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Advancing health equity through surgery

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Advancing health equity through surgery

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Table of contents

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Editorial: Advancing health equity through surgery: a review of recent contributions

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Editorial on the Research Topic
Advancing health equity through surgery: a review of recent contributions

The pursuit of health equity remains a moral imperative in modern surgical practice. The articles in this section contribute valuable insights into advancing health equity in various surgical disciplines. Each paper, whether explicitly or implicitly, serves to broaden our understanding of how surgical interventions can be both a tool and a metric for health equity.

Clinical studies with equity implications

Xiaobin et al. present a prediction model for hepatic alveolar hydatid disease, an ailment that disproportionately affects marginalized communities. This model could be an essential tool for equitable healthcare resource allocation. Similarly, Nie et al. discuss pyogenic liver abscesses, emphasizing their experience in a traditional Chinese hospital, thereby spotlighting the need for culturally-sensitive healthcare approaches.

Surgical techniques and health equity

Yao et al. explore the use of a trimodal prehabilitation model in lung cancer surgery. By tailoring preoperative care to patient-specific needs, they lay the groundwork for more equitable surgical outcomes. JinHua et al. examine a drainage technique for liver abscesses that could offer a more accessible treatment option for medically underserved populations.

Racial and ethnoracial considerations

Wu et al. and Lv et al. directly confront issues of ethnoracial disparity in organ transplantation. Their work contributes vital data to our understanding of how racial and ethnic factors influence both waiting-list and post-transplant prognosis. These studies serve as an urgent call to address these disparities systemically.

Age and comorbidity factors in health equity

Lv et al. delve into the often-overlooked subject of how age and metabolic syndrome affect treatment outcomes in prostate surgery, signaling the need for an equity-focused approach to comorbidity assessment. Bi et al. add to this discourse by investigating diastolic dysfunction in liver transplantation, highlighting a potential health equity consideration in transplant eligibility.

Optimizing care for vulnerable populations

Zhou et al. investigate optimal oxycodone dosing for elderly patients undergoing gastrointestinal cancer surgery. By focusing on a vulnerable demographic, their work underscores the importance of age-sensitive care protocols in advancing health equity.

Conclusion and future directions

The collective contributions in this section underscore the profound need for surgery to address health inequities. Future research must further delineate how surgical interventions can be optimized across diverse populations, thereby ensuring that the promise of health equity is not merely aspirational but actionable.

We look forward to additional submissions that explore the vast complexities of health equity in surgical practice, shedding light on the systemic changes required to ensure equitable surgical care for all.

By weaving these threads together, this section illustrates the multifaceted ways in which surgical research and practice can advance health equity. We invite future contributors to add to this crucial discourse.

Author contributions

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Conflict of interest

The author declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The predictive value of revised diastolic dysfunction in outcomes of liver transplantation: A propensity score matching analysis

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Background: Diastolic dysfunction (DD), one of the earliest signs of cirrhotic cardiomyopathy (CCM), is included in the revised 2019 CCM criteria. Nonetheless, relevant research regarding the effects of revised DD on post-liver transplantation (LT) outcomes remains limited.
Methods: This retrospective study enrolled patients who underwent LT for decompensated cirrhosis, from January 2018 to March 2021. Patients were divided into DD and non-DD groups. Clinical data were collected. Patients were followed up with, for at least 1 year post-LT; cardiovascular adverse events (AEs) and survival status were recorded. Risk factors were identified using 1:2 propensity score matching (PSM), after adjusting for confounding factors. The caliper value was set to 0.02.
Results: Of 231 patients, 153 were diagnosed with DD (male, 81.8%; mean age, 51.5 ± 9.5 years). Nineteen patients with DD died within 1 year, post-LT. After PSM, 97 and 60 patients were diagnosed with and without DD, respectively. Patients with DD had longer intensive care unit (ICU) stays, higher perioperative cardiovascular AEs, and higher mortality rates than those without DD. In a multivariate analysis, interventricular septum (IVS), left atrial volume index (LAVI), and potassium levels were independent prognostic factors of perioperative cardiovascular AEs, while a decreased early diastolic mitral annular tissue velocity (e'), increased neutrophil-to-lymphocyte ratio (NLR) and tumor markers were predictors of mortality within 1 year post-LT after PSM ($P < 0.05$).

Abbreviations

AEs, adverse events; AFP, alpha-fetoprotein; BUN, blood urine nitrogen; CCM, cirrhotic cardiomyopathy; CCC, cirrhotic cardiomyopathy consortium; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CRP, C-reactive protein; DD, diastolic dysfunction; e', early diastolic mitral annular tissue velocity; E/e', early diastolic trans-mitral flow to early diastolic mitral annular tissue velocity; EDV, end-diastolic volume; EDT, E-wave deceleration time; GLS, global longitudinal strain; ICU, intensive care unit; IVRT, isovolumetric relaxation time; IVS, interventricular septum; IVC, inferior vena cava; LT, liver transplantation; LAVI, left atrial volume index; LVDS, left ventricle end-systolic internal diameter; LVDD, left ventricle end-diastolic internal diameter; LVPW, left ventricular posterior wall; LVEF, left ventricular ejection fraction; MPA, main pulmonary artery; MELD, model for end-stage liver disease; NLR, neutrophil-to-lymphocyte ratio; PSM, propensity score matching; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; PASP, pulmonary arterial systolic pressure; QTc, QT interval after correction; RVW, right ventricle wall; SII, systemic immune-inflammation index; TRV, tricuspid regurgitation maximum velocity; TAPSE, tricuspid annular plane systolic excursion; TDE, time-delay estimation; TRV, tricuspid regurgitation maximum velocity.

Conclusion: Cardiac DD may contribute to perioperative cardiovascular AEs and mortality post-LT. Clinicians should be aware of decompensated cirrhosis in patients with DD.

KEYWORDS

decompensated cirrhosis, cirrhotic cardiomyopathy, liver transplantation, adverse events, mortality

Introduction

Cirrhotic cardiomyopathy (CCM) is defined as impaired contractility due to stress and/or diastolic dysfunction (DD) with electrophysiological abnormalities (1, 2), which is associated with a high incidence of complications and poor survival after liver transplantation (LT) (3, 4). The prevalence of CCM is approximately 33%–53% in patients on the transplant waiting list (5). Some studies have shown that early to late diastolic trans-mitral flow velocity (E/A), isovolumetric relaxation time (IVRT), and time-delay estimation (TDE) are prognostic markers of CCM (6).

DD, as one of the earliest signs of CCM, was entirely updated in the revised 2019 criteria (7) of the Cirrhotic Cardiomyopathy Consortium (CCC), including septal early diastolic mitral annular tissue velocity (e'), early diastolic trans-mitral flow to early diastolic mitral annular tissue velocity (E/e'), left atrial volume index (LAVI), and tricuspid

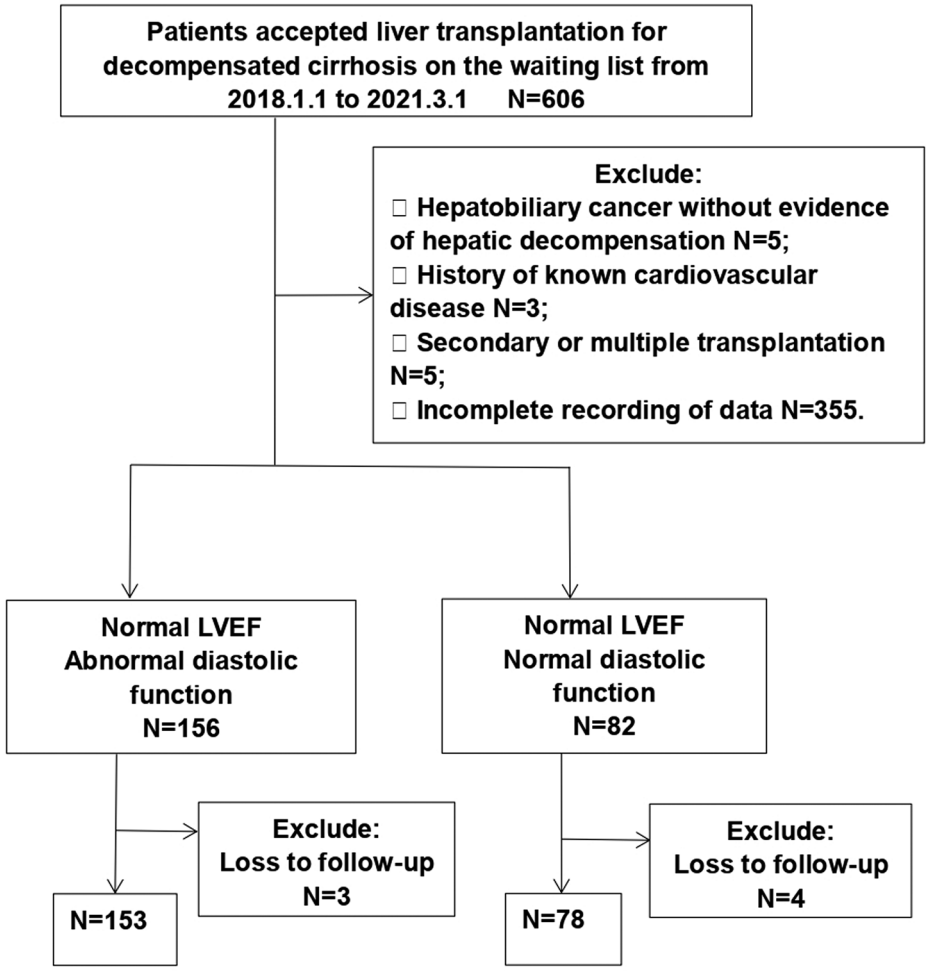

FIGURE 1
Patient flow diagram.

TABLE 1 Comparisons of baseline characteristics between patients with and without DD.

	Before PSM			After PSM		
	With DD $N = 153$	Without DD $N = 78$	P	With DD $N = 97$	Without DD $N = 69$	P
Age			0.004			0.724
<45	26 (17.0%)	24 (30.8%)		23 (23.7%)	17 (24.6%)	
45-	60 (39.2%)	38 (48.7%)		48 (49.5%)	37 (43.6%)	
55-	48 (31.4%)	12 (15.4%)		22 (22.7%)	11 (15.9%)	
65-	19 (12.4%)	4 (5.1%)		4 (4.1%)	4 (5.8%)	
Sex			0.131			0.946
Male	121 (79.1%)	68 (87.2%)		84 (86.6%)	60 (67.0%)	
Female	32 (20.9%)	10 (12.8%)		13 (13.4%)	9 (13.0%)	
BMI			0.074			0.143
<24	58 (37.9%)	38 (48.7%)		37 (38.1%)	35 (50.7%)	
24–27.9	73 (47.7%)	25 (32.1%)		44 (45.4%)	21 (30.4%)	
≥28	22 (14.4%)	15 (19.2%)		16 (16.5%)	13 (18.8%)	
Smoking	51 (33.3%)	33 (42.3%)	0.180	37 (38.1%)	27 (39.1%)	0.898
Alcohol	44 (28.8%)	30 (38.5%)	0.135	31 (32.0%)	25 (36.2%)	0.566
Hypertension	21 (13.7%)	2 (2.6%)	0.007	1 (1.0%)	1 (1.4%)	0.809
Diabetes	38 (24.8%)	9 (11.5%)	0.018	15 (15.5%)	6 (8.7%)	0.196
Anemia			0.073			0.050
No	54 (35.3%)	15 (19.2%)		37 (38.1%)	14 (20.3%)	
Mild	52 (34.0%)	31 (39.7%)		30 (30.9%)	27 (39.1%)	
Moderate	41 (26.8%)	27 (34.6%)		28 (28.9%)	23 (33.3%)	
Severe	6 (3.9%)	5 (6.4%)		2 (2.1%)	5 (7.2%)	
Etiology			0.627			0.854
Alcohol	12 (7.8%)	9 (11.5%)		9 (9.3%)	6 (8.7%)	
Hepatitis B	127 (83.0%)	63 (80.8%)		83 (85.6%)	58 (84.1%)	
Autoimmune	14 (9.2%)	6 (7.7%)		5 (5.2%)	5 (7.2%)	

PSM, propensity score matching; DD, diastolic dysfunction; BMI, body mass index. P-value < 0.05 was regarded as statistically significant using Chi-square test or Fisher's exact test.

regurgitation maximum velocity (TRV). Nonetheless, relevant research is limited.

This study aimed to investigate the effects and predictive value of revised DD on post-LT outcomes, based on the revised 2019 CCC criteria.

Materials and methods

Study design and participant selection

This retrospective study enrolled patients aged 18–70 years, diagnosed with decompensated cirrhosis (8) at the Affiliated Hospital of Qingdao University, Qingdao, China, between January 2018 and March 2021. Patients were divided into two groups (DD or non-DD group), according to echocardiographic examinations of cardiac diastolic function a week before operation, based on the revised 2019 CCC criteria (9–11). DD was determined if three of the following criteria were met: E/e' > 15, LAVI > 34 ml/m^2, e' < 7 cm/s or TRV > 2.8 m/s. Patients who had known heart disease pre-transplant were excluded. The flow diagram of the study is illustrated in **Figure 1**. The study was approved by Clinical Trials (NCT04976764) and the Ethics Committee of the Affiliated Hospital of Qing Dao University (QYFYWZLL 26462). All involved persons gave their

TABLE 2 Comparisons of routine laboratory test results and inflammatory markers between patients with and without DD.

	Before PSM			After PSM		
	With DD $N = 153$	Without DD $N = 78$	P	With DD $N = 97$	Without DD $N = 69$	P
Erythrocytes	3.5 (2.9,4.1)	3.0 (2.6,3.9)	0.007	3.5 (2.9,4.2)	3.0 (2.6,3.9)	0.009
Hemoglobin	107.3 ± 28.0	96.5 ± 23.7	0.004	108.6 ± 28.5	96.5 ± 23.5	0.004
Albumin	31.9 (28.0,36.8)	33.7 (29.0,38.0)	0.040	32.2 (28.1,37.9)	34.3 (29.0,38.0)	0.098
CA199	23.0 (12.5,51.2)	20.0 (7.7,38.5)	0.408	21.8 (9.7,50.7)	16.5 (7.4,34.0)	0.041
Inflammatory markers						
SII	233.7 (143.2,466.3)	239.4 (116.2,582.3)	0.286	240.3 (150.5,476.8)	231.1 (114.9,571.7)	0.681
NLR	2.9 (2.0,5.6)	3.4 (2.2,8.1)	0.256	3.1 (2.1,6.6)	3.4 (1.9,8.6)	0.866
PLR	85.0 (64.9,161.2)	98.3 (69.5,169.0)	0.200	86.0 (62.0,154.1)	96.3 (69.3,162.9)	0.219
PNI	37.1 (30.9,43.6)	38.6 (34.2,45.3)	0.139	37.5 ± 7.9	40.1 ± 7.8	0.187
C-reactive protein	9.2 (2.8,28.8)	13.5 (4.2,27.3)	0.942	8.4 (2.4,33.0)	14.0 (4.0,29.3)	0.969
Procalcitonin	0.7 (0.3,2.4)	0.5 (0.2,1.3)	0.152	0.7 (0.3,2.7)	0.5 (0.2,1.4)	0.112

CA19-9, carbohydrate antigen 19-9; SII, systemic immune-inflammation index; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index. P-value < 0.05 was regarded as statistically significant using Student's t-test or Mann-Whitney U test. Please see Appendix 1 Supplementary Table S1 for additional related results of routine laboratory test.

informed consent (written or verbal, as appropriate) prior to study inclusion.

Statistical analysis

Enumeration data are presented as frequencies (percentages) and the significance is determined by chi-square test or Fisher's exact test. Intergroup comparisons were performed using a Student's t-test or Mann-Whitney U test. Multivariate logistic regression analysis models were used to identify independent and predictive factors for poor outcomes. Survival status was assessed using Kaplan–Meier curves and the log-rank test. Significant variables in the univariate analysis were tested in a multivariate analysis using Cox's proportional hazard model, to identify the predictors of survival. The caliper value of propensity score matching (PSM), adjusted for confounders, was set to 0.02. A P-value < 0.05 was regarded as statistically significant. SPSS (version 26.0, IBM, New York, USA) was used to analyze the data.

Results

Baseline characteristics and serological indexes

Baseline characteristics of the 231 patients were collected (male, 81.8%; mean age 51.5 ± 9.5 years) (**Table 1**). A total of 153 (66.2%) patients in the DD group were diagnosed with DD with normal left ventricular ejection fraction, according to the 2019 CCC criteria. Before PSM, the patients with DD tended to be older ($P < 0.01$) and were more likely to have hypertension ($P < 0.01$) and diabetes ($P < 0.05$), in comparison to patients without DD. After PSM, there were 97 patients in the DD group and 69 patients in the non-DD group, with no notable differences in sex, age, smoking status, etiology, and basic diseases, including hypertension and diabetes.

