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ORIGINAL ARTICLE

Low seroprevalence of SARS-CoV-2 antibodies in a liver transplant cohort

Isabel Campos-Varela[1,2,3,4,5], Oscar Len[2,5,6], Ares Villagrasa[1,5], Ester Márquez-Algaba[2,5,6], Juliana Esperalba[2,5,7], Cristina Dopazo[4,5,8], Ibai Los-Arcos[2,5,6], Andrés Antón[2,5,7] & Lluís Castells[1,2,3,4]

1 Liver Unit, Hospital Universitari Vall d'Hebron, Barcelona, Spain
2 Vall d'Hebron Research Institute (VHIR), Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain
3 Centro de Investigación Biomédica de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Madrid, Spain
4 Facultat de Medicina, Universitat Autònoma de Barcelona, Bellaterra, Spain
5 Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain
6 Department of Infectious Diseases, Hospital Universitari Vall d'Hebron, Barcelona, Spain
7 Department of Microbiology, Hospital Universitari Vall d'Hebron, Barcelona, Spain
8 Department of Hepatobiliopancreatic Surgery and Transplantation, Hospital Universitari Vall d'Hebron, Barcelona, Spain

Correspondence
Isabel Campos-Varela MD, MPH and Oscar Len MD, PhD, Vall d'Hebron Institut de Recerca, Hospital Universitari Vall d'Hebron, Barcelona 08035, Spain.
Tel.: 34-932746140;
fax: 34-932746068;
e-mails: icampos@vhebron.net (I.C.-V.) and Oscar.len@vhir.org (O.L.)

SUMMARY

Solid organ transplant recipients might be at greater risk for acquisition and mortality because of SARS-CoV-2. There are no data regarding SARS-CoV-2 seroprevalence among liver transplant (LT) recipients, and whether it is different from that of the general population or other immunosuppressed groups. We evaluated the prevalence of IgG SARS-CoV-2 antibodies among LT recipients to estimate the frequency of asymptomatic SARS-CoV-2 infection using serological assays in our outpatient clinic. We conducted a cross-sectional analysis from 10 May to 26 October 2020 of all adult (>18 years) LT recipients that underwent a routine laboratory test for the outpatient clinic follow-up at the Hospital Universitari Vall d'Hebron (Barcelona) in which we included serological testing for SARS-CoV-2. Nine out of 294 LT recipients (3.1%) tested positive for anti-SARS-CoV-2 IgG antibodies. Five of them (55.5%) had suffered clinically symptomatic SARS-CoV-2 infection confirmed by RT-PCR, four (44.4%) had presented compatible symptoms but without microbiological confirmation and only one patient (1/9, 11.1%) tested positive without any previous symptom. SARS-CoV-2 seroprevalence among LT recipients in an area highly affected by the pandemic is lower than in the general population in the same area. These results render the possibility of asymptomatic infection in LT recipients very unlikely.

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Key words
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Introduction

Coronavirus disease 2019 (COVID-19) is a new emerging infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The main risk factors associated with worse outcomes include age and comorbidities such as hypertension, diabetes mellitus or chronic lung disease among others [1]. Because of the impairment in cell-mediated and humoral immunity caused by immunosuppressive agents, solid organ

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transplant (SOT) recipients might be also at greater risk for disease and mortality because of SARS-CoV-2 infection [2–5]. Otherwise, the impaired activation of naive B cells and B-cell antigen presentation as well as T-cell stimulus to T-cell dependent responses may prevent the development of antibodies against SARS-CoV-2 [6].

The impact of the current pandemic on SOT is being extraordinary, with early data showing a significant reduction in total waitlist additions and transplant surgeries across all transplant domains, with an increase in waitlist mortality for kidney, liver and lung transplant candidates [7].

Seroprevalence of SARS-CoV-2 antibodies in a certain population serves as a sensible measure of exposure risk. There are few data regarding SARS-CoV-2 seroprevalence among liver transplant (LT) recipients [8], and whether it is different from that of the general population or other immunosuppressed groups.

The aim of the present study was to systematically determine the presence of SARS-CoV-2 antibodies among LT recipients to evaluate the prevalence of asymptomatic SARS-CoV-2 infection using serological assays in our outpatient clinic.

