SARS-CoV-2 and Liver Transplant: How Has It Behaved in This Sixth Wave?

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Background. Since the declaration of a new variant of concern (VOC), Omicron, by the World Health Organization in November 2021, a quick spread has been documented worldwide, being the main VOC in the sixth wave in Spain. The Omicron variant has more transmissibility, lower virulence, and less risk of severe disease than previously described VOC. Here we analyze the current wave of severe acute respiratory syndrome coronavirus 2 infection in liver transplant recipients (LTRs). **Methods.** A retrospective observational study of 355 LTRs was conducted in La Rioja and Cantabria regions of Spain. Epidemiological and clinical parameters were gathered on the basis of clinical records and telephone interviews. **Results.** In the current wave of infection, a higher number of LTRs have been found to be infected than the sum of the previous 5 waves (30 versus 16 LTRs). Of the 30 infected LTRs, 29 (96.6%) had received 3 vaccine doses (mRNA based), in a median of 93 d (interquartile range, 86–108) before infection. Eight of 30 LTRs (24.0%) were asymptomatic and 21 LTRs (67.8%) were with mild symptoms with a mean duration of 4.6 d (interquartile range, 2.5–7), whereas in the unvaccinated LTRs, the symptoms were fever, nausea, vomiting, and diarrhea. Moreover, in the sixth wave, intrafamiliar transmission was the main route of infection (17/30; 56.6%), and nosocomial transmission was confirmed in 2 LTRs (6.6%). **Conclusions.** In our series, increased transmissibility of the Omicron variant was confirmed, including nosocomial infection, with a lower risk of severe disease in LTRs. These findings could be supported by the universal vaccination of LTRs and less virulence of the Omicron variant.

(*Transplantation* 2022;106: 1445–1449).

INTRODUCTION

Since its declaration by the World Health Organization and the European Centre for Disease Prevention and Control on November 26, 2021, a new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant of concern called (B.1.1.529)[1,2] was first detected in South Africa. This variant of concern has experienced rapid expansion and was estimated to be 81% of the variants isolated by November 2021 and 95% isolated by December 2021. In fact, Omicron was the most predominant variant of the sixth wave in Spain.[3] Accumulating scientific evidence supports the increased transmissibility of the Omicron variant and its greater immune escape capacity, as well as lower virulence and lower risk of causing severe disease and death than previous variants.[4] This study aimed to analyze the impact of SARS-CoV-2 infection on liver transplantation in the current wave from late November 2021 through February 23, 2022.

MATERIALS AND METHODS

This retrospective observational study included 355 liver transplant recipients (LTRs) from La Rioja and Cantabria undergoing regular follow-up at the Liver Transplant Unit of the Marqués de Valdecilla University Hospital and the Hepatology Unit of San Pedro Hospital. Clinical data, including comorbidities and immunosuppressive regimen, were obtained from patient's medical records. Epidemiological and clinical information, including contact details, date

Received 7 March 2022.

Accepted 9 March 2022.

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The authors declare no funding or conflicts of interest.

All authors had access to the study data and critically reviewed, revised, and approved the final article. A.C., D.S.S., E.F., J.C., T.H., and V.E. participated in the study design. A.C., A.M., A.O., B.L., E.F., M.d.B., T.H., and V.E. participated in the performance of the research. A.C., A.M., A.O., A.P., B.L., D.S.S., E.F., J.C., J.I.F., M.d.B., M.L.-H. T.H., and V.E. participated in interpretation of the data and drafting of the article.

Supplemental Visual Abstract; http://links.lww.com/TP/C419.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantjournal.com).

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ISSN: 0041-1337/20/1067-1445

DOI: 10.1097/TP.0000000000004157

<zdoi;10.1097/TP.0000000000004157>

onset, clinical severity, and disease course of SARS-CoV-2 infection, was gained via telephone survey. This study was approved by the Institutional Ethics Committee of Cantabria (Code 2022.038) and complied with the provisions of the Good Clinical Practice guidelines and the Declaration of Helsinki. The humoral response was evaluated using serum levels of anti–SARS-CoV-2 spike protein S1 immunoglobulin (Abbott SARS-CoV-2 antispike immunoglobulin G II assay, positive >50 AU/mL), and serum levels of anti–SARS-CoV-2 spike protein S1 immunoglobulin of ≥4160 AU/mL were chosen as surrogate measures of antibody neutralization.[5] Categorical variables were expressed as the number of cases (percentage), and continuous variables were expressed as the median (interquartile range [IQR]).

