**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 81889

**Manuscript Type:** REVIEW

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

Papa A *et al*. COVID-19 and GI diseases in elderly

Alfredo Papa, Marcello Covino, Sara Sofia De Lucia, Angelo Del Gaudio, Marcello Fiorani, Giorgia Polito, Carlo Romano Settanni, Andrea Piccioni, Francesco Franceschi, Antonio Gasbarrini

**Alfredo Papa, Sara Sofia De Lucia, Angelo Del Gaudio, Marcello Fiorani, Giorgia Polito, Antonio Gasbarrini,** CEMAD, Center for Diagnosis and Treatment of Digestive Diseases, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Roma 00168, Italy

**Alfredo Papa,** CEMAD, Università Cattolica del Sacro Cuore, Roma 00168, Italy

**Marcello Covino,** Department of Emergency, Università Cattolica del Sacro Cuore - Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome 00168, Italy

**Marcello Covino,** Emergency Medicine, Università Cattolica del Sacro Cuore, Roma 00168, Italy

**Carlo Romano Settanni,** Digestive Disease Center, Fondazione Policlinico Universitario A. Gemelli IRCCS - Università Cattolica del Sacro Cuore, Rome 00168, Italy

**Andrea Piccioni, Francesco Franceschi,** Department of Emergency, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Roma 00168, Italy

**Francesco Franceschi,** Department of Emergency, Università Cattolica del Sacro Cuore, Roma 00168, Italy

**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.

**Corresponding author: Marcello Covino, MD, PhD, Assistant Professor,** Department of Emergency, Università Cattolica del Sacro Cuore - Fondazione Policlinico Universitario A. Gemelli, IRCCS, Largo A. Gemelli 1, Rome 00168, Italy. marcello.covino@policlinicogemelli.it

**Received:** November 27, 2022

**Revised:** January 10, 2023

**Accepted:** March 20, 2023

**Published online:**

**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

Papa A, Covino M, De Lucia SS, Del Gaudio A, Fiorani M, Polito G, Settanni CR, Piccioni A, Franceschi F, Gasbarrini A. Impact of COVID-19 in individuals with and without pre-existent digestive disorders with a particular focus on elderly patients. *World J Gastroenterol* 2023; In press

**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.

**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 635 229 101 confirmed cases, including 6 602 552 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 autoptic 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](https://pubmed.ncbi.nlm.nih.gov/?term=Atalla%252520E%25255BAuthor%25255D) *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 antimicrobic 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, such as age, male sex, and comorbidities, are the same as observed in the general population. In IBD patients with COVID-19, an 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-α 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-α 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-α, 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]. Wetwittayakhlang *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 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 ≥ 5-times upper limit of normal (ULN), or increased level of ALP ≥ 2-times ULN (in the absence of bone pathology), or a simultaneous increase of ALT ≥ 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 × 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 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](https://pubmed.ncbi.nlm.nih.gov/?term=McNabb-Baltar%252520J%25255BAuthor%25255D) *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-α 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 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 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 aminopherase elevation with ALT levels > 5 ULN, all of which had elevated aminopherase 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 titersremained 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 38 000 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.

**REFERENCES**

1 **Liu YC**, Kuo RL, Shih SR. COVID-19: The first documented coronavirus pandemic in history. *Biomed J* 2020; **43**: 328-333 [PMID: 32387617 DOI: 10.1016/j.bj.2020.04.007]

2 **World Health Organization**. WHO Coronavirus (COVID-19) Dashboard. [cited 17 October 2022]. Available from: https://covid19.who.int/?gclid=CjwKCAiAlNf-

3 **Wiersinga WJ**, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA* 2020; **324**: 782-793 [PMID: 32648899 DOI: 10.1001/jama.2020.12839]

4 **Struyf T**, Deeks JJ, Dinnes J, Takwoingi Y, Davenport C, Leeflang MM, Spijker R, Hooft L, Emperador D, Domen J, Tans A, Janssens S, Wickramasinghe D, Lannoy V, Horn SRA, Van den Bruel A; Cochrane COVID-19 Diagnostic Test Accuracy Group. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19. *Cochrane Database Syst Rev* 2022; **5**: CD013665 [PMID: 35593186 DOI: 10.1002/14651858.CD013665.pub3]

5 **Chua AJ**, Charn TC, Chan EC, Loh J. Acute Olfactory Loss Is Specific for COVID-19 at the Emergency Department. *Ann Emerg Med* 2020; **76**: 550-551 [PMID: 32410763 DOI: 10.1016/j.annemergmed.2020.05.015]

6 **Carpenter CR**, Mudd PA, West CP, Wilber E, Wilber ST. Diagnosing COVID-19 in the Emergency Department: A Scoping Review of Clinical Examinations, Laboratory Tests, Imaging Accuracy, and Biases. *Acad Emerg Med* 2020; **27**: 653-670 [PMID: 32542934 DOI: 10.1111/acem.14048]

7 **Long B**, Carius BM, Chavez S, Liang SY, Brady WJ, Koyfman A, Gottlieb M. Clinical update on COVID-19 for the emergency clinician: Presentation and evaluation. *Am J Emerg Med* 2022; **54**: 46-57 [PMID: 35121478 DOI: 10.1016/j.ajem.2022.01.028]

8 **D'Amico F**, Baumgart DC, Danese S, Peyrin-Biroulet L. Diarrhea During COVID-19 Infection: Pathogenesis, Epidemiology, Prevention, and Management. *Clin Gastroenterol Hepatol* 2020; **18**: 1663-1672 [PMID: 32278065 DOI: 10.1016/j.cgh.2020.04.001]

9 **Aroniadis OC**, Wang X, Gong T, Forbes N, Yang JY, Canakis A, Elmunzer BJ, Yadav D; North American Alliance for the Study of Digestive Manifestations of Covid-19. Factors Associated with the Development of Gastrointestinal Symptoms in Patients Hospitalized with Covid-19. *Dig Dis Sci* 2022; **67**: 3860-3871 [PMID: 34751837 DOI: 10.1007/s10620-021-07286-7]

10 **Cholankeril G**, Podboy A, Aivaliotis VI, Tarlow B, Pham EA, Spencer SP, Kim D, Hsing A, Ahmed A. High Prevalence of Concurrent Gastrointestinal Manifestations in Patients With Severe Acute Respiratory Syndrome Coronavirus 2: Early Experience From California. *Gastroenterology* 2020; **159**: 775-777 [PMID: 32283101 DOI: 10.1053/j.gastro.2020.04.008]

11 **Wang Y**, Li Y, Zhang Y, Liu Y, Liu Y. Are gastrointestinal symptoms associated with higher risk of Mortality in COVID-19 patients? A systematic review and meta-analysis. *BMC Gastroenterol* 2022; **22**: 106 [PMID: 35255816 DOI: 10.1186/s12876-022-02132-0]

12 **Gupta A**, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, Bikdeli B, Ahluwalia N, Ausiello JC, Wan EY, Freedberg DE, Kirtane AJ, Parikh SA, Maurer MS, Nordvig AS, Accili D, Bathon JM, Mohan S, Bauer KA, Leon MB, Krumholz HM, Uriel N, Mehra MR, Elkind MSV, Stone GW, Schwartz A, Ho DD, Bilezikian JP, Landry DW. Extrapulmonary manifestations of COVID-19. *Nat Med* 2020; **26**: 1017-1032 [PMID: 32651579 DOI: 10.1038/s41591-020-0968-3]

13 **Zheng Z**, Peng F, Xu B, Zhao J, Liu H, Peng J, Li Q, Jiang C, Zhou Y, Liu S, Ye C, Zhang P, Xing Y, Guo H, Tang W. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. *J Infect* 2020; **81**: e16-e25 [PMID: 32335169 DOI: 10.1016/j.jinf.2020.04.021]

14 **Mueller AL**, McNamara MS, Sinclair DA. Why does COVID-19 disproportionately affect older people? *Aging (Albany NY)* 2020; **12**: 9959-9981 [PMID: 32470948 DOI: 10.18632/aging.103344]

15 **Goodman KE**, Magder LS, Baghdadi JD, Pineles L, Levine AR, Perencevich EN, Harris AD. Impact of Sex and Metabolic Comorbidities on Coronavirus Disease 2019 (COVID-19) Mortality Risk Across Age Groups: 66 646 Inpatients Across 613 U.S. Hospitals. *Clin Infect Dis* 2021; **73**: e4113-e4123 [PMID: 33337474 DOI: 10.1093/cid/ciaa1787]

16 **Chen Y**, Klein SL, Garibaldi BT, Li H, Wu C, Osevala NM, Li T, Margolick JB, Pawelec G, Leng SX. Aging in COVID-19: Vulnerability, immunity and intervention. *Ageing Res Rev* 2021; **65**: 101205 [PMID: 33137510 DOI: 10.1016/j.arr.2020.101205]

17 **Channappanavar R**, Perlman S. Age-related susceptibility to coronavirus infections: role of impaired and dysregulated host immunity. *J Clin Invest* 2020; **130**: 6204-6213 [PMID: 33085654 DOI: 10.1172/JCI144115]

18 **Papa A**, Covino M, Pizzolante F, Miele L, Lopetuso LR, Bove V, Iorio R, Simeoni B, Vetrone LM, Tricoli L, Mignini I, Schepis T, D'Alessandro A, Coppola G, Nicoletti T, Visconti E, Rapaccini G. Gastrointestinal symptoms and digestive comorbidities in an Italian cohort of patients with COVID-19. *Eur Rev Med Pharmacol Sci* 2020; **24**: 7506-7511 [PMID: 32706091 DOI: 10.26355/eurrev\_202007\_21923]

19 **Zou X**, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. *Front Med* 2020; **14**: 185-192 [PMID: 32170560 DOI: 10.1007/s11684-020-0754-0]

20 **Lin L**, Jiang X, Zhang Z, Huang S, Zhang Z, Fang Z, Gu Z, Gao L, Shi H, Mai L, Liu Y, Lin X, Lai R, Yan Z, Li X, Shan H. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. *Gut* 2020; **69**: 997-1001 [PMID: 32241899 DOI: 10.1136/gutjnl-2020-321013]

21 **Selva KJ**, Chung AW. Insights into how SARS-CoV2 infection induces cytokine storms. *Trends Immunol* 2022; **43**: 417-419 [PMID: 35537983 DOI: 10.1016/j.it.2022.04.007]

22 **Villapol S**. Gastrointestinal symptoms associated with COVID-19: impact on the gut microbiome. *Transl Res* 2020; **226**: 57-69 [PMID: 32827705 DOI: 10.1016/j.trsl.2020.08.004]

23 **Zhan T**, Tang Y, Han Z, Zhu Q, Tan J, Liu M, Cai Y, Huang M, Chen X, Cheng X, Deng J, Huang X, Tian X. Clinical Characteristics of 195 Cases of COVID-19 with Gastrointestinal Symptoms COVID-19 with Gastrointestinal Symptoms. *Turk J Gastroenterol* 2021; **32**: 148-154 [PMID: 33960938 DOI: 10.5152/tjg.2021.20379]

24 **Perisetti A**, Goyal H, Gajendran M, Boregowda U, Mann R, Sharma N. Prevalence, Mechanisms, and Implications of Gastrointestinal Symptoms in COVID-19. *Front Med (Lausanne)* 2020; **7**: 588711 [PMID: 33195352 DOI: 10.3389/fmed.2020.588711]

25 **Papadakis KA**, Prehn J, Nelson V, Cheng L, Binder SW, Ponath PD, Andrew DP, Targan SR. The role of thymus-expressed chemokine and its receptor CCR9 on lymphocytes in the regional specialization of the mucosal immune system. *J Immunol* 2000; **165**: 5069-5076 [PMID: 11046037 DOI: 10.4049/jimmunol.165.9.5069]

26 **Babic T**, Browning KN. The role of vagal neurocircuits in the regulation of nausea and vomiting. *Eur J Pharmacol* 2014; **722**: 38-47 [PMID: 24184670 DOI: 10.1016/j.ejphar.2013.08.047]

27 **Fang D**, Ma J, Guan J, Wang M, Song Y, Tian D, Li P. [Manifestations of digestive system of hospitalized patients with coronavirus disease 2019 in Wuhan, China: a single-center descriptive study]. Chin J Digestion 2020: 151-156

