Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Liver Transplantation 3 (2021) 100026

Contents lists available at ScienceDirect

Journal of Liver Transplantation

journal homepage: www.elsevier.com

Review

COVID-19 in liver transplant recipients

Juliana Piedade[a,b,c], Gustavo Pereira[a,b,c,*]

[a] Gastroenterology and Hepatology Unit, Bonsucesso Federal Hospital, (Ministry of Health), Avenida Londres 616 (21041-030), 3rd floor, Bonsucesso, Rio de Janeiro, RJ, Brazil
[b] Hepatobiliary Diseases and Liver Transplantation Division, Americas Medical City, Rio de Janeiro, Brazil
[c] Estácio de Sá University, School of Medicine, Rio de Janeiro, Brazil

ARTICLE INFO

Article History:
Received 7 July 2021
Accepted 21 July 2021
Available online 22 July 2021

Keywords:
COVID-19
Immunosuppressive agents
Liver transplantation
COVID-19 drug treatment
Vaccination

ABSTRACT

Coronavirus disease 2019 (COVID-19), an infection caused by severe acute respiratory syndrome coronavirus-type 2 (SARS-CoV-2), has emerged as a serious threat to public health. Liver transplant (LT) recipients may be at increased risk of acquisition of SARS-CoV-2 infection and higher morbidity and mortality due to constant contact with health-care services, the use of immunosuppressants and frequent comorbidities. In the first part of this review we discuss (1) the epidemiology and risk factors for SARS-CoV-2 infection in LT recipients; (2) the clinical and laboratory features of COVID-19 in this specific population, highlighting differences in presenting signs and symptoms with respect to general populations and (3) the natural history and prognostic factors in LT recipients hospitalized with COVID-19, with particular focus on the possible role of immunosuppression. Thereafter, we review the potential therapeutic options for COVID-19 treatment and prevention. Specifically, we give an overview of current practice in immunosuppressant regimen changes, showing the potential benefits of this strategy, and explore safety and efficacy issues of currently approved drugs in LT recipients. The last topic is dedicated to the potential benefits and pitfalls of vaccination.

Introduction

In December 2019 a novel Coronavirus designated severe acute respiratory syndrome coronavirus 2 (SARS CoV-2), responsible for a clinical condition named COVID-19, was first identified in Wuhan, China. Within a few months, the World Health Organization (WHO) declared a state of pandemic for COVID-19 [1]. About 20% of patients develop moderate to severe conditions and 5% progress to critical illness, the latter with a mortality rate reaching up to 49% [2]. Risk factors for worse prognosis including older age and the presence of comorbidities such as diabetes, hypertension, chronic kidney disease, morbid obesity, cardiovascular and chronic lung diseases were subsequently identified [3].

Initially, most studies did not include transplant recipients as a distinct population. However, this population has plenty of the high-risk comorbidities and is frequently hospitalized, in contact with health care assistance and under immunosuppression. Similar to other RNA respiratory viruses in immunosuppressed patients, SARS-CoV2 may present atypical and attenuated symptoms of infection, often leading to late presentations and missed diagnoses [4]. In short, COVID-19 infection could be a potential threat to transplant recipients and its clinical picture, immunosuppression management, prognosis and prophylaxis must be well understood. The aim of this study was to characterize COVID-19 evolution in patients who had previously received a liver transplant (LT).

Risk-factors associated with SARS-CoV2 infection in LT recipients

According to the literature, solid organ transplant (SOT) recipients have an increased risk of acquiring COVID-19 due to chronic immunosuppression [5]. More specifically, recent transplantation and kidney transplantation patients are more susceptible to SARS-CoV2 infection [6]. Considering that early post-transplant patients require higher doses of immunosuppressants and that liver transplant recipients usually require less immunosuppression than other forms of SOT, one can conclude that the risk of acquiring COVID-19 is immunosuppression dose dependent.

Abbreviations: ACE2, angiotensin-converting; CI, calcineurin inhibitors; CI, confidence interval; DILI, drug-induced liver injury; ECMO, extracorporeal membrane oxygenation; GI, gastrointestinal; HR, hazard ratio; ICU, intensive care unit; IL-6, interleukin-6; IS, immunosuppression; LT, liver transplant; MELD, Model for End-Stage Liver Disease; MMF, mycophenolate mofetil; OR, odds ratio; RCT, randomized controlled trial; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; SOT, solid organ transplant; ULN, upper limits of normal; WHO, World Health Organization

* Corresponding author at: Gastroenterology and Hepatology Unit, Bonsucesso Federal Hospital, (Ministry of Health), Avenida Londres 616 (21041-030), 3rd floor, Bonsucesso, Rio de Janeiro, RJ, Brazil.
E-mail addresses: pereira.gustavo@estacio.br, gustavo.pereira@prestadores.americasmc.com.br (G. Pereira).

https://doi.org/10.1016/j.liver.2021.100026

Male patients are more prone to develop acute respiratory distress syndrome and to progress to more severe outcomes [7]. Additionally, according to Colmenero et al. [5], the incidence rate of SARS-CoV2 infection increases in older people, particularly beyond 60 years of age. In this robust Spanish cohort, none of the patients had been infected by the liver donor. Lastly, a history of previous or active cancer, such as being transplanted for hepatocellular carcinoma, or having any cancer at the moment of COVID-19 diagnosis, was associated with a poor outcome [7].

