

78714_Auto_Edited-check.docx

Name of Journal: *World Journal of Transplantation*

Manuscript NO: 78714

Manuscript Type: MINIREVIEWS

Liver transplantation during COVID-19: Adaptive measures with future significance

Gyftopoulos A *et al.* Liver transplantation during COVID-19: Adaptive mechanisms

Abstract

Following the outbreak of coronavirus disease 2019 (COVID-19), a disease caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the field of liver transplantation, along with many other aspects of healthcare, underwent drastic changes. Despite an initial increase in waitlist mortality and a decrease in both living and deceased donor liver transplantation rates, through the implementation of a series of new measures, the transplant community was able to recover by the summer of 2020. Changes in waitlist prioritization, the gradual implementation of telehealth, and immunosuppressive regimen alterations amidst concerns regarding more severe disease in immunocompromised patients, were among the changes implemented in an attempt by the transplant community to adapt to the pandemic. More recently, with the advent of the Pfizer BNT162b2 vaccine, a powerful new preventative tool against infection, the pandemic is slowly beginning to subside. The pandemic has certainly brought transplant centers around the world to their limits. Despite the unspeakable tragedy, COVID-19 constitutes a valuable lesson for health systems to be more prepared for potential future health crises and for life-saving transplantation not to fall behind.

Key Words: Liver transplantation; COVID-19; SARS-CoV-2; Vaccine; Immunosuppression; Telehealth

Gyftopoulos A, Ziogas IA, Montenovo MI. Liver transplantation during COVID-19: Adaptive measures with future significance. *World J Transplant* 2022; In press

Core Tip: Several articles in the bibliography report on the state of liver transplantation during coronavirus disease 2019 (COVID-19). To our knowledge, this is the first review to retrospectively investigate the various changes that occurred throughout the pandemic, but also recognize which interventions, and to what extent, are possibly going to help the transplant community improve beyond the end of COVID-19; in the event of a major health crisis in the future, transplant programs should be able to adapt

even faster to the rapidly changing landscape, in order for life-saving transplantation not to fall behind.

INTRODUCTION

Since December 2019, the coronavirus disease 2019 (COVID-19) pandemic has changed the landscape for transplant programs across the United States^[1]. Although helpful, the experience gained from previous outbreaks, like the middle eastern respiratory syndrome coronavirus, could not quite compare to the full-scale pandemic of the last two years. Therefore, transplant programs were largely unprepared for the challenges of the current pandemic, as evidenced by the complex moral decision of temporarily holding life-saving transplantation for fear of COVID-19 transmission amongst immunocompromised patients, the healthcare personnel, and the community^[2]. Despite primarily being a respiratory pathogen, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) impacts liver biochemistry and many other organs^[3,4]. The S protein on the surface of SARS-CoV-2 binds the angiotensin-converting enzyme 2 receptor on the surface of hepatocytes, injecting its viral genome inside liver cells^[5]. Aside from its direct cytotoxic effect, SARS-CoV-2 may adversely affect the liver through its systemic inflammatory response and, indirectly, through many potentially hepatotoxic medications employed to combat COVID-19^[6]. At the same time, the effect of COVID-19 on cirrhotic patients can be especially severe due to their baseline immunosuppression in the setting of chronic liver disease^[7]. However, it is not uncommon for SARS-CoV-2 to cause only mild elevations in hepatic enzymes, with patients otherwise remaining asymptomatic, either due to the virus' minor hepatotoxicity or through COVID-19-related inflammation of the muscles, with little direct injury to the liver^[8].

Because of the significant health risks the new coronavirus poses to patients with chronic liver disease and liver transplant recipients, the transplant community had to adapt to the pandemic. In the spring of 2020, and in the states most severely affected by COVID-19, new listings were 11% lower than anticipated, there were 59% more deaths in patients waiting for a transplant than expected, and 34% fewer deceased donor liver

transplantations. Fear of transmission amongst patients and healthcare workers has led to a series of new measures, such as regular testing, mandatory protective equipment against the virus, and telehealth to replace in-person visits during the pandemic^[9]. At the same time, the race to develop new vaccines against SARS-CoV-2 has given hope that the end of the pandemic is slowly approaching. COVID-19 accelerated the implementation of measures already in motion in the transplant community, albeit at a slower pace.