RESULTS

In the current sixth wave, more LTRs have been found to be infected than the sum of the 5 previous waves (30 versus 16 LTRs; Figure 1). Table 1 shows the characteristics of these patients. Of these 30 LTRs, 29 were full vaccinated (96.6%) and received a third dose of Pfizer or Moderna mRNA vaccine between September 20, 2021, and December 27, 2021, in a median of 96 d (IQR, 87–111) before the diagnosis of the infection (from December 2, 2021, to February 17, 2022). It is noteworthy that the infection was asymptomatic in 8 LTRs (24%), the symptoms were mild in 21 LTRs (70%), and only 1 patient required hospitalization for pneumonia and finally died. The most common symptoms were cough (36.6%) and runny/stuffy nose (36.6%), followed by headache (23.3%), myalgia (20%), and fatigue (16.6%) with a mean duration of 4.6 d (IQR, 2.5–7). Whereas in the nonvaccinated patient, these symptoms were accompanied by fever, nausea, vomiting, and diarrhea. In a subgroup of 19 LTRs, we had the results of the humoral response in a median of 107 d (IQR, 93.75–119) after the third vaccine dose. Paradoxically, we observed in the LTRs with lower anti-S1 antibody titers (<4160 U/mL) more asymptomatic patients (4/8; 50%) than in the group of LTRs with a stronger humoral response (2/11; 18.1%), suggesting the possibility that LTRs developed cellular response capable of preventing or limiting severe coronavirus disease 2019 symptoms.[6] In contrast, of the 16 LTRs infected in the previous waves, 5 (31.25%) required hospital admission for pneumonia, and 2 of them (12.5%) died. In this sixth wave, intrafamilial transmission (17/30; 56.6%) was the main route of infection, and nosocomial transmission was demonstrated in 2 LTRs (6.6%). In 16 LTRs (53.3%), the initial diagnosis was made by a rapid antigen self-test taken at home[7,8] and subsequently confirmed by antigen test or by reverse transcription polymerase chain reaction, performed with nasopharyngeal swab in primary care centers. The outpatient follow-up protocol was similar to that of patients without any risk factors: without sending any patient to the hospital, neither performing blood tests nor chest radiology. In fact, only 12 LTRs (40%) contacted the Liver Transplant Unit.

DISCUSSION

In our series, the route of transmission was mainly intrafamilial, although we also observed nosocomial transmission because of the high rate of community transmission of the virus in this wave. It is noteworthy that asymptomatic cases represented 56.6% of all infected LTRs, percentage higher than reported by the Prevalence of SARS-CoV-2 in Spain study performed in the last months of the first wave in Spain.[9] Additionally, we confirmed that in this sixth wave, there is a greater transmissibility of the infection with a lower risk of producing serious illness in LTRs. This may be because of the practically universal vaccination with 3 vaccine doses of the LTRs together with the lower virulence of the Omicron variant. These findings together with those reported from South Africa, United Kingdom, and Canada, are consistent with experimental animal infection that Omicron causes less severe disease in mice and hamsters.[4,10]

