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REVIEW

SARS-CoV-2 infection: a hurricane that does not ignore chronic hepatitis

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Abstract

Background The COVID-19 pandemic significantly compromised screening, laboratory controls, clinical surveillance and treatment of chronic hepatitis patients and worsened their outcome, as evidenced by its significant correlation with advanced cirrhosis, liver decompensation and mortality.

Results This pandemic significantly impaired also the sector of liver transplantation, whose wards, operating rooms, outpatients' facilities, and healthcare personnel have been dedicated to patients with COVID-19. In addition, screening and treatment for HBV infection have been delayed or suspended in in most countries, with an increased risk of viral reactivation. Similar delay or suspension have also occurred for universal hepatitis B vaccination programs in many countries. Likewise, COVID-19 pandemic has made unreachable the goal of elimination of HCV infection as a worldwide public-health issue predicted for 2030 by the WHO.

Conclusion This review article demonstrates how COVID-19 pandemic is causing serious damage to the sector of liver disease, which has quickly lost the beneficial effects of years of study, research, and clinical and technological application, as well as considerable financial investments.

Keywords COVID-19 · SARS-CoV-2 · HBV infection · HCV infection · Viral hepatitis

Introduction

The novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) has devastated the healthcare systems of most countries worldwide. Many clinical facilities, originally dedicated to different pathologies, have been converted to coronavirus disease 2019 (COVID-19) assistance and many health care professionals of all areas of medicine have been reallocated to manage COVID-19 patients, thus reducing the care for those with other diseases, including chronic hepatitis. In addition, the enforcement of lockdown rules and the perceived risk of in hospital SARS-CoV-2 spread has acted as reducing factors of frequency of citizens in health facilities.

The impact of SARS-CoV-2 on the quality of care for patients with chronic hepatitis and the consequent damage to their health have been clarified only in part. It is well known, however, that chronic hepatitis patients require special attention and continuous follow-up.

Defining more accurately the real impact of this pandemic on such sensitive area of medicine seems useful to bring the health supply and the quality of care back to normal and properly plan new public health programs [1, 2].

This narrative review will evaluate the direct and indirect negative effects of COVID-19 on the sector of chronic hepatitis and on the lives of liver patients.

Methodologic premise

Although this is a narrative review, we prefer to give some information on methodology used. The PubMed and Embase databases were searched to identify studies on COVID-19 in chronic hepatitis patients, published in English between 2020 and 2021. A comprehensive literature search was

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performed using a combination of keywords, including the terms Medical Subject Headings (MeSH), identified for each construct and combined using the Boolean operators "OR" within the construct and "AND" between the constructs and free text words, including "severe acute respiratory syndrome coronavirus 2", "SARS-CoV-2", "COVID-19", "viral hepatitis", "chronic hepatitis", "hepatitis B", "hepatitis C", "alcoholic hepatitis", "autoimmune hepatitis", "symptoms", "therapy", and "outcome".

We evaluated prospective and retrospective studies, review articles, systematic reviews, meta-analysis, guidelines, recommendations, reports on the state of the art, case series and case reports. To identify suitable documents that may not have been retrieved from the search described above, the reference lists of the included articles were manually checked.

The search was conducted independently by two to authors, who identified and removed duplicates, reviewed the studies by title/abstract and then revised the full text, considering the inclusion and exclusion criteria for admissibility. Any discrepancies were resolved with the advice from a third author. Methodological assessment of article quality and risk of bias is a key step in systematic review and not in narrative review. However, it has been our commitment to identify the risks of publication bias, location bias, citation bias and outcome reporting bias, to evaluate the quality and reliability of the data reported.