Clinical picture

The vast majority of LT recipients are symptomatic and demonstrate radiologic evidence of COVID-19 on either chest x-ray or chest computed tomography [8]. Similar to the general population, the most common self-reported symptoms at the time of diagnosis were fever, cough, dyspnea, fatigue and myalgia. Anosmia and dysgeusia in turn were not frequently reported. In contrast, the proportion of patients with gastrointestinal (GI) symptoms, which include abdominal pain, diarrhea, nausea and/or vomiting, was higher among LT recipients than among the entire population [5,7,9,10]. **Table 1** describes in detail the proportion of symptoms related to COVID-19 in LT recipients according to the literature.

Belli et al. confirmed that GI symptoms, especially diarrhea, were at least twice as common in LT recipients than in the general population and proposed an association with the use of mycophenolate mofetil (MMF) [9]. Consequently COVID-19 should be one differential diagnosis in immunosuppressed patients with GI symptoms only, and SARS CoV-2 testing should be promptly considered. When considering time from liver transplantation, the terms long and short are adopted to distinguish patients who have been transplanted for more or less than five years, respectively. Becchetti et al. [7] compared both groups and concluded that of those symptoms at presentation, fever and dyspnea were more frequent among long-term recipients (91% vs. 63% and 59% vs. 29%, both $p < 0.05$, respectively). It might be possible that greater immunosuppression attenuates typical COVID-19 symptoms.

Among laboratory data, blood count, coagulation profile, serum biochemical tests including renal and liver function, creatine kinase and lactate dehydrogenase, myocardial enzymes, interleukin-6 (IL-6), serum ferritin, d-dimer and procalcitonin were analyzed in most COVID-19-related studies. Lymphocytopenia has been reported to be predictive of poor outcomes not only in LT recipients but also in non-transplanted COVID-19 patients [3,7,10]. Inflammatory biomarkers have been associated with severe disease. Higher values of procalcitonin and C-reactive protein levels have been described in patients requiring mechanical ventilation [10]. Alteration in liver enzymes can occur but are mostly found in hospitalized patients whose immunosuppression was decreased, exerting no impact on outcome [7].

Management of COVID-19

Management of LT recipients with COVID-19 has focused on 2 strategies: (1) reduction or withdrawal of immunosuppressive drugs used for the prevention of allograft rejection and (2) the use of drugs aimed at interfering with viral replication (e.g. Remdesivir) and inflammatory responses (e.g. high-dose corticosteroids) as well as immunomodulatory agents (e.g. Tocilizumab) as has been proposed in general populations. **Table 2** summarizes the data in the largest cohorts of LT recipients with COVID-19 [5,7,9,11–13]. Overall, data on more than 800 LT recipients with COVID-19 were reported. The majority of data derives from centers from the USA and Europe. Median time from LT to diagnosis of SARS-CoV-2 infection ranged from 3.8 to 8.75 years and only a small proportion of patients (less than 20%) received a liver graft in the previous 12 months.

Changes in immunosuppression

Immunosuppression and SARS-CoV-2 infection may have complex interactions. During the initial phase of infection, characterized

Table 1
The proportion of symptoms related to COVID-19 in LT recipients according to the literature.

Study, year	Origin	Patients (*n*)	Fever	Cough	Dyspnea	Fatigue or Myalgia	Anosmia or Dysgeusia	Gastrointestinal symptoms
Becchetti et al., 2020	Europe	57	44 (79%)	31 (55%)	26 (46%)	32 (56%)	4 (7%)	18 (33%)
Belli et al., 2021	Europe	243	190 (78%)	143 (59%)	82 (34%)	90 (37%)	21 (9%)	55 (23%)
Colmenero et al., 2021	Spain	111	83 (75%)	78 (70%)	46 (41%)	NA	NA	38 (34%)
Dumortier et al., 2021	France	91	55 (60%)	51 (56%)	45 (50%)	28 (31%)	9 (10%)	25 (27%)

Data expressed as *n* (%). NA: not available.

Table 2
Treatment of COVID-19 in LT recipients among different series.