Methods

Study population

Since 1988, our adult liver transplantation program has performed 1300 LT, and currently, we follow-up approximately 700 patients. We performed a cross-sectional analysis from 10 May to 26 October 2020 of all adult (>18 years of age) LT recipients that underwent a routine laboratory test for the outpatient clinic follow-up at the Hospital Universitari Vall d'Hebron (Barcelona) in which we added serological testing for SARS-CoV-2. There were no exclusion criteria.

During lockdown all outpatient visits were converted into telematic visits. Also, laboratory tests and other evaluations (image, endoscopy, etc.) were cancelled and rescheduled months later. Patients were instructed to follow lockdown restrictions and to stay at home as much as possible.

Data were prospectively collected in a database created for the study. All clinical information was extracted by experienced transplant physicians from reliable electronic medical data sources. Demographic data, comorbidities and transplant-related information including baseline immunosuppressant therapy were recorded. During the scheduled routine visit, all patients were asked about present or past symptoms compatible with COVID-19.

This study was approved by the Vall d'Hebron Institutional Review Board and conducted according to the 2000 Declaration of Helsinki as well the Declaration of Istambul 2008. All patients gave their informed consent prior to their inclusion in the study.

Serological testing for SARS-CoV-2 antibodies

During the study period, serological status could be determined by two commercial chemiluminescence immunoassays (CLIA) targeting specific SARS-CoV-2 antibodies: (i) Elecsys® Anti-SARS-CoV-2 (Roche Diagnostics, Mannheim, Germany) was performed on the Cobas 8800 system (Roche Diagnostics) for qualitative determination of total antibodies (including IgG, IgM and IgA) against nucleocapsid (N) SARS-CoV-2 proteins (the manufacturer reported sensitivity of 100% in patients with more than 14 days after infection, and specificity of 99.81%), and, (ii) Liaison SARS-CoV-2 S1/S2 IgG (DiaSorin, Saluggia (VC), Italy) was performed on the LIAISON® XL Analyzer (DiaSorin) for quantitative determination of the spike (S) glycoprotein subunits 1 and 2 (S1/S2) (the manufacturer reported sensitivity of 97.4% in patients with more than 15 days after infection, and specificity of 98.5%). According to the protocol of our Hospital, firstly, patients were screened with the determination of total antibodies against nucleocapsid. If the result was positive, or there was clinical or epidemiological suspicious, or the patient had a previous positive respiratory sample by real-time reverse transcription polymerase chain reaction (RT-PCR), the determination of IgG antibodies against spike was also performed.

Definitions

Confirmed-SARS-CoV-2 infection was diagnosed by RT-PCR assay of nasopharyngeal swab specimens following suggestive symptoms of acute presentation such as fever, cough, rhinorrhoea, sore throat, headache, dyspnoea, diarrhoea, anosmia or ageusia.

Suspected-SARS-CoV-2 infection was defined by the presence of symptoms described above, but without RT-PCR confirmation.

A patient was considered to have a positive serology against SARS-CoV-2 if either SARS-CoV-2 IgG anti-S1/S2 or SARS-CoV-2 Ig anti-N waspositive.

Statistical analysis

Descriptive statistics were expressed as medians and interquartile ranges (IQRs) for continuous variables and

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Table 1. Main characteristics of the cohort by SARS-CoV-2 antibody status.