28 **Jiménez E**, Fontán-Vela M, Valencia J, Fernandez-Jimenez I, Álvaro-Alonso EA, Izquierdo-García E, Lazaro Cebas A, Gallego Ruiz-Elvira E, Troya J, Tebar-Martinez AJ, Garcia-Marina B, Peña-Lillo G, Abad-Motos A, Macaya L, Ryan P, Pérez-Butragueño M; COVID@HUIL Working Group; COVID@HUIL Working Group. Characteristics, complications and outcomes among 1549 patients hospitalised with COVID-19 in a secondary hospital in Madrid, Spain: a retrospective case series study. *BMJ Open* 2020; **10**: e042398 [PMID: 33172949 DOI: 10.1136/bmjopen-2020-042398]

29 **Vuille-Dit-Bille RN**, Liechty KW, Verrey F, Guglielmetti LC. SARS-CoV-2 receptor ACE2 gene expression in small intestine correlates with age. *Amino Acids* 2020; **52**: 1063-1065 [PMID: 32627059 DOI: 10.1007/s00726-020-02870-z]

30 **Hashimoto T**, Perlot T, Rehman A, Trichereau J, Ishiguro H, Paolino M, Sigl V, Hanada T, Hanada R, Lipinski S, Wild B, Camargo SM, Singer D, Richter A, Kuba K, Fukamizu A, Schreiber S, Clevers H, Verrey F, Rosenstiel P, Penninger JM. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. *Nature* 2012; **487**: 477-481 [PMID: 22837003 DOI: 10.1038/nature11228]

31 **Liu Q**, Wang RS, Qu GQ, Wang YY, Liu P, Zhu YZ, Fei G, Ren L, Zhou YW, Liu L. Gross examination report of a COVID-19 death autopsy. *Fa Yi Xue Za Zhi* 2020; **36**: 21-23 [PMID: 32198987 DOI: 10.12116/j.issn.1004-5619.2020.01.005]

32 **de Souza CD**, de Arruda Magalhães AJ, Lima AJ, Nunes DN, de Fátima Machado Soares É, de Castro Silva L, Santos LG, Dos Santos Cardoso VI, Nobre YV, do Carmo RF. Clinical manifestations and factors associated with mortality from COVID-19 in older adults: Retrospective population-based study with 9807 older Brazilian COVID-19 patients. *Geriatr Gerontol Int* 2020; **20**: 1177-1181 [PMID: 33111433 DOI: 10.1111/ggi.14061]

33 **Marziliano A**, Burns E, Chauhan L, Liu Y, Makhnevich A, Zhang M, Carney MT, Dbeis Y, Lindvall C, Qiu M, Diefenbach MA, Sinvani L. Patient Factors and Hospital Outcomes Associated With Atypical Presentation in Hospitalized Older Adults With COVID-19 During the First Surge of the Pandemic. *J Gerontol A Biol Sci Med Sci* 2022; **77**: e124-e132 [PMID: 34279628 DOI: 10.1093/gerona/glab171]

34 **Ramos-Rincon JM**, Buonaiuto V, Ricci M, Martín-Carmona J, Paredes-Ruíz D, Calderón-Moreno M, Rubio-Rivas M, Beato-Pérez JL, Arnalich-Fernández F, Monge-Monge D, Vargas-Núñez JA, Acebes-Repiso G, Mendez-Bailon M, Perales-Fraile I, García-García GM, Guisado-Vasco P, Abdelhady-Kishta A, Pascual-Pérez MD, Rodríguez-Fernández-Viagas C, Montaño-Martínez A, López-Ruiz A, Gonzalez-Juarez MJ, Pérez-García C, Casas-Rojo JM, Gómez-Huelgas R; SEMI-COVID-19 Network. Clinical Characteristics and Risk Factors for Mortality in Very Old Patients Hospitalized With COVID-19 in Spain. *J Gerontol A Biol Sci Med Sci* 2021; **76**: e28-e37 [PMID: 33103720 DOI: 10.1093/gerona/glaa243]

35 **Lanthier N**, Mahiat C, Henrard S, Stärkel P, Gilard I, De Brauwer I, Cornette P, Boland B. Gastro-intestinal symptoms are associated with a lower in-hospital mortality rate in frail older patients hospitalized for COVID-19. *Acta Gastroenterol Belg* 2021; **84**: 135-136 [PMID: 33639706 DOI: 10.51821/84.1.824]

36 **Vrillon A**, Hourregue C, Azuar J, Grosset L, Boutelier A, Tan S, Roger M, Mourman V, Mouly S, Sène D, François V, Dumurgier J, Paquet C; for LRB COVID Group. COVID-19 in Older Adults: A Series of 76 Patients Aged 85 Years and Older with COVID-19. *J Am Geriatr Soc* 2020; **68**: 2735-2743 [PMID: 33045106 DOI: 10.1111/jgs.16894]

37 **Atalla E**, Zhang R, Shehadeh F, Mylona EK, Tsikala-Vafea M, Kalagara S, Henseler L, Chan PA, Mylonakis E. Clinical Presentation, Course, and Risk Factors Associated with Mortality in a Severe Outbreak of COVID-19 in Rhode Island, USA, April-June 2020. *Pathogens* 2020; **10** [PMID: 33374131 DOI: 10.3390/pathogens10010008]

38 **González González R**, Jacob J, Miró Ò, Llorens P, Jiménez S, González Del Castillo J, Burillo-Putze G, Martín A, Martín-Sánchez FJ, Lamberechts JG, Alquézar-Arbé A, Higa-Sansone L, Gayoso Martín S, Carbajosa V, Beddar Chaib F, Salido M, Marchena González MJ, Calvo López R, González Martínez F, Pavón Monzo J, Velarde Herrera DM, Niembro Valdés AP, Quero Motto E, Ferreras Amez JM, Piñera-Salmerón P; Spanish Investigators on Emergency Situations TeAm (SIESTA) Network. Incidence, Clinical Characteristics, Risk Factors, and Outcomes of Upper Gastrointestinal Bleeding in Patients With COVID-19: Results of the UMC-19-S12. *J Clin Gastroenterol* 2022; **56**: e38-e46 [PMID: 33252555 DOI: 10.1097/MCG.0000000000001465]

39 **Zhai Z**, Li C, Chen Y, Gerotziafas G, Zhang Z, Wan J, Liu P, Elalamy I, Wang C; Prevention Treatment of VTE Associated with COVID-19 Infection Consensus Statement Group. Prevention and Treatment of Venous Thromboembolism Associated with Coronavirus Disease 2019 Infection: A Consensus Statement before Guidelines. *Thromb Haemost* 2020; **120**: 937-948 [PMID: 32316065 DOI: 10.1055/s-0040-1710019]

40 **Tiwari NR**, Khatib KI, Dixit SB, Rathore PK, Melinkeri S, Ganapule A, Borawake KS, Mhatre U. Anticoagulation in COVID - 19: An Update. *J Crit Care Med (Targu Mures)* 2020; **6**: 217-223 [PMID: 33200092 DOI: 10.2478/jccm-2020-0033]

41 **Ion D**, Gherghinescu M, Andronic O, Andreescu CV, Păduraru DN, Bolocan A, Russu C, Aprodu S, Mationi G, Nicolescu C, Popa D. Prognosis Evaluation for Patients with Abdominal Trauma Using Usual Biological Parameters. *Chirurgia (Bucur)* 2021; **116**: 737-747 [PMID: 34967718 DOI: 10.21614/chirurgia.116.6.737]

42 **Dioscoridi L**, Giannetti A, Massad MT, Forti E, Pugliese F, Cintolo M, Bonato G, Rosa R, Mutignani M. A "double-hit" damage mechanism can explain self-limited GI bleeding in COVID-19 pneumonia. *Gastrointest Endosc* 2021; **93**: 1192-1193 [PMID: 33875144 DOI: 10.1016/j.gie.2020.12.022]

43 **Al-Samkari H**, Karp Leaf RS, Dzik WH, Carlson JCT, Fogerty AE, Waheed A, Goodarzi K, Bendapudi PK, Bornikova L, Gupta S, Leaf DE, Kuter DJ, Rosovsky RP. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood* 2020; **136**: 489-500 [PMID: 32492712 DOI: 10.1182/blood.2020006520]

44 **Ojetti V**, Saviano A, Covino M, Acampora N, Troiani E, Franceschi F; GEMELLI AGAINST COVID‐19 group. COVID-19 and intestinal inflammation: Role of fecal calprotectin. *Dig Liver Dis* 2020; **52**: 1231-1233 [PMID: 33060042 DOI: 10.1016/j.dld.2020.09.015]

45 **Ludvigsson JF**, Axelrad J, Halfvarson J, Khalili H, Larsson E, Lochhead P, Roelstraete B, Simon TG, Söderling J, Olén O. Inflammatory bowel disease and risk of severe COVID-19: A nationwide population-based cohort study in Sweden. *United European Gastroenterol J* 2021; **9**: 177-192 [PMID: 33704918 DOI: 10.1002/ueg2.12049]

46 **Amiot A**, Rahier JF, Baert F, Nahon S, Hart A, Viazis N, Biancone L, Domenech E, Reenears C, Peyrin-Biroulet L, Beaugerie L, Burisch J; I-CARE collaborator group. The Impact of COVID-19 on Patients with IBD in a Prospective European Cohort Study. *J Crohns Colitis* 2023; **17**: 37-48 [PMID: 35767639 DOI: 10.1093/ecco-jcc/jjac091]

47 **Maconi G**, Bosetti C, De Monti A, Boyapati RK, Shelton E, Piazza N, Carvalhas Gabrielli AM, Lenti MV, Bezzio C, Ricci C, Greco S, Romeo S, Giangregorio F, Gridavilla D, Tagliani F, Massari A, Pastorelli L, Di Sabatino A, Saibeni S, Alicante S, Ferretti F, Rizzardini G, Galli M, Ardizzone S. Risk of COVID 19 in patients with inflammatory bowel diseases compared to a control population. *Dig Liver Dis* 2021; **53**: 263-270 [PMID: 33483259 DOI: 10.1016/j.dld.2020.12.013]

48 **Papa A**, Gasbarrini A, Tursi A. Epidemiology and the Impact of Therapies on the Outcome of COVID-19 in Patients With Inflammatory Bowel Disease. *Am J Gastroenterol* 2020; **115**: 1722-1724 [PMID: 32826572 DOI: 10.14309/ajg.0000000000000830]

49 **Singh AK**, Jena A, Kumar-M P, Jha DK, Sharma V. Clinical presentation of COVID-19 in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Intest Res* 2022; **20**: 134-143 [PMID: 33440918 DOI: 10.5217/ir.2020.00108]

50 **Lee MH**, Li HJ, Wasuwanich P, Kim SE, Kim JY, Jeong GH, Park S, Yang JW, Kim MS, Yon DK, Lee SW, Koyanagi A, Jacob L, Kim EY, Cheon JH, Shin JI, Smith L. COVID-19 susceptibility and clinical outcomes in inflammatory bowel disease: An updated systematic review and meta-analysis. *Rev Med Virol* 2022: e2414 [PMID: 36504172 DOI: 10.1002/rmv.2414]

51 **Chen L**, Hu K, Cheng C, Hu Q, Zhang L, An T, Guo Y, Chen S, Duan G. Risk of adverse outcomes in inflammatory bowel disease patients infected with SARS-CoV-2: a systematic review and meta-analysis. *Int J Colorectal Dis* 2022; **37**: 2277-2289 [PMID: 36271206 DOI: 10.1007/s00384-022-04265-w]

52 **Bezzio C**, Saibeni S, Variola A, Allocca M, Massari A, Gerardi V, Casini V, Ricci C, Zingone F, Amato A, Caprioli F, Lenti MV, Viganò C, Ascolani M, Bossa F, Castiglione F, Cortelezzi C, Grossi L, Milla M, Morganti D, Pastorelli L, Ribaldone DG, Sartini A, Soriano A, Manes G, Danese S, Fantini MC, Armuzzi A, Daperno M, Fiorino G; Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD). Outcomes of COVID-19 in 79 patients with IBD in Italy: an IG-IBD study. *Gut* 2020; **69**: 1213-1217 [PMID: 32354990 DOI: 10.1136/gutjnl-2020-321411]

