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Impact of chronic liver disease on SARS-CoV-2 infection outcomes: Role of stage, etiology and vaccination

Nevola R *et al*. Chronic liver disease and SARS-CoV-2 infection

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Abstract

Since the first identification in December 2019, the fast spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has represented a dramatic global public health concern. Though affecting mainly the respiratory system, SARS-CoV-2 disease, defined as coronavirus disease 2019 (COVID-19), may have a systemic involvement leading to multiple organ dysfunction. Experimental evidences about the SARS-CoV-2 tropism for the liver and the increasing of hepatic cytolysis enzymes during infection support the presence of a pathophysiological relationship between liver and SARS-CoV-2. On the other side, patients with chronic liver disease have been demonstrated to have poor prognosis for COVID-19. In particular, patients with liver cirrhosis appear extremely vulnerable to infection. Moreover, also the etiology of liver disease and the vaccination status could affect the COVID-19 outcomes. This review analyzes the impact of the disease stage and the related causes on morbidity and mortality clinical outcomes during SARS-CoV-2 infection, as well as the efficacy of vaccination in patients with chronic liver disease.

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Core Tip: It has been observed, since the early months of pandemic, that pre-existing liver disease was associated with worsening of clinical outcomes in severe acute respiratory syndrome coronavirus 2 infection. A correlation exists between severity of liver disease and coronavirus disease 2019-related adverse outcomes. The etiology of liver disease could significantly affect mortality rates, as well as vaccination status.

INTRODUCTION

From December 2019 the fast spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new virus belonging to the Coronavirus family of respiratory pathogens, has represented a major public health problem worldwide, leading to the declaration of a pandemic status in March 2020 by the World Health Organization (WHO)[1]. Despite the enormous efforts by health personnel and organizations, coronavirus disease 2019 (COVID-19) has caused more than 6.5 millions of deaths worldwide to date[2]. While the new virus variants show a milder clinical picture with predominant involvement of the upper respiratory tract, the most severe form of SARS-CoV-2 infection characterized by acute respiratory distress syndrome (ARDS) still represent an important cause of morbidity and mortality[3-5]. As observed since the first pandemic phases, organ involvement in COVID-19 is not limited to the respiratory tract, but can result in systemic disease with cardiovascular, renal, neurological and, last but not least, hepatic involvement. In particular, increases in the indices of hepatic cytolysis or cholestasis [mean as an increase of aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubina totale (TBIL), gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) upper the range value] or a more severe acute liver injury (ALI) [defined as ALT and/or AST over 3 × upper limit of normal (ULN) or ALP, GGT, and/or TBIL over 2 × ULN] can be found in 14%-53% of SARS-CoV-2 infection[6]. The mechanism of COVID-19-associated ALI is probably multifactorial, given by the combination of direct viral cytopathic effect, cytokine-induced inflammatory damage, hypoxic and drug induced liver injury[7]. ALI has been demonstrated to be a predictor of unfavorable SARS-CoV-2 infection course[8,9]. High levels of AST and TBIL at hospital admission are associated with an increased risk of COVID-19 progression[10]. The coexistence of previous liver disease worsens itself the outcomes of COVID-19. In fact, if on one hand SARS-CoV-2 infection can determine liver injury[6], on the other hand chronic liver diseases (CLDs) are associated to immune system and hemostasis alterations[11] that are able to accelerate some pathogenetic mechanisms of SARS-CoV-2, as cytokine storm and prothrombotic state, affecting significantly the outcomes[12,13]. In particular, patients

with liver cirrhosis are at high risk of an unfavorable SARS-CoV-2 infection course, with significantly higher mortality rates than the general population[14,15]. The occurrence of ALI during COVID-19 in this population is an additional predictor of all-cause mortality[16]. The risk of adverse outcome in patients with chronic hepatitis is still poorly understood. Moreover, the etiology of CLD, the disease stage, potential concomitant therapies (*e.g.* immunosuppressive) and vaccination status could significantly impact on the outcomes of COVID-19.

