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Diagnosis, treatment protocols, and outcomes of liver transplant recipients infected with COVID-19

Liver transplant recipients and COVID-19

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Abstract

Several cases of fatal pneumonia during November 2019 were linked initially to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which the World Health Organization (WHO) later designated as Coronavirus disease 2019 (COVID-19). WHO designated COVID-19 as a pandemic on March 11, 2020. In the general population, COVID-19 severity can range from asymptomatic/mild symptoms to seriously ill in some patients. Its mortality rate could be as high as 49%. The Centers for Disease Control and Prevention (CDC) have acknowledged that people with specific underlying medical conditions, among those who need immunosuppression after solid organ transplantation (SOT), are at an increased risk of developing severe illness from COVID-19. Liver transplantation is the second most prevalent SOT globally. Due to their immunosuppressed state, liver transplant (LT) recipients are more susceptible to serious infections. Therefore, comorbidities and prolonged immunosuppression among SOT recipients enhance the likelihood of severe COVID-19. It is crucial to comprehend the clinical picture, immunosuppressive management, prognosis, and prophylaxis of COVID-19 infection because it may pose a danger to transplant recipients. This review describes the clinical and laboratory findings of COVID-19 in LT recipients and the risk factors for severe disease in this population group. In the following sections, we will discuss current COVID-19 therapy choices, review standard practice in modifying immunosuppressant regimens, and outline the safety and efficacy of currently licensed drugs for inpatient and outpatient management. Additionally, we will explore the clinical outcomes of COVID-19 in LT recipients and mention the efficacy and safety of vaccination use.

Core Tip: Liver transplant (LT) patients infected with SARS-CoV-2 have clinical, biochemical, and radiological features highly comparable to those of immunocompetent patients, except for a higher incidence of gastrointestinal symptoms. The prognosis of LT recipients is similar to non-LT patients and is not significantly affected by immunosuppression but rather by comorbidities. Considering the risk of organ rejection, it may not be wise to stop all immunosuppression after a COVID-19 diagnosis. All LT recipients should be vaccinated, considering booster doses augment vaccination immunogenicity. Still, a considerable proportion of patients remain at risk for Covid-19. Therefore, social isolation and other precautions must be maintained.

INTRODUCTION

Several cases of serious pneumonia during November 2019 were initially linked to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which the World Health Organization (WHO) later designated as Coronavirus disease 2019 (COVID-19) [1]. The infection was first discovered in Wuhan, Hubei Province, China [2]. WHO designated COVID-19 as a pandemic on March 11, 2020 [3].As of July 2022, COVID-19 has caused more than 6.3 million fatalities and over 560 million documented cases worldwide [4]. In the general population, COVID-19 severity can range from asymptomatic/mild symptoms to seriously ill in some patients [3]. The mortality rate in some patient populations has been reported to be as high as 49% [5].

The Centers for Disease Control and Prevention (CDC) have acknowledged that people with specific underlying medical conditions such as cancer, chronic kidney disease, liver disease, chronic obstructive pulmonary disease, obesity, type 2 diabetes mellitus, serious heart conditions, respiratory diseases, and immunocompromised status, including those who need immunosuppression after solid organ transplantation (SOT), are at an increased risk for developing severe illness from COVID-19 [6]. With a reported rate of 3.7 per million people, liver transplantation is the second most prevalent SOT globally, following kidney transplantation [7]. Due to their immunosuppressed state, recipients of SOT, especially liver transplant (LT) recipients, are more susceptible to

serious infections [1]. Therefore, comorbidities and prolonged immunosuppression among SOT recipients may enhance the likelihood of severe COVID-19 [8,9]. Additionally, LT cannot be postponed due to a greater waitlist mortality risk since SARS-CoV-2 can aggravate liver illness [10,11]. As a result, transplant centers have resumed solid organ transplantation worldwide [11,12].

SARS-CoV-2, like other RNA respiratory viruses, can cause (atypical) and attenuated infection symptoms in immunosuppressed patients, frequently resulting in delayed presentations and missed diagnoses [13]. It is crucial to recognize COVID-19 infection in this population to guide immunosuppressive management, prognosis, and prophylaxis in this disease associated with high morbidity/mortality [14].

This review describes the clinical and laboratory findings of COVID-19 in LT recipients and the risk factors for SARS-CoV-2 infection in those patients. We discuss current COVID-19 therapy choices, including a review of standard practice in modifying immunosuppressant regimens. Additionally, we will outline the safety and efficacy of the currently licensed drugs for inpatient and outpatient management of COVID-19 in LT recipients and the efficacy and safety of vaccination.