SARS-CoV-2 pandemic reduced diagnostic, management, and treatment opportunities for patients with chronic hepatitis

The measures meant to stop the spread of SARS-CoV-2 infection and to protect people from the COVID-19 pandemic have however adversely affected diagnostic procedures, access to treatments and routine monitoring of chronic liver disease (CLD). These adverse effects have had a different impact in different countries due to the substantial difference in levels of assistance between nations, high in industrialized countries, and low in developing countries, differences amplified by the profound health and economic worldwide crisis generated by the prolonged devastating COVID-19 pandemic. This has been made evident by several studies. The World Hepatitis Alliance (WHA), representing more than 300 member organizations across 99 countries, carried out a global online survey to assess the effects of COVID-19 crisis on viral hepatitis services and on people living with viral hepatitis. Of 132 self-selecting organizations responding to this online investigation, only 36% reported that people were able to access viral hepatitis testing and therapy due to closures during the lockdown. Lack of access to medications was more common in low-income and middle-income countries, further damaging already defied health care systems. Participants in India and Nigeria reported that travel restrictions made life very difficult for remote communities, where people living with viral hepatitis became unable to access medications [3]. Of 40 respondents from outside the USA, 22 (55%) felt that travel restrictions were the main reason people were unable to access treatment which also occurred in lower proportion in some USA geographic areas due to travel restriction [3]. Another main reason for lack of access to viral hepatitis testing and treatment was the fear of citizens to attend healthcare facilities during the waves of COVID-19 [2].

Some authors analyzed the consequences of the first three waves of COVID-19 pandemic. Tapper et al. [4] reported that all screening procedures for CLD stable patients were temporary delayed with an increase of first diagnoses in an advanced stage of the disease or at the onset of complications, which worsened the patients' outcome and life quality. These authors represented the evolution of events in three successive stages: the first one, temporally localized during the lockdown and/or other social distancing, characterized by high priority towards patients with COVID-19 and low priority or delay of elective and routine procedures for non-COVID-19 diseases; the second one, temporally located after the abolition of physical distancing, characterized by an increase in morbidity and decompensation of non-COVID-19 diseases and by the overload of healthcare facilities in carrying out what previously delayed; a protracted third stage burdened by the consequences of delayed or missed diagnosis, loss to follow-up and disease progression [4]. Mandel et al. [5] analyzed the effect of the COVID-19 pandemic waves on HBV and HCV testing in Ontario, Canada. HBsAg testing volumes decreased by 33% during the 1st wave, by 18% during the second and by 15% during the third one, paralleled by the decrease in HBV DNA testing by 37%, 27% and 20%, respectively. The same authors also reported a similar trend for anti-HCV testing, decreased by 35%, 21% and 19%, and for HCV RNA testing, decreased by 44%, 30% and 36%, during the first, second and third pandemic waves, respectively. These overtime reductions most probably reflect a better adaptation of citizens to the subsequent pandemic waves and the favorable effect of the progressive increase in COVID-19 vaccination coverage [5].

Other studies highlighted that clinic visits for patients with chronic hepatitis and surveillance imaging for HCC fell dramatically as the social distancing and lockdown measures were instituted [6]. These decreasing trends have been observed for both sexes, all race/ethnicity, all etiologies, and all stages of the disease [7]. It is common opinion that the reduction in screening activities and elective procedures such as imaging for HCC, endoscopy for esophageal varices and monitoring of encephalopathy will adversely affect the clinical course of CLD of any etiology.

The use of SARS-CoV-2 vaccines to confine the pandemic has been widespread in industrialized countries, but scarce in low-income countries and therefore the development of increasingly infectious viral variants has not been prevented. Even in industrialized countries vaccination coverage has not been completed, both because of the time required for the development, registration, production, and distribution of vaccines and of the refusal of vaccination by a minority but still consistent number of subjects. The consequence of this is the persistence of the pandemic, which is currently in its fourth wave. Reducing the circulation of SARS-CoV-2, COVID-19 vaccination will certainly exert a favorable effect on the management of chronic hepatitis, but its consistency is not fully assessable at present. In fact, even if many liver units and liver transplant centers have resumed full activity between the pandemic waves, they again have suffered strong limitations of space, personnel, and clinical activity in the next wave, and the fourth wave is in full swing in most geographic areas. Furthermore, the delay in screening and diagnosis and the interruptions of clinical activities for outpatients will produce serious but not yet predictable damages to national healthcare systems. Among the negative effects of COVID-19 we should also consider the damages due to the difficult access to nutritional programs, the damage to mental state and the increase in alcohol consumption.

