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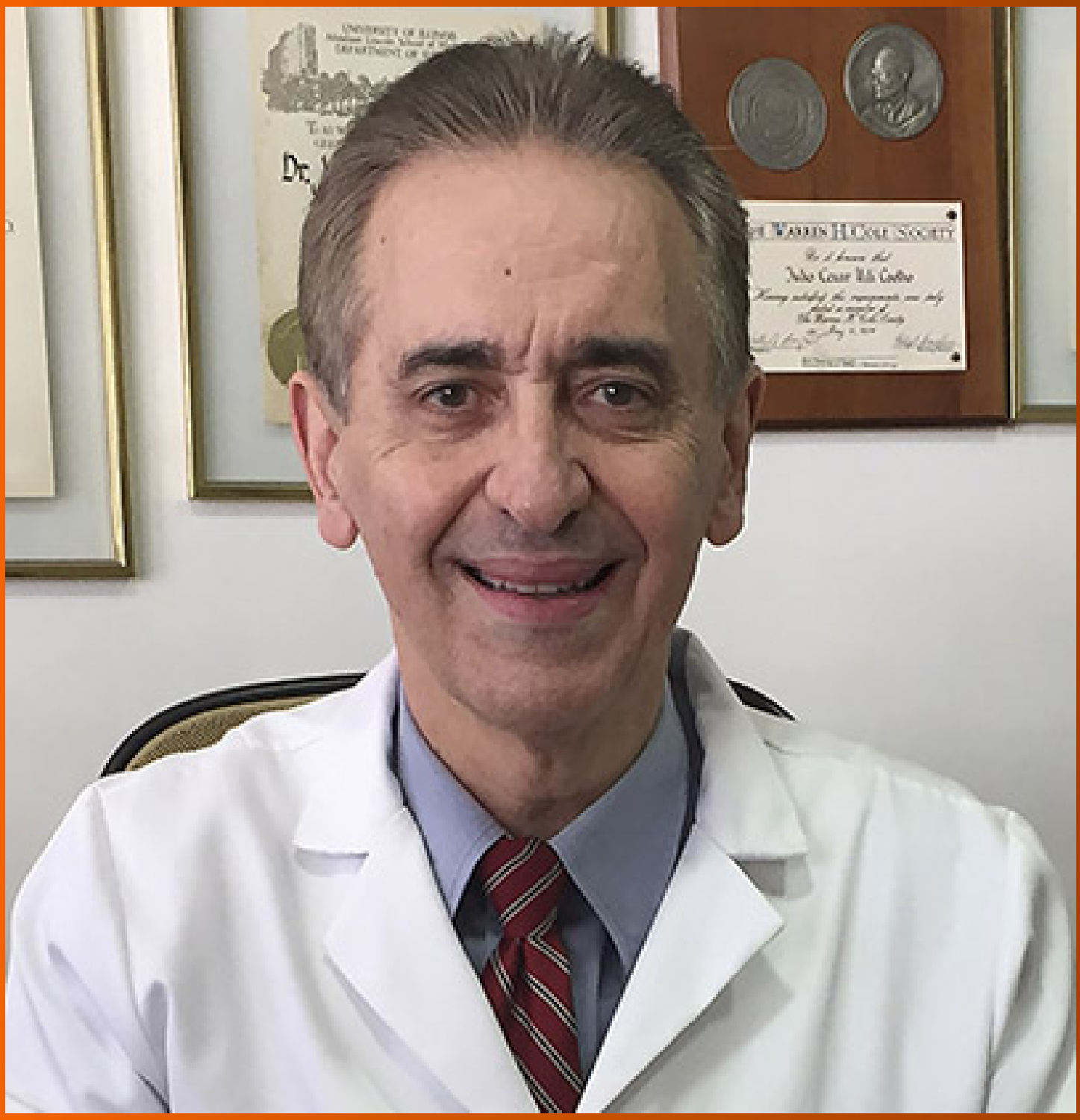

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MINIREVIEWS

Coronavirus disease 2019 in liver transplant patients: Clinical and therapeutic aspects

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has profoundly impacted liver transplant (LT) activity across the world, with notable decreases in the number of donations and procedures in most Western countries, in particular throughout the first wave. The cumulative incidence of COVID-19 in LT recipients (with estimates ranging from 0.34% to 1.56%) appears to be at least comparable to that observed for the general population. Clinical and radiological features at presentation are also similar to non-transplant patients. The risk of death among LT recipients requiring hospital admission is high (from 12% to 19%), although some authors have suggested that overall mortality may be actually lower compared to the general non-transplant population. It is likely that these poor outcomes may be mainly influenced by the older age and higher comorbidity burden of LT recipients, rather than by the transplant status itself. In fact, it has been hypothesized that post-transplant immunosuppression would exert a protective role, with special focus on tacrolimus-containing regimens. There is scarce evidence to guide the optimal management of post-transplant COVID-19 and the use of antiviral or immunomodulatory therapies, although both clinical practice and guidelines support the dose reduction or withdrawal of anti-proliferative agents such as mofetil mycophenolate. Preliminary reports suggest that the antibody response to messenger RNA vaccines is significantly impaired as compared to non-immunocompromised individuals, in line with other transplant populations. Finally, it is foreseeable that the future will be conditioned by the emerging variants of severe acute respiratory syndrome coronavirus 2 with

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increased transmissibility among LT recipients.