DIAGNOSIS OF SARS-COV-2

RT-PCR analysis of upper respiratory secretions, taken *via* nasopharyngeal swabs, is the current diagnostic test for COVID-19 [15]. However, it exhibits substantial false negative rates [16]. In addition to identifying prior asymptomatic infection, serological assays for SARS-CoV-2 IgG and IgM antibodies can diagnose individuals with a negative RT-PCR despite having COVID-like symptoms. [17]. Staff performing COVID-19 testing should be aware of the various essential steps and protocols that help confirm a diagnosis of COVID-19. The best available kits are 75% sensitive and 95% specific, which is attributed to various factors, including collection method of collection, duration of illness, collection site, illness severity, and sampling skill. False-negative results from viral mutations cause new infection outbreaks due to insufficient identification of positive cases. These can be avoided by amplifying several regions of the virus genome

to minimize the possibility of the probe and primer mismatch. [18,19]. The highest positive results are in bronchoalveolar lavage samples, sputum, nasopharyngeal swabs, and nasal swabs. The Cepheid GeneXpert platform, which qualitatively detects E and N protein genes in 45 min, can be used in emergency scenarios, such as liver transplantation for acute liver failure, where prompt viral detection results are required [18–20].

CLINICAL PICTURE

According to the CDC, COVID-19's clinical symptoms include cough and dyspnea, along with at least two of the following: fever, chills, muscle pain, headache, sore throat, and new loss of taste would put the medical terms in parentheses (dysgeusia) or smell (anosmia). There are also reports of diarrhea [8]. Most LT recipients have radiological evidence of COVID-19 on chest CT (contrast or non-contrast) or X-rays and are symptomatic [21]. Fever, cough, dyspnea, fatigue, and myalgia were the most frequently reported symptoms at the time of diagnosis, just like in the general population, with fever and cough being the two most frequently reported symptoms [22-29] and anosmia and dysgeusia the least reported [14]. A significant variation in the incidence of gastrointestinal symptoms in COVID-19 (ranging from 3 to 79 %) has been reported [30], with rates between 5 and 15% in 2 Large-scale studies [31,32]. Notably, gastrointestinal symptoms such as abdominal discomfort, diarrhea, nausea, and/or vomiting were more common in COVID-19 LT recipients [22,24,25,27,28,33], a piece of information that should be kept in mind when assessing LT patients at risk for SARS-CoV-2 [21]. Table (1) reports the prevalence of COVID-19 symptoms among LT recipients, as reported in the literature.

LABORATORY

Although laboratory testing cannot confirm COVID-19 infection, it can help evaluate the severity and progression of the illness. Typically, severe systemic inflammation is manifested by lymphopenia, the neutrophil-to-lymphocyte ratio of ≥3.13, thrombocytopenia, elevated C-reactive protein, ferritin, D-dimer, and interleukin (IL)-6, and elevated liver enzymes in more severe disease, indicating liver affections [34–36].

Studies have shown that patients who needed mechanical ventilation had higher levels of procalcitonin and CRP and that procalcitonin levels were identified as a predictor of poor outcomes [37,38].

RISK FACTORS FOR SEVERE DISEASE IN LT RECIPIENTS WITH COVID-19

Comorbidities

The probability of more severe COVID-19 disease in SOT, including LT patients, is increased by their long-term immunosuppression and comorbidities [9,39]. Still, the outcomes after liver transplants at a transplant center in India were the same during the COVID era and before its emergence.[40] Webb *et al* showed in their multinational registry study that the mortality risk of COVID-19 participants was not significantly increased by LT [absolute risk difference 1.4% (95% CI: 7.7–10.4)] [33]. The likelihood of developing severe COVID-19 and having a high mortality rate in the general population [31,41,42] and LT recipients [33] rises significantly with increasing age and comorbidities, including hypertension, type II diabetes, and obesity. Fraser *et al* showed that LT recipient patients 60 years or older with COVID-19 have a 3-fold higher risk for COVID-19-related death than those younger than 60 and a 2-fold higher risk of mortality if diabetic [21]. In contrast, a recent systematic review and meta-analysis showed that LT recipients with COVID-19 who were on immunosuppression and had comorbidities were not significantly associated with severity and mortality. These comorbidities included diabetes, hypertension, cardiovascular diseases, CKD, age > 60, the length of LT prior to the detection of COVID-19, and obesity. This was explained by the higher proportion of patients with mild illness in the included studies or the potential protective effects of immunosuppression in LT patients [43].

Cancer

A higher incidence of COVID-19 infection and a worse outcome were associated with having undergone a transplant for hepatocellular carcinoma (HCC) or having an active malignancy at the time of COVID-19 diagnosis [22]. Chinese national reports, including

more than 2000 confirmed cases of COVID-19 with a history of cancer, confirmed this finding [44,45].

