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Coronavirus infection and neutralizing antibody responses among liver transplant recipients: single-center study

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Abstract

Background Liver transplant (LT) recipients are classified as a high-risk group and should receive regular surveillance for COVID-19 and are expected to have higher viral load and prolonged viral shedding. Virus-specific neutralizing antibodies (NAb), induced by infection, can prevent viral infection by deactivating viral access to host receptors.

Aim To estimate the incidence of SARS-CoV-2 infections and ascertain the levels of NAb among LT recipients.

Method This cross-sectional study included LT recipients. The survey included 14 parameters about demography, date since operation, and immunosuppressant medications and 11 parameters about COVID-19 infection. NAb was done by electrochemiluminescence immunoassay.

Results Only 39 LT recipients responded to this survey. Their median age was 57, and 74.4% of them were men. Comorbidities were present in 64% of cases, and DM was the most common comorbidity. Immunosuppressants used were Tacrolimus in 56.4% and Tacrolimus with mycophenolate mofetil in 15.4%. Fifteen cases (38.5%) had suspected infection, and 2 (5.1%) had confirmed infection. Three patients (17.6%) were hospitalized with no mortality. NAb was done in 34 cases, and it was positive in 5 cases (14.7%) with a median level (range) of 0.075 (0.04–27). Three out of 5 cases with a positive NAb test did not give a history of either suspected or confirmed COVID-19 infection.

Conclusion COVID-19 surveillance in LT recipients is important and suggests a relatively favorable clinical course despite the presumed challenges of immunosuppression. COVID-19 was associated with low hospitalization in LT recipients. NAb indicates a potential immune response even in asymptomatic LT recipients.

Trial registration Clinical Trial.gov NCT04565782. September 15 2022.

Keywords Nabs, COVID-19, LT, Survey

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Introduction

Severe acute respiratory distress syndrome coronavirus-2 (SARS-CoV-2) was responsible for the coronavirus infectious disease 2019 (COVID-19) [1]. It soon spread to almost every country around the world, and the World Health Organization declared that COVID-19 was a public health emergency on January 30, 2020.

Liver transplant recipients are classified as a risk group and should receive regular surveillance for COVID-19. A great viral load and prolonged shedding in transplant recipients resulting in more infectivity and spread to others were anticipated [2].

Liu et al. [3] stated that liver transplant (LT) patients could be susceptible to SARS-CoV-2, with a worse prognosis compared to the normal population.

The LT society of India (LTSI) stated that SARS-CoV-2 can be transmitted to LT recipients and they can behave as asymptomatic carriers and sources of viral spread [4].

Virus-specific neutralizing antibodies (NAb), which are induced by infection or vaccination, can help to block viral infection later or during subsequent encounters with the pathogen [5, 6]. In general, Nabs help confer immunity by deactivating viral access to receptors used to enter host cells and/or binding to viral capsids so as to block the key step of uncoating the viral genome [7]. Neutralizing antibodies (NAbs) to SARS-CoV-2 can be found in most infected persons 10–15 days after the onset of presenting symptoms [8]. The titers of NAbs were variable in different patients [9].

Rational

It is essential to screen for the occurrence of SARS-CoV-2 infections among liver transplant recipients. To our understanding, no study to date has been undertaken in our country to determine levels of NAb in liver transplant recipients.

Aim of the study

The study was designed to estimate the occurrence of SARS-CoV-2 infections among liver transplant recipients. Also, to ascertain the levels of Nab in liver transplant recipients.

Methods

Type of the study

Prospective cross-sectional study.
Study setting: Al-Rajhi Liver Hospital.

Study subjects

Inclusion criteria

All liver transplant recipients in Al-Rajhi Liver Hospital who accept to participate.

Exclusion criteria

Those who refuse to participate in the study.

Ethical approval

The study protocol was reviewed and approved by the Committee of Medical Ethics of the Faculty of Medicine, Assiut University (IRB local approval number: 17300475). All participants gave their written consent to participate. Data collection was done in October, and November 2020, after obtaining the Ethical Approval.