53 **Ricciuto A**, Lamb CA, Benchimol EI, Walker GJ, Kennedy NA, Kuenzig ME, Kaplan GG, Kappelman MD, Ungaro RC, Colombel JF, Brenner EJ, Agrawal M, Reinisch W, Griffiths AM, Sebastian S. Inflammatory Bowel Disease Clinical Activity is Associated with COVID-19 Severity Especially in Younger Patients. *J Crohns Colitis* 2022; **16**: 591-600 [PMID: 34570886 DOI: 10.1093/ecco-jcc/jjab172]

54 **Tripathi K**, Godoy Brewer G, Thu Nguyen M, Singh Y, Saleh Ismail M, Sauk JS, Parian AM, Limketkai BN. COVID-19 and Outcomes in Patients With Inflammatory Bowel Disease: Systematic Review and Meta-Analysis. *Inflamm Bowel Dis* 2022; **28**: 1265-1279 [PMID: 34718595 DOI: 10.1093/ibd/izab236]

55 **Bezzio C**, Fiorino G, Ribaldone DG, Armuzzi A, Saibeni S; IG-IBD COVID-19 Study Group. IBD Flare in the COVID-19 Pandemic: Therapy Discontinuation Is to Blame. *Inflamm Bowel Dis* 2022 [PMID: 35972338 DOI: 10.1093/ibd/izac173]

56 **Papa A**, Papa V, Lopetuso LR, Gasbarrini A, Tursi A. Covid-19 and the management of patients with inflammatory bowel disease: a practical decalogue for the post-pandemic phase. *Therap Adv Gastroenterol* 2020; **13**: 1756284820968747 [PMID: 33149764 DOI: 10.1177/1756284820968747]

57 **Sturm A**, Maaser C, Mendall M, Karagiannis D, Karatzas P, Ipenburg N, Sebastian S, Rizzello F, Limdi J, Katsanos K, Schmidt C, Jeuring S, Colombo F, Gionchetti P. European Crohn's and Colitis Organisation Topical Review on IBD in the Elderly. *J Crohns Colitis* 2017; **11**: 263-273 [PMID: 27797918 DOI: 10.1093/ecco-jcc/jjw188]

58 **Hong SJ**, Katz S. The elderly IBD patient in the modern era: changing paradigms in risk stratification and therapeutic management. *Therap Adv Gastroenterol* 2021; **14**: 17562848211023399 [PMID: 34276809 DOI: 10.1177/17562848211023399]

59 **Brenner EJ**, Ungaro RC, Gearry RB, Kaplan GG, Kissous-Hunt M, Lewis JD, Ng SC, Rahier JF, Reinisch W, Ruemmele FM, Steinwurz F, Underwood FE, Zhang X, Colombel JF, Kappelman MD. Corticosteroids, But Not TNF Antagonists, Are Associated With Adverse COVID-19 Outcomes in Patients With Inflammatory Bowel Diseases: Results From an International Registry. *Gastroenterology* 2020; **159**: 481-491.e3 [PMID: 32425234 DOI: 10.1053/j.gastro.2020.05.032]

60 **Zabana Y**, Marín-Jiménez I, Rodríguez-Lago I, Vera I, Martín-Arranz MD, Guerra I, P Gisbert J, Mesonero F, Benítez O, Taxonera C, Ponferrada-Díaz Á, Piqueras M, J Lucendo A, Caballol B, Mañosa M, Martínez-Montiel P, Bosca-Watts M, Gordillo J, Bujanda L, Manceñido N, Martínez-Pérez T, López A, Rodríguez-Gutiérrez C, García-López S, Vega P, Rivero M, Melcarne L, Calvo M, Iborra M, Barreiro de Acosta M, Sicilia B, Barrio J, Pérez Calle JL, Busquets D, Pérez-Martínez I, Navarro-Llavat M, Hernández V, Argüelles-Arias F, Ramírez Esteso F, Meijide S, Ramos L, Gomollón F, Muñoz F, Suris G, Ortiz de Zarate J, Huguet JM, Llaó J, García-Sepulcre MF, Sierra M, Durà M, Estrecha S, Fuentes Coronel A, Hinojosa E, Olivan L, Iglesias E, Gutiérrez A, Varela P, Rull N, Gilabert P, Hernández-Camba A, Brotons A, Ginard D, Sesé E, Carpio D, Aceituno M, Cabriada JL, González-Lama Y, Jiménez L, Chaparro M, López-San Román A, Alba C, Plaza-Santos R, Mena R, Tamarit-Sebastián S, Ricart E, Calafat M, Olivares S, Navarro P, Bertoletti F, Alonso-Galán H, Pajares R, Olcina P, Manzano P, Domènech E, Esteve M, On Behalf Of The Eneida Registry Of Geteccu. Risk Factors for COVID-19 in Inflammatory Bowel Disease: A National, ENEIDA-Based Case-Control Study (COVID-19-EII). *J Clin Med* 2022; **11** [PMID: 36556155 DOI: 10.3390/jcm11247540]

61 **Wetwittayakhlang P**, Albader F, Golovics PA, Hahn GD, Bessissow T, Bitton A, Afif W, Wild G, Lakatos PL. Clinical Outcomes of COVID-19 and Impact on Disease Course in Patients with Inflammatory Bowel Disease. *Can J Gastroenterol Hepatol* 2021; **2021**: 7591141 [PMID: 34858891 DOI: 10.1155/2021/7591141]

62 **Gubatan J**, Levitte S, Patel A, Balabanis T, Sharma A, Jones E, Lee B, Manohar M, Swaminathan G, Park W, Habtezion A. Prevalence, risk factors and clinical outcomes of COVID-19 in patients with a history of pancreatitis in Northern California. *Gut* 2021; **70**: 440-441 [PMID: 32493828 DOI: 10.1136/gutjnl-2020-321772]

63 **Calafat M**, González-Muñoza C, Fortuny M, Roig C, Calm A, Mombiela A, Cañete F, Bertoletti F, González-González L, Teller-Martín M, Gordillo J, Mañosa M, Garcia-Planella E, Domènech E. Impact of immunosuppressants on SARS-CoV-2 infection in elderly patients with inflammatory bowel disease. *Aging Clin Exp Res* 2021; **33**: 2355-2359 [PMID: 34164799 DOI: 10.1007/s40520-021-01917-9]

64 **Geisz M**, Ha C, Kappelman MD, Martin CF, Chen W, Anton K, Sandler RS, Long MD. Medication Utilization and the Impact of Continued Corticosteroid Use on Patient-reported Outcomes in Older Patients with Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2016; **22**: 1435-1441 [PMID: 26978725 DOI: 10.1097/MIB.0000000000000747]

65 **Bernstein CN**, Singh H, Murthy SK, Nguyen GC, Benchimol EI, Bitton A, Kuenzig ME, Huang JG, Jones JL, Lee K, Targownik LE, Windsor JW, Mukhtar MS, Tandon P, Kaplan GG. Crohn's and Colitis Canada's 2021 Impact of COVID-19 and Inflammatory Bowel Disease in Canada: Seniors With IBD. *J Can Assoc Gastroenterol* 2021; **4**: S34-S39 [PMID: 34755037 DOI: 10.1093/jcag/gwab025]

66 **Kulkarni AV**, Kumar P, Tevethia HV, Premkumar M, Arab JP, Candia R, Talukdar R, Sharma M, Qi X, Rao PN, Reddy DN. Systematic review with meta-analysis: liver manifestations and outcomes in COVID-19. *Aliment Pharmacol Ther* 2020; **52**: 584-599 [PMID: 32638436 DOI: 10.1111/apt.15916]

67 **Mehta P**, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; **395**: 1033-1034 [PMID: 32192578 DOI: 10.1016/S0140-6736(20)30628-0]

68 **Li S**, Li J, Zhang Z, Tan L, Shao T, Li M, Li X, Holmes JA, Lin W, Han M. COVID-19 induced liver function abnormality associates with age. *Aging (Albany NY)* 2020; **12**: 13895-13904 [PMID: 32721928 DOI: 10.18632/aging.103720]

69 **Nardo AD**, Schneeweiss-Gleixner M, Bakail M, Dixon ED, Lax SF, Trauner M. Pathophysiological mechanisms of liver injury in COVID-19. *Liver Int* 2021; **41**: 20-32 [PMID: 33190346 DOI: 10.1111/liv.14730]

70 **Hamming I**, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004; **203**: 631-637 [PMID: 15141377 DOI: 10.1002/path.1570]

71 **Kumar P**, Sharma M, Kulkarni A, Rao PN. Pathogenesis of Liver Injury in Coronavirus Disease 2019. *J Clin Exp Hepatol* 2020; **10**: 641-642 [PMID: 32837092 DOI: 10.1016/j.jceh.2020.05.006]

72 **Zhao CL**, Rapkiewicz A, Maghsoodi-Deerwester M, Gupta M, Cao W, Palaia T, Zhou J, Ram B, Vo D, Rafiee B, Hossein-Zadeh Z, Dabiri B, Hanna I. Pathological findings in the postmortem liver of patients with coronavirus disease 2019 (COVID-19). *Hum Pathol* 2021; **109**: 59-68 [PMID: 33307078 DOI: 10.1016/j.humpath.2020.11.015]

73 **Xu Z**, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020; **8**: 420-422 [PMID: 32085846 DOI: 10.1016/S2213-2600(20)30076-X]

74 **Ibrahim N**, Hosri J, Bteich Y, Dib A, Abou Rached A. COVID-19 and Liver Dysfunction. *Cureus* 2022; **14**: e21302 [PMID: 35186564 DOI: 10.7759/cureus.21302]

75 **Cai Q**, Huang D, Yu H, Zhu Z, Xia Z, Su Y, Li Z, Zhou G, Gou J, Qu J, Sun Y, Liu Y, He Q, Chen J, Liu L, Xu L. COVID-19: Abnormal liver function tests. *J Hepatol* 2020; **73**: 566-574 [PMID: 32298767 DOI: 10.1016/j.jhep.2020.04.006]

76 **Săbiescu DM**, Kamal AM, Kamal CK, Alexandru DO, Mitruț P. Liver damage in the context of SARS-CoV-2. Covid-19 treatment and its effects on the liver. *J Med Life* 2022; **15**: 727-734 [PMID: 35928369 DOI: 10.25122/jml-2022-0177]

77 **Tokarczyk U**, Kaliszewski K, Kopszak A, Nowak Ł, Sutkowska-Stępień K, Sroczyński M, Sępek M, Dudek A, Diakowska D, Trocha M, Gajecki D, Gawryś J, Matys T, Maciejiczek J, Kozub V, Szalast R, Madziarski M, Zubkiewicz-Zarębska A, Letachowicz K, Kiliś-Pstrusińska K, Matera-Witkiewicz A, Pomorski M, Protasiewicz M, Sokołowski J, Adamik B, Kujawa K, Doroszko A, Madziarska K, Jankowska EA. Liver Function Tests in COVID-19: Assessment of the Actual Prognostic Value. *J Clin Med* 2022; **11** [PMID: 35956107 DOI: 10.3390/jcm11154490]

78 **Phipps MM**, Barraza LH, LaSota ED, Sobieszczyk ME, Pereira MR, Zheng EX, Fox AN, Zucker J, Verna EC. Acute Liver Injury in COVID-19: Prevalence and Association with Clinical Outcomes in a Large U.S. Cohort. *Hepatology* 2020; **72**: 807-817 [PMID: 32473607 DOI: 10.1002/hep.31404]

79 **Da BL**, Kushner T, El Halabi M, Paka P, Khalid M, Uberoi A, Lee BT, Perumalswami PV, Rutledge SM, Schiano TD, Friedman SL, Saberi B. Liver Injury in Patients Hospitalized with Coronavirus Disease 2019 Correlates with Hyperinflammatory Response and Elevated Interleukin-6. *Hepatol Commun* 2021; **5**: 177-188 [PMID: 33230491 DOI: 10.1002/hep4.1631]

80 **Pazgan-Simon M**, Serafińska S, Kukla M, Kucharska M, Zuwała-Jagiełło J, Buczyńska I, Zielińska K, Simon K. Liver Injury in Patients with COVID-19 without Underlying Liver Disease. *J Clin Med* 2022; **11** [PMID: 35054003 DOI: 10.3390/jcm11020308]

