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## Impact of COVID-19 in individuals with and without pre-existent digestive disorders with a particular focus on elderly patients

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### Abstract

Coronavirus disease 2019 (COVID-19) has several extrapulmonary symptoms. Gastrointestinal (GI) symptoms are among the most frequent clinical manifestations of COVID-19, with severe consequences reported in elderly patients. Furthermore, the impact of COVID-19 on patients with pre-existing digestive diseases still needs to be fully elucidated, particularly in the older population. This review aimed to investigate the impact of COVID-19 on the GI tract, liver, and pancreas in individuals with and without previous digestive diseases, with a particular focus on the elderly, highlighting the distinctive characteristics observed in this population. Finally, the effectiveness and adverse events of the anti-COVID-19 vaccination in patients with digestive disorders and the peculiarities found in the elderly are discussed.

**Key Words:** COVID-19; Elderly; Inflammatory bowel disease; Liver disease; Cirrhosis; Pancreatic disease

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**Core Tip:** Gastrointestinal symptoms are frequent in coronavirus disease 2019 (COVID-19), with more severe consequences reported in elderly patients. Patients with pre-existing liver disease are at an increased risk for worse outcomes, while no definitive conclusions can be drawn regarding patients with inflammatory bowel disease or pancreatic diseases. Elderly patients with digestive disorders, although the available data are limited, have no worse COVID-19 outcomes than those without these diseases.

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## INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the ongoing pandemic of coronavirus disease 2019 (COVID-19). Since its first report in December 2019 in Wuhan, China[1], COVID-19 has quickly spread worldwide with 635229101 confirmed cases, including 6602552 deaths according to the World Health Organization (WHO) at the moment of writing[2]. Although symptomatic COVID-19 patients exhibit various signs and symptoms, the typical clinical presentation has been predominantly respiratory[3]. The most common symptoms include cough (60%-86%), shortness of breath (53%-80%), and taste and smell alteration (64%-80%)[4-6]. However, as caseloads rise, many extrapulmonary effects have been observed, affecting the cardiovascular, neurologic, gastrointestinal (GI), and dermatologic systems. Liver and pancreatic impairment may also occur, especially in critically ill patients[7]. Although their exact prevalence is still the subject of debate, GI symptoms are more and more frequently reported[8]. However, it is impossible to exclude a bias thriving from the increased awareness of GI manifestations[9]. Some authors reported a prevalence of GI involvement of around 31.9%[10,11], while others up to 61%[12]. Regarding the impact of SARS-CoV-2 infection on older age, more severe outcomes are described [13,14]. The reason is the various age-related changes and the higher number of comorbidities typical of these patients. However, increasing evidence suggests that age is the most significant risk factor for worse outcomes[15]. Immunosenescence, the age-associated decline of immune system function, is the primary reason for the increased susceptibility to viral infection[16,17].

## Methods

Considering a broad topic such as SARS-CoV-2 infection, this narrative review aimed to provide an overview of current knowledge of its impact on the GI tract, liver, and pancreas, with a particular interest in the elderly population. First, we created a list of keywords related to our research question. Articles were searched in the PubMed, Scopus, and EMBASE databases using the following search terms: "COVID-19", "SARS-CoV2 infection", "Elderly people", "Elderly population", "Old people", "Gerontal population", "Extrapulmonary manifestations", "Gastrointestinal symptoms", "Gastrointestinal bleeding (GIB)", "Inflammatory bowel disease (IBD)", "Liver injury", "Liver dysfunction", "Chronic liver disease", "Drug liver injury", "Pancreatic involvement", "Acute pancreatitis" and "COVID-19 vaccination". We then synthesized, analyzed, and critically evaluated the related data to identify trends and patterns, in theory, debates, conflicts, and, most of all, persistent gaps in the existing knowledge.

## Mechanisms of GI involvement in COVID-19

It is well known that SARS-CoV-2 enters cells using angiotensin-converting enzyme 2 (ACE2)[8,18]. In addition to the respiratory tract, ACE2 has also been found in the GI tract, especially in the tongue, esophageal, gastric, and rectal mucosa[19]. Mechanisms underlying the probable pathological effect of SARS-CoV-2 are varied. First, the virus's entry into cells may lead to a direct cytopathic effect[20]. SARS-CoV-2 infection emphasizes inflammatory pathways determining the "cytokine storm", which is characterized by the overproduction of mediators such as interleukin-2 (IL-2), IL-7, tumor necrosis factor (TNF) and granulocyte monocyte colony-stimulating factors[21]. This condition could generate diarrhea due to the alteration of gut motility and GI flora[22]. Notably, gut microbiota alterations have been found in these patients, probably due to factors such as exposition to antimicrobial agents or expression of viral proinflammatory mediators. Moreover, ACE2 seems to be involved in the antimicrobial peptide secretion through target of rapamycin activity; an aberrant functioning of this pathway has been described during COVID-19[23]. In addition to this mechanism, disorders of the gut-lung axis may be involved in the pathophysiology of GI symptoms. For example, it has been reported that lung flora alteration can correlate with intestinal microbiota modifications, probably due to increased recruitment of lung-derived CCR9+CD4+T cells into the bowel[24,25]. Regarding nausea and vomiting, these symptoms are likely



related to SARS-CoV-2 infection of the vagus nerve and a cytokine-mediated stimulation of the central and autonomic nervous systems[26]. Moreover, anorexia might be related to nausea and vomiting or associated with acute viral prodrome and cytokine storm[27]. Some studies have identified a lower prevalence of GI symptoms in the elderly population. This finding could be related to differences in gene expression of the ACE2, which seems to be directly correlated with age[9,28,29]. Older patients showed higher intestinal ACE2 mRNA expression, which could modify susceptibility to GI symptoms by influencing intestinal immunity and microbiota composition[29,30]. However, studies on this relation are few and with uncertain results.

### **GI symptoms in patients with COVID-19**

In one-third of patients with COVID, GI symptoms occur as the first presentation. Nausea and vomiting may be present in up to two-thirds, diarrhea in up to 50%, loss of appetite in approximately 40%, and less than 10% present abdominal pain[7]. Moreover, extreme cases, such as the autptic finding of segmental dilatation and stenosis of the small intestine in an 85-year-old man with COVID-19, have been reported in the literature[31]. However, the causal role of SARS-CoV-2 has yet to be established.