	Patients (n)	Time from LT (years) (median)	Immunosuppression modification (Reduction or withdrawal)		Specific treatment		
			Calcineurin inhibitors	Antimetabolites	Corticosteroids	Remdesivir	Tocilizumab
Lee et al., 2020	38	3.8 (0.02–28.2)	Reduction: 15/24 (63%)	Reduction:13/13 (100%)	5/24 (21%)	NA	NA
Beccheti et al., 2020	57	6 (2–13)	Reduction: 24% (12/50) Withdrawal: 14% (7/50)	Reduction: 4% (1/26) Withdrawal: 31% (8/26)	19 (35%)	0	1 (2%)
Webb et al., 2020	151	NR	NR	NR	0 (0%)	6 (4%)	2 (1%)
Rabiee, Sadowski et al 2020	117	4 (11)	Reduction: 21/73 (29%)		4 (4%)	3 (3%)	NA
Colmenero et al., 2021	111	8.75 (3–14)	NR	NR	12 (13%)	1 (1%)	15 (16%) Mostly in severe cases
Belli et al., 2021	243	8 (3–15)	Reduction: 38/162 (23%); Withdrawal: 16/162 (10%)	Withdrawal: 35/119 (29%)	34(13%)	1 (0.5%)	15 (6%)
Dumortier et al., 2021	91	7,1 (2,8–14)	Withdrawal: 7 (13%)		6 (9%)	2 (3%)	1 (2%)

Data expressed as *n* (%). NA: not available.

Table 3
Predictors of mortality in LT recipients with COVID-19.

Study, year	Origin	Patients (n)	Risk-factors of mortality	Comments
Becchetti et al., 2020	Europe	57	History of previous or active cancer, such as being transplanted for HCC. Having cancer at COVID-19 diagnosis	Patients infected early after liver transplantation did not have a worse outcome
Webb et al., 2020	18 countries	151	Advanced age Increased baseline creatinine concentration Presence of non-liver cancer Presence of comorbidities	The type of immunosuppressants used and the time from transplantation were not independently associated with mortality.
Belli et al., 2021	Europe	243	Advanced age Serum creatinine >2 mg/dL, (trend)	Neither a specific comorbidity nor a combination of comorbidities emerged as independently associated with death. Use of TAC was confirmed as independently associated with a reduced mortality risk
Colmenero et al., 2021	Spain	111	Older age, male gender, increased comorbidities, raised D-dimer, serum ferritin and lymphocytopenia were associated with severe COVID-19	Adjusted mortality rates in patients older than 60 were similar in LT recipients and in the general population
Dumortier et al., 2021	France	91	Age Serum baseline creatinine (trend)	Independent risk factors for severe disease: dyspnea and fever

HCC: hepatocellular carcinoma; LT: liver transplantation; TAC: Tacrolimus

by viral replication, immunosuppression may lead to higher viral loads and consequently, potentially more severe disease. This has particularly been demonstrated in infections with other respiratory viruses [4]. However, in a later phase of infection, in which an intense inflammatory response ensues, a reduction in immune response could in theory be beneficial. Additionally, the type of immunosuppressant may be of concern, as CI and MMF, the most commonly used class of drugs, have distinct mechanisms of action. Among LT recipients, calcineurin inhibitors were the most common type of immunosuppressant drug, used by 60 to 100% of patients, followed by antimetabolites (46–60%; MMF in the vast majority of cases). Corticosteroids were used by 17 to 44% of patients, according to previously published series.

The baseline immunosuppression (IS) regimen may be of importance in prognosis. MMF use prior to diagnosis was associated with a higher probability of severe COVID-19 development. Patients using MMF at the time of diagnosis had an almost 4-fold higher probability of severe COVID-19 (defined as admission to the intensive care unit, mechanical ventilation, and/or death) than those who did not (HR 3.94, 95% CI 1.59–9.74), even after adjustment for other demographic and clinical variables, and for the Charlson comorbidity index [5]. This deleterious effect was particularly notable among those taking a daily dose higher than 1000 mg of MMF. A potential reversal of this deleterious effect through changes in the immunosuppression regimen is noted, as withdrawal of MMF in those taking full doses (i.e. 2000 mg/day) was associated with a trend toward less frequent development of severe COVID-19. On the other hand, the use of Tacrolimus may exert a beneficial effect. In a multicentric prospective European study, among hospitalized patients, the use of Tacrolimus was independently associated with lower mortality (HR 0.55; 95% CI, 0.31 – 0.99) [9]. This protective effect was particularly notable in older patients and in those with chronic kidney disease, two conditions associated with lower survival during the course of COVID-19. In these subgroups, mortality was dramatically lower among patients taking Tacrolimus, and comparable to patients without these comorbidities. The potential relation between Tacrolimus serum levels and mortality was not reported.

Due to a potentially detrimental effect upon the clinical course of disease, immunosupression regimens were commonly altered to maintain immune system defence against SARS-CoV-2 and avoid graft rejection. Modifications after COVID-19 diagnosis were reported in 5 studies (Table 3). Reduction and withdrawal of CIs were reported in approximately 25 and 12% of patients respectively. MMF was withdrawn in approximately 35% of patients. Interestingly, reduction or withdrawal of current IS regimen was not associated with acute liver injury [13], severity of infection or mortality [7]. Additionally, acute rejection was uncommon among LT recipients with COVID-19, being reported in 7 patients (out of 457, incidence of 1.5%). Taken together, these data strongly suggest that changes in IS regimen are feasible and may be of benefit in hospitalized patients. Preference should be given to the reduction or suspension of MMF, and the maintenance of Tacrolimus. This may be associated with less severe forms of infection and lower mortality, without putting these patients at risk of allograft rejection. Finally, modifications in immunosuppression regimens should not be performed in outpatients once the clinical course in these individuals is benign and marked by low probability of complications and need for hospitalization.