This review aims to retrospectively evaluate the status of liver transplantation during the pandemic, the effectiveness of multiple vaccine doses in liver transplant recipients, the recent change in the waitlist prioritization policy, potential alterations in immunosuppressive regimens for COVID-19 positive recipients, and explore the benefits and drawbacks of telehealth during and after the pandemic.

LIVER TRANSPLANTATION IN THE COVID-19 ERA

As the pandemic is slowly getting better controlled, the scientific community has a chance to evaluate how COVID-19 has affected liver transplantation programs during this unforeseen worldwide health crisis by tracing changes regarding vaccination protocols, waitlist prioritization, immunosuppression regimens, and the implementation of telehealth. These adaptive mechanisms may prove to be an invaluable lesson in the face of future health threats so that the rate of liver transplants will not descend again.

A query of the United Network for Organ Sharing database showed that, throughout the pandemic, whenever the number of new coronavirus cases peaked, primarily during the winter months, the number of transplants showed a concurrent decrease (Figure 1). In early 2020, from mid-March to mid-April, in states most severely affected by COVID-19, there were 11% fewer new listings, 49% fewer living donor transplantations, 9% fewer deceased donor liver transplantations, and 59% more deaths while waiting for a transplant than anticipated^[10]. Despite every successive COVID-19 wave inherently carrying different epidemiologic outcomes than those of the first wave,

transplant programs seemed to adapt to the changing landscape, as by August of the same year, except for deceased donor liver transplants, rates were within the expected range^[11]. The increased waitlist mortality, particularly during the first few months of 2020, can be explained by a multitude of factors, including deaths from end-stage liver disease while waiting for transplantation, the inability to admit patients facing complications of chronic liver disease, and the particularly severe impact of SARS-CoV-2 on obese patients with concurrent non-alcoholic steatohepatitis listed for transplantation^[12]. While SARS-CoV-2 has a direct toxic effect on the liver, the extent to which it can affect patients with chronic liver disease has not been definitively established; only mild elevations in liver enzymes are known to occur, with patients remaining otherwise asymptomatic^[13,14].

Observing how the transplant community managed to adapt relatively quickly by the summer of 2020, following a brief period of increased waitlist mortality and decreased living and deceased liver transplantation rates during the spring of 2020, it would be of great interest to investigate how the new liver transplant allocation policy change influenced that result. In December 2018, United Network for Organ Sharing approved a new allocation policy called the “acuity circle policy”, eventually implemented on February 4, 2020, coinciding with the beginning of the COVID-19 pandemic in late 2019^[15]. The new model would replace the “donation service area” distribution system, whereby one area was served by only one specific organ procurement organization. Under the new policy, the distance between donor and recipient was the primary determinant of organ allocation. Inevitably, states with lower COVID-19 incidence, where transplant centers were still active, received a larger volume of transplant patients from other, more heavily infested areas.

However, it is difficult to know the degree to which the changes that occurred after the acuity circle allocation policy resulted from the implementation of the new model or the concurrent outbreak of the coronavirus pandemic shifting the landscape for liver transplant allocation across the United States. By some preliminary estimates, under the new allocation system, adult patients with lower model for end-stage liver disease

(MELD) scores have received fewer transplants, while at high MELDs, transplantation rates were actually increased^[10]. According to Radhakrishnan and Goldberg, the new allocation policy has led to delays in procurement times due to the logistics involving procurement team travel, the challenges in working with new centers, and the increased number of possible local recipients^[16]. On the other hand, pediatric liver transplant recipients, median MELD/pediatric end-stage liver disease scores decreased under the new system, indicating that they were now receiving transplants earlier, thus avoiding the life-threatening risk of being diagnosed with late-stage disease by the time of transplantation^[17]. As the acuity circle allocation policy is relatively new, future studies may retrospectively prove its value during the outbreak of COVID-19 and may even display its usefulness after accounting for the drastic changes brought on by the pandemic. Regardless, seeing how the transplant community was able to adapt during the current pandemic, the acuity circle policy may prove to be a valuable tool, guiding efforts to improve waitlist mortality and deceased and living donor transplantation rates in the face of potential health crises in the future^[9,13].