A comparison of the serological indices and inflammatory markers in **Table 2** showed that erythrocyte, hemoglobin, and carbohydrate antigen (CA) 19-9 levels differed significantly between the groups, after PSM ($P < 0.05$). No differences were noted in the systemic immune-inflammation index (SII), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR) between the groups ($P > 0.05$). Additional results of routine laboratory tests, including complete blood cell counts, liver function, renal function, blood lipids, electrolytes, glucose, myocardial enzymes, coagulation function, and other tumor markers, are described in **Supplementary Table S1** of Appendix 1.

More echocardiographic abnormalities in patients with DD

There were significant differences in the septal e', E/e', and tricuspid regurgitation (TR) maximum velocity between the groups ($P < 0.01$). Moreover, it was found that pulmonary artery systolic pressure, left ventricular pulse wave, and interventricular septum (IVS) were higher in the DD group

TABLE 3 Comparisons of echocardiography parameters and QT interval between patients with and without DD.

	Before PSM			After PSM		
	With DD $N = 153$	Without DD $N = 78$	P	With DD $N = 97$	Without DD $N = 69$	P
LVEF	64.0 (62.0,66.0)	64.0 (62.0,66.0)	0.981	64.0 (62.0,66.0)	64.0 (62.0,66.0)	0.972
e'	6.3 (5.5,6.9)	7.9 (7.3,9.3)	0.000	6.3 (5.5,6.8)	8.0 (7.3,9.5)	0.000
E/e'	11.4 (9.7,12.9)	9.1 (8.2,10.6)	0.000	11.5 (10.0,13.1)	9.3 (8.2,10.0)	0.000
PASP	37.0 (34.8,38.0)	28.0 (25.0,30.0)	0.000	37.0 (34.8,38.0)	28.5 (25.0,30.8)	0.000
TRV	2.8 (2.8,2.9)	2.4 (2.2,2.5)	0.000	2.8 (2.8,2.9)	2.4 (2.2,2.5)	0.000
LAVI	24.7 (20.3,34.3)	22.8 (17.9,29.2)	0.275	24.6 (20.8,33.4)	23.4 (17.7,30.3)	0.350
LVDS	3.1 (2.9,3.2)	3.0 (2.8,3.2)	0.238	3.1 ± 0.3	3.1 ± 0.3	0.224
LVDD	4.8 (4.5,5.0)	4.7 (4.5,5.0)	0.707	4.7 (4.5,4.9)	4.7 (4.6,4.9)	0.309
EDV	108.5 (95.0,121.8)	103.0 (100.3,115.5)	0.051	102.0 (94.0,112.8)	103.0 (100.3,115.5)	0.146
EDT	184.7 ± 53.4	193.4 ± 46.8	0.390	183.0 ± 50.3	190.3 ± 49.6	0.444
LVPW	1.0 (1.0,1.0)	1.0 (1.0,1.0)	0.001	1.0 (1.0,1.0)	1.0 (1.0,1.0)	0.032
IVS	1.0 (1.0,1.2)	1.0 (1.0,1.0)	0.000	1.0 (1.0,1.1)	1.0 (1.0,1.0)	0.003
IVC	15.0 (14.0,16.0)	15.0 (14.5,16.0)	0.209	1.5 (1.5,1.7)	1.5 (1.5,1.7)	0.201
QT	446.3 ± 27.6	441.8 ± 31.7	0.104	403.6 ± 36.6	392.1 ± 29.9	0.149
QTc	444.5 (429.0,463.0)	440.0 (422.0,457.0)	0.085	443.5 (429.0,462.8)	440.0 (420.5,456.5)	0.563
TAPSE	2.2 (2.0,2.5)	2.3 (2.1,2.5)	0.162	2.3 (2.0,2.5)	2.2 (2.1,3.5)	0.117
RVW	0.4 (0.4,0.4)	0.4 (0.4,0.4)	0.978	0.4 (0.4,0.4)	0.4 (0.4,0.4)	0.919
MPA	2.4 (2.2,2.5)	2.3 (2.3,2.3)	0.670	2.4 (2.3,2.5)	2.3 (2.3,2.3)	0.250

LVEF, left ventricular ejection fraction; e', early diastolic mitral annular tissue velocity; E/e', early diastolic trans-mitral flow to early diastolic mitral annular tissue velocity; PASP, pulmonary arterial systolic pressure; TRV, tricuspid regurgitation maximum velocity; LAVI, left atrial volume index; LVDS, left ventricle end-systolic internal diameter; LVDD, left ventricle end-diastolic internal diameter; DD, diastolic dysfunction; EDV, end-diastolic volume; EDT, E-wave deceleration time; LVPW, left ventricular posterior wall; IVS, interventricular septum; IVC, inferior vena cava; QTc, QT interval after correction; TAPSE, tricuspid annular plane systolic excursion; RVW, right ventricle wall; MPA, main pulmonary artery; PSM, propensity score matching.
P-value < 0.05 was regarded as statistically significant using Student's t-test or Mann-Whitney U test.

TABLE 4 Comparison of scoring-based estimation and procedure-related data between patients with and without DD.

	Before PSM			After PSM		
	With DD $N = 153$	Without DD $N = 78$	P	With DD $N = 97$	Without DD $N = 69$	P
Child-Pugh			0.003			0.045
A	22 (14.4%)	25 (32.1%)		14 (14.4%)	21 (30.4%)	
B	90 (58.8%)	31 (39.7%)		51 (52.6%)	29 (42.0%)	
C	41 (26.8%)	22 (28.2%)		32 (33.0%)	19 (27.5%)	
Anhepatic time	53.0 (46.0,60.8)	51.5 (44.3,57.8)	0.220	53.5 (46.0,60.8)	51.0 (42.5,56.5)	0.089
Stay time in ICU	3.0 (3.0,5.0)	3.0 (2.0,4.0)	0.003	3.0 (3.0,5.0)	3.0 (2.0,4.0)	0.001
Cardiovascular adverse events						
Perioperative	24 (15.7%)	5 (6.4%)	0.044	15 (15.5%)	3 (4.3%)	0.023
1-year post-LT	28 (18.3%)	9 (11.5%)	0.185	17 (17.5%)	7 (10.1%)	0.183

DD, diastolic dysfunction; PSM, propensity score matching; ICU, intensive care unit; LT, liver transplantation.
P-value < 0.05 was regarded as statistically significant using chi-square test or Mann-Whitney U test.
Please see Appendix 1 Supplementary Table S2 for additional scoring-based estimation.

TABLE 5 Univariable and multivariable logistic regression analysis of perioperative cardiovascular adverse events.

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
(A) Before PSM				
Etiology		0.011		
Alcohol	Reference			
Hepatitis B	0.667 (0.180–2.473)	0.544		
Immune	3.231 (0.700–14.907)	0.133		
Sex	3.371 (1.452–7.824)	0.005		
BUN	1.182 (1.052–1.329)	0.005		
Anhepatic time	1.031 (1.009–1.054)	0.007	1.033 (1.003–1.063)	0.030
Potassium	1.918 (1.087–3.382)	0.025	2.302 (1.115–4.753)	0.024
Sodium	0.870 (0.801–0.944)	0.001		
Myoglobin	0.998 (0.997–1.000)	0.013		
e'	0.722 (0.520–1.001)	0.051		
E/e'	1.142 (0.976–1.335)	0.097		
IVS	1.802 (1.338–2.427)	0.000	1.594 (1.082–2.347)	0.018
LAVI	1.072 (1.021–1.125)	0.005		
Bleeding volume	1.000 (1.000–1.001)	0.035	1.001 (1.000–1.001)	0.046
Volume of blood transfusion				
Plasma	1.090 (1.033–1.151)	0.002		
Erythrocytes	1.001 (1.000–1.001)	0.021		
(B) After PSM				
Sex	4.125 (1.361–12.502)	0.012		
e'	0.558 (0.376–0.829)	0.004		
E/e'	1.289 (1.089–1.526)	0.003		
IVS	2.099 (1.416–3.109)	0.000	2.462 (1.153–5.046)	0.008
LAVI	1.090 (1.033–1.150)	0.002	1.090 (1.001–1.188)	0.047
BUN	1.217 (1.058–1.401)	0.006		
Potassium	2.642 (0.984–7.096)	0.054	14.135 (2.452–81.486)	0.003
Sodium	0.906 (0.819–1.003)	0.057		
Anhepatic time	1.041 (1.012–1.071)	0.005		
Bleeding volume	1.001 (1.000–1.001)	0.063		
Volume of blood transfusion				
Plasma	1.001 (1.000–1.002)	0.002		
Erythrocytes	1.099 (1.025–1.177)	0.008		

BUN, blood urine nitrogen; e', early diastolic mitral annular tissue velocity; E/e', early diastolic trans-mitral flow to early diastolic mitral annular tissue velocity; IVS, interventricular septum; LAVI, left atrial volume index; PSM, propensity score matching. *P*-value < 0.05 was regarded as statistically significant using univariable and multivariable logistic regression analysis.

than in the non-DD group, before and after PSM ($P < 0.01$). The median QT interval was not prolonged ($P > 0.05$). Other echocardiographic characteristics are presented in Table 3.

More serious liver diseases in patients with DD

Patients with DD had an increased Child-Pugh class score before and after PSM ($P = 0.003$ and $P = 0.045$, respectively). No significant differences were observed with respect to cardiac function class, model for end-stage liver disease (MELD) score, physician global assessment score, American Society of Anesthesiology score, bleeding volume, and volume of blood transfusion by PSM (Supplementary Table S2 of Appendix 1). Nonetheless, patients with DD had longer intensive care unit stays than those without DD ($P < 0.05$) (Table 4).

Poor post-LT outcomes in patients with DD

Enrolled patients were followed up, for at least 1 year. In total, 29 patients (12.6%) developed perioperative cardiovascular adverse events (AEs), 24 of whom had DD. Patients with DD frequently experienced perioperative cardiovascular events (15.7% vs. 6.4%, $P < 0.05$) (Table 4). In a multivariate analysis, anhepatic time ($P = 0.030$), potassium levels ($P = 0.024$), IVS ($P = 0.018$), and bleeding volume ($P = 0.046$) were found to be independent predictors of the incidence of perioperative cardiovascular AEs before PSM. Considering age, sex, etiology, smoking status, and basic diseases, IVS ($P = 0.008$), LAVI ($P = 0.047$), and potassium level ($P = 0.003$) were independently correlated with perioperative cardiovascular AEs after PSM (Table 5).

Twenty-one patients (9.10%) with DD died within the first year of follow-up. The causes were mainly AEs, graft rejection, progression of liver disease and sepsis (Table 6). But we found no statistically significant association between DD and each clinical event. The Kaplan–Meier curves in Figure 2 show that patients with DD had lower survival rates than those without DD. In a multivariable Cox regression analysis, carcinoembryonic antigen, e', and left ventricle end-systolic internal diameter were correlated with the occurrence of death, within 1-year post-LT. In the model adjusted by PSM, decreased e', increased NLR and tumor markers were associated with a greater 1-year mortality rate (Table 7).

IVS and e' were the strongest independent prognostic factors for perioperative cardiovascular AEs and mortality, respectively.

Discussion

In CCM, an occult onset process upon encountering environmental stress, such as transplantation, may contribute

TABLE 6 Categories of 1-year mortality post-LT.

	Before PSM			After PSM		
	With DD $N = 153$	Without DD $N = 78$	P	With DD $N = 97$	Without DD $N = 69$	P
Mortality	21 (13.73%)	2 (2.56%)	0.007	14 (14.43%)	2 (2.90%)	0.013
AEs	5 (3.27%)			4 (4.12%)		
Graft rejection	4 (2.61%)			2 (2.06%)		
Progression of liver disease	5 (3.27%)	1 (1.28%)		4 (4.12%)	1 (1.45%)	
Sepsis	6 (3.92%)	1 (1.28%)		4 (4.12%)	1 (1.45%)	
Other	1 (0.65%)					

DD, diastolic dysfunction; AE, adverse events; PSM, propensity score matching.
P-value < 0.05 was regarded as statistically significant using Fisher's exact test.

to rapid progression and even significant mortality rates. The primary outcome of this study showed that DD was related to the occurrence of perioperative cardiovascular AEs and mortality, before and after PSM. Among the echocardiographic parameters, IVS, and e' were the strongest independent prognostic factors for perioperative cardiovascular AEs and mortality, respectively. Upon encountering environmental stress, such as transplantation, impaired contractility fails to adapt to initial changes. Decreased vascular resistance and increased cardiac output increase cardiac preload, resulting in abnormal filling of the ventricle and blood redistribution (12, 13). Histological examination of a heart with CCM revealed edema, cardiomyocyte hypertrophy, nuclear vacuolization, and fibrosis, which occurred in conjunction with enhanced accumulation of collagen. However, we observed that ventricular wall stiffness would partially recover (14–16). Studies have demonstrated that DD increases the risk of cardiovascular AEs post-LT (5, 17). Nonetheless, few studies have reported such correlation based on the 2005 criteria (18).

Furthermore, elevated IVS was the strongest cardiac predictor, increasing the risk of perioperative cardiovascular AEs by 2.4-fold. These results may be attributed to myocardial remodeling, resulting in alterations in the cardiac structure, as onset was earliest in the IVS (19, 20). Decreased e' aided in confirming which patients were at an increasing risk of poor survival, in both univariate and multivariate regression analysis (6, 21). This may reflect progressive stiffness of the myocardium and deteriorating cardiac function (22). Prior studies have revealed association of E/A, E/e', and LAVI with poor survival post-LT (17, 23–26); however, it is not well-suited to apply the E/A ratio owing to its load- and age-dependence (27, 28). In comparison, some previous studies have failed to find any relevance (4, 29). The above mentioned studies did not rule out the influence of confounding factors. The present study adopted the 2019 criteria and performed PSM for risk factors, which reduced the bias in the results.

A prolonged QT interval is the main electrophysiological signature of CCM, which is associated with 30-day cardiovascular AEs and mortality, post-LT (30, 31). In the 2019 CCC consensus, QT prolongation was not warranted, because of its limited value in the diagnosis of CCM (32, 33). Potassium is the major predictive factor of perioperative cardiovascular AEs. Ischemia-reperfusion injury post-LT increase the level of extracellular potassium and reduce the concentration gradient between the inside and outside of the cell. Shortening action potential and impaired conductivity was attributed to altered gating of ion channels, predisposing to malignant arrhythmias (34, 35). Because of the limitations of current study population, possibilities of impaired ion channels cannot be completely excluded (11). Pulmonary arterial hypertension has been shown to be involved in liver fibrosis at the gene level and confers higher mortality (36–38). Cardiac dysfunction was first attributed to the direct effect of alcohol; however, it was revealed to be independent of the etiology (39, 40). Cardiac function deteriorated with the progression of cirrhosis, but showed limited progression with stable cirrhosis within 2 years (25, 28, 41). Pro-B-type natriuretic peptides and troponins have also been described as prognostic markers (42, 43). Nevertheless, this was contradicted by the results of our study. In contrast to the Child-Pugh score, the MELD score showed no impact on the presence of DD because of underestimation of the severity of end-stage liver disease on the waiting list for LT (44).

Given the increased risk of infectious complications, upregulation of inflammatory markers and downregulation of cnidarian complements in both the advancement of cirrhosis and development of CCM were associated with poor survival (21, 45–47). Similarly, NLR was considered an effector, along with SII and PLR, in this study. In addition, all enrolled patients had near-normal systolic function at a resting state maintained by the compensatory pathways of hyperdynamic circulatory state and low systemic vascular resistance (48). Additionally, a very low left ventricular ejection fraction is regarded as a contraindication to LT. Prior studies have

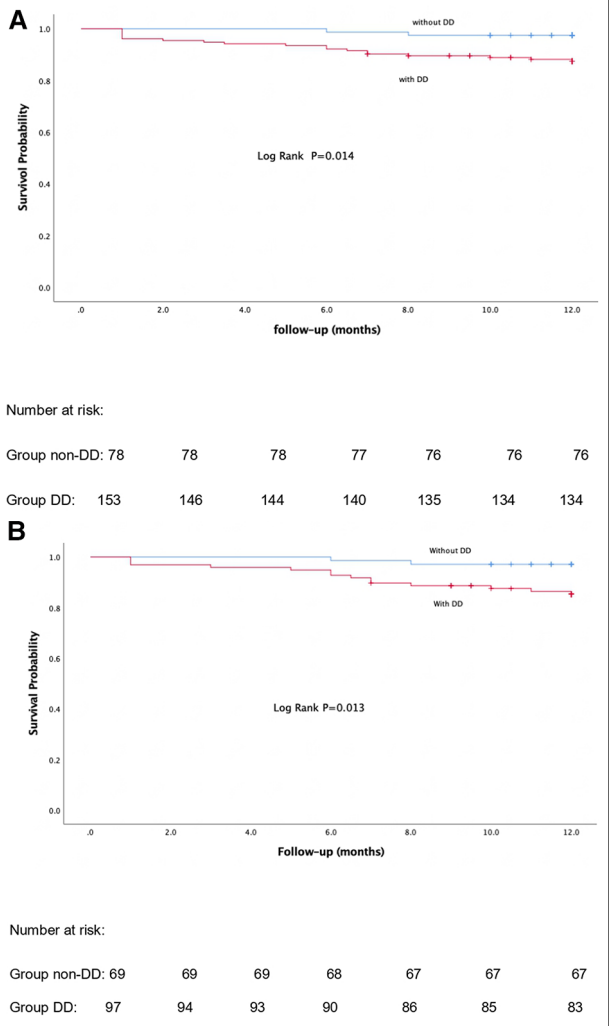

FIGURE 2
Kaplan-Meier curves of 1-year mortality post-LT before and after propensity score matching analysis. (**A**) Before-PSM. (**B**) After-PSM. *P*-value < 0.05 was regarded as statistically significant.

revealed associations between global longitudinal strain and poor survival (42, 49). Due to the limitations of diagnostic tools, we were unable to further confirm the influence of global longitudinal strain.