81 **Singh S**, Khan A. Clinical Characteristics and Outcomes of Coronavirus Disease 2019 Among Patients With Preexisting Liver Disease in the United States: A Multicenter Research Network Study. *Gastroenterology* 2020; **159**: 768-771.e3 [PMID: 32376408 DOI: 10.1053/j.gastro.2020.04.064]

82 **Wang Q**, Davis PB, Xu R. COVID-19 risk, disparities and outcomes in patients with chronic liver disease in the United States. *EClinicalMedicine* 2021; **31**: 100688 [PMID: 33521611 DOI: 10.1016/j.eclinm.2020.100688]

83 **Iavarone M**, D'Ambrosio R, Soria A, Triolo M, Pugliese N, Del Poggio P, Perricone G, Massironi S, Spinetti A, Buscarini E, Viganò M, Carriero C, Fagiuoli S, Aghemo A, Belli LS, Lucà M, Pedaci M, Rimondi A, Rumi MG, Invernizzi P, Bonfanti P, Lampertico P. High rates of 30-day mortality in patients with cirrhosis and COVID-19. *J Hepatol* 2020; **73**: 1063-1071 [PMID: 32526252 DOI: 10.1016/j.jhep.2020.06.001]

84 **Mallet V**, Beeker N, Bouam S, Sogni P, Pol S; Demosthenes research group. Prognosis of French COVID-19 patients with chronic liver disease: A national retrospective cohort study for 2020. *J Hepatol* 2021; **75**: 848-855 [PMID: 33992699 DOI: 10.1016/j.jhep.2021.04.052]

85 **Mohammed A**, Paranji N, Chen PH, Niu B. COVID-19 in Chronic Liver Disease and Liver Transplantation: A Clinical Review. *J Clin Gastroenterol* 2021; **55**: 187-194 [PMID: 33394628 DOI: 10.1097/MCG.0000000000001481]

86 **Magro F**, Nuzzo A, Abreu C, Libânio D, Rodriguez-Lago I, Pawlak K, Hollenbach M, Brouwer WP, Siau K. COVID-19 in gastroenterology: Where are we now? Current evidence on the impact of COVID-19 in gastroenterology. *United European Gastroenterol J* 2021; **9**: 750-765 [PMID: 34190413 DOI: 10.1002/ueg2.12115]

87 **Ekpanyapong S**, Bunchorntavakul C, Reddy KR. COVID-19 and the Liver: Lessons Learnt from the EAST and the WEST, A Year Later. *J Viral Hepat* 2022; **29**: 4-20 [PMID: 34352133 DOI: 10.1111/jvh.13590]

88 **Hoffmann C**, Gerber PA, Cavelti-Weder C, Licht L, Kotb R, Al Dweik R, Cherfane M, Bornstein SR, Perakakis N. Liver, NAFLD and COVID-19. *Horm Metab Res* 2022; **54**: 522-531 [PMID: 35468630 DOI: 10.1055/a-1834-9008]

89 **Boettler T**, Newsome PN, Mondelli MU, Maticic M, Cordero E, Cornberg M, Berg T. Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper. *JHEP Rep* 2020; **2**: 100113 [PMID: 32289115 DOI: 10.1016/j.jhepr.2020.100113]

90 **Sachdeva S**, Khandait H, Kopel J, Aloysius MM, Desai R, Goyal H. NAFLD and COVID-19: a Pooled Analysis. *SN Compr Clin Med* 2020; **2**: 2726-2729 [PMID: 33173850 DOI: 10.1007/s42399-020-00631-3]

91 **Berenguer J**, Ryan P, Rodríguez-Baño J, Jarrín I, Carratalà J, Pachón J, Yllescas M, Arriba JR; COVID-19@Spain Study Group; Fundación SEIMC-GESIDA; Hospital General Universitario Gregorio Marañón; Hospital Universitario La Paz; Hospital Infanta Leonor; Complejo Hospitalario Virgen de la Salud; Hospital Universitario Rafael Méndez; Hospital Universitario de Cruces; Hospital de Melilla; Hospital San Eloy de Barakaldo; Hospital Universitario Central de Asturias; Hospital General Universitario de Alicante; Hospital Virgen de la Victoria; Hospital Universitario Puerto Real; EOXI Pontevedra e Salnés; Hospital de Figueres; Hospital Sant Jaume de Calella; Hospital del Mar; Hospital Virgen de la Arrixaca; Hospital de Can Misses; Hospital de Sagunto; Hospital Clínico San Cecilio; Hospital Universitario Príncipe de Asturias; Parc Sanitari Sant Joan de Déu; Hospital Nuestra Señora de Gracia; HC Marbella Internacional Hospital; Hospital La Princesa; Hospital Josep Trueta; Hospital Dos de Maig; Hospital Arnau de Vilanova-Lliria; Hospital General Universitario de Elche; Hospital Clínico Universitario de Valencia; Complejo Asistencial de Ávila; Hospital Comarcal de Alcañiz; Hospital Universitario Marqués de Valdecilla; Hospital Quiron-Salud de Torrevieja; Hospital Universitario Miguel Servet; SCIAS, Hospital de Barcelona; Fundación Hospital Universitario Alcorcón; Hospital Álvaro Cunqueiro; Complejo Asistencial Universitario de Salamanca; Hospital Universitario Severo Ochoa; Hospital CIMA-Sanitas; Hospital HLA Inmaculada; Hospital Universitario Rio Hortega; Hospital de Guadalajara; Hospital Universitario Infanta Sofía; Hospital Comarcal de Blanes; Hospital Universitari de Tarragona Joan XXIII; Hospital Universitario Basurto; Hospital Universitario de Canarias; Hospital Universitario de Gran Canaria Dr Negrín; Hospital Son Espases; Hospital Universitario de Móstoles; Complejo Hospitalario Universitario A Coruña; Hospital Costa del Sol; Hospital Clínico Universitario Lozano Blesa; Hospital Mutua de Terrassa; Hospital de la Plana; Hospital Virgen de la Concha–Complejo Asistencial de Zamora; Complejo Hospitalario Universitario Insular Materno-Infantil; Hospital de la Marina Baixa; Hospital Universitario Virgen Macarena; Hospital Universitari de Bellvitge; Hospital Universitario y Politécnico la Fe; Hospital Universitario del Vinalopó; Hospital de Sabadell (Parc Tauli); Hospital Clinic de Barcelona; Hospital Universitario de la Ribera; Fundación Jiménez Díaz; Hospital Clínico Universitario de Valladolid; Hospital Clínico San Carlos; Hospital Santa Creu i Sant Pau; Clínica Universitaria de Navarra–Campus Madrid; Hospital Son Llatzer; Hospital General de la Defensa Gómez Ulla; Hospital Universitario de Álava; Hospital Santos Reyes; Hospital Dr José Molina Orosa; Hospital Vall d’Hebrón; Hospital Universitario Rey Juan Carlos; Complejo Hospitalario Universitario Santa Lucía; Hospital Santa Bárbara; Complejo Hospitalario Universitario de Ferrol; Hospital de l'Esperit Sant; Hospital Universitario los Arcos del Mar Menor; Hospital HLA Universitario Moncloa; Hospital Virgen del Puerto; Hospital Marina Salud de Dénia; Hospital Universitario de Jerez; Hospital Reina Sofía de Tudela; Hospital Clínico Universitario de Santiago de Compostela; Hospital Universitario del Henares; Hospital Universitario Lucus Augusti; Hospital de Donostia; Hospital de Urduliz Alfredo Espinosa; Hospital de Mendaro; Hospital Juan Ramón Jiménez; Hospital de Tortosa Virgen de la Cinta; Hospital Riotinto; Hospital Vega Baja; Hospital Puerta de Hierro; Hospital Universitario de Getafe; Hospital General de la Palma; Hospital El Bierzo; Fundación Hospital de Calahorra; Hospital Alto Deba; Hospital Universitario San Juan de Alicante; Hospital de Guadarrama; Hospital Universitario de Jaén; Hospital de Mataró; Hospital de Palamós; Hospital Universitario de Valme; Clínica Universitaria de Navarra–Campus Navarra; Hospital Clínica Benidorm; Hospital Doce de Octubre; Hospital Universitario Virgen del Rocío; Hospital Universitario Ramón y Cajal; Hospital Universitario San Pedro; Hospital Quirón A Coruña; HM Sanchinarro; Hospital Francesc de Borja; Complejo Hospitalario Universitario Nuestra Señora de La Candelaria; Hospital Universitario HM Montepríncipe; Hospital Universitario HM Puerta del Sur; Hospital Universitario HM Torrelodones; Hospital Universitario HM Madrid; Hospital Don Benito-Villanueva de la Serena; Hospital de Viladecans; Centro Nacional de Epidemiología. Characteristics and predictors of death among 4035 consecutively hospitalized patients with COVID-19 in Spain. *Clin Microbiol Infect* 2020; **26**: 1525-1536 [PMID: 32758659 DOI: 10.1016/j.cmi.2020.07.024]

92 **Marjot T**, Moon AM, Cook JA, Abd-Elsalam S, Aloman C, Armstrong MJ, Pose E, Brenner EJ, Cargill T, Catana MA, Dhanasekaran R, Eshraghian A, García-Juárez I, Gill US, Jones PD, Kennedy J, Marshall A, Matthews C, Mells G, Mercer C, Perumalswami PV, Avitabile E, Qi X, Su F, Ufere NN, Wong YJ, Zheng MH, Barnes E, Barritt AS 4th, Webb GJ. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: An international registry study. *J Hepatol* 2021; **74**: 567-577 [PMID: 33035628 DOI: 10.1016/j.jhep.2020.09.024]

93 **Karcz M**, Bankey B, Schwaiberger D, Lachmann B, Papadakos PJ. Acute respiratory failure complicating advanced liver disease. *Semin Respir Crit Care Med* 2012; **33**: 96-110 [PMID: 22447264 DOI: 10.1055/s-0032-1301738]

94 **Jeon D**, Son M, Choi J. Impact of liver cirrhosis on the clinical outcomes of patients with COVID-19: a nationwide cohort study of Korea. *Korean J Intern Med* 2021; **36**: 1092-1101 [PMID: 34399573 DOI: 10.3904/kjim.2020.486]

95 **Choi J**, Han S, Kim N, Lim YS. Increasing burden of liver cancer despite extensive use of antiviral agents in a hepatitis B virus-endemic population. *Hepatology* 2017; **66**: 1454-1463 [PMID: 28628942 DOI: 10.1002/hep.29321]

96 **Kim D**, Adeniji N, Latt N, Kumar S, Bloom PP, Aby ES, Perumalswami P, Roytman M, Li M, Vogel AS, Catana AM, Wegermann K, Carr RM, Aloman C, Chen VL, Rabiee A, Sadowski B, Nguyen V, Dunn W, Chavin KD, Zhou K, Lizaola-Mayo B, Moghe A, Debes J, Lee TH, Branch AD, Viveiros K, Chan W, Chascsa DM, Kwo P, Dhanasekaran R. Predictors of Outcomes of COVID-19 in Patients With Chronic Liver Disease: US Multi-center Study. *Clin Gastroenterol Hepatol* 2021; **19**: 1469-1479.e19 [PMID: 32950749 DOI: 10.1016/j.cgh.2020.09.027]

97 **Ghazanfar H**, Kandhi S, Shin D, Muthumanickam A, Gurjar H, Qureshi ZA, Shaban M, Farag M, Haider A, Budhathoki P, Bhatt T, Ghazanfar A, Jyala A, Patel H. Impact of COVID-19 on the Gastrointestinal Tract: A Clinical Review. *Cureus* 2022; **14**: e23333 [PMID: 35464519 DOI: 10.7759/cureus.23333]

98 **Olry A**, Meunier L, Délire B, Larrey D, Horsmans Y, Le Louët H. Drug-Induced Liver Injury and COVID-19 Infection: The Rules Remain the Same. *Drug Saf* 2020; **43**: 615-617 [PMID: 32514859 DOI: 10.1007/s40264-020-00954-z]

