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Contents

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REVIEW

- 255 Application of the cortical bone trajectory technique in posterior lumbar fixation
Peng SB, Yuan XC, Lu WZ, Yu KX
- 268 Allogeneic stem cell transplantation in the treatment of acute myeloid leukemia: An overview of obstacles and opportunities
Chen YF, Li J, Xu LL, Găman MA, Zou ZY
- 292 Idiopathic hirsutism: Is it really idiopathic or is it misnomer?
Unluhizarci K, Hacıoglu A, Taheri S, Karaca Z, Kelestimur F

MINIREVIEWS

- 299 Liver function in transgender persons: Challenges in the COVID-19 era
Milionis C, Ilias I, Koukkou E
- 308 Telenutrition for the management of inflammatory bowel disease: Benefits, limits, and future perspectives
Güney Coşkun M, Kolay E, Basaranoglu M
- 316 Liver transplantation amidst the COVID-19 era: Our center's experience
Khazaaleh S, Suarez ZK, Alomari M, Rashid MU, Handa A, Gonzalez AJ, Zervos XB, Kapila N
- 322 Prospects for the use of olfactory mucosa cells in bioprinting for the treatment of spinal cord injuries
Stepanova OV, Fursa GA, Andretsova SS, Shishkina VS, Voronova AD, Chadin AV, Karsuntseva EK, Reshetov IV, Chekhonin VP
- 332 Use of metaphors when treating unexplained medical symptoms
Seeman MV

ORIGINAL ARTICLE

Case Control Study

- 342 Microvesicles with mitochondrial content are increased in patients with sepsis and associated with inflammatory responses
Zhang HJ, Li JY, Wang C, Zhong GQ

Retrospective Study

- 357 Is fascial closure required for a 12-mm trocar? A comparative study on trocar site hernia with long-term follow up
Krittiyanitsakun S, Nampoolsuksan C, Tawantanakorn T, Suwatthanarak T, Srisuworanan N, Taweerutchana V, Parakonthon T, Phalanusitthepha C, Swangsri J, Akaraviputh T, Methasate A, Chinswangwatanakul V, Trakarnsanga A

- 366 Ten-year multicentric retrospective analysis regarding postoperative complications and impact of comorbidities in hemorrhoidal surgery with literature review

Moldovan C, Rusu E, Cochior D, Toba ME, Mocanu H, Adam R, Rimbu M, Ghenea A, Savulescu F, Godoroja D, Botea F

Observational Study

- 385 Tear inflammation related indexes after cataract surgery in elderly patients with type 2 diabetes mellitus

Lv J, Cao CJ, Li W, Li SL, Zheng J, Yang XL

CASE REPORT

- 394 Management of a rare giant cell tumor of the distal fibula: A case report

Fan QH, Long S, Wu XK, Fang Q

- 401 Repair of a giant inguinoscrotal hernia with herniation of the ileum and sigmoid colon: A case report

Liu SH, Yen CH, Tseng HP, Hu JM, Chang CH, Pu TW

- 408 Anti-leucine-rich glioma inactivated protein 1 encephalitis with sleep disturbance as the first symptom: A case report and review of literature

Kong DL

- 417 Fat-poor renal angiomyolipoma with prominent cystic degeneration: A case report and review of the literature

Lu SQ, Lv W, Liu YJ, Deng H

- 426 Perivascular epithelioid cell tumors of the liver misdiagnosed as hepatocellular carcinoma: Three case reports

Kou YQ, Yang YP, Ye WX, Yuan WN, Du SS, Nie B

- 434 H7N9 avian influenza with first manifestation of occipital neuralgia: A case report

Zhang J

- 441 Gefitinib improves severe bronchorrhea and prolongs the survival of a patient with lung invasive mucinous adenocarcinoma: A case report

Ou GC, Luo W, Zhang WS, Wang SH, Zhao J, Zhao HM, Qiu R

- 449 Habitual khat chewing and oral melanoacanthoma: A case report

Albagieh H, Aloyouny A, Alshagroud R, Alwakeel A, Alkait S, Almufarji F, Almutairi G, Alkhalaf R