Study tools

1- Survey included 21 parameters (14 parameters cover the demographic data, date since the operation, and immunosuppressant medications, and 11 parameters related to coronavirus infection). The authors developed and validated the survey used in this study. Internal validity was established in a pilot study of 10% of participants. Cronbach-α was found to be 0.72. SARS-CoV-2 infection was defined according to the Ministry of Health and population definitions of suspected and confirmed cases [10].
2- Serological test searching for Neutralizing Ab against SARS-Corona virus 2 in liver transplant recipients (whether who give symptoms or are asymptomatic) was done. It was detected by the Electrochemiluminescence immunoassay (ECLIA) method. For the measures of the presence of NAB in the serum samples, a Cobas 411 immunoassay analyzer that employed an electrochemiluminescence immunoassay (ECLIA) was used. Specifically, an Elecsys Anti-SARS-CoV-2 immunoassay kit was used for the in vitro qualitative detection of antibodies (including IgG) to SARS-CoV-2 in human serum and plasma. The assay used a recombinant protein representing the nucleocapsid (N) antigen in a double–antigen sandwich assay format. The test aids in the determination of the immune reaction to SARS-CoV-2. Elecsys Anti-SARS-CoV-2 detects antibody titers, which have been shown to positively correlate with neutralizing antibodies in neutralization assays. Results were considered non-reactive when kit values were < 1 and reactive when kit values were ≥ 1. The titers measured in reactive samples were recorded.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS version 17, SPSS Inc., Chicago, IL, USA). Continuous data were all presented

as the median and interquartile range, while categorical data were presented as frequencies and percentages.

Results

Fifty-one cases were subjected to living donor liver transplantation in our center from November 2014 to May 2019. Only 39 liver transplant recipients responded to this survey as 2 cases were non-Egyptian, and 10 cases refused to participate.

The median age of the respondents was 57 and 74.4% were men. 61.5% were living in rural areas. HCV-related LC was the most common cause of transplant in Egypt, followed by HCC in 35.9%. Comorbidity was present in 64% of cases and DM was the most common. Duration since transplant was (1 –3 years) in 53.8% and more than 3 years in 30.8%. The most common immunosuppressant is Tacrolimus only in 56.4% and Tacrolimus with mycophenolate mofetil in 15.4%. About 69.2% of the respondents did routine follow-up laboratory investigations and imaging in a regular manner despite the occurrence of the pandemic (Table 1).

Answers to parameters regarding COVID-19 infection among liver transplant recipients during the first wave of the pandemic are shown in Table 2.

About 17/39 (43.6%) had COVID-19 infection [15/39 cases (38.5%) had suspected coronavirus infection and 2/39 (5.1%)] had confirmed infection. Respiratory symptoms were present in 64.7% of cases with suspected or confirmed COVID-19 infection. Bilateral lower lobe pneumonic patches and ground glass were found in 5 cases and 1 of them also had segmental and subsegmental pulmonary emboli. Family members with confirmed COVID-19 were present in 8 cases (20.5%).

Out of 17 cases, only 3 were managed in the isolation hospital (17.6%). Reduction of the Tacrolimus dose was done in 4 cases (23.5%). Reduction of MMF or Everolimus doses was done in 9 cases (52.9%).

Neutralizing Ab test was done in 34 cases. Neutralizing Ab positivity was reported in only 5 cases out of 34 (14.7%) with a median (range) of 0.075 (0.04–27). Three out of 5 cases with positive neutralizing Ab test did not give a history of COVID-19 infection.

Complications occurred in 2 cases (ischemic hepatitis in 1 case and segmental and subsegmental pulmonary embolism in 1 case) and both improved and were discharged from the hospital. Three months later, the case with ischemic hepatitis died because of progressive liver failure.