99 **Kelly M**, O'Connor R, Townsend L, Coghlan M, Relihan E, Moriarty M, Carr B, Melanophy G, Doyle C, Bannan C, O'Riordan R, Merry C, Clarke S, Bergin C. Clinical outcomes and adverse events in patients hospitalised with COVID-19, treated with off-label hydroxychloroquine and azithromycin. *Br J Clin Pharmacol* 2021; **87**: 1150-1154 [PMID: 32687645 DOI: 10.1111/bcp.14482]

100 **Zhai G**, Li M, Wang Y, Wu J. Drug-Induced Liver Disturbance During the Treatment of COVID-19. *Front Pharmacol* 2021; **12**: 719308 [PMID: 34483929 DOI: 10.3389/fphar.2021.719308]

101 **Zampino R**, Mele F, Florio LL, Bertolino L, Andini R, Galdo M, De Rosa R, Corcione A, Durante-Mangoni E. Liver injury in remdesivir-treated COVID-19 patients. *Hepatol Int* 2020; **14**: 881-883 [PMID: 32725454 DOI: 10.1007/s12072-020-10077-3]

102 **Serviddio G**, Villani R, Stallone G, Scioscia G, Foschino-Barbaro MP, Lacedonia D. Tocilizumab and liver injury in patients with COVID-19. *Therap Adv Gastroenterol* 2020; **13**: 1756284820959183 [PMID: 33101458 DOI: 10.1177/1756284820959183]

103 **Teschke R**, Méndez-Sánchez N, Eickhoff A. Liver Injury in COVID-19 Patients with Drugs as Causatives: A Systematic Review of 996 DILI Cases Published 2020/2021 Based on RUCAM as Causality Assessment Method. *Int J Mol Sci* 2022; **23** [PMID: 35563242 DOI: 10.3390/ijms23094828]

104 **Stine JG**, Sateesh P, Lewis JH. Drug-induced liver injury in the elderly. *Curr Gastroenterol Rep* 2013; **15**: 299 [PMID: 23250699 DOI: 10.1007/s11894-012-0299-8]

105 **Gao S**, Yang Q, Wang X, Hu W, Lu Y, Yang K, Jiang Q, Li W, Song H, Sun F, Cheng H. Association Between Drug Treatments and the Incidence of Liver Injury in Hospitalized Patients With COVID-19. *Front Pharmacol* 2022; **13**: 799338 [PMID: 35387350 DOI: 10.3389/fphar.2022.799338]

106 **Sargiacomo C**, Sotgia F, Lisanti MP. COVID-19 and chronological aging: senolytics and other anti-aging drugs for the treatment or prevention of corona virus infection? *Aging (Albany NY)* 2020; **12**: 6511-6517 [PMID: 32229706 DOI: 10.18632/aging.103001]

107 **Yadav DK**, Singh A, Zhang Q, Bai X, Zhang W, Yadav RK, Singh A, Zhiwei L, Adhikari VP, Liang T. Involvement of liver in COVID-19: systematic review and meta-analysis. *Gut* 2021; **70**: 807-809 [PMID: 32669289 DOI: 10.1136/gutjnl-2020-322072]

108 **Khateri S**, Mohammadi H, Khateri R, Moradi Y. The Prevalence of Underlying Diseases and Comorbidities in COVID-19 Patients; an Updated Systematic Review and Meta-analysis. *Arch Acad Emerg Med* 2020; **8**: e72 [PMID: 33134968]

109 **Spearman CW**, Aghemo A, Valenti L, Sonderup MW. COVID-19 and the liver: A 2021 update. *Liver Int* 2021; **41**: 1988-1998 [PMID: 34152690 DOI: 10.1111/liv.14984]

110 **Metawea MI**, Yousif WI, Moheb I. COVID 19 and liver: An A-Z literature review. *Dig Liver Dis* 2021; **53**: 146-152 [PMID: 32988758 DOI: 10.1016/j.dld.2020.09.010]

111 **Ji D**, Qin E, Xu J, Zhang D, Cheng G, Wang Y, Lau G. Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study. *J Hepatol* 2020; **73**: 451-453 [PMID: 32278005 DOI: 10.1016/j.jhep.2020.03.044]

112 **Zhou YJ**, Zheng KI, Wang XB, Sun QF, Pan KH, Wang TY, Ma HL, Chen YP, George J, Zheng MH. Metabolic-associated fatty liver disease is associated with severity of COVID-19. *Liver Int* 2020; **40**: 2160-2163 [PMID: 32573883 DOI: 10.1111/liv.14575]

113 **Hartl L**, Haslinger K, Angerer M, Jachs M, Simbrunner B, Bauer DJM, Semmler G, Scheiner B, Eigenbauer E, Strassl R, Breuer M, Kimberger O, Laxar D, Trauner M, Mandorfer M, Reiberger T. Age-adjusted mortality and predictive value of liver chemistries in a Viennese cohort of COVID-19 patients. *Liver Int* 2022; **42**: 1297-1307 [PMID: 35412018 DOI: 10.1111/liv.15274]

114 **Ge J**, Pletcher MJ, Lai JC; N3C Consortium. Outcomes of SARS-CoV-2 Infection in Patients With Chronic Liver Disease and Cirrhosis: A National COVID Cohort Collaborative Study. *Gastroenterology* 2021; **161**: 1487-1501.e5 [PMID: 34284037 DOI: 10.1053/j.gastro.2021.07.010]

115 **Ioannou GN**, Liang PS, Locke E, Green P, Berry K, O'Hare AM, Shah JA, Crothers K, Eastment MC, Fan VS, Dominitz JA. Cirrhosis and Severe Acute Respiratory Syndrome Coronavirus 2 Infection in US Veterans: Risk of Infection, Hospitalization, Ventilation, and Mortality. *Hepatology* 2021; **74**: 322-335 [PMID: 33219546 DOI: 10.1002/hep.31649]

116 **Brozat JF**, Hanses F, Haelberger M, Stecher M, Dreher M, Tometten L, Ruethrich MM, Vehreschild JJ, Trautwein C, Borgmann S, Vehreschild MJGT, Jakob CEM, Stallmach A, Wille K, Hellwig K, Isberner N, Reuken PA, Geisler F, Nattermann J, Bruns T; LEOSS study group. COVID-19 mortality in cirrhosis is determined by cirrhosis-associated comorbidities and extrahepatic organ failure: Results from the multinational LEOSS registry. *United European Gastroenterol J* 2022; **10**: 409-424 [PMID: 35482663 DOI: 10.1002/ueg2.12232]

117 **Kandasamy S**. An unusual presentation of COVID-19: Acute pancreatitis. *Ann Hepatobiliary Pancreat Surg* 2020; **24**: 539-541 [PMID: 33234760 DOI: 10.14701/ahbps.2020.24.4.539]

118 **Schepis T**, Larghi A, Papa A, Miele L, Panzuto F, De Biase L, Annibale B, Cattani P, Rapaccini GL. SARS-CoV2 RNA detection in a pancreatic pseudocyst sample. *Pancreatology* 2020; **20**: 1011-1012 [PMID: 32498972 DOI: 10.1016/j.pan.2020.05.016]

119 **Aday U**, Gedik E, Kafadar MT, Özbek E. Acute Necrotizing Pancreatitis and Coronavirus Disease-2019 (COVID-19). *Korean J Gastroenterol* 2021; **78**: 353-358 [PMID: 34955513 DOI: 10.4166/kjg.2021.131]

120 **Tsai PH**, Lai WY, Lin YY, Luo YH, Lin YT, Chen HK, Chen YM, Lai YC, Kuo LC, Chen SD, Chang KJ, Liu CH, Chang SC, Wang FD, Yang YP. Clinical manifestation and disease progression in COVID-19 infection. *J Chin Med Assoc* 2021; **84**: 3-8 [PMID: 33230062 DOI: 10.1097/JCMA.0000000000000463]

121 **Khunti K**, Del Prato S, Mathieu C, Kahn SE, Gabbay RA, Buse JB. COVID-19, Hyperglycemia, and New-Onset Diabetes. *Diabetes Care* 2021; **44**: 2645-2655 [PMID: 34625431 DOI: 10.2337/dc21-1318]

122 **Wang F**, Wang H, Fan J, Zhang Y, Wang H, Zhao Q. Pancreatic Injury Patterns in Patients With Coronavirus Disease 19 Pneumonia. *Gastroenterology* 2020; **159**: 367-370 [PMID: 32247022 DOI: 10.1053/j.gastro.2020.03.055]

123 **Samanta J**, Gupta R, Singh MP, Patnaik I, Kumar A, Kochhar R. Coronavirus disease 2019 and the pancreas. *Pancreatology* 2020; **20**: 1567-1575 [PMID: 33250089 DOI: 10.1016/j.pan.2020.10.035]

124 **Bruno G**, Fabrizio C, Santoro CR, Buccoliero GB. Pancreatic injury in the course of coronavirus disease 2019: A not-so-rare occurrence. *J Med Virol* 2021; **93**: 74-75 [PMID: 32497298 DOI: 10.1002/jmv.26134]

125 **Liu F**, Long X, Zhang B, Zhang W, Chen X, Zhang Z. ACE2 Expression in Pancreas May Cause Pancreatic Damage After SARS-CoV-2 Infection. *Clin Gastroenterol Hepatol* 2020; **18**: 2128-2130.e2 [PMID: 32334082 DOI: 10.1016/j.cgh.2020.04.040]

126 **Stephens JR**, Wong JLC, Broomhead R, Stümpfle R, Waheed U, Patel P, Brett SJ, Soni S. Raised serum amylase in patients with COVID-19 may not be associated with pancreatitis. *Br J Surg* 2021; **108**: e152-e153 [PMID: 33793756 DOI: 10.1093/bjs/znaa168]

127 **Akkus C**, Yilmaz H, Mizrak S, Adibelli Z, Akdas O, Duran C. Development of pancreatic injuries in the course of COVID-19. *Acta Gastroenterol Belg* 2020; **83**: 585-592 [PMID: 33321015]

128 **McNabb-Baltar J**, Jin DX, Grover AS, Redd WD, Zhou JC, Hathorn KE, McCarty TR, Bazarbashi AN, Shen L, Chan WW. Lipase Elevation in Patients With COVID-19. *Am J Gastroenterol* 2020; **115**: 1286-1288 [PMID: 32496339 DOI: 10.14309/ajg.0000000000000732]

129 **Bansal P**, Margekar SL, Suman V, Sud R, Meena S, Sharma AK, Islam SY, Gurtoo A, Agrawal A, Pangtey GS, Prakash A. Pancreatic Injury in COVID-19 Patients. *J Assoc Physicians India* 2020; **68**: 58-60 [PMID: 33247644]

130 **Rasch S**, Herner A, Schmid RM, Huber W, Lahmer T. High lipasemia is frequent in Covid-19 associated acute respiratory distress syndrome. *Pancreatology* 2021; **21**: 306-311 [PMID: 33277183 DOI: 10.1016/j.pan.2020.11.023]

131 **Barlass U**, Wiliams B, Dhana K, Adnan D, Khan SR, Mahdavinia M, Bishehsari F. Marked Elevation of Lipase in COVID-19 Disease: A Cohort Study. *Clin Transl Gastroenterol* 2020; **11**: e00215 [PMID: 32764201 DOI: 10.14309/ctg.0000000000000215]

132 **Bacaksız F**, Ebik B, Ekin N, Kılıc J. Pancreatic damage in COVID-19: Why? How? *Int J Clin Pract* 2021; **75**: e14692 [PMID: 34331821 DOI: 10.1111/ijcp.14692]

133 **Hunt RH**, East JE, Lanas A, Malfertheiner P, Satsangi J, Scarpignato C, Webb GJ. COVID-19 and Gastrointestinal Disease: Implications for the Gastroenterologist. *Dig Dis* 2021; **39**: 119-139 [PMID: 33040064 DOI: 10.1159/000512152]

134 **Singh RR**, Chhabra P, Kumta NA. Does Hyperlipasemia Predict Worse Clinical Outcomes in COVID-19? A Multicenter Retrospective Cohort Study. *J Clin Gastroenterol* 2022; **56**: e227-e231 [PMID: 34294655 DOI: 10.1097/MCG.0000000000001590]

