

Coronavirus Pandemic

Clinical characteristics of liver transplant recipients with COVID-19 and analysis of risk factors for the severe disease

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Abstract

Introduction: Liver transplant (LT) recipients were at a high risk of infection during the coronavirus disease 2019 (COVID-19) pandemic. Our purpose was to compare the clinical characteristics of severe and non-severe groups of LT recipients with COVID-19, and to analyze their risk factors for severe disease.

Methodology: 79 LT recipients with COVID-19 were divided into a non-severe group (n = 60) and a severe group (n = 19), and differences in clinical characteristics, laboratory tests, and chest computed tomography (CT) performance were analyzed. Logistic regression was used to identify risk factors with severe COVID-19. Receiver operating characteristic (ROC) curves were plotted and the area under curve (AUC) values were calculated to assess the predictive value for severe COVID-19.

Results: Age was statistically different ($p < 0.001$) between the two groups. The difference in neutrophil-to-lymphocyte ratio (NLR), serum creatinine (Scr), D-dimer, urea, C-reactive protein (CRP), lactate dehydrogenase (LDH), and the number of lung segments involved in inflammation between the two groups were statistically significant ($p < 0.05$). The results revealed that age (OR = 1.255, 95% CI 1.079-1.460), NLR (OR = 1.172, 95% CI 1.019-1.348), and Scr (OR = 1.041, 95% CI 1.016-1.066) were independent risk factors for severe COVID-19. The ROC results showed that high values for age, NLR and Scr predicted severe COVID-19, with AUC values of 0.775, 0.841 and 0.820, respectively, and 0.925 for the three factors combined.

Conclusions: Advanced age, and elevated NLR and Scr are independent risk factors for severe COVID-19 in LT recipients.

Key words: liver transplantation; COVID-19; neutrophil-to-lymphocyte ratio; serum creatinine.

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Introduction

Coronavirus disease 2019 (COVID-19) has become a worldwide pandemic. Currently, the dominant strain is Omicron, which is known to be highly transmissible and capable of evading the immune system more effectively than other strains. COVID-19 causes acute respiratory distress syndrome in approximately 17-29% of cases, with the lungs being the primary organ affected. However, the virus can also affect other organs such as the liver and kidneys [1,2]. Older individuals, those with underlying medical conditions, and those with compromised immune systems are at a higher risk of developing severe or fatal respiratory illness due to COVID-19 [3,4]. Solid organ transplant recipients, including liver transplant (LT) recipients, take immunosuppressive drugs over a long-term, and are considered to be at a higher risk for developing severe COVID-19 due to their suppressed immune

status [5]. A study of LT recipients showed that the rate of intensive care unit (ICU) admission due to COVID-19 was as high as 28%, compared to only 8% in non-LT recipients [6], indicating a higher rate of ICU readmission among LT recipients. Additionally, Jering *et al* found that solid organ transplant recipients with COVID-19 had a higher mortality rate compared to the general population [7]. As a unique population, LT recipients on long-term immunosuppressive medications are at an unclear and increased risk for developing severe disease when combined with COVID-19, and few studies have been conducted in this area. This study aimed to investigate the risk factors for severe COVID-19 in LT recipients by dividing them into two groups, non-severe and severe, in order to provide early clinical identification and intervention treatment to reduce mortality.

Methodology

Study population

This retrospective study analyzed 79 LT recipients who were diagnosed with COVID-19 between December 2022 and March 2023 at the Ningbo Medical Center Lihuili Hospital. Among the patients, 56 were male and 23 were female, with ages ranging from 22 to 72 years, and a mean age of 56.7 ± 9.9 years. The reasons for LT included liver cancer (33 cases), cirrhosis B (30 cases), alcoholic cirrhosis (10 cases), and other reasons (6 cases). The diagnosis of COVID-19 was confirmed by real-time reverse transcription-polymerase chain reaction (RT-PCR) of nasopharyngeal swabs or sputum samples.

The inclusion criteria were (1) patients aged > 18 years and with a positive throat swab RT-PCR for COVID-19; (2) availability of complete laboratory and imaging data; and (3) signs of viral pneumonia on imaging studies. The exclusion criteria were (1) incomplete laboratory and imaging data; (2) LT recipients with other organ transplantation such as kidney transplantation.

