American Journal of BioMedicine
AJBM 2024;12 (1): 1-10
Research Article doi:10.18081/2333-5106/2024.12/1

The COVID-19 infection in liver transplant recipients: A Cohort Study

Arif Munawar [1], Naila Moin, Sara Sarwar [*]

Abstract

The immunosuppressed state of liver transplant recipients makes them vulnerable to infections after surgery. These infections are directly correlated with the net state of immunosuppression. Higher levels of immunosuppression mean a higher risk of infection, with rates of infection typically highest in the early post-transplant period. Coronavirus disease 2019 (COVID-19) vaccines have shown efficacy in generating specific immune responses. This study aims to describe the COVID-19 infection before and after vaccination in liver recipients. This was a cohort study including 77 liver transplant recipients with laboratory radiological confirmed COVID-19. COVID-19 infection was present before vaccination in 30 patients. The most frequent COVID-19 clinical presentations before vaccination were cough in 32 patients and myalgia in 21 patients; 27 cases had oxygen depletion and required supplemental oxygen. Of the 30 COVID-19 patients, 4 patients re-experienced the disease about three months after complete vaccination. 33 liver transplant patients had not experienced COVID-19 before vaccination, of which 32 patients received vaccination. In conclusion, liver transplant patients infected with SARS-CoV-2 are at greater risk of severe infection and death compared with immunocompetent individuals. Thus, COVID-19 vaccination for all liver recipients is of paramount importance.

Keywords: Liver transplant; COVID-19; Cohort Study

[*]Corresponding author email: sarwar23@skm.org.pk.
[1] Department of Epidemiology, Lahore, Pakistan.
Received 22 August 2023; revised 17 October 2023; accepted 04 December 2023; published 15 January 2024

Introduction

Liver transplantation (LT) is the only curative therapy for patients with decompensated cirrhosis, with one-year and 5-year survival of around 90% and 70%, respectively [1]. Survival following LT has improved over the years from a 1 and 5-year survival of 70% and 50% to 90% and 70%, respectively [2]. Significant improvement in surgical techniques, peri-operative care and immunosuppression therapy has translated in to better survival. However, the increasing complexity of patient selection and expansion of indications for liver transplantation may influence post-transplant outcomes [3]. Optimal immunosuppression is essential to maintain the balance between rejection and infection in the post-transplant period. Recurrent viral

Research Article doi:10.18081/2333-5106/2024.12/1

infection in the post-transplant has been a major obstacle in the previous era causing severe allograft dysfunction leading to graft failure and death [4]. Considering the long term immunosuppressive state, post-transplant patients are at a significant risk of '*de novo*' viral infections, defined as a new onset viral illness in the absence of previous exposure [5].

The source of *de novo* infection could be environmental or donor derived at the time of transplantation. In addition, there remains a significant risk of disease reactivation leading to 'recurrence' particularly in patients transplanted for viral hepatitis. Development of *de novo* or recurrent viral hepatitis can damage the liver allograft leading to a considerable impairment of graft and patient survival. Understanding the natural history of viral hepatitis in liver transplant recipients and the evolution of antiviral therapy has changed the long-term survival of these patients remarkably [6]. The current pandemic coronavirus disease (COVID-19) is caused by a new strain of corona virus named as SARS-CoV-2, with 80% similar phylogenetic homology to previous SARS-CoV. It is a single-positive stranded RNA virus belonging to the beta coronavirus genus and is a chimeric variant of bat coronavirus [7].

This disease initially started as a zoonotic infection from a seafood market of Wuhan in December 2019 causing potentially fatal pneumonia, with person-to-person droplet spread nuclei resulting in a rapid increase in infections across the world earning it a pandemic status by March 11, 2020 [8]. SARS-CoV-2 uses angiotensin-converting enzyme (ACE2) receptors for cell entry as it has a similar receptor binding domain to that of SARS-CoV [9]. ACE2 is abundantly expressed in alveolar type II cells and less commonly in bronchial epithelial cells of the lungs [10].

ACE2 is also expressed in stratified epithelial cells of the oral and esophageal mucosa, enterocytes of the small intestine and colon, liver, myocardial cells, vascular endothelium and smooth muscle cells [11]. SARS-CoV-2 has 10 to 20-fold higher affinity than SARS-CoV to ACE2 receptors. This disease can manifest with mild respiratory or gastrointestinal symptoms to interstitial pneumonia, acute respiratory distress syndrome (ARDS) and diffuse thromboembolic events leading on to multiorgan failure and death. Overall the case fatality of COVID-19 ranges from 5.65% to 15% with geographic heterogenicity [12].