Our study has several limitations. First, this was a single-center study, thus lacks representativeness. Moreover, it was limited by its retrospective and observational study design. Therefore, prospective and multicenter validation studies are required.

Conclusion

Decompensated cirrhosis with DD accelerates perioperative cardiovascular AEs and 1-year post-transplantation mortality

TABLE 7 Univariable and multivariable cox proportional hazard regression analysis of 1-year mortality post-LT.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
(A) Before PSM				
Platelet	9.379 (1.048–83.925)	0.002		
Neutrophils	1.006 (1.002–1.009)	0.018		
BUN	1.104 (0.988–1.234)	0.081		
SII	1.002 (1.000–1.004)	0.007		
PLR	1.000 (1.000–1.000)	0.005		
NLR	1.002 (1.001–1.004)	0.017		
CRP	1.001 (1.000–1.002)	0.004		
CEA	1.060 (1.009–1.113)	0.001	1.144 (1.031–1.269)	0.011
e'	0.573 (0.385–0.854)	0.006	0.610 (0.408–0.912)	0.016
LVDS	0.200 (0.045–0.883)	0.034	0.153 (0.028–0.824)	0.029
IVS	1.376 (1.021–1.855)	0.036		
Bleeding volume	1.000 (1.000–1.000)	0.037		
(B) After PSM				
Age		0.040		
<45	Reference			
45-	2.800 (0.337–23.256)	0.341		
55-	9.086 (1.118–73.857)	0.039		
65-	10.952 (0.993–120.800)	0.051		
e'	0.545 (0.376–0.788)	0.001	0.570 (0.331–0.981)	0.042
IVS	1.608 (1.179–2.192)	0.003		
Platelet	1.006 (1.003–1.010)	0.000		
SII	1.000 (1.000–1.000)	0.013		
PLR	1.003 (1.001–1.004)	0.005		
NLR	1.055 (0.997–1.118)	0.064	1.023 (1.003–1.043)	0.021
CRP	1.022 (1.008–1.037)	0.003		
AFP	1.000 (1.000–1.000)	0.007	1.000 (1.000–1.000)	0.016
CEA	1.179 (1.076–1.292)	0.000	1.262 (1.009–1.580)	0.042
CA199	1.002 (1.000–1.003)	0.031		
Bleeding volume	1.000 (1.000–1.000)	0.033		

BUN, blood urine nitrogen; SII, systemic immune-inflammation index; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; CEA, carcinoembryonic antigen; e', early diastolic mitral annular tissue velocity; LVDS, left ventricle end-systolic internal diameter; IVS, interventricular septum; AFP, alpha-fetoprotein; CA19-9, carbohydrate antigen 19-9; DD, diastolic dysfunction. *P*-value < 0.05 was regarded as statistically significant using univariable and multivariable cox proportional hazard regression analysis.

rates. Appropriate precedence in decompensated cirrhosis with DD on the waiting list should be considered to ensure timely diagnosis. In PSM analysis, multiple risk factors including IVS, LAVI, e', potassium, and NLR collectively contributed to perioperative cardiovascular AEs and 1-year mortality, highlighting the need for closer post-LT monitoring and management.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Affiliated Hospital of Qing Dao University (QYFYWZLL 26462). The patients/participants provided their written informed consent to participate in this study.

Author contributions

SB made the major contribution to draft the manuscript. YJ obtained institutional review board approval. XN contributed to the data acquisition. WZ and XL assisted in statistical analysis. XJ is the guarantor of the study and made a major contribution to the conception and design of the study and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.1072908/full#supplementary-material.

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Correlation between systemic immune inflammatory index and prognosis of patients with hepatic alveolar hydatid disease and establishment of a nomogram prediction model

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Background: To explore the evaluation value of systemic immune inflammation index (SII) in the prognosis of patients with alveolar hydatid disease, and establish a nomogram prediction model.

Methods: Collect the clinical data of 351 patients undergoing hepatic alveolar hydatid surgery admitted to the Department of Hepatobiliary and Pancreatic Surgery, Affiliated Hospital of Qinghai University from January 2015 to December 2020, calculate the SII value, and use the receiver operating characteristic curve (ROC curve) to determine According to the optimal clinical cut-off value of SII, patients were divided into two groups with high SII and low SII, and the relationship between SII and clinicopathological factors and prognosis of patients with alveolar echinococcosis was analyzed. Establish a nomogram prediction model based on independent risk factors for patient prognosis, and evaluate the prediction accuracy and discrimination ability of the nomogram through the consistency index (C-index) and calibration curve. The result is through the use of bootstrapping validation with 1,000 re-sampling Method for internal verification.

Results: The ROC curve was used to determine the optimal cut-off value of SII before operation 761.192, and patients were divided into low SII group ($n = 184$) cases and high SII group ($n = 167$) cases. The 1, 3, and 5-year survival rates of patients with hepatic alveolar hydatid in the low SII group and the high SII group were 98.90%, 96.90%, 86.50% and 98.20%, 72.50%, 40.30%, respectively. The survival rate of worm disease patients was significantly better than that of the high SII group, and the overall survival rate difference between the two groups was statistically significant ($P < 0.001$). Multivariate Cox regression model analysis results showed that intraoperative blood loss (HR = 1.810, 95%CI: 1.227–2.668, $P = 0.003$), SII (HR = 5.011, 95%CI: 3.052–8.228, $P < 0.001$), Complications (HR = 1.720, 95%CI: 1.162–2.545, $P = 0.007$) are independent risk factors for the prognosis of patients with alveolar hydatid disease. Draw a nomogram and include statistically significant factors in the multivariate Cox regression model to predict the overall survival rate

of patients with alveolar hydatid disease at 1, 3, and 5 years. The survival probability calibration curve is displayed. The nomogram is compared with The actual results have a high degree of agreement. The concordance index (C-index) of the nomogram model in the modeling sample is 0.777, and the C-index in the verification sample is 0.797, indicating that the nomogram model of this study has good accuracy and discrimination.

Conclusions: SII has a clear correlation to the prognosis of patients with alveolar echinococcosis. The nomogram prediction model constructed on this basis is beneficial to the clinically individualized analysis of the patient's prognosis.

KEYWORDS

systemic immune inflammatory, prognosis, risk factors, nomogram, hepatic alveolar echinococcosis

Introduction

Hydatid disease, also known as echinococcosis, is a zoonotic disease prevalent in the world. Currently, the number of infected people is as high as 4 million, and 60 million people are at risk of infection. It has become a serious threat to the public health and health of the world (1). There are two main types of hepatic hydatid disease in humans, cystic echinococcosis (CE) caused by E. alveolar echinococcosis, AE) (2–4). Although the incidence of hepatic alveolar echinococcosis is slightly lower than that of hepatic cystic echinococcosis, it often proliferates by budding or infiltrating, similar to tumor-like growth patterns (e.g., it is easy to invade adjacent organs and pass through blood vessels), lymphatic vessels and biliary tract and other ways of distant metastasis), so the pathogenicity is very strong, the morbidity and mortality rate are high, so it is called "worm cancer". At present, surgical treatment is the main treatment for hepatic alveolar echinococcosis. However, many postoperative complications often lead to poor prognosis of patients (5, 6). Hepatic alveolar hydatid disease patients with untreated or ineffective treatment have a fatality rate as high as 90% within 10–15 years after diagnosis, which seriously threatens human life and health (7). Therefore, at this stage, relevant researchers continue to explore, aiming to discover new simple, economical and accurate prognostic evaluation indicators similar to PNM classification, so as to better guide clinical treatment.

Studies have shown that the prognosis of tumor patients is related to inflammatory response and immune response, and the relevant circulating immune cells and inflammatory cells involved are mainly neutrophils (N), lymphocytes (L) and platelets (P). The Systemic Immune Inflammatory Index (SII) based on platelets, lymphocytes and neutrophils has been proved to be of great value in evaluating the prognosis of esophageal cancer, breast cancer, liver cancer and pancreatic cancer (8–11). In recent years, relevant studies have shown that inflammation is involved in the pathogenesis of hepatic alveolar echinococcosis. Based on this, this study collected clinical and follow-up data from patients with hepatic alveolar hydatid disease, and analyzed the relationship between SII and hepatic alveolar hydatid disease. To investigate the relationship between clinicopathological characteristics and prognosis of patients with hepatic alveolar echinococcosis, to explore the significance of SII in the prognosis of patients with hepatic alveolar echinococcosis, and to construct a nomogram prediction model for predicting the prognosis of patients with hepatic alveolar echinococcosis to provide clinical decision-making. In accordance with. To our knowledge, this is the first report on the application of nomogram for prognosis prediction in patients with hepatic alveolar echinococcosis.

Materials and methods

Data collection

The clinical data of patients with hepatic alveolar hydatid disease treated by hepatobiliary and pancreatic surgery in Qinghai University Affiliated Hospital from January 2015 to December 2020 were collected. Treatment options include radical resection of liver hydatid disease and palliative care. Inclusion criteria: (1) Hepatic alveolar hydatid disease was diagnosed by abdominal B-ultrasound and abdominal CT; (2) Preoperative treatment with albendazole anti-insect drugs was not targeted; (3) Preoperative acute and chronic diseases were not combined. Inflammation, the results of routine blood test were normal; (4) Child-Pugh grading of preoperative liver function was A or B. Exclusion criteria: (1) the postoperative pathological diagnosis was not hepatic alveolar hydatid disease; (2) the medical records were missing or lost to follow-up; (3) complicated with liver cirrhosis and liver tumor; (4) refused surgical treatment. All patients signed informed consent and this study protocol was approved by the Ethics Committee of Qinghai University Affiliated Hospital (batch number: PSL2018006).

Methods

The results of the first blood collection after admission were collected, and SII was calculated, SII = peripheral platelet × neutrophil/lymphocyte count. According to the optimal cut-off value of SII, patients were divided into two groups: low SII and high SII, and the relationship between SII and clinicopathological factors of patients was analyzed.

Follow up

All postoperative patients were followed up regularly, and the follow-up period was once every 3–6 months. The contents of follow-up included the current general condition of the patient, the recurrence of hepatic hydatid and the time of recurrence, the postoperative adjuvant therapy and treatment plan, and the time and cause of death of the patient who died. The follow-up deadline was June 1, 2022, when the patient died. Overall survival was defined as the time from postoperative day 1 to death or the end of follow-up.

Statistical analysis

SPSS 26.0 software and R software were used for statistical analysis of the data, and the χ^2 test was used to compare the qualitative variables between the two groups. The receiver operating characteristic curve (ROC curve) was used to determine the optimal critical value of SII, the Kaplan-Meier method was used to draw the survival curve, and the overall survival time of the two groups of patients was analyzed. Log-rank was used to compare the difference in survival time between the two groups; Cox regression model was used to analyze the relationship between SII and prognosis of patients with hepatic alveolar echinococcosis, and HR and corresponding 95% CI were calculated. According to the results of Cox multivariate analysis, the "rms" package in R software (version 3.6.0) was used to establish a nomogram prediction model (12). Model selection is done through a stepwise selection process following the Akaike Information Criterion (13). In addition, the Harrell Concordance Index (C-index) was used to quantify the discriminative performance of the predicted nomogram (14), and was evaluated by comparing the survival probability between the nomogram prediction and the actual Kaplan-Meier estimate, using a nomogram with 1,000 A sub-resampled bootstrapping validation method is used for internal validation to calculate the relative corrected C-index (15). The larger the C-index, the more accurate the prognosis prediction (16). $P < 0.05$ means the difference is statistically significant.

Results

General data

A total of 351 patients met the inclusion criteria, including 211 females (60.01%) and 140 males (39.89%), aged 7–73 years, with an average of (36.98 ± 12.5) years. All 351 patients were diagnosed with hepatic alveolar hydatid disease, and all patients were discharged after treatment. Among all patients, 296 patients (84.3%) received radical resection of liver hydatid, and 55 patients (15.7%) received palliative treatment. As of June 1, 2022, all 351 patients were followed up with a median follow-up time of 45 months, of which 110 (31.3%) died and 241 (68.7%) were still alive.

Determination of the optimal critical value of preoperative SII

Drawing the ROC curve of SII, the area under the ROC curve was 0.803 (95%CI: 0.757–0.850, $P < 0.001$), the Youden index was 0.485, and the corresponding optimal critical value was 761.192, which was sensitive to assessing the survival of postoperative patients. The specificity was 80.9% and the specificity was 67.6% (**Figure 1**). According to this critical value, 351 patients were divided into two groups, including 184 patients in the low SII group (SII ≤ 761.192) and 167 patients in the high SII group (SII > 761.192).

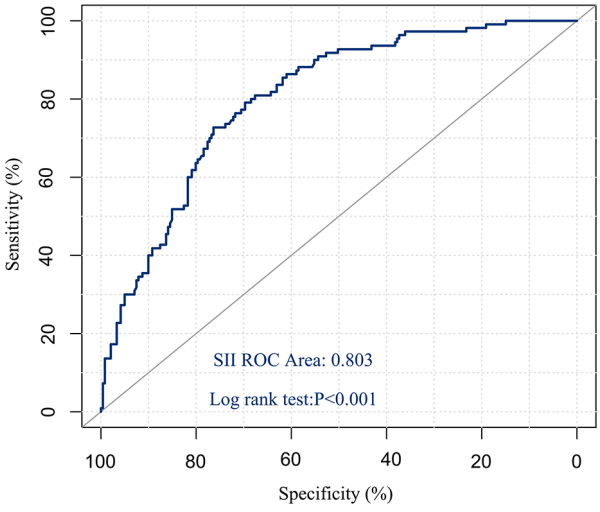

FIGURE 1
ROC curve of preoperative SII predicting overall survival in patients with hepatic hydatid disease.

TABLE 1 Relationship between SII and clinicopathological factors in patients with hepatic alveolar echinococcosis.

Variables	Low SII ($n = 184$)	High SII ($n = 167$)	χ^2	P
Age (year)	59		0.03	0.862
≤30		55		
>30	125	112		
Sex			0.018	0.894
Male	74	66		
Female	110	101		
Surgical approach			34.514	<0.001
Radical treatment	176	120		
Palliative care	8	47		
Intraoperative blood loss (ml)			50.751	<0.001
<1000	155	81		
≥1000	29	86		
PNM stages			28.971	<0.001
I, II	103	46		
≥III	81	121		
Child-Pugh			13.186	<0.001
A	113	81		
B	71	86		
Complication			7.516	0.003
Yes	116	81		
None	68	86		
ALT (U/l)			16.272	<0.001
≤40	122	75		
>40	62	92		
AST (U/l)			17.918	<0.001
≤40	129	80		
>40	55	87		
TBil (umol/l)			27.986	<0.001
≤34.2	146	88		
>34.2	38	79		
ALB (g/l)			30.931	<0.001
≤35	71	114		
>35	113	53		
ALP (U/l)			42.029	0.02
≤150	94	30		
>150	90	137		
PT (s)			6.947	0.001
≤16	166	123		
>16	18	44		
NE ($\times 10^9$/l)			16.517	0.232
≤6.3	171	138		
>6.3	12	29		
PLT ($\times 10^9$/l)			5.054	0.025
≤300	125	78		
>300	59	89		
WBC ($\times 10^9$/l)			11.445	0.001
≤10	170	138		
>10	8	25		
Whether to transfer			28.971	<0.001
Yes	103	46		
None	81	121		

Relationship between SII and clinicopathological factors in patients with hepatic alveolar echinococcosis

SII was related to surgical method, intraoperative blood loss, hydatid stage, Child-Pugh grade, complications, ALT, AST, TBil, ALB, ALP, PT, platelet, white blood cell count and metastasis (all $P < 0.05$). However, it was not related to age, gender and neutrophils (all $P > 0.05$) (Table 1).