The study was approved by the hospital's ethics committee with a specific ethics number (Approval No. KY2023PJ119)

Clinical classification

Clinical classification was done according to the diagnostic criteria of the Diagnostic Protocol for Pneumonia with Novel Coronavirus Infection (Trial Version 10) issued by the National Health and Wellness Commission [8]. Mild type included those with mild clinical symptoms and no imaging abnormalities. Moderate type included those with persistent fever (< 3 days), respiratory rate (RR) < 30 breaths/min, oxygen saturation $> 93\%$ in the resting state, and chest computed tomography (CT) with characteristic pneumonia manifestations of new coronavirus infection. Severe type included adults who had at least one of the following: RR ≥ 30 breaths/min, oxygen saturation $\leq 93\%$ in the resting state, arterial oxygen partial pressure (PaO₂) / inhaled oxygen concentration (FiO₂) ≤ 300 mmHg, progressive worsening of clinical symptoms, imaging showed a significant increase in lung inflammation of more than 50% within 24-48 hours. Critical type included adults with at least one of the following: respiratory failure, requiring mechanical ventilation, shock combined with other organ failure requiring ICU monitoring and treatment.

In this study, 0 patients were mild, 60 were moderate, 13 were severe, and 6 were critical. The study divided the patients into two groups: a non-severe group

($n = 60$) that included mild and moderate type patients, and a severe group ($n = 19$) that included severe and critical type patients.

Data collection

The data collected from the LT recipients with COVID-19 included: general information (gender, age, underlying disease, management of immunosuppression, and time of transplantation), laboratory tests data (C reactive protein (CRP), routine blood, biochemistry, and coagulation), and chest CT findings (number of lung segments involved in inflammation, the extent, and density of distribution of inflammation).

Statistical analysis

Statistical analysis was performed using the SPSS (version 22.0. Armonk, NY: IBM Corp) and MedCalc version 18.6 (MedCalc Software bv, Ostend, Belgium). The k-S test was conducted to determine whether the data conformed to normal distribution. Normally distributed data are presented as mean \pm standard deviation, while non-normally distributed data are reported as percentiles M (P25, P75). The independent sample t-test was used for normally distributed data, while the Mann-Whitney U test was used for non-normally distributed data. Statistical information was expressed as percentages and comparisons between two groups were made using the Chi-squared test or Fisher's exact probability method. The factors that were statistically significant in the univariate analysis were included in the multi-factor logistic regression analysis. Variables with $p < 0.1$ were selected for inclusion in the multifactorial analysis. The forward: LR method was used to select the variables ultimately included in the logistic regression equation. Variables with statistical significance were subjected to receiver operating characteristic (ROC) curves analysis to assess their predictive effectiveness, and the area under curve (AUC) values were recorded to obtain sensitivity and specificity. A p value of less than 0.05 was considered statistically significant.

Results

Clinical characteristics analysis

The study included 79 LT recipients with COVID-19, of which 56 (70.9%) were males and 23 (29.1%) were females. The mean age was 56.66 ± 9.93 years, and the range was 22 to 72 years. There were 60 cases in the non-severe group, with a mean age of 54.48 ± 10.21 years, and 19 cases in the severe group, with a mean age of 63.21 ± 5.09 years. There were no mild

cases, 60 were moderate, 13 were severe, and 6 were critical. The hospitalization rate was 78.5% (62/79), severity rate was 24.1% (19/79), ICU admission rate was 7.6% (6/79), and mortality rate was 3.8% (3/79). The main clinical symptoms were fever 62% (49/79), cough 74.7% (59/79), gastrointestinal symptoms (such as nausea, vomiting, diarrhea) 32.9% (26/79), myalgia 21.5% (17/79), headache 10.1% (8/79), and expectoration 17.7% (14/79). The common underlying comorbidities were hypertension 44.3% (35/79), diabetes mellitus 43% (34/79), chronic obstructive pulmonary disease 13.9% (11/79), coronary arterial disease 12.7% (10/79) and chronic kidney disease 2.5% (2/79). The main immunosuppressive agents used were tacrolimus 83.5% (66/79), mycophenolate mofetil 50.6% (40/79), sirolimus 36.7% (29/79), ciclosporin 11.4% (9/79), and prednisone 43% (34/79), because some patients are on multiple immunosuppressive drugs. Univariate analysis was performed to compare the two groups for various factors, including gender, age, time of transplantation, clinical symptoms, underlying comorbidities, and management of immunosuppression. The analysis revealed that there was no statistically significant difference between the two groups for five of the factors. The only factor that showed a statistical difference between the two groups was age, with the severe group having a significantly higher mean age compared to the non-severe group ($p < 0.001$, Table 1).