Some notes of cautions are warranted when analyzing these informations. In the majority of studies, median time from LT to diagnosis of SARS-CoV-2 was greater than 5 years and only a small proportion of patients (less than 20%) was composed of very short-term LT recipients (patients who received a liver graft in the previous 12 months). Consequently, it is very likely that the majority of them were under a low level of immunosuppression, as evidenced by a higher proportion of individuals taking only one drug for IS and a small proportion of patients without any IS at all. It is debatable whether the same conclusions are valid for individuals in the very early post-LT period, who receive more vigorous immunosuppression regimens. Furthermore, none of the studies evaluated the risk of opportunistic infections in individuals with COVID-19, a complication that frequently occurs in the first year after transplantation that may be triggered by viral infections like cytomegalovirus [14].

More information in these very short-term LT populations is warranted. If results in terms of frequency and severity of COVID-19 as well as recipient morbidity and graft function are comparable to those reported so far, transplant centers may feel confident in keeping LT programs fully active. Conversely, if very short-term recipients turn out to have increased morbidity and/or mortality, one may decide to transplant only patients with an urgent need for LT (such as those with fulminant hepatic failure) or those with advanced disease (such as decompensated cirrhotic patients), who otherwise have either very low short-term survival in the absence of LT and/or a high mortality rate in case of acquiring SARS-CoV-2 infection.

Drugs against COVID-19

Many drugs with potential efficacy against COVID-19 were used in LT recipients. This may reflect uncertainty in the first months of management of COVID-19 and an attempt to act at different stages of disease, with antivirals used in earlier infection and for milder disease,

and immunomodulatory agents being used in later infection and for more severe cases. However, the majority of them were proved to be ineffective or even detrimental in the management of the disease. Currently, the most recommended drugs for COVID-19 are Remdesivir, high-dose Dexamethasone and Tocilizumab [15]. There are promising data with respect to Anti-SARS-CoV-2 monoclonal antibody combinations [bamlanivimab plus etesevimab [16]; casirivimab plus imdevimab [17] for outpatients at risk of disease progression, as well as Janus kinase inhibitors Baracitinib [18] and Tofacitinib [19] in hospitalized patients requiring oxygen supplementation, but there are no studies including LT recipients using these drugs so far.

Remdesivir is an antiviral agent capable of inhibiting RNA-dependent RNA polymerase with *in vitro* activity against SARS-CoV-2. In a randomized, placebo-controlled trial, use of Remdesivir has been associated with a reduction in the length of hospital stay and a lower probability of new oxygen supplementation, non-invasive or invasive ventilation or extracorporeal membrane oxygenation (ECMO) use, but not of mortality [20]. Adverse events were common, but not different from placebo groups (25 vs. 32%). Specifically, alterations in liver function parameters were uncommon, being reported in 6 and 11% of patients receiving Remdesivir and a placebo respectively. Of note, patients with increases in aminotransferases greater than 5 times the upper limit of normal (ULN) at baseline were excluded from the study. This may not be an entirely uncommon situation in an LT setting, as demonstrated in 2 studies in which the frequency of so-called severe acute liver injury (defined as AST and/or ALT > 5X ULN) was 4 and 8% [9,12]. Elevations in aminotransferases may be due to multiple causes. Cholangiocytes and, to a lesser extent, hepatocytes express angiotensin-converting enzyme 2 (ACE2) receptor, to which SARS-CoV-2 spike protein binds in an initial step during cell entry [21]. Other potential contributing factors directly related to infection include systemic inflammatory response, hepatic congestion and release from extrahepatic tissues, like muscle. [22]. Lastly, patients treated for COVID-19 may develop drug-induced liver injury (DILI).

Antimicrobials/anti-infectives are the most common class of drugs associated with DILI in general populations [23], and antivirals may be an important cause of DILI among some populations, like individuals with HIV infection [24]. Incidence of DILI in LT patients has been reported to be as high as 2%, a frequency much higher than reported in general populations [25]. Patients with chronic liver disease and LT may be at increased risk of developing DILI (mainly due to alterations in drug pharmacokinetics, metabolism pathways, and drug-drug interactions) [26], and have lower survival when compared to patients without pre-existing liver disease who develop DILI [27]. Taken together, these data point to potential limitations for Remdesivir usage in LT recipients and have accounted, together with regulatory issues, for a very low percentage of COVID-19 patients using this drug in published series.