- 456 Systemic lupus erythematosus with multicentric reticulohistiocytosis: A case report

Liu PP, Shuai ZW, Lian L, Wang K

- 464 X-linked Charcot-Marie-Tooth disease after SARS-CoV-2 vaccination mimicked stroke-like episodes: A case report

Zhang Q, Wang Y, Bai RT, Lian BR, Zhang Y, Cao LM

- 472 Acute liver injury in a COVID-19 infected woman with mild symptoms: A case report

Lai PH, Ding DC

LETTER TO THE EDITOR

- 479** Incidence and clinical treatment of hypertriglyceridemic acute pancreatitis: A few issues

Yang QY, Zhao Q, Hu JW

- 482** Management of infected acute necrotizing pancreatitis

Pavlidis ET, Pavlidis TE

ABOUT COVER

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Liver transplantation amidst the COVID-19 era: Our center's experience

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Abstract

Coronavirus disease 2019 significantly impacted the liver transplant process worldwide. Consequently, it brought significant challenges and limitations to transplant policies and organ allocation forcing liver transplant centers to adjust their protocols to ensure maximum benefit and avoid harm to their patients. Our center, like many others, was obliged to adapt to the challenges. This paper provided an overview of the effects of coronavirus disease 2019 on liver transplantations and detailed our center's experience and efforts during this unprecedented pandemic to serve as a guide for future public health crises.

Key Words: COVID-19; Liver transplantation; Immunosuppression; Experience; Mortality

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Core Tip: The coronavirus disease 2019 pandemic gave rise to an exceptional situation for liver transplantation (LT) around the world, initially leading to a decline in LT followed by a rapid recovery. This robust response resulted from extensive efforts by various LT centers to offset these challenges in addition to emerging evidence and the provision of appropriate guidelines from major LT societies. It is of the utmost importance to share experiences among LT centers to improve outcomes and reduce graft loss.

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INTRODUCTION

The coronavirus (COVID-19) pandemic represented an unforeseen crisis to healthcare systems and transplant centers around the world, resulting in significant changes to solid organ transplant (SOT) practices[1,2]. At the beginning of the pandemic, a decrease in SOT was observed and attributed to multiple factors, which included a shortage of resources and staff, a saturation of critical care beds, changes to the donor pool, and uncertainty regarding optimal post-transplant immunosuppressive therapy. The stress on the health care system forced most of the transplant centers to reduce liver transplant (LT) activity to best utilize scarce resources.

LT centers that continued their activity had to adjust their policies and develop strategies that ensured the safety of their patients, including protocols regarding testing of donors and candidates, reorganization of clinical and isolation protocols to establish a coronavirus-free pathway, rearrangement of the waitlist based on priority, and promotion of telemedicine to minimize exposure to the virus[3-5]. The United States was not the exception, and the initial reduction in the number of LT performed at the beginning of 2020 was followed by a brisk comeback in the second half of 2020 and early 2021. The emergence of evidence and recommendations by the international transplant societies was crucial in guiding LT programs during these unprecedented times[6].

In this article, we discussed our center's experience with COVID-19 regarding its effects on LT patients, including the pretransplant, perioperative and post-transplant periods.

COVID-19 EFFECTS ON LT VOLUME AT OUR CENTER

Soon after the pandemic was declared we observed a decline in the number of LT performed at our center, which was similar to other LT centers across the nation[7]. From March 2020 to February 2021, 42 LT were performed, representing a reduction of 14.28% of the cases when compared to the same period 1 year earlier. Subsequently, from March 2021 to February 2022, a 38.77% decrease in LT was noted when compared to the period between March 2019 and February 2020 and a reduction of 28.57% when compared to the period between March 2020 and February 2021 (Figure 1).

COVID-19-RELATED LT CONSIDERATIONS

Prevention

General COVID-19 preventive measures for LT candidates are similar to those established for the general public. We continue to recommend that LT recipients maintain personal measures to minimize exposure to COVID-19, such as social distancing, masking, and avoiding gatherings whenever possible, regardless of vaccination status.