Comparison of the laboratory test results and chest CT performance between the two groups

Comparison of laboratory test results and chest CT performance revealed statistically significant differences between the two groups for seven factors: neutrophil-to-lymphocyte ratio, NLR ($p < 0.001$); serum creatinine, Scr ($p = 0.001$); urea ($p = 0.007$); D-dimer ($p = 0.002$); CRP ($p = 0.034$); lactate dehydrogenase, LDH ($p = 0.017$); and the number of lung segments involved in inflammation ($p = 0.011$). These results suggested that NLR, Scr, urea, CRP, D-dimer, LDH and the number of lung segments involved in inflammation were risk factors for severe COVID-19 in LT recipients (Table 2).

Logistic regression analysis between the two groups

The multifactorial logistic regression analysis concluded that age [(OR = 1.255, 95% CI = 1.079-1.460), $p < 0.05$; NLR (OR = 1.172, 95% CI = 1.019-1.348), $p < 0.05$; and Scr (OR = 1.041, 95% CI = 1.016-1.066), $p < 0.05$] were independent risk factors for LT recipients with severe COVID-19 (Table 3).

ROC curve analysis between the two groups

The factors that showed statistical significance in the multifactorial logistic regression analysis were analyzed using ROC curves.

Table 1. Analysis of general clinical characteristics between the severe and non-severe group.

Classification	Non-severe group	Severe group	p value
	(n = 60)	(n = 19)	
Age (years)	54.48±10.21	63.21±5.09	<0.001
Gender, n (%)			0.786
Male	43 (71.7)	13 (68.4)	
Female	17 (28.3)	6 (31.6)	
Time of transplantation (months)	24.5 (12,48.5)	33 (22,41)	0.266
Fever, n (%)	36 (60)	13 (68.4)	0.510
Cough, n (%)	43 (71.7)	16 (84.2)	0.371
Expectoration, n (%)	9 (15)	5 (26.3)	0.306
Gastrointestinal symptoms, n (%)	17 (28.3)	9 (47.4)	0.124
Myalgia, n (%)	14 (23.3)	3 (15.8)	0.749
Headache, n (%)	7 (11.7)	1 (5.3)	0.672
Hypertension, n (%)	26 (43.3)	9 (47.4)	0.758
Diabetes mellitus, n (%)	23 (38.3)	11 (57.9)	0.133
Chronic kidney disease, n (%)	2 (3.3)	0 (0.0)	1.000
Chronic obstructive pulmonary disease, n (%)	9 (15)	2 (10.5)	1.000
Coronary arterial disease, n (%)	9 (15)	1 (5.3)	0.437
Tacrolimus, n (%)	49 (81.7)	17 (89.5)	0.723
Ciclosporin, n (%)	6 (10)	3 (15.8)	0.443
Mycophenolate mofetil, n (%)	32 (53.3)	8 (42.1)	0.394
Sirolimus, n (%)	21 (35)	8 (42.1)	0.576
Prednisone, n (%)	25 (41.7)	9 (47.4)	0.662

Table 2. Comparison of laboratory test results and chest computed tomography (CT) images between the severe and non-severe groups.