The course of the illness in patients with chronic liver disease and COVID-19

SARS-CoV-2 binds to the angiotensin converting enzyme 2 (ACE2) receptor on hepatocytes and bile duct cells causing an organ damage which can be increased by hypoxia-induced oxygen free radicals. On the other hand, patients with advanced liver disease (mainly those with cirrhosis) often show a persistent systemic inflammation and a relevant proinflammatory cytokine production (typical hallmark of patients with metabolic associated fatty liver disease), which may increase the risk to develop a cytokine storm in patients with SARS-CoV-2 infection. Furthermore, some complications of cirrhosis (porto-pulmonary hypertension, hepato-pulmonary syndrome, hydrothorax) can worsen the respiratory failure associated with COVID-19 [8, 9].

The chronic liver disease prevalence among patients with COVID-19 varies between the published studies, in relation to the selection and sample size biases and to the geographic area where the studies were carried out. Racial factors have been infrequently investigated, but their relevance have been suggested by two studies showing that African American and Hispanic communities are at a higher risk to develop COVID-19 than Caucasians [10, 11]. In addition, most published reports have provided scarce information on the pre-existing liver conditions, on the etiology of liver disease and on the degree of viral replication in HBV- or HCV-cases.

In a large cohort study including more than 17 million adults, Williamson et al. [12] found CLD associated with COVID-19 hospital death (HR = 2.34, 95% CI 1.94–2.83). Similar data were obtained by Docherty et al. [13] who found the worst survival indexes associated to an older age, male sex and chronic comorbidities including moderate/severe liver disease. In a prospective observational cohort study on SARS-CoV-2-infected patients, Moon et al. [14] confirmed these findings and underlined that patient with cirrhosis experienced hepatic decompensation even in the absence of respiratory symptoms. In this study, patients with cirrhosis died of COVID-19 lung disease in 78.7% of cases, of liver disease in 12.2% and of heart related diseases in 4.3%, mortality being associated with the baseline Child–Pugh classes: 23.9% in patients in class A, 43.3% in those class B and 63.0% in those in class C, percentages much higher than the 12.2% registered in patients with CLD without cirrhosis [14]; in this study, even hepatic decompensation was found associated with the baseline Child–Pugh class [14].

Qi et al. [15] studied demographics, comorbidities, laboratory data, radiographic findings and clinical outcome of 21 SARS-CoV-2-infected patients with pre-existing liver cirrhosis and concluded that in most cases respiratory failure was the cause of death rather than an unfavorable progression of liver disease. Iavarone et al. [16] carried-out a multicenter retrospective analysis of a cohort of 50 patients with cirrhosis and severe acute respiratory SARS-CoV-2 infection and found a significant association between this infection and liver decompensation.

Several other studies have shown that COVID-19 infection aggravates the severity of liver cirrhosis. The APCOLIS study (APASL COVID-19 Liver Injury Spectrum Study) analyzed 228 patients with chronic liver diseases and COVID-19 from 13 Asian countries, 43 (18.9%) with cirrhosis and 185 (81.1%) without. Forty-three percent of patients without cirrhosis showed an acute liver injury and 20.6% of those with cirrhosis had either acute-on-chronic liver failure (ACLF), 11.6%, or acute decompensation (9%); liver injury progressed to death in 43% of cases with decompensated cirrhosis [17]. Other studies performed to assess the rate of cirrhotic patients who developed acute liver decompensation during COVID-19, showed percentages ranging from 9.3 to 61.5%, most probably reflecting differences in sample selection [14, 17–20]. In these studies, jaundice, worsening of ascites, variceal bleeding, hepatic encephalopathy, and spontaneous bacterial peritonitis were the more frequent clinical events first highlighting acute decompensation [14, 17–20].

Marjot et al. [18] evaluated the impact of COVID-19 on 745 patients with pre-existing CLD, 386 with and 359 without liver cirrhosis. The fatality rate was 8% in

those without cirrhosis and 32% in cirrhotic patients ($p < 0.001$), with an increasing trend according to the original Child–Pugh class, 19% in class A, 35% in class B and 51% in class C, the main cause of death being respiratory failure (71%) [18]. The factors independently associated with death in this CLD cohort were an older age, alcoholic etiology, and presence of cirrhosis (either in class Child–Pugh A, B or C). Acute hepatic decompensation occurred in 46% of patients with cirrhosis, of whom 21% had no respiratory symptoms [18].