Time from LT to the diagnosis of COVID-19

Data on the effect of the interval between LT and COVID-19 diagnosis on the disease severity and mortality are conflicting. As LT recipients are on higher doses of immunosuppression in the first year, which is slowly tapered as a maintenance dosage, it may contribute to an increase in viral load and a delayed recovery from COVID-19 in the first year of LT. Secondly, the outcomes of LT recipients with COVID-19 can be adversely impacted by the increasing frequencies of comorbidities brought on by chronic immunosuppression the longer the transplant duration [43].

Guarino *et al* found that the asymptomatic group had a significantly shorter time from LT to COVID-19 diagnosis (8.62 years compared to 16.81 years in symptomatic patients) ($P = 0.031$) [26]. Several studies showed that the time between LT till SARS-CoV-2 infection does not affect the probability of developing severe COVID-19 or fatality [33,43,46]. On the contrary, Data from the European Liver and Intestine Transplant Association /European Liver Transplant Registry COVID-19 registry suggests that mortality increases in long-term LT recipients [47], and that they have more frequent comorbidities such as hypertension and CV disease [2,48], and present more frequently with fever and dyspnea than short term LT recipients. Risk factors for severe COVID - 19 disease in LT recipients are shown in figure 1.

COVID-19 TREATMENT IN LT RECIPIENTS

During the current pandemic, major international liver societies advised restricting liver transplants to patients with advanced hepatocellular carcinoma or high MELD scores. According to the American Association for the Study of Liver Diseases (AASLD), transplantation is not advised for liver transplant candidates with active COVID-19 infection [49]. Treatment of COVID-19 relies on the understanding of its pathophysiology. In the early phase of COVID-19 infection, viral clearance occurs due to the immunological response. In the second phase, dysregulation of CD4+ T cells and

activation of CD8+ T cells and macrophages may ensue, accompanied by a cytokine storm [50]. Immunomodulatory drugs could reduce this detrimental immune response, but this could increase the viral load and slow disease recovery. Two approaches have been prioritized for the management of LT recipients infected with COVID-19: (1) reducing or discontinuing immunosuppressive medications used to prevent allograft rejection and (2) using antiviral (such as Remdesivir), anti-inflammatory (such as high-dose corticosteroids), and immunomodulatory therapies (such as tocilizumab), as indicated in general populations [14]. Immunosuppression management and its effect on COVID-19 outcomes present significant challenges [51]. Excessive immunosuppression might increase the viral load and postpone recovery, whereas a healthy immune system can worsen the condition [52]. The standard treatment for COVID-19 infection of different severity can be administered to LT recipients, albeit cautiously [53,54]. In most cases, it is advised to maintain immunosuppression, preferably the minimum effective regimen, to prevent rejection and help recovery from COVID-19 [55]. Systematic reviews and meta-analyses showed that the most commonly used immunosuppressant in LT recipients with COVID-19 were calcineurin inhibitors (CNI), followed by antimetabolites (mainly mycophenolate mofetil MMF), and finally corticosteroids. Unless there is a severe, progressing illness, the immunosuppression dosage should not be changed [11,21,56]. Management of liver transplantation recipients infected with COVID-19 si summarized in figure 2.

Calcineurin Inhibitors

Tacrolimus (TAC) -containing immunosuppression improved survival in LT patients with COVID-19 [47]. TAC, and CNIs in general, can reduce human Coronavirus replication *in vitro* by acting on the cyclophilin pathway [57]. By moderating T-cell activation, CNIs may also reduce the harmful effects of the late COVID-19 inflammatory phase [52]. It is recommended to decrease but not stop CNI in LT recipients with COVID-19-related lymphopenia, fever, or deteriorating pulmonary status [58]. In patients with renal impairment, it is recommended to use a higher

corticosteroid dose while reducing or stopping CNI until kidney functions are normalized [55].

Antimetabolites

MMF and SARS-CoV-2 may have a negative synergistic effect on reducing peripheral lymphocytes since both have a cytostatic effect on activated lymphocytes [59,60]. Mycophenolate mofetil therapy was an independent, dose-dependent predictor of a severe infection outcome. Until complete recovery from COVID-19, a dose reduction or momentary switch to everolimus or calcineurin inhibitors may be contemplated [46]. Lowering the dosage of azathioprine or mycophenolate should be considered when COVID-19-induced lymphopenia, fever, or worsening pneumonia are present [58].

Corticosteroids

Since most patients with severe COVID-19 have elevated levels of inflammatory mediators, corticosteroids have been advocated as an anti-inflammatory medication to prevent or reduce a systemic inflammatory response [61]. The National Institutes of Health (NIH) discourages the routine use of systemic corticosteroids for the treatment of COVID-19 in hospitalized patients with COVID-19 who have undergone a transplant unless they are in the (intensive care unit) ICU [62]. Proper prednisone dose adjustment is required to prevent adrenal insufficiency [58]. Critically ill patients with COVID-19 who require oxygen therapy have better outcomes after receiving corticosteroids [63]. During active infection with COVID-19, reducing or discontinuing immunosuppressive medicines has not been shown to enhance the risk of rejection in LT recipients, as long as liver functions are followed up [48,64–66].

