Virology Journal

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Risk factors for SARS-CoV-2 pneumonia among renal transplant recipients in Omicron pandemic—a prospective cohort study

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Abstract

Background The coronavirus disease (COVID-19) pandemic is a global health emergency, and SARS-CoV-2 pneumonia poses significant challenges to health systems worldwide. Renal transplant recipients (RTRs) are a special group and are more vulnerable to viral pneumonia. However, few studies have elucidated the risk factors of SARS-CoV-2 pneumonia in RTRs infected with COVID-19. This study aimed to build a risk prediction model for SARS-CoV-2 pneumonia among RTRs based on demographic and clinical information.

Methods We conducted a prospective cohort study among 383 RTRs (age ≥ 18 years) diagnosed with COVID-19 from December 21, 2022, to March 26, 2023. Patients' demographic and clinical information was collected through a questionnaire survey combined with electronic medical records. A stepwise logistic regression model was established to test the predictors of SARS-CoV-2 pneumonia. We assessed the diagnostic performance of the model by calculating the area under the curve (AUC) of the receiver operating characteristic (ROC) and calibration using the Hosmer–Lemeshow (HL) goodness-of-fit test.

Results Our study showed that the incidence of SARS-CoV-2 pneumonia among RTRs was 31.1%. Older age (OR = 2.08–3.37,95%CI:1.05–7.23), shorter post-transplantation duration (OR = 0.92,95% CI: 0.87,0.99), higher post-transplant Charlson Comorbidity Index (CCI) (OR = 1.84, 95%CI: 1.14,2.98), pulmonary infection history (OR = 3.44, 95%CI: 1.459, 8.099, $P = 0.005$), fatigue (OR = 2.11, 95%CI: 1.14, 3.90), cough (OR = 2.03, 95%CI: 1.08, 3.81), and lower estimated glomerular filtration rate (eGFR) at COVID-19 diagnosis (OR = 0.98, 95%CI:0.97,0.99) predicted a higher risk for SARS-CoV-2 pneumonia. The model showed good diagnostic performance with Chi-Square = 10.832 ($P > 0.05$) and AUC = 0.839 ($P < 0.001$).

Conclusions Our study showed a high incidence of SARS-CoV-2 pneumonia among RTRs, and we built a risk prediction model for SARS-CoV-2 pneumonia based on patients' demographic and clinical characteristics. The model can help identify RTRs infected with COVID-19 at high risk of SARS-CoV-2 pneumonia to inform timely, targeted, and effective prevention and intervention efforts.

Keywords SARS-CoV-2, Pneumonia, Omicron, Renal transplant recipients, Risk factors, Risk prediction model

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Introduction

The coronavirus disease (COVID-19) outbreak, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an unprecedented global health emergency [1]. Due to the high transmission rate and high mortality rate, COVID-19 has caused a tremendous disease burden to the world health systems and incurred significant disturbances to the physical, mental, and social wellbeing of the world population [2–4]. According to the World Health Organization (WHO), COVID-19 has infected 775 million people worldwide and caused 7.05 million deaths as of May 22, 2024 [5]. Patients with COVID-19 can develop pneumonia, diffuse alveolar damage, severe symptoms of acute respiratory distress syndrome (ARDS), and multiple organ failure, which can eventually lead to death [6, 7].

Omicron (B.1.1.529) is among the latest COVID-19 variants of SARS-CoV-2 and the most highly mutated strain compared to the other four variants (Alpha, Beta, Gamma, and Delta) [8]. Initially identified in Botswana, Omicron has spread quickly worldwide and has become the dominant strain in many countries, posing new challenges to the prevention and control of COVID-19 [8]. In December 2022, the Chinese government fully relaxed its COVID-19 prevention and control policies, and the Omicron has caused large-scale population infections and hospitalizations, placing a significant burden on the limited medical resources [9].

Although most patients have gradually recovered, there is a high risk of reinfection due to the strong transmissibility and increased immune evasion ability of Omicron [10]. Many people have persistent symptoms after the acute phase of Omicron infection, which has long-term adverse effects on their health [11]. Although Omicron mainly affects the upper airways, such as the nose and pharynx, it can easily lead to frequent hospitalizations, thus increasing the risk of coinfections or superinfections involving the lower respiratory tract and leading to pulmonary complications such as pneumonia [12]. Research shows that Omicron pneumonia is caused by lung epithelium and endothelium injuries due to direct viral toxicity and immune response [13]. Lower lung infections are more common in patients with comorbidities, such as cardiovascular or kidney disease [14]. Among all patients with Omicron pneumonia, 70–80% have mild symptoms, including fever, cough, and nasal congestion [13, 15]. However, 20-30% of patients may develop moderate or severe pneumonia, with symptoms such as shortness of breath and dyspnea, leading to ARDS and even death [13, 15].

Immune ability is closely associated with COVID-19 progression, and renal transplant recipients (RTRs) are particularly vulnerable to critical COVID-19 complications, such as pneumonia [16]. Due to the long-term use of immunosuppressants, RTRs have impaired immune response, which, combined with preexisting comorbidities, can lead to greater susceptibility and more rapid progression to pneumonia [17]. Compared to influenza virus pneumonia, SARS-CoV-2 pneumonia is more severe and fatal, especially among RTRs [14]. Several large cohort studies showed that among RTRs infected with Omicron, 37-40% developed dyspnea, 13-14% developed hypoxemia, 65.1-73% required hospitalization, 34.6-40% required intensive care unit (ICU) admission, 24.9-29% required mechanical ventilation (MV), and finally, the mortality rate ranged from 17 to 21.0% [18, 19]. A study in Brazil showed that the COVID-19-associated mortality rate among RTRs was over seven times higher than in the general population [20].