The aim of this review is to describe the role of liver disease during COVID-19, analyzing if and how much the stage of the disease and the related etiology can affect the SARS-CoV-2 infection outcomes and examine what is known on the clinical efficacy of vaccination in patients with CLD to date.

COVID-19 OUTCOMES AND LIVER DISEASE

Despite the prevalence of a pre-existing liver disease in COVID-19 patients appears low (between 0.6% and 3.4%)[17-19] and not significantly related to the risk of contracting SARS-CoV-2 infection[20], the first studies already showed that the presence of CLD was associated with an increase in both hospitalization rate and overall mortality[14]. In this regard, Singh *et al*[14] reported a relative risk (RR) for death in patients with pre-existing liver disease of 2.8 (95%CI: 1.9-4.0). Similarly, also Williamson *et al*[19] and Galiero *et al*[21] found a significant association between liver disease and COVID-19 mortality. A meta-analysis including about 25000 patients confirmed that CLDs were significantly associated with more severe COVID-19 course [odds ratio (OR): 1.48; 95%CI: 1.17-1.87] and overall mortality (OR: 1.78; 95%CI: 1.09-2.93)[20]. Other studies instead did not show this association[22,23]. For example Simon *et al*[22] reported that patients with CLD show an increased risk of hospitalization for COVID-19 but not an increased mortality. Furthermore, in a recent retrospective case-control study, patients with CLD did not show more need for invasive mechanical ventilation, as well as admission to intensive care unit (ICU) and overall mortality, compared to patients without liver disease[23].

Therefore, data on the association between liver disease and increase of mortality rates related to COVID-19 are conflicting. However, the spectrum of CLDs is very heterogeneous both for etiology and for stage disease. In fact, the risk appears directly related to the latter. Studies that evaluated all liver disease stages could have been affected by different mortality rates in patients with CLD, greater in cirrhosis stage, particularly if in decompensation. In this regard, Mallet et al[15] more recently reported, on a large French cohort, a significative increase in the need for mechanical ventilation (OR: 1.54; 95%CI: 1.44-1.64) and mortality rate (OR: 1.79; 95%CI: 1.71-1.87) in patients with CLD. However, when stratified by disease severity, authors observed that patients with decompensated liver cirrhosis showed a significantly higher mortality rate whereas patients with mild liver disease or compensated cirrhosis were not at increased risk of COVID-19-related mortality[15]. These data have been confirmed by meta-analysis of Middleton et al[24], in which liver cirrhosis has been shown to be associated to an increased risk of all-cause mortality in COVID-19 compared to non-cirrhotic patients. Current evidences on the role of disease stage, aetiology, and vaccination on COVID-19 outcomes are summarized in Figure 1.

LIVER CIRRHOSIS AND COVID-19 CLINICAL OUTCOMES

Regardless of the etiology, the stage of liver cirrhosis is characterized by a high degree of patient frailty. The impairment of immune system, the cuncurrent increase of both thrombotic and hemorrhagic risk and the protein-calorie malnutrition make the patient suffering from cirrhosis vulnerable to various kind of injuries. The frailty of the cirrhotic patient in the setting of COVID-19 is expressed by an excess of mortality and hospitalization rate compared to patients without CLD[14,15,19]. Extracting data of the subgroup of cirrhotic patients, Singh et al[14] had already reported that the risk of death in these patients was 4.6 fold increased compared to the ones without liver disease. As already mentioned, mortality rate appears higher in patients with cirrhosis not only compared to patients without CLD but also when compared to patients with CLD but without cirrhosis (32% vs 8%, respectively; $P < 0.001$)[25]. In particular, compared to