135 **Inamdar S**, Benias PC, Liu Y, Sejpal DV, Satapathy SK, Trindade AJ; Northwell COVID-19 Research Consortium. Prevalence, Risk Factors, and Outcomes of Hospitalized Patients With Coronavirus Disease 2019 Presenting as Acute Pancreatitis. *Gastroenterology* 2020; **159**: 2226-2228.e2 [PMID: 32860787 DOI: 10.1053/j.gastro.2020.08.044]

136 **Karaali R**, Topal F. Evaluating the effect of SARS-Cov-2 infection on prognosis and mortality in patients with acute pancreatitis. *Am J Emerg Med* 2021; **49**: 378-384 [PMID: 34246968 DOI: 10.1016/j.ajem.2021.06.045]

137 **Dirweesh A**, Li Y, Trikudanathan G, Mallery JS, Freeman ML, Amateau SK. Clinical Outcomes of Acute Pancreatitis in Patients With Coronavirus Disease 2019. *Gastroenterology* 2020; **159**: 1972-1974 [PMID: 32721439 DOI: 10.1053/j.gastro.2020.07.038]

138 **Pandanaboyana S**, Moir J, Leeds JS, Oppong K, Kanwar A, Marzouk A, Belgaumkar A, Gupta A, Siriwardena AK, Haque AR, Awan A, Balakrishnan A, Rawashdeh A, Ivanov B, Parmar C, M Halloran C, Caruana C, Borg CM, Gomez D, Damaskos D, Karavias D, Finch G, Ebied H, K Pine J, R A Skipworth J, Milburn J, Latif J, Ratnam Apollos J, El Kafsi J, Windsor JA, Roberts K, Wang K, Ravi K, V Coats M, Hollyman M, Phillips M, Okocha M, Sj Wilson M, A Ameer N, Kumar N, Shah N, Lapolla P, Magee C, Al-Sarireh B, Lunevicius R, Benhmida R, Singhal R, Balachandra S, Demirli Atıcı S, Jaunoo S, Dwerryhouse S, Boyce T, Charalampakis V, Kanakala V, Abbas Z, Nayar M; COVID PAN collaborative group. SARS-CoV-2 infection in acute pancreatitis increases disease severity and 30-day mortality: COVID PAN collaborative study. *Gut* 2021; **70**: 1061-1069 [PMID: 33547182 DOI: 10.1136/gutjnl-2020-323364]

139 **Ye C**, Zhang S, Zhang X, Cai H, Gu J, Lian J, Lu Y, Jia H, Hu J, Jin C, Yu G, Zhang Y, Sheng J, Yang Y. Impact of comorbidities on patients with COVID-19: A large retrospective study in Zhejiang, China. *J Med Virol* 2020; **92**: 2821-2829 [PMID: 32543710 DOI: 10.1002/jmv.26183]

140 **Miró Ò**, Llorens P, Jiménez S, Piñera P, Burillo-Putze G, Martín A, Martín-Sánchez FJ, Lamberechts J, Alquézar-Arbé A, Jacob J, Noceda J, Cano Cano MJ, Fortuny Bayarri MJ, Marín Porrino JM, Meléndez N, Pérez García C, Brasó Aznar JV, Ponce MC, Díaz Fernández E, Ejarque Martínez L, Peiró Gómez A, Tost J, Domínguez MJ, Teigell Muñoz FJ, González Del Castillo J; Spanish Investigators on Emergency Situations TeAm (SIESTA) network. A case-control emergency department-based analysis of acute pancreatitis in Covid-19: Results of the UMC-19-S(6). *J Hepatobiliary Pancreat Sci* 2021; **28**: 953-966 [PMID: 33259695 DOI: 10.1002/jhbp.873]

141 **Akarsu C**, Karabulut M, Aydin H, Sahbaz NA, Dural AC, Yegul D, Peker KD, Ferahman S, Bulut S, Dönmez T, Asar S, Yasar KK, Adas GT. Association between Acute Pancreatitis and COVID-19: Could Pancreatitis Be the Missing Piece of the Puzzle about Increased Mortality Rates? *J Invest Surg* 2022; **35**: 119-125 [PMID: 33138658 DOI: 10.1080/08941939.2020.1833263]

142 **Huang BZ**, Sidell MA, Wu BU, Setiawan VW, Chen Z, Xiang AH. Pre-Existing Pancreatitis and Elevated Risks of COVID-19 Severity and Mortality. *Gastroenterology* 2022; **162**: 1758-1760.e3 [PMID: 35149034 DOI: 10.1053/j.gastro.2022.02.005]

143 **Hadi Y,** Shah-Khan SM, Sohail AH, Jannat FRU, Syed A, Humphries CE, Daum TL, Malik A, Krafft MR, Bilal M, Thakkar S, Singh S. Su1270: Chronic pancreatitis and COVID-19: Incidence and outcomes. A multicenter research network analysis. *Gastroenterology* 2022; **162**: S-564-S-565

144 **Georgakopoulou VE**, Gkoufa A, Garmpis N, Makrodimitri S, Papageorgiou CV, Barlampa D, Garmpi A, Chiapoutakis S, Sklapani P, Trakas N, Damaskos C. COVID-19 and Acute Pancreatitis: A Systematic Review of Case Reports and Case Series. *Ann Saudi Med* 2022; **42**: 276-287 [PMID: 35933608 DOI: 10.5144/0256-4947.2022.276]

145 **Xin MJ**, Chen H, Luo B, Sun JB. Severe acute pancreatitis in the elderly: etiology and clinical characteristics. *World J Gastroenterol* 2008; **14**: 2517-2521 [PMID: 18442198 DOI: 10.3748/wjg.14.2517]

146 **Kara B**, Olmez S, Yalcın MS, Tas A, Ozturk NA, Sarıtaş B. Update on the effect of age on acute pancreatitis morbidity: a retrospective, single-center study. *Prz Gastroenterol* 2018; **13**: 223-227 [PMID: 30302167 DOI: 10.5114/pg.2018.75677]

147 **Quero G**, Covino M, Fiorillo C, Rosa F, Menghi R, Simeoni B, Potenza A, Ojetti V, Alfieri S, Franceschi F. Acute pancreatitis in elderly patients: a single-center retrospective evaluation of clinical outcomes. *Scand J Gastroenterol* 2019; **54**: 492-498 [PMID: 30905212 DOI: 10.1080/00365521.2019.1588369]

148 **Yu B**, Li N, Li J, Wan J, He W, Zhu Y, Lu N. The Clinical Characteristics of Acute Pancreatitis in Gerontal Patients: A Retrospective Study. *Clin Interv Aging* 2020; **15**: 1541-1553 [PMID: 32982192 DOI: 10.2147/CIA.S259920]

149 **Márta K**, Lazarescu AM, Farkas N, Mátrai P, Cazacu I, Ottóffy M, Habon T, Erőss B, Vincze À, Veres G, Czakó L, Sarlós P, Rakonczay Z, Hegyi P. Aging and Comorbidities in Acute Pancreatitis I: A Meta-Analysis and Systematic Review Based on 194,702 Patients. *Front Physiol* 2019; **10**: 328 [PMID: 31001131 DOI: 10.3389/fphys.2019.00328]

150 **Bulthuis MC**, Boxhoorn L, Beudel M, Elbers PWG, Kop MPM, van Wanrooij RLJ, Besselink MG, Voermans RP. Acute pancreatitis in COVID-19 patients: true risk? *Scand J Gastroenterol* 2021; **56**: 585-587 [PMID: 33715577 DOI: 10.1080/00365521.2021.1896776]

151 **Meyers MH**, Main MJ, Orr JK, Obstein KL. A Case of COVID-19-Induced Acute Pancreatitis. *Pancreas* 2020; **49**: e108-e109 [PMID: 33122538 DOI: 10.1097/MPA.0000000000001696]

152 **Karimzadeh S**, Manzuri A, Ebrahimi M, Huy NT. COVID-19 presenting as acute pancreatitis: Lessons from a patient in Iran. *Pancreatology* 2020; **20**: 1024-1025 [PMID: 32576441 DOI: 10.1016/j.pan.2020.06.003]

153 **Gadiparthi C**, Mohapatra S, Kanna S, Vykuntam V, Chen W. Acute pancreatitis in a patient with COVID-19: a case report. *Transl Gastroenterol Hepatol* 2021; **6**: 65 [PMID: 34805587 DOI: 10.21037/tgh-20-234]

154 **Wifi MN**, Nabil A, Awad A, Eltatawy R. COVID-induced pancreatitis: case report. *Egypt J Intern Med* 2021; **33**: 10 [PMID: 33716498 DOI: 10.1186/s43162-021-00039-y]

155 **Gonzalo-Voltas A**, Uxia Fernández-Pérez-Torres C, Baena-Díez JM. Acute pancreatitis in a patient with COVID-19 infection. *Med Clin (Engl Ed)* 2020; **155**: 183-184 [PMID: 32835111 DOI: 10.1016/j.medcle.2020.05.010]

156 **Reick-Mitrisin V**, Mukhtar K, Khan ZH. Acute Pancreatitis in a Patient With Recent History of SARS-CoV-2 Infection. *Cureus* 2022; **14**: e29032 [PMID: 36237820 DOI: 10.7759/cureus.29032]

157 **Acherjya GK**, Rahman MM, Islam MT, Alam AS, Tarafder K, Rahman MM, Ali M, Deb SR. Acute pancreatitis in a COVID-19 patient: An unusual presentation. *Clin Case Rep* 2020; **8**: 3400-3407 [PMID: 33363941 DOI: 10.1002/ccr3.3412]

158 **Alves AM**, Yvamoto EY, Marzinotto MAN, Teixeira ACS, Carrilho FJ. SARS-CoV-2 leading to acute pancreatitis: an unusual presentation. *Braz J Infect Dis* 2020; **24**: 561-564 [PMID: 32961108 DOI: 10.1016/j.bjid.2020.08.011]

159 **Shinohara T**, Otani A, Yamashita M, Wakimoto Y, Jubishi D, Okamoto K, Kanno Y, Ikeda M, Ishigaki K, Nakai Y, Harada S, Okugawa S, Koike K, Moriya K. Acute Pancreatitis During COVID-19 Pneumonia. *Pancreas* 2020; **49**: e106-e108 [PMID: 33122537 DOI: 10.1097/MPA.0000000000001695]

160 **Kumaran NK**, Karmakar BK, Taylor OM. Coronavirus disease-19 (COVID-19) associated with acute necrotising pancreatitis (ANP). *BMJ Case Rep* 2020; **13** [PMID: 32900752 DOI: 10.1136/bcr-2020-237903]

161 **Chen T**, Dai Z, Mo P, Li X, Ma Z, Song S, Chen X, Luo M, Liang K, Gao S, Zhang Y, Deng L, Xiong Y. Clinical Characteristics and Outcomes of Older Patients with Coronavirus Disease 2019 (COVID-19) in Wuhan, China: A Single-Centered, Retrospective Study. *J Gerontol A Biol Sci Med Sci* 2020; **75**: 1788-1795 [PMID: 32279081 DOI: 10.1093/gerona/glaa089]

162 **Imrie CW**. Prognosis of acute pancreatitis. *Ann Ital Chir* 1995; **66**: 187-189 [PMID: 7668494]

163 **Brikman S**, Denysova V, Menzal H, Dori G. Acute pancreatitis in a 61-year-old man with COVID-19. *CMAJ* 2020; **192**: E858-E859 [PMID: 32719021 DOI: 10.1503/cmaj.201029]

164 **Jena A**, James D, Singh AK, Dutta U, Sebastian S, Sharma V. Effectiveness and Durability of COVID-19 Vaccination in 9447 Patients With IBD: A Systematic Review and Meta-Analysis. *Clin Gastroenterol Hepatol* 2022; **20**: 1456-1479.e18 [PMID: 35189387 DOI: 10.1016/j.cgh.2022.02.030]

165 **Bhurwal A**, Mutneja H, Bansal V, Goel A, Arora S, Attar B, Minacapelli CD, Kochhar G, Chen LA, Brant S, Seril D. Effectiveness and safety of SARS-CoV-2 vaccine in Inflammatory Bowel Disease patients: a systematic review, meta-analysis and meta-regression. *Aliment Pharmacol Ther* 2022; **55**: 1244-1264 [PMID: 35355306 DOI: 10.1111/apt.16913]