In response to such high hospitalization and mortality rates of COVID-19 infection among RTRs, transplant physicians have employed multiple measures to manage patients, including COVID-19 vaccination, immunosuppressant adjustment, and use of specific drugs, such as nirmatrelvir, ritonavir, and immunoglobulins [21, 22]. However, the COVID-19 vaccine has only limited effects on RTRs, nirmatrelvir and ritonavir have the potential risk of drug interactions, and there is a lack of robust evidence to verify the effectiveness of immune globulin [23–25]. The risk of breakthrough infection in RTRs is still high [26]. It is thus crucial to identify the risk factors of SARS-CoV-2 pneumonia among RTRs to guide effective and targeted prevention and intervention efforts.

Previous research, mainly derived from cross-sectional studies in the general population, identified multiple risk factors for pneumonia, including older age, poor immunity, pneumonia history, and comorbidities such as chronic respiratory disease, cytomegalovirus infection, diabetes, kidney disease, and anemia [27–29]. Still, there is a lack of evidence on the risk factors of Omicron pneumonia among RTRs. Additionally, the existing evidence is mainly derived from cross-sectional studies, which cannot establish robust causal relationships between risk factors and pneumonia. To fill the research gap, we conducted a prospective cohort study to investigate the predictors of SARS-CoV-2 pneumonia among RTRs infected with Omicron, based on which we aimed to build a risk prediction model for SARS-CoV-2 pneumonia. Our findings would help identify RTRs at high risk for SARS-CoV-2 pneumonia to guide early interventions to reduce mortality and improve health outcomes among RTRs.

Methods

Study design, settings, and participants

This prospective cohort study was conducted at Xiangya Hospital of Central South University, China, from December 21, 2022, to March 26, 2023. The predominant variant circulating during this study period was Omicron.

Xiangya Hospital is the first hospital in Hunan Province to carry out kidney transplantation and one of the first hospitals in China to carry out organ donations. Xiangya Hospital performs more than 100 kidney transplants each year and ranks third in Hunan Province in terms of organ donations and kidney transplants. The Organ Transplant Center in Xiangya Hospital has 40 beds, divided into general areas and isolation areas. After kidney transplantation, patients are monitored in the isolation area (4 beds) of the transplant ward. The hospital ICU includes five areas, and the main first area contains 33 beds, among which eight beds are for the Organ Transplant Center.

A total of 478 RTRs with COVID-19 infection who were eligible for the study inclusion were consecutively recruited during the study period. The participants were followed up for three months. The inclusion criteria were as follows: [1] age≥18 [2], completed kidney transplant with functional transplanted kidney [3], COVID-19 positivity defined as a positive result in a nucleic acid amplification test (NAAT) or an antigen test of nasal and/or pharyngeal swab specimens [4, 30] with normal cognitive and mental function to complete the questionnaire survey. We excluded participants with the following conditions: [1] combined organ transplantation (n=3) [3], high allergic sensitization (n=5) [4], unable to complete the questionnaire survey due to severe physical or mental illness (n=27), and [5] loss-to-follow up (n=60). Finally, 383 RTRs completed the study and were included for analysis, with an effective response rate of 80.1%.

Procedures

The study was approved by the Ethics Committee of Xiangya Hospital of Central South University (No.: 2021101000). The research team was comprised of one physician and four licensed nurses working in the Organ Transplant Center of Xiangya Hospital, who had received unified training on research conduction and data collection. The research team approached the eligible participants and explained the study's purpose, procedure, benefits, and risks in detail. All participants were informed that they could withdraw from the study at any time during the survey period, which would not affect their treatment at the hospital. After providing written informed consent, the participants were invited to complete a questionnaire survey based on face-to-face or telephone interviews at the patients' convenience. The total questionnaire took 20–35 min to complete.

Measures

Based on questionnaires combined with patient medical records, the researchers collected the following demographic and clinical information: sex, age, body mass index (BMI), post-transplantation duration, donor types, immunosuppression regimens, COVID-19 vaccination status, COVID-19 prevention measures, pre-infection renal function, and pre-transplant and post-transplant comorbidities. As of November 21, 2022, seven vaccines have been approved in mainland China, among which Sinovac and Sinopharm vaccines are the two most common COVID-19 vaccines in China. COVID-19 prevention measures mainly include personal protection (such as wearing a face mask, washing hands frequently, avoiding crowds, and minimizing going out) and drug prevention (such as taking Ursodeoxycholic and Bailing capsules). Renal function was assessed using the estimated glomerular filtration rate (eGFR) based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Eq. [31]. Comorbidities were assessed using the Charlson Comorbidity Index (CCI) for any comorbid conditions [32].

The outcome indicator was SARS-CoV-2 pneumonia, confirmed by CT scanning (MDCT-Sensation 64, Siemens Healthcare, Forchheim, Germany) by experienced radiologists after SARS-CoV-2 infection. The following typical CT manifestations were considered suggestive of SARS-CoV-2 pneumonia: ground-glass opacities, consolidation, reticular pattern, and crazy paving pattern [33]. In this study, SARS-CoV-2 pneumonia diagnosis relied solely on imaging.

In addition, we collected information on RTRs' maximum body temperature, clinical manifestations related to COVID-19 infection (such as fever, fatigue, cough, sore throat, and headache), treatment for COVID-19 infection (including the administration of immunosuppressants during COVID-19 infection, therapeutic drugs, and hospitalization), and outcomes after COVID-19 infection (including renal allograft dysfunction and eGFR at COVID-19 diagnosis).

