Retrospective Cohort Study

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Impact of preoperative infection on the outcomes of liver transplant recipients: a national propensity score-matched retrospective cohort study in China

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Background: Impact of preoperative infection on liver transplantation (LT) needs further investigation.
Materials and methods: From 1 January 2015 to 31 December 2022, 24 122 eligible patients receiving LT were enrolled from the China Liver Transplant Registry database. The outcomes of LT were compared after using the propensity score-matched analysis.
Results: Compared to the noninfection group, patients in the infection group were more likely to have postoperative effusion, infection, abdominal bleeding, and biliary complications (all $P < 0.01$), and they had shorter 30-day, 90-day survival, and overall survival (all $P < 0.01$). Cox proportional hazards regression analysis revealed that MELD score and cold ischemia time were risk factors for the overall survival in the infection group (both $P < 0.05$). Besides, compared to the nonpulmonary group, patients in the pulmonary group were more likely to have postoperative effusion and infection (both $P < 0.0001$), and less likely to have postoperative abscess and early allograft dysfunction (both $P < 0.05$). Patients in the nonabdominal group also had a higher proportion of postoperative infection than those in the abdominal group ($P < 0.05$). Furthermore, compared to the number = 1 group, patients in the number ≥ 2 group were more prone to postoperative effusion and infection (both $P < 0.01$), and they also had shorter 30-day and 90-day survival (both $P < 0.05$).
Conclusion: Preoperative infection can result in a higher incidence of early postoperative complications and shorter survival in liver transplant recipients. The types and number of infection sites will also influence the prognosis of liver transplant recipients.

Keywords: early complications, liver transplantation, overall survival, preoperative infection, short-term survival

Introduction

Liver transplantation (LT) is an effective treatment for patients with end-stage liver diseases[1–3]. In recent years, with the fast development of surgical techniques, intraoperative and postoperative management, the overall survival (OS) of liver transplant recipients has been greatly improved[4,5]. Nevertheless, the outcomes of liver transplant recipients may also be significantly affected by preoperative risk factors. Nowadays, infection before surgery deserves attention with the increasing severity of multidrug resistance[6–8]. If not detected and prevented in time, preoperative infection will lead to serious consequences during and after surgery. There exist many studies on the impact of preoperative infection, indicating that it will cause a poor prognosis in patients undergoing transplantation, including kidney[9], heart[10], and lung[11,12] transplantation. In addition, active infection should be avoided and needs adequate treatment before

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LT according to the international guidelines[13]. Hence, preoperative infection in LT should also be emphasized, and the impact of preoperative infection on the outcomes of liver transplant recipients needs further exploration.

Several studies have preliminarily explored the impact of preoperative infection on patients receiving LT. Sun *et al*.[14] compared post-transplant outcomes between patients with and without preoperative nonviral infection. There was no significant difference between these two groups in short-term survival, and patients with preoperative sepsis needed more care before and after LT. Bertuzzo *et al*.[15] also demonstrated that preoperative infection can lead to a higher possibility of infection following LT, but not a worse short-term survival outcome. Moreover, acute-on-chronic liver failure patients who underwent living donor LT with preoperative infection were proved to have a shorter 1-year survival compared to those without preoperative infection[16]. However, these studies did not discuss whether different infection sites and the number of infection sites can influence the outcomes of LT. Besides, these studies all pointed out that they were limited to few centers and small sample sizes, and few studies compared the outcomes of liver transplant recipients with or without preoperative infection using the paired-matched method. The conclusions need to be further verified, and more studies are urgently required.

Therefore, based on a national retrospective cohort in China, the present study further explored the impact of preoperative infection on the outcomes of liver transplant recipients using the propensity score-matched (PSM) analysis, aiming to provide new insights into the accurate management of preoperative infection in LT.

HIGHLIGHTS

- Preoperative infection can result in a higher incidence of early postoperative complications in liver transplant recipients.
- Preoperative infection can lead to shorter survival in liver transplant recipients.
- Different infection sites will affect the prognosis of liver transplant recipients.
- The number of infection sites will influence the prognosis of liver transplant recipients.

Patients and methods

Study populations

The China Liver Transplant Registry (CLTR) database is a scientific research institution responsible for national liver transplant data gathering in China. From 1 January 2015 to 31 December 2022, adult patients ($\geq$ 18 years old) receiving LT were identified (n = 33 922) in the CLTR database. Patients with donor age less than 18 years or missing (n = 1780), living donor transplantation (n = 463), retransplantation (n = 721), and multiple organ transplantation (n = 234) were excluded, those with missing essential data were excluded, including recipient characteristics (n = 657), donor characteristics (n = 2817), and surgical characteristics (n = 2488), and those with incomplete follow-up (n = 640) were also excluded. Finally, 24 122 patients were included for analysis, and the median follow-up time was 27.1 months. The flow chart of the enrolled cohort was shown in Figure 1.

The study has been reported in line with the strengthening the reporting of cohort, cross-sectional, and case–control studies in surgery (STROCSS) criteria[17] (Supplemental Digital Content 1, http://links.lww.com/JS9/B780). This study was performed in accordance with the Declaration of Helsinki and approved by the CLTR database (No. 20230007). Informed consent was waived as previously collected data that did not include personally identifiable information were used.

Data collection

Recipient and donor characteristics were collected. Recipient characteristics included age, sex, BMI, blood group, etiology of