cirrhotic/SARS-CoV-2 negative patients and to non-cirrhotic/SARS-CoV-2 positive patients, those with liver cirrhosis and COVID-19 had 2.38 and 3.31 times adjusted hazard ratio of 30-d death, respectively[26]. Similar results was found also by Ioannou et al[27]. Overall, the 30-d COVID-19-related mortality rate in patients with cirrhosis is very high, ranging from 32% to 47% of cases[25,28,29]. In fact, liver cirrhosis has been proven to be an independent risk factor for COVID-19 related mortality (OR: 3.1)[29]. However, no updated mortality data are available for the new viral variants, with an apparently lower lethality rate than the wild type. Although most studies consider liver cirrhosis as an independent predictor of the risk of COVID-19-related death[15,24,26,29,30], some data would indicate that the high mortality rates in patients with cirrhosis and COVID-19 result from cirrhosis-associated comorbidities and extrahepatic organ failure rather than liver disease itself[31]. After propensity score matching for age, sex, and extra-hepatic comorbidities, mortality rate during COVID-19 appears to be similar between patients with and without cirrhosis (28.8% vs 26.1%, respectively; P = 0.644). These results still could have been affected by the typology of matching and the methodology of data collection through registers. Among patients with liver cirrhosis the coexistence of obesity and diabetes would further worsen the outcomes[16].

Similarly to what recently reported for kidney failure[32], COVID-19-related mortality risk was strongly associated with the stage of liver impairment. Overall, the 30-d mortality risk is significantly increased in patients with decompensated liver cirrhosis hospitalized for COVID-19[15,30]. Mortality rate increased according to Child-Pugh (CP) class, raising from 19% of class A (OR: 1.90), to 35% of class B (OR: 4.14) up to 51% of class C (OR: 9.32)[25]. In particular a CP score ≥ 9 at hospital admission would be predictive of high mortality[16]. Compared to patients without liver disease, a CP class B and C cirrhosis would bring an additional mortality rate of +20% and +38.1%, respectively[25]. In this regard, it seems that the Chronic Liver Failure Consortium had better performance in predicting 28-d mortality than CP score and model for end-stage liver disease-Na in patients with cirrhosis and COVID-19[29]. Moreover, in cirrhotic patients an increasing

trend of bilirubin and AST/ALT ratio[16] or the occurrence of liver injury[10,21] would be predictive of mortality.

The most frequent cause of mortality in patients with liver cirrhosis and COVID-19 remains the respiratory failure (71%)[25]. However, acute liver decompensation occurred in up to 46% of patients, even without respiratory symptoms. Liver related complications increased according to stage of liver disease[16]. It is known that infections (bacterial more than viral) may lead to liver decompensation, hepatorenal syndrome and portosystemic encephalopathy, and are one of the most frequent causes of acute-on-chronic liver failure (ACLF) and death in patients with cirrhosis. Conclusive data on the comparison between the SARS-CoV-2 infection outcomes and those of other infectious precipitants are currently not available. However, some data indicate that in-hospital mortality rates would be significantly higher in cirrhotic patients with COVID-19 than in those with other bacterial infections[28]. Overall about 45% of patients with CLD develop ACLF[16]. Higher rates are reported for patients with liver cirrhosis. Moreover, cirrhotic patients with diabetes or obesity had higher ACLF rates than non-diabetic or normal weight patients (OR: 2.1 and 8.9, respectively)[16]. Similarly to other viral infections, ACLF during COVID-19 could result from an immune-mediated response to viral antigens in the context of cytokine storm[33], as well as a direct cytopathic effect or iatrogenic injury. Multiorgan damage caused by SARS-CoV-2 is significantly more frequent in immunocompromised patients[34]. The impairment of immune system in case of liver cirrhosis due to bone marrow suppression, lower protein synthesis and cirrhosis associated immune dysfunction syndrome, could explain the high rates of ACLF and the severe course in cirrhotic patients.

If in-hospital COVID-19-related mortality was significantly increased in patients with liver cirrhosis, little is known about post-acute outcomes. Recently Vaishnav et al[35] analyzed the post-discharge mortality of cirrhotic patients with SARS-CoV-2 infection. The data indicate that mortality rates within two months of discharge among COVID-19 survivors are comparable between patients with liver cirrhosis and those without.

Hepatocellular carcinoma

Little data are currently available on SARS-CoV-2 infection clinical course and outcomes in patients with hepatocellular carcinoma (HCC). Indeed, in studies performed during the first pandemic phase on COVID-19-related outcomes in cancer patients, those with HCC were underrepresented[36,37].