Statistical analysis

Statistical analysis was performed using SPSS version 26.0. The Kolmogorov–Smirnov test was used to evaluate the distribution of continuous variables. Normally distributed continuous variables were described as means±standard deviations and compared using the independent-sample t-test between the pneumonia and non-pneumonia groups. Non-normally distributed continuous variables were expressed as medians and interquartile ranges and compared using the non-parametric test Wilcoxon rank sum test between two groups. Categorical variables were described as numbers and percentages and compared using the chi-square test between the two groups. To test the predictive factors of pneumonia in RTRs, we conducted a stepwise logistic regression model with pneumonia as the dependent variable and variables with statistical significance in group comparisons and variables that were clinically meaningful as independent variables (α_{in}=0.05, α_{out}=0.10).

The Hosmer-Lemeshow goodness of fit test was used to assess the model fitting index. The Hosmer–Lemeshow test is a statistical test for goodness of fit used frequently in risk prediction models and logistic regression models. It assesses whether or not the observed event rates match expected event rates in subgroups of the model population by identifying subgroups as the deciles of fitted risk values. The Hosmer–Lemeshow test can determine if the differences between observed and expected proportions are significant, with a significant p value indicating a lack of model fit and a nonsignificant p value indicating good model fit. A receiver operating characteristic (ROC) curve was plotted to calculate the area under the curve (AUC) and further verify the diagnostic performance of the model. Two-sided $P<0.05$ was considered statistically significant.

Results

Sample characteristics between pneumonia and non-pneumonia groups

Table 1 shows the sample characteristics and their comparisons between the pneumonia and non-pneumonia groups. The primary indication for renal transplantation is end-stage renal disease (ESRD), the final, permanent stage of chronic kidney disease, where the kidneys can no longer function on their own, presented with an eGFR of less than 15 mL/min. Among the 383 RTRs included in the study, 229 (59.8%) were male and 154 (40.2%) were female. Their average age was 44.1±10.5 years (range:18–74), and their median post-transplantation duration was 4.67 years (interquartile range, IQR: 2.42,7.67). Most had cadaveric donors (81.7%), and 93 RTRs (24.3%) were overweight with body mass index (BMI)≥24 kg/m^2. The most common comorbidities before transplantation were severe anemia (n=76, 19.8%), followed by Hepatitis B virus (HBV) infection (n=27,7.0%). The most common comorbidities after transplantation were post-transplantation diabetes mellitus (PTDM, n=68, 17.8%), followed by pulmonary infection history (n=59,15.4%). Most patients received Calcineurin Inhibitors+Mycophenolate Mofetil+Prednisone immunosuppressive treatment (82.5%). The majority of patients (70.8%) were unvaccinated against COVID-19 due to concerns about the side effects and lack of vaccine-related knowledge. Instead, they took personal protection (91.1%) and drug prevention (13.6%) to prevent COVID-19 infection. With the success of kidney transplantation, the CCI decreased from 1.95±1.17 preoperative to 0.53±0.72 postoperative. The eGFR before COVID-19 infection was 62.91±23.35 ml/min/1.73 m^2.

A total of 119 (31.1%) patients developed SARS-CoV-2 pneumonia during the follow-up period. The pneumonia and non-pneumonia groups showed significant differences in age, donor type, pre-transplant comorbidities, post-transplant comorbidities, pre-infection eGFR, and post-transplant CCI. Compared to the non-pneumonia group, the pneumonia group was older ($P<0.001$) and more likely to have cadaveric donors(89.9% vs. 78.0%, $P=0.005$), pre-transplant myocardial infarction (4.2% vs. 0.0%, $P=0.004$), post-transplant BK virus nephropathy (9.2% vs. 3.8%, $P=0.030$), and pulmonary infection history (37.0% vs. 5.7%, $P<0.001$).In addition, the pneumonia group had significantly lower pre-infection eGFR (53.78±21.26 vs. 67.02±23.12, $P<0.001$) and significantly higher post-transplant CCI (0.93±0.82 vs.0.35±0.58, $P<0.001$).

Clinical indicators between pneumonia and non-pneumonia groups

Table 2 shows patients' clinical manifestations, treatment, and outcomes related to COVID-19 infection and their comparisons between the pneumonia and non-pneumonia groups. The most common clinical symptom was fever (81.5%), with the highest median body temperature being 38.5 °C (IQR:37.6, 39.0), and most patients' duration of fever was ≤72 h (89.4%). Most patients continued their regular use of immunosuppressants during COVID-19 infection (69.5%), while 8.6% had reduced immunosuppressants, and 21.9% had discontinued immunosuppressants. Physicians also developed personalized treatment plans based on the patient's condition, including symptoms-relieving drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) (55.4%), Chinese patent medicines (41.8%), Bailing Capsules (27.7%), etc. Among the 383 patients, 26.9% required hospitalization, and 55.9% suffered varying degrees of renal allograft dysfunction. The eGFR at COVID-19 diagnosis was 61.60±23.77 mL/min/1.73 m^2.

The pneumonia and non-pneumonia groups showed significant differences in clinical manifestations, treatment, and outcomes related to COVID-19 infection. Compared to the non-pneumonia group, the pneumonia group was more likely to suffer from the following clinical symptoms associated with COVID-19 infection: fatigue (73.9% vs. 53.0%, $P<0.001$), cough (76.5% vs. 56.4%, $P<0.001$), expectoration (63.9% vs. 38.6%, $P<0.001$), diarrhea (26.1% vs.11.4%, $P<0.001$), anorexia (57.1% vs.34.8%, $P<0.001$), hypogeusia (40.3% vs.23.9%, $P=0.001$), shortness of breath after activity (46.2% vs.16.3%, $P<0.001$), and dyspnea (23.5% vs.4.9%, $P=0.001$). Regarding COVID-19-related treatment, the pneumonia group was more likely to discontinue immunosuppressants (57.1% vs. 6.1%, $P<0.001$) and use NSAIDs (63.0% vs. 51.9%, $P=0.043$), nirmatrelvir/ritonavir (32.8% vs. 0.4%, $P<0.001$), Azvudine (6.7% vs.0.4%, $P=0.001$), and Gamma globulin (15.1% vs.0.0%, $P<0.001$) than the non-pneumonia group. As for COVID-19-related outcomes, the pneumonia group was more likely