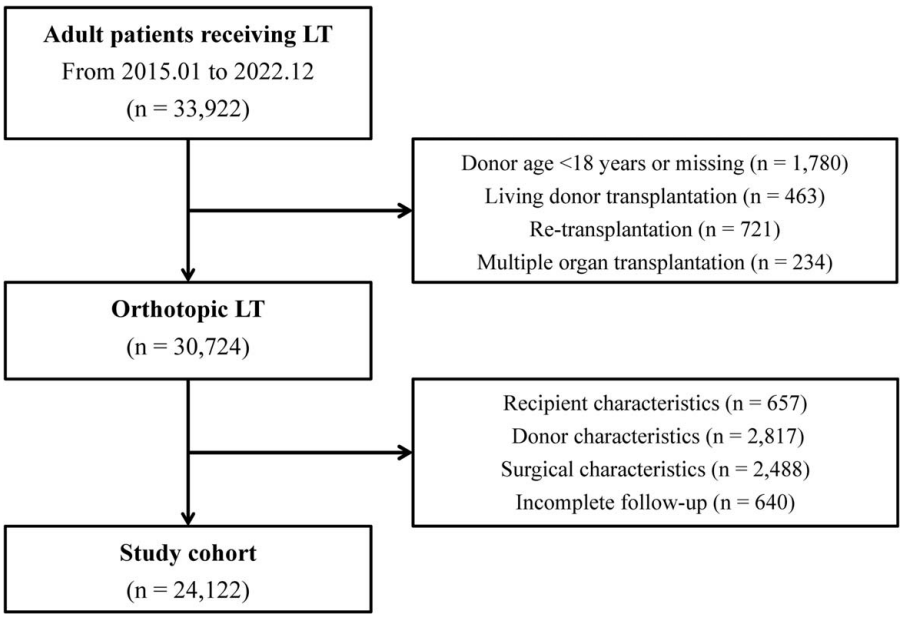

Figure 1. Flowchart of the enrolled cohort.

Table 1

Baseline characteristics of the enrolled patients.

	Before PSM			After PSM		
Variables	**Noninfection group ($n=23465$)**	**Infection group ($n=657$)**	***P***	**Noninfection group ($n=657$)**	**Infection group ($n=657$)**	***P***
Recipient characteristics						
Age (years)	50.63 ± 10.16	49.46 ± 10.50	0.0036	49.08 ± 10.53	49.46 ± 10.50	0.5174
Sex (male, %)	18 944 (80.73)	539 (82.04)	0.4020	511 (77.78)	539 (82.04)	0.0539
BMI (kg/m^2)	23.52 ± 3.53	23.21 ± 3.53	0.0296	23.07 ± 3.62	23.21 ± 3.53	0.4524
Etiology of liver diseases (%)[a]						
Hepatitis B	16 789 (71.55)	469 (71.39)	0.0176	435 (66.21)	469 (71.39)	0.0095
Hepatitis C	522 (2.22)	13 (1.98)		15 (2.28)	13 (1.98)	
NASH	1502 (6.40)	25 (3.81)		54 (8.22)	25 (3.81)	
Alcoholic	1724 (7.35)	55 (8.37)		55 (8.37)	55 (8.37)	
Autoimmune	1198 (5.11)	30 (4.57)		43 (6.54)	30 (4.57)	
Others	1730 (7.37)	65 (9.89)		55 (8.37)	65 (9.89)	
Blood group (%)						
O	7082 (30.18)	220 (33.49)	0.3227	179 (27.25)	220 (33.49)	0.0848
A	7283 (31.04)	190 (28.92)		16.06 (32.12)	190 (28.92)	
B	6666 (28.41)	182 (27.70)		189 (28.77)	182 (27.70)	
AB	2434 (10.37)	65 (9.89)		78 (11.87)	65 (9.89)	
MELD score (%)						
< 30	13 980 (59.58)	272 (41.40)	< 0.0001	281 (42.77)	272 (41.40)	0.6150
≥ 30	9485 (40.42)	385 (58.60)		376 (57.23)	385 (58.60)	
Child-Pugh score (%)						
A	2302 (9.81)	13 (1.98)	< 0.0001	11 (1.67)	13 (1.98)	0.1464
B	6346 (27.04)	69 (10.50)		92 (14.00)	69 (10.50)	
C	61.43 (63.15)	575 (87.52)		554 (84.32)	575 (87.52)	
Ascites (%)[a]						
Absent	6613 (28.18)	48 (7.31)	< 0.0001	109 (16.59)	48 (7.31)	< 0.0001
Slight/Moderate	12 255 (52.23)	330 (50.23)		385 (58.60)	330 (50.23)	
Severe	4597 (19.59)	279 (42.47)		163 (24.81)	279 (42.47)	
Donor characteristics						
Age (years)	45.17 ± 14.96	42.84 ± 14.19	< 0.0001	42.03 ± 15.69	42.84 ± 14.19	0.3239
Sex (male, %)	19 334 (82.40)	523 (79.60)	0.0644	525 (79.91)	523 (79.60)	0.8908
BMI (kg/m^2)	23.32 ± 3.39	22.96 ± 3.17	0.0040	22.61 ± 3.34	22.96 ± 3.17	0.0535
Blood group (%)						
O	8730 (37.20)	271 (41.25)	0.1695	231 (35.16)	271 (41.25)	0.0556
A	6635 (28.28)	168 (25.57)		198 (30.14)	168 (25.57)	
B	6313 (26.90)	173 (26.33)		169 (25.72)	173 (26.33)	
AB	1787 (7.62)	45 (6.85)		59 (8.98)	45 (6.85)	
Donation type (%)						
DBD	9899 (42.19)	374 (56.93)	< 0.0001	357 (54.34)	374 (56.93)	0.1234
DCD	8800 (37.50)	181 (27.55)		213 (32.42)	181 (27.55)	
DBCD	4766 (20.31)	102 (15.53)		87 (13.24)	102 (15.53)	
Death cause (%)						
Trauma	5224 (22.26)	265 (40.33)	< 0.0001	285 (43.38)	265 (40.33)	0.2634
Others	18 241 (77.74)	392 (59.67)		372 (56.62)	392 (59.67)	
Surgical characteristics						
CIT (%)						
< 8 h	17 742 (75.61)	507 (77.17)	0.3586	488 (74.28)	507 (77.17)	0.1189
≥ 8 h	5723 (24.39)	150 (22.83)		169 (25.72)	150 (22.83)	
Anhepatic phase (min)	54.59 ± 21.64	51.69 ± 19.37	0.0002	52.39 ± 18.83	51.69 ± 19.37	0.5066
Operation time (h)	7.18 ± 1.90	7.18 ± 2.03	0.9956	7.10 ± 1.99	7.18 ± 2.03	0.4723

Etiology of liver diseases and ascites are associated with preoperative infection, which are not included in the PSM analysis.