Although data are not univocal[25], several studies include the presence of HCC among the independent predictors of COVID-19-related mortality[15,30,38]. Among patients with CLD and COVID-19, HCC patients had 3.31 times hazard of death for all causes, regardless of the presence of liver cirrhosis[30]. Beyond the association with mortality, according to Mallet *et al*[15] the presence of HCC is also predictive of a severe course of COVID-19 and a greater need for mechanical ventilation. Muñoz-Martínez *et al*[38] evaluated the SARS-CoV-2 infection course in 250 patients with primary liver cancer (218 with HCC and 32 with intrahepatic cholangiocarcinoma). In patients with HCC, a 30-d mortality rate of 18.4% was observed, with a statistically significant trend according to the stage of cirrhosis (assessed by CP) and tumor [assessed by Barcelona Clinic Liver Cancer (BCLC)]. In particular, the mortality rates increased from 6.10% for BCLC-0/A, to 11.76% for BCLC-B, to 20.69% for BCLC-C and 34.52% for BCLC-D[38].

The high COVID-19 related mortality in patients with HCC could result from the link between viral infection and the impairment of immune-system secondary to active neoplasm, antineoplastic therapy and the frequent coexistence of liver cirrhosis.

Liver transplant recipients

In the analysis of the correlation between SARS-CoV-2 infection and CLD, patients undergone liver transplant (LT) represent a separate group, due to the effects of chronic immunosuppressive therapy. The hypothesis that this therapy could increase the susceptibility to SARS-CoV-2 has been suggested from some population studies[39-41]. Observational studies on western populations have reported a mortality of 16%-22% in hepatotransplant patients with SARS-CoV-2 infection[42,43] in liver-transplant patients with SARS-CoV-2 infection, finding an increased survival in short term LT recipients (<

2 years), usually treated with full doses of immunosuppressants. This data support the hypothesis that, more than the immunosuppressive effect itself, the main cause of death in these patients is represented by the long-term cardio-metabolic effects induced by immunosuppressive drugs[44].

The study of the correlation between the type of immunosuppressive drug and COVID-19 outcomes in patients undergone LT has led to non-univocal results. During the first pandemic wave, Colmenero *et al*[39] reported that mycophenolate mofetil therapy in liver-transplant patients with SARS-CoV-2 infection was associated to an increased risk of severe course of COVID-19 (RR 3.94, P = 0.003)[39]. Therapies with calcineurin inhibitors or everolimus, instead, have been shown to be not associated with an increased likelihood of adverse outcome. Furthermore, discontinuation of immunosuppressive therapy did not show benefits[39]. On the contrary, Webb *et al*[45] did not find any correlation between the type of immunosuppressant and mortality rate in patient with previous LT and SARS-CoV-2 infection. They highlighted that LT seems to not increase significantly COVID-19-related mortality rate. These data are supported by the results of a meta-analysis including the main studies performed on LT patients with SARS-CoV-2 infection[46]. In these patients the 30-d mortality was comparable to the mortality rate found in the general population (OR: 0.90, 95%CI: 0.55-1.47). In light of unavailability of univocal data, European Association for the Study of the Liver suggests to personalize immunosuppressive therapy changes based on patient's medical history, disease severity and the type of ongoing immunosuppressive therapy[47].

CHRONIC HEPATITIS AND COVID-19 CLINICAL OUTCOMES

As mentioned above, if liver cirrhosis is associated with high rates of COVID-19-related mortality, several data indicate that patients with chronic hepatitis do not show an increased risk[15]. However, in addition to the stage of the disease, the different etiology could also affect the COVID-19 outcomes (Figure 1).