Table 1 Sample characteristics between the pneumonia and non-pneumonia groups

Variable	Total($n=383$)	Pneumonia Group	Non-Pneumonia Group	*P* value
Sex, n (%)				0.166
Male	229(59.8)	65(54.6)	164(62.1)	
Female	154(40.2)	54(45.4)	100(37.9)	
Age, years, n(%)				< 0.001
<40	135(35.2)	25(21.0)	110(41.7)	
40–49	126(32.9)	40(33.6)	86(32.6)	
50–59	91(23.8)	42(35.3)	49(18.6)	
≥ 60	31(8.1)	12(10.1)	19(7.2)	
BMI ≥ 24 kg/m^2, n (%)				0.316
No	290(75.7)	94(79.0)	196(74.2)	
Yes	93(24.3)	25(21.0)	68(25.8)	
Post-transplantation duration, years, median (IQR)	4.67(2.42,7.67)	4.33(1.92,7.25)	4.79(2.60,8.08)	0.149
Donor type, n (%)				0.005
Cadaveric donor	313(81.7)	107(89.9)	206(78.0)	
Living donor	70(18.3)	12(10.1)	58(22.0)	
Pre-transplant comorbidities, n (%)				
Cerebrovascular disease	9(2.3)	4(3.4)	5(1.9)	0.608
Myocardial infarct	5(1.3)	5(4.2)	0(0.0)	0.004
Congestive heart failure	16(4.2)	6(5.0)	10(3.8)	0.770
HBV	27(7.0)	9(7.6)	18(6.8)	0.792
Digestive ulcer disease	10(2.6)	5(4.2)	5(1.9)	0.335
Severe anemia	76(19.8)	26(21.8)	50(18.9)	0.509
Tumor	1(0.3)	0(0.0)	1(0.4)	1.000
Tuberculosis	3(0.8)	0(0.0)	3(1.1)	0.555
Immunosuppressive regimen, n (%)				0.171
Calcineurin Inhibitors + Mycophenolate Mofetil + Prednisone	316(82.5)	102(85.7)	214(81.1)	
Calcineurin Inhibitors + Mycophenolate Mofetil	31(8.1)	5(4.2)	26(9.8)	
Other	36(9.4)	12(10.1)	24(9.1)	
Post-transplant comorbidities, n (%)				
Cerebrovascular disease	9(2.3)	5(4.2)	4(1.5)	0.214
Transplanted kidney rejection	15(3.9)	6(5.0)	9(3.4)	0.633
Transplanted kidney nephritis or kidney disease	13(3.4)	6(5.0)	7(2.7)	0.373
BK nephropathy	21(5.5)	11(9.2)	10(3.8)	0.030
Pulmonary infection history	59(15.4)	44(37.0)	15(5.7)	< 0.001
Tuberculosis	3(0.8%)	0(0.0)	3(1.1)	0.555
Tumour	5(1.3)	3(2.5)	2(0.8)	0.357
PTDM	68(17.8)	27(22.7)	41(15.5)	0.090
Hypertension	34(8.9)	11(9.2)	23(8.7)	0.866
Other	28(7.3)	7(5.9)	21(8.0)	0.471
COVID-19 vaccination status, n (%)				0.703
No	271(70.8)	86(72.3)	185(70.1)	
1 dose	27(7.0)	9(7.6)	18(6.8)	
2 doses	32(8.4)	7(5.9)	25(9.5)	
3–4 doses	53(13.8)	17(14.3)	36(13.6)	
Preventive measures, n (%)				
No	20(5.2)	5(4.2)	15(5.7)	0.547
Bailing Capsules	26(6.8)	12(10.1)	14(5.3)	0.085
ursodeoxycholic	26(6.8)	10(8.4)	16(6.1)	0.399
Personal protection (e.g., wear face mask)	349(91.1)	110(92.4)	239(90.5)	0.544
Other	4(1.0)	0(0.0)	4(1.5)	0.420
Pre-infection eGFR, mL / min / 1.73 m^2, **mean (SD)**	62.91 ± 23.35	53.78 ± 21.26	67.02 ± 23.12	< 0.001

Table 1 (continued)

Variable	Total($n=383$)	Pneumonia Group	Non-Pneumonia Group	*P* value
Pre-transplant CCI, mean (SD)	1.95 ± 1.17	2.13 ± 1.22	1.88 ± 0.14	0.051
Post-transplant CCI, mean (SD)	0.53 ± 0.72	0.93 ± 0.82	0.35 ± 0.58	< 0.001

Abbreviations: IQR, Interquartile range; SD: standard deviation; BMI, body mass index; HBV, Hepatitis B virus; PTDM, post-transplantation diabetes mellitus; CCI, Charlson comorbidity index; eGFR, estimated glomerular filtration rate

Table 2 Clinical manifestations, treatment, and outcomes related to COVID-19 infection between the pneumonia and non-pneumonia groups