Relationship between SII and overall survival in patients with hepatic alveolar echinococcosis

The cumulative survival rate in the low SII group was >50%, and the average survival time was 68.256 months (95%CI: 66.255–70.257); the cumulative survival rate in the high SII group was <50%, and the average survival time was 51.28 months (95% CI: 47.990–54.570), and the median survival time was 53 months (95%CI: 45.324–60.676). The 1-, 3-, and 5-year survival rates in the low SII group were 98.90%, 96.90%, and 86.50%, respectively; the 1-, 3-, and 5-year survival rates in the high-SII group were 98.20%, 72.50%, and 40.30%, respectively, and the survival rates in the low SII group were It was better than the high SII group, and there was a statistically significant difference in the overall survival rate between the two groups ($P < 0.001$) (Figure 2).

Analysis of influencing factors for prognosis of patients with hepatic alveolar hydatid disease

Univariate analysis showed that surgical methods, intraoperative blood loss, ALB, SII, and complications were all prognostic factors for patients with hepatic alveolar hydatid disease (all $P < 0.05$). Moderate bleeding volume (HR = 1.810, 95%CI: 1.227–2.668, $P = 0.003$), SII (HR = 5.011, 95%CI: 3.052–8.228, $P < 0.001$), complications (HR = 1.720, 95%CI: 1.162–2.545, $P = 0.007$) was an independent risk factor for the prognosis of patients with hepatic alveolar hydatid disease, as shown in Table 2.

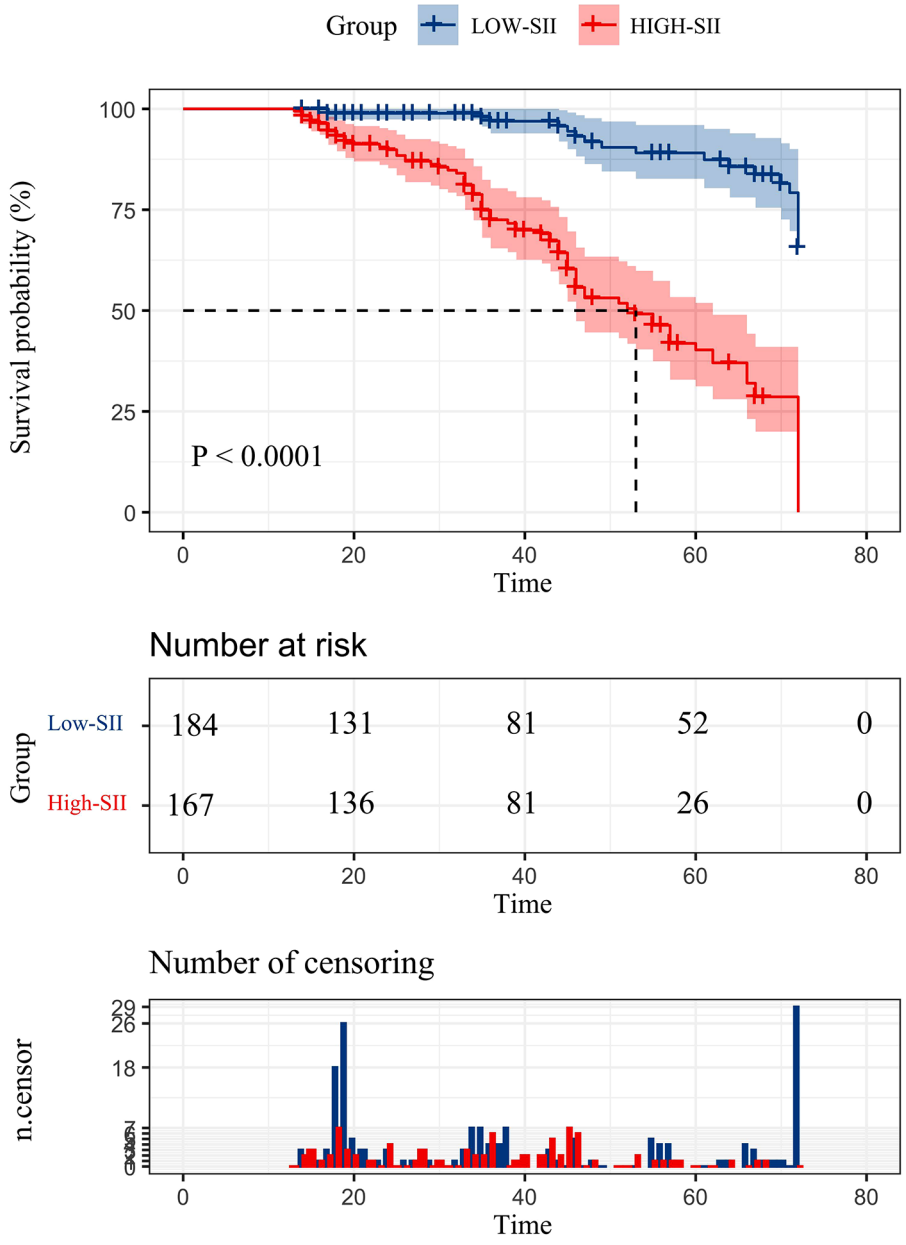

FIGURE 2
Postoperative overall survival curve of patients with hepatic alveolar hydatid disease in two groups.

Predictive effect of nomogram prediction model on cumulative survival rate of patients with hepatic alveolar hydatid disease

The prediction effect of the cumulative survival rate of patients with hepatic alveolar hydatid disease was displayed by drawing a nomogram, and the prediction model was established according to the independent risk factors (intraoperative blood loss, SII, complications) screened out by the Cox regression model, and listed in the column The line plot shows that the total score for each patient was assigned by drawing a vertical line from the corresponding point of each predictor variable to the score table, and adding these scores to obtain the total score, for patients with alveolar hydatid disease The 1-year, 3-year, and 5-year survival rates were predicted, and the consistency index (C-index) was 0.777 (Figure 3). The calibration curves are all very close to the ideal curve (Figure 4), indicating that the predicted values obtained from the nomogram prediction

TABLE 2 Univariate and multivariate analysis on the survival of patients with hepatic alveolar hydatid disease.

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Age (≤30 vs. >30)	1.164 (0.765–1.772)	0.479		
Sex (Male vs. Female)	0.875 (0.599–1.278)	0.490		
Surgical approach (radical treatment vs. palliative care)	1.980 (1.294–3.032)	0.002		
Intraoperative blood loss (≤1,000 vs. >1,000)	2.705 (1.856–3.942)	0.001	1.810 (1.227–2.668)	0.003
PNM stages (I, II vs. ≥III)	1.100 (0.692–1.747)	0.687		
Child-Pugh (A vs. B)	2.013 (1.214–4.571)	0.053		
ALT (≤40 vs. >40)	0.956 (0.656–1.392)	0.813		
AST (≤40 vs. >40)	1.116 (0.767–1.623)	0.566		
ALB (≤35 vs. >35)	0.654 (0.436–0.981)	0.040		
TB (≤34.2 vs. >34.2)	1.079 (0.737–1.579)	0.696		
PT (≤16 vs. >16)	0.928 (0.577–1.494)	0.759		
SII (≤761.192 vs. >761.192)	6.361 (3.935–10.281)	0.001	5.011 (3.052–8.228)	0.001
Whether to transfer (none vs. yes)	1.100 (0.692–1.747)	0.687		
Complication (none vs. yes)	2.410 (1.641–3.539)	0.001	1.720 (1.162–2.545)	0.007

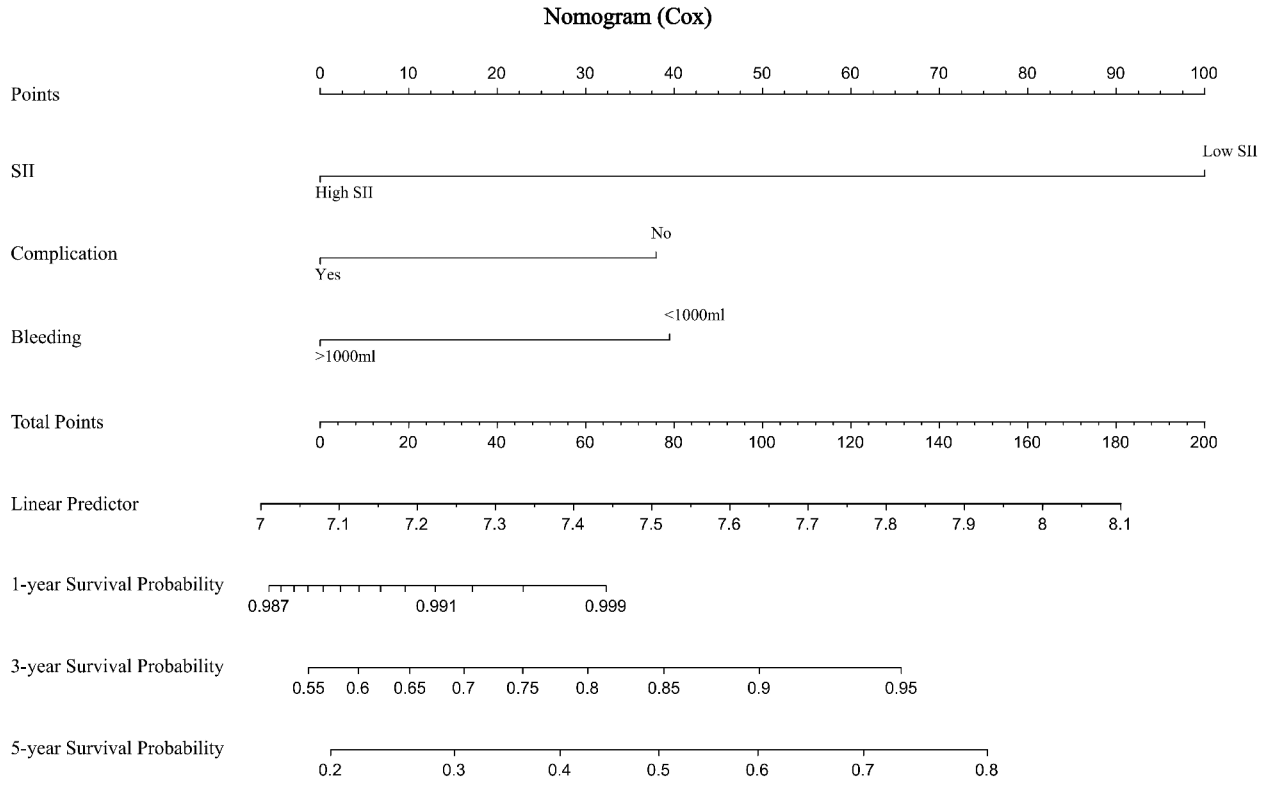

FIGURE 3
Prediction of 1-, 3-, and 5-year survival rates of patients with hepatic alveolar hydatid disease by nomogram.

model can better represent the actual values. In the internal validation cohort, the validation C-index was 0.797 by bootstrapping validation analysis, which indicates that the model has good discriminative power. The calibration curve also performed well in the validation set, as shown in Figure 5.

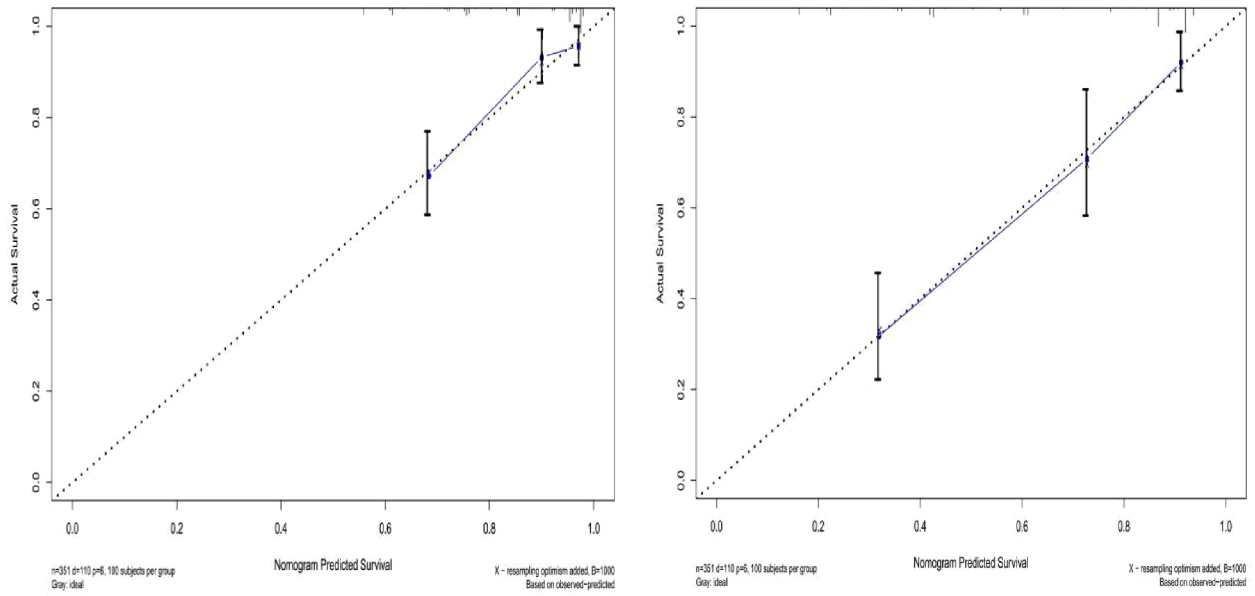

FIGURE 4
Survival calibration curve of patients with hepatic alveolar echinococcosis. A is 3-year survival, B is 5-year survival, and the probability of nomogram-predicted overall survival is plotted on the *x*-axis; actual overall survival is plotted on the *y*-axis.

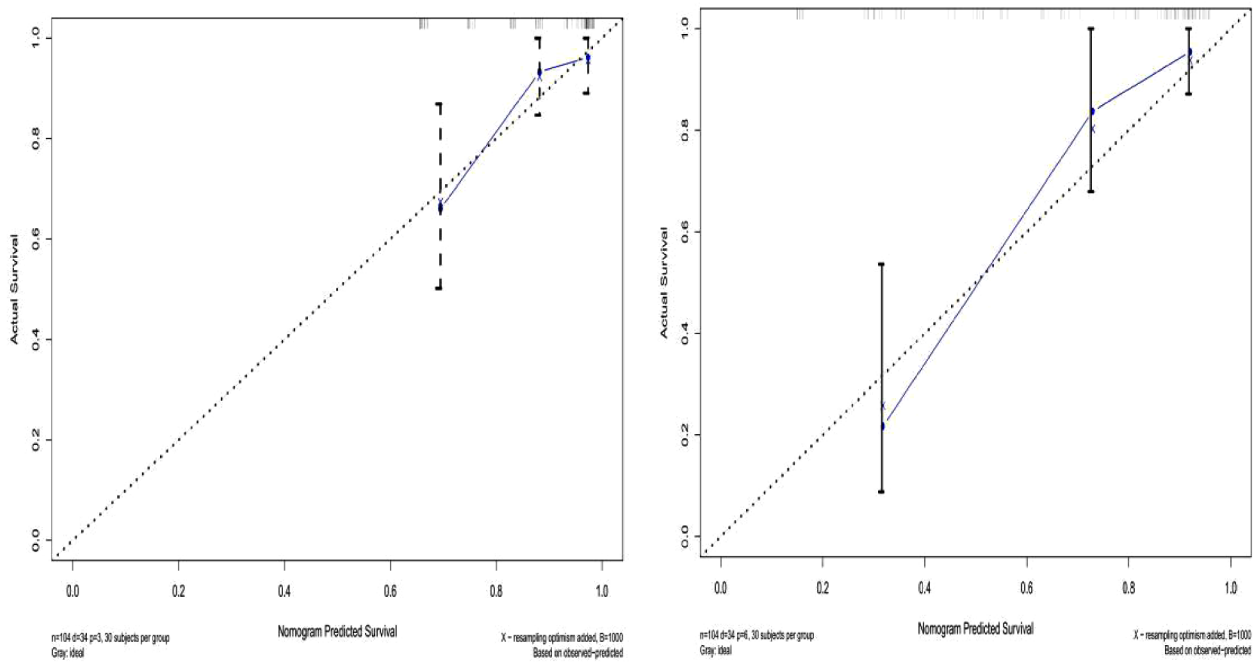

FIGURE 5
Validation set survival calibration curve for patients with hepatic alveolar echinococcosis.

Discussion

In recent years, more and more studies have shown that inflammatory response plays an important role in disease progression and is also involved in the regulation of host immune function. Some biomarkers such as C-reactive protein, α1-acid glycoprotein, neutrophils Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are closely related to the prognosis of cancer patients and have potential clinical significance for monitoring the prognosis of cancer patients (17, 18). Among them, SII is a comprehensive index based on lymphocytes, platelets and neutrophils, reflecting the body's inflammatory response index. Compared with other indexes, this inflammatory index reflects the balance between the host's immune state and inflammatory state more comprehensively. It has been proved that It is a valuable prognostic indicator for tumor patients (19, 20). Recent studies (11, 17, 18) have shown that high levels of SII are associated with poor prognosis in malignancies such as hepatocellular, gastric, breast and pancreatic cancers.