CIT, cold ischemia time; DBCD, donation after brain and cardiac death; DBD, donation after brain death; DCD, donation after circulatory death; MELD, Model for End-Stage Liver Disease; PSM, propensity score-matched.

liver diseases, Model for End-Stage Liver Disease (MELD) score, Child-Pugh score, ascites, and preoperative infection-related information. Donor characteristics included age, sex, BMI, blood group, donation type, and death cause. Cold ischemia time (CIT), anhepatic phase and operation time were enrolled as surgical characteristics. Moreover, immunosuppressive regimens were also collected, including tacrolimus (FK506), cyclosporin A (CSA), mycophenolate mofetil (MMF), and glucocorticoid. In addition, early (< 30 days) complications after LT were enrolled based on diagnosis and treatment specification for postoperative complications after LT in China[18], and short-term (30-day and 90-day) survival and OS were also collected.

Table 2

Early postoperative complications between the noninfection and infection groups.

Types of early postoperative complications	Noninfection group ($n=657$)	Infection group ($n=657$)	P
Effusion (%)	137 (20.85)	436 (66.36)	< 0.0001
Abscess (%)	109 (16.59)	97 (14.76)	0.3626
Infection (%)	92 (14.00)	440 (66.97)	< 0.0001
Abdominal bleeding (%)	28 (4.26)	51 (7.76)	0.0076
Acute rejection (%)	16 (2.44)	17 (2.59)	0.8601
EAD (%)	151 (22.98)	148 (22.53)	0.8435
Biliary complications (%)	12 (1.83)	31 (4.72)	0.0032
Vascular complications (%)	13 (1.98)	17 (2.59)	0.4600

EAD, early allograft dysfunction.

Definition of preoperative infection

An exhaustive effort was made to identify all pretransplant infections and categorize them based on symptom presentation, infection site, pathogen type, and so on. Stringent criteria were employed for precise infection definition. The identified infections were classified into pulmonary, abdominal, biliary tract, bloodstream, and urinary tract infections[19,20].

Diagnosis of pulmonary infections must include the following criteria: (1) respiratory symptoms (cough and dyspnea) or hypoxemia develops, and chest radiography shows new or progressive infiltrates, consolidation, cavitation, or pleural effusion. (2) One of the following: (a) bacteria are isolated from purulent sputum in large quantities; (b) isolation of pathogens from specimens obtained by tracheal aspiration, bronchial brushing, or biopsy; (c) virus isolation or detection of viral antigens in respiratory secretions; (d) a fourfold increase in single antibody titers (IgM) or paired serum samples (IgG) of the diagnostic pathogen. (3) The diagnosis of CMV pneumonia is based on pneumonia with fever for at least 2 days, the presence of neutropenia or thrombocytopenia, and the detection of CMV DNA in the blood.

Abdominal infections include the following criteria: (1) rapid onset of abdominal pain and symptoms of gastrointestinal dysfunction (loss of appetite, nausea, vomiting, bloating, and/or constipation) with or without inflammatory symptoms (pain, tenderness, fever, tachycardia, and/or shortness of breath). (2) Isolation of organisms from cultures of purulent material in the abdominal cavity during surgery or needle aspiration. If peritoneal polymorphonuclear cells are $>200/\mu l$ and pathogen was isolated, abdominal infection was diagnosed. In cases where cell counts were not obtained, gram staining of peritoneal fluid showing ≥ 1 polymorphonuclear cells per unit was sufficient. (3) Spontaneous bacterial peritonitis is defined as a pleomorphic cell count of 250 cells/mm^3 or more in ascitic fluid, regardless of bacterial growth in the medium and signs of peritoneum such as muscle protection and/or rebound tenderness from abdominal distention. Infection is classified as primary when the source is unknown and secondary when the site is identified.

Diagnosis of biliary tract infections includes the following criteria: (1) fever or chills, pain in the right upper quadrant. (2) Cholestasis and jaundice or abnormal liver tests. (3) Imaging evidence such as biliary dilatation.

Bloodstream infections must meet the following criteria: (1) one of the following: fever, chills, or hypotension, without any associated infection at other sites. (2) Pathogens like *S aureus*, *Enterococcus* spp, *Escherichia coli*, *Pseudomonas* spp, *Klebsiella* spp, or *Candida* spp should be isolated from at least one blood culture. For other pathogens, isolation of the bacterium is required in two blood cultures or in one positive blood culture and a culture from a known site of infection. (3) Recognized pathogens isolated from blood cultures should not be associated with infection at other sites.

Gold standard for diagnosis of urinary tract infections is urine culture, and the traditional definition of significant bacteriuria is 10^5 colony forming unit/ml. The classifications of urinary tract infections are as follows: (1) uncomplicated urinary tract infection; (2) complicated urinary tract infection; (3) recurrent urinary tract infection; (4) catheter-associated urinary tract infection; (5) urosepsis.

Immunosuppressive regimens

Immunosuppressive regimens used in liver recipients are individualized based on the clinical assessment. In general, transplant centers in China adopt the calcineurin inhibit (CNI)-based immunosuppressive regimen combined with antiproliferative drugs such as MMF and/or glucocorticoids according to Diagnosis and treatment specification for immunosuppressive therapy and rejection of LT in China[21]. CNI mainly includes FK506 and CSA.

FK506

When used in combination, the dosage of FK506 is generally 0.05–0.15 mg/kg/d. The plasma concentration of FK506 is determined according to the trough value, which is 8–12 ng/ml within 3 months after LT, 7–10 ng/ml within 3–6 months, 6–8 ng/ml within 6–12 months and maintains around 5 ng/ml after 12 months.

CSA

The dosage of CSA is generally 6–8 mg/kg/d when used in combination. The plasma concentration of CSA is determined based on the trough value. It maintains around 200 ng/ml within 1 months after LT, around 150 ng/ml within 1–6 months and 100–150 ng/ml within 6–12 months, and thereafter maintained at a low concentration.

MMF

When used in combination, the loading dosage should be taken for the first time (three times the maintenance dosage). The recommended loading dosage is 6 mg/d and the maintenance dosage is 2 mg/d. Using conventional dosage, adult recipients generally do not need to monitor the plasma concentration, while pediatric recipients, those with impaired liver function, and those whose cyclosporine dosage is significantly reduced or discontinued need.

Glucocorticoid

The initial dosage after LT is 30 mg/d, and then is reduced at a rate of 5 mg/d according to the condition until maintaining 5–10 mg/d.