### **GI manifestations in elderly patients with COVID-19**

Anorexia and diarrhea were the most frequent symptoms reported in the elderly, with variable frequencies depending on the study. In a large Brazilian cohort of 9807 patients, low frequencies of GI symptoms were reported, with diarrhea being registered only in 2% of patients[32]. Marziliano *et al*[33] reported a prevalence of GI symptoms of near 9% in a population of older adults (65 years and older). Ramos-Rincon *et al*[34] reported that very old patients (age > 80 years old) had higher frequencies of GI symptoms, with diarrhea presenting in 14% and vomiting in 5%, and anorexia in nearly 21% of patients. In the studies mentioned above, GI symptomatology did not impact mortality. Other studies pointed out an inverse correlation between age and the prevalence of GI symptoms[9,28]. Aroniadis *et al*[9] reported that older COVID-19 patients were less likely to exhibit digestive symptoms. A lower prevalence of GI symptoms was reported in 70 and older patients compared with those < 70 years (32% *vs* 41%). This potential age-related protective effect is found in a dysregulation of the immune system activation and a different expression of the ACE2 receptor in the digestive system [28]. Surprisingly, some studies highlighted a possible protective role of GI symptoms in COVID-19. Belgian research observed a prevalence of 30% of GI symptoms in frail older patients (aged over 80 years) and a positive correlation between their presence and patients' survival[35]. These results were also aligned with those of Vrillon *et al*[36], who described a positive outcome in older people presenting with GI symptoms, whereas younger adults with digestive symptoms had a higher prevalence of complications. On the contrary, Atalla *et al*[37] in their retrospective study, revealed a higher incidence of loss of appetite (83.3% *vs* 44.4%) and diarrhea (50% *vs* 28.6%) in the deceased patients than in those who survived. However, the onset of diarrhea during hospitalization was not necessarily related to SARS-CoV-2 infection, and the etiological analyses are not presented in the article[37]. Patients with SARS-CoV-2 infection are also at risk of other potential causes of diarrhea, such as *Clostridium difficile* infection and antibiotic-associated diarrhea due to frequent antimicrobial therapy and hospitalization. These could be confounding factors that alter the analysis of GI symptoms during SARS-Cov-2 infection, especially when they appear during infection and not at onset[18,24]. GI bleeding (GIB) in COVID-19 patients can represent a fatal complication. In the literature, a rate of GIB between 1.1% and 13% during SARS-CoV-2 infection has been reported[38]. However, the actual incidence and prevalence of GIB in COVID-19 patients are extremely difficult to assess. The underlying mechanisms for GI hemorrhage in COVID-19 patients could involve conditions that increase the risk of thromboembolism, such as dehydration, which may follow fever or diarrhea[39]. Anticoagulation drugs prescribed for preventing thrombotic events should be considered additional risk factors[40]. Although Ion *et al*[41] sustained that the use of anticoagulation or antiplatelet agents was not a risk factor for GIB, at least in hospitalized COVID-19 patients. Stress ulcers may be another major cause of bleeding unrelated to SARS-COV-2[41]. Furthermore, assisted ventilation techniques could cause stress ulceration and generate GIB[42]. However, rates of thrombosis and bleeding related to COVID-19 were congruent to those reported in hospitalized patients with comparable grades of critical illness. Except for case reports, no elective studies on the elderly population are available in the literature[43]. An overview of the analyzed studies is shown in Table 1.

### **COVID-19 in inflammatory bowel disease patients**

Due to the immunosuppressive therapies, malnutrition, and chronic inflammation, patients affected by inflammatory bowel disease (IBD) are potentially at augmented risk for SARS-CoV-2 infections and complications due to the immunosuppressive therapies, malnutrition, and chronic inflammation[44,45]. However, various studies have investigated the incidence of COVID-19 in IBD patients, concluding that it is not increased compared to the general population [46-48]. Interestingly, COVID-19 in IBD patients has a clinical presentation similar to the general population. A recent meta-analysis found that the most common symptoms in these patients are extraintestinal, such as fever and cough[49]. However, GI manifestations appear more common than in the general population. Diarrhea can occur in 27.2% of patients, followed by abdominal pain, nausea, and vomiting, with a pooled prevalence rate of 13%, 10%, and 8.8%, respectively, and sporadically GI symptoms can be the only clinical presentation, which could be challenging to differentiate from IBD reactivation[49]. The prognosis of COVID-19 patients affected by IBD is not different from that of the general population. A recent meta-analysis observed that IBD was not correlated with augmented risk of death, intensive care unit (ICU) admission, or hospitalization related to COVID-19, and the pooled odds ratios were 0.67 [95% confidence interval (CI): 0.32-1.42], 1.09 (95% CI: 0.27-4.47), and 0.58 (95% CI: 0.28-1.18), respectively[50]. On the other hand, another meta-analysis found that in IBD patients affected by COVID-19, the risk ratio (RR) of adverse outcomes was increased (RR = 1.32; 95% CI: 1.06-1.66) compared to patients without IBD[51]. The risk factors for worse outcomes of COVID-19,

**Table 1 Overview of studies evaluating the course of gastrointestinal symptoms during severe acute respiratory syndrome coronavirus 2 infection in the elderly population**

Ref.	n	Age (yrs)	GI symptoms	Diarrhoea	Nausea/vomiting	Anorexia	Abdominal pain	Outcomes
de Souza <i>et al</i> [32]	9807	70.21 ± 8	-	2%	-	-	-	No association
Ramos-Rincon <i>et al</i> [34]	2772	86.3 ± 3	-	14%	5%	22%	-	No association
Marziliano <i>et al</i> [33]	4961	77 ± 8	9%	-	-	-	-	No association
Atalla <i>et al</i> [37]	111	87.0 median (IQR: 77.0-92.0)	-	7% (38% all ages)	2%	17% (61% all ages)	-	Mortality was associated with a disease course beginning with a loss of appetite, and the incidence of diarrhea was more frequent in the deceased
Lanthier <i>et al</i> [35]	50	88 median (IQR: 83-92)	30%	24%	6%	10%	6%	Digestive symptoms were associated with a favorable outcome
Aroniadis <i>et al</i> [9]	434	Age > 70	31%	19%	-	-	-	Older patients were less likely to exhibit gastrointestinal symptoms
Zhan <i>et al</i> [23]	39	Age > 75	36%	-	-	-	-	No association
Vrillon <i>et al</i> [36]	76	90 median (IQR: 86-92)	22%	-	-	-	-	Digestive symptoms were associated with a favorable outcome

The sample's age was expressed either by the mean or the median in the studies analyzed. For some non-specific studies performed on older people, only the characteristics of the population mentioned above have been shown in the table. However, some of these have yet to express a category-specific significant trend measure. For example, the relationship between the course of the infection and the outcome was reported in the last column. SD: Standard deviation; IQR: Interquartile range; GI: Gastrointestinal.

such as age, male sex, and comorbidities, are the same as observed in the general population. In IBD patients with COVID-19, an active disease was considered a risk factor for poor outcome[52,53], and in a cohort of 79 patients with IBD and COVID-19, active IBD, especially in elderly patients, was correlated with worse outcomes such as pneumonia, hospitalization, respiratory support, and death[52]. Another study reported that the correlation between IBD activity and the risk of severe COVID-19 appears to vary with age and is more relevant in younger patients[53]. The impact of IBD medications on the course of COVID-19 is still under investigation. A meta-analysis by Tripathi *et al*[54] has shown that the therapy with TNF- $\alpha$  antagonists is associated with favorable hospitalization and mortality outcomes, while the use of mesalamine was correlated with worse outcomes in terms of hospitalization, ICU admissions, and death. Another recent study, including 6144 patients, found that systemic corticosteroids were associated with severe COVID-19, while mesalamine and sulfasalazine were not associated with adverse outcomes[55]. In addition, combination therapy with TNF- $\alpha$  antagonists plus thiopurines was correlated with an augmented risk of hospitalization or death, but not the combination with methotrexate. Moreover, biologics were not associated with worse COVID-19 outcomes and could have a protective effect without differences when comparing biologic classes such as TNF- $\alpha$ , IL-12/23, or integrin antagonists [56]. Therefore, the correct management of IBD therapy is relevant because SARS-CoV-2 is not correlated with the risk of IBD relapse. Conversely, the discontinuation or delay of the IBD therapy, regardless of SARS-CoV-2 infection, is significantly associated with the disease activity[55,56] (Table 2).