Dexamethasone has been recommended for hospitalized patients receiving oxygen supplementation or mechanical ventilation, as a large RCT has shown a reduction in 30-day mortality (29 and 23% in patients receiving mechanical and oxygen ventilation vs. 41 and 26% in patients in control groups) and in the need for mechanical ventilation among those receiving supplemental oxygen (RR 0.88, 95% CI 0.80 − 0.97) [28]. Previous diagnosis of diabetes mellitus was common, being reported in 24% of patients, and despite this significant proportion of individuals and a high-dose dexamethasone regimen for a median of 7 days, development of hyperglycaemia and other common complications of corticosteroids, like gastrointestinal bleeding, were infrequent. These results may be of interest in LT recipients, as they may encourage the use of high-dose steroids in patients with respiratory insufficiency as a preferred or solely immunosuppressive regimen. Corticosteroids were used at therapeutic dosages in a minority of LT patients (4 to 35%), which may either suggest a measure of caution to avoid stimulating viral replication, or that patients were not ill enough to merit intensive therapeutic measures. This however, is unlikely, as a substantial number of patients needed respiratory support in LT published series. Of note, very few patients with previous liver disease were included in the trial (approximately 2%), and frequency and severity of subsequent infections were not reported. In general populations with COVID-19, development of a subsequent infection was common, being observed in 24% of patients. The majority of infectious episodes were due to bacteria (83%, most commonly *Acinetobacter spp.*), but fungal (mainly *Candida sp.*) and viral superinfections were also reported. Of concern, patients who developed superinfection were at increased risk of death (OR = 3.54, 95% CI 1.46 − 8.58) [29]. This may be of particular concern as SOT patients are at increased risk of bacterial and fungal infections, and the potential effect of this high-dose corticosteroid in terms of frequency and severity of infections is unknown. SOT recipients have been shown to be at high risk of invasive fungal infections, especially *Aspergillus fumigatus*, in a recently published observational study [30].

Tocilizumab, an IL-6 inhibitor, was evaluated in hospitalized patients with COVID-19 and was associated with a reduction in the need for mechanical ventilation in patients not requiring non-invasive or invasive ventilation and SpO2 ≥ 94% at baseline, without effects on mortality [31]. Of note, the majority (80%) of patients in both arms of this RCT received corticosteroids and approximately 50% also received remdesivir. No data with respect to the proportion of patients with pre-existing liver disease was provided. Frequency of bacterial infections and septic shock were comparable between Tocilizumab and control groups (10 vs. 13% and 2 vs. 2.4% respectively). A second study, including patients with a SpO2 ≤ 93% or PO2 / FiO2 ratio < 300 mm Hg, did not show benefits in terms of mortality in the entire group [32]. Nevertheless, among patients not receiving mechanical ventilation, occurrence of a composite endpoint including death, initiation of mechanical ventilation or ICU transfer was less frequent in the tocilizumab group. The proportion of patients receiving concomitant treatment with corticosteroids and antivirals was lower in the tocilizumab group (19 vs. 28% and 24 vs. 29%), which may have contributed to the negative results of the trial. Infections and liver events (defined according to aminotransferase and bilirubin levels) were reported in 38 and 2% of patients receiving Tocilizumab, a frequency comparable to that described in the placebo group. Nevertheless, similar to Remdesivir, Tocilizumab usage is contraindicated in patients with aminotransferase levels > 5X ULN. Five studies reported the frequency of Tocilizumab use in LT recipients, with great variability among them. Overall, 5% of LT patients received treatment with Tocilizumab. No specific information is available in this population with respect to safety. The role of tocilizumab in management of COVID-19 remains debatable in general as well as in liver transplant populations.

Clinical outcomes in LT recipients with COVID-19

Most of the largest studies [7,9,12] describe hospitalization rates in LT recipients around 80% with mortality rate ranging between 12 and 23%. These values are in agreement with the general population (mortality rate 15−22%) [33,34].

Webb et al. included 151 LT recipients and 627 non-LT recipients from 18 different countries, all with laboratory-confirmed SARS CoV-2 infection. The proportion of hospitalized patients was similar between the LT cohort and the comparison group (82% vs. 76%, p = 0.10). In contrast, the proportion of patients admitted to the intensive care unit (ICU) and given invasive ventilation were higher in LT patients than in those who had not received a LT, 28% vs. 8%, $p < 0.001$ and 20% vs. 5 %, $p < 0.0001$, respectively. Lastly, liver transplantation was not associated with an increased risk of mortality, 19% vs. 27 %, p = 0.046, which is concordant with the literature [12]. The dominant cause of death in both groups was lung-related and no

Table 4
Vaccination against COVID-19 in SOT.

		Vaccine		Efficacy		Adverse effects	
SOT	Patients (*n*)	Doses	Type	Overall	LT	Local	Systemic
Boyarsky et al, 2021	658 [LT: 129 (20%)]	2	BNT162b2: 51%; mRNA-1273: 40%	D1: 15%; D2: 54%	D1: 32%; D2: 80%	NA	10 (17%)
Marion et al, 2021	950 [367 received 2 doses and tested (LT: 58 -16%)]	1 dose: 376; 2 doses: 576	BNT162b2 (Pfizer-BioNTech): 942	D1: 6%; D2: 34% (out of 367)	D2: 50%	NA	1 LT with paresthesia
Ou et al, 2021	741 [LT:140(19%)]		BNT162b2: 54% mRNA-1273: 46%	NR		D1: 78% D2: 85% Most common: pain at the injection site	D1 49% D2 69% Most common: fatigue and headache
Kamar et al, 2021	101 LT:12(12%)		BNT162b2:100%	D1: 4%; D2: 40% D3: 68%		NA	NA
LT recipients							
Rabinowich et al, 2021	117	2 doses	BNT162b2	D2: 48% (vs. 100% in control group)	D1: 60% D2: 53%	20%	

Data expressed as *n* (%). D1: after first dose; D2: after second dose; D3: after third dose; LT: liver transplant; NA: not available; SOT: Solid-organ transplant.

liver-related deaths occurred in the LT group. Liver transplantation was not independently associated with death, while increased age and comorbidities were.