In a multi-center USA observational cohort study on 867 adult CLD patients with COVID-19, Kim et al. [19] reported a severe course of COVID-19 in 61.7% of cases and a 14.0% all-cause mortality, alcohol-related liver disease (ALD) (HR = 2.42, 95% CI 1.29–4.55), decompensated cirrhosis (HR = 2.91, 95% CI 1.70–5.00) and presence of HCC (HR = 3.1, 95% CI 1.53–7.16) being the liver-specific independent predictors of mortality. Considering that patients with ALD often develop immune system dysregulation that can lead to the production of proinflammatory cytokines, the authors speculated that a supervening cytokine storm induced by SARS-CoV-2 infection may result in an increased risk of poor survival and mortality. This association raises further concern regarding the increase in alcohol consumption during the COVID-19 pandemic. This study also showed a relationship between SARS-CoV-2 infection and the advanced stage of cirrhosis, liver decompensation and mortality [19].

A large-scale collaborative registry project has been organized to collect data on COVID-19 patients with chronic hepatitis at any stage or liver transplanted, both hospitalized and managed in the community. The latest update of this study includes 957 patients, of whom 63% were men and 88% have been hospitalized [20]. The median age was 59 years. Among the 957 patients, 425 had liver cirrhosis and 372 lacked clinical, laboratory and ultrasound sign of cirrhosis. Alcohol intake was the major etiologic factor (31% of cases), followed by NASH (22%), HCV or HBV infection, and autoimmunity. Among cirrhotic patients, 46% experienced a new episode of ascites, others developed encephalopathy (26%) or variceal hemorrhage (4%) and 160 underwent liver transplantation. The rate of hospitalization, admission to intensive care unit (ICU) and invasive ventilation was similar among non-cirrhotic, transplanted, and cirrhotic patients, but the fatality rates were 7%, 19%, and 32%, respectively [20].

Some of the above-mentioned studies also showed that patients with cirrhosis and COVID-19 developed ACLF with a frequency ranging from 4.8 to 34.6%, a high variability probably reflecting differences in sample selection [14, 17–20]. Worth of mention is the possibility that hepatotoxic effects due to drug-to-drug interactions might have negatively impacted on patients' outcome, particularly during the 1st wave of COVID-19, when various therapies with no scientific basis were attempted worldwide.

Information on the course of the diseases and outcome of NALFD patients with COVID-19 is limited. In a study by Ji et al. [21], compared with non-NAFLD patients those with NAFLD had a higher risk of COVID-19 progression, 44.7% of 76 patients versus 6.6% of 126 ($p < 0.0001$), higher frequency of abnormal liver function, 70% vs 11.1% ($p < 0.0001$) and a longer SARS-CoV-2 shedding time (17.5 ± 5.2 days vs 12.1 ± 4.4; $p < 0.0001$) [21].

Only a few data are currently available on the interaction between of COVID-19 and autoimmune hepatitis (AIH). A study performed in northern Italy reported that AIH patients under immunosuppressant treatment have a similar prevalence of COVID-19 than those in the general population of the same geographic area [22]. In a phone-based survey in Flanders, Belgium, Verhelst et al. [23] found that 7 out of the 85 AIH patients investigated declared symptoms compatible with Covid-19 suggesting that COVID-19 pandemic should not stop immunosuppressive treatment [23]. Finally, a small study reported that COVID-19 in patients with AIH treated with immunosuppression appears to have a disease course like that observed in general population [24]. Currently, EASL, AASLD, and APASL guidelines suggest great caution in withdrawing immunosuppression in AIH patients with COVID-19, as it may lead to hepatitis flares.

Racial factors influencing COVID-19 outcome have been analyzed in a few studies. Among patients with CLD and COVID-19, Kim et al. [19] found Hispanic ethnicity independently associated with the risk for severe COVID-19 (OR = 2.33, 95% CI 1.47–3.70. Comparing three groups of patients, 224 Hispanic, 297 non-Hispanic white, and 276 non-Hispanic black, Adeniji et al. [25] observed that the Hispanic group had a higher rate of hospitalization than the non-Hispanic white group (OR = 1.7, CI 1.2–2.4), but no significant difference in the severity of the diseases (oxygen requirement, mechanical ventilation, admission to ICU and mortality) was observed between these three groups of patients. The limited knowledge provided by these studies does not allow to express an opinion on the influence of race/ethnicity on the outcome of CLD patients with COVID-19 [25].

