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Original Article

Clinical characteristics and outcomes of liver transplant recipients infected by Omicron during the opening up of the dynamic zero-coronavirus disease policy in China: A prospective, observational study

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ABSTRACT

We analyzed the characteristics, risk factors, outcomes, and post–coronavirus disease 2019 (COVID-19) symptoms in liver transplant recipients in China's late 2022 COVID-19 wave. Recipients with COVID-19 were enrolled from December 1, 2022, to January 31, 2023, and followed up until May 31, 2023. Baseline and characteristic data were collected. A total of 930 recipients were included, with a vaccination rate (non-mRNA) of 40.0%. Among 726 (78.1%) recipients with COVID-19, 641 (88.3%) patients were treated at home, 81 (11.2%) patients required hospitalization in general wards, 4 (0.6%) patients required intensive care, and 1 (0.1%) patient died because of COVID-19. Severe acute respiratory syndrome coronavirus 2 infection was related to close contact with confirmed cases ($P < .001$) and the condition of end-stage kidney disease ($P < .046$). Older age, male sex, less vaccination, and hypertension were independent risk factors for hospitalization. Fatigue (36.9%) was the most common symptom post-COVID-19, followed by memory loss (35.7%) and sleep disturbance (23.9%). Two doses of vaccines had a protective effect against these post-COVID-19 symptoms ($P < .05$). During this Omicron outbreak, liver transplant

Abbreviations: COVID-19, coronavirus disease 2019; HBV, hepatitis B virus; ICU, intensive care unit; IQR, interquartile range; LT, liver transplant; MELD, model for end-stage liver disease; PCR, polymerase chain reaction; UDCA, ursodeoxycholic acid.

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recipients were susceptible to COVID-19, with frequent hospitalization but low mortality. Two doses of non-mRNA COVID-19 vaccines could protect against liver transplant recipient hospitalization and post-COVID-19 symptoms.

Introduction

After the coronavirus disease 2019 (COVID-19) policy adjustment, the number of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected patients increased rapidly in China.[1] Genome sequencing showed that all local cases of COVID-19 were caused by Omicron variants from September 26, 2022, to January 23, 2023, in China, and BA.5.2 and BF.7 were the major epidemic strains in this wave.[1]

Solid organ transplant (SOT) recipients are susceptible to COVID-19 because of their immunosuppressive state and low antibody response to vaccines.[2-4] Meanwhile, they are considered a particularly vulnerable group to the COVID-19 pandemic because of their high prevalence of comorbidities, such as hypertension, renal dysfunctions, and diabetes.[2,5] With the development of timely diagnosis and advances in vaccines and treatments, the severity of COVID-19 in liver transplant (LT) recipients has changed.[6-8] In the initial phase of the COVID-19 pandemic, up to 80% of LT recipients required hospitalization, with mortality rates as high as 20%.[8,9] In more recent studies, mortality and hospitalization rates declined, with hospitalizations below 30% and within-month mortality rates ranging from 0% to 5.1%.[6,7,10,11]

The variation in the characteristics and outcomes of COVID-19 in transplant recipients might also be related to the different prevalent viral variants.[2,12] Since the end of 2021, the Omicron variant has been the dominant strain worldwide. Omicron has significantly higher transmissibility and ability to escape the immune system than the original strain but is less likely to cause severe disease.[13] However, the disease severity in hospitalized patients remains high.[14] Few studies have focused on the disease characteristics, disease progression, and optimal treatment of LT recipients infected with the Omicron strain. Thus, there is a need for further evidence. Particularly, the characteristics of LT recipients infected with the Omicron strain in the late 2022 COVID-19 wave in China might differ from previous studies, due to the variations in the types of COVID-19 vaccinations administered across different countries.[4,15] Non-mRNA COVID-19 vaccines are the mainstream vaccines used in China, mainly including inactivated vaccines and recombinant protein vaccines,[1,16] which differ from the widely used mRNA COVID-19 vaccines in many countries.[4,15] In this study, we aimed to analyze the characteristics, risk factors, outcomes, and post-COVID-19 symptoms in liver transplant recipients in the late 2022 COVID-19 wave in China. To achieve this purpose, we conducted a prospective and observational study in our center through follow-up of recipients who underwent liver transplantation from 2016 to 2022. Data from these patients might provide different and important information about COVID-19 in this population.