Classification	Non-severe group	Severe group	p value
	(n = 60)	(n = 19)	
C-reactive protein, mg/L, mean ± SD	26.40 ± 15.77	42.53 ± 29.83	0.034
White blood cell count (× 10 ⁹ /L), mean ± SD	4.78 ± 1.91	5.74 ± 4.05	0.326
Neutrophil-to-lymphocyte ratio, NLR, median (IQR)	3.83 (2.30, 4.92)	7.00 (5.50, 9.90)	< 0.001
Hemoglobin, g/L, mean ± SD	121.88 ± 21.25	115.05 ± 12.90	0.097
Platelet count (× 10 ⁹ /L)	154.50 (112.00, 236.25)	124.00 (89.00, 215.00)	0.160
Albumin, g/L, mean ± SD	39.98 ± 6.96	37.14 ± 8.63	0.148
Aspartate aminotransferase, U/L, median (IQR)	33.00 (23.00, 48.25)	32.00 (22.00, 43.00)	0.435
Alanine aminotransferase, U/L, median (IQR)	35.50 (19.00, 52.75)	42.00 (30.00, 76.00)	0.191
Alkaline phosphatase, U/L, mean ± SD	198.38 ± 255.86	140.63 ± 52.33	0.333
Total bilirubin, μmol/L, median (IQR)	14.20 (8.78, 23.23)	19.50 (10.00, 32.80)	0.09
Glucose, mmol/L, median (IQR)	5.85 (5.09, 6.99)	7.97 (5.23, 11.50)	0.075
Serum creatine, μmol/L, mean ± SD	76.64 ± 26.21	123.59 ± 53.00	0.001
Urea, mmol/L, mean ± SD	5.42 ± 1.62	8.63 ± 4.58	0.007
Uric acid, μmol/L, mean ± SD	344.10 ± 113.22	323.68 ± 162.68	0.615
D-dimer, ng/mL, mean ± SD	210.25 ± 119.86	278.95 ± 62.73	0.002
Lactate dehydrogenase, U/L, mean ± SD	212.33 ± 63.32	279.47 ± 107.32	0.017
Involved lung segments, n (%)			0.011
Segments 1-6	25 (41.7)	1 (5.3)	
Segments 7-12	22 (36.7)	10 (52.6)	
Segments 13-18	13 (21.6)	8 (42.1)	
Density of the lesion, n (%)			0.064
Density of pure ground glass	15 (25)	1 (5.3)	
Ground glass-consolidation	37 (61.7)	12 (63.2)	
Consolidation	8 (13.3)	6 (31.5)	
Extent of the lesion, n (%)			0.171
Peripheral	36 (60)	8 (42.1)	
Peripheral-central	24 (40)	11 (57.9)	

Table 3. Logistic regression analysis between the severe and non-severe groups.

Parameter	B	SE	Wald value	p value	OR value	95% CI
Age	0.227	0.077	8.666	0.003	1.255	1.079~1.460
NLR	0.159	0.071	4.969	0.026	1.172	1.019~1.348
Scr	0.040	0.012	10.925	0.001	1.041	1.016~1.066
Constant	-19.932	5.620	12.579	0.000	0.000	-

NLR: neutrophil-to-lymphocyte ratio; Scr: serum creatinine; SE: standard error; OR: odds ratio; CI: confidence interval.

Table 4. ROC curve analysis between the severe and non-severe groups.

Parameter	AUC	95% CI	Sensitivity (%)	Specificity (%)
Age	0.775	0.667~0.861	89.5	55
NLR	0.841	0.741~0.913	84.2	78.3
Scr	0.820	0.717~0.897	84.2	65
Combination of the three factors	0.925	0.844~0.972	94.7	73.3

ROC: receiver operating characteristic; AUC: area under curve; CI: confidence interval; NLR: neutrophil-to-lymphocyte ratio; Scr: serum creatinine.

The analysis revealed that age, NLR, and Scr had AUC values of 0.775, 0.841, and 0.820, respectively, indicating that they had good predictive value for severe COVID-19 in LT recipients. The combination of age, NLR, and Scr showed the highest predictive value, with an AUC value of 0.925 (Table 4, Figure 1).

Discussion

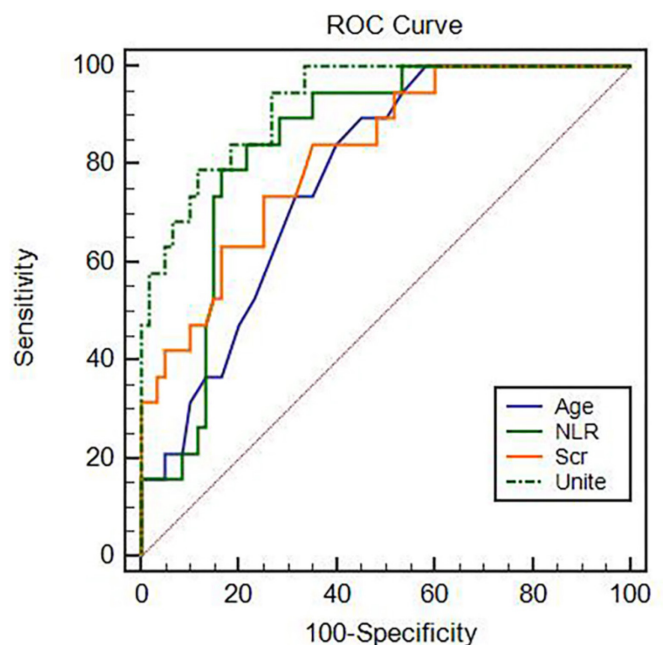
COVID-19 has emerged as a global public health crisis because it is a highly contagious respiratory infection. The virus is spread through the respiratory tract or by contact with surfaces contaminated with the virus. While there is a growing body of literature on the clinical presentation, pathogenesis and management of the virus in the general population, there has been less attention paid to certain special populations, such as organ transplant recipients who are on long-term immunosuppressive therapy. These individuals have suppressed immune systems, and the severity of their COVID-19 disease has been rarely reported. Therefore, this study aimed to investigate the risk factors for severe COVID-19 in LT recipients.