OUTPATIENT MANAGEMENT OF COVID-19 IN LT PATIENTS

Hydroxychloroquine (with or without azithromycin), azithromycin alone, and lopinavir/ritonavir are all treatments that have been proven ineffective or even hazardous [67].

Lopinavir/Ritonavir

Protease inhibitors, mainly lopinavir/ritonavir, were considered effective against other coronaviruses, but no benefit was seen in a recently published clinical trial involving individuals with severe COVID-19 [68].

Antimalarial Agents

Chloroquine and hydroxychloroquine (HCQ) were the cornerstones of treatment throughout the early days of the pandemic. In vitro, they have antiviral activity against SARS-CoV-2, and their immunomodulatory properties may decrease the host's inflammatory response [69]. Early observational data revealed that azithromycin might be helpful when added to HCQ [70]. However, HCQ with or without azithromycin did not improve clinical outcomes; instead, it had increased adverse events, according to research including nearly 500 patients randomly assigned to receive either HCQ or HCQ with azithromycin, or the standard of treatment [71]. In June 2020, the Food and Drug Administration (FDA) canceled its EUA (emergency use authorization) because of the significant number of controlled trials that failed to demonstrate any advantage from HCQ [70–75].

Ritonavir-boosted nirmatrelvir (Paxlovid)

Nirmatrelvir is an orally administered protease inhibitor that blocks MPRO, a viral protease crucial to viral replication [76]. For optimal pharmacokinetic performance, nirmatrelvir is combined with ritonavir (in the form of Paxlovid), a potent inhibitor of cytochrome P450 (CYP) 3A4. To achieve therapeutic concentrations of nirmatrelvir, coadministration of ritonavir is necessary. On December 22, 2021, the FDA approved nirmatrelvir with ritonavir as an emergency therapy for COVID-19 [77].

All human-infecting coronaviruses have been shown to be susceptible to its antiviral effects [78]. Despite the absence of clinical efficacy data, it is anticipated that ritonavir-boosted nirmatrelvir will be efficacious against all Omicron subvariants [79–81].

A 5-day regimen of ritonavir-boosted nirmatrelvir is one of the preferred treatments for mild to moderate COVID-19 among outpatients at risk of disease progression. During treatment and for ≥ 3 days after ritonavir is ended, ritonavir may raise concentrations of some concurrent medicines, including calcineurin and mTOR inhibitors. Significant

elevations in these medications' concentrations may result in severe and occasionally fatal drug toxicity [82]. Anti-SARS-CoV-2 monoclonal antibodies or remdesivir are recommended as first-line therapy for nonhospitalized transplant patients who are also on calcineurin or mTOR inhibitors for antirejection. If these medications are unavailable, ritonavir-boosted nirmatrelvir may be administered cautiously, with thorough patient monitoring and transplant specialist consultation [83].

Until sufficient data are available to determine the optimum dose, the EUA advises against ritonavir-boosted nirmatrelvir for patients with an eGFR of <30 mL/min [77]and those with significant hepatic impairment (Child-Pugh Class C) and to be taken with caution in patients with pre-existing liver disorders, liver enzyme abnormalities, or hepatitis [82].

Compared to a placebo in the EPIC-HR study, ritonavir-boosted nirmatrelvir significantly decreased the risk of hospitalization or mortality by 88% in unvaccinated, nonhospitalized persons with laboratory-confirmed SARS-CoV-2 infection [77,84]. This outcome is similar to that seen in similar patient populations for remdesivir (87% relative reduction) [85] and better than that seen for molnupiravir (31% relative reduction) [86].

Molnupiravir

Molnupiravir is the oral prodrug of beta-D-N4-deoxycytidine (NHC), a ribonucleoside with antiviral activity *in vitro* and clinical trials against SARS-CoV-2 [87,88]. When viral RNA-dependent RNA polymerases take in NHC, it leads to mutations in the virus and lethal mutagenesis [89,90]. The FDA approved an EUA for molnupiravir on December 23, 2021, to treat adults with mild to moderate COVID-19 within five days of symptom onset, who are at high risk of progressing to severe disease, and for whom alternative antiviral treatments are not available or clinically acceptable [91,92]. Molnupiravir is effective against Omicron subvariants, as shown by *in vitro* and animal trials [81,88,93,94].