Interestingly, the mortality rate was lower in LT recipients than reported among cirrhotic patients with COVID-19 [35]. Patients with cirrhosis, especially those with higher Child Pugh and MELD scores, presented particularly high rates of hepatic decompensation and death due to COVID-19. One of the hypotheses to explain these findings includes the association of cirrhosis to immune dysfunction. Liver transplantation and immunosuppression itself do not seem to confer an increased risk of mortality in COVID-19 [36].

Age, dyspnea, fever, C-reactive protein level, lymphocyte count, a partial pressure of oxygen < 95% on admission, acute kidney injury and moderate/severe lung involvement were significantly associated with severe COVID-19 according to Dumortier et al. [10]. Moreover, Fraser et al. highlighted age and diabetes as potential risk-factors to poorer outcomes [8]. LT recipients who are 60 years of age or older presented 3-fold greater risk for COVID-19 related mortality when compared to LT recipients < 60 years of age. Older-age was a well-described risk-factor not only for in-hospital mortality but also to severe infection. Diabetes in turn has been associated with more than 2-fold risk for ICU admission and 3-fold risk for in-hospital death. Details are shown in **Table 3**.

Immunization

Since the emergence of the COVID-19 pandemic, there has been an outstanding program of development, testing, approval and large-scale distribution of vaccines based on diverse platforms, like mRNA (Pfizer/BioNTech BNT162B1/2 and Moderna mRNA-1273), replication deficient adenovirus (Oxford Astra-Zeneca ChAdOx1-S-nCoV and Janssen, Ad26.COV2.S), recombinant adenovirus (Gamaleya, Gam-COVIDVac) and inactivated virus (Sinovac, CoronaVac/PiCoVac) [37].

Vaccination against SARS-CoV-2 offers a real possibility of reducing SARS-CoV-2 circulation and transmission and, most importantly, development of severe infection and death. In general populations, vaccination against COVID-19 is associated with an overall efficacy between 66 and 95%, defined as avoidance of development of COVID-19 confirmed by molecular testing. Also, vaccines were safe, with a low incidence of serious adverse events, comparable to that observed in control groups in RCT. That said, one should keep in mind that SOT patients in general have a lower probability of response for other commonly used vaccines against respiratory viruses, like Influenza [38], probably due to concomitant comorbidities and immunosuppression.

Few studies have evaluated the results of vaccination against COVID-19 in SOT recipients [39–42] (**Table 4**). Overall, only mRNA-based vaccines were evaluated. Seroconversion is considerably lower than non-SOT recipients, even though, among them, LT recipients are the group with the highest probability of response. Vaccines are associated with local and systemic reactions, in the vast majority of cases mild and transient. Of interest, in this population, local reactions were associated with a higher probability of antibody response. Only a small study exclusively evaluated LT recipients. Seroconversion after 2 doses of Pfizer/BioNTech BNT162B1/2 was lower than for a control group of healthcare workers (48 vs. 100%), and median antibody titer was lower among LT recipients, indicating a less frequent and strong vaccinal response. Older age, MMF use and triple immunosuppression therapy were predictors of non-response. Frequency and severity of adverse events were similar between groups [43]. Despite the relative paucity of data, both AASLD and EASL recommend vaccination of LT recipients, preferably 3 months after transplantation [44,45]. Also, changes in immunosuppression in order to achieve higher rates of seroconversion are not recommended.

Some important questions are still pending with respect to vaccination in LT recipients. All of the studies conducted in SOT used mRNA-based vaccines, which were associated with highest efficacy in general populations. It remains to be determined if other commonly used, non-mRNA vaccines, are capable of achieving advised rates of seroconversion in a population with considerably lower vaccinal efficacy. Additionally, studies in SOT only described efficacy in terms of serological response, contrary to RCT in which efficacy was defined on a clinical basis. Also, cellular response, which may be as important as a humoral response for adequate protection against SARS-CoV-2 infection and may be particularly compromised in LT recipients, was not specifically evaluated. Finally, with increasing vaccinal coverage in this population, some rare but potentially serious effects concerning allograft function may become more frequent, as evidenced by a recent report of acute cellular rejection within 2 weeks of the first dose of vaccination [46].