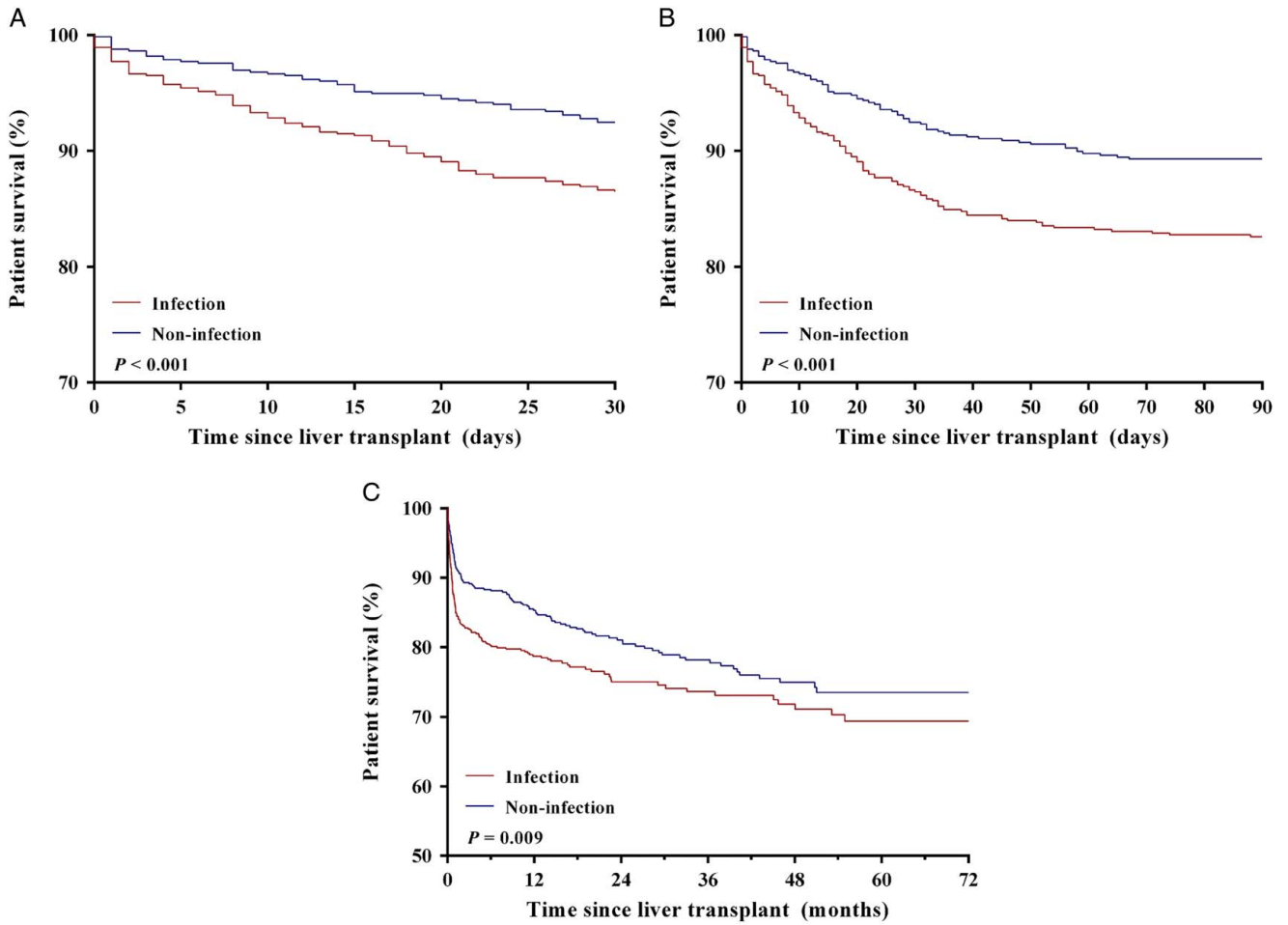

Figure 2. Short-term survival and OS between the noninfection and infection groups. (A). Patients in the infection group had shorter 30-day survival than those in the noninfection group ($P < 0.001$); (B). Patients in the infection group had shorter 90-day survival than those in the noninfection group ($P < 0.001$); (C) Patients in the infection group had shorter OS than those in the noninfection group ($P = 0.009$).

Statistical analysis

In this study, normally distributed continuous variables were expressed as mean ± SD, and *t*-test was conducted between two groups. Non-normally distributed continuous variables were expressed as median (quartile), and Mann–Whitney *U* test was used between two groups. Categorical variables were compared using χ^2 test or Fisher's exact test. The survival probability curves were generated with the nonparametric Kaplan–Meier estimation and then compared with log-rank test. The potential variables were selected by univariate Cox proportional hazards regression analysis, and then these variables were incorporated in the multivariate Cox proportional hazards regression analysis to explore the significant ones associated with recipients' OS. PSM was performed to balance the significant difference in the baseline characteristics that could impact outcomes[22]. *P*-value <0.05 was statistically significant.

Results

Baseline characteristics of the enrolled patients

According to the presence or absence of preoperative infection, 24 122 patients were firstly divided into the noninfection ($n = 23\,465$) and infection ($n = 657$) groups, as shown in Table 1.

Recipient age in the noninfection group was older than that in the infection groups ($P = 0.0036$). Recipient BMIs were 23.52 ± 3.53 kg/m^2 in the noninfection group and 23.21 ± 3.53 kg/m^2, respectively ($P = 0.0296$). There existed a great difference in etiology of liver diseases ($P < 0.0001$). Recipients in the noninfection group had better MELD and Child-Pugh scores than those in the infection group (both $P < 0.0001$). Besides, ascites also differed significantly between two groups ($P < 0.0001$). Donor age in the noninfection group was also older than that in the infection group ($P < 0.0001$), and donor BMIs were 23.32 ± 3.39 kg/m^2 in the noninfection group and 22.96 ± 3.17 kg/m^2 in the infection group ($P = 0.0040$). Donation type and death cause also differed significantly between these two groups (both $P < 0.0001$). Anhepatic phase showed a great difference between these two groups ($P = 0.0002$).

PSM analysis of the noninfection and infection groups

To minimize the confounding factors that may influence the outcomes of LT, the noninfection and infection groups were matched using the PSM analysis. There were 657 patients in the noninfection group and 657 in the infection group. As expected, all possible confounding factors lost significance after the PSM analysis ($P > 0.05$, Table 1).