Alcohol-related liver disease

During pandemic, the relationship between alcohol and SARS-CoV-2 infection has been shown to be bidirectional. On one hand, the isolation and socio-economic uncertainties resulting from COVID-19 pandemic have led to an increase in alcohol consumption[48], already on the rise in the last twenty years[49]. On the other hand, several studies reported that alcohol-related liver disease (ALD) seems to be associated to poorer prognosis for COVID-19 than the other etiologies[15,25,30,50]. In this regard, Marjot *et al*[25] showed ALD to be an independent risk factor for death from COVID-19 (OR: 1.79; 95%CI: 1.03-3.13). Similar results have been obtained from Mallet *et al*[15] and Kim *et al*[30]. More recently Bailey *et al*[50] confirmed that alcohol use disorders (AUDs) worsen the COVID-19 course and are associated to an increased hospitalization rate and all-cause mortality compared to patients with SARS-CoV-2 infection but without AUDs.

AUDs are an already known risk factor for ARDS and ARDS-related multiorgan failure[51]. In fact, chronic alcohol consumption has been demonstrated to cause significative alterations in epithelial and endothelial cell function, surfactant synthesis and secretion, lung matrix composition and alveolar-capillary barrier function. Such alterations could increase susceptibility to respiratory pathogens, like SARS-CoV-2, leading to higher ARDS rate and adverse outcomes compared to patients without AUDs. Furthermore, ethanol exposure could stimulate the activity of key inflammatory mediators with a pro-inflammatory response further exacerbated by SARS-CoV-2 infection, resulting in a more severe course of COVID-19[52].

Chronic viral hepatitis

Several studies analyzed the mutual interaction between chronic hepatitis B virus (HBV) and SARS-CoV-2 infection, investigating whether the underlying viral disease could determine a worse prognosis in the COVID-19 course. Numerous data suggest that patients with chronic HBV infection have similar characteristics to HBV-negative patients in prevalence of laboratory abnormalities (changes in cytolysis and cholestasis liver markers), severity of the COVID-19 course and mortality[53-55]. The absence of a significative correlation between COVID-19-related outcomes and chronic viral hepatitis

is confirmed by meta-analysis of Sarkar et al[56], in which the Authors found no significant impact on overall mortality during SARS-CoV-2 infection. Neither the degree of HBV replicative activity seems to affect the SARS-CoV-2 infection outcomes: inactive carriers or patients with previous infection have ALI and mortality rates comparable to patients with active hepatitis[57,58]. As further demonstration of the absence of correlation between HBV replicative activity and COVID-19-related outcomes, antiviral therapy for HBV is not able to determine a significant impact on mortality, need for admission to ICU and hospitalization length[59]. Apparently conflicting with these data, Yang et al[60] showed that the HBeAg-positive chronic HBV hepatitis is associated with a higher rate of hospitalization in ICU and mortality. However, the Authors did not stratify the study cohort in relation to disease stage and the impact of the presence of liver cirrhosis and organ failure on these results is unknown. Finally, the role and safety of immunosuppressive therapies (e.g. corticosteroids, IL-6 pathway inhibitors such as tocilizumab) used in case of SARS-CoV-2-related ARDS were evaluated about the risk of HBV reactivation in patients with biohumoral signs of previous infection (HBsAg-negative, HBcAb-positive). In these patients, the risk of HBV reactivation following immunosuppressive treatment for COVID-19 appears negligible and not influenced by any antiviral prophylaxis[61].

Little data are available to date on the association between severity of COVID-19 course and chronic hepatitis C virus (HCV) infection. Some studies would report an excess of mortality for patients with chronic HCV infection[62]. However, also in this case, the proportion of patients with liver cirrhosis and the related impact on outcomes is unknown. Butt et al[63] show similar COVID-19-related mortality rates among HCV-positive patients compared to HCV-negatives, despite a higher hospitalization rate. However, in the study population, HCV patients show a higher prevalence of liver cirrhosis than those not HCV (8.1% vs 1.4%, respectively; $P < 0.0001$). At last, Cerbu et al[64] investigated the differences in outcomes between patients with active HCV infection and those who were under treatment or achieved sustained virological response. They found that patients with active infection showed overall worse prognosis in terms of

hospitalization, severe COVID-19 course, ICU admission and all-cause mortality compared to non-viraemic patients. Regarding this, the early treatment with sofosbuvir/velpatasvir combination (used for HCV infection) in patients with COVID-19 has been shown to be effective in speeding up the clearance of SARS-CoV-2 and preventing disease progression[65].