LT centers faced significant ethical challenges of vaccine skepticism and uncertainty regarding if it should be mandatory for all candidates on the waitlist[8]. Based on guidance from international transplant societies, vaccination against COVID-19 was strongly recommended for patients with chronic liver disease[9]. However, SOT recipients were found to mount a lower humoral response to COVID-19 vaccination, for which the administration of booster doses was deemed necessary to achieve acceptable immunity[10,11].

On August 12th, 2021, the Food and Drug Administration approved a three-dose mRNA vaccine series for immunocompromised patients, including SOT recipients[12]. In addition, the Advisory Committee on Immunization Practices recommended that all immunocompromised adults should be vaccinated at least 3 mo after the third inoculation of the mRNA vaccine or 2 mo after the initial sequence of the Johnson and Johnson vaccine[13]. We agree with these recommendations, and in our

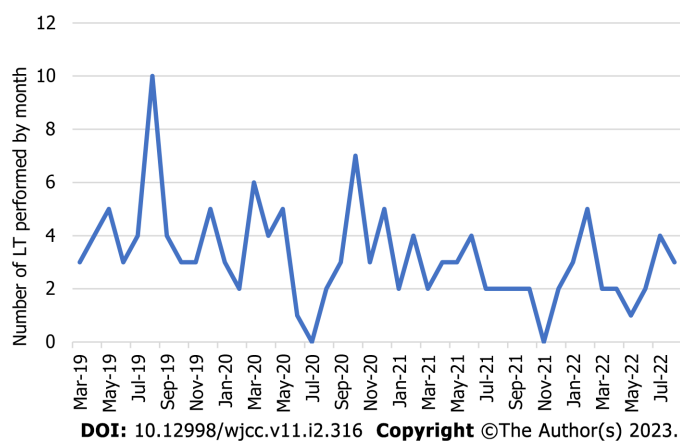


Figure 1 Number of liver transplants performed per month in our center between March 2019 and July 2022. LT: Liver transplant.

center we highly recommend that all patients listed for LT receive at least three doses of an mRNA vaccine before transplant.

At the beginning of 2022, the Food and Drug Administration published an Emergency Use Authorization for tixagevimab/cilgavimab (Evusheld), a long-acting monoclonal antibody for pre-exposure prophylaxis of COVID-19 in patients with moderate to severe immunosuppression[14]. Evusheld became an attractive armamentarium for protection against COVID-19 infection in LT recipients who may not be able to mount an appropriate immune response to the vaccine[15]. In a retrospective study that followed 378 patients with hematologic malignancies, less than 60% of patients seroconverted after the third vaccine dose, regardless of the therapy used. Thirty-three patients (8.8%) eventually developed COVID-19 infection, and among them 3 patients died due to severe infection. Importantly, no deaths occurred among patients who achieved seroconversion, and none of the patients who received Evusheld ($n = 25$) developed COVID-19 infection[10]. Although data on the use of Evusheld may be lacking in the SOT population, at our center we adopted the use of Evusheld in all patients who undergo LT, irrespective of vaccination status.

COVID-19 in LT candidates

Early case reports from Korea and India studied the viability of conducting an LT after 14-28 d of a positive COVID-19 infection in asymptomatic or minimally symptomatic patients[16,17]. In addition, a retrospective multicenter study from 11 European countries reported 26 patients who received an LT after a median of 78.5 d from an initial positive test for COVID-19. Even though LT candidates with symptomatic COVID-19 were at higher risk of early mortality when compared to counterparts with similar Model for End-stage Liver Disease scores, those who underwent LT had a favorable short-term survival of 96%. This study showed that once patients recover from COVID-19, LT is safe and encouraged[18].

In our center, patients on the waitlist who have a positive PCR test for COVID-19 are temporarily inactivated until becoming asymptomatic and 3 wk have elapsed since their initial positive test. Subsequently, if the patient had respiratory symptoms, we perform a contrast-enhanced computed tomography of the chest and pulmonary function tests before waitlist reactivation. Conversely, if the patient did not develop any respiratory symptoms, they are reactivated without further testing.