Conclusions

Emergence of the COVID-19 pandemic has profoundly changed LT centers and raises important questions for the management of LT recipients. Population-based studies have demonstrated the increased susceptibility of LT recipients for SARS-CoV-2 acquisition, possibly reflecting constant contact with healthcare resources and immunosuppression. Clinical, laboratory and radiological features are very similar to that of immunocompetent patients, except for a

higher frequency of digestive symptoms, the presence of which, even in the absence of respiratory symptoms, should demand evaluation for SARS-CoV-2 infection. Management is based on the appropriate use of drugs approved for general populations and changes in immunosuppression. Caution is warranted especially due to potential limitations of using antivirals in patients with elevations in liver enzymes and potential risk of infections, opportunistic or not, in more ill patients receiving dexamethasone or anti IL-6. Changes in immunosuppressive regimens may be of benefit, particularly the reduction in MMF dosage and maintenance of Tacrolimus as the preferred or sole drug. Prognosis is similar to non-LT patients, and is related not to immunosuppression but to the burden of comorbidities. Vaccination should be offered to all LT recipients, preferably after the first months post-LT and achievement of stable IS dosage. Nevertheless, lower efficacy in comparison to immunocompetent patients should be expected.

Author contributions

JP and GP wrote and contributed to this paper equally. Final review and approval were provided by all authors.

Disclosure statement

The authors have no conflicts of interest to disclose related to this topic.

Grant support

Gustavo Pereira received funding from Estácio de Sá University [Programa Pesquisa e Produtividade UNESA]. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] WHO. Coronavirus disease (COVID-19) pandemic. WHO; 2021. Available: https://www.who.int in.
[2] Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 2020;323(18):1775–6.
[3] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395(10229):1054–62.
[4] Manuel O, Estabrook M. RNA respiratory viruses in solid organ transplantation. Am J Transplant 2013;13(Suppl 4):212–9 Suppl 4.
[5] Colmenero J, Rodríguez-Perálvarez M, Salcedo M, Arias-Milla A, Muñoz-Serrano A, Graus J, et al. Epidemiological pattern, incidence, and outcomes of COVID-19 in liver transplant patients. J Hepatol 2021;74(1):148–55.
[6] Ravanan R, Callaghan CJ, Mumford L, Ushiro-Lumb I, Thorburn D, Casey J, et al. SARS-CoV-2 infection and early mortality of waitlisted and solid organ transplant recipients in England: a national cohort study. Am J Transpl 2020;20(11):3008–18.
[7] Becchetti C, Zambelli MF, Pasulo L, Donato MF, Invernizzi F, Detry O, et al. COVID-19 in an international European liver transplant recipient cohort. Gut 2020;69(10):1832–40.
[8] Fraser J, Mousley J, Testro A, Smibert OC, Koshy AN. Clinical presentation, treatment, and mortality rate in liver transplant recipients with coronavirus disease 2019: a systematic review and quantitative analysis. TransplProc 2020;52(9):2676–83.
[9] Belli LS, Fondevila C, Cortesi PA, Conti S, Karam V, Adam R, et al. Protective role of tacrolimus, deleterious role of age and comorbidities in liver transplant recipients with COVID-19: results from the ELITA/ELTR Multi-center European Study. Gastroenterology 2021;160(4):1151–63 e3.
[10] Dumortier J, Duvoux C, Roux O, Altieri M, Barraud H, Besch C, et al. Covid-19 in liver transplant recipients: the French SOT COVID registry. Clin Res Hepatol Gastroenterol 2021;45(4):101639.
[11] Lee BT, Perumalswami PV, Im GY, Florman S, Schiano TD. COVID-19 in liver transplant recipients: an initial experience from the US epicenter. Gastroenterology 2020;159(3):1176–8 e2.
[12] Webb GJ, Marjot T, Cook JA, Aloman C, Armstrong MJ, Brenner EJ, et al. Outcomes following SARS-CoV-2 infection in liver transplant recipients: an international registry study. Lancet Gastroenterol Hepatol 2020;5(11):1008–16.
[13] Rabiee A, Sadowski B, Adeniji N, Perumalswami PV, Nguyen V, Moghe A, et al. Liver injury in liver transplant recipients with coronavirus disease 2019 (COVID-19): U.S. multicenter experience. Hepatology 2020;72(6):1900–11.
[14] Kumar R, Ison MG. Opportunistic infections in transplant patients. Infect Dis Clin North Am 2019;33(4):1143–57.
[15] Berlin DA, Gulick RM, Martinez FJ. Severe COVID-19. N Engl J Med 2020;383(25):2451–60.
[16] Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, Morris J, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. JAMA 2021;325(7):632–44.
[17] Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with COVID-19. N Engl J Med 2021;384(3):238–51.
[18] Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus Remdesivir for hospitalized adults with COVID-19. N Engl J Med 2021;384(9):795–807.
[19] Guimarães PO, Quirk D, Furtado RH, Maia LN, Saraiva JF, Antunes MO, et al. Tofacitinib in patients hospitalized with COVID-19 pneumonia. N Engl J Med 2021 Online ahead of print. doi: 10.1056/NEJMoa2101643.
[20] Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of COVID-19 - final report. N Engl J Med 2020;383(19):1813–26.
[21] Pirola CJ, Sookoian S. SARS-CoV-2 virus and liver expression of host receptors: putative mechanisms of liver involvement in COVID-19. Liv Int 2020;40(8):2038–40.
[22] Jothimani D, Venugopal R, Abedin MF, Kaliamoorthy I, Rela M. COVID-19 and the liver. J Hepatol 2020;73(5):1231–40.
[23] Stephens C, Robles-Diaz M, Medina-Caliz I, Garcia-Cortes M, Ortega-Alonso A, Sanabria-Cabrera J, et al. Comprehensive analysis and insights gained from long-term experience of the Spanish DILI registry. J Hepatol 2021;75(1):86–97.
[24] Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. JAMA 2000;283(1):74–80.
[25] Sembera S, Lammert C, Talwalkar JA, Sanderson SO, Poterucha JJ, Hay JE, et al. Frequency, clinical presentation, and outcomes of drug-induced liver injury after liver transplantation. Liv Transpl 2012;18(7):803–10.
[26] Tischer S, Fontana RJ. Drug-drug interactions with oral anti-HCV agents and idiosyncratic hepatotoxicity in the liver transplant setting. J Hepatol 2014;60(4):872–84.
[27] Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, et al. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN prospective study. Gastroenterology 2015;148(7):1340–52 e7.
[28] Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in hospitalized patients with COVID-19. N Engl J Med 2021;384(8):693–704.
[29] Musuuza JS, Watson L, Parmasad V, Putman-Buehler N, Christensen L, Safdar N. Prevalence and outcomes of co-infection and superinfection with SARS-CoV-2 and other pathogens: a systematic review and meta-analysis. PLoS ONE 2021;16(5):e0251170.
[30] Fekkar A, Lampros A, Mayaux J, Poignon C, Demeret S, Constantin JM, et al. Occurrence of invasive pulmonary fungal infections in patients with severe COVID-19 admitted to the ICU. Am J Respir Crit Care Med 2021;203(3):307–17.
[31] Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, et al. Tocilizumab in patients hospitalized with COVID-19 pneumonia. N Engl J Med 2021;384(1):20–30.
[32] Rosas IO, Bräu N, Waters M, Go RC, Hunter BD, Bhagani S, et al. Tocilizumab in hospitalized patients with severe COVID-19 pneumonia. N Engl J Med 2021;384(16):1503–16.
[33] Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020;180(7):934–43.
[34] Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA 2020;323(20):2052–9.
[35] Marjot T, Moon AM, Cook JA, Abd-Elsalam S, Aloman C, Armstrong MJ, et al. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: an international registry study. J Hepatol 2021;74(3):567–77.
[36] Marjot T, Webb GJ, ASt B, Moon AM, Stamataki Z, Wong VW, et al. COVID-19 and liver disease: mechanistic and clinical perspectives. Nat Rev Gastroenterol Hepatol 2021;18(5):348–64.
[37] McDonald I, Murray SM, Reynolds CJ, Altmann DM, Boyton RJ. Comparative systematic review and meta-analysis of reactogenicity, immunogenicity and efficacy of vaccines against SARS-CoV-2. NPJ Vaccines 2021;6(1):74.
[38] Eckerle I, Rosenberger KD, Zwahlen M, Junghanss T. Serologic vaccination response after solid organ transplantation: a systematic review. PLoS ONE 2013;8(2):e56974.
[39] Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, et al. Antibody response to 2-dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. JAMA 2021;325(21):2204–6.

