padmavathi Srivoleti, Kirtan Chauhan, Simcha Weissman, Erik A. Holzwanger, Rohit Dhingra, Aaron Dickstein, Nimisha K. Parekh, James H. Tabibian, Osama Altayar, Matthew A. Ciorba, Jessica X. Yu, Lea Ann Chen, Liu Yang, Berkeley N. Limketkai,	EUA	Retrospective Study	1896	18+
5.	Zaid Imam, Inayat Gill, Bana Antonios, Andrew Aneese, Guarav Kakked, Faisal Kamal, Bara El Kurdi, Alexandra Halalau,	EUA	Retrospective Study	301	-
6.	Raffaele Pezzilli, Stefano Centanni , Michele Mondoni	Italy	Observational study	110	18+
7.	Muhammad Abrar Jeelani, Hafiz; Sheikh, Muhammad Mubbashir; Samuel, Shirly Susan; Omotosho, Yetunde Bernice; Sharko, Artem; Albetar, Rami.	-	Case Report	1	24 anos

It is important to point out that the studies reported that, among the main gastrointestinal symptoms, patients had abdominal pain, nausea, vomiting, and/or diarrhea, whether alone or in groups. In addition, the vomiting presented was mostly non-bilious, as for abdominal pain, it was possible to infer that some were well localized, such as the pain in the right iliac fossa presented by some patients, or even diffuse (Table 2).

Table 2 - Distribution of the results of the articles according to the method of diagnostic confirmation of COVID-19, Environment of clinical evolution, gastrointestinal signs and symptoms presented, main pancreatic repercussions presented, and main conclusions of the authors related to the pancreatic involvement of the patients.

Nº	COVID-19 diagnostic confirmation method	Clinical evolution	Gastrointestinal symptoms	Pancreatic repercussions	Conclusion
1.	RT-PCR	Infirmary	Pain in the right iliac fossa associated with bilious vomiting	Heterotopic pancreatitis Acute pancreatitis	We hypothesize that the simultaneous presence of heterotopic pancreatitis and COVID-19 infection in our patient may not be a coincidental finding.
2.	RT-PCR	ICU	Abdominal pain and diarrhea	Pancreatic injury. Hyperlipidemia	There is a high prevalence of hyperlipidemia without clinical pancreatitis in COVID-19 disease.
3.	RT-PCR	Infirmary	Nausea, vomiting, abdominal pain, and diarrhea	ECA-2; hyperlipasemia	Hyperlipidemia in patients with COVID-19 was not associated with a prolonged hospital course, need for mechanical ventilation
4.	RT-PCR	ICU	Nausea, vomiting, diarrhea and Abdominal pain	ECA-2; hyperlipasemia	There is significant variability in the prevalence of GI symptoms associated with COVID-19 in the United States
5.	RT-PCR	ICU	Abdominal pain, diarrhea, nausea, vomiting.	Hyperlipidemia. Acute Pancreatitis	Acute pancreatitis in patients with COVID-19 are rare, while hyperlipidemia is common.
6.	Antibody: IgM-IgG	ICU	Nausea/ Vomiting/ Diarrhea	Increased lipase and amylase	Serum amylase is more often elevated than serum lipase
7.	-	-	Abdominal pain, nausea, vomiting, loose stools, epigastric pain, and tenderness to deep palpation	Increased lipase, and increased fluid in the peripancreatic area	-

In addition to the aforementioned gastrointestinal symptoms, studies have shown some pancreatic alterations, whether structural or enzymatic. Among these alterations, the presence of acute pancreatitis was noticed, which was found in about 24% of the studies included in the review, and it was seen that these patients needed oxygen, through mechanical ventilation or a nasal catheter.

Among the complications, there was an important consensus among the studies that high levels of the pancreatic lipase enzyme were related to a worse prognosis. However, in a smaller number of studies, an increase in the pancreatic amylase enzyme was also reported.

Despite the findings indicating possible correlations between COVID-19 infection and the presence of pancreatic lesions, the authors highlighted that the patients did not develop typical signs of acute pancreatitis. Additionally, it is worth emphasizing that these findings were found, for the most part, in patients considered to be in a serious condition requiring referral to the Intensive Care Unit (ICU).