In the pre-Omicron era, the MOVe-OUT trial found that compared to a placebo, molnupiravir reduced the rate of hospitalization or death by 31% among

nonhospitalized adults who were unvaccinated and at high risk of progression to severe disease [77,86]. A subset of patients who received molnupiravir in the MOVe-OUT trial and subsequently required hospitalization had a lower likelihood of requiring respiratory interventions than those who got a placebo[95]. When ritonavir-boosted nirmatrelvir and remdesivir are not accessible, feasible, or clinically acceptable, the COVID-19 Treatment Guidelines recommend using molnupiravir orally for five days as an alternate therapy in nonhospitalized adult patients with mild to moderate COVID-19 who are at high risk of disease progression. After the onset of symptoms, treatment should begin as soon as feasible and no later than five days [82]. Molnupiravir therapy should be continued for the entire five days. Whether a shorter course of treatment results in poorer efficacy or is linked to the development of molnupiravir-resistant mutations remains unanswered. The whole course of molnupiravir treatment can be completed even if hospitalization is necessary during treatment [82].

Anti-SARS-CoV-2 Monoclonal Antibodies
Monoclonal antibodies (MABs), one of the weapons in the arsenal against COVID-19, block the virus' ability to attach to the angiotensin-converting enzyme receptor on host cells and impede internalization [96]. FDA has granted EUAs for several anti-SARS-CoV-2 MABs for the treatment of COVID-19 and post-exposure prophylaxis [97-99].

Treatment of Mild-Moderate COVID-19
Antibodies against SARS-CoV-2 are now approved for treating mild-to-moderate COVID-19 and post-exposure prophylaxis, and SOT recipients are included [100]. As of October 2021, the FDA EUA has authorized casirivimab-imdevimab (C-I), bamlanivimab-etesevimab (B-E), and sotrovimab for the treatment of outpatients diagnosed with mild to moderate COVID-19 and are at high risk of developing a severe illness or requiring hospitalization. Once positive results of the SARS-CoV-2 antigen or nucleic acid amplification test (NAAT) are obtained, and no later than ten days after the onset of symptoms, treatment with MABs should be initiated [100]. When administered early in the course of COVID-19 (median four days after the beginning of symptoms),

MABs reduce hospitalization and mortality by 70% and viral load [101-103]. MABs appear more effective in patients with high viral loads [103] but ineffective in hospitalized patients with severe COVID-19 [104]. The use of MABs in SOT recipients was related to a low incidence of emergency department visits, hospitalizations, mechanical breathing, and the need for intensive care, and fatality was observed over a 28-30-day post-infusion follow-up period. A further decreased incidence of subsequent ED visits or hospitalization was linked to early MAB delivery (four vs. six days)[105]. Casirivimab-imdevimab was used to treat COVID-19 in 25 SOT recipients; none suffered worsening symptoms or needed to be hospitalized [105]. The use of MAB (75.3 % bamlanivimab) for the treatment of COVID-19 in 73 SOT recipients was described in a retrospective analysis by Yetmar *et al* Of these patients, 12.3 percent were hospitalized, although none required intubation, died, or had rejection[106]. Since the appearance of the Omicron variant in December 2021, most of the previously available MABs have shown drastically reduced activity, except for sotrovimab, which is effective against Omicron BA.1 and BA.1.1 subvariants, in addition to previous variants. However, it is less effective against the BA.2 subvariant [107].

Bebtelovimab, which was found to be effective against Omicron BA.1, BA.1.1, and BA.2 subvariants, was granted an EUA by the United States FDA in February 2022, [108] and revoked in November 2022 because it was not expected to neutralize omicron subvariants BQ.1 and BQ.1.1. [109].

Post-exposure Prophylaxis

FDA EUA permits the utilization of C-I and B-E for post-exposure prophylaxis (PEP) as of October 2021. In high-risk exposure, an incomplete vaccination schedule or an insufficient immunological response to complete vaccination, as observed in immunocompromised persons, are indicators for PEP administration. For optimum response, the administration should be within seven days [100]. No major transfusion-related adverse events were observed after the administration of MABs in SOT recipients. This includes no cases of acute allograft rejection, overreactions to the immune system, or anaphylaxis. Preliminary findings suggest promising outcomes,

such as a reduction in COVID-19-related hospitalizations and deaths [100]. The likelihood of emerging resistant strains may increase in immunocompromised people with a higher viral burden. This danger may be reduced with the timely and appropriate administration of these MABs [100].