Variable	Total ($n=383$)	Pneumonia Group	Non-Pneumonia Group	*P* value
Maximum body temperature, median (IQR)	38.5(37.6,39.0)	38.5(37.8,39.0)	38.4(37.5,39.0)	0.570
Symptoms, n (%)				
Fever	312(81.5)	99(83.2)	213(80.7)	0.558
Fatigue	228(59.5)	88(73.9)	140(53.0)	< 0.001
Cough	240(62.7)	91(76.5)	149(56.4)	< 0.001
Expectoration	178(46.5)	76(63.9)	102(38.6)	< 0.001
Sore throat	124(32.4)	39(32.8)	85(32.2)	0.911
Muscle soreness	227(59.3)	68(57.1)	159(60.2)	0.570
Headache	176(46.0)	53(44.5%)	123(46.6)	0.709
Diarrhea	61(15.9)	31(26.1)	30(11.4)	< 0.001
Nausea or vomiting	62(16.2)	23(19.3)	39(14.8)	0.263
Anorexia	160(41.8)	68(57.1)	92(34.8)	< 0.001
Nasal congestion or runny nose	111(29.0)	36(30.3)	75(28.4)	0. 713
Hypogustia	111(29.0)	48(40.3)	63(23.9)	0.001
Anosmia	50(13.1)	19(16.0)	31(11.7)	0.256
Shortness of breath after activity	98(25.6)	55(46.2)	43(16.3)	< 0.001
Dyspnea	41(10.7)	28(23.5)	13(4.9)	< 0.001
Other	11(2.9)	4(3.4)	7(2.7)	0.957
Administration of immunosuppressants during COVID-19 infection, n (%)				< 0.001
Normal use	266(69.5)	44(37.0)	222(84.1)	
Drug reduction	33(8.6)	7(5.9)	26(9.8)	
Discontinuation	84(21.9)	68(57.1)	16(6.1)	
Therapeutic drugs, n (%)				
NSAIDs	212(55.4)	75(63.0)	137(51.9)	0.043
Chinese patent medicine	160(41.8)	52(43.7)	108(40.9)	0.609
Bailing Capsules	106(27.7)	34(28.6)	72(27.3)	0.793
Ursodeoxycholic	33(8.6)	14(11.8)	19(7.2)	0.140
Metformin	9(2.3)	5(4.2)	4(1.5)	0.214
Nirmatrelvir/ritonavir	40(10.4)	39(32.8)	1(0.4)	< 0.001
Azvudine	9(2.3)	8(6.7)	1(0.4)	0.001
Gamma globulin	18(4.7)	18(15.1)	0(0.0)	< 0.001
Other	25(6.5)	12(10.1)	13(4.9)	0.059
Hospitalization, n (%)				< 0.001
No	280(73.1)	32(26.9)	248(93.9)	
Yes	103(26.9)	87(73.1)	16(6.1)	
Renal allograft dysfunction after COVID-19 infection, n (%)				0.737
No	169(44.1)	51(42.9)	118(44.7)	
Yes	214(55.9)	68(57.1)	146(55.3)	
eGFR at diagnosis, ml/min/1.73 m2, mean (SD)	61.60 ± 23.77	51.18 ± 21.47	66.30 ± 23.28	< 0.001

Abbreviations: IQR, Interquartile range; SD: standard deviation; NSAIDs: Nonsteroidal anti-inflammatory drugs

to be hospitalized (73.1% vs. 6.1%, $P<0.001$) and had lower eGFR at COVID-19 diagnosis (51.18±21.47 vs.66.30±23.28, $P<0.001$).

Establishment of a risk prediction model for SARS-CoV-2 pneumonia

In the subsequent stepwise logistic regression analysis, we built a risk prediction model for SARS-CoV-2 pneumonia by including the significant factors in the previous group comparison analysis as independent variables as follows: age, donor type, pre-transplant myocardial infarction, post-transplant BK virus nephropathy, pulmonary infection history, pre-infection eGFR, post-transplant CCI, clinical symptoms related to COVID-19 infection (fatigue, cough, expectoration, diarrhea, anorexia, hypogeusia, shortness of breath after activity, and dyspnea), COVID-19-related treatment (immunosuppressants, NSAIDs, nirmatrelvir/ritonavir, Azvudine, and Gamma globulin), and COVID-19-related outcomes (hospitalization and eGFR at COVID-19 diagnosis). Considering that BMI and post-transplantation duration are clinically important factors that may affect patient outcomes, we also included them in the multivariable analysis. This model aimed to predict SARS-CoV-2 pneumonia incidence among RTRs with COVID-19 infection.

The final model showed the following predictors of SARS-CoV-2 pneumonia: age (40–49 years: OR=2.08, 95%CI:1.05, 4.14, $P=0.036$; 50–59 years, OR=3.37, 95%CI: 1.57, 7.23, $P=0.002$), post-transplantation duration (OR=0.92,95% CI: 0.87,0.99, $P=0.017$), post-transplant CCI (OR=1.84, 95%CI: 1.14,2.98, $P=0.013$), pulmonary infection history (OR=3.44, 95%CI: 1.459, 8.099, $P=0.005$), fatigue (OR=2.11, 95%CI: 1.14, 3.90, $P=0.017$), cough (OR=2.03, 95%CI: 1.08, 3.81, $P=0.027$), and eGFR at COVID-19 diagnosis (OR=0.98, 95%CI:0.97,0.99, $P=0.008$) (Table 3).

The Hosmer-Lemeshow goodness of fit test showed good model fit with Chi-Square=10.832, $P>0.05$. Fig. 1 shows the ROC curve with AUROC=0.839, $P<0.001$, which further verified that the diagnostic performance of the model was good.

Discussion

Summary of the findings

To our knowledge, this was the first prospective cohort study reporting the incidence and risk factors of SARS-CoV-2 pneumonia among kidney transplant patients during the Omicron variant pandemic in China. We proposed a risk prediction model for SARS-CoV-2 pneumonia based on patient demographic and clinical information easily obtained from questionnaires and electronic medical records. Our study showed that the incidence of SARS-CoV-2 pneumonia among RTRs was 31.1%. We also found that older age, shorter post-transplant duration, higher post-transplant CCI, a history of pulmonary infection, clinical symptoms of fatigue and cough related to COVID-19 infection, and lower eGFR at COVID-19 diagnosis were independent risk factors for SARS-CoV-2 pneumonia. The Hosmer-Lemeshow goodness-of-fit test and AUROC proved that the model was reliable.