Variable	Total (*N* = 294)	SARS-CoV-2 (+) (*N* = 9; 3.1%)	SARS-CoV-2 (−) (*N* = 285; 96.9%)	*P*-value
Age at LT (years)	54 (46–61)	53 (48–55)	54 (46–61)	0.83
Age at serology testing (years)	63 (56–70)	66 (65–69)	63 (56–70)	0.38
Time from LT to SARS-CoV-2 serology (years)	9.6 (3.2–16.0)	13.7 (3.2–14.1)	9.5 (3.2–16.0)	0.75
Sex				
Male	211 (71.8%)	6 (66.7%)	205 (71.9%)	0.72
Aetiology of liver disease				
Alcohol	75 (25.5%)	2 (22.2%)	73 (25.6%)	0.62
HCV	105 (35.7%)	2 (22.2%)	103 (36.1%)	
HBV	31 (10.6%)	2 (22.2%)	29 (10.2%)	
NASH	10 (3.4%)	0 (0%)	10 (3.5%)	
Other	73 (24.8%)	3 (33.4%)	70 (24.6%)	
HCC as indication of LT	98 (33.3%)	1 (11.1%)	97 (34.0%)	0.28
Blood type				
A	140 (48.0%)	4 (44.5%)	136 (48.1%)	0.05
B	25 (8.6%)	1 (11.1)	24 (8.5%)	
O	117 (40.0%)	2 (22.2%)	115 (40.6%)	
AB	10 (3.4%)	2 (22.2%)	8 (2.8%)	
Arterial hypertension	157 (53.4%)	5 (55.6%)	152 (53.3%)	1.00
Diabetes	113 (38.4%)	6 (66.7%)	107 (37.5%)	0.09
Chronic renal failure (GFR <60 ml/min/1.73 m^2)	65 (22.1%)	3 (33.3%)	62 (21.7%)	0.42
HIV infection	10 (3.4%)	0 (0%)	10 (3.5%)	1.00
Simultaneous liver-kidney transplant	10 (3.4%)	0		1.00
Cardiac disease	33 (11.2%)	1 (11.1%)	32 (11.23%)	1.00
Immunosuppressant therapy				
Tacrolimus	268 (91.2%)	7 (77.8%)	261 (91.6%)	0.18
Cyclosporine	14 (4.8%)	1 (11.1%)	13 (4.6%)	0.36
Mofetil Mycofenolate	106 (36.1%)	3 (33.3%)	103 (33.1%)	1.00
Everolimus	51 (17.4%)	3 (33.3%)	48 (16.8%)	0.19

GFR, glomerular filtration rate; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV; human immunodeficiency virus; IQR, IQR, interquartile range; LT, liver transplantation; NASH, nonalcoholic steatohepatitis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Data are presented as median (IQR) or *n* (%).

absolute numbers (percentages) for categorical variables. Comparisons among LT recipients with a positive or negative serology were performed using Wilcoxon rank-sum for continuous variables and the chi-square test or Fisher exact test for categorical variables. Two-sided *P* values of <0.05 were considered to indicate statistical significance. STATA v13 (College Station, TX, USA) was used for all statistical analyses.

Results

During the study period, we obtained sera samples during regular outpatient visits in 294 adult LT recipients for serological testing. Patient demographics are presented in Table 1. Recipients were more frequently men (71.8%), and had a median age of 54 years (IQR 46–61) at LT and a median age at serology assessment of 63 years (IQR 56–70). At assessment, median time since LT was 9.6 years (IQR 3.2–16.0). The aetiology of liver disease was chronic hepatitis C infection (35.7%), alcoholic cirrhosis (25.5%), chronic hepatitis B infection (10.5%), nonalcoholic steatohepatitis (NASH; 3.4%), and other (24.8%). Hepatocellular carcinoma (HCC) was the indication of LT in 33.3% of cases. Regarding immunosuppressant therapy, 91.2% of patients were on a tacrolimus-based therapy, 36.1% and 17.4% were on mycophenolate-mofetil (MMF) and everolimus treatment, respectively, both in combination with tacrolimus or cyclosporine or in monotherapy.

Nine out of 294 LT recipients (3.1%) tested positive for anti-SARS-CoV-2 Ig antibodies (all nine patients were SARS-CoV-2 IgG anti-S1/S2 positive and eight were SARS-CoV-2 anti-N positive). Five of them (5/9, 55.5%) had suffered clinically symptomatic SARS-CoV2

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infection confirmed by RT-PCR (three were hospitalized, and none of them was admitted to the intensive care unit), four (4/9, 44.4%) had presented compatible symptoms but without microbiological confirmation and only one patient (1/9, 11.1%) tested positive without any previous symptom. Median time from diagnosis of COVID-19 to anti-SARS-CoV-2-Ig antibodies determination was 66 days (IQR 39–99).