### COVID-19 in elderly patients with IBD

Elderly-onset IBD is defined as onset at 60 years or older[57], and up to 30% of the IBD population is older than 60 years, while 15% of IBD patients have been diagnosed after age 65. It has been observed that in elderly-onset IBD, there is a different natural history and disease phenotype. The disease outcomes are less influenced by genetics, while frailty, immunosenescence, and dysbiosis have a more significant role[58]. In IBD patients, as in the general population, age and comorbidities increase the risk of severe COVID-19 and disease-related mortality[45,59]. A prospective observational study that included 482 patients confirmed that age over 60 years was correlated with severe COVID-19 [odds ratio (OR) = 4.59, 95%CI: 1.3-15.9] and was an independent risk factor related to death (OR = 7.1, 95%CI: 1.8-27.4), as to have two or more comorbidities (OR = 3.9, 95%CI: 1.3-11.6)[60]. Wetwittayakhleng *et al*[61] examined a cohort of 3516 IBD patients, of whom 82 were diagnosed with COVID-19 infection, and they observed that age over 55 years was an independent risk factor for developing severe COVID-19. The study by Brenner *et al*[59], through an extensive international registry, corroborates these observations, finding that advanced age [adjusted OR (aOR) = 1.04; 95%CI: 1.01-1.06] and having at

**Table 2 Risk of severe coronavirus disease 2019 in elderly inflammatory bowel disease patients**

Ref.	Total number of IBD patients	Number of COVID-19-positive IBD patients	Age threshold considered (yrs)	Risk of severe COVID-19
Ludvigsson <i>et al</i> [45]	67292	179 (hospitalized patients)	60	HR = 1.42; 95%CI: 0.94-2.13
Brenner <i>et al</i> [59]	SECURE-IBD database	525	Increasing age on multivariable analysis	OR = 1.04; 95%CI: 1.01-1.06
Zabana <i>et al</i> [60]	53682	482	60	OR = 4.59, 95%CI: 1.3-15.9, <i>P</i> = 0.02
Wetwittayakhleng <i>et al</i> [61]	3516	82	55	OR = 11.09, 95%CI: 1.81-68.09, <i>P</i> = 0.02

OR: Odds ratio; CI: Confidence interval; IBD: Inflammatory bowel disease; COVID-19: Coronavirus disease 2019; HR: Hazard ratio.

least two comorbidities (categorized into lung disease, cardiovascular disease, hypertension, history of stroke, cancer, liver disease, kidney disease, and diabetes) (aOR = 2.9; 95%CI: 1.1-7.8) were positively associated with severe COVID-19.

Regarding the risk of SARS-CoV-2 infection, a study by Gubatan *et al*[62] observed that IBD patients older than 66 years have an augmented risk of acquiring SARS-CoV-2 infection compared to younger patients. On the other hand, a retrospective cohort study by Calafat *et al*[63] that included 418 IBD patients over 65 years of age, of whom 32 were diagnosed with COVID-19, found that the incidence of COVID-19 in elderly IBD patients is similar to that reported in the age-adjusted general population. Furthermore, the incidence of COVID-19 was not influenced by the use of immunosuppressants, but the authors observed a worse prognosis among the patients who did not use immunosuppressants. Medication use in older patients with IBD differs from younger ones since they are treated less often with biological agents and immunosuppressants. However, corticosteroid use is similar[63,64], and it is possible to hypothesize that these differences could have a role in the course of SARS-CoV-2 infection. Overall, in the elderly population, IBD does not seem to increase the risk of SARS-CoV-2 infection or severe COVID-19[65] (Table 2).

## LIVER MANIFESTATIONS ASSOCIATED WITH COVID-19

### Introduction

Among the extrapulmonary manifestations of SARS-CoV-2, abnormal liver function reflecting hepatocellular and cholangiocellular injury is often reported[12,66]. COVID-19-associated liver injury includes any liver abnormality due to the disease course or the treatment. Indeed, it is not always possible to determine whether the liver injury is due to the infection or other concomitant conditions, such as the co-administration of hepatotoxic agents or ischemic hepatitis from severe and prolonged hypotension. Moreover, the cytokines storm observed in the severe forms of COVID-19 and caused by systemic hyper-inflammation may result in multiple severe organs injury and, in turn, it represents another cause of liver damage[67]. However, the frequency of liver dysfunction in COVID-19 infection has not yet been well understood [68].

### Liver test abnormalities

Among abnormal liver function, liver test abnormalities have often been described. The incidence of elevated liver transaminases, alanine transaminase (ALT), and aspartate aminotransferase (AST) in COVID-19 patients range from 2.5% to 76.3%[69]. A systemic review pointed out that elevated liver chemistries occurred in 23.1% of adult patients with COVID-19 at initial presentation[66]. In comparison, 24.4% develop elevated liver chemistries during the illness, and up to 10.7% have severe liver injury[66]. In detail, the pooled incidence of AST and ALT elevation at initial presentation of COVID-19 was 22.5% and 17.9%, respectively[66]. The incidence of hyperbilirubinemia at the onset of symptoms was 13.4%, while the incidence of alkaline phosphatase (ALP) and gamma-glutamyltransferase (gamma-gt) was 6.1% and 21.1%, respectively[66]. In addition, hypoalbuminemia ranged from 1.1% to 45.8% in non-severely infected patients, reaching 72.9% in those severely infected[66].

The cause of the elevated liver enzymes in COVID-19 patients without pre-existent liver diseases still needs to be well elucidated. In the study of Kulkarni *et al*[66], only 3.6% of the analyzed patients had underlying chronic liver disease (CLD), suggesting that liver damage might be directly caused by the viral infection of liver cells. It is believed that SARS-CoV-2 could penetrate the liver cells thanks to the ACE2 receptor, which is expressed in the liver and bile duct cells[70]. Recent data show that ACE2 is expressed in 2.6% of hepatocytes and 59.7% of cholangiocytes. The level of ACE2 expression in cholangiocytes was similar to type 2 alveolar cells of the lungs. Therefore, liver dysfunction may result from SARS-CoV-2 attachment to ACE2 on cholangiocytes[71]. Of note, studies on both mice and humans reveal an increased ACE2 expression in hepatocytes when liver fibrotic/cirrhotic conditions are present[69]. This finding leads us to believe that preexisting liver injury could exacerbate SARS-CoV-2 hepatic tropism. Although COVID-19 may contribute to liver dysfunction directly through an inflammatory response, postmortem pathological findings of the liver suggest that COVID-19-related liver dysfunction may be mainly caused by secondary liver damage by respiratory distress syndrome-induced hypoxia, multiple organ failure, and the use of potentially hepatotoxic drugs[72]. Microscopically, the most



significant findings in postmortem hepatic tissue of patients with COVID-19 were microvesicular steatosis and mild lobular inflammation[73]. Zhao *et al*[72] presented unique findings, such as platelet-fibrin microthrombi in hepatic sinusoids, central vein or portal vein, histolytic hyperplasia in portal tracts, and megakaryocytic in sinusoids.

### **Liver test abnormalities and COVID-19 outcomes**

Liver test abnormalities can predict the severity of COVID-19 disease[74]. Patients with abnormal liver tests at admission or during hospitalization, classified as hepatocyte type or mixed type, had significantly higher risks of progressing to severe COVID-19 and mortality when compared to patients with normal liver tests[66,75]. Elevated liver enzyme levels are linked to adverse manifestations such as shock, admission to an ICU, and mechanical ventilation. Although, Săbiescu *et al*[76] proved that only elevation over five times the upper limit is strongly correlated with high mortality risk. Also, hypoalbuminemia is a strong predictor of severe COVID-19 course and, in combination with AST or total bilirubin (TBIL), has a remarkable association with mortality[77], even in patients without chronic illness[78]. Furthermore, Da *et al* [79] reported a correlation between ALT levels and levels of inflammatory markers such as C-reactive protein, D-dimers, ferritin, and IL-6.