166 **Kennedy NA**, Lin S, Goodhand JR, Chanchlani N, Hamilton B, Bewshea C, Nice R, Chee D, Cummings JF, Fraser A, Irving PM, Kamperidis N, Kok KB, Lamb CA, Macdonald J, Mehta S, Pollok RC, Raine T, Smith PJ, Verma AM, Jochum S, McDonald TJ, Sebastian S, Lees CW, Powell N, Ahmad T; Contributors to the CLARITY IBD study. Infliximab is associated with attenuated immunogenicity to BNT162b2 and ChAdOx1 nCoV-19 SARS-CoV-2 vaccines in patients with IBD. *Gut* 2021; **70**: 1884-1893 [PMID: 33903149 DOI: 10.1136/gutjnl-2021-324789]

167 **Lin S**, Kennedy NA, Saifuddin A, Sandoval DM, Reynolds CJ, Seoane RC, Kottoor SH, Pieper FP, Lin KM, Butler DK, Chanchlani N, Nice R, Chee D, Bewshea C, Janjua M, McDonald TJ, Sebastian S, Alexander JL, Constable L, Lee JC, Murray CD, Hart AL, Irving PM, Jones GR, Kok KB, Lamb CA, Lees CW, Altmann DM, Boyton RJ, Goodhand JR, Powell N, Ahmad T; CLARITY IBD study. Antibody decay, T cell immunity and breakthrough infections following two SARS-CoV-2 vaccine doses in inflammatory bowel disease patients treated with infliximab and vedolizumab. *Nat Commun* 2022; **13**: 1379 [PMID: 35296643 DOI: 10.1038/s41467-022-28517-z]

168 **McMahan K**, Yu J, Mercado NB, Loos C, Tostanoski LH, Chandrashekar A, Liu J, Peter L, Atyeo C, Zhu A, Bondzie EA, Dagotto G, Gebre MS, Jacob-Dolan C, Li Z, Nampanya F, Patel S, Pessaint L, Van Ry A, Blade K, Yalley-Ogunro J, Cabus M, Brown R, Cook A, Teow E, Andersen H, Lewis MG, Lauffenburger DA, Alter G, Barouch DH. Correlates of protection against SARS-CoV-2 in rhesus macaques. *Nature* 2021; **590**: 630-634 [PMID: 33276369 DOI: 10.1038/s41586-020-03041-6]

169 **Xu AM**, Li D, Ebinger JE, Mengesha E, Elyanow R, Gittelman RM, Chapman H, Joung S, Botwin GJ, Pozdnyakova V, Debbas P, Mujukian A, Prostko JC, Frias EC, Stewart JL, Horizon AA, Merin N, Sobhani K, Figueiredo JC, Cheng S, Kaplan IM, McGovern DPB, Merchant A, Melmed GY, Braun J. Differences in SARS-CoV-2 Vaccine Response Dynamics Between Class-I- and Class-II-Specific T-Cell Receptors in Inflammatory Bowel Disease. *Front Immunol* 2022; **13**: 880190 [PMID: 35464463 DOI: 10.3389/fimmu.2022.880190]

170 **Li D**, Xu A, Mengesha E, Elyanow R, Gittelman RM, Chapman H, Prostko JC, Frias EC, Stewart JL, Pozdnyakova V, Debbas P, Mujukian A, Horizon AA, Merin N, Joung S, Botwin GJ, Sobhani K, Figueiredo JC, Cheng S, Kaplan IM, McGovern DPB, Merchant A, Melmed GY, Braun J. The T-Cell Response to SARS-CoV-2 Vaccination in Inflammatory Bowel Disease is Augmented with Anti-TNF Therapy. *Inflamm Bowel Dis* 2022; **28**: 1130-1133 [PMID: 35397000 DOI: 10.1093/ibd/izac071]

171 **Tabesh E**, Soheilipour M, Rezaeisadrabadi M, Zare-Farashbandi E, Mousavi-Roknabadi RS. Comparison the effects and side effects of Covid-19 vaccination in patients with inflammatory bowel disease (IBD): a systematic scoping review. *BMC Gastroenterol* 2022; **22**: 393 [PMID: 35987619 DOI: 10.1186/s12876-022-02460-1]

172 **Botwin GJ**, Li D, Figueiredo J, Cheng S, Braun J, McGovern DPB, Melmed GY. Adverse Events After SARS-CoV-2 mRNA Vaccination Among Patients With Inflammatory Bowel Disease. *Am J Gastroenterol* 2021; **116**: 1746-1751 [PMID: 34047304 DOI: 10.14309/ajg.0000000000001342]

173 **Derhovanessian E**, Pawelec G. Vaccination in the elderly. *Microb Biotechnol* 2012; **5**: 226-232 [PMID: 21880118 DOI: 10.1111/j.1751-7915.2011.00283.x]

174 **Soiza RL**, Scicluna C, Thomson EC. Efficacy and safety of COVID-19 vaccines in older people. *Age Ageing* 2021; **50**: 279-283 [PMID: 33320183 DOI: 10.1093/ageing/afaa274]

175 **Collier DA**, Ferreira IATM, Kotagiri P, Datir RP, Lim EY, Touizer E, Meng B, Abdullahi A; CITIID-NIHR BioResource COVID-19 Collaboration, Elmer A, Kingston N, Graves B, Le Gresley E, Caputo D, Bergamaschi L, Smith KGC, Bradley JR, Ceron-Gutierrez L, Cortes-Acevedo P, Barcenas-Morales G, Linterman MA, McCoy LE, Davis C, Thomson E, Lyons PA, McKinney E, Doffinger R, Wills M, Gupta RK. Age-related immune response heterogeneity to SARS-CoV-2 vaccine BNT162b2. *Nature* 2021; **596**: 417-422 [PMID: 34192737 DOI: 10.1038/s41586-021-03739-1]

176 **Karamese M**, Tutuncu EE. The effectiveness of inactivated SARS-CoV-2 vaccine (CoronaVac) on antibody response in participants aged 65 years and older. *J Med Virol* 2022; **94**: 173-177 [PMID: 34427924 DOI: 10.1002/jmv.27289]

177 **Kappelman MD**, Weaver KN, Zhang X, Dai X, Watkins R, Adler J, Dubinsky MC, Kastl A, Bousvaros A, Strople JA, Cross RK, Higgins PDR, Ungaro RC, Bewtra M, Bellaguarda EA, Farraye FA, Boccieri ME, Firestine A, Chun KY, Fernando M, Bastidas M, Zikry M, Long MD. Factors Affecting Initial Humoral Immune Response to SARS-CoV-2 Vaccines Among Patients With Inflammatory Bowel Diseases. *Am J Gastroenterol* 2022; **117**: 462-469 [PMID: 35029167 DOI: 10.14309/ajg.0000000000001619]

178 **Classen JM**, Muzalyova A, Nagl S, Fleischmann C, Ebigbo A, Römmele C, Messmann H, Schnoy E. Antibody Response to SARS-CoV-2 Vaccination in Patients with Inflammatory Bowel Disease: Results of a Single-Center Cohort Study in a Tertiary Hospital in Germany. *Dig Dis* 2022; **40**: 719-727 [PMID: 34915480 DOI: 10.1159/000521343]

179 **Alexander JL**, Liu Z, Muñoz Sandoval D, Reynolds C, Ibraheim H, Anandabaskaran S, Saifuddin A, Castro Seoane R, Anand N, Nice R, Bewshea C, D'Mello A, Constable L, Jones GR, Balarajah S, Fiorentino F, Sebastian S, Irving PM, Hicks LC, Williams HRT, Kent AJ, Linger R, Parkes M, Kok K, Patel KV, Teare JP, Altmann DM, Goodhand JR, Hart AL, Lees CW, Boyton RJ, Kennedy NA, Ahmad T, Powell N; VIP study investigators. COVID-19 vaccine-induced antibody and T-cell responses in immunosuppressed patients with inflammatory bowel disease after the third vaccine dose (VIP): a multicentre, prospective, case-control study. *Lancet Gastroenterol Hepatol* 2022; **7**: 1005-1015 [PMID: 36088954 DOI: 10.1016/S2468-1253(22)00274-6]

180 **Cornberg M**, Buti M, Eberhardt CS, Grossi PA, Shouval D. EASL position paper on the use of COVID-19 vaccines in patients with chronic liver diseases, hepatobiliary cancer and liver transplant recipients. *J Hepatol* 2021; **74**: 944-951 [PMID: 33563499 DOI: 10.1016/j.jhep.2021.01.032]

181 **Fix OK**, Blumberg EA, Chang KM, Chu J, Chung RT, Goacher EK, Hameed B, Kaul DR, Kulik LM, Kwok RM, McGuire BM, Mulligan DC, Price JC, Reau NS, Reddy KR, Reynolds A, Rosen HR, Russo MW, Schilsky ML, Verna EC, Ward JW, Fontana RJ; AASLD COVID-19 Vaccine Working Group. American Association for the Study of Liver Diseases Expert Panel Consensus Statement: Vaccines to Prevent Coronavirus Disease 2019 Infection in Patients With Liver Disease. *Hepatology* 2021; **74**: 1049-1064 [PMID: 33577086 DOI: 10.1002/hep.31751]

182 **Sripongpun P**, Pinpathomrat N, Bruminhent J, Kaewdech A. Coronavirus Disease 2019 Vaccinations in Patients With Chronic Liver Disease and Liver Transplant Recipients: An Update. *Front Med (Lausanne)* 2022; **9**: 924454 [PMID: 35814781 DOI: 10.3389/fmed.2022.924454]

183 **Marjot T**, Eberhardt CS, Boettler T, Belli LS, Berenguer M, Buti M, Jalan R, Mondelli MU, Moreau R, Shouval D, Berg T, Cornberg M. Impact of COVID-19 on the liver and on the care of patients with chronic liver disease, hepatobiliary cancer, and liver transplantation: An updated EASL position paper. *J Hepatol* 2022; **77**: 1161-1197 [PMID: 35868584 DOI: 10.1016/j.jhep.2022.07.008]

184 **Ai J**, Wang J, Liu D, Xiang H, Guo Y, Lv J, Zhang Q, Li J, Zhang X, Li Q, Liang J, Guo X, Feng Y, Liu L, Zhang X, Qin W, Wang X, Rao W, Zhang Q, Tian Q, Zhang Y, Xie F, Jiang S, Yan Y, Qiu Y, Wu H, Hou Z, Zhang N, Zhang A, Ji J, Yang J, Huang J, Zhao Z, Gu Y, Bian L, Zhang Z, Zou S, Ji H, Ge G, Du X, Hou A, Zhu Y, Cong Q, Xu J, Zu H, Wang Y, Yan Z, Yan X, BianBa Y, Ci Q, Zhang L, Yang S, Gao X, Zhong L, He S, Liu C, Huang Y, Liu Y, Xu D, Zhu Q, Xu X, Lv M, Zhang W, Qi X. Safety and Immunogenicity of SARS-CoV-2 Vaccines in Patients With Chronic Liver Diseases (CHESS-NMCID 2101): A Multicenter Study. *Clin Gastroenterol Hepatol* 2022; **20**: 1516-1524.e2 [PMID: 34942370 DOI: 10.1016/j.cgh.2021.12.022]

185 **Noor MT**, Manoria P. Immune Dysfunction in Cirrhosis. *J Clin Transl Hepatol* 2017; **5**: 50-58 [PMID: 28507927 DOI: 10.14218/JCTH.2016.00056]

186 **Chen Z**, Zhang Y, Song R, Wang L, Hu X, Li H, Cai D, Hu P, Shi X, Ren H. Waning humoral immune responses to inactivated SARS-CoV-2 vaccines in patients with severe liver disease. *Signal Transduct Target Ther* 2022; **7**: 174 [PMID: 35654782 DOI: 10.1038/s41392-022-01032-9]

187 **Thuluvath PJ**, Robarts P, Chauhan M. Analysis of antibody responses after COVID-19 vaccination in liver transplant recipients and those with chronic liver diseases. *J Hepatol* 2021; **75**: 1434-1439 [PMID: 34454993 DOI: 10.1016/j.jhep.2021.08.008]