Table 1 Demographic data, cause of liver transplant, comorbidity, and immunosuppressant regimens of liver transplant recipients

Variable	Number	Percentage
Age[a]		
Median (range)		57(24–68)
Sex		
Men	29	74.4%
Women	10	25.6%
Address		
Urban	15	38.5%
Rural	23	61.5%
Smoking status		
Smokers	3	7.7%
Non-smokers	36	92.3%
Cause of transplant		
HBV-related LC	5	12.8%
HCV-related LC	16	41%
HCC	14	35.9%
Autoimmune	3	7.7%
Cryptogenic LC	1	2.6%
Comorbidity		
Yes	25	64%
No	14	36%
Type of comorbid disease		
Hypertension	7	17.9%
DM	10	25.6%
Both DM and hypertension	7	17.9%
Other (chronic myeloid leukemia)	1	2.6%
Period since transplant		
Less than 1 year	6	15.4%
1 year–3 years	21	53.8%
More than 3 years	12	30.8%
Immunosuppressants		
Tacrolimus only	22	56.4%
Tacrolimus and steroid	5	12.8%
Tacrolimus and mycophenolate mofetil	6	15.4%
Tacrolimus and mycophenolate mofetil and steroid	4	10.3%
Tacrolimus and Everolimus	2	5.1%
Doing routine follow-up laboratory investigations:		
Yes, regularly	27	69.2%
Yes, but not regularly	5	12.8%
No	7	17.9%

Number = 39

[a] Data were expressed as median and range/mean ± SD

Discussion

Neutralizing antibody (NAb) evaluations are useful for the determination of individual or herd immunity against SARS-CoV-2, vaccine efficacy, and long-term humoral protective response [9]. Serological assays represent the test of choice to determine prior exposure to SARS-CoV-2. However, whether the detected antibodies can neutralize the virus and provide protection on subsequent exposure remains a point of debate. Antibodies against

Table 2 Response to parameters regard COVID-19 infection among liver transplant recipients

Variable	Number	Percentage
Do you have a coronavirus infection?		
Yes, confirmed	2	5.1%
Yes, suspected	15	38.5%
No	22	56.4%
How do you know?		
-Respiratory symptoms	11	64.7%
-GIT symptoms	2	11.8%
-Clinical, laboratory, and radiological	5	29.4%
-Clinical, laboratory findings, and contacts of confirmed cases and PCR	2	11.8%
CT chest		
-Not done	6/17	35.3%
-Bilateral lower lobe pneumonic patches and ground glass	4/17	23.5%
-Bilateral lower lobe pneumonic patches and ground glass and segmental and subsegmental emboli	1/17	5.9%
-Normal	6	35.3%
Family members with confirmed COVID-19		
Yes	8	20.5%
No	31	79.5%
Son	3	37.5%
Daughter	3	37.5%
Wife	2	25%
Place of treatment		
Home	14/17	82.4%
Hospital	3/17	17.6%
ICU admission		
None	0/17	0%
Reduction of tacrolimus dose		
Yes	4/17	23.5%
No	13/17	76.5%
Mycophenolate mofetil/Everolimus dose reduction		
Yes	9/17	52.9%
Anticoagulant		
Yes	2/17	11.7%
Neutralizing Ab positivity	5/34	14.7%
Neutralizing Ab titer[a]		
Median (range)	0.075 (0.04–27)	

Number of liver transplant recipient = 39, while neutralizing Ab titer was done in 34 cases only

[a] Data were expressed as median and range

RBD of the S protein have been shown to be the primary source of neutralizing antibodies against the virus [11, 12].

This single-center study was designed to estimate the occurrence of SARS-CoV-2 infections among liver transplant recipients and to ascertain the levels of Nab in liver transplant recipients.