In this study, univariate and multivariate Cox regression analysis confirmed that intraoperative blood loss, complications, and SII were independent risk factors affecting the prognosis of patients with alveolar hydatid disease, which had important clinical significance. Agid et al. (21) found that the risk of complications was significantly related to the prognosis of hepatic alveolar echinococcosis, reflecting the survival rate of patients to some extent, which was consistent with the results of this paper, by discussing the relationship between postoperative complications of hepatic alveolar echinococcosis, surgical methods and Child-Pugh grading of liver function before operation. In addition, the results of this study suggest that the amount of intraoperative blood loss is the key factor affecting the prognosis of patients with hepatic alveolar echinococcosis, which is consistent with the results of Ma Hailin (22). By analyzing the influencing factors of postoperative survival time of patients with end-stage hepatic alveolar echinococcosis treated by excised hepatectomy and autotransplantation, Ma Hailin found that the amount of intraoperative blood loss (RR = 0.096, 95% CI: 0.020–0.450, $P = 0.003$). In addition, the liver is an important blood storage organ, and excessive intraoperative blood loss will lead to postoperative liver function decline to a certain extent. Hanazaki et al. (23) pointed out that for radical surgery of hepatocellular carcinoma (HCC), even if a small amount of blood is infused during operation, the risk of postoperative recurrence of HCC may increase. Subsequently, Eiji Tsujita et al. (24) found that intraoperative blood loss was an independent risk factor for the prognosis of recurrent hepatocellular carcinoma (HCC) by studying the adverse prognostic factors of the second operation.

This study shows that the survival time of patients with hepatic alveolar echinococcosis in the high SII group is significantly shorter than that in the low SII group. The author considers that the higher level of SII mostly represents the higher level of neutrophils and platelets and the lower level of lymphocytes. On the one hand, platelet-derived TGFβ1 can induce epithelial mesenchymal transition and synergistically promote the transfer of worms by activating NF-κB and TGFβ/Smad pathways (25); on the other hand, lymphocytes, as immune cells, can inhibit the growth and metastasis of worms (26); finally, neutrophils can aggravate local inflammatory reaction by activating complement and coagulation system, leading to tissue damage. Parasites can induce neutrophils to have oxidative and non-oxidative killing reactions, which will aggravate the progress of the disease (27). These are the main factors leading to poor prognosis of patients with hepatic alveolar echinococcosis.

In this study, a nomogram was constructed according to the independent risk factors of prognosis screened by Cox regression model, and the prognosis of patients with hepatic alveolar echinococcosis was predicted and evaluated by nomogram. The accuracy of nomogram is evaluated by C-index and calibration chart, which proves that nomogram has high predictive value. The nomogram provides the specific scores of each influencing factor, and the final probability of the outcome can be predicted by adding the scores of each factor. At the same time, the nomogram transforms the complex regression equation into a simple visual graph, which makes the prediction results of the prediction model more readable. Medical staff can predict the prognosis of patients with hepatic alveolar echinococcosis more quickly and conveniently according to nomograms, which is conducive to prevention work in advance and has high clinical application value.

There are some limitations in this study. On the one hand, the sample size of this study is small, and the regression model constructed may have some bias, and there is no test set for external verification of survival model and nomogram. Therefore, further samples should be collected for further research in the future. In addition, it is not clear whether the high level of SII before operation means promoting or inhibiting peripheral neutrophils, lymphocytes and platelets, and the related mechanism needs further research to confirm.

In conclusion, the results of this study indicate that SII is expected to be a prognostic indicator for patients with hepatic alveolar hydatid disease due to its simplicity, non-invasiveness, and low cost. In addition, the nomogram has high clinical application value, which can intuitively predict the prognosis of patients with hepatic alveolar hydatid disease, and help clinicians formulate or adjust a reasonable diagnosis and treatment plan in a timely manner.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

CX and XZ: Designed the research and wrote the paper; CX, YJ: Revised the paper; CX, WZ and FH: Participated in research work; CX, ZY, LZ, RL and PM: Collected samples; CX and XZ: Analyzed data and constructed figures; FH and WZ: Responsible for project guidance. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Clinical characteristics and management of 106 patients with pyogenic liver abscess in a traditional Chinese hospital

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This is a retrospective study of clinical data from 106 patients with pyogenic liver abscess (PLA) treated in a traditional Chinese hospital during the eight years preceding this publication. We aimed to provide evidence to improve the diagnosis accuracy and the treatment strategies for PLAs. We collected records of patients treated at the Guangxing Hospital, which is affiliated to the Zhejiang Traditional Chinese University in Hangzhou, and we collected their general background information, laboratory and imaging features, and clinical manifestations and outcomes to perform a retrospective analysis. Diabetes mellitus (45.3%, 48/106), biliary calculi (36.8%, 39/106), and history of abdominal surgery (15.1%, 16/106) were the three most common PLA risk factors present in our cohort. Fever and chills (95.3%, 101/106), right upper quadrant pain/epigastric discomfort (68.9%, 73/106), nausea and vomiting (38.8%, 41/106), and cough and sputum (14.2%, 15/106) were the most common clinical manifestations of PLA. Most patients had the abscesses in the right liver lobe, and the most commonly found bacteria were *Klebsiella pneumoniae* (54.8%, 42/76), *Escherichia coli* (35.1%, 27/76), and *Streptococcus pneumoniae* (3.9%, 3/76). Liver Doppler ultrasound is a conventional and effective method to identify liver abscesses. Most patients were treated using a percutaneous puncture under B-ultrasound guidance. Most patients ($n = 104$ or 98.1%) were cured, one patient (0.9%) died, and one was discharged with multiple abscesses post treatment.

KEYWORDS

pyogenic liver abscess, clinical features, pathogenic bacteria, outcomes, laboratory features

Introduction

Pyogenic liver abscesses (PLAs) are reported globally, but their incidence varies significantly between countries (from 8 to 22 patients per 1,000,000 people) (1). The incidences of PLA in Asia are higher than those in western countries, with the highest being in Taiwan, China (2, 3). Medical technological progress has reduced the PLA mortality risk. However, regional differences in the application of these technologies have caused the mortality rate to remain high. A review by Chan KS et al. of 16 PLA articles showed mortality rates ranging from 0% to 15.7% (11 articles) (4).

In the early 20th century, the most common route of PLA infection was portal phlebitis, often secondary to acute appendicitis, and the total mortality rate was as high as 80% (5). However, the different infection routes described since then include biliary calculi, the portal vein, hepatic artery, cryptogenic pathway, and adjacent infections (6). Some studies have reported diabetes mellitus as a risk factor for PLA (2). Recent studies have shown that biliary tract alterations (including acute cholecystitis, common bile duct stones, chronic pancreatitis, and tumoral biliary obstructions) are the main route of infection for PLA (7, 8). The number of cryptogenic liver abscess cases has been on the rise, and Thomas McNeil et al. found no predisposing conditions (cryptogenic) for 14 (18%) of the patients in their cohort (9).

The clinical manifestations of PLA are nonspecific. The main symptoms are fever and chills, and there may be right upper quadrant pain/epigastric discomfort, but sometimes the signs are unclear. Early PLA diagnoses depend mainly on imaging examinations. B-ultrasound is the first choice, followed by abdominal computed tomography (CT) and magnetic resonance imaging (MRI). The risk factors for PLA include age, male sex, diabetes mellitus, biliary calculi, immunodeficiency, and the use of proton pump inhibitors (1, 10). And, the pathogens associated with PLA are mostly gram-negative bacilli, but reports of mixed infections of *Streptococci* and anaerobic bacteria exist.

The diagnosis and management of PLA have changed substantially in the past few decades. Due to the advent of advanced imaging techniques and accurate chemical tests, early diagnosis, precise localization, image-guided percutaneous aspiration, and drainage of abscesses can be achieved easily. However, many patients are missed due to the nonspecific clinical features of PLA, and a high degree of suspicion is the cornerstone of misdiagnosis prevention and prognosis improvement. We present here a retrospective analysis of 106 patients with PLAs managed in a Chinese hospital over the course of the eight years preceding the publication of this study. We analyzed demographic, clinical, laboratory, pathogenic, and management outcomes.

Materials and methods

We obtained the medical records of inpatients with a principal diagnosis of a liver abscess between June 2013 and June 2021 from the clinical document database of the Guangxing Hospital affiliated to the Zhejiang Traditional Chinese University in Hangzhou. All the patients were diagnosed as having liver abscesses, and all were adults older than 18 years. The data could be found in **Supplementary materials**.

PLA was diagnosed if: (1) the results of microbial cultures (blood or pus cultures) were positive, or antimicrobial treatment was effective; and/or, (2) after percutaneous liver puncture or surgical treatment, a lesion with suppurative infection caused by bacteria was confirmed; and, (3) clinical manifestations such as fever, liver discomfort, abdominal pain, and percussion pain in liver area were present; and/or, (4) hepatic abscesses or lesions were diagnosed using liver Doppler ultrasound, CT, or MR images.

To decrease biases, we excluded patients with liver liquefaction infarctions, hepatic echinococcosis, amebic liver abscesses, tuberculous liver abscesses, and liver abscesses caused by other factors; patients lacking clinical data; and patients who had undergone radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE), or who had had postoperative hepatic tumor-associated infections.

We extracted the following demographic data and clinical information from each patient's record: age, sex, presenting symptoms and signs, comorbidities, the imaging modality they had been diagnosed with, the abscess characteristics (size, location, and number of abscesses), whether percutaneous aspiration was performed, whether a drainage catheter was inserted, the hospital stay duration, and the treatment outcome. We retrieved the following laboratory variables for analysis: white blood cell count (WBC); neutrophil/leukocyte ratio; platelet count; serum levels of C-reactive protein (CRP), procalcitonin (PCT), albumin, total bilirubin, alkaline phosphatase (ALP), fibrinogen, and alanine transaminase (ALT), and creatine kinase (CK); and prothrombin time (PT).

All measurement data were normally distributed and we expressed them as means ± SDs. We expressed count data as frequencies (percentages).

Results

Basic features

During the period from June 2013 to June 2021, 106 patients were diagnosed as having PLA at the Zhejiang Chinese Medical University. We analyzed data from all the patients with available and complete records. The data belonged to 71 men and 35 women (male-to-female ratio, 2.03:1) with an age range between 18 and 87 years (mean ± SD, 64 ± 13 years). The age group with the most patients was the 60–69-year-old group, followed by the 70–79-year-old group.

Clinical manifestations

As shown in **Table 1**, the most common presenting features were fever and chills in 101 patients (95.3%), followed by right upper quadrant pain in 73 patients (68.9%), nausea and vomiting in 41 patients (38.8%), cough and sputum in 15 patients (14.2%), and scleral icterus/yellow urine in 6 patients

TABLE 1 Clinical features of PLA.

Clinical features	Number of patients (%)
Fever (≥37.5°C) and chills	101 (95.3%)
High Fever (≥39°C)	77 (74.8%)
Nausea and vomiting	41 (38.8%)
Cough and sputum	15 (14.2%)
Scleral icterus/yellow urine	6 (5.7%)
Right upper quadrant pain/epigastric discomfort	73 (68.9%)
Diabetes mellitus	48 (45.3%)
Biliary calculi	39 (36.8%)
History of abdominal surgery	16 (15.1%)
Hepatic cyst	15 (14.2%)
Shock	15 (14.2%)
Gastrointestinal tumor	5 (4.7%)
Endophthalmitis	1 (0.94%)

(5.7%). High fever (>39°C) was present in 77 patients (74.8%) on admission. The body temperatures ranged from 36.3°C to 41.3°C (mean ± SD, 39.3 ± 0.9°C).

The most common comorbidities included diabetes mellitus (48 patients, 45.3%), and biliary calculi (39 patients, 36.8%). We found 16 patients (15.1%) with a history of abdominal surgeries, 15 (14.2%) with hepatic cysts, and 2 (1.9%) with hepatic cysts complicated with bacterial infections. Our cohort included 15 patients (14.2%) with septic shock and 5 patients (4.7%) with gastrointestinal tumors. One patient, had had three different hepatic abscesses at different times without other intestinal lesions on contrast-enhanced CT images, but with a malignant tumor in the hepatic flexure of the colon (as seen during a colonoscopy). Another patient who felt eye discomfort after two weeks was diagnosed with endophthalmitis with Klebsiella pneumoniae being found in both the aqueous and pus cultures. Other comorbidities in our cohort included hypertension, senile stroke, ischemic heart disease, congestive heart failure, and malignant diseases.

Laboratory features

The most common laboratory abnormality in our cohort of patients was CRP elevation in 105 of 106 patients (99.1%; Table 2), followed by decreased albumin levels in 98 of 103 patients (95.1%), elevated procalcitonin (PCT) levels in 71 of 85 patients (83.5%), elevated neutrophil/leukocyte ratio in 87 of 106 patients (82.1%), and abnormal WBCs in 74 of 106 patients (72.6%). We found high leukocyte counts in 71 patients (67.0%) and low counts in 3 patients (2.8%). Notably, infection-induced thrombocytopenia had occurred in 18 patients (17.0%), while we found elevated levels of ALP in 56 patients (52.8%), ALT in 54 patients (50.9%), and total bilirubin in 20 patients (18.9%). These last patients had mild to moderate liver function impairments. Additionally, 98 patients (92.5%) had elevated fibrinogen levels, 28 (26.4%) had elevated PTs, and 17 (16.0%) had high CK levels.

The hemocultures or liver abscess fluid cultures of 76 patients were positive (Table 3) with 42 cases of *K. pneumoniae* (the most common pathogen in our cohort), 27 of *Escherichia coli*, 3 of *Streptococcus pneumoniae*, 2 of *Streptococcus intermedius,* 1 of *Lactococcus lactis* subspecies, 1 of *Enterobacter cloacae*, and 1 of *Citrobacter braakii*.

TABLE 2 Laboratory features of PLA.

Abnormal Laboratory Values	Number of patients (%)	Mean ± SD	Range
Albumin (high)	98/103 (95.1%)	32.4 ± 5.2	21.1–48.9
CRP (high)	105 /106 (99.1%)	161.3 ± 81.9	5.63–313
Neutrophil/leukocyte ratio	87/106 (82.1%)	82.9 ± 8.0	62.5–96.8
PCT (high)	71/85 (83.5%)	16.40 ± 30.48	0.04–100
WBC (abnormal)	74/106 (69.8%)	12.24 ± 5.21	0.98–32.46
WBC (high)	71/106 (67.0%)		
WBC (low)	3/106 (2.8%)		
Infection-induced thrombocytopenia	18/106 (17.0%)	81.9 ± 18.3	51–109
ALP (high)	56/106 (52.8%)	151.8 ± 98.0	47–687
ALT (high)	54/106 (50.9%)	61.5 ± 47.3	11–295
Bilirubin (high)	20/106 (18.9%)	19.2 ± 12.1	5.3–70.2
Fibrinogen (high)	98/106 (92.5%)	5.90 ± 1.61	2.93–13.19
PT (high)	28/106 (26.4%)	13.2 ± 1.6	9.7–17.8
CK (high)	17/106 (16.0%)	117 ± 133	12–747

CRP, C-reactive protein; WBC, white blood cell; PCT, procalcitonin; ALP, alkaline phosphatase; ALT, alanine transaminase; PT, prothrombin time; CK, creatine kinase.

TABLE 3 Results of hemocultures or liver abscess fluid cultures of patients with PLA.

Pathogen	Number of patients (%)
Klebsiella pneumoniae	42 (54.5%)
Escherichia coli	27 (35.1%)
Streptococcus pneumoniae	3 (3.9%)
Streptococcus intermedius	2 (2.6%)
Lactococcus lactis subspecies	1 (1.3%)
Enterobacter cloacae	1 (1.3%)
Citrobacter braakii	1 (1.3%)

TABLE 4 Location and number of PLA.

Location	Number of patients (%)
Left lobe	27 (26.2%)
Right lobe	66 (62.3%)
Left and right lobes	13 (12.3%)
Single abscess	83 (78.3%)
Multiple abscesses	23 (21.7%)

Imaging features

Ultrasound alone was the diagnostic tool of choice in 62 patients (58.5%). CT scans or MRI were performed as appropriate for differential diagnoses of liver cancer or cancer with infections. The abscess diameters ranged from 1 to 12.7 cm (mean ± SD, 5.6 ± 2.4 cm). The PLAs were confined mostly to the right hepatic lobe (66 patients, 62.3%) due to the portal vein anatomy, high hepatic mass, and dense network of bile canaliculi in this lobe. We found 27 patients (26.2%) with PLAs in the left hepatic lobe. The PLAs in 13 patients (12.3%) were either in the right lobe, or in the right and left lobes, while two patients had PLAs in the caudate lobe. We found single abscesses in 83 patients (78.3%), and multiple abscesses in 23 patients (21.7%) (**Table 4**).