Drugs used in COVID-19 treatment can cause liver injury and drug interactions. Remdesivir, was initially considered in the management of COVID-19 but a recent randomized controlled trial failed to show clinical benefit in COVID-19 treatment. Unfortunately, 10–13% of patients developed drug induced liver injury [13]. This may lead to allograft dysfunction in LT recipients. Similarly, lopinovir-ritonovir inhibits cytochrome P450 leading to significant drug interaction particularly CNI trough level in post LT patients [14].

Patients and Methods

Research Article doi:10.18081/2333-5106/2024.12/1

Materials and Methods Study design and participants This was a single center cohort study including 77 liver transplant recipients with laboratory or radiologically confirmed COVID-19 who were hospitalized from January 2020 to December 2022. Demographic and clinical data were collected and analyzed for each patient from the patients' medical records or call interview, including age, sex, and medical history, clinical presentations, laboratory data, therapeutic management, and outcomes before and after COVID-19 vaccines. The vaccination protocol consisted of the administration of two doses one month apart. This study followed the ethical guidelines of the Declaration of Helsinki.

Statistical Analysis

Quantitative data are presented as mean ± SD, and qualitative data were evaluated as percentages. The data was analyzed using SPSS software version 22

Results

Patients' characteristics In this descriptive cohort study, 95 liver transplant recipients, at a mean time after transplant of 6 years (range, 5 months to 15 years), were enrolled. The mean ±SD age of the patients was 46.5514± years73. patients (76.84%) were male. 41 (43.15%) patients had underlying diseases with the most frequency of diabetes mellitus (68.29%) and hypertension (41.46%) (Table 1). Before vaccination COVID-19 infection before vaccination was present in 33 (35.78%) patients. The most frequent COVID-19 clinical presentations before vaccination were cough in 21 (63.63%) and myalgia in 19 (57.57%) patients; 12 (36.36%) were hospitalized; 17 (51.51%) cases had oxygen depletion and required supplemental oxygen; none of them needed invasive ventilation. 20 (60.60%) patients showed ground-glass opacification with occasional consolidation in the periphery in their chest CT scans as the predominant imaging pattern; 70% of them were bilateral (Figure 1). Vaccination 96.8% of all enrolled patients were fully vaccinated with two doses, which included all of the COVID-19 affected patients and 59 of 62 patients in negative COVID-19 group.

Of the entire 33 COVID-19 patients, two patients (6.06%) re-experienced the disease about two months after complete vaccination. Finally, both of them were recovered. The most immunosuppressive regimen was tacrolimus and mycophenolate in 63 (66.31%) and 71 (74.73%) patients, respectively. The medication regimen in 20 patients was not changed, but in 45 patients was reduced temporarily. The results indicated that two male patients experienced transplant rejection, which had a positive COVID-19 PCR test and also at least one symptom; but they were not hypoxemic and hospitalized and had recovered after a few days.

In this study, the lymphocyte subsets were evaluated in patients with different severities of COVID-19. Materials and Methods: In this prospective study, the frequencies of peripheral lymphocyte subsets (CD3+, CD4+, and CD8+ T cells; CD19+ and CD20+ B cells; CD16+/CD56+ NK cells, and CD4+/CD25+/ FOXP3+ regulatory T cells and in our study, five

Research Article doi:10.18081/2333-5106/2024.12/1

patients (5.26%) passed away; two people were injected with two doses of vaccine and the others were unvaccinated.

Table 1.

Demographic characteristics of liver transplant patients

		Percent	Frequency
Age	< 18	2.10	1
	19-30	11.20	7
	31-40	14.20	15
	41-50	25.30	20
	51-60	28.20	22
	> 61	13.20	12
Sex	Male	70.00	66
	Female	30.00	34
Hypertension	Yes	40.00	15
	No	60.0	11
Diabetes Mellitus	Yes	59.23	29
	No	41.54	35
Chronic Kidney Disease	Yes	19.10	8
	No	81.20	40
Liver Disease	Yes	5.00	2
	No	95.00	6

Discussion

Vaccines against COVID-19 have recently become available, and are increasingly accessible nationwide. While no studies have been conducted specifically in patients with chronic liver disease or after liver transplantation, vaccination is recommended [15]. For liver transplant candidates, society guidelines recommend vaccination in patients and their household contacts, to be completed at least two weeks prior to transplantation. Liver transplant recipients should also complete vaccination, which can be administered at least three months after transplantation in patients receiving B or T cell ablative therapies. Solid organ transplant recipients receiving immunosuppression may have a less robust immune response to vaccination, as to natural COVID-19 infection, than other patients; as such, vaccine administration before transplant is preferred when possible [16].