Key Words: COVID-19; Liver transplantation; Clinical features; Therapy; Immunosuppression; SARS-CoV-2

Core Tip: Coronavirus disease 2019 incidence and clinical and radiological features are similar in liver transplant recipients and the general population. Reported mortality in hospitalized patients is 12%-19%. Risk factors are older age and comorbidity. Tacrolimus could be protective, but anti-proliferative agents such as mycophenolate mofetil should be avoided.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) produced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China in December 2019[1,2]. The initial outbreak rapidly spread all over the world, being declared a pandemic by the World Health Organization by March 11, 2020, with 118000 cases declared in 114 countries and 4291 deaths at that time[3]. The pandemic has now affected more than 172 million people and has reached a death toll exceeding 3.7 million[4,5].

Liver transplant (LT) recipients are considered susceptible to infectious complications due to their long-term immunosuppression (IS)[6]. At the time COVID-19 was first described, the potential impact of this emerging condition on this patient population was unpredictable. Previous experiences with related coronaviruses, such as SARS-CoV or Middle East respiratory syndrome coronavirus (MERS-CoV), did not clearly show an increased incidence or case-fatality rate among immunocompromised patients[7,8]. A systematic review and meta-analysis that summarized the literature available between January and April 2020 identified hypertension, diabetes, cardiovascular disease, chronic obstructive pulmonary disease, malignancy, cerebrovascular disease, and human immunodeficiency virus infection as risk factors for severe COVID-19 in the Chinese population. Of note, chronic liver disease was not identified in this preliminary study[9]. Nevertheless, a systematic review focused on solid organ transplantation (SOT), which pooled 60 studies from January to October 2020 and 2772 unique patients, including 505 LT recipients, revealed high rates of both hospitalization (81.0%) and all-cause mortality (18.6%)[10].

In the present review, we summarize the current experience regarding COVID-19 in LT recipients, with particular focus on clinical and therapeutic aspects. Early experiences from different locations all over the world led to the scientific societies to develop guidelines for the management of these patients. This pandemic has exerted a deep impact on the transplant activity. There remain concerns about the medium- and long-term outcomes of infected recipients as well as on the optimal management of IS.

EARLY EXPERIENCES

On April 19, 2020 it was reported from Wuhan a 50-year-old male patient that had undergone LT in 2017 and developed SARS-CoV-2 pneumonia with mild respiratory failure by the end of January. Tacrolimus was restarted 4 wk later, with normal liver function. The authors suggested that reduction or temporary withdrawal of IS may be beneficial for the reconstitution of the immune response[11]. Huang *et al*[12] subsequently reported a second 59-year-old LT recipient that died on 45 d of

admission due to multiorgan failure in the setting of suspected chronic rejection and septic shock.

During March 2020, three long-term (> 10 years) LT recipients that were receiving low-dose IS and rapidly developed acute respiratory distress syndrome (ARDS) requiring mechanical ventilation died at the Istituto *Nazionale dei Tumori di Milano* between 3 and 12 d after the onset of symptoms. Three other recipients that developed COVID-19 less than 2 years from transplantation had an uneventful disease. This led the authors to suggest that post-transplant IS might be protective, whereas metabolic-related comorbidities would be associated with an increased risk of severe infection [13].

Six LT recipients from our institution had been admitted by March 23, 2020. Two of them died due to ARDS associated to renal failure and refractory shock, respectively. Both patients were receiving mycophenolate mofetil (MMF) at admission, associated to everolimus in the first case. Two further LT recipients were treated as outpatients. Two patients were temporarily converted to tacrolimus, MMF was halted in one patient, and no modifications were made in the remaining three[14].

Some of the earliest cases of post-transplant COVID-19 from the United States were reported on March 22, 2020. These 4 cases included a 67-year-old man that had undergone LT 19 years before. The patient was initially admitted to the intensive care unit (ICU), cyclosporine therapy was continued without adjustment, and he was discharged home after 6 d[15]. A report from New York City described the initial experience at two centers during the first weeks of the outbreak, including 13 LT recipients, four of them with severe disease. Sixteen out of 90 SOT recipients died, resulting in an overall case-fatality rate of 18%, 24% for hospitalized patients and 52% for those admitted to the ICU[16].

Shortly after the outbreak of the pandemic, first experiences with recent transplant recipients started to be reported. For instance, a 69-year-old patient admitted for LT on January 28, 2020 in Iran became febrile on post-transplant day 4, being diagnosed with hospital-acquired pneumonia. He developed respiratory failure and loss of consciousness on day 9. A brain computerized tomography (CT) scan revealed a hypodensity in the right parietal lobe suggestive of middle cerebral artery ischemic stroke. The patient died on day 23 after transplantation, with SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) being reported positive on the next day[17]. Qin *et al*[18] reported a 37-year-old male patient that underwent LT on January 21, 2020. He started with persistent fever on post-transplant day 9, and a thoracic CT scan revealed minor changes. A second scan performed 9 d later showed multiple ground glass opacification in the left lobes. Tacrolimus and steroids were maintained though titrated to lower doses, and supplemental oxygen therapy through high-flow nasal cannula maintained oxygen saturation ranging from 95% to 99%. The patient was successfully discharged 51 d after transplantation[18].

COVID-19 AND THE LIVER

Although COVID-19 is primarily a respiratory disease, SARS-CoV-2 may also infect the digestive system through its viral receptor angiotensin-converting enzyme 2 (ACE2). The ACE2 cell surface receptor is more strongly expressed in cholangiocytes, at a similar level in fact than type 2 alveolar cells in the lungs, than hepatocytes (59.7% *vs* 2.6%, respectively)[19]. Increased transaminases is a common laboratory finding in COVID-19, and liver injury has been associated to drug-induced liver toxicity, systemic hyperinflammatory response, or hypoxia-ischemia reperfusion injury[20], rather than direct viral cytopathic effect[21]. Coagulopathy and liver endotheliopathy have been suggested to be at least partially driven by interleukin (IL)-6 trans-signaling, which would lead to the expression of procoagulant (such as factor VIII or von Willebrand factor) and proinflammatory factors as well as increased platelet attachment in liver sinusoidal endothelial cells. Interestingly, these effects were blocked by soluble gp130, which acts as an IL-6 trans-signaling inhibitor, and the janus kinase inhibitor ruxolitinib, providing support for these therapeutic approaches[22]. Histopathologic features suggestive of some level of cytopathic injury, however, have been also observed in liver biopsies[23].