Fatality rate in patients with CLD and COVID-19

The data from the articles that we believe mainly directed to identify the fatality rate in patients with CLD and COVID-19 will be analyzed in this chapter.

Reports from cirrhosis registries operating during the COVID-19 pandemic (Secure Cirrhosis Registry, COVID-Hep.net, COVID Cirrhosis.org, and

COVID-Cirrhosis-CHESS) found a relationship between SARS-CoV-2 infection, advanced stage of cirrhosis (MELD > 14, Child-Turcotte-Pugh C), liver decompensation and mortality [26]. In a multicenter study on 2,780 COVID-19 patients, Singh et al. [27] identified 250 (9%) patients with preexisting CLD; in this study the fatality risk for COVID-19 was higher for patients with CLD than for those without, a difference remained significant after the propensity matching between patients with and without liver diseases (RR = 3.0, 95% CI 1.5–6.0; $p = 0.001$). An analysis performed in the UK on 17 million patients from the OpenSAFELY platform showed that chronic liver disease was a risk factor for in-hospital death from COVID-19 (HR|= 2.3995% CI 2.06–2.77) [28]. A previously mentioned Italian study reported that 17 (34%) out of 50 patients with cirrhosis died 4–13 days (median 10 days) after COVID-19 was diagnosed, mortality being independently predicted by the severity of both COVID-19 and liver diseases [16]. The COVOCA study [29] is a retrospective observational cohort study involving 18 COVID-19 centers throughout Campania Region in southern Italy; among the 618 patients hospitalized for COVID-19 the fatality rate was 23.1%. At a multivariable logistic analysis, presence of chronic hepatitis was strongly associated with COVID-19 mortality (OR = 5.88, 95% CI 2.39–14.46; $p < 0.001$) [29]. An Asian multinational study found that cirrhotic patients with a Child-Turcotte-Pugh score of 9 or more at presentation were at higher risk for COVID-19-related mortality than those with a lower score [3]. In an American multicenter study, decompensated cirrhosis was identified as an independent risk factor for mortality in patients with liver cirrhosis and COVID-19 [19].

Some investigators failed to show an increased fatality rate in patients with CLD and COVID-19, even in the presence of cirrhosis. Bajaj et al. [30] investigated 37 patients with cirrhosis and COVID-19 in comparison with 108 with COVID-19 alone and 127 with cirrhosis alone, collected in seven participating centers. Patients with cirrhosis and COVID-19 had a higher fatality rate than those with COVID-19 alone (30% vs 13%, $p = 0.03$), while compared with those with cirrhosis alone the difference did not reach statistical significance (30 vs 20%); it should be underlined, however, that a larger group of patients with CLD and COVID-19 would have allowed for a more balanced statistical analysis. In addition, Yip et al. [31] did not observe an association between past or present HBV infections and higher rates of liver injury and mortality in a territory-wide retrospective cohort study on COVID-19 patients performed in Hong Kong. We must consider all the published data as useful for formulating a conclusive opinion on this matter, but today the prevalent opinion is that liver cirrhosis a factor associated with COVID-19 mortality.

For an integrated assessment of the reciprocal negative interaction between CLD and COVID-19, we should consider that liver cirrhosis has been found associated with the development of serious complications of COVID-19, including ARDS, need of mechanical ventilation, shock, renal failure requiring organ replacement, need for extracorporeal membrane oxygenation, transfer in ICU and mortality [13, 19, 32–35].

Specific action of COVID-19 pandemic on HBV AND HCV chronic hepatitis

(a) **SARS-CoV2 pandemic has reduced the levels of care for HBV-related chronic hepatitis**

It has been estimated that half families living in low- and middle-income countries have become unable to access healthcare facilities for diagnosis, clinical evaluation, and treatment of HBV diseases during COVID-19 pandemic, mostly because of movement restrictions, reduced earnings for the loss of job, and patients' anxiety to get infected with SARS-CoV-2 [24].