Table 3 Logistic regression analysis of predictors of pneumonia ($n=383$)

Variables	OR (95%CI)	*P* value
Age, years		
<40 (Ref.)		
40–49	2.082(1.048,4.140)	0.036
50–59	3.365(1.565,7.232)	0.002
≥60	2.438(0.842,7.059)	0.100
BMI ≥ 24, kg/m^2		
No (Ref.)		
Yes		
Post-Transplantation duration, years	0.924(0.866,0.986)	0.017
Post-transplant Comorbidities		
Pulmonary infection history	3.437(1.459,8.099)	0.005
Post-transplant CCI	1.842(1.138,2.980)	0.013
Symptoms		
Fatigue	2.111(1.143,3.902)	0.017
Cough	2.031(1.082,3.813)	0.027
eGFR at COVID-19 Diagnosis	0.983(0.970,0.995)	0.008

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; eGFR, estimated glomerular filtration rate

Note: the following variables were not significant in the multivariable analysis and were thus not listed in the table: donor type, pre-transplant myocardial infarction, post-transplant BK nephropathy, pre-infection eGFR, post-transplant CCI, expectoration, diarrhea, anorexia, hypogeusia, shortness of breath after activity, dyspnea, immunosuppressants, NSAIDs, Nirmatrelvir/ritonavir, Azvudine, Gamma globulin, and hospitalization

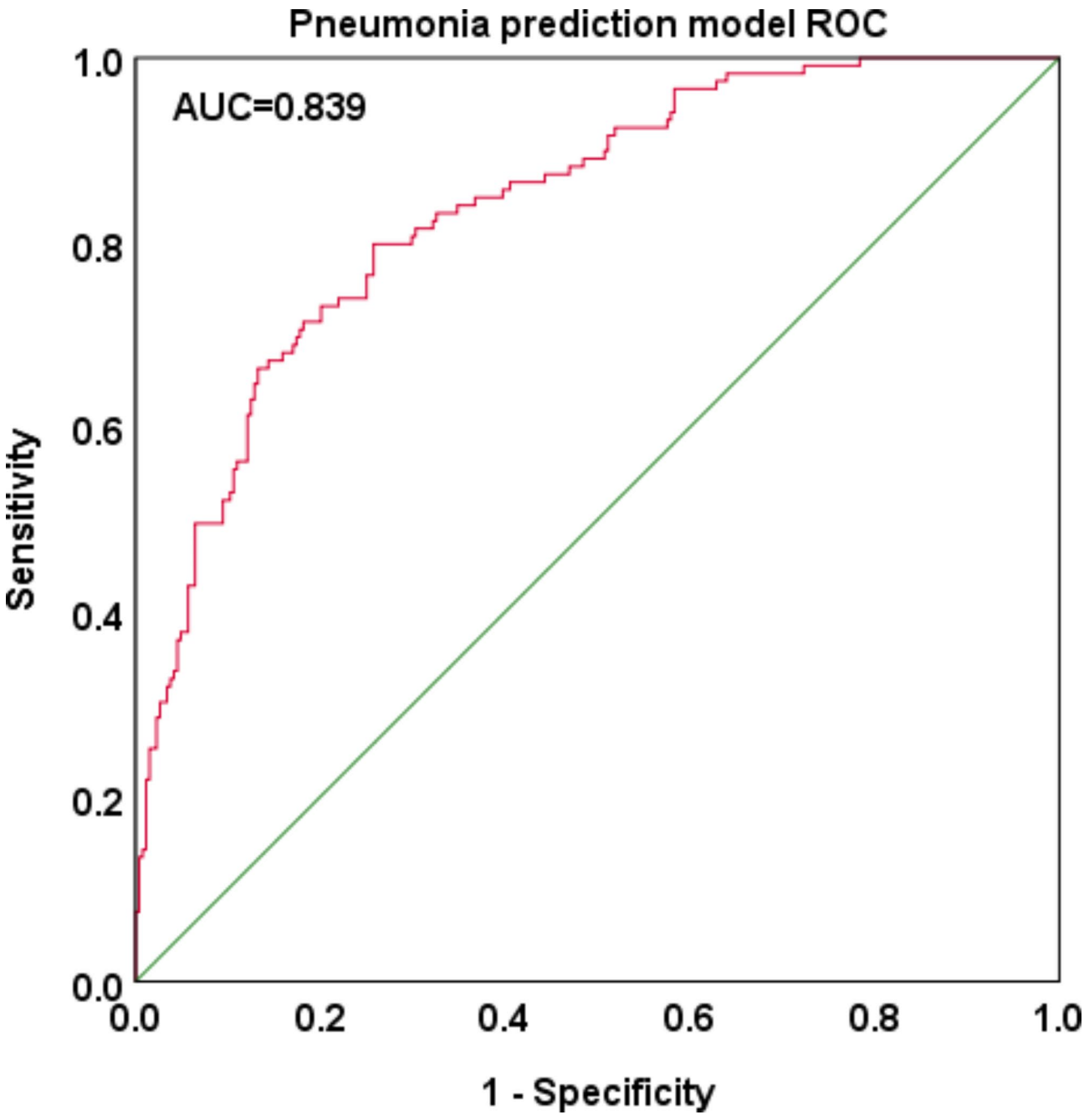

Fig. 1 The receiver operating characteristic (ROC) curve

The incidence of SARS-CoV-2 pneumonia

Our study showed that 31.1% of RTRs developed SARS-CoV-2 pneumonia after COVID-19 infection, consistent with the literature showing pulmonary infection as a common complication after kidney transplantation. For instance, Mangalgi et al. [34] reported that the incidence rate of pulmonary infection involving different COVID-19 variants in the first year, 1–5 years, and 5 years after kidney transplantation were 32.3%, 31.4%, and 36.3%, respectively. Omicron variant infection is a respiratory disease mainly affecting the upper respiratory tract and is characterized by an acute phase and a short course [35]. However, RTRs infected with Omicron often have a longer course of disease and more severe symptoms, leading to serious complications such as pneumonia and even death [36]. The high incidence of SARS-CoV-2 pneumonia among RTRs after Omicron infection may be explained by the decreased immunity of these patients, leading to combined bacterial, viral, and fungal infections [37]. Our findings suggest that SARS-CoV-2 pneumonia

is a common complication among RTRs after COVID-19 infection, which warrants special attention and timely response.