Donor COVID-19 positivity

During the beginning of the pandemic, transplant societies recommended against SOT in situations where donors tested positive for COVID-19 due to the likelihood of developing complications, such as acute respiratory distress syndrome or thrombosis of the graft. However, as the pandemic continued, the Organ Procurement and Transplantation Network Ad Hoc Disease Transmission Advisory Committee recommended that the decision to transplant organs from donors with active infection of COVID-19 should take into consideration the likelihood of death of the recipient for delaying the procedure and the risk of transmission to members of the transplant team.

Nevertheless, studies revealed that, unlike lung transplant recipients, the chance of disseminating COVID-19 infection from the donor to the recipient was low in LT patients[19]. The degree of viral load in the blood is usually low, and therefore blood-borne transmission does not represent a significant risk [20]. In our center, we actively consider liver grafts from donors who are COVID-19 positive at the time of organ donation.

COVID-19 in LT recipients

Initial reports suggested that LT recipients could be at an increased risk of acquiring severe COVID-19,

given their immunosuppressed status, with the inherent risk of long-term viral shedding[21,22]. Although some studies showed an increased infection rate among SOT recipients, this was not associated with worse clinical outcomes. The Spanish Society for Liver Transplantation conducted a prospective nationwide study that included 111 LT recipients and concluded that these patients were twice as likely to be infected with COVID-19 compared to age- and sex-matched individuals (standardized incidence: 191.2; 95% confidence interval: 190.3-192.2)[23]. However, another prospective study from Italy followed 30 LT recipients with COVID-19 and suggested that LT recipients were more symptomatic yet with no increased risk of hospitalization or death[24].

The approach to management varies based on the severity of the COVID-19 infection and largely stems from experts' opinions. It is generally advised to lower the cumulative dose of immunosuppression, particularly mycophenolate mofetil, if possible[23]. Immunosuppression was found to be an independent predictor of severe COVID-19 disease as it may interfere with mounting a humoral response to COVID-19 vaccination[25]. Commonly used agents for outpatient management of COVID-19 infection include oral antivirals such as molnupiravir and nirmatrelvir/ritonavir (Paxlovid). Molnupiravir appears to be effective, safe, and well-tolerated in LT patients[26]. Nonetheless, Paxlovid strongly interacts with calcineurin inhibitors, so concomitant use is contraindicated due to the potential for calcineurin inhibitor toxicity[27]. For those requiring inpatient management of COVID-19, the nucleotide analog remdesivir is our preferred therapeutic option. It has been shown to shorten the duration of illness and hospitalization, especially when given to patients on supplemental oxygen within 10 d of symptom onset[28].

We also use COVID-19-specific antibodies in LT recipients with COVID-19, mainly in the outpatient setting and selected patients in the inpatient setting. In a single-center, retrospective study that included liver and kidney transplant recipients, COVID-19 monoclonal antibody (casirivimab-imdevimab or bamlanivimab) reduced hospitalization from 32% to 15% ($P = 0.045$) with no mortality (13% *vs* 0%, $P = 0.04$)[29].

Impact on LT medical staff

Healthcare providers are well-known to be at an additional risk of contracting COVID-19 when compared to the general population[30]. At our center, we adopted a strategy of decreasing interactions among team members to mitigate the risk of COVID-19 transmission. All meetings, including LT selection and multidisciplinary tumor boards, were transitioned to an online platform. A strict departmental protocol was implemented for caregivers who developed symptoms to allow them to undergo testing and appropriate isolation. Outpatient visits, when necessary, were shifted to an online platform to minimize unnecessary exposure and protect patients and staff members.

CONCLUSION

The COVID-19 pandemic has impacted transplant centers globally. Despite the burden, LT centers have been forced to adopt protocols to ensure patient and caregiver safety. A limitation of this review is that it only provides the experience of one LT center in the United States. In the future, emerging evidence will further guide LT centers toward the creation of contingency plans to provide optimal pretransplant, perioperative, and post-transplant care in future public health crises.

FOOTNOTES

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