Furthermore, there has been a worldwide consistent reduction in the number of healthcare facilities and healthcare personnel usually dedicated to patients with HBV or HCV infection, devolved to the assistance of patients with COVID-19 during the pandemic. A web-based survey performed by the members of the Italian association for the study of the liver (AISF) revealed that a quarter of the hepatology wards had become COVID-19 wards and that a quarter of outpatient hepatology services had been interrupted. In particular, the start of treatment of HBV infection was postposed in 23% of centers, and only 18% of patients with hepatocellular carcinoma and 32% of those with decompensated cirrhosis experienced continuity of service delivery [2].

In this regard, it should be emphasized that all international guidelines emphasize that nucleo(t)side therapy to suppress HBV replication in patients with HBsAg positive chronic hepatitis should start at the time of its first identification and therefore continued over time for the real risk of a dangerous reactivation in case of treatment discontinuation [36, 37].

Indeed, reactivation of HBV replication can also be induced by tocilizumab and corticosteroids, drugs often administered to patients with COVID-19 [38].

Another dramatic consequence of COVID-19 pandemic has been its detrimental effect on the universal vaccination programs against hepatitis B in low- or middle-income countries. The Institute for Health Metrics and Evaluation revealed that the overall global vaccination coverage levels observed in 2020 has dropped

at the levels of 1990s, losing 25 years of progress in just a few months, a reduction that could increase the transmission rates of HBV infection [39].

The reduction in prevention, diagnosis and treatment of chronic hepatitis B induced by COVID-19 pandemic will postpone the goal of worldwide eradication of HBV infection by many years. Hence, the healthcare organizations of all nations should ensure the greatest possible attention to the management of HBV hepatitis during COVID-19 pandemic not to lose in a short time the advantages obtained with a long period of struggle, great sacrifices, and considerable costs.

(b) **SARS-COV-2 pandemic could slow down HCV eradication**

WHO set a goal for HCV elimination as public-health issue by 2030, goal hardly achievable after 2 years of COVID-19 pandemic. A standardized analysis led in Italy and United Kingdom, studied the impact of COVID-19 on HCV infection considering two hypothetical scenarios, one in which HCV treatment was going on without interruption and another one in which HCV treatment has been delayed by 3, 6, 9 or 12 months, having as outcomes the number of incident cases of advanced liver disease and the number of HCV related deaths on 1000 standardized patients in a perspective view of 5 years. In Italy the number of cases of ALD would have increased by 2, 5, 7 and 10 times in 3, 6, 9 and 12 months of delay in diagnosis, respectively, as well as the number of deaths. For the UK, ALD cases would have increased by 3, 8, 12 and 17 times in 3, 6, 9 and 12 months of delay in diagnosis, respectively, as well as the number of deaths [40].

The effect of the delay in accessing care for patients with chronic HCV infection due to the COVID-19 pandemic was also evaluated in another mathematical model aimed at hypothesizing the worldwide possible reduction in the number of patients treated and the changes in the number of cases with HCV liver cancer and of liver-related deaths, following a 3 month, 6 month, or 1 year delay in the hepatitis elimination programs [41]. In the "1 year delay" scenario 746,000 patients would start treatment with a delay of one year, with an excess of 44,800 (95% CI 43,800–49,300) cases of HCC and 72,300 (95% CI 70,600–79,400) deaths from liver disease in the period 2020–2030. A shorter delay would result in fewer events, 50,600 excess deaths predicted under the 6-month delay scenario and 25,300 excess deaths under the 3 month delay scenario. To similar conclusions they come Buti et al. who performed an analogous simulation using clinical data of a Spanish cohort of 15,859 patients: an 18 month delay in HCV diagnosis and treatment would increase the number of HCC, decompensated cirrhosis, and liver-related deaths in this series, by 73, 118 and 117 cases, respectively [41].

The scarce stocks of COVID-19 vaccines destined for low- to middle-income areas will not help to achieve the many goals that medicine has set itself in recent years, including the worldwide elimination of HCV infection as public health problem by 2030. In addition, recent estimates indicate that only a few countries are in line with the WHO program.