Methods

Study design and participants

This prospective, observational, and real-world study was conducted in the liver transplantation center of the First Affiliated Hospital of Zhejiang University from December 1, 2022, to May 31, 2023. The enrollment period of recipients with COVID-19 was from December 1, 2022, to January 31, 2023. The inclusion criteria were as follows: (1) adult recipients ($\geq$18 years old) who underwent liver transplantation from January 1, 2016, to November 30, 2022, and had been discharged after liver transplantation (LT recipients in the perioperative period were not included); (2) no history of major psychiatric or neurologic disorders; and (3) agreed to participate in the study and to comply with protocol-specified criteria. Recipients with confirmed or suspected COVID-19 were followed up regularly until May 31, 2023.

The study was conducted following the principles of the Helsinki Declaration of 1975 and followed the statement of Strengthening the Reporting of Observational Studies in Epidemiology. Ethical approval was obtained from the authorized ethics committee of the First Affiliated Hospital of Zhejiang University (IIT20230020B). All participants provided informed consent. Since January 1, 2015, organ procurement from executed prisoners has ceased entirely in China. No organs from executed prisoners were used in any case involved in this study. All organs were donated voluntarily with written informed consent, and this was conducted in accordance with the Declaration of Istanbul.

Diagnosis of COVID-19

Patients diagnosed through PCR or antigen tests were defined as having a confirmed diagnosis. Suspected diagnosis of COVID-19 for LT recipients was carried out in accordance with a previously published study[17] and should meet all the following criteria: (1) Intimate contact with patients with COVID-19 or clustered cases; (2) fever and clinical signs of acute respiratory infection, such as cough, shortness of breath, fatigue, headache, muscle or body aches, sore throat, and diarrhea. Confirmed diagnosed and suspected diagnosed cases were all included in the COVID-19 group.

Data collection, vaccines, and follow-up

During follow-up, an online data collection tool was used to collect information. Demographic data (such as age, sex, weight, body mass index), medical history (primary liver disease, underlying disease), procedure-related information (model for end-stage liver disease [MELD] score, graft information, and

transplant date), drug information (immunosuppressive regimes and combined medications), vaccination status, clinical symptoms, and outcomes of COVID-19 were collected.

The vaccines provided locally included inactivated vaccines and recombinant vaccines (produced using chinese hamster ovary cells). Fully immune was defined as the completion of vaccination according to the government recommendation (2 doses of the vaccines). Vaccines in China were provided by the government through the community, instead of medical centers. Thus, detailed vaccine information for every patient was not required.

Our transplantation center employs a scheduled 3-month follow-up plan for recipients. Follow-up was conducted by a special follow-up team. All patients previously marked as lost to follow-up were excluded.

Outcomes

The primary outcomes were 1-month mortality after infection, rate of hospitalization, and intensive care unit (ICU) admission. The secondary outcomes were the characteristics of LT recipients with COVID-19 and the risk factors for infection, hospitalization, and death.

Statistical analysis

Statistical tests were performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp). Continuous variables were summarized as the mean (± standard deviation [SD]) or median (with the interquartile range [IQR]), and categorical variables were expressed as the frequency (percentage). Univariate comparisons were conducted using the χ^2 or Fisher exact test for categorical variables, and Student's t-test or the Mann-Whitney U-test for continuous variables, as appropriate. Univariate and multivariate logistic regression analyses were applied to explore the risks for severe disease. After univariate comparisons, factors with a P value $< .05$ were entered into the multivariate logistic regression analysis (using forward selection). Two-sided $P < .05$ was considered statistically significant.

Results

Baseline characteristics of recipients with COVID-19 infection

Demographic and characteristic data of the enrolled recipients are shown in Table 1. A total of 930 adult LT recipients were included. The mean age of the included recipients was 51.0 years (SD ± 10.6), and 724 (77.8%) were male. During the study period, 726 (78.1%) patients developed COVID-19 (Fig. 1). Methodologically, 251 (34.6%) cases were diagnosed through PCR tests, 165 (22.7%) cases were diagnosed through antigen tests, 70 (9.6%) cases were diagnosed based on both PCR and antigen tests, and 240 (33.1%) were suspected diagnosed cases. The occurrence of COVID-19 in LT recipients is shown in Figure 2.

Among the COVID-19 group, the primary indication for LT was hepatitis B virus (HBV)/alcoholic cirrhosis (42.4%), hepatocellular carcinoma (29.6%), and other liver diseases (28.0%). The median time between transplantation and COVID-19 infection was 3.3 years (IQR: 1.7-4.6). Hypertension (n = 141, 19.4%) was the most common comorbidity of LT, followed by biliary complications (n = 114, 15.7%), diabetes mellitus (n = 58, 8.0%), vascular complications (n = 42, 5.8%), end-stage kidney disease (n = 21, 2.9%), and tumor recurrence (n = 18, 2.5%). At the time of enrollment, 461 (63.5%) recipients used a single type of immunosuppressant, 246 (33.9%) used 2 types of immunosuppressants, and 16 (2.2%) patients used 3 or more types of immunosuppressants. Tacrolimus (n = 629, 86.6%) and mycophenolate mofetil (MMF) (n = 225, 31.0%) were the predominant immunosuppressants. For vaccination status, more than half of the recipients were not vaccinated (428, 59.0%), 268 (36.9%) received a complete series of vaccines (2 doses), and 30 (4.1%) received a single dose.