The risk prediction model for SARS-CoV-2 pneumonia

We built a risk prediction model for SARS-CoV-2 pneumonia based on the following demographic and clinical indicators: age, transplantation duration, post-transplant CCI, history of pulmonary infection, fatigue, cough, and eGFR at COVID-19, which were independent risk factors for COVID-19, each discussed below:

Pulmonary infection history

In our study, a history of pulmonary infection showed the strongest predicting effect on SARS-CoV-2 pneumonia among RTRs. This finding was in line with the abundant evidence showing previous pulmonary infection was associated with an increased risk of subsequent pneumonia [27, 29, 38]. All these studies indicate that chronic pulmonary infection is a risk factor for pneumonia and requires great attention, yet there is limited evidence of its impact on SARS-CoV-2 pneumonia among RTRs. Our study identified a strong predicting effect of pulmonary infection history on SARS-CoV-2 pneumonia among RTRs. One possible explanation may be that RTRs are more likely to be infected with viruses such as CMV and influenza due to immunosuppressive treatment [39]. Studies have shown that CMV is not only independently associated with Pneumocystis pneumonia but can also invade the respiratory system and cause organizational pneumonia [40, 41]. Additionally, colonization and prophylactic agents like cotrimoxazole, commonly used to prevent pulmonary infections among immunocompromised individuals such as RTRs, can also contribute to pulmonary infections. Studies show that long-term use of cotrimoxazole prophylaxis can alter the normal bacterial flora in the lungs, eventually leading to colonization with resistant bacteria and multi-drug resistance in pneumococci and increasing the risk of pulmonary infection [42, 43]. Furthermore, the high risk of pulmonary infection may be explained by the use of induction immunosuppression, which is a high-dose, intensive therapy of immunosuppressive drugs given at the time of transplantation to prevent acute rejection early [44]. While effective in preventing rejection, induction therapy can also increase the risk of infections due to significant immune suppression [44].

Age

Our study showed that RTRs in the age groups of 40–49 years and 50–59 years were at higher risk of developing SARS-CoV-2 pneumonia than RTRs aged < 40 years old. This finding was congruent with previous studies showing age was closely associated with the occurrence of pneumonia due to COVID-19 infection [45, 46]. RTRs with older age have lower immunity, are more susceptible to viral infections, and thus have an increased risk of pneumonia [45, 46]. Lyons et al. [47] constructed a SARS-CoV-2 pneumonia prediction model for hospitalized patients and found that age was the most important predictor. A large population-based cohort study of middle-aged and older adults also demonstrated similar results [29]. However, Xiang et al. [27] showed that age ≥ 60 was an independent risk factor for postoperative pneumonia, which differed from our study showing a higher risk of pneumonia in those aged 40–59. This discrepancy may be explained by the generally younger age of RTRs in our study (average age 44.1 ± 10.5 years), with more than half (56.7%) in the age group of 40–59 years old. In contrast, only 8.1% of patients were ≥ 60 years old, and there may be a lack of power to detect statistical significance due to the sample size being too small.

Clinical symptoms related to COVID-19 infection

In addition, we observed that COVID-19-related clinical symptoms of fatigue (OR = 2.11) and cough (OR = 2.03) were significant predictors of SARS-CoV-2 pneumonia, and their effects were only secondary to a pulmonary infection history (OR = 3.44) and age (OR = 2.08–3.37). A meta-analysis including 7,840 patients revealed a high risk of persistent fatigue and cough among those infected with COVID-19, especially among those with severe initial diseases [48]. Another large meta-analysis including 53,659 patients found that cough and fatigue were common predictors of COVID-19 infection [49]. The performance of a single indicator in predicting COVID-19 infection is limited, but combined indicators such as cough, fatigue, fever, and comorbidities can enhance the screening for potential COVID-19 infection and severe outcomes [49]. Aboumrad et al. [50] developed a clinical risk score including fatigue and cough to predict individualized 30-day hospitalization risk following COVID-19 diagnosis, which showed good discrimination and calibration. However, these findings have not been extensively validated among RTRs, and there is a lack of evidence for predicting SARS-CoV-2 pneumonia risk among RTRs. Our findings added novel evidence by unraveling the impact of clinical symptoms related to COVID-19 infection on predicting pneumonia risk to inform early intervention strategies.

Post-transplant CCI

RTRs were in a state of ESRD before transplantation and had a high CCI. With the success of kidney transplantation, their postoperative CCI decreased significantly. Our study demonstrated that higher post-transplant CCI predicted a higher risk of SARS-CoV-2 pneumonia among RTRs, which was consistent with published research

results. Vo-Pham-Minh et al. [51] conducted a study on patients hospitalized in intensive care units with nosocomial pneumonia. They found that nosocomial pneumonia occurred in 7.12% of chronic renal failure, and CCI≥3 was associated with a worse prognosis of nosocomial pneumonia [51]. Nguyen et al. [52] also found that higher CCI was associated with a higher risk of in-hospital mortality with an OR of 1.28. Similarly, Varol et al. [53] found that CCI was a prognostic factor for mortality among COVID-19 patients hospitalized due to pneumonia, based on which they developed a novel COVID-19 mortality score to predict mortality. All these findings support the inclusion of CCI in predicting the outcomes of SARS-CoV-2 pneumonia among RTRs.