It appears evident that liver injury in COVID-19 patients is linked to the severity of the hyperinflammatory response, thus, reinforcing the hypothesis that the entity of liver damage is related to the severe forms of SARS-CoV-2 infection. Pazgan-Simon *et al*[80] reported that liver injury in patients with COVID-19 with no underlying liver disease did not correlate with higher mortality. On the other hand, patients with preexisting liver disease, particularly those with cirrhosis, have a higher risk of death than those without any known liver pathology[81].

### **Impact of SARS-CoV-2 infection on patients with CLD**

Wang *et al*[82] showed an increased risk of COVID-19 infection in patients with a recent diagnosis of CLD. A multicentric retrospective study revealed that nearly one-fifth of hospitalized COVID-19 patients had CLD[82]. However, the elevated aminotransferases on admission were higher in patients with CLD than those without CLD. On the contrary, during hospitalization, the aminotransferase level did not differ between patients with or without CLD. Iavarone *et al*[83] described the impact of SARS-CoV-2 infection on ALT levels in cirrhotic patients, revealing that acute liver injury was observed in almost 50% of patients with previously average ALT values. However, more data are necessary to clarify the impact of an ALT increase on the natural history of cirrhosis and COVID-19. It has been described that CLD can negatively influence the clinical outcomes of patients with COVID-19[84,85]. The overall mortality rate of COVID-19 is estimated at 0%-2% in these patients[86]. However, currently, there is no convincing evidence that patients with stable CLD without advanced fibrosis/cirrhosis, primary biliary cholangitis, or primary sclerosing cholangitis have increased susceptibility to severe COVID-19 infection[87]. Contradictory data exist on the risk of developing severe illnesses of non-alcoholic fatty liver disease (NAFLD)[88]. Patients with NAFLD often suffer from metabolic comorbidities such as diabetes, hypertension, and obesity and, for this reason, present an increased risk of a severe course of COVID-19[89]. However, Sachdeva *et al*[90] affirmed that NAFLD might represent a predictor of severe COVID-19, even after adjusting to the presence of confounding factors. The risk of a worse prognosis of COVID-19 is directly related to the severity of the liver disease, and cirrhosis may appear independently associated with an increased risk of death in patients hospitalized with COVID-19[91]. A large multinational cohort study determined that baseline liver disease severity is the primary determinant of SARS-CoV-2 infection outcome[92]. This study resulted in a mortality of 32% in patients with cirrhosis compared to only 8% of those with CLD without cirrhosis. In addition, patients with CLD without cirrhosis appear to have a similar risk of SARS-CoV-2 infection-related mortality compared to patients without liver disease. Furthermore, since only 19% of cirrhosis patients' mortality was related to liver complications, the leading cause of death remained COVID-19-related lung injury. Patients with cirrhosis may also have underlying complications such as hepato-pulmonary syndrome, porto-pulmonary hypertension, or hepatic hydrothorax, which can increase the risk of respiratory failure[93]. On the contrary, a Korean cohort study showed no significant association between developing severe complications from COVID-19, including mortality, or the presence of liver cirrhosis[94]. A possible explanation could be attributed to the different etiologies of cirrhosis in the patients analyzed. In particular, chronic hepatitis B is responsible for more than 70% of cirrhosis cases in Korea[95], and NAFLD and alcoholic liver disease are the most common etiologies of liver cirrhosis in Europe and North America. Consequently, the different etiologies of cirrhosis may play a critical role in developing severe complications from COVID-19. For example, a United States multicentric study pointed out that, among patients with CLD, those with decompensated cirrhosis, alcohol-related liver disease, and hepatocellular carcinoma (HCC) were more vulnerable to adverse outcomes from COVID-19. These patients also had a higher risk for all-cause mortality from COVID-19[96] (Table 3).

### **Drug-induced liver injury caused by COVID-19 treatment**

Liver injury can be caused by several medications used in the treatment of COVID-19. Drug metabolites can cause cellular stress that can lead to apoptosis or necrosis of liver cells[97]. Since most of these drugs cause an elevation of liver enzymes alone, it is important to correctly define acute liver injury to avoid withdrawing this medication improperly[98]. Drug-induced liver injury (DILI) is defined as an increased level of ALT  $\geq$  5-times upper limit of normal (ULN), or increased level of ALP  $\geq$  2-times ULN (in the absence of bone pathology), or a simultaneous increase of ALT  $\geq$  3-times ULN and TBIL concentration  $>$  2-times ULN. While analyzing the different medications used for COVID-19 infection, liver-related adverse effects were more common in patients who used hydroxychloroquine and azithromycin and those who did not receive any targeted therapy[99]. In contrast, drugs, including lopinavir/ritonavir (LPV/v), were associated with 4  $\times$  higher odds of liver injury[75]. According to another study, no apparent side effects were found in the LPV/r group, except for transient ALT elevation ( $<$  125 U/L)[96]. A meta-analysis revealed that the incidence of DILI in patients treated

**Table 3 Summary of studies on the relationship between liver disease and coronavirus disease 2019 in elderly patients**

Ref.	Outcome considered	Results
Khateri <i>et al</i> [108]	Incidence of acute liver injury in patients affected by COVID-19	Acute liver injury has no relationship with age
Metawea <i>et al</i> [110]	Mortality of patients with hepatocellular carcinoma infected with COVID-19	Age is associated with poorer outcomes and higher mortality
Ji <i>et al</i> [111]	Severe COVID-19 in patients affected by NAFLD	Associated in patients older than 60 yr
Zhou <i>et al</i> [112]	Severe COVID-19 in patients affected by NAFLD	Associated in patients younger than 60 yr
Hartl <i>et al</i> [113]	Liver-related death due to COVID-19 between different age groups	More frequent in the 40-69 years old group than in the over 70 years old group (6.5% vs 2.2%)
Ioannou <i>et al</i> [115]	Predictors of mortality among patients with cirrhosis and SARS-CoV-2 infection	Advanced age was one of the main risk factors for mortality among patients with cirrhosis and SARS-CoV-2 infection
Brozat <i>et al</i> [116]	The case fatality rate in patients with cirrhosis and SARS-CoV-2 infection	The case fatality rate in cirrhotic patients and SARS-CoV-2 infection aged 65 yr and older was nearly three times that in patients younger than 65 yr (43.6% vs 16.1%)

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019; NAFLD: Non-alcoholic fatty liver disease.

with remdesivir was 15.2%, while the incidence of DILI in patients treated with LPV/v was 37.2% [66]. Although some extensive reviews concluded that remdesivir does not affect liver function [100], AST and ALT elevations have been described in a cohort of patients treated with remdesivir. However, in most cases, elevated levels of AST and ALT do not progress to severe liver injury [101]. Hepatotoxicity is documented among the possible Tocilizumab-related side effects. In registration trials, serum aminotransferase elevations occurred in up to 40% of patients receiving tocilizumab. After its licensure, it has been linked to several instances of clinically apparent liver injury with jaundice. Also, liver failure and transplantation may occur in patients treated with tocilizumab [102]. Interestingly, the median age of COVID-19 patients with DILI ranged from 54.3 to 56 years; therefore, age does not appear to significantly influence the risk of developing DILI [103]. Although animal studies have demonstrated changes in hepatic physiology that affect drug metabolism in the aging liver, there is no evidence that this leads to any appreciable deterioration of liver function in healthy elder patients. Moreover, several large international DILI registries do not support elder age as an independent risk factor for developing hepatic injury [104]. On the contrary, it has been described that age does affect the incidence rates of liver injury in COVID-19 patients. Older patients have a higher incidence of liver injury. In addition, impaired liver function in the elderly increases the drug concentrations in their livers. The decline in liver function also explains the higher incidence of DILI in the elderly [105]. Therefore, intensive liver function monitoring should be considered for patients treated with drugs such as remdesivir, LPV/v, and tocilizumab.