INPATIENT MANAGEMENT OF COVID-19 IN LT PATIENTS

Remdesivir:

Remdesivir is a nucleoside analog that showed anti-SARS-CoV-2 activity in human cell lines[110]. On October 22, 2020, the FDA approved remdesivir for treatment in adult and pediatric patients with COVID-19 who require hospitalization and are >12 years old and >40 kg [58]. It appears to be most efficient when administered to individuals on oxygen within ten days of the onset of symptoms, even if no mortality advantage has been shown. It also tends to minimize the length of illness and hospitalization [111]. Hospitalized patients with liver illnesses or LT recipients who need supplemental oxygen and have COVID-19 should get remdesivir for five days. However, if their condition worsens and they require mechanical ventilation, it should not be given [58]. Both patients and healthy volunteers who were given remdesivir showed increased levels of amino transaminases after taking the drug. Liver biochemistry should be checked before starting remdesivir and then regularly throughout treatment; if any tests show elevations >10x ULN or indicate liver inflammation, the medicine should be stopped [58].

Dexamethasone

Hospitalized COVID-19 patients who need supplemental oxygen have a lower death rate when dexamethasone is administered at a dose of 6 mg per day for up to 10 days [63]. People who needed mechanical ventilation benefited the most; patients who did not need supplemental oxygen had a deteriorating tendency, and patients who had been experiencing their symptoms for longer than seven days did not benefit. In the absence of dexamethasone, an alternate corticosteroid in a comparable dosage may be used [58]. Besides oxygenation, particular biochemical markers may be relevant in evaluating who

may benefit from corticosteroids. Although Keller *et al* found no association between steroid use and overall mortality benefit, they found a substantial reduction in mortality risk in individuals whose baseline C-reactive protein was greater than 20 mg/dL. (OR, 0.23; 95%CI, 0.08-0.70) [112].

IL-6 inhibitors (e.g., tocilizumab, sarilumab)

FDA has authorized the use of the IL-6 inhibitors tocilizumab and sarilumab to treat autoimmune disorders and chimeric antigen receptor T cell (CAR-T) driven cytokine release syndrome. Evidence from case series published during the early stages of the COVID-19 pandemic revealed that suppressing the inflammatory state experienced by some COVID-19 patients by blocking IL-6 could improve their prognoses [113]. Contradictory results were reported in randomized studies. In general, patients with recent (within 24 h) or imminent requirements for mechanical ventilation and raised inflammatory markers (CRP levels > 75mg/L) may benefit from the addition of tocilizumab to dexamethasone (limited data available for sarilumab) [114,115]. Tocilizumab may help certain patients whose conditions are rapidly deteriorating and who are already getting corticosteroids, but there is insufficient data to make any recommendations regarding its usage in patients with liver disease or solid organ transplantation at this time [58].

Baricitinab

Baricitinab is an FDA-approved Janus Kinase (JAK) inhibitor for treating refractory rheumatoid arthritis. In patients with COVID-19, kinase inhibitors reduce inflammation, which may aggravate organ dysfunction, and may have direct antiviral activities [58]. In the ACTT-2 trial, hospitalized COVID-19 patients received baricitinib + remdesivir or remdesivir alone. Baricitinib-treated patients recovered faster, especially those on high-flow oxygen or noninvasive ventilation. No mortality benefit was observed, and total mortality was low [116]. Baricitinib may be an option for individuals with liver disease or transplant recipients who are intolerant to corticosteroids and yet fulfill their requirements [58].

Convalescent Plasma

Neutralizing antibodies are detectable in the sera of people who have recovered from the infection, as evidenced by earlier coronavirus outbreaks [117]. Passive antibody therapy using convalescent plasma is another potential treatment for COVID-19, acting by viral neutralization [118]. Recent evidence shows that individuals who received plasma early in their illness had a much lower 30-day mortality rate [119]. In addition, the mortality rate was lower for patients who were given plasma with higher antibody levels than those who were given plasma with lower antibody levels. Accordingly, The FDA issued a EUA for convalescent plasma for hospitalized COVID-19 patients on August 23, 2020, and updated it on February 3, 2021, to exclude low-titer plasma [58]. Subsequently, the EUA was updated. The present EUA restricts convalescent plasma products containing high levels of anti-SARS-CoV-2 antibodies to patients with COVID-19 who have an immunosuppressive condition or are receiving immunosuppressive therapy. This restriction applies to both inpatients and outpatients [82]. A Chinese randomized trial found a trend toward clinical improvement with plasma therapy (51.9 vs 43.1%) but failed to reach statistical significance (P = 0.26), presumably because of underpowering as the study was terminated early due to a decline in COVID cases in China [120]. Data from 804 patients with COVID-19 from RCTs, matched control studies, and case series were combined and analyzed. Results demonstrated that patients who received plasma had a significantly lower risk of death than those who received standard care (13% vs 25%; P<0.001) [121].

Nonetheless, despite these optimistic preliminary results, a recent randomized trial of 464 patients, with moderate COVID-19, given convalescent plasma, showed no improvement in mortality or illness progression [122]. Hospitalized patients with liver illness or LT recipients rarely benefit from receiving convalescent plasma [58]. Using high-titer plasma in patients with recent symptoms, mild disease, and risk factors for a progressive disease may be beneficial [122-124].