A study with 436 solid organ recipients evaluated the immune response to the first dose of mRNA vaccines and found anti-Spike IgG antibodies in only 17% of the participants after a

Research Article doi:10.18081/2333-5106/2024.12/1

median follow-up of 20 days [17]. In our study, there was seropositivity in all liver transplant patients who were assessed; also, no serious adverse event was reported after vaccination. In a case series study conducted by other researcher, management of immunosuppressive medications was similar in all the patients. Mycophenolate was held in all the patients since lymphopenia is associated with worse outcomes in COVID-19 patients and all of them had lymphopenia on admission labs, calcineurin inhibitors were also continued unless trough levels were supratherapeutic [18]. In our study, the most immunosuppressive regimen was tacrolimus and mycophenolate. The medication regimen in twenty patients was not changed, but in 33 patients was reduced temporarily. There are some limitations to this study. This was a single-center analysis; also, there was poor patient compliance for antibody evaluation due to the accessibility difficulties.

During the COVID-19 pandemic, liver transplant programs were also impacted by alcohol consumption. Harmful drinking rose significantly, while the purchase of alcoholic beverages increased by as much as 400% [19]. Furthermore, 17% of abstinent patients with a history of alcohol use disorder relapsed under lockdown conditions [20]. Currently, ALD accounts for 40% of transplant listings in North America, more than nonalcoholic steatohepatitis and chronic hepatitis C combined. The severity of liver disease at the time of liver transplant was worse, with higher MELD scores during the COVID-19 pandemic [21]. Lockdown conditions resulted in patients following a harmful lifestyle, with reduced physical activity, excess calorie intake, and consumption of unhealthy foods. Thus, an increased prevalence of obesity and NAFLD was also observed [22].

Regarding the outcome of surgical procedures that were performed during the COVID-19 pandemic, published data revealed that liver transplant patients infected with SARS-CoV-2 who underwent surgery experienced significant postoperative morbidity and mortality [23]. In a large international study of SARS-CoV-2-infected patients who underwent emergent or elective nontransplant surgeries, the 30-day mortality was found to be 21%, with nearly half of those patients developing pulmonary complications [24]. Surgical stress can lead to a cytokine release syndrome, resulting in severe complications, such as superimposed infections and graft loss [25].

Active SARS-CoV-2 infection in the early postoperative period may be complicated by arterial or venous thromboses, myocarditis or myocardial infarction, renal failure or respiratory failure [26]. Furthermore, SARS-CoV-2 infection can cause acute hepatitis (a reference to SARS-CoV-2 in biopsy) with an elevation of transaminases up to 3 times the upper limit of normal, while in some cases it can progress to acute liver failure [27]. Thus, distinguishing acute rejection from viral-induced hepatitis in LT patients could be challenging [28].

To date, all suggested medications are under investigation, with no proven efficacy against COVID-19. These medications include Remdesivir, hydroxychloroquine/chloroquine, azithromycin, hydroxychloroquine, convalescent plasma, tocilizumab, favipiravir, interferon beta, and lopinavir/ritonavir. Most of our cohort were hospitalized and could not be managed at

home due to the severity of the disease. They were managed with hydroxychloroquine (42.9%), antibiotics (35.7%), lopinavir/ritonavir (28.6%), INF-a,b (28.6%), intravenous methylprednisolone (21.4%), intravenous immunoglobulin (14.3%), oseltamivir (14.3%), azithromycin (7.1%), and tocilizumab (7.1%). COVID-19 causes pneumonia that can be severe enough to be lethal, especially in patients with advanced age or underlying medical comorbidities [29].