[40] Marion O, Del Bello A, Abravanel F, Couat C, Faguer S, Esposito L, et al. Safety and immunogenicity of anti-SARS-CoV-2 messenger RNA vaccines in recipients of solid organ transplants. Ann Intern Med 2021 May 25; M21-1341.Online ahead of print. doi: 10.7326/M21-1341.
[41] Ou MT, Boyarsky BJ, Motter JD, Greenberg RS, Teles AT, Ruddy JA, et al. Safety and reactogenicity of 2 doses of SARS-CoV-2 vaccination in solid organ transplant recipients. Transplantation 2021 021 Apr 9. Online ahead of print. doi: 10.1097/TP.0000000000003780.
[42] Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three doses of an mRNA COVID-19 vaccine in solid-organ transplant recipients. N Engl J Med 2021 Jun 23;NEJMc2108861. Online ahead of print. doi: 10.1056/NEJMc2108861.
[43] Rabinowich L, Grupper A, Baruch R, Ben-Yehoyada M, Halperin T, Turner D, et al. Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients. J Hepatol 2021 Aug; 75(2):435–438. Epub 2021 Apr 21. doi: 10.1016/j.jhep.2021.04.020.
[44] Fix OK, Blumberg EA, Chang KM, Chu J, Chung RT, Goacher EK, et al. AASLD expert panel consensus statement: vaccines to prevent COVID-19 infection in patients with liver disease. Hepatology 2021 Feb 12;10.1002/hep.31751. Online ahead of print. doi: 10.1002/hep.31751.
[45] 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(4):944–51.
[46] Vyhmeister R, Enestvedt CK, VanSandt M, Schlansky B. Steroid-resistant acute cellular rejection of the liver after severe acute respiratory syndrome coronavirus 2 mRNA vaccination. Liver Transpl 2021 May 16;10.1002/lt.26097. Online ahead of print. doi: 10.1002/lt.26097.