Outcomes and treatments during 1 month of follow-up after infection

During the enrollment period, 726 (78.1%) patients developed COVID-19 (Fig. 1). The occurrence of COVID-19 in LT recipients is shown in Figure 2. The most common symptoms included fever (73.8%), fatigue (55.5%), myalgia (40.9%), cough/phlegm (39.4%), pharyngalgia (28.8%), and ageusia (22.5%). Of the 726 infected patients, 261 (35.9%) patients received nonsteroid antiinflammatory drugs (NSAIDs), 29 (4.0%) patients received steroids, 32 (4.4%) patients received small molecule antivirals (including nirmatrelvir/ritonavir, azvudine, and molnupiravir), and 49 (6.7%) patients received antibacterial drugs.

After developing COVID-19, 641 (88.3%) patients were treated at home, 81 (11.2%) patients required hospitalization in general wards, and 4 (0.6%) patients required ICU admission (Fig. 1). One (0.1%) patient admitted to the ICU died, and all others survived. In patients who required hospitalization, fever, fatigue, diarrhea, and dyspnea occurred more frequently than in patients treated at home (Fig. 3, $P < .05$).

Compared with patients treated at home, hospitalized patients more frequently received small molecule antivirals (25.9% vs 1.6%), antiinfective agents (21.2% vs 4.8%), and steroids (21.2% vs 1.7%, $P < .001$, Table 2); however, the use of NSAIDs was similar between the 2 groups (38.8% vs 35.6%, $P = .550$). Among the 85 LT recipients requiring hospitalization, 31 were admitted to our hospital (including 4 patients who required ICU care), whereas 54 recipients were admitted to other hospitals (all in general wards). The median hospital stay of LT recipients in our hospital was 9 (IQR: 6.5-16) days. Seven recipients (22.6%) did not require oxygen support, 7 recipients (22.6%) needed noninvasive ventilation or humidified high-flow nasal cannula support, and 2 (6.5%) recipients were intubated, including 1 patient supported with extracorporeal membrane oxygenation who ultimately died.

Risk factors for SARS-CoV-2 infection

The demographic and characteristic data were compared between recipients with or without COVID-19. The age, sex ratio, primary liver disease, vaccination status, ursodeoxycholic acid (UDCA) usage, immunosuppressant usage, comorbidities, and

Table 1
Demographic and clinical characteristics of the study participants.

Characteristics	Total (n = 930)	Infection group (n = 726)	Noninfection group (n = 204)	*P*
Age, y	51.0 ± 10.6	50.8 ± 10.3	51.4 ± 11.5	.475
BMI, kg/m^2	23.1 ± 3.6	23.1 ± 3.5	23.1 ± 3.7	.780
Male sex, n (%)	724 (77.8)	567 (78.1)	157 (77.0)	.729
MELD at LT	20.9 ± 9.5	20.7 ± 9.4	21.4 ± 9.7	.338
Tx to infection/end of follow-up, y	3.2 (IQR: 1.6-4.5)	3.3 (IQR: 1.7-4.6)	3.1 (IQR: 1.4-4.3)	.820
Etiology, n (%)				.646
HCC	273 (29.4)	215 (29.6)	58 (28.4)	
HBV/Alcoholic cirrhosis	390 (41.9)	308 (42.4)	82 (40.2)	
Others	267 (28.7)	203 (28.0)	64 (31.4)	
Vaccination, n (%)				.339
None	558 (60.0)	428 (59.0)	130 (63.7)	
Single dose	40 (4.3)	30 (4.1)	10 (4.9)	
Fully immune	332 (35.7)	268 (36.9)	64 (31.4)	
Close contacts, n (%)				<.001
None	124 (13.3)	57 (7.9)	67 (32.8)	
1-2	383 (41.2)	292 (40.2)	91 (44.6)	
>3	423 (45.5)	377 (51.9)	46 (22.5)	
Anti-HBV medication, n (%)	643 (69.1)	506 (69.7)	137 (67.2)	.488
UDCA, n (%)	374 (40.2)	299 (41.2)	75 (36.8)	.255
Tac, n (%)	811 (87.2)	629 (86.6)	182 (89.2)	.330
CsA, n (%)	27 (2.9)	21 (2.9)	6 (2.9)	.962
MMF, n (%)	288 (31.0)	225 (31.0)	63 (30.9)	.976
Steroids, n (%)	25 (2.7)	19 (2.6)	6 (2.9)	.800
Sirolimus, n (%)	137 (14.7)	107 (14.7)	30 (14.7)	.989
Numbers of immunosuppressants, n (%)				.917
None	4 (0.4)	3 (0.4)	1 (0.5)	
Single	585 (62.9)	461 (63.5)	124 (60.8)	
Two	320 (34.4)	246 (33.9)	74 (36.3)	
Three or more	21 (2.3)	16 (2.2)	5 (2.5)	
Comorbidities, n (%)				
Hypertension	177 (19.0)	141 (19.4)	36 (17.6)	.568
Diabetes	75 (8.1)	58 (8.0)	17 (8.3)	.873
ESKD	22 (2.4)	21 (2.9)	1 (0.5)	.046
Biliary complication	143 (15.4)	114 (15.7)	29 (14.2)	.624
Tumor recurrence	25 (2.7)	18 (2.5)	7 (3.4)	.458
Vascular complications	53 (5.7)	42 (5.8)	11 (5.4)	.841
Nearest laboratory values before symptoms				
WBC, $\times 10^9$/L	5.4 ± 2.0	5.4 ± 2.0	5.3 ± 1.8	.608
Neutrophil, $\times 10^9$/L	3.0 ± 1.3	3.0 ± 1.3	3.1 ± 1.2	.609