Table 3

Cox proportional hazards regression model analysis of risk factors for the OS in the infection group.

	Univariate		Multivariate	
Variables	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Recipient characteristics				
Age (years)	1.00 (0.99–1.02)	0.70		
Sex (male, %)	1.15 (0.78–1.71)	0.48		
BMI (kg/m^2)	0.98 (0.94–1.02)	0.34		
Etiology of liver diseases (%)				
Hepatitis B	Reference			
Hepatitis C	0.59 (0.15–2.40)	0.46		
NASH	1.69 (0.86–3.34)	0.13		
Alcoholic	1.42 (0.86–2.35)	0.17		
Autoimmune	0.82 (0.36–1.88)	0.65		
Others	1.20 (0.73–1.98)	0.48		
Blood group (%)				
O	Reference			
A	0.93 (0.63–1.37)	0.72		
B	0.72 (0.47–1.09)	0.12		
AB	1.07 (0.63–1.82)	0.80		
MELD score (%)				
<30	Reference		Reference	
≥ 30	1.50 (1.08–2.09)	0.02	1.62 (1.16–2.27)	0.02
Child-Pugh score (%)				
A	Reference			
B	2.44 (0.32–18.69)	0.39		
C	3.57 (0.50–25.50)	0.21		
Ascites (%)				
Absent	Reference			
Slight/Moderate	0.63 (0.37–1.10)	0.10		
Severe	0.96 (0.56–1.65)	0.89		
Donor characteristics				
Age (years)	1.01 (1.00–1.02)	0.24		
Sex (male, %)	0.76 (0.50–1.16)	0.20		
BMI (kg/m^2)	0.98 (0.94–1.03)	0.49		
Blood group (%)				
O	Reference			
A	0.86 (0.58–1.28)	0.46		
B	0.82 (0.55–1.21)	0.32		
AB	0.95 (0.50–1.79)	0.87		
Donation type (%)				
DBD	Reference			
DCD	1.23 (0.86–1.75)	0.26		
DBCD	1.04 (0.67–1.62)	0.85		
Death cause (%)				
Trauma	Reference			
Others	0.97 (0.71–1.33)	0.86		
Surgical characteristics				
CIT (%)				
<8 h	Reference		Reference	
≥ 8 h	1.46 (1.04–2.06)	0.03	1.46 (1.04–2.05)	0.03
Anhepatic phase (min)	1.00 (1.00–1.01)	0.16		
Operation time (h)	1.00 (0.93–1.09)	0.93		

CIT, cold ischemia time; DBCD, donation after brain and cardiac death; DBD, donation after brain death; DCD, donation after circulatory death; HR: hazard ratio; MELD, Model for End-Stage Liver Disease; OS, overall survival; PSM, propensity score-matched.

The early postoperative complications were compared in the PSM cohort (Table 2). Patients in the infection group were more likely to have postoperative effusion (noninfection group: 20.85 vs. infection group: 66.36%, $P<0.0001$), infection (noninfection group: 14.00 vs. infection group: 66.97%, $P<0.0001$), abdominal bleeding (noninfection group: 4.26 vs. infection group: 7.76%, $P=0.0076$), and biliary complications (noninfection group: 1.83 vs. infection group: 4.72%, $P=0.0032$). However, there existed no significant difference in postoperative abscess, acute rejection, early allograft dysfunction (EAD), and vascular complications between these two groups (all $P>0.05$).

The median follow-up time was 25.3 months for the noninfection group and 18.1 months for the infection group. We compared the short-term survival between the noninfection and infection groups, including 30-day and 90-day survival. Patients in the infection group had shorter 30-day and 90-day survival than those in the noninfection group (Fig. 2A, B, both $P<0.001$). In addition, the OS between the two groups was also explored. Patients in the infection group also had shorter OS than those in the noninfection group (Fig. 2C, $P=0.009$).

Cox proportional hazards regression analysis of the risk factors for the OS in the infection group

Since patients in the infection group had shorter OS, we explored the risk factors for the OS in the infection group using the univariable and multivariable Cox proportional hazards regression analyses (Table 3).

In the univariate analysis, it was shown that MELD score and CIT were significantly different (both $P<0.05$), and the multivariate analysis further revealed that MELD score and CIT were risk factors for the OS in the infection group (MELD score, HR = 1.62, 95% CI: 1.16–2.27, $P=0.02$; CIT, HR = 1.46, 95% CI: 1.04–2.05, $P=0.03$).

Impact of infection sites on the prognosis of LT patients

In the infection group, 657 patients had 534 pulmonary, 193 abdominal, 62 biliary tract, 28 bloodstream, 11 urinary tract and 34 other infections (Table S1, Supplemental Digital Content 2, http://links.lww.com/JS9/B781). To investigate the infection site on the prognosis of LT, we divided the infection group into the nonpulmonary ($n=123$) and pulmonary ($n=534$) groups, the nonabdominal ($n=464$) and abdominal ($n=193$) groups and the nonbiliary tract ($n=595$) and biliary tract ($n=62$) groups.

As shown in Table S2 (Supplemental Digital Content 2, http://links.lww.com/JS9/B781), it was found that patients in the pulmonary group were more likely to have postoperative effusion (nonpulmonary group: 50.41 vs. pulmonary group: 70.04%, $P<0.0001$) and infection (nonpulmonary group: 34.15 vs. pulmonary group: 74.53%, $P<0.0001$), and less likely to have postoperative abscess (abscess, nonpulmonary group: 34.96 vs. pulmonary group: 10.11%, $P<0.0001$) and EAD (nonpulmonary group: 30.08 vs. pulmonary group: 20.79%, $P=0.0261$) than those in the nonpulmonary group. No significant difference was found in both short-term survival and OS between these two groups (Figure S1A, B, C, Supplemental Digital Content 2, http://links.lww.com/JS9/B781, all $P>0.05$).

Besides, no difference was observed except for a higher proportion of postoperative infection in the nonabdominal group (Table S2, Supplemental Digital Content 2, http://links.lww.com/JS9/B781, nonabdominal group: 69.61 vs. abdominal group: 60.62%, $P=0.0256$). Similarly, no significant difference was found in both short-term survival and OS between these two groups (Figure S2A, B, C, all $P>0.05$, Supplemental Digital Content 2, http://links.lww.com/JS9/B781).