### COVID-19 liver manifestations in elderly patients

It has been debated if age may represent a risk factor in developing severe complications of SARS-CoV-2 infection in patients with CLD. Several studies demonstrated that older patients are more susceptible to developing severe COVID-19 [106] but are also more likely to develop liver function abnormalities [68]. However, advanced age as a risk factor for more severe forms of COVID-19 has not yet been well assessed. Older patients with COVID-19 have a higher risk of liver injury [107]. Indeed, Khateri *et al* [108] have revealed that the prevalence of acute liver injury has no relationship with age. Spearman *et al* [109] have pointed out that age represents one of the main risk factors for adverse outcomes in individuals with CLD and COVID-19. In patients with HCC infected with COVID-19, age is considered one of the factors responsible for poorer outcomes and higher mortality [109,110]. In a Chinese retrospective study of patients with COVID-19, NAFLD and age over 60 years were associated with a more severe course of COVID-19 [111]. On the contrary, Zhou *et al* [112] demonstrated that the association between metabolic-associated fatty liver disease and the development of severe COVID-19 was significant in patients aged less than 60 years. The higher prevalence of severe COVID-19 in patients aged under 60 years with NAFLD compared to those without NAFLD may be attributed to hepatic and systemic immune responses caused by NAFLD, which may increase the severity of the cytokine storm in younger patients with COVID-19. Hartl *et al* [113] analyzed the frequency and the predictive role of abnormal liver chemistries in different age groups. Interestingly, the study revealed that patients aged 40-69 years had a significant risk for COVID-19-associated liver injury. The median levels of hepatocellular injury were highest in patients aged between 40 and 69 years, while cholestatic liver injury was similar within both groups (40-69 years and > 70 years). However, the patients aged over 70 had the highest risk of COVID-19-related mortality; liver-related death due to COVID-19 occurred significantly more often in 40-69-year-old patients than those aged over 70 years (6.5% vs 2.2%) [113]. Moreover, this study revealed that increased AST levels were linked to a shorter survival time in patients older than 70, while elevated AST seems to predict a severe course of COVID-19 in all age strata [113]. Of all patients with liver-related death, only 1.7% had no preexisting liver disease. Another study pointed out that among patients with CLD, the highest risk of death was found in their eighth decade of life [92]. Age was associated with higher 30-d mortality in patients with cirrhosis and SARS-CoV-2 infection compared with patients without SARS-CoV-2 infection [114]. Ioannou *et al* [115] also highlighted that higher age, decompensation,

and high model for end-stage liver disease scores were mortality predictors. Also, a more recent study pointed out that older age > 65 and Child-Pugh class C were associated with a high mortality rate[116]. In contrast, Marjot *et al*[92] revealed that mortality in patients with cirrhosis was more evenly distributed across age categories, including a high mortality rate under age 40. A multicentric retrospective Italian study confirmed that the outcomes of cirrhosis patients with COVID-19 were poor. According to a previous study, cirrhotic patients had a higher mortality rate and lower age at death[83].

In summary, COVID-19 is frequently associated with liver function abnormality. However, liver dysfunction may predict a severe form of COVID-19. Therefore, special attention should be paid to older patients, especially those with preexisting CLD and after using hepatotoxic agents. Lastly, cirrhotic patients deserve special attention because they have a high risk of liver function deterioration and mortality with COVID-19 infection, regardless of age (Table 3).

### **Pancreatic manifestations associated with COVID-19 in elderly patients**

The pancreatic involvement of COVID-19, both in terms of clinical implications and underlying mechanisms, is highly manifold and individual-specific[97]. Clinical presentations may range from asymptomatic increases in pancreatic enzyme levels to episodes of acute pancreatitis (AP) and its related complications included pseudocyst formation, peripancreatic fluid collection, pancreatic necrosis, and walled-off necrosis[97,117-119]. Several studies also reported the impact of COVID-19 on metabolic and endocrinologic pancreatic function; manifestations include the development of glucose intolerance and the exacerbation of hyperglycemia, both leading to the development of new-onset diabetes[120, 121].

### **COVID-19 and AP: Examining the causality**

The mechanisms underlying COVID-induced pancreatic damage can be direct, due to the cytopathic effect of local SARS-CoV-2 replication, or indirect, caused by the infection's systemic inflammatory and immune response. Moreover, drug-induced pancreatic injury resulting from antipyretics, anti-inflammatories, and corticosteroids, should also be considered as an additional risk factor[122,123]. However, despite several proposed explanations, no comprehensive theory of COVID-induced pancreatic impairment is universally accepted. The most accredited theory views the engagement of several complexes and interrelated processes. For example, whether the pancreatic injury is caused by SARS-CoV-2 or is just an epiphenomenon is often unclear.

### **Incidence of COVID-induced pancreatic impairment**

From an analysis of the present literature, it can be inferred that the range of incidence of COVID-19-caused pancreatic damage is susceptible to the definition of pancreatic impairment itself. Studies accounting for amylase or lipase serum level increases as an index of pancreatic involvement report an incidence level of 8.5%-17.3%[122,124]. When the more stringent Atlanta criteria are considered, lower incidence values of 1.7%-1.8% are reported[125-127]. An example of this can be found in McNabb-Baltar *et al*[128]'s work; who pointed out that despite mild hyperlipasemia being observed in 9 out of 71 patients (12.1%), only 2 of those (2.8%) had levels more than three times higher than the ULN and that none of them showed any characteristic imaging findings of AP. Similar conclusions are supported by the works of Bansal *et al* [129], Rasch *et al*[130], Barlass *et al*[131], and Bacaksiz *et al*[132], all of which call out for caution when addressing the interrelation between the alteration of pancreatic enzymes and COVID-induced pancreatic impairment. Despite the increase in pancreatic biomarkers typical of COVID-19 patients, no direct correlation to pancreatic impairment is established, as these imbalances could result from concurrent clinical conditions[86,133].

On the other hand, many authors have recognized and described a significant prognostic role of amylase and lipase levels in poor outcomes in COVID-19. Liu *et al*[125] reported a pancreatic enzyme alteration incidence about nine times higher in patients with severe COVID conditions compared to those with non-severe disease (17.4% *vs* 1.85%). Barlass *et al*[131] showed an association between lipase elevation and worse disease outcomes, especially in terms of the need for intensive care (92.9% in patients with elevated lipase levels *vs* 32.8% in those with lower levels) and rate of intubation (78.6% *vs* 23.5%). Ultimately, the multicenter retrospective cohort study by Singh *et al*[134] played a vital role in strengthening this theory, and if its findings are confirmed, serum lipase can be utilized as a marker of disease severity in patients with COVID-19.