CLINICAL OUTCOMES IN LT RECIPIENTS WITH COVID-19
Infection Rate

SARS-CoV-2 infection rates are lower among liver transplant patients than among other solid organ recipients. Heart and lung transplant recipients tend to have the highest risk of infection, while liver transplant recipients appear to have the lowest risk [125,126].

Hospitalization Rate

Despite having a similar need for ICU care, ventilatory support, and severe COVID-19 infection, when compared to the general population, LT patients infected with COVID-19 were reportedly more frequently hospitalized [at a rate ranging from 71 to 86.5%] [22,23,28,33,46,125], which may be ascribed to safety precautions [127,128], especially if they have additional risk factors for a more severe COVID-19 course like hypertension, diabetes or obesity [129]. Guarino *et al*, on the other side, reported a significantly lower rate of hospitalization, 16.66% [26], attributing this discrepancy to the period of COVID-19 infection during which the study was enrolled. This was during the second pandemic wave (from September 2020 to January 2021), when expertise and skills in managing infections in immunosuppressed patients improved, indicating a better understanding of patients and less worry among clinicians about the potential effects of the COVID-19 disease course on LT recipients.

Mortality rates

In the general population of Wuhan, China, the COVID-19 mortality rate was first reported to be 1.4% [130]. Mortality increased considerably among hospitalized patients (10%) [38] and ICU patients (26%) [131]. The mortality rate of SARS-CoV-2 infection in the LT cohort reported by literature ranges from 12 to 22.3%. Webb *et al* [33] and Colmenero *et al* [24] reported 19% and 18% mortality rates, respectively, lower than matched control groups. The estimated mortality rate reported on 57 LT recipients in a European cohort was 12% (95%CI 5% to 24%), which increased to 17% (95%CI 7%−32%) among hospitalized patients [22].

Ravanan *et al* conducted a comparative study between patients waitlisted for transplants and SOT recipients and described a mortality rate of 20.3 % among LT recipients, which was lower than reported by other SOT. The highest mortality rates were reported in heart and lung transplant recipients [126]. Heart transplant recipients

reported an overall mortality rate of 15%-33% and a rate of 25%-41% among hospitalized patients, according to data from four studies with small sample sizes (13-28 patients). [132-135] This was supported by Trapani *et al*, who found that the liver is more resistant to COVID-19 infection than other organs and has a lower mortality rate (15.7%) with mortality rates of 35.8% and 40% for heart and lung transplant recipients respectively. They hypothesized that LT recipients' immunosuppressive therapy was milder than usual, and they had a higher immune tolerance than other SOT recipients [125]. Data from an Italian transplant center in Lombardy showed a remarkably low mortality rate among LT recipients with COVID-19, primarily related to metabolic syndrome comorbidities [48].

Kidney transplant recipients infected with COVID-19 have higher hospitalization rates and mortality rates when compared to LT recipients. This is attributed to chronic immunosuppression together with associated comorbidities. [8]

IMMUNIZATION

Since the COVID-19 pandemic started, an excellent program of vaccine research, testing, approval, and wide-scale dissemination has been implemented using a variety of platforms, including 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, GamCOVIDVac) and inactivated virus (Sinovac, CoronaVac/PiCoVac) [138]. Vaccination is a crucial way to avoid getting SARS-CoV-2 and a severe illness. Early vaccine trials for COVID-19 in the general population were very effective, with reported response rates of 95% for BNT162b2 and 94% for mRNA-1273. However, these trials did not include people taking immunosuppressant drugs [39,139,140]. On the other hand, Ad26.COV2.S recombinant adenovirus vaccine prevented moderate to severe-critical COVID-19 in the general population by 66.1%, excluding people on immunosuppression [141]. The health authorities of numerous countries have prioritized SOT recipients for vaccination with mRNA vaccines. Antirejection drugs inhibit T-cell activation, interact with antigen-

presenting cells, and reduce B-cell memory responses in SOT recipients, making SARS-CoV-2 vaccines less effective in this population [142-144]. In addition to diminished vaccine efficiency, considerably lower anti-spike IgG antibodies have been found in completely vaccinated liver, kidney, heart, and lung transplant recipients following mRNA vaccination [145-148]. While measuring humoral immune response as a surrogate marker for vaccine effectiveness has received significant attention, the clinical endpoints, such as immunity to SARS-CoV-2 infection and severe/acute disease, are the most critical outcomes. Outcomes were explicitly examined in COVID-19 vaccine studies in the general population but not in immunosuppressed patients [139-141]. Ignoring cellular immunity is one way in which antibody measurements alone may not fully predict clinical protection from SARS-CoV-2 vaccination. Studies showed that SOT recipients had worse cellular immunity after SARS-CoV-2 immunization than healthy controls [120,121]. In the same studies, cellular and humoral immune responses did not correlate; some patients had a solid cellular response but no humoral response. The role of T-cells in vaccinations is poorly understood due to a paucity of commercially available tests [149].