Despite the use of immunosuppressive drugs, neutralizing Ab positivity was reported in only 5 cases out of 34 (14.7%) with a median (range) of 0.075 (0.04–27). Three out of 5 cases with positive neutralizing Ab test did not give a history of COVID-19 disease. Therefore, even asymptomatic liver transplant recipients after SARS-CoV-2 infection can give a neutralizing Ab response. Becchetti et al. (2021) demonstrated neutralizing activity in 82.9% of 35 LT recipients which significantly differed from the COVID-19-Immunocompetent group where neutralizing activity was found in all patients. This result suggests that not all LT recipients develop functional antibodies [13].

Among the present cohort of liver transplant recipients, about 17 /39 (43.6%) had COVID-19 infection [15/17 cases (88.2%) had suspected coronavirus infection and 2/17 (11.8%)] had confirmed infection. While, Anwar et al. (2021) in another center in Lower Egypt reported 21/255 (8.23%) recipients had COVID-19 infection, and recipients were classified into 17 (80.5%) confirmed, 4 (19.04%) suspected and reduction or stoppage of current immunosuppressive was only in 19% [14]. However, in the current study, reduction of the tacrolimus dose was done in 4 cases (23.5%) and reduction of Mycophenolate mofetil or Everolimus doses was done in 9 cases (52.9%).

The national Egyptian protocol for living donor liver transplantation (LDLT) recommended reduction/ hold of calcineurin inhibitors (CNI) dose, according to disease severity and radiological findings in CT chest. It is essential to consider reducing azathioprine or mycophenolate dosages [15].

Kulkarni et al. (2021), in their systematic review and meta-analysis, reported that immunosuppression was modified in 55.9% of patients after COVID-19 infection [16].

Only 17.6% of our cases need hospital admission; however, none of them need ICU admission. High numbers of infected cases in Egypt pass officially undetected and homely recovered [17]. The incidence rate of hospitalization for COVID-19 was 14.4% in the general population in Italy [18]. While in the study of Anwar et al. (2021), 42.6% of LT cases need hospitalization and only one of them needs ICU admission [14]. Their cases were recruited from March 2020 to August 2020, while our cases were recruited in October and November 2020. LT and non-LT patients with COVID-19 infection have a similar risk of adverse outcomes in a systematic review and meta-analysis [16].

Chronic immunosuppression is considered a double-edged sword in COVID-19.

While it may facilitate viral replication in the early phase of the infection, it could also, ameliorate the aberrant immune response which is responsible for the most severe forms of the disease [19]. Liver transplant recipients show a lower prevalence of anti-SARS-CoV-2 antibodies and more pronounced antibody levels decline [20].

Limitations of the study

First, this was a single-center study. Second, the absence of a control group comprising immunocompetent individuals makes it challenging to compare the outcomes of liver transplant recipients with the general population and assess the impact of immunosuppression on COVID-19 severity. Third, although the study assesses neutralizing antibodies, it does not provide comprehensive data on the overall immune response, such as T cell responses, which could contribute to a more thorough understanding of immune protection.

Conclusion

COVID-19 infection surveillance in LT recipients is important and suggests a relatively favorable clinical course despite the presumed challenges of immunosuppression. COVID-19 infection was associated with low hospitalization. NAb indicates a potential immune response even in asymptomatic LT recipients.

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Authors' contributions

NAM shared in writing the protocol and data collection from the participants. Also, she did the statistical analysis and shared it in the literature review and in the writing of the manuscript. AAM shared in study design, and writing the protocol. She also shared in doing all laboratory work and in the writing of the method section. MAM shared the idea of the work, literature review, and writing of the manuscript. AS shared in data collection and sampling from the participants. AFE shared in literature review and writing of the manuscript. HAM was a major contributor in writing the manuscript and supervision of the work. BAF revised the protocol and revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data and material are available on request.

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Committee of Medical Ethics of the Faculty of Medicine, Assiut University (IRB local approval number: 17300475). All participants gave their written consent to participate.

Consent for publication

All authors and participants gave their consent for publication.

Competing interests

All authors declare that they have no competing interests.

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