### **Prevalence and outcomes of acute and chronic pancreatitis in COVID-19**

After carefully examining the existing literature, a bidirectional relationship between COVID-19 disease and AP can be inferred, at least in terms of outcomes. As part of their retrospective observational cohort study, Inamdar *et al*[135] reported the point prevalence, risk factors, and outcomes among hospitalized patients with pancreatitis with or without COVID-19. This work illustrated a point prevalence of pancreatitis of 0.27%, a higher need for intensive care (mechanical ventilation), and a longer length of hospital stay (OR = 5.65 and OR = 3.22, respectively) among COVID-19 patients. Comparable data were obtained in the works of Karaali and Topal[136], Dirweesh *et al*[137], and from the COVID PAN collaborative study[138], the last of which reported longer length of hospital-stay, persistent organ failure, and higher 30-d mortality in patients with SARS-CoV-2 co-infection. As clearly described by Ye *et al*[139], COVID-19 patients with comorbidities had worse clinical outcomes and greater risk of adverse events proportionally to the number of comorbidities. Focusing on AP, only two studies have compared outcomes in COVID-19 patients with and without pancreatic impairment. Mirò *et al*[140] found comparable results for these two groups, except for the former, being more frequently in need of hospitalization. Similarly, Akarsu *et al*[141] reported that COVID-19 patients who suffered from pancreatitis were more likely to have higher hospitalization and mortality rates. Gubatan *et al*[62] were the first to evaluate the prevalence and outcomes of COVID-19 among patients with a history of pancreatitis. As thoroughly



described by Huang *et al*[142], preexisting pancreas condition was associated with an increased risk of COVID-19 hospitalization and mortality compared to pancreatitis-free patients. Specifically, the highest hospitalization and ICU admission rates were registered in those with a history of chronic pancreatitis. Multicenter research by Hadi *et al*[143] have confirmed that COVID-19 patients with convalescent plasma (CP) bear higher hospitalization rates despite showing no difference in mortality and critical care need. A plausible explanation looks at the higher pancreatic fibrosis grade and the lower inflammatory state, typical of these patients, as predisposing agents to the burden of comorbidities and worse COVID-19 outcomes (Tables 4 and 5).

### **Distinctive features of COVID-19-associated AP in elderly patients**

Focusing on the elderly population, it seems that AP has some particular clinical features that lead to a clinically severe evolution, systemic complications, and, therefore, higher mortality rates[145]. AP has been increasing globally because of an aging population. However, it is worth noting that even if the WHO's definition of elderly is over > 65 years, the age cut-off used for "elderly" in AP prevalence studies differs. In detail, the highest prevalence was found in subjects between 55 and 65 years of age[145-147]. The non-specific presentation and the last occurrence of the symptoms typical of elderly patients make the clinical assessment more difficult for physicians. For example, the typical abdominal pain radiating to the back is absent or mild in 53.8% of cases[148]. For these reasons and the overlap of coexisting comorbidities, AP is often clinically indistinguishable from other clinical conditions in this population. Márta *et al*[149] reported that aging greatly influenced AP's outcome. Their work demonstrated a direct relationship between age and the mortality rate with mortality increase of 0.08% per year between the ages of 20 and 59 and up to 0.76% per year between 59 and 70[149]. These findings, suggesting the involvement of additional deteriorating factors in the elderly population, led the way to other/further studies. COVID-19-induced AP in the elderly population is increasingly reported. Unfortunately, no studies account for only COVID-19 elderly patients with pancreatic impairment, and the few data available are insufficient to draw general conclusions. In Wang *et al*[122]'s work, which describes the incidence of comorbidities in a COVID-19-affected population, the nine patients with pancreatic damage had an average age of 55 years, ranging from 25 to 71 years. Similar data are reported in Inamdar *et al*[135]'s (average age of 54 years), Bruno *et al*[124]'s (average age of 56), and Bulthuis *et al*[150]'s work (60 years). Moreover, a systematic review of case reports and case series pointed out that COVID-19-associated AP affected primarily females with a median age of 53.5 years[144]. The average age of all these study populations aligns with the definition mentioned above of elderly in AP, but the range does not[145]. Conversely, from what was stated before about geriatric patients solely affected by AP[142], 11 case reports of AP in COVID-19-affected elderly patients showed the typical clinical presentation with all the patients experiencing abdominal pain radiating to the back[151-160]. However, these findings are insufficient to suggest a direct or, most likely, indirect effect of SARS-CoV-2 infection on AP's clinical presentation. Therefore, further studies are necessary to establish a causative role. As previously reported, aging is considered a risk factor for a worse outcome not only in COVID-19 disease[161] but also in pancreatitis[149]. Advancing age is one of the 8 modified Glasgow Imrie severity Criteria for AP [162]. Three or more positive criteria, generally assessed within 48 h from admission, are indicative of severe pancreatitis and may require transfer to an intensive care unit[163]. Three of the 11 case reports had to be excluded from the analysis for insufficient data availability. Half of the remaining reports showed a result equal to or higher than three, suggesting severe pancreatitis. However, it is essential to highlight that due to the intrinsic limitation of retrospective analysis, information about the specific timings of the blood test is missing. To the authors' knowledge, no studies evaluating the isolated impact of age as a risk factor for severe prognosis exist for specific subgroups of patients like COVID-19 and AP. Moreover, in the aforementioned prognostic studies[136-138], the demographic composition of the age of the analyzed groups was so similar that no meaningful information could be inferred on the topic.

### **Impact of SARS-CoV-2 vaccines on patients with IBD**

Initially, SARS-CoV-2 vaccines caused hesitancy in the IBD, mainly due to fear of poor response and safety concerns. IBD represents impaired immune function due to the disease and the therapies used to control this illness[60]. Jena *et al*[164] in a systematic review and meta-analysis, analyzed the response to complete vaccination in IBD patients. They reported positive seroconversion rates (95%), although these rates were slightly lower than non-IBD controls (98%). However, if considering only mRNA vaccines, the seroconversion data overlapped between the two populations. Similar results are reported by Bhurwal *et al*[165], which confirmed the adequate response to vaccination in the IBD population (96%), again showing improved outcomes with mRNA vaccines. Moreover, these two meta-analyses found no significant difference in seroconversion concerning the therapy administered (anti-TNF alone, vedolizumab, ustekinumab, or JAK inhibitors), in contrast to other studies which found lower responses to vaccination during anti-TNF alpha and JAK inhibitors therapy [166,167]. In addition, the analysis of breakthrough infections suggests an overall frequency similar to the general population. Nevertheless, a more rapid decline in antibody titers is described in IBD patients, particularly those treated with anti-TNF, immunomodulators, or a combination of these drugs[164]. Another parameter used to assess the efficacy of vaccination is the T cellular response, which plays an essential role in preventing disease progression[168]. Patients with IBD maintain this response even when receiving immune-targeted therapies, confirming that the immunocompromised state does not necessarily prevent a response to vaccination[169,170]. Interestingly, the T cellular response appears to be increased in patients taking anti-TNF- $\alpha$  due to unclear mechanisms[170]. Regarding the safety of vaccinations, several studies have observed similar side effect frequencies between the IBD population and the general population. However, no worsening or flare-up of the disease following vaccination has been proved. Thus, vaccines are considered a safe and well-tolerated strategy for IBD patients[171,172].

Focusing on the elderly population, it is well known that the response to vaccines may be lower than in young people [173], which may also occur with SARS-CoV-2 vaccines. This is probably the result of immune-senescence phenomena, which leads to quantitative and qualitative alterations in the immune system, including a reduction in naive T