Cai *et al*[24] reported in a large cohort that individuals with abnormal liver tests were at a higher risk of progression to severe COVID-19. Abnormal liver function was observed in 76.3% of patients, with 21.5% of them developing liver injury. The detrimental effect on liver function was mainly related to therapies used during hospitalization, which should be closely monitored and evaluated.

In a retrospective study from Wuhan, 1282 out of 2073 patients (61.8%) had abnormal liver function test during hospitalization, and 14.3% experienced some degree of liver injury. Increased aspartate aminotransferase (AST) and direct bilirubin levels at admission were independent predictors of all-cause mortality, whereas the presence of hepatitis B virus infection did not increase the risk of poor outcome[25].

In a retrospective cohort comprising 234 patients hospitalized in two referral hospitals in France, the rate of abnormal liver function tests at admission was as high as 66.6% and was associated with in-hospital aggravation [odds ratio (OR): 4.1: 95% confidence interval (CI): 1.5-10.8; $P = 0.004$] and mortality (OR: 3.3; 95%CI: 1.04–10.5; $P = 0.04$). A minority of patients (3.8%) had underlying liver disease, and there were no significant differences in the prevalence of alcohol consumption or metabolic syndrome between patients with or without abnormal liver tests on admission, suggesting that this finding may be COVID-19-related and not due to pre-existing liver disease[26].

In a retrospective cohort from New York that included 2273 patients, acute liver injury was common and categorized as mild [alanine transaminase (ALT) levels < 2 times the upper limit of normal (ULN)] in 45% of the cases, moderate (ALT levels two to five times the ULN) in 21%, and severe (ALT levels > 5 times the ULN) in 6.4%. In the multivariate analysis adjusted for age, body mass index, comorbidities, and requirement of invasive mechanical ventilation (IMV) and renal replacement therapy, peak ALT levels were significantly associated with death or discharge to hospice (OR: 1.14; $P = 0.044$)[27].

Underlying cirrhosis has been identified as a risk factor for increased severity of COVID-19, with mortality rates ranging from 12% to 43%[28]. Indeed, SARS-CoV-2 may produce acute-on-chronic liver failure (ACLF) among cirrhotic patients[29]. The mortality in 20 patients with ACLF reported from India reached 30%, as compared to 5% among cirrhotic patients without ACLF[30]. Metabolic dysfunction-associated fatty liver disease has been also associated with the severity of SARS-CoV-2 infection in patients below 60 years (OR: 4.07; 95%CI: 1.20–13.79; $P = 0.02$)[31].

In the earlier post-mortem examinations, Xu *et al*[32] found moderate microvesicular steatosis and mild inflammatory infiltrates in the hepatic lobule and portal tract. Mild sinusoidal dilatation, focal macrovesicular steatosis, and mild lobular lymphocytic infiltration has been also reported[33]. Fiel *et al*[23] described the biopsies of two patients that successfully recovered from COVID-19, showing a mixed inflammatory infiltrate with prominent bile duct damage, endothelitis, and numerous apoptotic bodies. *In situ* hybridization and electron microscopy suggested the intrahepatic presence of SARS-CoV-2, thus supporting the possibility of a direct cell injury.

Macrovesicular steatosis was the most common finding (75%) in 40 liver biopsies from patients that died due to a complicated COVID-19 course. Mild lobular necroinflammation and portal inflammation were present in 20 cases each (50%), whereas viral RNA was detected by RT-PCR on liver tissue in 55% of patients tested[34].

Both the diagnosis and treatment of cancer have been negatively affected by the COVID-19 pandemic and the resulting pressure on the health care services worldwide. Patients with hepatocellular carcinoma (HCC) represent a vulnerable population with a significant treatment delay. In a multicenter, retrospective study performed in Paris, Amaddeo *et al*[35] found a significant decrease in the number of patients with HCC presented to the multidisciplinary tumor committee. The proportion of patients that experienced a treatment delay longer than 1 mo increased between 2019 and 2020 from 9.5% to 21.5%.

IMPACT OF COVID-19 ON LT ACTIVITY

The effect of the pandemic has been heterogeneous in terms of donation and transplant activity. Nevertheless, a notable reduction has been reported from most institutions across Europe and North America during the peak of COVID-19 incidence, mainly related to the burden of patients admitted to the ICU and the associated effects on candidate referral and perioperative care[36]. Such a decrease in LT activity was particularly profound in March and April 2020, during the first wave that affected many Western countries. De Simone described the reorganization of LT units carried out in so many centers worldwide during the first wave: Cancellation of routine patient follow-up, outpatient care limited to recent LT recipients, pre-transplant referral limited to priority patients after telephone triage, follow-up by means of phone calls on the waiting list, and implementation of health care worker (HCW) safety

policies[36]. This rapid reorganization allowed for maintaining the activity of a high-volume center in Pisa during the Italian national lockdown (February 18 to May 4, 2020), despite the marked drop observed between March 16 and April 5. This was achieved due to the increase in ICU bed capacity, systematic screening for SARS-CoV-2, creation of COVID-19-dedicated ICUs, recruitment of additional medical and nurse staff, rescheduling of elective surgery to priority cases, and continuation of LT activities in COVID-19-free areas[37].