About HCV treatment during COVID-19 pandemic, ASLD guidelines recommend evaluating whether chronic HCV patients are infected with SARS-CoV-2 before treating them with DAAs during COVID-19 pandemic. In fact, DAAs therapy is highly recommended for patients with HCV chronic infection lacking SARS-CoV-2, while for those SARS-CoV-2 positive it should be deferred until the nasopharyngeal swab has become stably negative [42]. HCV patients who have developed COVID-19 while on therapy with DAAs should be strictly monitored, mainly for possible interactions with COVID-19 medications.

Influence of SARS-COV-2 pandemic on liver transplantation sector

Liver transplantation (LT) is a life-saving procedure for patients with decompensated cirrhosis not manageable with medical therapy, for those with acute liver failure, and for selected patients with HCC. The liver transplant sector has faced significant hardships during COVID-19 pandemic, A significant decrease in organ donation and liver transplantation have been reported by many worldwide organ-sharing organizations since the start of COVID-19 pandemic [3, 33, 42, 43].

As an example, 149 centers affiliated with European Liver Transplant Registry (ELTR) were recruited for an internet-based survey to investigate the impact of COVID-19 on liver transplant activity: 6% of the centers temporarily halted all transplant activity due to lack of donors and/or other collateral effects of the pandemic, nearly two thirds of centers used more strict criteria to admit patients to liver transplantation and nearly one third did not apply COVID-19 related restriction [44].

A main reason for the significant decrease in organ donation and liver transplantation has been identified in the strong organizational pressure exerted by the spread of COVID-19 pandemic on the healthcare systems of most countries, which resulted in the need for reserving ICU units, other healthcare facilities and healthcare staff for COVID-19 patients. Other main reasons for reducing LT during COVID-19 pandemic have been identified in the increased mortality rate of patients undergoing elective surgery while incubating COVID-19 infection, the potential risk of starting

immunosuppressive therapies during the COVID-19 pandemic, the patients' fear of becoming infected during their stay in hospital or in other health facilities, and in lockdown measures.

COVID-19 has also exerted its impact on patients waitlisted for liver transplantation, decreasing their opportunities to be transplanted and posing significant mortality risk. To provide them with a wider opportunity for liver transplantation, transplant centers should adapt their strategies to the COVID-19 emergency, increasing safety within the hospital and adopting appropriate communication systems with patients. During each hospital stay, liver transplant recipients and those on the transplant list must have dedicated SARS-CoV-2-free healthcare personnel and SARS-CoV-2-free dedicated accesses, paths, outpatient facilities, wards, and operation rooms, far away from the areas dedicated to the assistance of patients with SARS-CoV-2 infection.

The above-mentioned report from ELTR gave other interesting information on the transplant activity of the 149 affiliated transplant centers. All centers declared they did not transplant livers from donors who experienced SARS-CoV-2 infection and only 3% of them admitted they could consider this option only in case of urgency. Centers performing LT from living donors have delayed LT for any SARS-CoV-2 donor positivity of at least 2 weeks after donors' complete recovery, and of at least four weeks in some centers [37]. In the same study, the incidence of symptomatic COVID-19 infection was significantly higher in LT candidates (57 of the 5,440, 1.05%), than in LT recipients (36 of the 244, 0.3%) ($p < 0.001$). Out of patients with symptomatic COVID-19, 10 of the 57 (18%) LT candidates and 36 of the 244 (15%) LT recipients had died of COVID-19 ($p < 0.001$) [37].

Telemedicine for liver patients during COVID-19 pandemic

In the last 20 years there has been a growing use of telemedicine in clinical practice [4, 45], with a sharp surge in the last 2 years, due to the lockdown and other social distancing measures made necessary to stem COVID-19 pandemic. An AASLD expert panel consensus statement and an EASL—ESCMID position paper have recommended the use of remote assistance during the COVID-19 pandemic for both patients with CLD, those in the waiting list for liver transplantation and liver transplant recipients [46, 47].