(*continued on next page*)

Table 1 (*continued*)

Characteristics	Total (n = 930)	Infection group (n = 726)	Noninfection group (n = 204)	*P*
Lymphocyte, $\times 10^9$/L	1.7 ± 0.9	1.7 ± 1.0	1.6 ± 0.8	.235
NLR	2.1 ± 1.3	2.0 ± 1.2	2.2 ± 1.3	.175
ALT, U/L	18 (IQR: 12-26)	17 (IQR: 12-26)	18 (IQR: 12-28)	.058
Tac concentration, ng/mL	5.2 ± 2.3	5.2 ± 2.4	5.0 ± 1.9	.322
Sirolimus concentration, ng/mL	5.4 ± 2.1	5.3 ± 1.8	5.4 ± 2.8	.983

Data are mean ± SD or median (interquartile range [IQR]) or n (%).
Abbreviations: ALT, alanine transaminase; BMI, body mass index; CsA, cyclosporin A; ESKD, end-stage kidney disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; MMF, mycophenolate sodium enteric-coated tablets or mycophenolate mofetil; NLR, neutrophil-to-lymphocyte ratio; Tac, tacrolimus; Tx, transplant; UDCA, ursodeoxycholic acid; WBC, white blood cell.

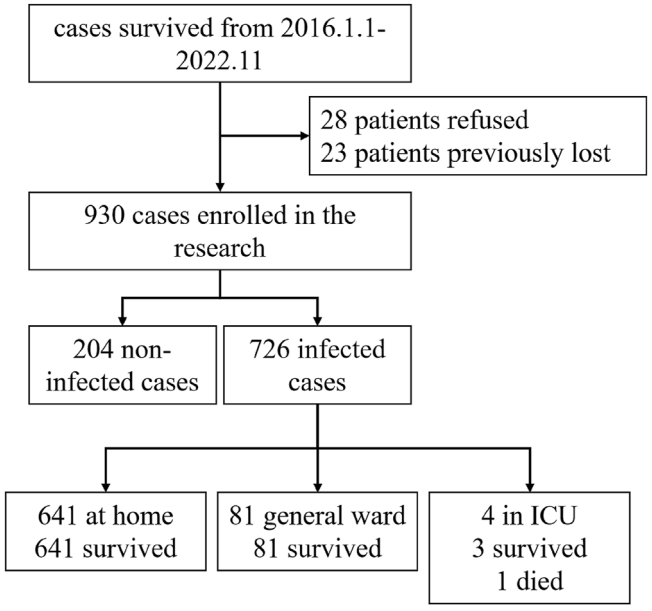

Figure 1. Flow chart of the present research.