**Table 4 Evidence regarding pancreatic involvement in coronavirus disease 2019 patients**

Ref.	Study design	No. of patients with pancreatic injury/total no. of patients	Remarks
Wang <i>et al</i> [122]	CHS	9/52 (4.68%)	Potential mild pancreatic involvement in patients with COVID-19 pneumonia
Bruno <i>et al</i> [124]	CHS	6/70 (8.5%)	Pancreatic involvement in hospitalized patients with documented COVID-19
Liu <i>et al</i> [125]	RS	13/121 (10.74%)	Pancreatic enzyme alteration incidence was higher in patients with severe COVID-19-related conditions than those with the non-severe disease. However, only a minority of patients with pancreatic enzyme alteration had a confirmed diagnosis of AP as defined by the AC
Stephens <i>et al</i> [126]	RS	158/234 (67.5%)	Raised serum amylase in patients with COVID-19 may not be associated with pancreatitis
Akkus <i>et al</i> [127]	RS	127/309 (15.7%)	Pancreatic injuries or AP are frequent during COVID-19 infection, especially in those with pre-existing DM
McNabb-Baltar <i>et al</i> [128]	RS	9/71 (12.1%)	Although a mild elevation in serum lipase was observed in some patients with COVID-19, acute clinical pancreatitis was not seen, according to the AC
Bansal <i>et al</i> [129]	RS	14/42 (33%), 7/29 patients (24.1%)	Pancreatic injury showed no statistically significant relation to the severity or outcome of COVID-19
Rasch <i>et al</i> [130]	CHS	22/38 (57.8%)	Patients with lipasemia needed more extended periods of mechanical ventilation than patients with COVID-19-associated ARDS
Barlass <i>et al</i> [131]	CCS	14/83 (16.8%)	Elevated lipase is associated with worse disease outcomes and increased ICU admission and intubation
Bacaksiz <i>et al</i> [132]	RS	316/1378 (23%)	Hyperamylasemia was significantly associated with COVID-19 severity
Magro <i>et al</i> [86]	Review	NA	Increased amylase or lipase levels might not be associated with AP in COVID-19 and may be a consequence of concurrent clinical conditions
Hunt <i>et al</i> [133]	Review	NA	No direct correlation between COVID-19 and pancreatic impairment could be established
Singh <i>et al</i> [134]	MS	1406/435731 (0.32%)	Worse clinical outcomes
Inamdar <i>et al</i> [135]	MS	189/11.883 (0.01%)	COVID-19 patients with pancreatitis were more likely to require mechanical ventilation and had a more extended hospital stay than patients without COVID-19
Karaali and Topal[136]	RS	189/562 (33.6%)	COVID-19 patients with AP had a higher rate of severe AP and a higher need for ICU admission
Dirweesh <i>et al</i> [137]	RS	75/339 (22.1%)	Higher mortality, MOF, and POF rates were registered in patients with AP and coexisting COVID-19
Pandanaboyana <i>et al</i> [138]	CHS	149/1777 (8.3%)	SARS-CoV-2 infection in acute pancreatitis increases 30-d mortality and disease severity
Mirò <i>et al</i> [140]	MS	45/63.822 (0.0007%)	Higher need for hospitalisation in COVID-19 patients with pancreatitis
Akarsu <i>et al</i> [141]	CCS	40/316 (12.6%)	Higher mortality rate and increased need for hospitalisation in COVID-19 patients with pancreatitis
Gubatan <i>et al</i> [62]	RS	100% total population 14235	Patients with a history of pancreatitis may be more susceptible to COVID-19
Huang <i>et al</i> [142]	RCS	4706/326993 (1.4%)	Pre-existing pancreatitis was associated with an increased risk of COVID-19-related hospitalisation and mortality
Hadi <i>et al</i> [143]	CS	2/3 (66.6%)	COVID-19 patients with CP bear higher hospitalisation rates
Georgakopoulou <i>et al</i> [144]	RS	100%	COVID-19-associated acute pancreatitis affected primarily females with a median age of 53.5 yr

CS: Case series; CR: Case reports; RS: Retrospective studies; RCS: Retrospective cohort study; MS: Multicentric study; CCS: Case-control study; CHS: Cohort study; CSS: Cross-sectional study; NA: Not available; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019; AC: Atlanta criteria; CP: Convalescent plasma; ICU: Intensive care unit; MOF: Multiple-organ failure; POF: Persistent organ failure; ARDS: Acute respiratory distress syndrome.

lymphocytes available to respond to a vaccine, a significant decrease in CD8 T cells, and a reduction in the T helper follicular cell response[174-176]. Unfortunately, there are currently no studies evaluating vaccination efficacy and safety in elderly patients with IBD. However, in many studies, older age has been associated with attenuated responses, with an earlier decline of the antibody title and reduction differences in the overall strength of the T-cell, although in most of



**Table 5 Case reports regarding pancreatic involvement in old coronavirus disease 2019 patients**

Ref.	Study design	Age (yrs)	Remarks
Meyers <i>et al</i> [151]	CR	67	COVID-19 can cause clinical AP. Typical abdominal pain radiating to the back. Increase lipase serum level. Evidence of AP in abdominal CT scan. Glasgow Acute Pancreatitis Score: NA
Karimzadeh <i>et al</i> [152]	CR	65	COVID-19 presents as mild AP. Typical abdominal pain radiating to the back. Increase lipase serum level. Negative abdominal CT scan. Glasgow Acute Pancreatitis Score: 1 point
Gadiparthi <i>et al</i> [153]	CR	74	AP in a patient with COVID-19 with SARS-CoV-2 as the possible etiological agent. Typical abdominal pain radiating to the back. Increase lipase serum level. Evidence of AP in abdominal CT scan. Glasgow Acute Pancreatitis Score: 1 point
Wifi <i>et al</i> [154]	CR	72	Emphasises the importance of measuring serum amylase and lipase in patients with COVID-19. Typical abdominal pain radiating to the back. Increase lipase and amylase serum levels. Negative abdominal CT scan. Glasgow Acute Pancreatitis Score: 3 points
Gonzalo-Voltas <i>et al</i> [155]	CR	76	A case of AP that could be related to COVID-19 infection. Typical abdominal pain radiating to the back. Increase amylase serum level. Evidence of AP in abdominal CT scan. Glasgow Acute Pancreatitis Score: NA
Reick-Mitrison <i>et al</i> [156]	CR	71	AP should be considered in differential abdominal pain in patients with active or recent SARS-CoV-2 infection. Typical abdominal pain. Increase lipase serum level. Evidence of AP in abdominal CT scan. Glasgow Acute Pancreatitis Score: 3 points
Brikman <i>et al</i> [163]	CR	61	Unresolved abdominal pain occurring late during COVID-19 warrants a thorough workup. Typical abdominal pain. Increase lipase serum level. Evidence of AP in abdominal CT scan. Glasgow Acute Pancreatitis Score: 2 points
Acherjya <i>et al</i> [157]	CR	57	Pay attention to the atypical presentations of SARS-CoV-2, including AP. Typical abdominal pain radiating to the back. Increase lipase serum level. Evidence of AP in abdominal CT scan. Glasgow Acute Pancreatitis Score: 4 points
Alves <i>et al</i> [158]	CR	56	Physicians should be aware that asymptomatic or mildly gastrointestinal symptomatic patients with COVID-19 require pancreatic enzymes and even abdomen imaging to diagnose pancreatitis. Typical abdominal pain. Increase lipase and amylase serum levels. Evidence of AP in abdominal CT scan. Glasgow Acute Pancreatitis Score: 3 points
Shinohara <i>et al</i> [159]	CR	58	Extrapulmonary clinical characteristics of COVID-19 remain unclear. Typical abdominal pain. Increase amylase serum level. Evidence of AP in abdominal CT scan. Glasgow Acute Pancreatitis Score: NA
Kumaran <i>et al</i> [160]	CR	67	Importance of considering COVID-19 as a potential cause in patients presenting with idiopathic pancreatitis. Typical abdominal pain. Increase amylase serum level. Evidence of AP in abdominal CT scan. Glasgow Acute Pancreatitis Score: 2 points

AP: Acute pancreatitis; CR: Case reports; CT: Computed tomography; NA: Not available; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

them, the presence of IBD does not influence these findings[169,170,177,178].

In conclusion, most of the studies mentioned above agree on the potential benefit of a further vaccine booster dose in patients with IBD, especially if elderly or on specific immunosuppressive therapies, such as anti-TNF alpha or JAK inhibitors. To date, studies reporting response rates with additional doses of COVID-19 vaccine in IBD are limited; however, current data suggest a significant boost in antibody binding levels from a third vaccine dose, even during immunosuppressive therapies, but patients receiving infliximab or tofacitinib show a lower response than healthy controls[179].

