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.

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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 antispikel 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. 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 fully 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. 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 home7,8 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. 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.
| S. No. | Age  | Sex | Transplant  | Date of liver transplant | Comorbidities                                      | Immunosuppressive regimen | Date of third dose | 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          | –                | 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          | –                | 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          | –                | Intrafamiliar | No       | Cough, headache                | 3         | 86                      | No              | Primary care | No    |
| 4     | 47   | Male   | Liver      | 08/11/2015              | None                                               | Tacrolimus                | 10/05/2021          | –                | Intrafamiliar | 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          | –                | Unknown      | No       | Cough, headache                | 3         | 97                      | No              | Primary care | No    |
| 6     | 64   | Male   | Liver      | 02/03/2015              | Diabetes, CKD2                                     | Tacrolimus                | 09/20/2021          | –                | Intrafamiliar | Yes      | Asymptomatic                    | 0         | 97                      | No              | Primary care | No    |
| 7     | 65   | Male   | Liver      | 07/12/2002              | Diabetes, hypertension                             | MMF                       | 12/27/2021          | –                | Intrafamiliar | No       | Fever, myalgias, fatigue       | 10        | 14                      | No              | Primary care | No    |
| 8     | 72   | Male   | Liver      | 20/09/2015              | Diabetes, hypertension, CKD3a                      | Tacrolimus                | 09/28/2021          | 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          | 461              | 01/11/2022    | Unknown      | No       | Asymptomatic                    | 0         | 104                     | No              | Primary care | No    |
| 10    | 72   | Male   | Liver      | 15/12/2005              | Diabetes, hypertension                             | MMF                       | 09/28/2021          | 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          | 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          | 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          | 21.019          | 01/09/2022    | Intrafamiliar | Yes      | Headache, sore throat, fatigue  | 6         | 103                     | No              | Primary care | No    |
| 14    | 35   | Male   | Liver      | 23/02/2018              | Polycythemia vera, CKD3a                            | Tacrolimus                | 09/28/2021          | 40.000          | 01/12/2022    | Intrafamiliar | Yes      | Runny/stuffy nose, headache     | 7         | 106                     | No              | Primary care | No    |
| 15    | 67   | Male   | Liver      | 30/12/2006              | Diabetes, hypertension                             | Tacrolimus + MMF          | 09/27/2021          | 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          | 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          | 25.452          | 01/17/2022    | Unknown      | No       | Runny/stuffy nose               | 5         | 111                     | No              | Primary care | No    |

**Continued next page**
| 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 | Days since vaccination | Hospitalization | Following | Death  |
|--------|------|-------|----------------|--------------------------|--------------------------------|---------------------------|----------------------|-----------------|------------------|--------------|----------|----------|----------------------|----------------|-----------|--------|
| 18     | 72   | Female| Liver          | 24/05/2018               | Diabetes, hypertension, obesity | Tacrolimus                | 10/28/2021           | 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           | 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           | –               | 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           | –               | 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           | 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           | 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           | –               | 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           | 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           | 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           | 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             | 85              | 02/15/2022       | Unknown      | No       | Cough, runny/stuffy nose, sore throat, diarrhea | 5               | 141 No | Primary care No  |
| 30     | 36   | Female| Liver          | 06/06/1995               | None                        | Tacrolimus                | 09/28/2021           | 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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