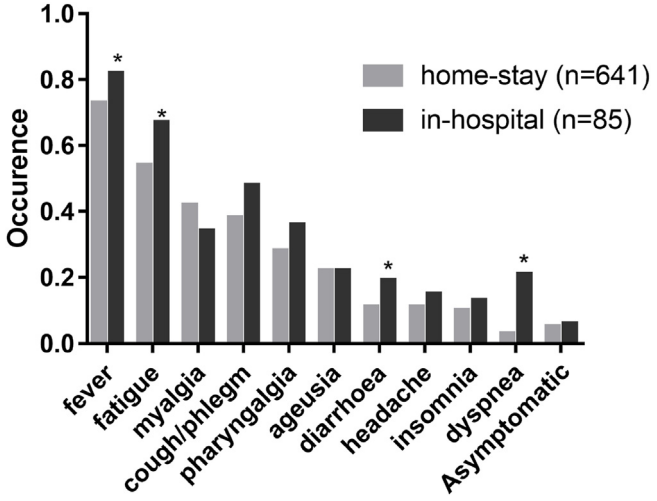

Figure 3. Symptoms according to the home-stay group and hospitalized group. * $P < .05$ ($P = .046$ for fever, $P < .001$ for diarrhea, $P = .032$ for fatigue, $P < .001$ for dyspnea).

laboratory values were similar between the 2 groups. Significant differences were seen in the rate of close contact ($P < .001$) and end-stage kidney disease (ESKD, $P < .046$). More than 90% of infected recipients had an exposure history that was significantly greater than recipients without infections (67.1%), and there was a significantly higher rate of infections among recipients with ESKD.

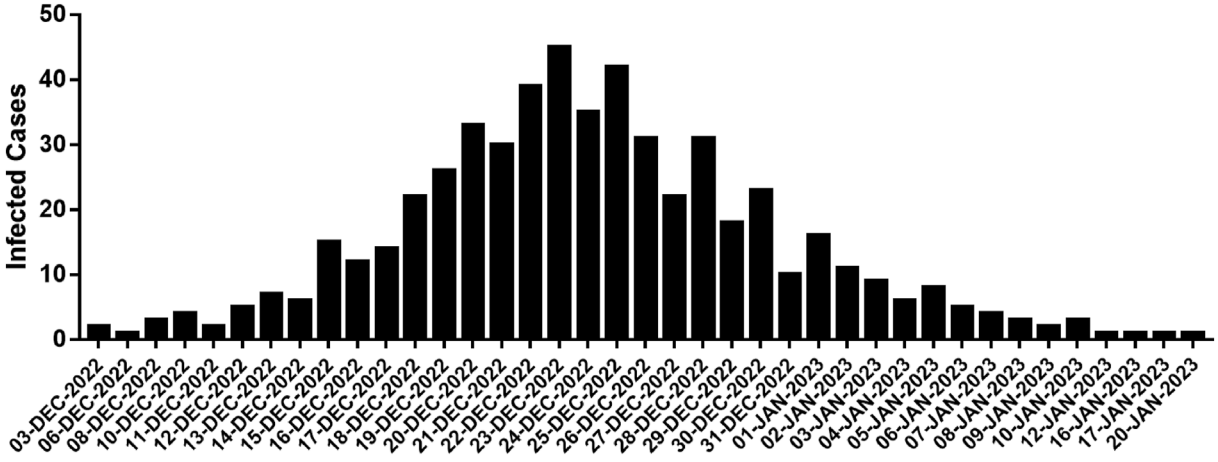

Figure 2. Infection time according to the time of the research (time was defined as the date of the antigen or polymerase chain reaction test for patients with confirmed coronavirus disease 2019, and the onset of the symptoms for patients with suspected coronavirus disease 2019. Infection time was identified in 549 recipients.).

Table 2
Characteristics of the risk factors for hospitalization.