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is currently the most frequent etiology of liver disease worldwide, affecting approximately 32.5% of global population[66]. It is closely associated to metabolic comorbidities as obesity, diabetes mellitus, arterial hypertension and chronic kidney failure[67]. Such comorbidities related to NAFLD have been shown to play a predictive role for adverse outcomes in COVID-19, being associated to higher rates of hospitalization, mechanical ventilation and mortality[19,68]. For these reasons great attention has been paid to determine whether NAFLD itself could represent an independent prognostic factor in COVID-19. However, studies in this setting are affected by the variability in the definition of NALFD patients, using for this purpose clinical-anamnestic or radiological (by ultrasound or computed tomography) criteria or score [hepatic steatosis index (HSI)] in different ways. Data currently available are not univocal. In one of the very first reports, Ji *et al*[69] showed that, net of comorbidities, NAFLD (diagnosed by ultrasound or by a value > 36 of the sum of HSI and body mass index) was an independent predictor of COVID-19 progression (OR: 6.4; 95%CI: 1.5-31.2). Furthermore, NAFLD was associated to higher prevalence of ALI during hospital stay and a slower viral clearance compared to control group without NAFLD. Mahamid *et al*[70] later confirmed these data, despite the small cohort size. Conversely, in a recent case control study, NAFLD was not found to be associated to higher in-hospital mortality rates, need for ventilatory support, ICU admission, or overall length of hospital stay[71]. Similar results have been obtained by Marjot *et al*[25] and Kim *et al*[30]. Also in the study by Vrsaljko *et al*[72], NAFLD is not shown to be independently correlated to a severe course of COVID-19 and to mortality rate in the multivariate analysis, while it appears

significantly related to the hospitalization length and the incidence of pulmonary thrombosis.

Moreover, the nomenclature of NALFD recently has been changed to metabolic associated fatty liver disease (MAFLD)[73]. At the same time, the diagnostic criteria have been redefined, results that do not overlap with the previous ones. These new criteria have been recently applied also in the setting of patients with SARS-CoV-2 infection, showing conflicting data in this case as well. In this regard, Vázquez-Medina et al[74] reported that patients with MAFLD, but not those with NAFLD, have higher mortality rates (55.0% vs 38.3%, P = 0.02) than the control group not MAFLD/not NAFLD, whereas both MAFLD and NAFLD are associated with a higher rate of orotracheal intubation. Gao et al[75] confirmed that MAFLD increases by 4 times the risk of severe course of COVID-19 and the association remains even after adjusting for age, sex, and comorbidities. Surprisingly, some preliminary data would indicate that the correlation between MAFLD and severity of COVID-19 course is more significative in patients under 60[76]. In contrast to the above mentioned studies, Campos-Murguía et al[77] observed that fibrosis rather than MAFLD is associated with a severe course of COVID-19 (increased need for mechanical ventilation, increased incidence of acute kidney injury), and higher mortality. However, in most of these studies enrolled patients were not evaluated for the possible presence of liver cirrhosis. This could represent a significant bias with a potential impact on the results. As expected, the presence of intermediate or advanced liver fibrosis in patients with MAFLD is indeed associated with a higher risk of severe COVID-19[78]. In this regard, advanced fibrosis has been shown to determine a significant increase in mortality risk both in patients diagnosed with MAFLD and in those diagnosed with NAFLD compared to patients without CLD[74] and patients with mild or moderate liver fibrosis[79].

Recently, a large-scale 2-sample Mendelian randomization analysis has been carried out in order to provide possible conclusive data on the association between NAFLD and the COVID-19 course[80]. Although NAFLD is associated with a severe course of SARS-CoV-2 infection in univariate analysis, this association disappears after adjustment for

age, sex, and comorbidities. Therefore, the Authors conclude that there are no evidence supporting that NAFLD is a causal risk factor for severe COVID-19. The results favoring this association are probably attributable to the correlation between NAFLD and obesity.