During the study period, we had 14 RT-PCR confirmed cases of SARS-CoV-2 infection in LT recipients. Five are still in quarantine and had not yet been tested for serology, three died, and six recovered and are followed at the outpatient clinic and were included in the study. Five of the six patients who had confirmed COVID-19, tested positive for anti-SARS-CoV-2 IgG antibodies (83.3%) as have been described above, while in only one case (1/6, 16.7%), the serology was negative 1 and 3 months after the acute infection. This patient presented a mild curse of the disease. None of the patients received convalescent plasma or intravenous immunoglobulin.

There were no differences in seroprevalence according to age, sex, aetiology of liver disease, HCC as indication of LT, immunosuppressant therapy, comorbidities, or being a carrier of a simultaneous liver-kidney transplant. SARS-CoV-2 antibodies were less frequently positive among LT recipients with blood group O (two patients, 22.2%, $P = 0.05$).

Discussion

The results of the present study show that the seroprevalence of SARS-CoV-2 among LT recipients is low (3.1%) in the line of results from general population. Seroprevalence in the Spanish population in the same period of time was 5%, and specifically in the area of the present study, Barcelona, seroprevalence was 6.8%, even higher than the general average [9]. Moreover, only one patient out of 294 (0.3%) fulfils the diagnosis of SARS-CoV-2 asymptomatic infection. These results, confirm that, even in Spain, one of the European countries most affected by the COVID-19 pandemic, asymptomatic infection among LT recipients is practically nonexistent. Studies of SARS-CoV-2 seroprevalence in other populations at risk have shown discordant results, probably related to the specific characteristics of the different patient populations studied. While in a Spanish study among cancer outpatients, SARS-CoV-2 prevalence was 31.4% [10], among patients on haemodialysis in the United States and the United Kingdom (UK) it was 8.0% and 36.2%, respectively [11,12], and 8.1% in kidney transplant recipients in the UK [13].

These differences may be related to true geographic differences and the different degree of assistance to medical centres during the pandemic. In this sense, cancer patients and patients on haemodialysis are among the groups of patients who maintained their regular attendance to medical facilities, with the consequent risk of nosocomial infection, along with the risk associated with traveling [14]. On the contrary, in liver or kidney transplant recipients, in a situation of clinical stability, the follow-up was mainly done by telematic means during the pandemic which significantly reduced their exposure to the virus in medical settings.

Despite the fact that LT recipients accumulate many potential risk factors (diabetes mellitus, chronic renal failure, arterial hypertension, immunosuppressant drugs), this low seroprevalence may be partly explained by the early recommendation towards our LT recipients to limit the face-to-face contacts and the high compliance with the isolation and personal cleanliness measures (social distancing, hand washing and use of masks).

However, a previous study carried out in the same area has shown that LT recipients presented an incidence of COVID-19 disease double than in the general population [3]. There might be several explanations regarding this discrepancy. First, it could be that in the middle of the first wave, LT recipients acutely ill, were diagnosed in a greater proportion than in the general population, when because of a collapsed system, many individuals remained at home without a COVID-19 diagnosis confirmed, while immunosuppressed patients were admitted to hospital and tested against SARS-CoV-2 infection more often than other populations without significant comorbidities. This under diagnosis would have been less significant in the LT population. Another explanation might be an impaired immune response of LT recipients, limiting their capacity to generate antibodies against SARS-CoV-2 virus, or even in a titre enough to be detected, despite a true higher incidence of SARS-CoV-2 infection. This later hypothesis might be supported by the known inferior response to vaccination against hepatitis B virus in LT recipients [15–17]. Also, time since LT and type of immunosuppression might play a role in the ability to generate a measurable immune response. In a recent study including 70 SOT recipients (10 LT recipients) infected with SARS-CoV-2, only 51% were antibody positive, three months after the infection. However, among the 10 LT recipients, 8 (80%) had developed SARS-CoV-2 antibodies [18]. This study shows an important discrepancy among the rate of seropositivity among the different organs evaluated that deserves further evaluation. A

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similar study conducted by Boyarsky *et al.* [19] reported a series of 18 SOT recipients with SARS-CoV-2 PCR-confirmed, in which 78% of the patients were able to develop and maintain SARS-CoV-2 antibodies 98 days (IQR 55–147) after the COVID-19 infection. Despite the relevance of the data, both are small series, including only 16 LT recipients (or liver-kidney) recipient, whose results would have to be confirmed.