Those comorbidities include cardiovascular disease, diabetes mellitus, HTN, chronic lung disease, cancer, chronic kidney disease, and obesity (body mass index ≥30) [30]. Liver transplant patients infected with COVID-19 are a fragile and high-risk group due to immunosuppression and common comorbidities. In this review, 60% of patients had comorbidities. These comorbidities predispose these patients to a more severe COVID-19 infection. The attendant IS is an additional risk factor for severe disease. Liver transplant recipients and candidates are in a high-risk group due to the high incidence and prevalence of hypertension, renal failure, diabetes, obesity, and advanced age in this group [31]. It was previously reported that a progressive decline in lymphocyte count was observed in non-survivors compared to more stable levels in survivors [22]. In the present study, 100% of patients who died had lymphopenia. Given the fact that ISM can induce lymphopenia, many liver transplant patients have baseline lymphopenia that might further deteriorate and worsen the prognosis [12].

Several studies and a report from the Chinese Center for Disease Control and Prevention have classified COVID-19 severity in the general population [32] as mild, severe, and critical disease in 81%, 14%, and 5% of patients, respectively. In this report, severe disease defined by SOB and/or hypoxemia was reported in 31.3% of patients. The WHO reported that recovery time appears to be around 2 weeks for mild infections and 3 to 6 weeks for severe disease [33]. In the present study, we found that 72% of patients recovered clinically from the COVID-19, with a median duration of illness of 17 (6–53) days. Rates of ICU admission were reported to range between 5% and 12% in the general population [34]. In our cohort, 28.6% of patients were admitted to the ICU.

Conclusions

Liver transplant patients infected with SARS-CoV-2 are at greater risk of severe infection and death compared with immunocompetent individuals. Thus, COVID-19 vaccination for all liver recipients is of paramount importance.

Conflict of Interest

No conflicts of interest were declared by the authors.

Financial Disclosure

The authors declared that this study has received no financial support.

Ethics Statement

Not applicable.

Authors' contributions

All authors shared in the conception and design and interpretation of data, drafting of the manuscript and critical revision of the case study for intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

Open access

References

1. Oyelade T, Alqahtani J, Canciani G. Prognosis of COVID-19 in patients with liver and kidney diseases: an early systematic review and meta-analysis. Trop Med Infect Dis. 2020;5(2).
2. Mokdad AA, Lopez AD, Shahraz S, et al. Liver cirrhosis mortality in 187 countries between 1980 and 2010: A systematic analysis. BMC Med. 2014;12:145.
3. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. J. Hepatol. 2019;70:151–171.
4. Kottgen A, Glazer NL, Dehghan A, et al. Multiple loci associated with indices of renal function and chronic kidney disease. Nat. Genet. 2009;41:712–717.
5. Suleymanlar G, Utas C, Arinsoy T. et al. A population-based survey of Chronic REnal Disease In Turke—The CREDIT study. Nephrol. Dial. Transplant. 2011;26:1862–1871.
6. Hashemi N, Viveiros K, Redd WD, et al. Impact of chronic liver disease on outcomes of hospitalized patients with COVID-19: a multicentre United States experience. Liver Int. 2020;40(10):2515–2521.
7. Qi X, Liu Y, Wang J, et al. COVID-Cirrhosis-CHESS Group Clinical course and risk factors for mortality of COVID-19 patients with pre-existing cirrhosis: a multicentre cohort study. Gut. 2021;70(2):433–436.
8. Fan Z, Chen L, Li J, Cheng X, Yang J, Tian C, Zhang Y, Huang S, Liu Z, Cheng J. Clinical features of COVID-19-related liver functional abnormality. Clin Gastroenterol Hepatol. 2020;18(7):1561–1566.