Treatment

The 106 patients in our cohort received anti-infection therapy. In addition, those with liver damage received liver protection therapy, and those with septic shock received rapid rehydration and anticoagulation therapy. Under the guidance of B-ultrasound, 76 patients underwent puncturing and draining of abscesses with either one or more drainage tubes inserted; however, one patient had to undergo continued percutaneous aspiration due to lack of an appropriate drainage tube insertion space (**Figure 1**). Nine patients (8.5%) were treated with piperacillin sodium and tazobactam sodium, 42 (39.6%) with third generation cephalosporins combined with quinolones/nitrazole antibiotics, and 28 (26.4%) with third generation cephalosporins alone. In 27 patients (25.5%), the infections were controlled with the initial use of carbapenems, and the subsequent use of third generation cephalosporins and other antibiotics. Thirty patients (28.3%) were treated with anti-infectives alone, 76 (71.7%) were treated with ultrasound-guided puncture and drainage, and no one required surgical resection.

Outcome

The patients' hospital stays lasted between 3 and 43 days, with the average length of stay at 19.9 ± 10.2 days. A total of 104 patients (98.2%) were cured. Despite careful treatment, an elderly patient with severe hypertension, diabetes mellitus, heart failure, and hypoproteinemia died. The mortality rate was 0.9%. Another patient, whose abscess was treated with ultrasound-guided puncture and drainage and who had a normal body temperature and hemogram, developed multiple small abscesses near the primary abscess as observed by CT and MRI techniques two weeks later (**Figure 1**).

Discussion

Hippocrates described the first liver abscess in the year 400 BC. PLA remains a major public health problem due to its severe morbidity and mortality. PLA is an infective disease caused by various pathogens, and it often occurs in patients with impaired immunity such as those with diabetes mellitus and malignancies (11–13). In this study, we reviewed and analyzed the background features, clinical manifestations, laboratory and imaging features, and outcomes of 106 patients with PLA. One patient with multiple organ disease died, and one patient whose abscess was spread after treatment requested to be discharged.

The average age of the patients with PLA in our study was 64 years. This supports the findings of other studies indicating that the risk of PLA increases with age (14, 15). Also, our cohort had mostly men.

In patients with liver abscesses, large numbers of bacteria and toxins from the purulent cavity cause systemic sepsis with symptoms such as chills and fever. The presenting symptoms of PLAs are multiple and nonspecific, and include fever, right upper abdominal pain, vomiting, nausea, and asthenia. Fever and pain in the right upper abdomen have been found to be the main clinical symptoms (1, 15, 16). However, symptoms such as nausea and vomiting, cough and sputum, and the yellowing of the eyes have also been observed. In our study, 101 patients (95.3%) had fever [77 patients (78.7%) had mainly high fever]; while other common clinical manifestations included right upper quadrant pain (73 patients, 68.9%), nausea and vomiting (41 patients, 38.8%), and cough and sputum (15 patients, 14.2%). Atypical clinical symptoms (mostly in middle-aged and elderly patients with relatively slow responses) included sensitivity to pain combined with basic diseases generating discomfort such as abdominal pain; and, weakness, especially in patients with diabetes mellitus and visceral autonomic dysfunction, with an increased pain threshold (17, 18).

Comorbid illnesses included biliary calculi, diabetes mellitus, history of abdominal surgery, hepatic cysts, colon tumor, and endophthalmitis. Biliary calculi and diabetes mellitus were the predominant causes of PLAs (19). Biliary calculi were present in most patients (55%) of a different study (1), and yet another study reported coexistence rates for

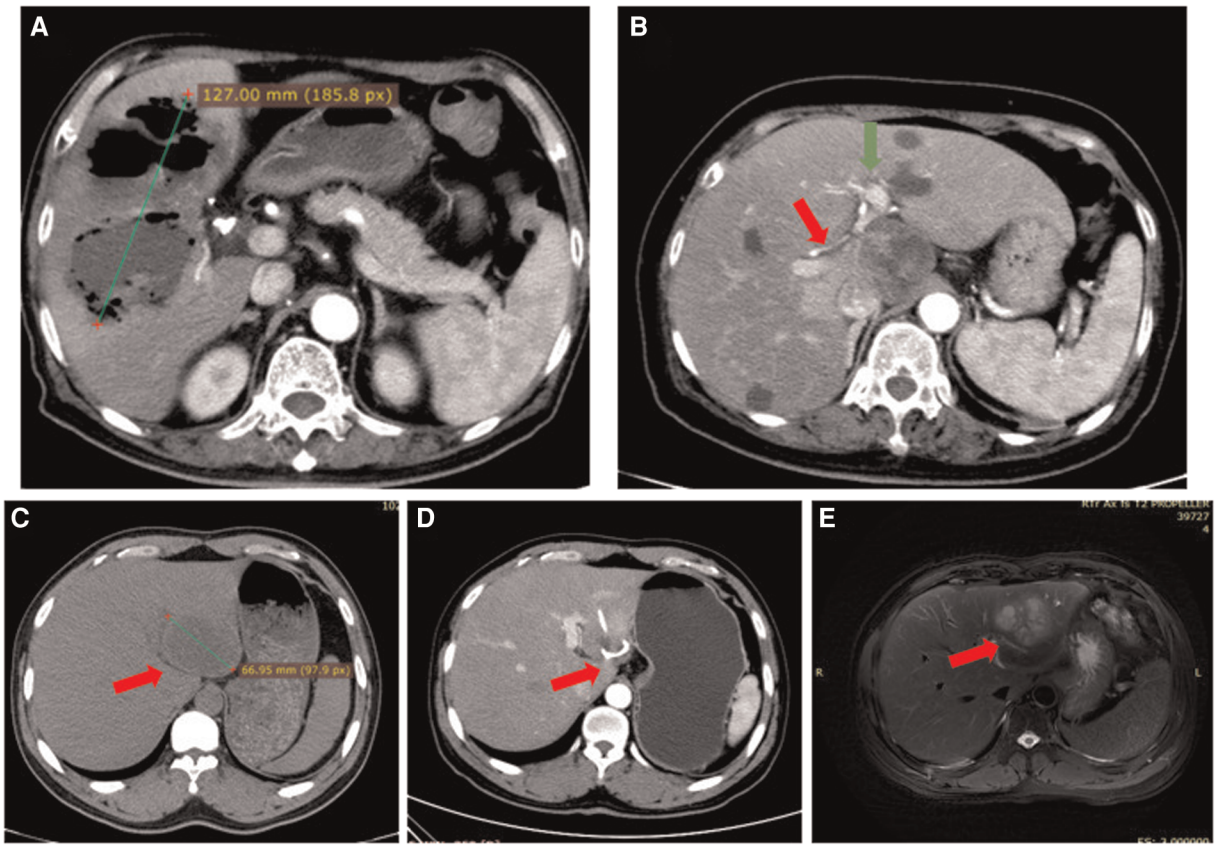

FIGURE 1
(A) case #1. Irregular low-density shadows were observed in the liver with clear boundaries and uneven internal density. Scattered gas density shadows were observed, and some gas-liquid planes were observed with a large cross section of approximately 127 mm. (B) Case #2. Image showing the lack of a space to place a drainage tube; The red arrow points to the right hepatic artery, The green arrow points to the left hepatic artery. (C) Case #3. The left lobe of the liver is a round low-density focus, approximately 53 mm in size. (D) Case #3. A drainage duct shadow was seen in the left lobe of the liver, with a few adjacent patchy low-density shadows. (E) Case #3. Recurrent abscess after treatment of liver abscess: A multilocular cystic solid long T2 signal shadow was seen in the left lobe of the liver, the maximum cross-section was 66 mm, and the boundaries were blurred. Left lobe lesion of the liver, abscess considered.

biliary calculi of 40.95%. The recurrence rates for patients with biliary PLAs have been recorded at percentages between 23% and 37%, and between 2% and 4% for those without biliary PLAs (20). This high recurrence risk may be clinically targeted; thus, patients with biliary PLAs need special attention. Diabetes mellitus is a risk factor for PLAs with a hazard risk rate ranging from 3.6 to 9-fold (21), and the disease is relatively common in patients with PLA; the reported coexistence rates are 30% in Hong Kong, 31% in Canada, 28.7% in a single center in Xi'an (China), 23% in Italy (1, 22), and 45.3% in our study. The morbidity of patients with PLAs and diabetes is high, and this may be due to their impaired immunity, neutrophil chemotaxis, mononuclear phagocyte activation, and/or opsonization. In addition, hyperglycemia can promote bacterial growth in tissues; and, metabolic disorders impact the liver, gut, pancreas, stomach, and intestine (14). Cryptogenic liver abscesses may be associated with gastrointestinal malignancies (23); and, colonoscopies are necessary for patients with cryptogenic liver abscesses, especially in eastern Asia, where gastrointestinal malignancies occur frequently. We found three patients with PLA and colon cancer in our study. Cryptogenic liver abscess has been mentioned in many studies, but the incidence of cryptogenic liver abscesses is difficult to calculate. Cryptogenicity is determined by how thoroughly one investigates to find the aetiology, e.g. Ultrasound scan to check for gallstones, EUS to check for microlithiasis, colonoscopy to check for polyps, cancer or diverticula, gastroscopy to check for gastric tumor, routine CT to check for appendicitis, cholecystitis, diverticulitis, colitis, or small bowel mass, or abscess formation *via* extension from a contiguous focus like the kidney. In addition, portal phlebitis, cholangitis, inflammatory bowel disease, infected liver cysts, and abdominal surgical infections. should be excluded. If one does not perform these tests, one will likely conclude to be cryptogenic.

Most patients had abnormal WBCs; elevated neutrophil/leukocyte ratios ratios, CRP, and PCT levels; and, abnormal liver function test results; however, the CRP and PCT levels were abnormal more often than the WBCs. We found elevated levels of CRP (in 99.1% of patients), PCT (in 83.5% of patients), neutrophil/leukocyte ratios (in 82.1% of patients), and WBCs (in 69.8% of patients). In our study, CRP was the most sensitive inflammatory response indicator. We used it to reveal the degree of inflammation caused by the infection and to evaluate the effect of the anti-infective treatment. CRP level reductions to a normal value can be used as an indicator of appropriateness of drug treatment cessation (24). Interestingly, we found three patients (2.8%) with low WBCs; a sign that can be present in patients with severe infections and that highlights the importance of diagnosing infections by means other than the WBC. During thrombocytopenia, CRP values >200 mg/L and PCT values >10 μg/L often indicate severe infection resulting in sepsis, hemodynamic disorders, organ dysfunction, and poor prognoses. We found 15 patients (14.2%) with shock out of the 106 patients in our cohort. Some of the patients with PLAs in our study had liver injuries; however, the degree of injury was mild and showed significant improvement after the implementation of infection control. In another study of 246 patients with PLA, the levels of CRP, PCT, and WBC showed no significant differences between the diabetes mellitus and the non-diabetes mellitus groups (15). In that paper, patients with diabetes mellitus showed significantly higher levels of ALP and γ-glutamyl transferase than their counterparts without diabetes mellitus.

Ultrasound, the first choice for the examination of liver abscesses because it is simple and accurate, and does not lead to radiation exposure, needs to be performed by experienced radiologists. The ultrasound examination is simple and noninvasive, and it displays the shape, size, quantity, location, liquefaction, and separation of abscesses in real time. Although the specificity of ultrasound can reach more than 85%, there are deviations in the observations of air cavities and the separation of the abscesses. The specificity of CT is higher than 95%, and liver abscesses with diameters of approximately 0.5 cm can be clearly detected. The "Petal sign" and "cluster sign" and other indirect signs of biliary tract problems can be diagnostic criteria for atypical liver abscesses during CT examinations. Some studies have shown that for *K. pneumoniae*-associated liver abscesses, the most frequent imaging manifestations are right lobe single abscesses in the liver parenchyma, with unclear boundaries, which are mostly solid and multilocular, and with air volumes in the abscess that are significantly larger than those usually seen in non-*K. pneumoniae* liver abscesses (25). The specificity and sensitivity of MRI scans are not as clear, but the "ring target sign" from MRI scans is an important clue for the diagnosis of a liver abscess.

In our cohort, the use of ultrasound-guided percutaneous aspiration followed by continuous catheter drainage along with parenteral antibiotic therapy showed a high success rate. Since 1953, administration of intravenous antibiotics after liver abscess puncture and drainage has become a classic method for the treatment of bacterial liver abscesses (26). The indications for puncture or catheter drainage are the following: (1) liver abscess with ineffective drug treatment or continuous increase of body temperature; (2) liver abscess with wall formation and liquefaction tending to mature; (3) abscess with a diameter of 3–5 cm that can be punctured and drained, and abscess with a diameter larger than 5 cm that can be drained with a tube; (4) liver abscess in patients with normal coagulation function and intolerance to operation. For abscesses larger than 10 cm, two drainage tubes can be placed from different angles to facilitate full drainage and flush the pus cavity as necessary. A meta-analysis reported success rates of 77.8% for percutaneous needle aspiration (PNA) and of 96.1% for percutaneous catheter drainage (PCD). PNA or PCD achieved clinical remission in a shorter time than antibiotic therapy alone. PCD is the first choice for the treatment of liver abscesses, not only because it is simple and cheap, but also because even for multiple liver abscesses that are difficult to treat, the treatment success rate is higher than 90% (27). Saleem Ahmed found that PCD is safe and sufficient even for patients with giant PLAs (28). We removed drainage tubes after the patient's laboratory examination and clinical performance results had returned to normal, the drainage fluid output was less than 5 ml/day, and imaging results had confirmed that the diameter of the pus cavity after drainage was smaller less than 2 cm. The study by Vishal G. Shelat followed a similar protocol (29).

In our study, the microbiological yield including both the pus and blood cultures was 72.6% (77/106), a number similar to that in a Singaporean study (30). The main isolates were *K. pneumoniae* (42 cases 54.5%) and *E. coli* (27 cases 35.1%). Over the past three decades, *K. pneumoniae* has emerged as the major pathogen and the single leading cause of PLAs in southern and eastern Asia, including in India, Korea, Singapore, Hong Kong, mainland China, and Taiwan. In a nationwide prospective study of PLAs in Korea, *K. pneumoniae* was the major etiological organism (7). Highly invasive *K. pneumoniae* strains possess genes responsible for a hypermucoviscosity phenotype associated with the serotypes K1 and K2. This highly invasive *K. pneumoniae* strains can cause intestinal colonization in healthy individuals that may lead to pathogenesis by opportunistic pathogens after the resulting microbiota compositional changes, especially the reduction in *Lactobacilli* abundance (31). When this occurs during bacterial translocation, pathogens can circulate to the liver through the portal vein, causing liver abscesses. After the gastrointestinal colonization by *K. pneumoniae* through

environmental exposure or the fecal-to-oral transmission, the bacteria may cross the intestinal barrier to invade the liver (32). Asian populations may be predisposed to intestinal colonization by highly toxic *K. pneumoniae* strains, a fact that may explain the high prevalence of *K. pneumoniae* in patients with PLA in Asia. *E. coli* is the most common biliary liver abscess pathogen, accounting for 20%–35% of patients infected by *E.coli* alone (20), followed in frequency by *K. pneumoniae*. This may be the main reason for the differences in the etiologies between Asia and Europe. The main pathogen found in Europe was *E. coli*, accounting for 60% of PLAs. Vishal G. Shelat et al. found that in multimodal care settings, outcomes of *E. coli* PLA are comparable to those of *K. pneumoniae* PLAs (29). Moreover, multi-bacterial infections and multi-drug resistant bacteria are common, and their causes are associated with biliary tract diseases and abnormal bile duct anatomies. Abnormal endogenous intestinal flora compositions caused by infections are associated with the use of broad-spectrum antibiotics. Interestingly, Vishal G. Shelat et al. found that even though *K. pneumoniae* PLAs and culture-negative PLAs present demographic and clinical differences, their overall outcomes are equivalent, and they recommend treating culture-negative PLAs with empirical antibiotics targeting *K. pneumoniae* (30).

According to the recommended treatment scheme in the Sanford Guide to Antimicrobial Therapy of 2016, the first choice for PLA treatment is metronidazole combined with ceftriaxone, or cefoxitin, or piperacillin tazobactam, or ciprofloxacin, or levofloxacin; and, the alternative is metronidazole combined with imipenem/meropenem/donipenem. The patients in our cohort received third generation cephalosporins combined with metronidazole.

The optimal length of intravenous administration and subsequent oral maintenance remains unclear. Researchers in the USA and Chinese mainland have recommended that the intravenous administration be prolonged for 2–3 weeks, and the oral administration for 1–2 weeks. The course of treatment is determined by the response of the patient to treatment and should be adjusted according to the ultrasound findings, body temperature, and WBC counts (7, 8). If complicated with endophthalmitis, systemic venous and intravitreal anti-infection must be started, and ceftriaxone can be considered. For high-risk patients with advanced age, diabetes mellitus, intensive care unit (ICU) hospitalization, and catheterizations, carbapenem should be the first choice to treat suspected PLA infections. The empiric antibiotic treatment should be adjusted once the culture results become available.