A preliminary analysis of the impact on Italian LT programs was done by means of a survey issued on March 16, 2020 and completed by 22 centers[38]. There were two major geographical areas with different incidence of SARS-CoV-2 infection, north-central Italy and south-central Italy. Between February 15 and March 15, all transplant programs reduced their outpatient activity by 68% in terms of pre-transplant evaluation and 100% in the post-transplant face-to-face follow-up. A reduction in transplant activity was also seen in northern-central Italy during the first 2 wk of March, but not in the southern-central area. Recovered donors dropped by 46% during the first peak (the 4-wk period after February 23) as compared to the preceding 8-wk period[39].

In Spain, according to data provided by the Spanish National Transplant Organization [Organización Nacional de Trasplantes (ONT)], the mean number of donors declined since the national state of alarm was declared on March 13 from 7.2 to 1.2 per day, and the mean number of transplants from 16.1 to 2.1 per day[40]. There was a saturation of the health care system and ICU capacities (although most hospitals had increased the number of ICU beds), and many HCWs became infected (15.5% of the infected population at that time) or forced to quarantine. The number of potential donors declined due to the decrease in neurocritical patients or due to a positive result in SARS-CoV-2 screening. In addition, logistical problems arose as a consequence of the restricted mobility and declining organ offers following a risk assessment that included the clinical situation of the recipients, and even human resources were reduced due to cases of COVID-19 among HCWs. Finally, in the pandemic scenario, some candidates refused transplantation after informed consent[40].

The impact of the first wave on the LT activity in France resulted in an overall 28% decrease in the number of donations when comparing the first 4 mo of 2019 with the corresponding period of 2020, whereas the number of LT effectively performed dropped by 22%. The north-eastern region of the country (with the highest incidence rate of COVID-19) experienced reductions in multiorgan procurement and LT activity of 33% and 26%, respectively[41].

A national state of emergency was declared in the United States by March 13, 2020. A retrospective analysis of data collected from January 5 to September 5, 2020 by the Organ Procurement and Transplantation Network revealed a decrease of 37% in the number of LT procedures performed between March 8 and April 5[42]. Since mid-March, many waitlist patients were placed in temporarily inactive status due to COVID-19 concerns. This practice affected over 2000 waitlist registrations during the week of March 22. LiveOnNY, the organ procurement organization for the greater New York metropolitan area, suffered a drop to 10 donors in April 2020 from 26 in March, although this figure recovered to 18 donors in May[43].

A multinational study performed in India, the United Kingdom, and the United States compared the weekly organ donation and LT numbers over a 3-mo period (February 17 to May 17, 2020) and the LT activity in six centers with varying local COVID-19 caseload[44]. Peak reduction ranged from 25% in the United States to more than 80% in the United Kingdom and India.

On the contrary, the impact of COVID-19 on LT activity has been reported to be almost negligible in other countries. Lee concluded that establishing safe processes and procedures can be beneficial in reducing the negative effects of the national lockdown and saving patients' lives, as he analyzed LT procedures performed in South Korea[45]. He compared the MERS outbreak, the COVID-19 pandemic, and the average number of LT performed throughout the prior 5 years. There was a significant decrease of 11% in the LT activity during the MERS outbreak, although the number of procedures was maintained from January to March 2020. In addition, none of the 401 patients undergoing LT during the COVID-19 outbreak were confirmed to be infected with SARS-CoV-2. Some Italian centers located in medium- or high-incidence areas were also able to maintain a stable LT activity by means of appropriate screening and isolation practices, dedicated COVID-19-free routes, and reorganization of ICU resources[36,46,47].

A great variability in the adaptation of LT practices in response to the COVID-19 pandemic has been observed within the same country and even the same region[48]. On the other hand, the detrimental impact on LT activity seems to have been not

restricted to those areas facing the highest COVID-19 burden. According to Agopian *et al*[48] such differences across centers likely reflect variations in the allocation and prioritization of hospital resources, local capacities to timely screen for SARS-CoV-2 infection among SOT candidates and recipients, and concerns with respect to donors (*e.g.*, accuracy of testing), recipients (*e.g.*, role of baseline IS), and transplant team members (*e.g.*, risk of hospital-acquired COVID-19).

The effect on the LT waiting list in the United States has been studied by Strauss *et al*[49] using data from the Scientific Registry of Transplant Recipients. From March 15 to April 30, new listings were 11% lower than expected, and deceased donor LTs (DDLTs) decreased by 9%. In May, new listings were 21% lower and living donor LTs were 42% lower, whereas DDLTs increased by 13%. In states with the highest incidence of COVID-19, the number of deaths in the waiting list increased by 59%. By August, waitlist outcomes were occurring at expected rates except for DDLT. According to the authors, these results reflect the adaptability of the transplant community in addressing the COVID-19 pandemic and applying new knowledge to patient care.

Putzer *et al*[50] found a 29% decrease in the number of LT procedures performed in the Eurotransplant area between mid-March and mid-June 2020, with regards to the corresponding periods from 2015 to 2019. Of note, the activity in Germany continued at the same pace during the initial phase of the crisis, likely thanks to the higher number of ICU beds in that country. However, the number of LTs increased slowly compared to the first month of observation.