188 **Bakasis AD**, Bitzogli K, Mouziouras D, Pouliakis A, Roumpoutsou M, Goules AV, Androutsakos T. Antibody Responses after SARS-CoV-2 Vaccination in Patients with Liver Diseases. *Viruses* 2022; **14** [PMID: 35215801 DOI: 10.3390/v14020207]

189 **Willuweit K**, Frey A, Passenberg M, Korth J, Saka N, Anastasiou OE, Möhlendick B, Schütte A, Schmidt H, Rashidi-Alavijeh J. Patients with Liver Cirrhosis Show High Immunogenicity upon COVID-19 Vaccination but Develop Premature Deterioration of Antibody Titers. *Vaccines (Basel)* 2022; **10** [PMID: 35335009 DOI: 10.3390/vaccines10030377]

190 **Voysey M**, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, Angus B, Baillie VL, Barnabas SL, Bhorat QE, Bibi S, Briner C, Cicconi P, Collins AM, Colin-Jones R, Cutland CL, Darton TC, Dheda K, Duncan CJA, Emary KRW, Ewer KJ, Fairlie L, Faust SN, Feng S, Ferreira DM, Finn A, Goodman AL, Green CM, Green CA, Heath PT, Hill C, Hill H, Hirsch I, Hodgson SHC, Izu A, Jackson S, Jenkin D, Joe CCD, Kerridge S, Koen A, Kwatra G, Lazarus R, Lawrie AM, Lelliott A, Libri V, Lillie PJ, Mallory R, Mendes AVA, Milan EP, Minassian AM, McGregor A, Morrison H, Mujadidi YF, Nana A, O'Reilly PJ, Padayachee SD, Pittella A, Plested E, Pollock KM, Ramasamy MN, Rhead S, Schwarzbold AV, Singh N, Smith A, Song R, Snape MD, Sprinz E, Sutherland RK, Tarrant R, Thomson EC, Török ME, Toshner M, Turner DPJ, Vekemans J, Villafana TL, Watson MEE, Williams CJ, Douglas AD, Hill AVS, Lambe T, Gilbert SC, Pollard AJ; Oxford COVID Vaccine Trial Group. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021; **397**: 99-111 [PMID: 33306989 DOI: 10.1016/S0140-6736(20)32661-1]

191 **Liang CK**, Lee WJ, Peng LN, Meng LC, Hsiao FY, Chen LK. COVID-19 Vaccines in Older Adults: Challenges in Vaccine Development and Policy Making. *Clin Geriatr Med* 2022; **38**: 605-620 [PMID: 35868676 DOI: 10.1016/j.cger.2022.03.006]

192 **US Food Drug Aaministration**. Vaccines and Related Biological Products Advisory Committee. [cited 15 October 2022]. Available from: https://www.fda.gov/advisory-committees/blood-vaccines-and-other-biologics/vaccines-and-related-biological-products-advisory-committee

193 **Parkash O**, Sharko A, Farooqi A, Ying GW, Sura P. Acute Pancreatitis: A Possible Side Effect of COVID-19 Vaccine. *Cureus* 2021; **13**: e14741 [PMID: 34084669 DOI: 10.7759/cureus.14741]

194 **Dey RK**, Ilango H, Bhatta S, Shaheed A, Dole S, Zooshan A, Faisham M, Murad M. Acute pancreatitis in pregnancy following COVID-19 vaccine: a case report. *J Med Case Rep* 2022; **16**: 354 [PMID: 36175940 DOI: 10.1186/s13256-022-03607-0]

195 **Ozaka S**, Kodera T, Ariki S, Kobayashi T, Murakami K. Acute pancreatitis soon after COVID-19 vaccination: A case report. *Medicine (Baltimore)* 2022; **101**: e28471 [PMID: 35029194 DOI: 10.1097/MD.0000000000028471]

196 **Cacdac R**, Jamali A, Jamali R, Nemovi K, Vosoughi K, Bayraktutar Z. Acute pancreatitis as an adverse effect of COVID-19 vaccination. *SAGE Open Med Case Rep* 2022; **10**: 2050313X221131169 [PMID: 36313269 DOI: 10.1177/2050313X221131169]

197 **Kantar A**, Seminara M, Odoni M, Dalla Verde I. Acute Mild Pancreatitis Following COVID-19 mRNA Vaccine in an Adolescent. *Children (Basel)* 2021; **9** [PMID: 35053654 DOI: 10.3390/children9010029]

198 **Kalra RK**, Jayadeep S, Ball AL. Acute Pancreatitis in an Adolescent Following COVID Vaccination. *Clin Pediatr (Phila)* 2022; **61**: 236-240 [PMID: 35081801 DOI: 10.1177/00099228211067678]

199 **Patel AH**, Amin R, Lalos AT. Acute liver injury and IgG4-related autoimmune pancreatitis following mRNA-based COVID-19 vaccination. *Hepatol Forum* 2022; **3**: 97-99 [PMID: 36177105 DOI: 10.14744/hf.2022.2022.0019]

200 **Walter T**, Connor S, Stedman C, Doogue M. A case of acute necrotising pancreatitis following the second dose of Pfizer-BioNTech COVID-19 mRNA vaccine. *Br J Clin Pharmacol* 2022; **88**: 1385-1386 [PMID: 34423463 DOI: 10.1111/bcp.15039]

201 **Cieślewicz A**, Dudek M, Krela-Kaźmierczak I, Jabłecka A, Lesiak M, Korzeniowska K. Pancreatic Injury after COVID-19 Vaccine-A Case Report. *Vaccines (Basel)* 2021; **9** [PMID: 34205898 DOI: 10.3390/vaccines9060576]

202 COVID-19 mRNA Pfizer- BioNTech vaccine analysis print. [cited 15 October 2022]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\_data/file/1072043/COVID-19\_mRNA\_Pfizer-\_BioNTech\_vaccine\_analysis\_print.pdf

203 Enquête de pharmacovigilance du vaccin Pfizer-BioNTech Comirnaty. [cited 15 October 2022]. Available from: https://ansm.sante.fr/uploads/2021/10/22/20211021-covid-19-vaccins-pfizer-focus-1-2.pdf

204 **World Health Organization**. VigiAccess. [cited 17 October 2022]. Available from: https://www.vigiaccess.org/

205 **Guda NM**, Trikudanathan G, Freeman ML. Idiopathic recurrent acute pancreatitis. *Lancet Gastroenterol Hepatol* 2018; **3**: 720-728 [PMID: 30215363 DOI: 10.1016/S2468-1253(18)30211-5]

**Footnotes**

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Corresponding Author’s Membership in Professional Societies:** Società Italiana di Medicina Interna; Società Italiana Medicina Emergenza Urgenza.

**Peer-review started:** November 27, 2022

**First decision:** December 27, 2022

**Article in press:**

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Italy

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B, B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Sharma V, India; Shrestha MR, Nepal **S-Editor:** Wang JJ **L-Editor:** Ma JY-MedE  **P-Editor:** Wang JJ

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

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Age****(yrs)** | **GI symptoms** | **Diarrhoea** | **Nausea/vomiting** | **Anorexia** | **Abdominal pain** | **Outcomes** |
| de Souza et al[32], *n* = 9807 | 70.21 ± 8) | - | 2% | - | - | - | No association |
| Ramos-Rincon *et al*[34], *n* = 2772 | 86.3 ± 3) | - | 14% | 5% | 22% | - | No association |
| Marziliano *et al*[33], *n* = 4961 | 77 mean (± 8) | 9% | - | - | - | - | No association |
| [Atalla](https://pubmed.ncbi.nlm.nih.gov/?term=Atalla%252520E%25255BAuthor%25255D) *et al*[37], *n* = 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 *et al*[35], *n* = 50 | 88 median (IQR: 83-92) | 30% | 24% | 6% | 10% | 6% | Digestive symptoms were associated with a favorable outcome |
| Aroniadis *et al*[9], *n* = 434 | Age > 70  | 31% | 19% | - | - | - | Older patients were less likely to exhibit gastrointestinal symptoms |
| Zhan *et al*[23], *n* = 39 | Age > 75  | 36% | - | - | - | - | No association  |
| Vrillon *et al*[36], *n* = 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.

**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 *et al*[45] | 67 292 | 179 (hospitalized patients) | 60  | HR = 1.42; 95%CI: 0.94-2.13 |
| Brenner *et al*[59] | SECURE-IBD database | 525 | Increasing age on multivariable analysis | OR = 1.04; 95%CI: 1.01-1.06 |
| Zabana *et al*[60] | 53 682 | 482 | 60  | OR = 4.59, 95%CI: 1.3-15.9, *P* = 0.02 |
| Wetwittayakhlang *et al*[61] | 3516 | 82 | 55  | OR = 11.09, 95%CI: 1.81-68.09, *P* = 0.02 |

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

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

|  |  |  |
| --- | --- | --- |
| **Ref.** | **Outcome considered** | **Results** |
| Khateri *et al*[108] | Incidence of acute liver injury in patients affected by COVID-19 | Acute liver injury has no relationship with age |
| [Metawea](https://pubmed.ncbi.nlm.nih.gov/?term=Metawea+MI&cauthor_id=32988758) *et al*[110] | Mortality of patients with hepatocellular carcinoma infected with COVID-19 | Age is associated with poorer outcomes and higher mortality |
| Ji *et al*[111] | Severe COVID-19 in patients affected by NAFLD | Associated in patients older than 60 yr |
| Zhou *et al*[112] | Severe COVID-19 in patients affected by NAFLD | Associated in patients younger than 60 yr |
| Hartl *et al*[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 *et al*[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 *et al*[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.

**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 *et al*[122] | CHS | 9/52 (4.68%) | Potential mild pancreatic involvement in patients with COVID-19 pneumonia |
| Bruno *et al*[124] | CHS | 6/70 (8.5%) | Pancreatic involvement in hospitalized patients with documented COVID-19 |
| Liu *et al*[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 *et al*[126] | RS | 158/234 (67.5%) | Raised serum amylase in patients with COVID-19 may not be associated with pancreatitis |
| Akkus *et al*[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](https://pubmed.ncbi.nlm.nih.gov/?term=McNabb-Baltar%252520J%25255BAuthor%25255D) *et al*[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 *et al*[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 *et al*[130] | CHS | 22/38 (57.8%) | Patients with lipasemia needed more extended periods of mechanical ventilation than patients with COVID-19-associated ARDS |
| Barlass *et al*[131] | CCS | 14/83 (16.8%) | Elevated lipase is associated with worse disease outcomes and increased ICU admission and intubation |
| Bacaksiz *et al*[132] | RS | 316/1378 (23%) | Hyperamilasemia was significantly associated with COVID-19 severity |
| Magro *et al*[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 *et al*[133] | Review | NA | No direct correlation between COVID-19 and pancreatic impairment could be established |
| Singh *et al*[134] | MS | 1406/435731 (0.32%) | Worse clinical outcomes |
| Inamdar *et al*[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 *et al*[137] | RS | 75/339 (22.1%) | Higher mortality, MOF, and POF rates were registered in patients with AP and coexisting COVID-19 |
| Pandanaboyana *et al*[138] | CHS | 149/1777 (8.3%) | SARS-CoV-2 infection in acute pancreatitis increases 30-d mortality and disease severity |
| Mirò *et al*[140] | MS | 45/63.822 (0.0007%) | Higher need for hospitalisation in COVID-19 patients with pancreatitis |
| Akarsu *et al*[141] | CCS | 40/316 (12.6%) | Higher mortality rate and increased need for hospitalisation in COVID-19 patients with pancreatitis |
| Gubatan *et al*[62] | RS | 100% total population 14235 | Patients with a history of pancreatitis may be more susceptible to COVID-19 |
| Huang *et al*[142] | RCS | 4706/326993 (1.4%) | Pre-existing pancreatitis was associated with an increased risk of COVID-19–related hospitalisation and mortality |
| Hadi *et al*[143] | CS | 2/3 (66.6%) | COVID-19 patients with CP bear higher hospitalisation rates |
| Georgakopoulou *et al*[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.

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

|  |  |  |  |
| --- | --- | --- | --- |
| **Ref.** | **Study design** | **Age (yrs)** | **Remarks** |
| Meyers *et al*[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 *et al*[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 *et al*[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 *et al*[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 *et al*[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-Mitrisin *et al*[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 *et al*[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 *et al*[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 *et al*[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 *et al*[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 *et al*[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.