There are limitations to our study. This was a retrospective analysis performed in a single center, some patients were excluded due to missing data, important and relevant details may not have been documented, and cases data were collected at the time of admission, and the actual changes in some indicators could not be judged by comparing baseline levels. However, our findings are based on a large number of cases and should be valuable to other investigators and clinicians.

Conclusions

The common clinical manifestations of bacterial liver abscesses are fever and chills, right upper quadrant pain/epigastric discomfort, nausea and vomiting, and cough and sputum. Liver Doppler ultrasound was a conventional and effective method to diagnose PLAs in our study. *K. pneumoniae* is the most commonly isolated pathogen in PLAs. Percutaneous puncture under B-ultrasound guidance was the most commonly used treatment.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary Material**.

Ethics statement

The studies involving human participants were reviewed and approved by Research Ethics Committee of Guangxing Hospital affiliated to the Zhejiang Traditional Chinese University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Study conception and design: SN and XL. Literature search and acquisition of data: DL. Analysis and interpretation of data and drafting of manuscript: SN. Critical revision of manuscript: XL. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.1041746/full#supplementary-material.

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Application and practice of trimodal prehabilitation model in preoperative management of patients with lung cancer undergoing video-assisted thoracoscopic surgery

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Lung cancer is one of the malignant tumors with high mortality worldwide. To date, the most effective treatment of non—small cell lung cancer (NSCLC) is still surgical resection. Video-assisted thoracoscopic surgery has become the main surgical approach. Tumor patients are the high-risk perioperative population. At present, how to optimize perioperative management measures to improve the patient's body function and promote the rehabilitation after video-assisted thoracoscopic surgery is a hot research topic for medical staff. In this study, 148 patients with lung cancer were selected as the research object, to analyze and discuss the application value of trimodal prehabilitation model in preoperative management of patients with lung cancer undergoing video-assisted thoracoscopic surgery.

KEYWORDS
lung cancer, trimodal prehabilitation, rapid rehabilitation surgery, functional capabilities, prognosis

Introduction

Lung cancer has become one of the common malignant tumors in clinic, and the incidence rate of lung cancer is increasing year by year (1). Video-assisted thoracoscopic surgery (VATs) has become the main surgical approach for chest diseases due to its advantages of less trauma and rapid recovery of patients. The latest guidelines issued by the National Comprehensive Cancer Network (NCCN) in 2018 proposed that video-assisted thoracoscopic surgery should be preferred for patients with NSCLC (2). However, due to impaired lung function, obesity, and weakness, some patients with lung cancer have poor body reserve function, which cannot ensure the efficacy of the operation and increases the risk of postoperative complications (3). Therefore, it is urgent to find effective methods to fight for more patients' operation opportunities, improve the operation efficacy, reduce postoperative complications and improve the prognosis in clinical practice.

The study found that compared with the traditional rehabilitation measures which only carry out postoperative rehabilitation, maintaining a good physiological and

psychological state before surgery is more conducive to increasing the reserve function and making the body in a better functional state (4, 5). Pre-rehabilitation is an emerging preoperative management strategy based on the enhanced recovery aftersurgery (ERAS). The new preoperative optimization strategy proposed in this scheme mainly includes the trimodal prehabilitation measures of exercise, nutritional support and psychological intervention in the preoperative stage, aiming to improve the body function of patients to withstand the stress of surgery, accelerate the rehabilitation process and improve the clinical outcome of patients (6). As a new pre-operative intervention mode, trimodal prehabilitation is being accepted by scholars both in China and abroad, and has been verified by many studies that pre-operative intervention in surgical patients can promote their rehabilitation (7). However, it still lacks its application value in thoracoscopic surgery for lung cancer in China. This study analyzed the application of trimodal prehabilitation model in preoperative management of patients with lung cancer undergoing video-assisted thoracoscopic surgery. The report is as follows.

Information and methods

General information

A total of 160 patients who received video-assisted thoracoscopic surgery for lung cancer in the inpatient department of Shanghai Chest Hospital from June 2021 to December 2021 were selected. According to the inclusion and exclusion criteria, 148 patients were finally taken as research subjects and randomly divided into an intervention group and a control group, with 74 cases in each group. All patients signed informed consent forms, and this study has been approved by the Medical Ethics Committee of our hospital.

Inclusion criteria

① According to the 2020 NCCN Guidelines for the Diagnosis and Treatment of Non-small Cell Lung Cancer and the eighth edition of international lung cancer pathological staging criteria, all patients were stage I-II lung cancer patients with feasible surgical resection; ② Patients who underwent video-assisted thoracoscopic surgery; ③ The patient has no physical activity disorder, is conscious, and can understand and cooperate with medical staff; ④ Age ≤75 years old.

Exclusion criteria

① Patients with lung cancer in which the tumor has invaded the peripheral organs and extensive adhesion to the pleura; ② Patients with a previous history of ipsilateral pulmonary surgery; ③ Lung tumors cannot undergo one-lung ventilation; ④ Patients with severe complications before operation, including patients with severe hematological and immune system diseases; ⑤ Patients with cardiac function ≥Class ≥III; ⑥ Patients with compact adhesion of thoracic cavity explored during operation and tumor invading thoracic wall; ⑦ Patients who switched from video-assisted thoracoscopic surgery to thoracotomy due to massive hemorrhage; ⑧ Patients who underwent pneumonectomy by changing the operation mode during the operation; ⑨ Pet-name ruby postoperative patients with active bleeding tendency; ⑩ Patients with incomplete or untrue clinical data were excluded.

Research methods

Patients in the control group received routine perioperative intervention. They completed medical history inquiry, laboratory and physical examination before hospital admission and assessment of general preoperative conditions. Routine nursing measures and health guidance were given during the perioperative period, including hospital admission propaganda and education, diet guidance, respiratory function exercise, preoperative patient preparation and postoperative precautions.

The intervention group was given trimodal prehabilitation intervention strategy on the basis of the control group. ① Firstly, a triple pre-rehabilitation group is set up, with the head nurse of our department as the team leader, and the team members included two experienced nursing supervisors and several responsible nurses. Under the group leader's organization, all team members were trained in the pre-rehabilitation nursing practice program, and after confirming that all ward nurses had mastered the program operation process, the intervention group patients were given nursing measures. ② On the day of hospitalization for patients with pre rehabilitation guidance, distribution of pre rehabilitation guidance manual, and guidance will be recorded daily activities, guidance form including oral, manual and demonstration. ③ After the operation, the physical condition of the patient was evaluated, and the physician wrote the exercise prescription and gave the patient exercise support. Ways of exercise: a. aerobic exercise: you can arrange exercises according to your actual situation. the common exercise ways are floor training, fast walking and jogging. Stair-climbing training: Climbing 45 steps at the normal stair-climbing speed constituted one group of sports, with two to three groups in succession. 20 min each time, 2 times/day. Brisk walking or jogging can also be performed. The duration of exercise can be initially set at 10–20 min, and finally increased to 30 min, 2 times/day. It was advisable for patients to exercise without increasing obvious fatigue, and when the degree of self-

perceived fatigue was heavy, the exercise intensity could be reduced. The target heart rate was calculated based on the patient's age, i.e., target heart rate = (220−age) × (70%–80%). b. Respiratory trainer Deep breathing training: 10–15 min/time, 3 times/day. c. Abdominal breathing exercise: The patient was guided to the abdominal breathing method at 10–15 min/time, 3 times/day. ④ Nutrition support by combined medical care and establishment of ward nutrition intervention group composed of competent doctor, responsible nurse and dietician. The NRS 2000 scale was used to assess the nutritional status of patients. The patients with a score of <3 points ate a balanced diet, and the patients with a score of ≥3 points were malnourished. After evaluation, intervention was carried out, and the group made dietary plan according to the patient's situation. 20 g whey protein was added into the beverage 1 h after exercise. ⑤ Professional scale was used to evaluate the psychological state of patients and psychological consolation was carried out accordingly. At the same time, to guide patients to carry out relaxation training, the specific content is as follows. Patients were required to empty their stools and wear loose clothes before training. Keep the room quiet, neat, the light is appropriate. Instruct patients to close their eyes and concentrate in the most comfortable position. Breathe naturally, and slowly clenched his fist when inhaling to feel the muscle tension (about 5–10 s), and then slowly loosen your fist when exhaling to feel the muscle relaxation (about 10–30 s). The feelings of muscle groups of arm, head and face, neck, shoulder, chest, abdomen, back, hip, lower limbs and both feet were felt orderly until the muscles of the whole body were relaxed, which lasted for about 20 min. At the same time, take listening to music to relax training. Keep the indoor environment quiet and comfortable, and use headphones. Wearing headphones, the music volume should be kept under 60 dB, and instrumental music such as Chinese classical folk music and world famous music will be played. The intervention of the two groups was ended after the first week of operation.

Observation indicators

(1) Activity capacity: The results of the 6-minute walking test (6 MWT) before intervention, 1 d before operation and 30 days after operation in the two groups were compared. The patients of the two groups walked in a straight line in a corridor with a length of 30 m for 6 min, and the total walking distance of the patients was finally measured and recorded as 6 MWT (8). During testing, put three chairs in the corridor for rest. During the test, attention was paid to the presence of warning signs of fall. During the test, the patient's oxygen saturation, heart rate and Brog score were continuously monitored. Once the patient developed dyspnea, chest pain and chest tightness, and progressive decline in oxygen saturation, the test was immediately stopped. Experimental preparation of epinephrine and nitroglycerin tablets and other rescue medication, abnormal timely notify the doctor.

(2) Psychological status: The results of Hospital Anxiety and Depression Scale (HADS) before intervention, 1 d before operation and 30 days after operation between the two groups were compared. HADS consisted of anxiety (anxiety, a) and depression (depression, d) sub-scales, with 7 questions for anxiety and depression respectively, which were rated by the patients themselves with a total score of 21 points. 0–7 points indicate no anxiety and depression symptoms, 8–10 points indicate possible anxiety and depression, and 11–21 points indicate affirmation of anxiety and depression (9).

(3) Nutrition status: Elbow venous blood was collected before intervention, 1 day before operation and 30 days after operation, and once before the patient was discharged. All automated hematology analyzer was used to test the nutritional indicators of the patients. Serum albumin (albumi, ALB) was detected by bromocresol green method, prealbumin (PA) was detected by rate nephelometry, and transferrin (TRF) level was detected by nephelometry.

(4) Comparison of the incidence of postoperative complications and the postoperative hospital stay between the two groups.

(5) Evaluate the patient's nursing satisfaction at discharge. According to the specific situation of our department, a satisfaction questionnaire was designed to obtain the satisfaction data of patients' families from the monthly satisfaction survey conducted by our department. The content of the satisfaction survey included safety, environment, comfort, accessibility, respect for patients, nursing technology, health education, communication and so on. The full score of the satisfaction questionnaire was 100. The higher the score was, the higher the patients' satisfaction with the nursing care would be.

Data statistics

SPSS Statistics 22.0 software was used for statistical analysis. Measurement data were expressed as $(\bar{x} \pm S)$. Paired-samples *t*–test was used for intra-group comparison before and after treatment, and *t*-test was used for inter-group comparison. The count data were expressed as *n* (%) using the χ^2 test. For inter-group comparison at multiple time points, the overall difference was analyzed using the repeated measures analysis of variance. $P < 0.05$ was considered as the difference with statistical significance.

TABLE 1 Comparison of two groups of general data.

Group	Age (years old)	Gender (n)		Surgical approach (n)			ASA grading (n)	
		Male	Female	Pulmonary lobe	Lung segment	Wedge	I	II
Intervention group ($n = 74$)	53.59 ± 5.74	43	31	59	6	9	46	28
Control group ($n = 74$)	54.18 ± 5.66	40	34	62	4	8	43	31
t/χ^2	0.630	0.247		0.533			0.254	
P	0.530	0.619		0.766			0.615	

Result

Comparison of general information

The general data of the two groups were not statistically significant ($P > 0.05$), and they were comparable, as shown in Table 1.

Comparison of activity abilities of patients between the two groups before and after intervention

There was no significant difference in 6 MWT between the two groups before intervention ($P > 0.05$). One day before surgery, the 6 MWT in both groups was higher than that before intervention and higher in the intervention group than in the control group. On the 30th day after surgery, the 6 MWT values in the two groups were lower than that one day before surgery, but it was higher in the intervention group than in the control group ($P < 0.05$), as shown in Figure 1.

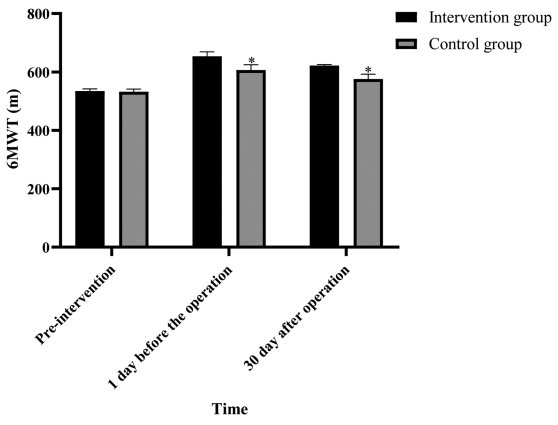

FIGURE 1
Comparison of 6 MWT between the two groups at different times (Note: compared with the intervention group, *$P < 0.05$).

Comparison of psychological states of patients between the two groups before and after intervention

There was no significant difference in HADS scores between the two groups before intervention ($P > 0.05$). One day before surgery, the scores of the two groups were higher than those before intervention, but the scores in the intervention group were lower than those in the control group. The HADS scores of the two groups were lower than those of the one-day intervention group and the control group 30 days after the operation ($P < 0.05$), as shown in Figure 2.

Comparison of ALB, PA and TRF levels between the two groups before and after intervention

Before intervention, the levels of ALB, PA and TRF in the two groups were not statistically significant ($P > 0.05$). One day before surgery, the levels of ALB, PA and TRF in the intervention group were higher than those before intervention

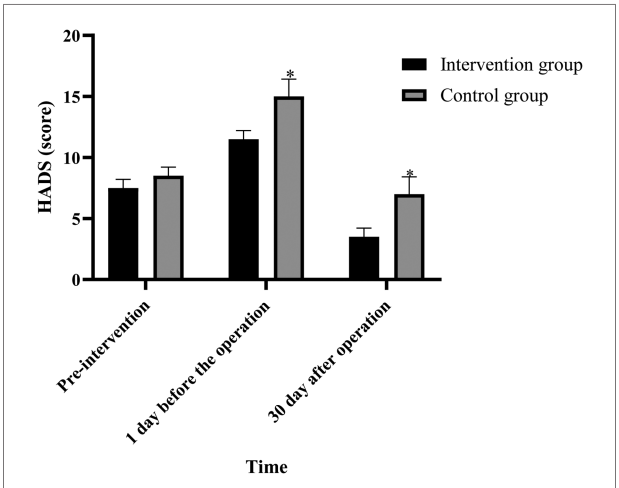

FIGURE 2
Comparison of HADS scores in two groups at different times (Note: compared with the intervention group, *$P < 0.05$).

($P < 0.05$), but the levels of ALB, PA and TRF in the control group were not statistically significant as compared with those before intervention ($P > 0.05$). On the 30th day after surgery, the levels of ALB, PA and TRF in the intervention group were lower than those on the 1st day before surgery ($P < 0.05$), but their levels were not statistically significant as compared with those before intervention ($P > 0.05$). The levels of ALB, PA and TRF in the control group were lower than those 1 day before surgery and before intervention ($P < 0.05$). The levels of ALB, PA and TRF in the intervention group were higher than those in the control group one day before surgery and 30 days after surgery ($P < 0.05$), as shown in Figures 3–5.

Comparison of the incidence of postoperative complications and postoperative hospital stay between the two groups before and after intervention

The incidence of complications in the intervention group was lower than that in the control group, and the postoperative hospital stay was shorter than that in the control group ($P < 0.05$), as shown in Table 2.

Comparison of nursing satisfaction between the two groups

The nursing satisfaction degree in the intervention group was higher than that in the control group ($P < 0.05$), as shown in Table 3.

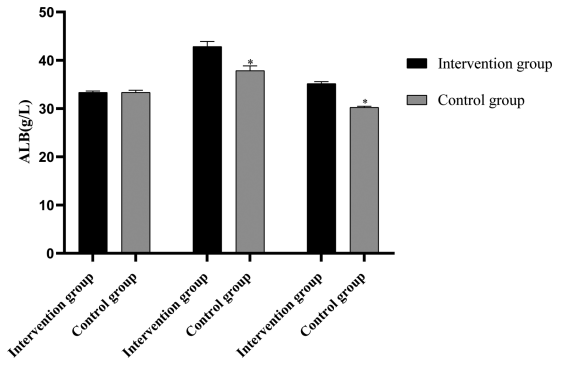

FIGURE 3
Comparison of ALB levels between the two groups before and after intervention (Note: compared with the intervention group, *$P <$ 0.05).