INCIDENCE OF COVID-19 IN LT RECIPIENTS

According to the survey performed by the European Liver and Intestine Transplantation Association (ELITA) and the European Liver Transplant Registry (ELTR), the crude incidence of SARS-CoV-2 infection among LT candidates and recipients during the first wave in Europe has been overall estimated in 1.05% (range: 0.5%-20%) and 0.34% (range: 0.1%-4.8%), respectively[51]. One hundred nine out of 149 (73.2%) ELTR centers located in 28 European countries responded to the survey. Eighty-eight centers reported the diagnosis of COVID-19 in 57 LT candidates and 272 recipients. The highest numbers of infected recipients were reported from Spain (77), Italy (66), and France (59). Crude case fatality rates in candidates and recipients were 18% and 15%, respectively. The authors concluded that both LT candidates and recipients are at high risk of COVID-19 and highlighted the need for an early and proactive screening for SARS-CoV-2 infection in these populations.

Cumulative incidence of COVID-19 has been highly variable across European countries. The King´s College group only reported 5 cases out of about 4500 LT recipients (0.1%) followed-up in their institutional cohort during the first wave[52]. In fact, LT recipients appeared to have a lower incidence of COVID-19, with less severe symptoms, as compared to the general population or other SOT populations, likely due to the better individual adherence to self-isolation recommendations or the optimal level of IS, which would favorably modulate the response against SARS-CoV-2.

A nationwide study promoted by the Spanish Liver Transplantation Society (SETH) recruited 111 LT patients from February 28 to April, 7 2020 and revealed a higher incidence of COVID-19 compared to the general population, almost doubling the expected number of cases[53]. A preliminary experience from our institution showed a cumulative incidence from March 15 to May 5 of 1.6% (19 out of 1200) among LT recipients compared to 0.95% in the general population of Madrid, although potential underreporting due to limited diagnostic capacities at that time could not be ruled out [54].

A detailed study carried out in the United Kingdom comprised SOT recipients diagnosed with SARS-CoV-2 infection in England up to May 20, 2020 and showed a cumulative incidence of 1.3% and 0.7% (64 out of 8734) for the specific group of LT recipients[55].

As the pandemic evolved during 2020, different institutions and groups have provided updated epidemiological data. On the basis of data collected by the Italian Information Transplant System until June 22, Trapani *et al*[56] found a cumulative incidence of 1.02% among SOT recipients as compared to 0.4% in the non-transplant population ($P < 0.05$). This figure was lower (0.63%) for LT recipients. Authors from the Shiraz University of Medical Sciences in Iran, one of the largest transplant centers in the world, published their results by mid-July[57]. They found 85 cases of COVID-

19 among abdominal transplant recipients (66 in LT recipients). As of July 2020, 0.32% of the population of the country was infected, with a mortality rate of 5.1%. Among 6969 SOT recipients followed-up at their center, 85 (1.21%) had been diagnosed with COVID-19, and 17 (20%) had died. Their conclusion was that LT and kidney transplant recipients face a poorer outcome due to COVID-19.

Not surprisingly, cumulative incidence has steadily increased over the last months, reflecting variations in the epidemiology of COVID-19 in the general population. In our institution, we have registered 67 cases of SARS-CoV-2 infection by the end of January 2021, accounting for more than 5% of followed-up LT recipients (data not published).

RISK FACTORS FOR SEVERE COVID-19 IN LT RECIPIENTS

In an early retrospective, multicenter cohort study, Zhou *et al*[58] reported detailed clinical course and risk factors for mortality in 191 non-transplant patients with COVID-19 from Wuhan that had been discharged or died by January 31, 2020. Hypertension (30%), diabetes (19%) and coronary heart disease (8%) were the most common comorbidities in the general population. The authors found that older age, higher Sequential Organ Failure Assessment score and D-dimer levels above 1 μg/mL on admission were associated with in-hospital death at multivariable regression.

Mainly reflecting the risk factors identified in the general population, older age, the presence of chronic comorbidities (congestive heart failure, chronic obstructive pulmonary disease, or obesity), lymphopenia (absolute lymphocyte count < 0.5 x 10^9 cells/L), and abnormal chest imaging at admission were independently associated with mortality (20.5%) in a cohort study comprising 482 SOT recipients (73 LT recipients) from more than 50 United States centers[59].

Preliminary data from the ELITA/ELTR registry on 103 LT recipients diagnosed with COVID-19 between March 1 and April 24, 2020 revealed the following co-morbidities: Overweight (56%), hypertension (51%), diabetes (41%), chronic renal impairment (serum creatinine level > 2 mg/dL) (15%), smoking history (13%), and coronary artery disease (7%). After a median follow-up of 18 d, overall all-cause mortality rate was 16%, but it reached 22% among patients ≥ 60 years and 44% in those requiring IMV[60]. Although the difference did not achieve statistical significance, mortality was found to be lower among patients that had undergone LT within the previous 2 years as compared to those with longer intervals since transplantation (5% *vs* 18%). Of note, all deaths occurred among patients aged 60 years or older.

In the SETH study the most common comorbidity was hypertension (57.7%), whereas risk factors for severe COVID-19 among hospitalized patients included Charlson comorbidity index, male gender, dyspnea at diagnosis, and baseline immunosuppression containing MMF, particularly at doses higher than 1000 mg/d [53].

The assessment of SARS-CoV-2-attributable mortality after LT must take into account the impact of baseline conditions. A multicenter study from the COVID-Hep and SECURE-Cirrhosis international registries performed between March 25 and June 26, 2020 compared the outcomes of 151 adult LT recipients and 627 patients with SARS-CoV-2 infection who had not undergone transplantation. Older age, serum creatinine levels, and non-liver cancer were associated with mortality. In a propensity score-matched analysis (adjusted for age, sex, major comorbidities, and ethnicity), LT did not significantly increase the risk of death in patients (absolute risk difference: 14%; 95%CI: -7.7–10.4)[61]. Similar findings have been also reported for kidney transplant recipients[62].