In addition, there existed no significant difference in early postoperative complications between the nonbiliary tract and biliary tract groups (Table S2, Supplemental Digital Content 2, http://links.lww.com/JS9/B781, all $P > 0.05$), and both short-term survival and OS had no significant difference between these two groups (Figure S3A, B, C, all $P > 0.05$, Supplemental Digital Content 2, http://links.lww.com/JS9/B781).

Impact of the number of infection sites on the prognosis of LT patients

Based on the number of infection sites, we further divided the infection group into the number = 1 ($n = 482$) and number ≥ 2 ($n = 175$) groups. Firstly, we compared the early postoperative complications between the number = 1 and number ≥ 2 groups (Table 4). Patients in the number ≥ 2 group were more likely to have postoperative effusion (number ≥ 2 group: 75.43 vs. number = 1 group: 63.07%, $P = 0.0030$) and infection (number ≥ 2 group: 75.43 vs. number = 1 group: 63.90%, $P = 0.0055$) than those in the number = 1 group.

Secondly, it was revealed that patients in the number ≥ 2 group had shorter 30-day and 90-day survival than those in the number = 1 group (Fig. 3A, B, both $P < 0.05$). Besides, the OS had no significant difference between these two groups (Fig. 3C, $P > 0.05$).

Table 4

Early postoperative complications between the number = 1 and number ≥ 2 groups.

Types of early postoperative complications	Number = 1 group ($n = 482$)	Number ≥ 2 group ($n = 175$)	*P*
Effusion (%)	304 (63.07)	132 (75.43)	0.0030
Abscess (%)	74 (15.35)	23 (13.14)	0.4803
Infection (%)	308 (63.90)	132 (75.43)	0.0055
Abdominal bleeding (%)	37 (7.68)	14 (8.00)	0.8910
Acute rejection (%)	12 (2.49)	5 (2.86)	0.7931
EAD (%)	115 (23.86)	33 (18.86)	0.1749
Biliary complications (%)	25 (5.19)	6 (3.43)	0.3475
Vascular complications (%)	15 (3.11)	2 (1.14)	0.1599

EAD, early allograft dysfunction.

Subgroup analysis

Infections were found to increase mortality fourfold in patients with cirrhosis[23]. Moreover, several studies have reported that

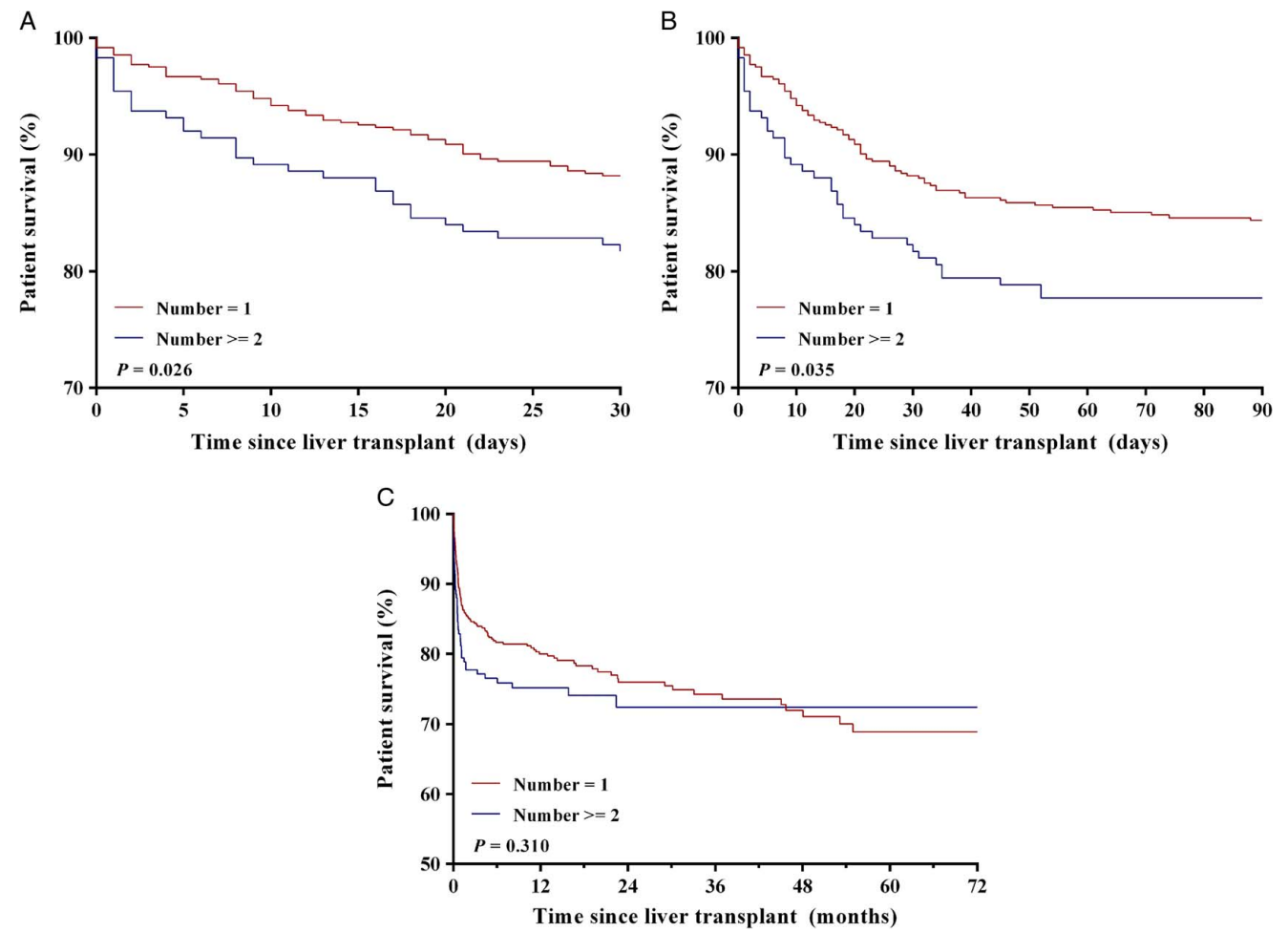

Figure 3. Short-term survival and OS between the number = 1 and number ≥ 2 groups. (A). Patients in the number ≥ 2 group had shorter 30-day survival than those in the number = 1 group ($P = 0.026$); (B). Patients in the number ≥ 2 group had shorter 90-day survival than those in the number = 1 group ($P = 0.035$); (C). OS had no significant difference between the number = 1 and number ≥ 2 groups ($P > 0.05$).