### **Impact of SARS-CoV-2 vaccines on patients with CLD**

As mentioned above, cirrhotic patients are at high risk of severe COVID-19 infection. Therefore, vaccination against SARS-CoV-2 represents a significant protective measure in patients with CLD, which must be administered as early as possible[180,181]. Moreover, due to vaccinations, patients should not discontinue any of their medications for liver disease or delay any local or regional treatments for HCC[182]. Current COVID-19 vaccines are safe, but a rare vaccine-triggered immune-mediated hepatitis is reported after COVID-19 vaccination. These events are described in the literature in association with mRNA platforms, but cases have also been described for vector-based vaccines. These cases of liver injury are sporadic and respond to corticosteroid treatment. Therefore, liver injury after vaccination should not represent a limit to further vaccination[183]. Furthermore, a Chinese multi-centric study analyzed the safety and immunogenicity of inactivated SARS-CoV-2 vaccines in patients with CLDs[184]. These vaccines are safe in patients with CLD, as there was no significant difference in adverse reactions among the non-cirrhotic CLD, compensated cirrhosis, and decompensated cirrhosis subgroups. Pain was the most common local adverse reaction, while fever was the most commonly systematic adverse reaction reported. Among laboratory findings, only three patients of 437 with CLD had significant aminophosphatase elevation with ALT levels > 5 ULN, all of which had elevated aminophosphatase at baseline. Only one of the three patients required hospitalization. Nevertheless, it is impossible to attribute his adverse reaction to the vaccine for certainty since this patient had a history of discontinuing anti-hepatitis B virus therapy before the SARS-CoV-2 vaccination. In addition, patients with CLD often present an inadequate immune response, which may cause an incomplete immediate and long-term protective response[185]. Therefore, although these vaccines are safe in patients with CLD, they do not guarantee such patients equal antibody levels if compared to healthy controls. However, the difference in the positive rate of SARS-CoV-2 neutralizing antibodies between patients with CLD and healthy control groups is statistically significant (77.3% *vs*

90.3%) despite the adjustment for age, gender, and body mass index[184]. While there was no significant difference in positive rate between non-cirrhotic CLD patients (76.8%), compensated cirrhosis patients (78.9%), and decompensated cirrhosis patients (76.7%). Chen *et al*[186] confirmed in their study that inactivated SARS-CoV-2 vaccines are safe and well tolerated in patients with severe liver disease (such as cirrhosis or HCC). However, they also stressed the necessity to assign priority to vaccine patients with severe liver disease, which may have worse antibody responses than those with non-severe CLDs. Thuluvath *et al*[187] instead, analyzed the antibody response in CLD patients after administration of 2 doses of mRNA vaccines or a single dose of viral vector vaccine. This study revealed that only 24% of patients with CLDs had poor antibody responses. More in detail, 15.8% of patients who received the vector vaccine Johnson & Johnson had a good response, and the mRNA Moderna vaccine showed a better response than the mRNA Pfizer vaccine (76.4% *vs* 64.4%). Moreover, analyzing patients' characteristics, it emerged that those with undetectable antibodies (< 0.4 U/mL) had the highest mean age (64.8 years). In line with Thuluvath *et al*[187], Bakasis *et al*[188] highlighted that CLD was not associated with mRNA vaccine hypo-responsiveness. Only 4% of patients with CLD did not respond to SARS-CoV-2 vaccination, with statistically significant differences between cirrhotic and non-cirrhotic patients. The presence of liver disease showed no correlation with antibody titers or neutralizing activity, while age was negatively correlated with neutralizing activity. According to Willuweit *et al*[189], up to 96% of patients with liver cirrhosis presented an antibody response after receiving two doses of the mRNA-based vaccine. Unfortunately, antibody titers remained relatively stable in the control group while showing a rapid and significant decrease in patients with liver cirrhosis, with any differences stratifying cirrhotic patients according to age. The studies mentioned above do not focus on the differences between safety and efficacy among age (patients under 65 and over 65 years old or following stratification of groups according to age). Moreover, the studies conducted to evaluate the safety and efficacy of SARS-CoV-2 vaccination include a limited number of older adults[190]. Therefore, considering that older adults are more inclined to develop vaccine-related adverse events[191] and the lack of older adults in specific SARS-CoV-2 vaccination studies, further research is recommended to evaluate the safety and efficacy of COVID-19 vaccines in older people.

### COVID-19 vaccines and pancreatic involvement

To the best of our knowledge, no published work evaluates the COVID-19 vaccination response in older adults suffering from pancreatic diseases. On the other hand, according to Pfizer's data, only 2 cases of AP as an adverse reaction (among 38000 participants) were reported during the clinical trial of the COVID-19 mRNA vaccine[192]. Since the Pfizer-BioNTech mRNA vaccine was approved for COVID-19 infection, AP has been reported in a few case reports[193-201]. Data inferred from United Kingdom databases (up to November 2022) for the same vaccine report 21 cases of pancreatitis, 19 cases of AP, and 3 cases of necrotizing pancreatitis[202]. The National Agency for the Safety of Medicines and Health Products reports 164 cases of pancreatitis up to February 10, 2022[203]. Data released from Vigibase, the WHO's global database, show 1093 cases of pancreatitis[204]. Currently, there is no evidence supporting a direct relationship between the vaccine and AP; even assuming the existence of vaccine-related pancreatic injury, its mechanism would still be unclear[194]. Moreover, considering the high rate of idiopathic pancreatitis[205], the available data are even more challenging to analyze. Considering the higher vaccination prevalence, fewer cases of AP following vaccination may suggest the involvement of different mechanisms in developing a vaccine-related pancreatic injury[196]. The benefits of vaccination against COVID-19 are unquestionable and not disputed in this paper. However, by reporting this evidence, we aim to make all healthcare workers aware of these possible adverse effects and to highlight the importance of not underestimating any abdominal pain after vaccination. As far as we know, the current literature does not include studies evaluating the safety and efficacy of SARS-CoV-2 vaccines in patients with CP. As mentioned above[142,143], CP may be associated with an increased risk of complications from COVID-19 infection leading to worse outcomes. Thus, reducing that risk by having the vaccine would be advisable.

## CONCLUSION

Literature data confirm that the digestive manifestations of COVID-19 are frequent and often impact the clinical course of affected patients. In particular, patients with pre-existing liver disease, including cirrhosis or HCC, are at increased risk for worse outcomes. On the contrary, no definitive conclusions can be drawn for patients with IBD or pancreatic diseases. As for elderly patients with digestive disorders, although the available data are limited and extrapolated from studies not designed for this specific issue, there seems to be no evidence of worse COVID-19 outcomes than those without digestive diseases. As expected, this review confirms that age represents one of the main risk factors for poorer outcomes and higher mortality for COVID-19. Moreover, considering the under-representation of older adults in SARS-CoV-2 vaccination studies, further studies are necessary to evaluate better the safety and efficacy of COVID-19 vaccines, especially in frail older people with chronic digestive diseases.

## FOOTNOTES

**Author contributions:** Papa A and Covino M contributed to the conception and design of this study, analysis and interpretation of data; De Lucia SS, Del Gaudio A, Fiorani M, Polito G, and Settanni CR were involved in the acquisition and collection of data; Papa A, Covino M, De Lucia SS, Del Gaudio A, Fiorani M, Polito G, Settanni CR, Franceschi F, and Gasbarrini A drafted the paper or revised it critically for intellectual content; and all authors approved the final version of the manuscript to be published.

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