COVID-19 PRESENTATION IN THE SETTING OF LT

There is a male predominance across different series of LT recipients with COVID-19, from 68%[61] to 78.8%[57]. Median age in adult patients ranges from 60[59] to 65 years [53,60]. Low-grade fever was the most frequent symptom in the earlier reports from Wuhan, followed by cough, fatigue, myalgia, and digestive symptoms (diarrhea, nausea, or vomiting)[58]. Among LT recipients with COVID-19, the presence of fever is also reported in 62.7%[57] to 79%[62] of cases. Cough (with rates ranging from 40.9% [57] to 70.3%[52]), myalgia (37%[60] to 45.5%[57]), fatigue (40.9%[57] to 56%[62]), dyspnea (30.3%[57] to 46%[63]), gastrointestinal symptoms (22.6%[60] to 39.4%[57]), and smell and taste disorders (7%[63]) are also common at presentation.

Becchetti *et al*[63] observed a higher prevalence of fever and dyspnea in long-term LT recipients (more than 10 years from the procedure), whereas the presence of fever and cough was significantly less likely among very short-term recipients (≤ 1 year) [63]. Asymptomatic patients are scarce. In the SETH series they accounted for 6.3% of cases only, whereas most of the patients admitted to the hospital (66%) required some type of respiratory support[52].

Chest X-ray or computed tomography scan showed typical features of COVID-19 in 62% of patients in the series by Belli *et al*[60] and 78.4% in the SETH cohort (unilateral in 19.8% and bilateral in 58.6%)[52]. Becchetti *et al*[63] reported typical radiological features (bilateral, peripheral, consolidation, or ground glass opacities) in 43% of computed tomography scans and 40% of X-ray examinations performed[63].

Only 8% of the patients reported by Becchetti *et al*[63] had a significant increase in transaminases (AST and/or ALT > 2 times the ULN), whereas this figure reached 14.7% in the series by Colmenero *et al*[53]. Mean lymphocyte and platelet counts were decreased in patients with severe disease. Lymphopenia was present in 68.8% of the patients reported by Malekhosseini *et al*[57] and 76% of those reported by Becchetti *et al*[63]. The nadir of absolute lymphocyte count during hospital stay was 0.31 x 10^9 cells/L among severe cases (versus 0.5 × 10^9 cells/L in the non-severe forms of infection; P = 0.013). Other markers as D-dimers of ferritin levels were significantly higher in severe cases[53], although data were not available for most patients[63].

OUTCOME IN LT RECIPIENTS WITH COVID-19

The percentage of mild cases managed as outpatients varied in different series from 13.5%[53] to 42.4%[57]. Most of the published cohorts reported rates of hospitalization in the range of 66% to 82%[60,61,63], with a mean hospital stay of 9-10 d[57,63]. Notable variation was observed in the proportion of ICU admission (from 10%[63] to 31.6%[57] of hospitalized patients), which likely reflect regional differences in the availability of critical care resources. Regarding respiratory support, invasive or non-invasive mechanical ventilation was used in 10%[63] to 20%[61] of recipients, including extracorporeal membrane oxygenation in 10.6% of the patients in one series [57].

Reported mortality rates ranged between 12%[61] and 19%[61], close to those observed in large series in the general population (15-21%)[1,64]. Colmenero *et al*[53] showed that, after adjusting for age and gender, the number of observed deaths among LT patients was slightly lower than expected in the general population, resulting in a standardized mortality ratio of 95.55 (95%CI: 94.25–96.85).

Four out of 5 patients that contracted COVID-19 within the first month after transplantation in Shiraz died[57]. The authors attributed this dismal outcome to the higher amount of IS given during the very early post-transplant period. On the other hand, there are several reports on successful recovery in patients diagnosed with SARS-CoV-2 infection very shortly after LT[65-69].

Bhoori *et al*[13] were the first to suggest that long-term LT survivors on minimal IS therapy would face a greater risk of death following COVID-19 infection, thus proposing that a higher IS level could play a protective role. A systematic review pooling outcomes of 223 LT recipients from case-series and cohorts published up to June 15, 2020, however, revealed no significant differences in mortality rates between recent (< 2 years) and remote (≥ 2 years) LT recipients (16.7% *vs* 21.9%, respectively; P = 0.5)[70].

THERAPEUTIC APPROACHES IN LT RECIPIENTS WITH COVID-19

Antiviral therapies

Most LT recipients included in the series reported during the first pandemic wave were treated with repurposed drugs with *in vitro* activity against SARS-CoV-2, despite the lack of supporting clinical evidence at that time. For instance, the use of hydroxychloroquine (HCQ) (66%), azythromycin (33%), and lopinavir/ritonavir (LPV/r) (17%) was common among LT recipients recruited in the ELITA/ELTR registry between March 1 and April 24, 2020[60]. These rates were even higher in the SETH registry, with as many as 88% and 40% of patients receiving HCQ and LPV/r, respectively[53]. Of note, no differences in the use of these agents were observed according to the severity of COVID-19. In addition, the multicenter registry collected by the ONT in Spain showed that the proportion of recipients treated with protease inhibitors

(mainly LPV/r), HCQ, and azithromycin was similar across different SOT populations, suggesting that the therapeutic approach in LT recipients did not substantially differ from that used in patients usually exposed to a higher level of IS, such as heart or lung transplant recipients[71]. As expected, the management of drug-to-drug interactions between LPV/r, a potent cytochrome P450 3A4 inhibitor, and calcineurin or mammalian target of rapamycin (mTOR) inhibitors was particularly challenging[16,72]. In our experience, two LT recipients under everolimus were converted to low-dose prolonged-release tacrolimus (0.5 mg/wk) in order to facilitate the adjustment of IS during hospitalization[54].