In this study, 79 LT recipients with COVID-19 were included. A comparison of the general clinical characteristics between the two groups revealed that 70.9% of LT recipients were males. This may be due to the higher incidence of end-stage liver disease in males, resulting in a higher number of LT recipients in males [9]. Comparison between the two groups also showed no significant association between the duration of transplantation and the occurrence of severe COVID-19 in LT recipients, which is consistent with the results of a meta-analysis [10]. In our study, approximately 32.9% of those who received LT and had COVID-19 developed gastrointestinal symptoms (such as nausea, vomiting, diarrhea). Mansoor *et al.* [11] found that 30% of LT with COVID-19 had gastrointestinal symptoms, which is similar to the results of the present study. Comparison of clinical characteristics of the two groups indicated that age was the only identified risk factor for severe COVID-19 in LT recipients ($p < 0.001$). LT recipients with severe COVID-19 were older than those in the non-severe group (63.21 years vs. 54.48 years), and the differences were statistically significant. Bhoori *et al.* [12] demonstrated that LT recipients who were > 60 years old, and who were infected with COVID-19 had a higher risk of mortality, with increasing age being associated with even higher mortality. Reduced resistance to the organism, combined with immunosuppression, increased the risk of infection in those with advanced age. Such COVID-19 cases are more likely to become severe and have a higher

mortality rate, which is consistent with the results of some other studies [13,14].

When the novel coronavirus infects the body, neutrophils become activated and migrate to target organs (such as the lungs and kidneys), where they release large amounts of reactive oxygen species that damage cellular DNA and cause the virus to be released from cells. Other immune cells, such as NK cells, also play a role in fighting the virus by killing infected cells and stimulating both cellular and humoral immunity [15]. Meanwhile, the lymphatic system is also activated, and lymphocytes work to combat the virus. However, this can lead to a decrease in the number of lymphocytes, particularly CD4+ T lymphocytes, and an increase in CD8+ T lymphocytes [16]. This decrease in lymphocytes has been found to be positively correlated with the severity of the infection [17]. Damage to lymphocytes by the virus can weaken the body's immunity and increase the risk of severe or critical illness. NLR is a marker of the body's systemic inflammatory response, and normal or decreased levels of neutrophils, decreased levels of lymphocytes, and a slightly elevated NLR are observed in the early stages of the disease. In LT recipients, viral infections can damage the tracheal mucosal barrier and upregulate

Figure 1. ROC curve analysis was performed to assess the predictive effectiveness of severe COVID-19 in LT recipients. The AUC values for age, NLR, Scr and the combination of the three were 0.775, 0.841, 0.820 and 0.925 respectively, with the highest predictive effectiveness of the combination of the three.



ROC: receiver operating characteristic; COVID-19: coronavirus disease 2019; LT: liver transplant; AUC: area under curve; NLR: neutrophil-to-lymphocyte ratio; Scr, serum creatinine

airway adhesion molecules, making them more susceptible to bacterial and fungal infections [4]. As the infection progresses, LT recipients are at an increased risk of bacterial co-infections, elevated neutrophil levels, progressive lymphocyte depletion, increased NLR, and progression to severe or critical disease. In this way, inflammation caused by the virus can increase the NLR value, and an increased NLR value can in turn promote disease progression. In this study, NLR was statistically different between the two groups, with significantly higher values in the severe group compared to the non-severe group {7 (5.50, 9.90) vs 3.83 (2.30, 4.92)}. NLR alone had an AUC of 0.841, a sensitivity of 84.2%, and a specificity of 78.3%, when used as a risk factor for predicting disease severity, demonstrating a higher predictive value than Scr or age alone. Studies have shown that an NLR value greater than 19.9 is an independent risk factor for death in COVID-19 patients [18], indicating that a higher NLR value is associated with a greater risk of developing severe COVID-19 in LT recipients, which is similar to the findings of this study.