IMMUNOSUPPRESSION AND COVID-19 IN LIVER TRANSPLANT RECIPIENTS

At the beginning of the pandemic, it was postulated that the use of immunosuppressive regimens in liver transplant recipients would predispose them to a higher risk for severe disease following COVID-19 infection. In a study of 39 solid organ transplant recipients, reported mortality following COVID-19 was 37.5% in the liver group^[18]. Despite the limited number of patients, mortality was significantly higher in immunosuppressed patients than in other studies. In a nationwide Korean study by Baek *et al*^[19] that included a total of 6435, both immune-competent and immunocompromised subjects, mortality in the immunocompromised group was 9.6% - including patients who had undergone transplantation in the last three years, were taking steroids or other immunosuppressants, were diagnosed with human immunodeficiency virus/acquired immunodeficiency syndrome or had a known malignancy^[19]. The potential risk of post-transplant immunosuppression regimens

contributing to a more severe clinical course in SARS-CoV-2 infected patients had to be balanced against the inevitable risk of rejection following reduction of the treatment. An individualized approach to immunosuppressive regimen alteration in the setting of COVID-19 was stressed by Giannis *et al*^[20], whereby not all transplant recipients, and certainly not all COVID-19 positive patients, are the same; in other words, COVID-19 complicated the already individualized approach to transplant regimen selection and therapeutic-range dose regulation even further^[20]. An Iranian study recruiting 265 liver transplant recipients with a median time since transplantation of 68 mo identified 25 patients who contracted COVID-19, four of whom eventually died. For fear of organ rejection, the patients' immunosuppressive regimens were only slightly modified, with mycophenolate mofetil (MMF) dose being reduced to limit liver enzyme level elevation. While previous studies have argued in favor of lowering immunosuppression during COVID-19, Sheikhalipour *et al*^[21], among others, have shown that despite minimal alterations in the patients' immunosuppressive regimen, most participants fully recovered from COVID-19^[22]. Ethical considerations regarding the risk of acute rejection following a significant reduction in the immunosuppressive regimen make randomized control trials investigating the role of immunosuppression discontinuation or decrease in the setting of COVID-19 inherently challenging.

The choice of immunosuppression has proven to variably affect postoperative mortality for coronavirus-positive liver transplant recipients. Tovikkai *et al*^[23] conducted a large retrospective study including 3837 liver transplant recipients from the United Kingdom. They showed cardiovascular disease and non-hepatic malignancy amongst transplant recipients were the primary determinants of mortality within 10 years after transplantation^[23]. Interestingly, in a study by Becchetti *et al*^[24], coronavirus-positive liver transplant recipients did not necessarily have worse outcomes than other solid transplant recipients, while only active extra-hepatic cancer was associated with increased mortality from SARS-CoV-2 infection, but cardiovascular disease did not predispose to a worse outcome. Immunosuppression was reduced in 39% of patients and discontinued in 7% - primarily in patients taking MMF^[24]. Importantly, patients

who did not require hospitalization due to COVID-19-related complications had no change in their immunosuppressive regimen, arguing that maintaining the immunosuppressant dose stable may not negatively impact outcomes in liver transplant recipients infected with SARS-CoV-2^[20]. Colmenero *et al*^[25] conducted a cohort study including 111 liver transplant recipients who tested positive for COVID-19, whom they followed for 23 d. Out of the 96 patients requiring admission, there was an 18% mortality rate, which was actually lower than that of the general population (28% and 42% in patients requiring high-dependency unit and intensive care unit admission, respectively), pointing towards a potential anti-viral effect of immunosuppressive therapy, with the exception of MMF^[26]. Although immunosuppressive regimen modification is a complex decision, one to be made by the transplant center regarding each individual patient, MMF has been associated with increased rates of severe COVID-19 at doses greater than 1000 mg per day, perhaps explained by the peripheral CD4⁺ depleting effect of MMF acting in synergy with the cytotoxic T-cell effect of SARS-CoV-2^[25]. On the contrary, mammalian target of rapamycin inhibitors have memory T-cell boosting effects, while calcineurin inhibitors are postulated by *in vitro* studies to tone down the cytokine storm responsible for acute respiratory distress syndrome in patients with COVID-19^[27,28].