No outcome benefit has been demonstrated from the use of LPV/r, HCQ, or subcutaneous interferon-β in the setting of randomized controlled trials (RCTs) conducted over the past months[73-75]. The RNA-dependent RNA polymerase inhibitor remdesivir is the only antiviral agent currently approved for the treatment of COVID-19, in view of the shorter time to clinical recovery obtained with this agent as compared to placebo[76]. The clinical experience with remdesivir in LT recipients, nevertheless, is scarce, with only a few treated patients in large multicenter cohorts[53,71]. Since remdesivir and its main active metabolite GS-441524 are mainly excreted by the kidney, no major drug-to-drug interactions with tacrolimus, MMF, or mTOR inhibitors are to be expected, whereas limited experience with cirrhotic patients has revealed no new safety signals[28]. Abnormal liver function test was not reported as a common adverse event in the ACTT-1 trial, although exclusion criteria included the presence of ALT or AST levels > 5 times the ULN[76].

Immunomodulatory therapies

The clinical course of severe forms of COVID-19 is characterized by the presence of an excessive inflammatory response triggered by SARS-CoV-2 and orchestrated by the host immune system, which contributes to the development of tissue damage, multiorgan failure, and ARDS[77]. Such a pathogenic mechanism has led to the widespread use of various immunomodulatory strategies aimed at blocking this "cytokine storm", including corticosteroids[78], anti-IL-6 (such as tocilizumab or sarilumab)[79] and anti-IL-1β (canakinumab or anakinra)[80] agents, or janus kinase inhibitors (baricitinib)[81]. With the exception of low-to-intermediate-dose systemic corticosteroids (*i.e.* dexamethasone 6 mg daily for 10 d), which have been shown to decrease 28-d mortality in patients requiring respiratory support[82], there remains controversy regarding the clinical benefit to be expected from these agents in the general population with COVID-19, with conflicting results from observational studies and RCTs.

The available evidence supporting the use of immunomodulatory therapies in SOT recipients is even more limited[83]. Nevertheless, multicenter registries revealed that anti-IL-6 agents were commonly administered during the first pandemic wave (with overall rates ranging from 13%[59] to 21%[71]). In the specific group of LT recipients, 5% and 1% of patients included in the ONT registry as of July 2020 had received tocilizumab and anakinra, respectively[71]. The off label use of tocilizumab in other cohorts ranged from 6.2% in the ELITA/ELTR registry[84] to 15.6% in the SETH registry[53]. As previously stated, no RCTs have assessed to date the role of therapeutic IL-6 blockade in the setting of post-transplant COVID-19 with cytokine release syndrome. A small retrospective study compared 29 SOT recipients treated with tocilizumab for severe COVID-19 (including one single LT recipient) with a matched control group of recipients who did not receive this agent. No significant differences were observed in terms of in-hospital mortality (41% *vs* 28%, respectively; $P = 0.27$), hospital discharge (52% *vs* 72%; $P = 0.26$), or secondary infections (34% *vs* 24%; $P = 0.55$), although the higher rates of IMV and renal replacement therapy observed in the tocilizumab group suggest some degree of confounding by indication not completely controlled by the matching process[85].

Management of immunosuppression

As commented above, some preliminary reports showing a worse outcome among long-term LT recipients on minimal immunosuppressive regimen (as compared to recently transplanted, fully immunosuppressed patients)[15] led to propose during the first weeks of the pandemic that post-transplant IS might be actually protective in severe COVID-19[86]. Clinical experience accumulated over the past months, however, does not seem to confirm this hypothesis. Indeed, the SETH registry demonstrated the deleterious impact of baseline MMF-containing regimens (particularly when given at doses higher than 1000 mg/d). This negative effect was not observed for calcineurin or mTOR inhibitors. Complete MMF withdrawal during hospitalization showed a trend towards a reduced risk of progression to severe COVID-19 (41.7% *vs* 69.2%; $P = 0.16$)

[53].

The most common adjustment of baseline IS among more than 600 SOT recipients enrolled within the ONT registry was the withdrawal of the anti-metabolite drug (MMF or azathioprine), whereas calcineurin inhibitors were generally managed with dose reduction[71]. It is likely that the impact of baseline IS on the outcome of SARS-CoV-2 infection differ according to individual drugs. Belli *et al*[84] have recently shown that the use of tacrolimus was independently associated with a reduced mortality risk in the ELITA/ELTR registry (hazard ratio: 0.55; 95%CI: 0.31–0.99). The authors propose that tacrolimus could exert a direct antiviral effect through the immunophilin FK506-binding proteins[87].

In accordance with the survival benefit demonstrated for dexamethasone in the RECOVERY trial[82], baseline corticosteroid dose was usually maintained or increased in most LT recipients hospitalized due to COVID-19. In addition, corticosteroids boluses were given in 12.5% of patients in the SETH registry (4.9% and 25.7% of those with non-severe or severe COVID-19, respectively)[53].