Characteristics	Home-stay group (n = 641)	Hospitalized group (n = 85)	*P*
Age, y	50.4 ± 10.3	54.3 ± 9.6	.001
BMI, kg/m^2	23.1 ± 3.5	23.5 ± 3.8	.271
Male sex, n (%)	492 (76.9)	75 (88.2)	.016
MELD at LT	20.6 ± 9.4	21.2 ± 9.3	.601
Tx to infection/end of follow-up, y	3.3 (IQR: 1.8-4.6)	2.5 (IQR: 1.2-4.7)	.179
Etiology, n (%)			.702
HCC	193 (30.0)	22 (25.9)	
HBV/Alcoholic cirrhosis	271 (42.3)	37 (43.5)	
Others	177 (27.7)	26 (30.6)	
Vaccination, n (%)			.024
None	370 (57.8)	58 (68.2)	
Single dose	24 (3.8)	6 (7.1)	
Fully immune	247 (38.5)	21 (24.7)	
Close contacts, n (%)			.626
None	48 (7.5)	9 (10.6)	
1-2	259 (40.4)	33 (38.8)	
>3	334 (52.2)	43 (50.6)	
Anti-HBV medication, n (%)	449 (70.0)	57 (67.1)	.573
UDCA, n (%)	261 (40.7)	38 (44.7)	.483
Tac, n (%)	563 (87.8)	66 (77.6)	.010
CsA, n (%)	18 (2.8)	3 (3.5)	.709
MMF, n (%)	204 (31.8)	21 (24.7)	.182
Steroids, n (%)	16 (2.5)	3 (3.5)	.575
Sirolimus, n (%)	91 (14.2)	16 (18.8)	.258
Numbers of immunosuppressants, n (%)			.025
None	1 (0.2)	2 (2.4)	
Single	403 (63.0)	58 (68.2)	
Two	222 (34.6)	24 (28.2)	
Three or more	15 (2.3)	1 (1.2)	
Comorbidities, n (%)			
Hypertension	115 (17.9)	26 (30.6)	.006
Diabetes	46 (7.1)	12 (14.1)	.027
ESKD	17 (2.7)	4 (4.7)	.288
Biliary complication	97 (15.2)	17 (20.0)	.254
Tumor recurrence	14 (2.2)	4 (4.7)	.160
Vascular complications	40 (6.3)	2 (2.4)	.146
Nearest laboratory values before symptoms			
WBC, $\times 10^9$/L	5.3 ± 1.9	5.6 ± 2.5	.237
Neutrophil, $\times 10^9$/L	3.0 ± 1.3	3.2 ± 1.7	.097
Lymphocyte, $\times 10^9$/L	1.7 ± 1.0	1.7 ± 0.9	.519
NLR	2.0 ± 1.2	2.4 ± 1.6	.029
ALT, U/L	17 (IQR: 12-25)	18 (IQR: 12-27)	.354
Tac concentration, ng/mL	5.2 ± 2.3	5.1 ± 2.6	.716
Sirolimus concentration, ng/mL	5.4 ± 1.9	5.0 ± 1.2	.427
Treatments, n (%)			
NSAIDs	228 (35.6)	33 (38.8)	.550
Small molecule antivirals	10 (1.6)	22 (25.9)	<.001
Steroids	11 (1.7)	18 (21.2)	<.001
Antiinfective agents	31 (4.8)	18 (21.2)	<.001

Data are mean ± SD or median (interquartile range [IQR]) or n (%).
Abbreviations: ALT, alanine transaminase; BMI, body mass index; CsA, cyclosporin A; ESKD, end-stage kidney disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; MMF, mycophenolate sodium enteric-coated tablets or mycophenolate mofetil; NLR, neutrophil-to-lymphocyte ratio; Tac, tacrolimus; Tx, transplant; UDCA, ursodeoxycholic acid; WBC, white blood cell.

Risk factors for hospitalization among infected patients

The demographic and characteristic data of recipients who required hospitalization are shown in Table 2. Compared with recipients treated at home, recipients who required hospitalization were characterized by older age (home-stay group vs hospitalized group, 50.3 ± 10.3 vs 54.3 ± 9.6 years, $P = .001$, Table 2), a higher proportion of males (76.9% vs 88.2%, $P = .016$), fewer vaccinations (none: 57.8% vs 68.2%, single dose: 3.8% vs 7.1%, and 2 doses: 38.5% vs 24.7%, $P = .024$). The incidence of hypertension and diabetes was significantly higher in the hospitalized group ($P < .05$). For drug usage, tacrolimus was less frequently used in patients admitted to hospitals (87.8% vs 77.6%, $P = .010$); there was no statistical difference in the use of UDCA. The most recent laboratory examination before symptoms appeared showed a higher neutrophil-to-lymphocyte ratio in the hospitalized group (2.0 ± 1.2 vs 2.4 ± 1.6, $P = .029$).

Eight groups of variables were further analyzed through multivariate regression analysis to examine the independent risk factors for hospitalization. The results are shown in Table 3 and revealed that older age (odds ratio [OR] = 1.039, 95% confidence

Table 3
Univariate and multivariate analysis of risk factors for hospitalization.

Characteristics	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age, y	1.041 (1.016-1.066)	.001	1.039 (1.012-1.068)	.005
Male sex, n (%)	2.256 (1.137-4.475)	.020	3.080 (1.409-6.731)	.005
Vaccination, n (%)				
None	2.929 (1.078-7.956)	.035	3.274 (1.128-9.501)	.029
Single dose	1.836 (1.087-3.103)	.023	1.946 (1.091-3.472)	.024
Fully immune	-	-	-	-
Tac, n (%)	0.482 (0.275-0.846)	.011	0.542 (0.295-0.998)	.049
No. of immunosuppressants, n (%)				
None	-			
Single	0.072 (0.006-0.806)	.033		
Two	0.054 (0.005-0.621)	.054		
Three or more	0.033 (0.001-0.770)	.034		
Hypertension, n (%)	2.033 (1.229-3.365)	.006	1.971 (1.130-3.438)	.017
Diabetes, n (%)	2.174 (1.099-4.297)	.026		
NLR	1.201 (1.016-1.421)	.032		