Furian *et al* identified a link between anti-SARS-CoV-2 antibody production and T cell responses in kidney and LT recipients after SARS-CoV-2 vaccination. Patients with antibody seroconversion had more significant amounts of IFN-producing T cells [150]. These findings support and add to earlier research [151,152]. However, they found serological converts who did not have anti-SARS-CoV-2 IFN-γ T cell responses [150]. This supports the concept that anti-SARS-CoV-2 antibody production is at least partially independent of T cells [153]. Oddly, immunosuppression impacted anti-SARS-CoV-2 IFN-γ T cell responses more negatively than antibody production [150]. Severe cases of COVID-19 have also been reported in transplant recipients who had received two doses of the vaccine [154]. Due to concerns regarding insufficient protection with a two-dose series, extra vaccination doses have been observed to improve antibody response for SOT recipients [155,156]. Based on these findings, the FDA allowed a third vaccination

dosage for immunocompromised people on August 12, 2021, and the CDC revised their recommendations consequently [157].

Moreover, The CDC proposed a fourth booster dose three months after the original series, but only some real-world data support this. In comparison to the placebo, the third dosage of the mRNA vaccine was considered safe among 60/120 adult SOT recipients and was linked to higher levels of specific T-cells (432 vs. 67 cells per 106 CD4+ T-cells), median virus neutralization (71 % vs. 13 %), and anti-receptor-binding domain antibodies of at least 100 U/mL in more patients (55 % vs. 18 %) [158]. These results suggest that even a third vaccination dose is insufficient to protect SOT recipients from COVID-19. Therefore, further measures will be required to safeguard these vulnerable patients against COVID-19. This can entail passive immunization and/or reducing immunosuppression in some patients [100]. Zhen *et al* attempted to assess the effectiveness and safety of COVID-19-inactivated vaccinations in LT patients. The immunological response to the inactivated COVID-19 vaccination is markedly suboptimal. The predictors of negative antibody response were a shorter duration post-LT, the usage of a mycophenolate acid derivative, and IL-2R activation during LT. However, no serious adverse reactions to the inactivated vaccination or graft rejection were reported. So, they concluded that LT recipients need booster vaccination [159]. Despite limited evidence, the AASLD and European Association for the Study of the Liver (EASL) advise vaccinating LT patients three months after transplantation [160,161].

Pre-exposure prophylaxis

FDA has authorized the long-acting combination MABs tixagevimab-cilgavimab (EVUSHELD™) for pre-exposure prophylaxis to prevent COVID-19 commencing in December 2021. In the United States, this agent is the only one to have received an EUA for this use [107]. Those who are not likely to produce an effective immune response to vaccination may nevertheless benefit from this medication's protective effects, such as those who are immunocompromised due to a medical condition or immunosuppressive medication, as well as those for whom COVID-19 vaccination is not recommended due to a history of severe adverse reaction to COVID-19 vaccine [162].

However, it is currently unknown whether or not tixagevimab/cilgavimab is effective in preventing COVID-19 in SOT recipients. The combination is more effective than either tixagevimab or cilgavimab alone against omicron, and it appears to be more effective *in vitro* against BA.2 than against BA.1 or BA.1.1 subvariants [163].

CONCLUSION

LT patients with SARS-CoV-2 infection have clinical, biochemical, and radiological features that are highly comparable to those of immunocompetent patients, except for a higher incidence of gastrointestinal symptoms. Particular focus should be given to gastrointestinal symptoms as a diagnostic indicator for COVID-19 among LT patients with COVID-19, even in the absence of fever or respiratory symptoms. Even if the risk of infection appears to be considered after a liver transplant, alterations in innate and adaptive immunity induced by immunosuppressants cause the severity of COVID-19 to remain low. The prognosis of LT recipients is similar to non-LT patients and is not affected by immunosuppression but rather by comorbidities. Considering the risk of organ rejection, it may not be wise to stop all immunosuppression after a COVID-19 diagnosis. However, depending on the severity of the disease, MMF may be withdrawn or substituted from an immunosuppressive regimen with CNIs or mTOR inhibitors in some selected LT patients with COVID-19. All LT recipients should be vaccinated. The administration of a booster dose considerably enhances the vaccine's immunogenicity. However, many patients continue to be at risk for Covid-19. Consequently, social isolation and other protective measures must be maintained for these individuals.

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