Our result is consistent with the 3.2% SARS-CoV-2 seroprevalence described in another cohort of LT recipients evaluated between May and August 2020 [8], but significantly, in an area, as it was Germany during the evaluated period, much less affected by the pandemic, where the estimated seroprevalence was 1.3–3.2%. Hence, in this study the seroprevalence in LT recipients was the same as in the general population. However, the SARS-CoV-2 seroprevalence reported in the present study came from an area as Barcelona with a SARS-CoV-2 seroprevalence twice as high as that found in our cohort (3.1% vs. 6.8%). Taking as true the seroprevalence figures, we can only assume that patients evaluated in the present cohort, within a much more affected area, were less exposed to the virus, thanks to isolation and personal cleanliness measures, which were the first premises that the LT team tried to ensure in these patients, as well as keeping them out of the hospital, if possible. This reinforces the paramount importance of observing social distancing, disinfection measures and masking.

Another important fact is that, in our cohort of 294 patients, we were only able to identify one asymptomatic case (0.3%), and the remaining patients had clinical manifestations, previously confirmed or not by RT-PCR. These results make the possibility of asymptomatic infection in LT recipients very unlikely. Probably, if a LT recipient is infected by SARS-CoV-2 develops clinical manifestations of the disease. Whether clinical manifestations would be more severe than in general population is still under discussion, with discordant results [2,3,19]. Besides, other studies from high incidence areas, like London, have shown a low incidence of SARS-CoV-2 infection among LT recipients, supporting our findings, with a seroprevalence half the rate found in the Spanish population [20].

However, and despite the aforementioned data, we have seroprevalence figures from SARS-CoV-2 infection and postvaccination studies in LT and SOT recipients that support the concept that immunological response is lower in these patients. In a Spanish study, including 71 LT recipients and 71 controls, with RT-PCR confirmed SARS-CoV-2 infection, lower incidence and lower levels of anti-nucleocapsid IgG antibodies at 3 and 6 months after infection in the LT group have been found [21]. Similarly, in a US cohort of 658 SOT recipients, antibody response after the two doses of mRNA vaccines was of 54%, representing a significant reduction when compared to the robust response demonstrated among the general population [22].

The relation between ABO and Rh blood type and COVID has been described with contradictory results. First studies pointed to a protector effect from nontype A group [23]. However, later studies have questioned this premise, showing contradictory results [24,25], and moreover, a large prospective study has not found any association among ABO blood type, risk of infection or its severity [26]. Our limited in size cohort, does not provide much information, but seems that the proportion of patients with non-A blood type have a lower proportion of SARS-CoV-2 antibodies.

Our study has some limitations. It is a single-centre study, but carried out in an area highly affected by the SARS-CoV-2 pandemic. It is a descriptive study and does not have enough cases to evaluate risk factors associated with a higher rate of infection. However, it has also some strengths. Data were prospectively collected, including all consecutive patient visited in the outpatient clinic, limiting the loss of information and selection bias. Likewise, serological diagnosis in consecutively tested patients is not affected by the rate of report of the disease.

In conclusion, SARS-CoV-2 seroprevalence among LT recipients in an area highly affected by the pandemic is as low as 3.1% and is reduced to 0.3% for the asymptomatic infection. These results make the design of futures strategies to face the next phases of the pandemic, including vaccination, highly needed and reinforce the need to maintain public health measures and surveillance to protect the general population and LT recipients.

Authorship

IC-V: study concept and design, interpretation of data, drafting of manuscript, critical revision of the manuscript for important intellectual content and statistical analysis. OL: study concept and design, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content. AV: data collection, interpretation of data and critical revision of the manuscript for important intellectual content. EM-A: data collection, interpretation of data and critical revision of the manuscript for important intellectual content. JE, CD, ILA and AA: data collection, interpretation of data and critical revision of the manuscript for important intellectual content. LC: study concept and

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design, data collection, interpretation of data, drafting of manuscript and critical revision of the manuscript for important intellectual content.

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Conflict of interest

The authors have no conflicts of interest to disclose.

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