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; Tac, tacrolimus.

interval [CI]: 1.012-1.068), male sex (OR = 3.080, 95% CI: 1.409-6.731), vaccination (none vs 2 doses: OR = 3.274, 5% CI: 1.128-9.501; single dose vs 2 doses: OR = 1.946, 95% CI: 1.091-3.472), hypertension (OR = 1.971, 95% CI: 1.130-3.438), and usage of tacrolimus (OR = 0.542, 95% CI: 0.295-0.998) were significantly related to the risk for hospitalization after COVID-19 development.

Extended follow-up clinical situations and post-COVID-19 symptoms

Extended follow-up was performed for patients with COVID-19 from March 1, 2023, to May 31, 2023. No patient died due to COVID-19 during the extended follow-up period. One patient died because of hepatocellular carcinoma recurrence. Long-term COVID symptoms were further assessed through the post-COVID-19 symptom survey. Eight recipients refused to provide post-COVID-19 symptoms and 8 cases were lost to contact during this follow-up period. A total of 708 cases responded to the survey (Supplementary Table). Fatigue (36.9%) was the most common symptom reported, followed by memory loss (35.7%), sleep disturbance (23.9%), abdominal pain/diarrhea (15.0%), cough (13.3%), chest pain/palpitation (105, 14.8%), and dyspnea (6.6%). Complete immunity had a protective effect against memory loss ($P < .001$), sleep disturbance ($P = .027$), and fatigue ($P = .030$).

Discussion

During the COVID-19 pandemic, the characteristics and mortality of LT recipients continued to change over time. The Omicron strains are associated with lower risks of severe outcomes than the Delta and original strains.[13] However, data concerning Omicron infections in LT recipients are limited, especially in China. To the best of our knowledge, this is the largest single cohort study to date to assess the characteristics, risk factors, and outcomes of LT recipients with COVID-19 in an outbreak of the Omicron strain. Our study revealed that LT recipients were susceptible to COVID-19 after close contact with other confirmed cases. Compared with the initial phase of the COVID-19 pandemic,[8,9] the disease severity in this Omicron strain outbreak seemed mild, with 0.6% of patients requiring ICU admission, and 0.1% dying from COVID-19. Importantly, we first found that 2 doses of non-mRNA COVID-19 vaccines were associated with substantial reductions in COVID-19 hospitalization among LT recipients and had a protective effect against post-COVID-19 symptoms during the Omicron wave. UDCA, a promising drug to improve COVID-19 outcomes,[18] was not found to be related to the risk of hospitalization.

After the adjustment of the zero-COVID policy, surges of COVID-19 cases occurred in China. In the current Omicron wave, about 80% of LT recipients in our center developed COVID-19 during the enrollment period. The infection rate is substantially higher compared with studies carried out before Omicron variant predominance, which ranged from 2.4% to 12.6%.[15,19-25] Further analysis indicated that close contact with other confirmed cases and having ESKD were related to the infection risk. Currently used vaccines might be insufficient to prevent Omicron infections in LT recipients because the infection rates were similar among recipients who received different vaccine doses. Insufficient response to mRNA SARS-CoV-2 vaccines in LT recipients was

reported in several studies,[26-29] and the infection rate in vaccine recipients was slightly lower than that in unvaccinated recipients.[2,4] Meanwhile, neutralization for the Omicron variant dramatically declined in vaccinated individuals.[30] Few studies have examined the clinical efficacy of non-mRNA COVID-19 vaccines in the breakthrough of COVID-19. Inactivated vaccines are widely used in China. A multicenter study in China showed that inactivated vaccines accounted for 98.4% of the vaccines used in LT recipients.[31] In our previous study,[16] we evaluated the immunologic response of inactivated COVID-19 vaccines and found 17.1% of LT recipients were seropositive for IgG antibodies against SARS-CoV-2 one month after the last vaccination. Another study found that 41.2% of cases had positive serology of total neutralizing antibodies against SARS-CoV-2 after inactivated vaccination.[32] A multicenter retrospective study evaluated the prophylactic efficacy of COVID-19 vaccines (mainly inactivated vaccines) and revealed a poor protection rate (2.59%) against Omicron infection.[31] Based on the present results, behavior modifications are still strongly recommended for vaccinated LT recipients, such as mask wearing in public settings, social distancing from confirmed cases, and handwashing.