Autoimmune liver disease

The incidence of COVID-19 in patients with autoimmune hepatitis (AIH) is comparable to that of the general population[81,82]. Despite available data are limited, the main studies agree that patients with AIH do not present significant differences in hospitalization rates, disease severity and mortality during SARS-CoV-2 infection compared to patients with non-AIH CLD and the general population[83,84]. However, steroid treatment during COVID-19, when not indicated, can cause a more severe course of the disease. While steroids represent a cornerstone in the therapy of SARS-CoV-2-related ARDS[85,86], particularly when associated to antiviral drugs[87], their use is not recommended in absence of respiratory failure due to lack of benefit and potential worsening of outcomes[85,86]. In this regard, Efe *et al*[88] recently highlighted that the use of corticosteroids or azathioprine for AIH therapy is associated with a significant increase in the risk of severe form of COVID-19 (OR: 4.73; 95%CI: 1.12-25.89), even after adjusting for demographic characteristics, comorbidities and presence of liver cirrhosis. However, in absence of conclusive data, any remodulation of immunosuppressive therapy during SARS-CoV-2 infection should be personalized after a careful assessment of the risks and benefits[47].

Role and efficacy of vaccination in patients with CLD and liver cirrhosis

The global availability of anti-SARS-CoV-2 vaccines in the last months of 2020 has resulted in reduction of hospitalization and mortality rates from COVID-19 despite the succession of different viral variants[89]. Given their vulnerability profile in case of SARS-CoV-2 infection, such vaccines have been strictly recommended in LT recipients and patients with CLD, with priority to cirrhotic patients and those with HCC or ALD (Figure 1)[90-92]. In this setting vaccines have found to be generally safe[93-95], although sporadic

cases of post-vaccinal ALI are reported, with predominantly hepatocellular and immune-mediated injury due to a probable aberrant response of the immune system after vaccine stimulation[96].

Despite the strong indication, patients with CLD (particularly those with liver cirrhosis) appear underrepresented in phase III trials of anti-SARS-CoV-2 vaccines, both for mRNA and viral vector ones[97-99]. In fact, CLD and in particular the presence of significant liver fibrosis could negatively affect the production of innate immunity proteins and the count and performance of B and T lymphocytes[100]. For this reason in the last 2 years a growing number of clinical studies have investigated the efficacy of anti-SARS-CoV-2 vaccines in patients with CLD. Anti-SARS-CoV-2 vaccines are able to determine both a T-cell and a humoral response, stimulating the production of antibodies directed against the Spike protein (seroconversion) and neutralizing antibodies[101,102]. Prospective studies compared the immunological response induced by a full course of mRNA vaccines and/or viral vector vaccines in patients with liver cirrhosis and controls[93-95]. Almost all patients with liver cirrhosis showed production of anti-Spike antibodies and a neutralizing antibody activity, similar to patients without liver cirrhosis[93]. A recent meta-analysis confirmed comparable seroconversion rates between cirrhotic patients and patients with CLD without cirrhosis[100]. Despite comparable seroconversion rates, Iavarone *et al*[95] reported a statistically significant difference in the antibody titer developed by patients with liver cirrhosis after vaccination compared to controls (1751 *vs* 4523 U/mL, $P = 0.012$). In particular, CP classes B and C and the presence of HCC would appear to be independently associated with low levels of antibody titer. We hypothesize that this suboptimal vaccine response could potentially indicate partial protection against SARS-CoV-2 infection and a reduction in its duration, particularly in patients with decompensated cirrhosis. Furthermore, with regard to the cellular response induced by the vaccine, the production of interferon-gamma after spike-specific stimulation of T lymphocytes is detectable only in 65.4% of patients with liver cirrhosis, against 100% of controls[94].