The COVID-19 pandemic has had a negative impact on the care of patients with CALD, delaying diagnosis, elective procedures and treatment decision during its waves and forced the liver units to dispose of the arrears between one wave and another [48]. A wider use of telemedicine will be useful in reducing or preventing these negative events from happening in subsequent waves of the pandemic. It has also been pointed out that the use of telemedicine is useful in simplifying the management of liver transplant recipients and in improving their outcome [46, 47, 49–52], as well as allowing a multi-disciplinary approach for early diagnosis and monitoring of HCC in cirrhotic patients [53]. However, a poor ability to use internet and other audiovisual media can be an obstacle to a wide use of telemedicine, as verified by a retrospective cohort study performed by Wegermann et al. [49] showing a low ability of the elderly and non-Hispanic blacks to use telemedicine.

Strengthened by the experiences gained during the COVID-19 pandemic, telemedicine could be included in ordinary integrated programs of prevention, diagnosis, and clinical-therapeutic follow-up, and will be of extraordinary utility in rural areas and for people who have difficulty in reaching a liver unit.

Conclusions

The first defenses placed to counter COVID-19 pandemic have been local or national lockdowns, social distancing, use of face masks and frequent hand washing, defenses rigorously applied in some countries, intermittently in many others and never in some low-income areas. Consequently, SARS-CoV-2 infection has continued to spread and to cause countless hospitalizations and, up to date, 6 million deaths worldwide. This has required significant changes in healthcare organization in all nations and forced many clinical facilities and health care professionals, originally dedicated to different pathologies including chronic hepatitis, to be converted to the needs of COVID-19. The availability of effective vaccines and drugs directed against SARS-CoV-2 is recent history almost exclusively concerning nations with good health services and sufficient economic resources.

Focusing on CLD, COVID-19 pandemic has induced a delay in screening procedures with shift of first diagnosis in the more advanced stages of the illness and a remarkable reduction in laboratory and clinical checks, and in surveillance for HCC, esophageal varices, and encephalopathy. This has worsened the clinical course of the disease in many patients, as testified by the correlation between COVID-19 and advanced cirrhosis, liver decompensation and mortality.

Several reports have underlined a significant worldwide reduction in number of liver transplantation attributable to COVID-19 pandemic, which subtracted from this sector wards, operating rooms, outpatients' facilities, and healthcare personnel. To maintain an adequate level of activity, centers performing cadaveric or living LT should increase the security within their center, ensuring healthcare personnel vaccinated against SARS-CoV-2 and free of this infection, dedicated entrances, pathways, wards operating rooms and outpatients' sectors far away from the areas intended

for SARS-CoV-2 infection. It is also advisable to carry out a continuous careful vigilance that those who for any reason enter a LT center have a behavior suitable to avoid becoming infected and passing SARS-CoV-2 infection to others. In addition, doctors and psychologists should advise all subjects who are expected to enter a transplant center to undergo a complete cycle of vaccination against COVID-19. Adopting the necessary precautions, the activity of the liver transplant centers could continue without decline.

During COVID-19 pandemic, HBsAg screening and start of treatment to suppress HBV replication have been delayed in a quarter of liver centers of high-income countries and stopped in many low- or middle-income countries, with the risk of dangerous and sometime life-threatening HBV reactivation. Furthermore, an appropriate assistance was provided to less than one-third of patients with HCC or with decompensated cirrhosis during COVID-19 pandemic. Another unfavorable effect of COVID-19 pandemic is the strong damage to the universal vaccination programs against hepatitis B in low- or middle-income countries, where the coverage level has shrunk considerably in 2020, destroying 25 year work in a short time and increasing the risks of HBV transmission.

Similarly, the goal of achieving the elimination of HCV infection as a worldwide public-health issue, predicted for 2030 by the WHO, should now be considered unattainable, due to the delay in accessing to screening and DAA-treatment induced worldwide by COVID-19 pandemic.

COVID-19 pandemic has caused and will continue to cause for years serious damage to the various sectors of medicine, including that of chronic hepatitis which has lost in a short time the beneficial effects of several years of study, research and of clinical and technological application, as well as of considerable financial investments. Wider use of telemedicine could reduce the negative impact of COVID-19 pandemic. Today, our hope is based on the commitment of health organizations to adequately support the whole sector of liver disease and on the worldwide adequate distribution of effective vaccines against SARS-CoV-2 infection.

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