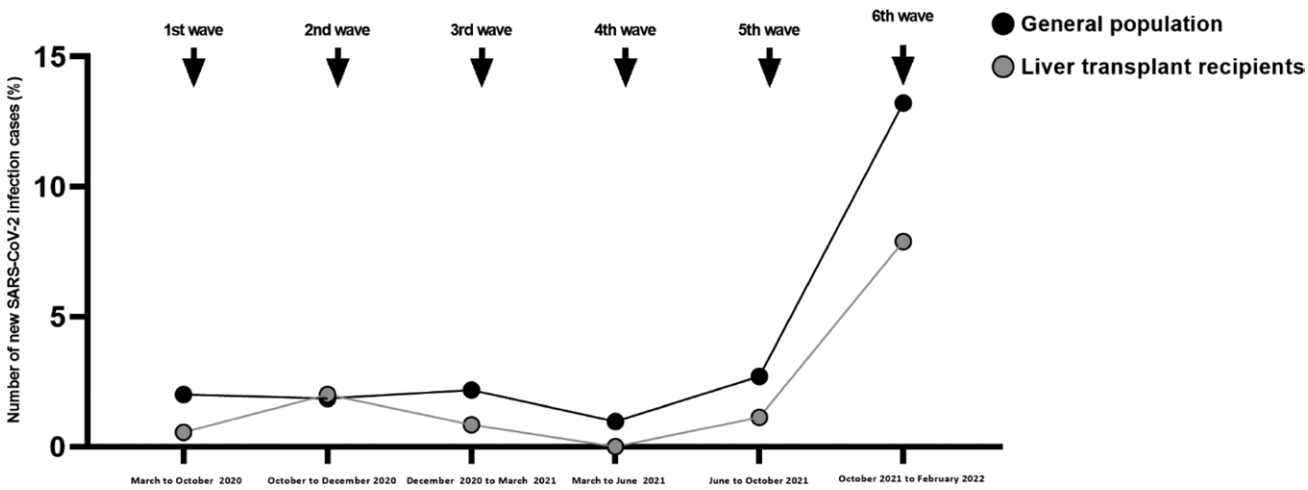

FIGURE 1. Evolution of SARS-CoV-2 infection since the pandemic declaration in the general population and liver transplant recipients from Cantabria and la Rioja. The timeline of the frequency of new cases of SARS-CoV-2 infection in the general population (black circles) and liver transplant recipients (gray circles) are depicted. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

TABLE 1.

Epidemiological and clinical data of liver transplant recipients in the sixth wave of SARS-CoV-2 infection

S. No.	Age	Sex	Transplant	Date of liver transplant	Comorbidities	Immunosuppressive regimen	Date of third dose	Anti-S1 (AU/mL)	Date of infection	Transmission	Autotest	Symptoms	Duration	Days since vaccination	Hospitalization	Following	Death
1	74	Female	Liver	21/07/2012	Diabetes, hypertension,CKD3a	Tacrolimus	09/27/2021 (Moderna)	–	12/24/2021	Intrafamiliar	Yes	Cough, runny/ stuffy nose	5	88	No	Primary care	No
2	45	Male	Liver	17/01/2015	Ulcerative colitis	Tacrolimus + MMF + P	10/03/2021 (Moderna)	–	12/02/2021	Intrafamiliar	No	Cough, runny/ stuffy nose	5	60	No	Primary care	No
3	65	Male	Liver	16/03/2015	Diabetes, hypertension, celiac disease	Tacrolimus	09/27/2021 (Pfizer)	–	12/22/2021	Intrafamiliar	No	Cough, headache	3	86	No	Primary care	No
4	47	Male	Liver	08/11/2015	None	Tacrolimus	10/05/2021 (Moderna)	–	12/30/2021	Unknown	Yes	Runny/stuffy nose, headache	2	86	No	Primary care	No
5	67	Male	Liver	15/02/2018	Diabetes, CKD 3a, CVD	Tacrolimus + EV	09/22/2021 (Moderna)	–	12/28/2021	Unknown	No	Cough, headache	3	97	No	Primary care	No
6	64	Male	Liver	02/03/2015	Diabetes, CKD2	Tacrolimus	09/20/2021 (Pfizer)	–	26/12/2021	Intrafamiliar	Yes	Asymptomatic	0	97	No	Primary care	No
7	65	Male	Liver	07/12/2002	Diabetes, hypertension	MMF	12/27/2021 (Moderna)	–	01/10/2022	Unknown	Yes	Fever, myalgias, fatigue	10	14	No	Primary care	No
8	72	Male	Liver	20/09/2015	Diabetes, hypertension, CKD3a	Tacrolimus	09/28/2021 (Moderna)	39 975	01/03/2022	Unknown	No	Asymptomatic	0	97	No	Primary care	No
9	48	Male	Liver	06/10/2020	Diabetes, CKD2	Tacrolimus + EV	09/29/2021 (Moderna)	461	01/11/2022	Intrafamiliar	No	Asymptomatic	0	104	No	Primary care	No
10	72	Male	Liver	15/12/2005	Diabetes, hypertension, CKD 4	MMF	09/28/2021 (Moderna)	10 665	01/11/2022	Intrafamiliar	Yes	Cough, runny/ stuffy nose	5	105	No	Primary care	No
11	58	Male	Liver	24/07/2015	Hypertension obesity	EV	09/29/2021 (Moderna)	12 513	12/31/2021	Social	Yes	Myalgias, fatigue	8	93	No	Primary care	No
12	69	Male	Liver	31/08/2009	CVD	Tacrolimus	10/05/2021 (Moderna)	29 164	01/09/2022	Unknown	Yes	Cough, runny/ stuffy nose	5	96	No	Primary care	No
13	51	Female	Liver	10/05/2012	Polycythemia vera, CKD3a	Tacrolimus + MMF + P	09/28/2021 (Moderna)	21 019	01/09/2022	Intrafamiliar	Yes	Headache, sore throat, fatigue	6	103	No	Primary care	No
14	35	Male	Liver	23/02/2018	None	Tacrolimus	09/28/2021 (Moderna)	40 000	01/12/2022	Intrafamiliar	Yes	Runny/stuffy nose, headache	7	106	No	Primary care	No
15	67	Male	Combined liver and kidney	30/12/2006	Diabetes, hypertension	Tacrolimus + MMF	09/27/2021 (Moderna)	33	01/11/2022	Unknown	Yes	Cough, runny/ stuffy nose, nausea	7	106	No	Primary care	No
16	70	Female	Liver	24/11/2020	Diabetes, hypertension, CKD3a	Tacrolimus + MMF + P	09/28/2021 (Moderna)	853	01/16/2022	Intrafamiliar	Yes	Cough, headache, fatigue, myalgias	7	110	No	Primary care	No
17	65	Male	Liver	06/08/2015	Obesity, CKD3b	Tacrolimus + MMF	09/28/2021 (Moderna)	25 452	01/17/2022	Unknown	No	Runny/stuffy nose	5	111	No	Primary care	No