liver transplant recipients with hepatocellular carcinoma (HCC) had worse long-term survival than those without[24,25]. To avoid the impact of HCC on OS, we explored further the impact of non-HCC cirrhosis on the prognosis of LT patients in the subgroup analysis. Of the 657 patients who had preoperative infection, there were 304 non-HCC cirrhotic patients. The PSM analysis was also conducted, and all variables with significant differences initially also lost significance between the noninfection ($n = 301$) and infection ($n = 301$) groups. The baseline characteristics were shown in Table S3 (Supplemental Digital Content 2, http://links.lww.com/JS9/B781) before and after the PSM analysis.

The early complications after LT were also compared in Table S4 (Supplemental Digital Content 2, http://links.lww.com/JS9/B781). Patients in the infection group had a higher proportion of postoperative effusion (noninfection group: 23.92 vs. infection group: 61.46%, $P < 0.0001$), infection (noninfection group: 14.62 vs. infection group: 59.14%, $P < 0.0001$), abdominal bleeding (noninfection group: 3.65 vs. infection group: 8.97%, $P = 0.0073$), and acute rejection (noninfection group: 0.66 vs. infection group: 3.32%, $P = 0.0197$) than those in the noninfection group. No significant difference was observed in postoperative abscess, EAD, biliary, and vascular complications (all $P > 0.05$).

The median follow-up time was 26.4 months for the noninfection group and 24.3 months for the infection groups. Patients in the infection group were also found to have shorter 30-day and 90-day survival than those in the noninfection group (Fig. 4A, B, both $P < 0.001$). In addition, patients in the infection group had shorter OS than those in the noninfection group as well (Fig. 4C, $P = 0.007$).

Discussion

Nowadays, many studies have made great efforts in surgical site infection, which provides new insight into the prevention, diagnosis, and treatment of surgical site infection[26–28]. Preoperative infection can also cause damage to patients who receive surgery, which should also be taken seriously. Nevertheless, current understanding of preoperative infection in liver recipients remains incomprehensive. Therefore, based on a national retrospective cohort in China, this study investigated the impact of preoperative infection on liver transplant recipients' prognosis using the PSM analysis. In particular, we also discussed the influence of the types and number of infection sites on the outcomes of LT, which can provide more accurate management

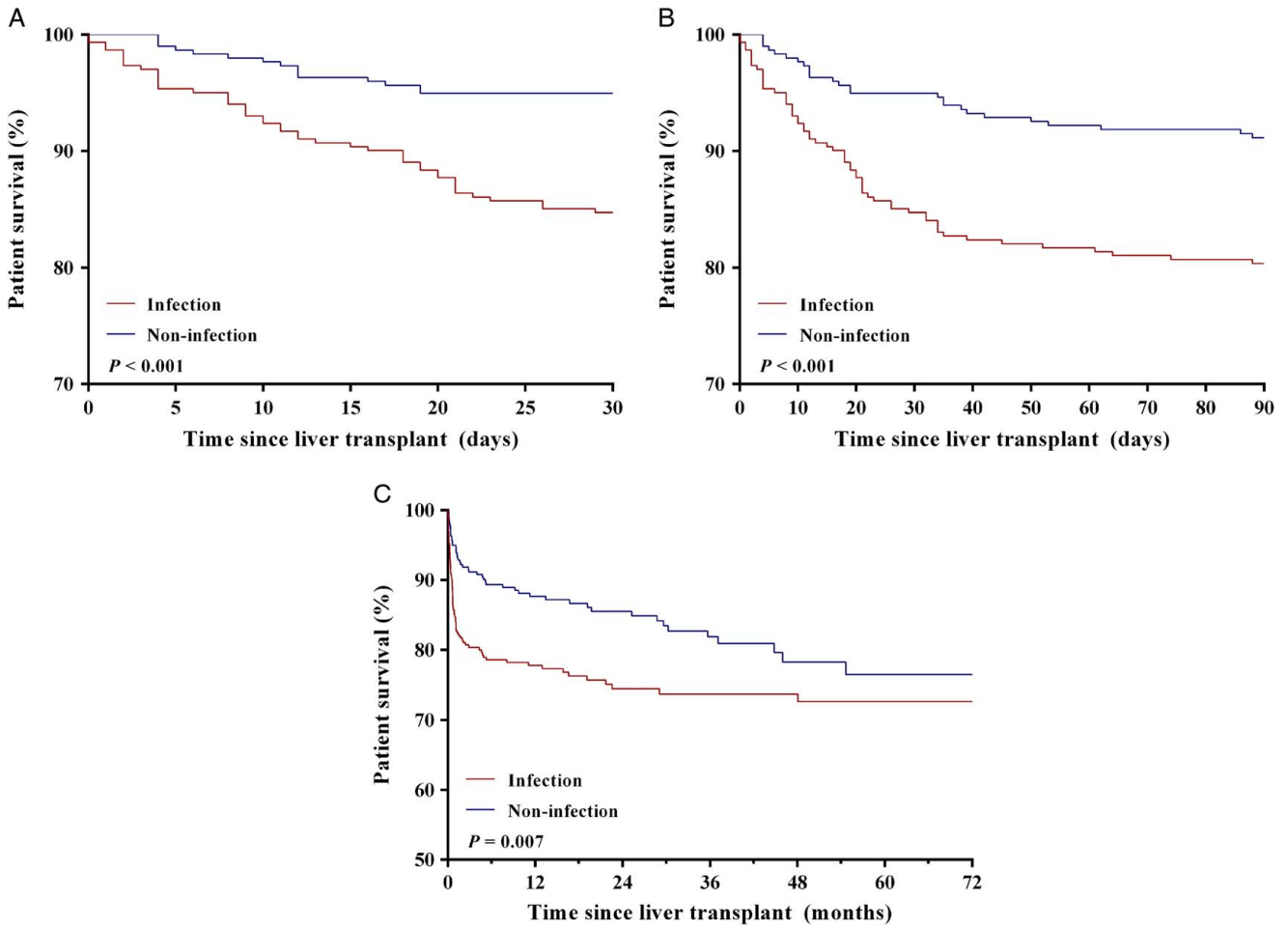

Figure 4. Short-term survival and OS between the noninfection and infection groups with cirrhosis. (A). Patients in the infection group were found to have shorter 30-day survival than those in the noninfection group ($P < 0.001$); (B). Patients in the infection group were found to have shorter 90-day survival than those in the noninfection group ($P < 0.001$); (C). Patients in the infection group had shorter OS than those in the noninfection group ($P = 0.007$).

measures for liver transplant recipients with preoperative infection.