COVID-19 VACCINATION IN LIVER TRANSPLANT RECIPIENTS

With the advent of the BNT162b2 vaccine, a safe and effective preventive strategy against COVID-19 was made available to transplant recipients. In a study by Hardgrave *et al*^[29], amongst 103 unvaccinated liver transplant recipients, before vaccination had been made widely available, 90-d mortality was 10%, with age > 60, use of belatacept and cyclosporin being associated with an increased risk, and tacrolimus acting as a protective factor. Interestingly, comorbidities (hypertension, diabetes, obesity) were not significantly associated with high mortality rates amongst unvaccinated individuals^[29]. Prior studies have demonstrated the safety and efficacy of inactivated and subunit vaccines against various pathogens in solid transplant recipients^[30]. It is not unlikely,

however, for immunocompromised patients to be unable to mount an adequate immune response following vaccination. Interestingly, liver transplant recipients have shown better immune response rates to SARS-CoV-2 vaccination than other solid organ recipients. Out of the 43 liver transplant recipients who received the second dose of the BNT162b2 vaccine, 79% developed antibodies, compared to 100% of immunocompetent individuals, but their response was reportedly superior to that of other solid organ recipients in the bibliography^[31]. According to the recent Global Hepatology Society Statement and the European Association for the Study of the Liver, liver transplant recipients are strongly encouraged to get vaccinated with any approved COVID-19 vaccine, as the benefits outweigh the risks of SARS-CoV-2 infection^[32-34].

The BNT162b2 vaccine is an mRNA vaccine that has proven to be safe, albeit with low immunogenicity, particularly following its second dose, in specific categories of liver transplant patients^[35]. In a group of 107 patients, just 76% achieved immunity six months following their second vaccine. However, after receiving their third dose, 91% of patients had sufficient antibody titers against SARS-CoV-2^[36]. Various factors have been reported to affect the degree of immunogenicity following vaccination in liver transplant patients (Figure 2). Combined immunosuppression with a calcineurin inhibitor and another agent, either MMF, steroids, or mammalian target of rapamycin inhibitors (double or triple regimen), were risk factors for a reduced immune response after the second dose of the BNT162b2 vaccine^[37,38]. Renal impairment was also associated with lower vaccine responses following the second dose, with a mean estimated glomerular filtration rate of 56 mL/min amongst patients who were unable to mount an adequate immune response *vs* 75 mL/min amongst patients who had a positive immunoglobulin G spike^[35]. Interestingly, renal toxicity is one of the key side effects of calcineurin inhibitors - the predominant immune suppressive agents used post-transplantation, which have even been shown to harbor a protective effect against severe COVID-19 disease^[39]. Older age is another significant risk factor for lower immunogenicity, with one study showing a mean age of 63 years in liver transplant recipients with a negative immune response, compared to 58 years in positive vaccine

responders^[35]. Furthermore, in a group of 365 patients, a higher body mass index (mean 27.7 in seronegative recipients *vs* 26.7 in positive vaccine responders, $P = 0.031$) and a shorter time since liver transplantation (11.9 years in seronegative recipients *vs* 14.7 years in seropositive transplant patients, $P = 0.031$) were also significant risk factors for attenuated vaccine response, according to Guarino *et al*^[40]. Mazzola *et al*^[41] identified diabetes as an additional risk factor for a negative response after the second dose of the SARS-CoV-2 BNT162b2 vaccine in a study that included 133 liver transplant recipients, with 46 out of 55 diabetic patients in the study group not mounting an adequate immune response following the second dose.

The variable effectiveness following each dose of the COVID-19 vaccine may reflect a different effect on T and B cell populations after every booster, with each cell type playing a different role in the immune system's defense against SARS-CoV-2. Despite the importance of humoral immunity in preventing infection following vaccination, the role of T-cell-mediated immunity has not been established^[42]. Although T cells (CD4, CD8) are theoretically implicated in the defense against SARS-CoV-2, a recent study by Ruether *et al*^[43] showed decreased rates of cellular immunity in liver transplant recipients following the second BNT162b2 vaccine dose^[38]. On the contrary, in 74 patients treated with rituximab, only 39% of patients seroconverted, indicating that CD19⁺ B cells seem primarily responsible for the immune response generated following the second vaccine dose. Interestingly, according to Davidov *et al*^[44], after receiving the third dose, 98% of patients seroconverted, compared to only 56% following the second dose. At the same time, T-cell counts increased significantly in all 12 liver transplant recipients who were evaluated^[44]. A similar T-cell amplifying effect was demonstrated by Schrezenmeier *et al*^[45] in a study of 25 kidney transplant recipients who had been unable to mount an adequate humoral response after their second dose. Thirty-six percent of those patients eventually generated humoral immunity, with CD4⁺ T-cell levels significantly increased in the same patients^[45]. In recipients with lower humoral titers following vaccination, a T-cell response may instead protect against the virus. Fernández-Ruiz *et al*^[46] demonstrated that 22% of liver transplant recipients had an