Beyond humoral response, little data are available on clinical efficacy of anti-SARS-CoV-2 vaccines in patients with CLD. The most important knowledges on this issue have been acquired from Veterans Outcomes and Costs Associated with Liver Disease cohort[103] and National COVID Cohort Collaborative registers[104]. In the first study, John et al[103] compared overall and COVID-19-related mortality 60 d after SARS-CoV-2 infection in cirrhotic patients receiving mRNA vaccine and cirrhotic patients not previously vaccinated. Unequivocally, postvaccination COVID-19 was associated with reduced mortality rates (HR: 0.21; 95%CI: 0.11-0.42) compared to unvaccinated patients with liver cirrhosis, with an overall reduction in the risk of death of approximately 80%. The benefit of vaccination is also statistically significant in patients with decompensated cirrhosis and in those who have not completed the vaccination course[103]. Similar results have been reported also by Ge et al[104], whose study is available only in "pre-print" version to date. This study, carried out during SARS-CoV-2 alpha and delta variants predominance, describes a 66% reduction in 30-d mortality in vaccinated cirrhotic patients compared to unvaccinated patients with liver cirrhosis. Furthermore, the administration of the third dose of mRNA vaccine in cirrhotic patients seems to lead to 80% reduction in case of SARS-CoV-2 infection (symptomatic or asymptomatic) and a 100% reduction in severe forms of COVID-19 and related death compared to the administration of two doses, overcoming the hyporesponsiveness to vaccines in these patients[105]. The impact of the third vaccine dose appears stronger among patients with compensated rather than decompensated cirrhosis.

If patients with liver cirrhosis show overall suboptimal but effective seroconversion rates on protection against risk of death and a severe COVID-19 course, data obtained from LT recipients appear less encouraging. In fact, LT recipients show lower vaccine response[94,100,106]. Seroconversion rates in these patients range from 47.5% and 65%, significantly lower than controls[94,107]. Overall, 28% of patients undergoing LT did neither develop a T-cell nor a humoral response after vaccination[94]. An optimal humoral response is developed in only one third of liver transplant patients[107]. Among the factors associated with vaccine response rate in this setting, studies agree in identifying

advanced age, alcoholic etiology of liver disease, and immunosuppressive therapy as independent predictors of reduced antibody response[93,106,108]. Conclusive data on the correlation with the specific immunosuppressive regimen are not available to date. Some studies would indicate that the reduced antibody response is particularly significant for patients treated with mycophenolate mofetil[106,108] or high doses of steroids[106]. Other manuscripts reported instead a negative correlation with calcineurin inhibitors compared to other immunosuppressive drugs[94]. Thuluvath *et al*[107] highlights that the use of ≥ 2 immunosuppression drugs is associated with poor immune response.

Finally, at the moment few data are available about the influence of CLD etiology on vaccine-induced immune responses. Among the various etiologies, despite the high seroconversion rates, AIH patients show a significantly lower antibody titer than both patients with autoimmune cholestatic liver disease and controls, independently from the presence of liver cirrhosis and the ongoing immunosuppressive therapy[109]. Despite this, clinical benefit of vaccination appears consistently also in AIH patients, showing a significative reduction in hospitalization, severe course and COVID-19-related mortality rates (adjusted OR: 0.20)[110].

CONCLUSION

Patients with CLD are more vulnerable to SARS-CoV-2 infection. In particular patients with liver cirrhosis show higher hospitalization rates, severe COVID-19 course and mortality than the general population. Mortality rate increases according to stage of cirrhosis. Among etiologies, ALD is the most frequently associated to adverse outcomes. Patients with NAFLD have high mortality rates and severe COVID-19 course in relation to the high burden of comorbidities. Anti-SARS-CoV-2 vaccination is safe and effective in patients with CLD: in particular patients with liver cirrhosis benefit from a complete vaccination course. Patients undergone liver transplant show higher mortality rates and a reduced humoral response to vaccination. In any case, vaccination should be encouraged in all patients with CLD, particularly for those at higher risk due to disease stage and related etiology.

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3	Jonathan F. Brozat, Frank Hanses, Martina Haelberger, Melanie Stecher et al. "COVID‐19 mortality in cirrhosis is determined by cirrhosis‐associated comorbidities and extrahepatic organ failure: Results from the multinational LEOSS registry", United European Gastroenterology Journal, 2022 Crossref	30 words —	**1%**
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