Novel coronaviruses primarily attach to the angiotensin-converting enzyme 2 (ACE2) receptors located on the surface of target organs, resulting in disease. ACE2 receptors are mainly present in the lungs, gastrointestinal tract, and kidneys [19]. Renal tubular epithelial cells express high levels of ACE2 receptors, approximately 100 times higher than alveolar epithelial cells [20], and COVID-19 has a strong affinity for ACE2 [21]. The virus can directly damage the kidneys by binding to the ACE2 receptor on the kidney's surface via the S protein. Additionally, critically ill patients experience an activated inflammatory response that produces inflammatory metabolites, which can damage the kidneys and increase the risk of acute kidney injury (AKI). This study found that the severe group had higher Scr and urea levels than the non-severe group, and there was a statistically significant difference between the two groups. The severe group had no patients with chronic kidney disease, which excluded the effect of chronic kidney disease on Scr and urea levels. Scr alone as a predictor of severe COVID-19 had an AUC of 0.820, a sensitivity of 84.2%, and a specificity of 65%. Ali *et al.* found that up to 53.3% of abdominal organ transplant patients, including liver and kidney transplant recipients with COVID-19, developed elevated Scr levels [22]. A meta-analysis study of LT patients with COVID-19 found that 104 of 313 LT patients developed AKI, with an incidence rate of 33.22% [10], indicating a higher AKI incidence rate in LT recipients

with COVID-19. Elevated Scr levels have been identified as a risk factor for mortality in patients who have undergone LT with COVID-19 [6], and Scr is considered the gold standard for diagnosing and assessing AKI [23]. Therefore, if a LT recipient has a combination of COVID-19 and an elevated Scr level, they may be at risk of developing AKI.

The novel coronavirus binds to ACE2 receptors on alveolar epithelial cells, resulting in alveolar edema, capillary leakage, and infiltration of inflammatory cells, which can lead to lung injury and subsequent pneumonia. In non-severe cases, chest CT scans frequently show ground-glass opacities and interstitial changes in the peripheral lung bands, which can progress to multiple subsolid infiltrative opacities and solid changes in the bilateral lungs in severe cases. In this study, all the patients underwent chest CT scans and showed varying degrees of pneumonia. The severity of pneumonia detected by CT has been found to be positively correlated with the severity of COVID-19 [24]. The number of lung segments involved in pneumonia was found to be statistically significant in univariate analysis between the two groups, with patients having more lung segments involved being more likely to develop severe disease. However, multifactorial regression analysis did not indicate significance for this factor, which may be due to the small sample size and the fact that the study was conducted at a single center.

In this study, researchers conducted a multifactorial logistic regression analysis and found that three factors - NLR, Scr, and age - were independent risk factors for LT recipients with severe COVID-19. The ROC curve analysis showed that none of these factors alone had an AUC higher than 0.850 to predict severe COVID-19. However, when the three factors were combined to predict severe COVID-19, the AUC was as high as 0.925, indicating a high predictive value. The sensitivity was 94.7% and specificity was 73.3%. These findings have important implications for clinical management and prevention strategies for LT patients with COVID-19, who are a vulnerable population. They may also help with the early identification of severe cases and targeted interventions for treatment, which could improve the prognosis of these patients.

This study has some limitations that should be considered. Firstly, the study was retrospective, and although all patients were screened in accordance with the same inclusion and exclusion criteria, the possibility of selection bias cannot be excluded. The inclusion of a smaller number of LT cases, particularly those with severe COVID-19 may affect the statistical results. Secondly,

this study was conducted at a single center, and further multi-center studies with larger sample sizes are needed to confirm the findings.

Conclusions

In conclusion, the study's results suggest that age, NLR, and Scr are important independent risk factors for severe COVID-19 in LT recipients, with the combination of these factors having the highest predictive effectiveness. Therefore, it is crucial to closely monitor LT patients who are older and have elevated NLR and Scr levels for the development of severe COVID-19 and to implement timely interventions to improve their prognosis.

Acknowledgements

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Ethics committee approval

The study was conducted in accordance with the Helsinki Declaration and ethical standards of the research Ethics Committee of Ningbo Medical Center Lihuli Hospital (Approval No. KY2023PJ119). A waiver for the informed consent requirement was granted by the Ethics Committee since the study was retrospective.

Authors' contributions

DC: design and supervision; SF: materials, data collection, processing, literature search, writing manuscript; YZ and MW: analysis and interpretation. All authors approved the final submitted version.

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