4 DISCUSSION

From reading the articles, it is notorious to realize that the USA was the country that presented the highest number of surveys carried out. This is due to the high availability of resources since it is a major world power (BBC, 2021). In addition, because of being the greatest democracy, data collection and dissemination regarding the SARS-CoV-2 virus infection are carried out with greater transparency (BLAUER, 2021). Another important point that contributes to the vast studies carried out in the USA is the fact that it is one of the epicenters of the pandemic with more than 34 million confirmed cases and 605,000 deaths (WHO, 2021).

Several factors collaborate in research patients with COVID-19 since it is a new disease and difficult to control since the SARS-CoV-2 virus has a high transmissibility capacity (BULFONE, 2021). Among these factors, there is the outcome of the patient, as it is noticeable that many die before the end of the research (BRASIL, 2020). In addition, it has the presence of intercurrences due to clinical treatments without consolidated effectiveness and research withdrawal, affecting the quantitative final sample of the study (BRASIL, 2021). For this reason, the variation in the number of patients in the different surveys included is notorious.

It is possible to notice that all the analyzed studies were descriptive, which justifies the fact that it is a worldwide studied disease (ADIL, 2021) and, in this sense, despite being considered less elaborate studies, they are fundamental for initial understanding and raising new hypotheses of the study. (CALDEIRA et al., 2018).

From the diagnostic confirmation of COVID-19 infection, all studies used the RT-PCR test as a method. According to Trindade and Fortes (2021), it constitutes a robust technique, well protocoled and accepted by the medical community, considered the 'gold standard' of the diagnosis of COVID-19, in addition to being used to quantify the viral load even before the manifestation of symptoms. symptoms. (WOTTRICH et al., 2021)

Among the surveys included, there was consensus and correlation between the presence of gastrointestinal signs and symptoms associated with patients with COVID-19 infection. For CHEUNG and collaborators (2020). This correlation is because, since the gastrointestinal tract has ACE-2 receptors, they are more present in the small intestine, specifically, in the enterocytes that are located in its proximal and

distal region. These receptors are responsible for modulating the intestinal inflammatory process, which allows the SARS-CoV-2 virus to promote physiological changes and, consequently, the development of gastrointestinal symptoms, since the virus has an affinity for these receptors.

As mentioned above, this affinity of the SARS-CoV-2 virus for ACE2 receptors is also noted in pancreatic acinar cells, which contributes to changes in the organ resulting from this virus (ADIL, 2021). In addition, there was a presentation of a probable chance of pancreatic injury belonging to this relationship (RAMSEY, 2021, PATEL, 2020; JEELANI, 2021). Among these alterations, acute pancreatitis was observed, resulting in enzymatic alterations, such as hyperlipidemia and hyperamylasemia.

It was identified that viral particles initially affect the respiratory tract, and subsequently infect other cells, thus causing the production of cytokine storms in the body (GUO, 2020), thus justifying the serious condition of patients with COVID-19. With this, it is possible to infer the relationship that most patients with pancreatic repercussions need oxygen (IMAM, 2021).

Additionally, it was possible to identify some pancreatic repercussions among patients diagnosed with SARS-CoV-2 virus infection, which proved to be interesting. However, we expected another outcome with a broader spectrum of research demonstrating a correlation between these repercussions and the SARS-CoV-2 virus. There were important limitations such as the search for studies only in English, Spanish, and Portuguese, in addition to the exclusion of studies with patients who had previous pancreatic pathologies.

5 CONCLUSION

Based on a large part of the studies, it was possible to analyze that patients infected with the SARS-CoV-2 virus, diagnosed using the RT-PCR method, who presented alterations at the pancreatic level, had elevated serum lipase and the minority cited an increase in amylase, in addition to some having had the outcome of pancreatitis. Furthermore, it was noted the presence of gastric symptoms being very prevalent. However, research is still inconclusive and lacks information on the subject, which makes it necessary to carry out further studies in the area.

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