adequate T-cell spike response following their third vaccine dose. The role of T-cell mediated cellular immunity against SARS-CoV-2 as a complementary or second-line defense mechanism against the virus is yet to be investigated by future studies.

TELEHEALTH IN LIVER TRANSPLANTATION

SARS-CoV-2 has had a profound effect on nearly all aspects of medicine. Liver transplant centers, among others, have had to adjust their practices to the new landscape^[47]. High-volume centers were notably affected the most; the number of transplants performed had decreased initially, and the time spent on the waitlist had shortened. With approximately 15% of organs originating from coronavirus-positive donors, protocols and treatment regimens had to change. Notably, telemedicine emerged as a solution to the consecutive lockdowns and the unavoidable halt to in-person patient visits^[25]. While it is not without its downsides, there is a clear consensus on the benefits telehealth can have in liver transplant programs during the pandemic. As new protocols are implemented, telehealth is proving to be an effective alternative to in-person visits even after the end of the pandemic.

Proper follow-up, along with improvements in perioperative care, surgical technique, and immunosuppression, is largely responsible for the improved outcomes in liver transplant recipients over the last decades^[48]. Survival after transplantation is slowly approaching that of the general population, but at the same time, there is an increasing number of patients requiring postoperative follow-up. In the first five years following transplantation, major causes of mortality include cardiovascular disease and infection, while death after that time is usually attributed to malignancy, renal failure, and cardiovascular disease^[49]. Therefore, the importance of regular follow-up to ensure compliance with treatment, proper imaging, and biochemical studies cannot be understated. While cooperation between primary care providers, transplantation centers, and liver clinics is crucial, especially for patients living further away from the transplant hospital, telehealth may offer another option^[50].

Prior studies have demonstrated the usefulness of telehealth in heart failure and diabetic glucose regulation, exhibiting similar results to telephone follow-up and in-patient visits^[51]. With regards to liver transplantation, one study showed that long-term follow-up *via* telehealth had comparable outcomes to in-person follow-up, with the only drawback of requiring stricter control over tacrolimus levels^[52]. Importantly, 75% of physically stable transplant patients expressed interest in telemonitoring, with distance from the hospital being a major contributing factor. A different study by Le *et al*^[53] involving a small number of matched patients followed *via* telehealth underlined the increased satisfaction from shorter wait times and complete absence of travel, with 90% of patients stating they would opt for telemedicine again. In an interesting approach toward new technologies, Levine *et al*^[54] had 108 patients assigned to regular in-person follow-up, app-assisted follow-up in the form of tacrolimus level monitoring, and app-plus-smartwatch groups (mean ages 53, 52, and 50, respectively), demonstrating no significant difference in tacrolimus levels overall. Moreover, telehealth can impact multiple constituents of post-transplant patient care, from immunosuppression to lifestyle modification, as demonstrated by Barnett *et al*^[55] in a group of 19 liver transplant recipients, in whom telemedicine effectively promoted adherence to dietary and exercise recommendations.