Research Article doi:10.18081/2333-5106/2024.12/1

9. Phipps MM, Barraza LH, LaSota ED, et al. Acute liver injury in COVID-19: prevalence and association with clinical outcomes in a large US cohort. Hepatology. 2020;72:807–817.
10. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. 2020;323(20):2052–2059.
11. Goyal P, Choi JJ, Pinheiro LC,et al. Clinical characteristics of Covid-19 in New York City. N Engl J Med. 2020;382(24):2372–2374.
12. Pereira MR, Antinori S, Cossu MV, et al. Compassionate remdesivir treatment of severe Covid-19 pneumonia in intensive care unit (ICU) and Non-ICU patients: clinical outcome and differences in post-treatment hospitalisation status. Pharmacol Res. 2020;158:104899.
13. Aversa MM, Farr MA, Miko BA, et al. Tocilizumab for severe COVID-19 in solid organ transplant recipients: a matched cohort study. Am J Transplant. 2020;20(11):3198-205.
14. Montastruc F, Thuriot S, Durrieu G. Hepatic disorders with the use of remdesivir for coronavirus 2019. Clin Gastroenterol Hepatol. 2020;18(12):2835–2836.
15. Laracy JC, Verna EC, Pereira MR. Antivirals for COVID-19 in solid organ transplant recipients. Curr Transplant Rep. 2020:1–11.
16. Neidlinger NA, Smith JA, D'Alessandro AM, et al. Organ recovery from deceased donors with prior COVID-19: a case series. Transpl Infect Dis. 2020:e13503.
17. Niess H, Borner N, Muenchhoff M, et al. Liver transplantation in a patient after COVID-19—rapid loss of antibodies and prolonged viral RNA shedding. Am J Transplant. 2021;21(4):1629–1632.
18. Zhang C, Shi L, Wang F-S. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol 2020;5:428–30.
19. Gacouin A, Locufier M, Uhel F, et al. Liver cirrhosis is independently associated with 90-day mortality in ARDS patients. Shock 2016;45:16–21.
20. Jepsen P, Vilstrup H, Andersen PK, et al. Comorbidity and survival of Danish cirrhosis patients: a nationwide population-based cohort study. Hepatology 2008;48:214–20.
21. Rabinowich L, Grupper A, Baruch R, et al. Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients. J Hepatol. 2021;75:435–438.
22. Ruether DF, Schaub GM, Duengelhoef PM, et al. SARS-CoV2-specific humoral and T-cell immune response after second vaccination in liver cirrhosis and transplant patients. Clin Gastroenterol Hepatol. 2022;20:162–172.
23. Levin MJ, Ustianowski A, De Wit S, et al. PROVENT Study Group. Intramuscular AZD7442 (Tixagevimab-Cilgavimab) for prevention of Covid-19. N Engl J Med. 2022;386:2188–2200.
24. Al Jurdi A, Morena L, Cote M, Bethea E, Azzi J, Riella LV. Tixagevimab/cilgavimab pre-exposure prophylaxis is associated with lower breakthrough infection risk in vaccinated

solid organ transplant recipients during the omicron wave. Am J Transplant. 2022;22:3130–3136.

25. Shah VK, Firmal P, Alam A, Ganguly D, Chattopadhyay S. Overview of immune response during SARS-CoV-2 infection:lessons from the past. Front Immunol. 2020;11:1949.
26. Timsit JF, Sonneville R, Kalil AC, et al. Diagnostic and therapeutic approach to infectious diseases in solid organ transplant recipients. Intensive Care Med. 2019;45:573–591.
27. Colmenero J, Rodríguez-Perálvarez M, Salcedo M, et al. Epidemiological pattern, incidence, and outcomes of COVID-19 in liver transplant patients. J Hepatol. 2021;74:148–155.
28. Webb GJ, Marjot T, Cook JA, et al. Outcomes following SARS-CoV-2 infection in liver transplant recipients:an international registry study. Lancet Gastroenterol Hepatol. 2020;5:1008–1016
29. Fraser J, Mousley J, Testro A, Smibert OC, Koshy AN. Clinical presentation, treatment, and mortality rate in liver transplant recipients with coronavirus disease 2019:a systematic review and quantitative analysis. Transplant Proc. 2020;52:2676–2683.
30. Huang JF, Zheng KI, George J, et al. Fatal outcome in a liver transplant recipient with COVID-19. Am J Transplant. 2020;20:1907–1910.
31. Yousif NG, Fullerton J, Cabrera V. Special considerations for leukemic patients during the COVID-19 pandemic: meta-analysis study. NeuroQuantology. 2022;20(8): 7509-7515.
32. Mohammed A, Paranji N, Chen PH, Niu B. COVID-19 in chronic liver disease and liver transplantation:a clinical review. J Clin Gastroenterol. 2021;55:187–194.
33. Elens L, Langman LJ, Hesselink DA, et al. Pharmacologic treatment of transplant recipients infected with SARS-CoV-2:considerations regarding therapeutic drug monitoring and drug-drug interactions. Ther Drug Monit. 2020;42:360–368.
34. AL-Hussein AJ, Alruda GM, Yousif NG, Increased neutrophil-lymphocyte ratio in patients with COPD: case-control study. American Journal of Biomedicine. 2023;11(3): 144-157.

Research Article doi:10.18081/2333-5106/2024.12/1

American Journal of BioMedicine
Journal Abbreviation: AJBM
ISSN: 2333-5106 (Online)
DOI: 10.18081/issn.2333-5106
Publisher: BM-Publisher
Email: editor@ajbm.net