Post-transplantation duration

Of note, we found that post-transplantation duration predicted the development of SARS-CoV-2 pneumonia. As the time post-transplantation increased, the incidence of pneumonia caused by COVID-19 among RTRs significantly reduced. Ying et al. [54] found that the mortality decreased steadily among RTRs over 10 years post-transplant, and long-term RTRs in 2018 were 12% less likely to die than patients in 2010–2014, suggesting a continuous improvement in the long-term outcomes of RTRs. Compared to RTRs in early post-transplant periods with higher complications, RTRs with longer post-transplantation duration had passed the high-risk window and thus presented with better prognostic outcomes [55]. Our findings suggest that post-transplantation duration impacts patient clinical outcomes and contributes to the prediction of SARS-CoV-2 pneumonia among RTRs. Therefore, physicians should develop personalized treatment plans based on different post-transplantation durations when managing patients to achieve the best treatment effect.

eGFR

In this study, the pneumonia group had an eGFR of <60 ml/min/1.73 m2, which was lower than that of the non-pneumonia group. In addition, the pneumonia group had lower eGFR at COVID-19 diagnosis than before COVID-19 infection. The subsequent logistic regression model showed that lower eGFR at COVID-19 diagnosis predicted a higher risk of SARS-CoV-2 pneumonia, which aligned with the literature. Cei et al. [56] found that an eGFR value<60 mL/min/1.73 m^2 was associated with increased in-hospital mortality in a large sample of consecutive acutely ill COVID-19 hospitalized patients. Lai et al. [57] also found that eGFR<60 ml/min/1.73 m^2 predicted increased mortality and shorter overall survival among hospitalized COVID-19 patients. However, these studies only focused on the impact of eGFR on mortality risk among the general population and did not provide detailed insights into the risk of pneumonia due to low eGFR among RTRs. Our study added further evidence on the predicting effect of eGFR on SARS-CoV-2 pneumonia among RTRs. In the early stages of COVID-19 infection, patients' renal function declined significantly with decreased eGFR [58]. Creatinine is the most important indicator for evaluating renal function and can be obtained during routine physical checks, and eGFR calculation is also straightforward. Our findings suggest that dynamic monitoring of eGFR levels can help physicians identify high-risk RTRs for SARS-CoV-2 pneumonia and take timely interventions.

Limitations

Our study has several limitations. First, this was a single-center study with a small sample size, and the results could not be generalized to all Chinese RTRs. Future multicenter studies at a national level are needed to expand the study population and enhance the generalizability of the findings. Second, we excluded patients who were lost to follow-up since the outcome variable was unavailable for them. The high attrition rate of 19.9% may limit the generalizability of our study findings. Future studies should consider retaining those patients and run further sensitivity analyses for a more robust conclusion. Third, we had a relatively short follow-up time and may not obtain enough data. Future studies should follow up with the patients for a more extended period to observe the long-term impacts. Fourth, most information was collected based on patients' self-reported questionnaires, which is subject to bias. Future studies should consider combining more objective indicators to get a more accurate assessment. Fifth, the outcome indicator was defined as the occurrence of pneumonia due to COVID-19 infection but did not consider the impact of symptoms lasting more than three months on the long-term prognosis of patients. Future studies should include long-term symptoms to provide a more comprehensive evaluation. Finally, we did not collect the time between SARS-CoV-2 diagnosis and pneumonia onset, which may also affect the outcomes and should be explored by future studies.

Conclusion

Our study showed a high incidence of SARS-CoV-2 pneumonia among RTRs at 31.1%, and we built a risk prediction model for SARS-CoV-2 pneumonia. Older age, shorter post-transplant duration, higher post-transplant CCI, history of pulmonary infection, fatigue, cough, and lower eGFR at COVID-19 diagnosis were independent risk factors for SARS-CoV-2 pneumonia. The model can help identify RTRs infected with COVID-19 at high risk of SARS-CoV-2 pneumonia to inform timely, targeted, and effective prevention and intervention efforts.

Abbreviations

AUC	The area under the curve
ARDS	Acute respiratory distress syndrome
BMI	Body mass index
CCI	Charlson Comorbidity Index
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	Novel coronavirus disease
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
HBV	Hepatitis B virus
IQR	Interquartile range
MV	Mechanical ventilation
NAAT	Nucleic acid amplification test
PTDM	Post-transplantation diabetes mellitus
ROC	Receiver operating characteristic
RTRs	Renal transplant recipients
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
WHO	World Health Organization

Acknowledgements
The authors would like to thank all the patients for participating in this study and the staff from the Transplantation Center at Xiangya Hospital of Central South University for their collaboration and support.

Author contributions
SZ: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Visualization; Roles/Writing - original draft. XD: Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing - review & editing. CG: Data curation; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing - review & editing.HZ: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing - review & editing. All authors approved the final version of the manuscript for submission and publication.

Funding
This work was funded by a grant from the Natural Science Foundation in Hunan Province of China (Grant Number 2022JJ70083) in support of Hong Zhang, Natural Science Foundation in Hunan Province of China (Grant Number 2021JJ31057) in support of Xiang Ding and Enhanced Inclusive Policy and Innovative Environment Development Initiative in Hunan Province of China (Grant Number 2023ZK4058) in support of Hong Zhang.

Data availability
The datasets and codes used for analyses are available from the corresponding author at Zhong2800@csu.edu.cn upon reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from the Institutional Review Committee of the Xiangya Hospital of Central South University (No.: 2021101000). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All participants provided written informed consent before the study.

Consent for publication
NA.

Competing interests
The authors declare no competing interests.

Received: 4 July 2024 / Accepted: 28 November 2024
Published online: 04 December 2024

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