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TABLE 1. (Continued)

S. No.	Age	Sex	Transplant	Date of liver transplant	Comorbidities	Immunosuppressive regimen	Date of third dose	Anti-S1 (AU/mL)	Date of infection	Transmission	Autotest	Symptoms	Duration	Days since vaccination	Hospitalization	Following	Death
18	72	Female	Liver	24/05/2018	Diabetes, hypertension, obesity	Tacrolimus	10/28/2021 (Moderna)	2706	01/14/2022	Social	No	Fatigue	1	78	No	Primary care	No
19	65	Male	Liver	12/05/2012	Diabetes, hypertension, CVD, CPD	Tacrolimus	18/10/2021 (Pfizer)	19 937	24/12/2021	Nosocomial	No	Asymptomatic	0	67	No	Primary care	No
20	74	Male	Combined liver and kidney	26/02/2007	Diabetes, hypertension, CKD4	Tacrolimus + MMF	11/22/2021 (Pfizer)	–	12/31/2021	Intrafamiliar	No	Fever, cough, headache, diarrhea, pneumonia	46	69	Yes	Intensive care unit	Yes
21	77	Male	Liver	01/07/2007	Diabetes, CKD3a	Tacrolimus + MMF + P	10/26/2021 (Pfizer)	–	01/12/2022	Nosocomial	No	Asymptomatic	0	78	No	Primary care	No
22	59	Male	Liver	01/05/2007	Diabetes, CKD3a	MMF	09/27/2021 (Moderna)	1042	01/24/2022	Unknown	No	Asymptomatic	0	119	No	Primary care	No
23	66	Male	Liver	14/11/2016	None	Tacrolimus	10/19/2021 (Moderna)	1467	01/15/2022	Intrafamiliar	No	Asymptomatic	0	88	No	Primary care	No
24	39	Female	Liver	13/05/2016	None	Tacrolimus + azathioprine	11/16/2021 (Pfizer)	–	01/16/2022	Intrafamiliar	Yes	Runny/stuffy nose	2	61	No	Primary care	No
25	64	Male	Liver	04/04/2018	Hypertension	EV	10/05/2021 (Moderna)	40 000	02/02/2022	Intrafamiliar	Yes	Myalgias	2	120	No	Primary care	No
26	66	Female	Liver	22/10/2011	None	Tacrolimus + MMF	10/05/2021 (Moderna)	40 000	12/31/2021	Intrafamiliar	Yes	Cough, sore throat, headache, myalgias	7	87	No	Primary care	No
27	65	Female	Liver	07/04/2019	Hypertension, CKD3a	Tacrolimus	Not vaccinated	–	20/01/2021	Intrafamiliar	No	Fever, headache, sore throat, nausea, vomiting, diarrhea	7	–	No	Primary care	No
28	56	Male	Liver	23/03/2011	CKD2	Tacrolimus	10/05/2021 (Moderna)	1304	02/04/2022	Intrafamiliar	Yes	Asymptomatic	0	122	No	Primary care	No
29	58	Male	Liver	25/04/2021	Diabetes	Tacrolimus	09/27/21 (Moderna)	85	02/15/2022	Unknown	No	Cough, runny/ stuffy nose, sore throat,	5	141	No	Primary care	No
30	36	Female	Liver	06/06/1995	None	Tacrolimus	09/28/2021 (Moderna)	39 242	02/17/2022	Intrafamiliar	Yes	Runny/stuffy nose, diarrhea	2	142	No	Primary care	No

CKD, chronic kidney disease categories according to KDIGO; CPD, chronic pulmonary disease; CVD, cardiovascular disease; EV, everolimus; KDIGO, Kidney Disease: Improving Global Outcomes; MMF, mycophenolate mofetil; P, prednisone.

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