Although LT recipients required more frequent hospitalization than non-LT patients after SARS-CoV-2 infection,[33,34] the severity was mild and declined significantly compared with data from SOT recipients in the early pandemic.[5,35,36] However, post-COVID-19 symptoms were frequent, such as fatigue, memory loss, sleep disturbance, and abdominal pain/diarrhea. Compared with home-treated recipients, recipients who required hospitalization were older, had a higher proportion of males, had more frequent hypertension, and had less tacrolimus usage. These risk factors are consistent with previously published studies.[11,25] Interestingly, in contrast to the weak protective effect of vaccines against COVID-19, we found that 2 doses of non-mRNA vaccines could be effective in protecting against COVID-19 hospitalization and post-COVID-19 symptoms; even a single dose of the vaccine could reduce the risk of hospitalization. Such a protective role of the non-mRNA vaccines in LT recipients has not been reported previously. The underlying mechanism is unclear. A recent study found that although the neutralization for Omicron was dramatically compromised when using mRNA vaccines, CD4+ or CD8+ T cell responses were similar between the wild-type virus and Omicron, suggesting that the escape probability at the level of T cells was very low.[30] Therefore, vaccines might limit severe COVID-19 by preserving T cell immunity against the Omicron variant. Our results showed that non-mRNA vaccination still has a significant benefit in LT recipients. However, over half of the LT recipients did not receive COVID-19 vaccines. The level of vaccination in our center was lower than the average national rate,[1] but was similar to the level in LT recipients reported in a recent study.[31] Given the benefits of vaccines, additional interventions are needed to promote COVID-19 vaccination among LT recipients.

UDCA is a promising drug against COVID-19, which acts by downregulating angiotensin-converting enzyme 2 in human lungs and liver perfused ex situ.[18] Patients who received UDCA showed better outcomes, such as fewer deaths, hospitalizations, and ICU admissions after SARS-CoV-2 infection.[18] The positive outcome of UDCA was independently confirmed in a small sample cohort (96 patients) of LT recipients. However, the result remains to be confirmed prospectively in LT recipients. We analyzed the role of UDCA in our cohort with a larger sample and found no such protective result. It would be interesting to determine whether the role of UDCA depends on different ethnicities or viral variants in future studies.

Some limitation exists in the present study. Firstly, the SARS-CoV-2 variants and sublineages that infected our LT recipients were not determined, and some COVID-19 cases were diagnosed as suspected based on symptoms and exposure history. To avoid infection, LT recipients were encouraged to maintain social distancing. Therefore, it was not feasible to conduct genetic testing for all LT recipients. Diagnosis based on clinical symptoms, which is highly feasible in real-world studies, was recommended in some studies and considered informative.[17] Other flu-like diseases in winter can also cause similar symptoms. The incidence of flu during the peak period of this COVID-19 outbreak was below 1%, according to the Chinese Center for Disease Control and Prevention.[1] Combining symptoms and exposure history can further reduce the possibility of including cases infected by other flu-like viruses. According to the national report in China, all genome sequencing of local cases of COVID-19 identified Omicron variants from September 26, 2022, to January 23, 2023. The mainstream epidemic strains were the highly transmissible BA.5.2 (70.2%) and BF.7 (28.3%). The prevalence status might represent the epidemic strains in our center. Secondly, we did not collect data related to certain lifestyle variables (such as job nature, institutionalization, mask wearing, and outdoor dining), which are known to be related to the risk for SARS-CoV-2 infection. The main aim of the study was to evaluate the severity of COVID-19 and its impact on LT recipients; therefore, we did not include behavioral lifestyle variables in the original design, and the retrospective collection of data regarding mask wearing and outdoor dining would be difficult and might lead to recall bias. Another limitation is that the risk of death was not investigated. Mortality was low; therefore, this analysis cannot be taken further. Finally, it should be noted that LT recipients in the perioperative course were not included, because their characteristics and risks differed from stable patients. Therefore, our results cannot be extrapolated to these LT recipients.

Conclusion

During this Omicron wave, LT recipients were susceptible to COVID-19, with frequent hospitalizations, but low mortality. Non-mRNA COVID-19 vaccines effectively protected LT recipients from hospitalization. Further efforts are needed to improve the low prevalence of vaccination in LT recipients.

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Author contributions

Concept and design: T.L., X.B., W.Z.; Acquisition, analysis, or interpretation of data: P.J., R.W., Y.Z.; Figure preparation: X.Y., W.W.; Drafting of the manuscript: R.W., P.J., W.Z.; Reviewing the manuscript: all authors.

Declaration of competing interest

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation. The clinical activities being reported are consistent with the principles of the Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

Data availability

All data associated with this study are presented in the paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajt.2023.09.022.

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