SARS-COV-2 VACCINATION IN LT RECIPIENTS

Whereas messenger RNA SARS-CoV-2 vaccines provide excellent rates of seroconversion and clinical effectiveness in the general population[88,89], immunogenicity in the setting of SOT appears to be severely compromised. Most available reports, however, are focused on kidney[90-92] or lung transplant recipients[93]. In addition, only a few studies have assessed the development of SARS-CoV-2-specific T-cell-mediated immunity in addition to antibody responses[94,95]. Rabinowich *et al*[96] tested for SARS-CoV-2 immunoglobulin G antibodies against the SARS-CoV-2 spike glycoprotein 10-20 d after the administration of the second BNT162b2 vaccine dose in 80 LT recipients. Detectable humoral response was demonstrated in 47.5% of patients only (as compared to 100% of HCWs used as control group). In addition, the mean antibody titer was significantly lower in LT recipients (95.41 AU/mL *vs* 200.5 AU/mL, respectively). Older age, lower estimated glomerular filtration rate, and treatment with MMF or high dose steroids were associated with the lack of vaccine response, with no apparent impact of the time since transplantation. The vaccine was well tolerated, and there were no episodes of suspected or confirmed graft rejection during the follow-up [96]. This disappointing immunogenicity is, however, in line with the rates reported for other SOT populations. The deleterious effect of the anti-metabolite drug has been also shown for kidney and lung transplant recipients[90,93].

GUIDELINES FOR THE MANAGEMENT OF LT DURING THE COVID-19 PANDEMIC

On November 9, 2020, the American Association for the Study of Liver Diseases (AASLD) issued updated guidelines for LT providers in the current pandemic scenario [97]. Regarding the management of the waiting list, the document recommends to continue to prioritize the initial evaluation of patients with HCC or those with severe disease and high Model for End-stage Liver Disease (MELD) scores who are more likely to benefit from immediate LT listing. Some listed patients should be still seen in person according on the local incidence of SARS-CoV-2 infection and individual patient factors (such as their Model for End-stage Liver Disease score). Telemedicine alternatives may be considered for the remaining candidates. In addition, the AASLD guidelines recommend to develop hospital-specific policies for organ acceptance, taking into account the availability of ICU beds and other hospital resources. Potential donors and recipients must be screened for SARS-CoV-2 exposure and clinical symptoms compatible with COVID-19 (regardless of test results or availability). In addition, all donors and recipients should be screened for SARS-CoV-2, by means of nasopharyngeal swab, bronchoalveolar lavage, or both, taking into account the risk of false negative results, disease prevalence, and testing turnaround time in your area. Alternatives to RT-PCR-based testing such as chest X-ray may also be also considered. Ideally, LT in SARS-CoV-2-positive candidates should be delayed for at least 14-21 d after symptom resolution and one or two negative SARS-CoV-2 diagnostic tests. Of note, the decision to ultimately proceed with LT in a candidate recovering from COVID-19 must be individualized based on several factors (such as the urgency of transplantation, the presence of respiratory symptoms, and the risk of exposing HCWs

to SARS-CoV-2).

Regarding the approach to LT recipients diagnosed with COVID-19 in the AASLD guidelines, it should be considered lowering the overall level of IS (particularly anti-metabolite doses) based on general principles for managing post-transplant infections and in order to decrease the risk of secondary infection. The risk of COVID-19-associated kidney injury should be also taken into account and calcineurin inhibitor levels must be closely monitored. Likely due to the lack of supporting evidence, no clear recommendations are provided regarding the optimal regimen and timing for antiviral and immunomodulatory therapies.

In addition, the AASLD expert panel advises against making anticipatory adjustments in current immunosuppressive regimens in LT recipients with no diagnosis of SARS-CoV-2 infection. Prevention measures (*e.g.*, hand washing, cleaning frequently touched surfaces, staying away from large crowds, *etc*.) should be emphasized in this at-risk population[97].

Finally, although specific guidelines on the optimal vaccination strategy are scarce and based on low-level evidence, the Italian Association for the Study of the Liver recommends that LT candidates should be prioritized due to the high risk of mortality in the waiting list. Vaccination of the partners and caregivers of cirrhotic patients and LT recipients should be also encouraged[98].

CONCLUSION

Although with geographical differences across countries, COVID-19 has exerted a negative impact on LT transplant activity (both in the number of donors and procedures) during the first months of the pandemic, with decreases ranging from 28% to 46%[38,40,42,43]. The cumulative incidence of SARS-CoV-2 infection in LT recipients has been estimated between 0.34%[50] to 1.56%[52]. These figures appear to be comparable to that observed for the general population, although some studies suggest that the incidence of COVID-19 after LT would be lower as compared to other types of SOT[54]. The clinical and radiological characteristics of COVID-19 at presentation are overall similar to non-transplant patients, including predictive factors of poor outcomes. All-cause mortality among hospitalized recipients is high (from 12%[61] to 19%[59]), and great heterogeneity in the rates of ICU admission is observed across different series (10%[61] to 31.6%[55]). It has been also proposed that the risk of death may be actually lower compared to the non-transplant population[51]. The outcome of post-transplant COVID-19 seems to depend mainly on the age of the recipient and the number of chronic comorbidities, rather than by the transplant status itself[59]. Some studies have suggested that post-transplant IS —in particular tacrolimus-containing regimens— may play a protective role by abrogating the deleterious effect of the cytokine release syndrome occurring during the course of SARS-CoV-2 infection or through a direct antiviral activity[83]. To date, there is scarce evidence to guide the use of antiviral or immunomodulatory therapies for COVID-19 after LT, including the potential effectiveness and safety of remdesivir or anti-IL-6 agents[82]. Both clinical experience and guidelines recommend the dose reduction of IS or withdrawal of MMF and other anti-proliferative agents[51,87]. Although specific studies are still scarce, messenger RNA vaccines seem to be safe in LT recipients in terms of serious adverse events or risk of alloimmunity, although the magnitude of SARS-CoV-2-specific immunoglobulin G antibody response is severely decreased as compared to non-immunocompromised individuals[97].

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