Firstly, we evaluated the impact of preoperative infection on the outcome of all liver transplant recipients using the PSM analysis. Compared to recipients without preoperative infection, those with preoperative infection were more likely to have early postoperative complications, including effusion, infection, abdominal bleeding, and biliary complications. The previous study by Ying *et al*.[20] has also shown that preoperative infection within 2 weeks can cause postoperative infection in liver transplant recipients, which is consistent with the conclusions in Bertuzzo *et al*.'s study[15]. Similarly, septic shock within 28 days before LT was associated with higher mortality 90 days after LT. In our series, recipients with preoperative infection also had shorter OS than those without[29]. Hence, it was concluded that preoperative infection can result in more early postoperative complications and shorter survival.

Secondly, we further explored the risk factors for the OS of liver transplant recipients with preoperative infection using the Cox proportional hazards regression analysis. MELD score and CIT were risk predictors for the OS. It was inferred that the higher MELD score and longer CIT, the shorter OS. It is generally believed that MELD score and CIT can influence the OS of LT in several studies[30,31]. Moreover, the use of immunosuppressive regimens will limit the host ability to resist pathogens[32], thereby affecting the outcomes of liver transplant recipients. Therefore, the use of immunosuppressive regimens in patients with preoperative infection should also receive individualized attention.

Thirdly, since recipients with preoperative infection had different infection sites, it is interesting to explore the impact of infection sites on the prognosis of LT. Unlike other studies[14–16], pulmonary infections account for the majority in this study, followed by abdominal and biliary tract infections. Compared to recipients with preoperative infection at other sites, the proportions of early postoperative complications were different in those with preoperative pulmonary infection, and both short-term survival and OS showed no great differences. Besides, only the proportion of postoperative infection was found to be significantly different between recipients with preoperative abdominal infection and with infection at other sites, and short-term survival and OS also showed no great differences. Moreover, no significant differences were found in early postoperative complications, short-term survival and OS between recipients with preoperative biliary tract infection and with infection at other sites. In view of this, different preoperative infection sites may influence the early postoperative complications in liver transplant recipients, rather than survival.

Furthermore, we also assessed the impact of the number of infection sites on the prognosis of LT liver transplant recipients. It was found that recipients with multiple-site infection were more likely to have postoperative effusion and infection than those with single-site infection. In addition, recipients with multiple-site infection also had shorter short-term survival than those with single-site. Although relatively less common, multisite infection can cause more severe consequences than single-site infection[33,34]. Hence, it was speculated that the number of infection sites can also influence both early postoperative complications and survival in liver transplant recipients. Different infection sites and the number of infection sites can have different effects on the outcomes of liver transplant recipients, and hierarchical and refined management is required.

Patients with cirrhosis are prone to develop infection, which may further cause organ failure and even death[35,36]. The impact of cirrhosis on the prognosis of liver transplant recipients with preoperative infection was further explored in the subgroup analysis. After the PSM analysis, it was revealed that recipients with preoperative infection were more likely to have postoperative effusion, infection, abdominal bleeding, and acute rejection than those without. Incicco *et al*.[37] also found that preoperative infection was an independent risk factor of postoperative infection in cirrhotic patients receiving LT. There exist no significant difference in either short-term or long-term survival in their study, while we found that recipients with preoperative infection had shorter survival than those without. Patients without preoperative infection had a higher prevalence of HCC than those with in their study, and liver transplant recipients with HCC have been reported to have worse long-term survival compared to those without[24,25], which may lead to different results. Furthermore, the short-term mortality of cirrhosis patients with preoperative infection was found to be higher compared to all infected patients in our study. Hence, patients with cirrhosis may need more care if they are infected before LT.

There existed several limitations in this study. Firstly, although we considered that all liver transplant recipients with preoperative infection received treatment since Chinese experts' consensus on prevention and control of multidrug resistance organism healthcare-associated infection was published in 2015[38], preoperative infection treatment is not recorded in the CLTR database and treatment methods may be different in different centers. Secondly, the aetiologies of preoperative infection are not fully recorded, hence this study did not consider whether the preoperative infection was caused by bacterial, fungal infections, or other aetiologies. Finally, some preoperative variables and late postoperative complications were missing, and some patients were excluded, which may cause some bias in this study. Therefore, more clinical data needs to be collected to further explore the impact of preoperative infection on the outcomes of liver transplant recipients.

Conclusion

In summary, preoperative infection can result in a higher incidence of early postoperative complications and shorter survival in liver transplant recipients. Different infection sites and the number of infection sites will also influence the prognosis of liver transplant recipients. Early preoperative infection prevention is recommended in liver transplant recipients.

Ethical approval

This study was performed in accordance with the Declaration of Helsinki and approved by the CLTR database (No. 20230007).

Consent

Informed consent was waived as previously collected data that did not include personally identifiable information were used.

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Author contribution

X.X.: the guarantor of this work; Z.X., Y.S., and J.L.: study design and manuscript drafting; C.X. and Z.Z.: statistical analysis; J.L., R.S., W.S., and Z.L.: data acquisition, analysis, and interpretation; S.Z., Y.Y., J.Y., and X.W.: critical revision of the manuscript.

Conflicts of interest disclosure

The authors have declared no conflicts of interest.

Research registration unique identifying number (UIN)

Not applicable. This study did not involve human participants.

Guarantor

Xiao Xu.

Data availability statement

All data relevant to the study are included in the article.

Provenance and peer review

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