Despite all the benefits telemedicine has to offer, especially amidst a pandemic, there are undeniable downsides to its use (Table 1). One study involving 98 young adults (*i.e.*, individuals acquainted with new technologies), who had undergone liver transplantation in childhood, showed that during the COVID-19 pandemic, of the 12 patients who were followed up *via* video calls, nine had experienced rejection episodes and were using telehealth as an adjunct to in-person visits^[56]. Delman *et al*^[57] also pointed out a rather concerning drawback regarding increased readmissions following telemonitoring. Despite not being statistically significant (41.9% *vs* 61.5% 30-d readmission rate in patients followed by telehealth), the exhibited difference could be partly explained by the lack of a physical exam; still, hospital length-of-stay was significantly shorter in the telemedicine group. Another possible drawback of new

technologies is the relative lack of access, as not all centers and not all patients can afford newer computer systems. At the same time, the learning curve may also prove to be a challenge for healthcare professionals and patients alike, who are not acquainted with the new technologies^[57]. Despite being more adept at embracing emerging technologies, young people may actually be the ones more challenged regarding adherence, therefore constantly being at risk of rejection^[58]. Lower socioeconomic status may further contribute to inequalities in the use of new technologies; namely, internet access is not always available; many patients may lack an appropriately private setting for the physician-patient encounter to take place; they may have limited English proficiency, or limiting visual or hearing impairment that may hinder proper physician-patient communication^[59]. Furthermore, technical problems often arise, as demonstrated by a recent randomized control trial recruiting 54 patients; only 17% of patients could attend all appointments without technical issues. Regardless, patients agreed that video appointments saved them time and money, were easier to attend, and limited the exposure of immunocompromised individuals to COVID-19 during the peak of the pandemic^[60]. All in all, the ideal use of new technologies may entail their co-implementation with the classic processes (*i.e.*, outpatient visits), especially as pandemic-related restrictions are slowly being lifted, contrary to telehealth replacing in-person appointments entirely. An interesting point could be made regarding the need for general physicians “closer to home” to be more deeply involved in the care of transplant recipients, complementing the role of telehealth and perhaps aiding the transplant community to overcome certain limitations associated with its use (*i.e.*, lack of a physical exam, software and hardware-related issues, accessibility difficulties)^[61].

CONCLUSION

Overall, during the last two-and-a-half years, the COVID-19 pandemic has significantly changed liver transplant programs worldwide. It is fair to say that certain changes, such as updated vaccination protocols or immunosuppressive regimen modifications, would never have happened had it not been to ameliorate the effect of COVID-19 on transplant

recipients. Other changes, however, such as the reformed waitlist prioritization policy and the implementation of telehealth, were accelerated by the pandemic. It is up to the scientific community to assess the outcome of these measures now that the pandemic is slowly subsiding; what was initially viewed as a “necessary evil” by many physicians could be a unique opportunity to overcome limitations and address pitfalls in the current system. In addition to the already existing problems, such as liver donor shortage, future health crises are now becoming a pressing concern, threatening to make the work of transplant centers even more challenging than it already is. The COVID-19 pandemic could be an invaluable lesson as, despite its terrible implications, perhaps it catalyzed significant changes in the transplant community that will help surgeons adapt in the face of significant health crises in the future.

ORIGINALITY REPORT

1 %

SIMILARITY INDEX

PRIMARY SOURCES

- | | | |
|--|--|------------------|
| <div style="background-color: red; color: white; padding: 5px; display: inline-block; width: 30px; height: 30px; text-align: center; line-height: 30px;">1</div> | debuglies.com
<small>Internet</small> | 16 words — < 1 % |
| <hr/> | | |
| <div style="background-color: magenta; color: white; padding: 5px; display: inline-block; width: 30px; height: 30px; text-align: center; line-height: 30px;">2</div> | Amy G. Feldman, Lara A. Danziger-Isakov. "The impact of COVID-19 on the pediatric solid organ transplant population", Seminars in Pediatric Surgery, 2022
<small>Crossref</small> | 13 words — < 1 % |
| <hr/> | | |
| <div style="background-color: purple; color: white; padding: 5px; display: inline-block; width: 30px; height: 30px; text-align: center; line-height: 30px;">3</div> | www.frontiersin.org
<small>Internet</small> | 12 words — < 1 % |
| <hr/> | | |
| <div style="background-color: teal; color: white; padding: 5px; display: inline-block; width: 30px; height: 30px; text-align: center; line-height: 30px;">4</div> | www.spandidos-publications.com
<small>Internet</small> | 12 words — < 1 % |

EXCLUDE QUOTES ON

EXCLUDE BIBLIOGRAPHY ON

EXCLUDE SOURCES < 12 WORDS

EXCLUDE MATCHES < 12 WORDS