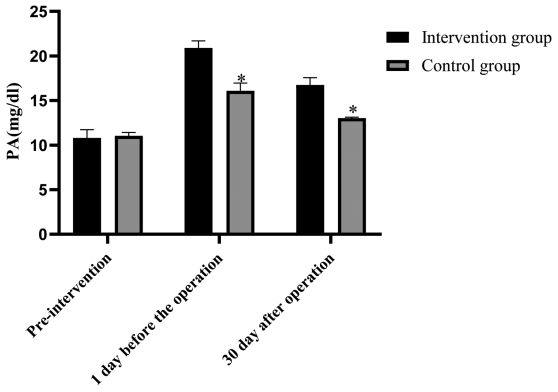

FIGURE 4
Comparison of PA levels between the two groups before and after intervention (Note: compared with the intervention group, *$P < 0.05$).

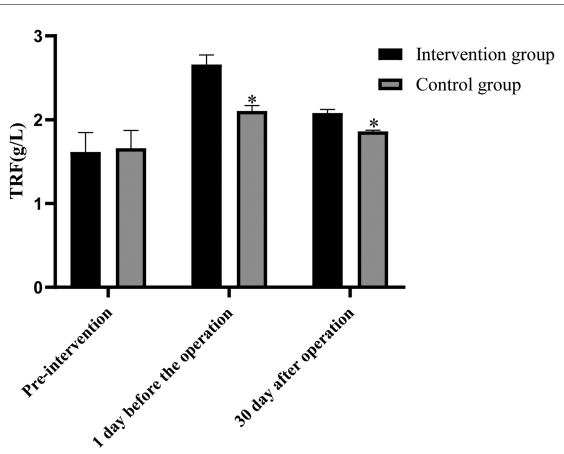

FIGURE 5
Comparison of TRF levels between the two groups before and after intervention (Note: compared with the intervention group, *$P < 0.05$).

Discussion

Studies have shown that the incidence of postoperative complications in lung cancer patients undergoing minimally invasive surgery is still as high as 26.2%–36.3% (10, 11). The core of ERAS concept is to reduce the trauma and stress on patients in each stage of the perioperative period, in order to shorten the treatment time, reduce complications and reduce the mortality rate (12). In recent years, the concept of ERAS has become a consensus in the field of surgery. However, previous efforts of ERAS to improve the prognosis of patients have mainly focused on the intraoperative (laparoscopic surgery, epidural anesthesia, etc.) and postoperative (analgesia, early feeding, rehabilitation activities, etc.), without

TABLE 2 Comparison of postoperative complications and hospitalization duration between the two groups before and after intervention.

Group	Postoperative complications						Postoperative hospitalization time (d)
	Atelectasis	Empyema	Bronchopleural fistula	Subcutaneous emphysema	Pulmonary infarction	Total	
Intervention group ($n = 74$)	1 (1.35)	0 (0.00)	0 (0.00)	1 (1.35)	0 (0.00)	2 (2.70)	7.16 ± 1.55
Control group ($n = 74$)	3 (4.05)	1 (1.35)	1 (1.35)	2 (2.70)	1 (1.35)	8 (10.81)	9.57 ± 1.27
t/χ^2						3.861	10.346
P						0.049	<0.001

TABLE 3 Comparison of nursing satisfaction between the two groups ($\bar{x} \pm S$, score).

Group	Nursing satisfaction
Intervention group ($n = 74$)	13.95 ± 3.14
Control group ($n = 74$)	13.18 ± 3.16
t	1.175
P	0.243

preoperative intervention (13). The trimodal prehabilitation strategy is a new concept of preoperative management proposed based on ERAS (14).

There is increasing evidence that objective assessment of physical fitness and nutritional status can predict postoperative recovery. This study showed that after intervention, the motor function, psychological state and nutritional state of patients in the two groups were significantly improved compared with those before intervention. However, the levels of MWT, ALB, PA and TRF in the intervention group were higher than those in the control group at 6 MWT one day before surgery and 30 days after surgery, and the postoperative hospital stay in the intervention group was shorter than that in the control group. This indicates that the trimodal prehabilitation model has a significant effect on improving the physiological and psychological state of patients with lung cancer undergoing video-assisted thoracoscopic surgery, and can shorten the postoperative treatment time.

To further analyze the cause value of triple pre-rehabilitation model in thoracoscopic surgery for lung cancer. On the one hand, the first step of the triple pre-rehabilitation model is to establish a triple pre-rehabilitation model team, which can help to the functional state of the patient at a high level throughout the surgery and recover to the preoperative baseline level more quickly after surgery by developing a reasonable optimization plan in accordance with the specific situation of the patient before the surgery (15). On the other hand, different from the control group that only carried out health education, the intervention group that received triple pre-rehabilitation mode was based on exercise training, and at the same time carried out nutritional support and psychological intervention measures, which can adjust the preoperative functional status of patients with lung cancer undergoing video-assisted thoracoscopic surgery from different aspects (16). Among them, aerobic exercise is the main form of exercise training, which includes two complementary exercise types of endurance and strength training. Moreover, there are many methods of aerobic exercise in the intervention group, including climbing training, brisk walking, jogging, etc., to avoid the decrease of compliance caused by boring training, which is helpful to enhance the aerobic metabolic capacity and muscle strength of patients, enhance their physiological reserves, and facilitate postoperative rehabilitation (17). In addition to exercise, respiratory exercise is also an important component of exercise support for patients undergoing video-assisted thoracoscopic surgery for lung cancer (18). Low respiratory muscle strength is one of the risk factors of pulmonary complications after thoracoscopic surgery for lung cancer. Respiratory exercise can strengthen the strength of respiratory muscles, facilitate the discharge of sputum, increase vital capacity and prevent the incidence of postoperative pulmonary complications such as atelectasis during perioperative period. In addition, preoperative nutritional support is also one of the key measures for pre-rehabilitation (19). Different degrees of malnutrition are common in patients with lung cancer, and the patients are in stress state of high catabolism after surgery, which further aggravates the malnutrition of the body and seriously affects the postoperative rehabilitation. Therefore, nutritional support for patients undergoing video-assisted thoracoscopic surgery for lung cancer can increase their preoperative nutritional reserve, simultaneously provide the basis for exercise training and postoperative nutritional consumption, and reduce the incidence of postoperative infection.

In addition, studies have reported that anxiety and depression significantly inhibit immune function and can affect postoperative wound healing, leading to adverse outcomes (20). Therefore, psychological intervention for lung cancer patients undergoing thoracoscopic surgery is very important to reduce stress response and enhance the effect of pre-rehabilitation. In this study, the perioperative anxiety and

depression were effectively relieved by individualized explanation of perioperative plan and related knowledge, as well as psychological intervention, relaxation training and respiratory training. In the trimodal prehabilitation model, sports and psychological support are mutually reinforcing. Physical exercise accompanied by sympathetic excitation, blood flow and oxygen consumption increased, resulting in changes in excitatory neurotransmitters, good stimulation of the central nervous system, can make people feel better, from which to obtain a sense of exercise pleasure, satisfaction and self-confidence, but also conducive to the improvement of anxiety and depression before surgery (21). In this study, the HADS scores of the intervention group were lower than those of the control group 1 day and 30 days after operation ($P < 0.05$), further verifying that the application of the triple pre-rehabilitation mode in the pre-operative management of lung cancer patients undergoing video-assisted thoracoscopic surgery can improve the psychological state of patients and facilitate the postoperative recovery.

Notably, some important issues were also found in the application of the triple pre-rehabilitation model. Patients undergoing video-assisted thoracoscopic surgery for lung cancer may have a number of pre-operative conditions that hinder exercise planning, including anxiety, depression, malnutrition, comorbidities, and the tumor itself, all of which can affect their compliance with treatment and intervention. Therefore, before the trimodal prehabilitation, adequate education and education on the content of pre-rehabilitation are needed to encourage patients to timely adjust their mentality before surgery and strictly follow the strategy of the triple pre-rehabilitation model. At the same time, when carrying out sports training, it is necessary to avoid excessive exercise intensity, so as to avoid fatigue, injury or poor compliance. For continuous improvement of physical strength, the intensity of exercise should be slowly and gradually increased. In addition, it is necessary to maintain the diversity of plans and adjust the physical and mental state of patients from multiple aspects. In addition, the influence of no difference in complications between the two groups on the postoperative treatment time of the two groups needs to be confirmed by a larger sample size.

In summary, the application of trimodal prehabilitation model in preoperative management of patients with lung cancer undergoing video-assisted thoracoscopic surgery is conducive to improving the functional state and psychological state of patients, preventing complications, and improving nursing satisfaction.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by This study was approved by the ethics committee of our hospital.. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LY, HC: are the mainly responsible for the writing, research design of the article. The corresponding author is BX, and she is responsible for ensuring that the descriptions are accurate and agreed by all authors. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Simpson's paradox and the impact of donor-recipient race-matching on outcomes post living or deceased donor kidney transplantation in the United States

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Background: Race is a prognostic indicator in kidney transplant (KT). However, the effect of donor-recipient race-matching on survival after KT remains unclear.
Methods: Using the United Network for Organ Sharing (UNOS) database, a retrospective study was conducted on 244,037 adults who received first-time, kidney-alone transplantation between 2000 and 2019. All patients were categorized into two groups according to donor-recipient race-matching, and the living and deceased donor KT (LDKT and DDKT) were analyzed in subgroups.
Results: Of the 244,037 patients, 149,600 (61%) were race-matched, including 107,351 (87%) Caucasian, 20,741 (31%) African Americans, 17,927 (47%) Hispanics, and 3,581 (25%) Asians. Compared with race-unmatching, race-matching showed a reduced risk of overall mortality and graft loss (unadjusted hazard ratio (HR) 0.86, 95% confidence interval (CI) 0.84–0.87; and unadjusted HR 0.79, 95% CI: 0.78–0.80, respectively). After propensity score-matching, donor-recipient race-matching was associated with a decreased risk of overall graft loss ($P < 0.001$) but not mortality. In subgroup analysis, race-matching was associated with higher crude mortality (HR 1.12, 95% CI: 1.06–1.20 in LDKT and HR 1.11, 95% CI: 1.09–1.14 in DDKT). However, race-matching was associated with a decreased risk of graft loss in DDKT (unadjusted HR 0.97, 95% CI: 0.96–0.99), but not in LDKT. After propensity score-matching, race-matching had better outcomes for LDKT (patient survival, $P = 0.047$; graft survival, $P < 0.001$; and death-censored graft survival, $P < 0.001$) and DDKT (death-censored graft survival, $P = 0.018$). Nonetheless, race-matching was associated with an increased adjusted mortality rate in the DDKT group ($P < 0.001$).

Conclusion: Race-matching provided modest survival advantages after KT but was not enough to influence organ offers. Cofounding factors at baseline led to a contorted crude conclusion in subgroups, which was reversed again to normal trends in the combined analysis due to Simpson's paradox caused by the LDKT/DDKT ratio.

KEYWORDS

kidney transplantation, race-matching, Simpson's paradox, patient survival, graft survival

Introduction

For most patients with end-stage renal disease (ESRD), kidney transplantation (KT) is the preferred treatment because it has a superior survival to dialysis (1). In the United States, KT has shown an annual increasing trend. Additionally, a large body of literature (2–6) has focused on the effect of donor and/or recipient race on post-transplant outcomes, albeit with inconsistent results. Donor-recipient race-matching is considered a potential prognostic factor for organ transplant outcomes, since receiving organs from the same race increases the possibility of genetic and physiological similarities between donors and recipients and thereby reduces the possibility of rejection events (7). However, few studies (8–12) have investigated the impact of donor-recipient race-matching on post-transplant survival, especially in KT. Although some studies have noted reduced survival of patients or grafts in race-unmatched organ transplantation, conflicting results have been reported in several studies. In addition, most prior studies are now outdated, and the different population classifications affect comparability among different studies. Understanding the impact of race-matching on patient and graft survival is crucial for improving KT outcomes.

Therefore, we performed the present study to evaluate the potential implication of donor-recipient race-matching on post-KT patient and graft survival utilizing United Network for Organ Sharing (UNOS) database. We hypothesized that donor-recipient race-matching in KT would improve patient and graft survival compared with unmatching, due to genetic and physiological similarities.

Methods and materials

Data source and study design

We obtained the data from the UNOS database. Our institutional review board (IRB) deemed this study exempt from IRB approval because no patients or center identifiers were included in this analysis. We retrospectively examined adults (≥18 years) who received a first-time, kidney-alone transplant from January 1, 2000 to December 31, 2019. The cohort was classified into race-matched and unmatched groups according to whether the donors and recipients were of the same ethnicity. In addition, we performed subgroup analyses by donor type (living and deceased). Specific races (Caucasian, African American, Hispanic, and Asian) were investigated, and other races (including American Indian, Pacific Islander, and unknown races) were excluded because of small sample sizes.

Variables examined and outcome measures

The present study included recipient, donor, and transplant period variables. The primary covariates of interest were the races of recipients and donors. Demographic factors of recipient and donor included age, body mass index (BMI), gender and race. The primary causes of ESRD were classified into five groups [glomerular disease, diabetes mellitus (DM), hypertension, and polycystic kidneys and other]. We also checked other recipient information, such as insurance type, education level, dialysis before transplant, and days on the waitlist. Donor type and cause of death for deceased donors were also examined. Finally, transplant factors were also evaluated as covariables, including transplant time periods, human leukocyte antigen (HLA) mismatch, delayed graft function (DGF), cold ischemic time, and reported any acute rejection.

The endpoints were crude and were adjusted for patient and graft survival, and death-censored graft survival in both LDKT and DDKT.

Statistical analysis

Comparison of clinical and demographic characteristics between the race-matched and unmatched groups was performed using Student's *t*-test (for continuous variable) and χ^2 test (for categorical variable). We censored recipients who lost to follow-up prior to death. The cumulative survival rate was evaluated with Kaplan–Meier curves, and log-rank tests were used to determine survival differences. Survival analysis was conducted with Cox proportion hazard ratio regression models for the overall data and for subgroups to determine the magnitude of difference. Considering statistically significant differences in clinical factors between the race-matched and unmatched cohorts, we used propensity score-matching for 1 : 1 matching of race-matched and unmatched patients. Data missing patients were exclude from the matching model. In the subgroup analysis, propensity scores were calculated using recipient covariates (age, BMI, gender, race,

causes of ESRD, primary insurance, education level, and dialysis before KT) and donor covariates (age, BMI, gender, and race), as well as organ-specific factors (HLA mismatch, DGF, cold ischemic time, and acute rejection), but with the addition of donor type as a covariate in the overall analysis. In addition, a balance diagnosis was performed by comparing the baseline characteristics between race-matching and race-unmatching groups (**Supplementary Figure S1**).

For all analyses, all *P*-values were 2-sided, and statistical significance was set at $P < 0.05$. Means are presented with standard deviations (SD), and hazard ratios (HR) are presented with 95% confidence intervals (CI). All analyses were conducted using R (version 3.6.2) within RStudio (version 1.1.456).

Results

Cohort statistics

From January 1, 2000 to December 31, 2019, 342,990 patients undergoing KT were identified in the United States according to UNOS. Excluding previous transplants ($n = 35,630$), children ($n = 35,351$), multiple organ transplantation (9,490), dual KT ($n = 5,102$), ABO incompatibility ($n = 2,276$), foreign donors ($n = 7$), and minorities ($n = 11,097$), the final study subjects of 244,037 were enrolled in the study. The mean age of donors and recipients was 40.21 ± 14.60 years and 51.68 ± 13.38 years with percentages of male being 52.89% ($n = 129,072$) and 61.06% ($n = 149,008$), respectively.

The race distribution of recipients was as follows: Caucasian ($n = 123,646$, 50.67%), African American ($n = 67,610$, 27.70%), Hispanic ($n = 38,280$, 15.69%), and Asian ($n = 14,501$, 5.94%). The racial distribution of donors was as follows: Caucasian ($n = 171,632$, 70.33%), African American ($n = 31,589$, 12.94%), Hispanic ($n = 33,789$, 13.85%), and Asian ($n = 7,027$, 2.88%) (**Figure 1**).

Overall, 149,600 (61.30%) patients received kidneys from race-matched donors, whereas 94,437 (38.70%) patients received kidneys from race-unmatched donors. A total of 107,351 (86.82%) Caucasians, 20,741 (30.68%) African Americans, 17,927 (46.83%) Hispanics, and 3,581 (24.69%) Asians received race-matched kidneys (**Table 1**). The percentage of annual donor-recipient race-matching varied from 55.16% to 66.99%, with a decreasing trend over time. The number of KT cases ranged from 8,722 to 17,809 during

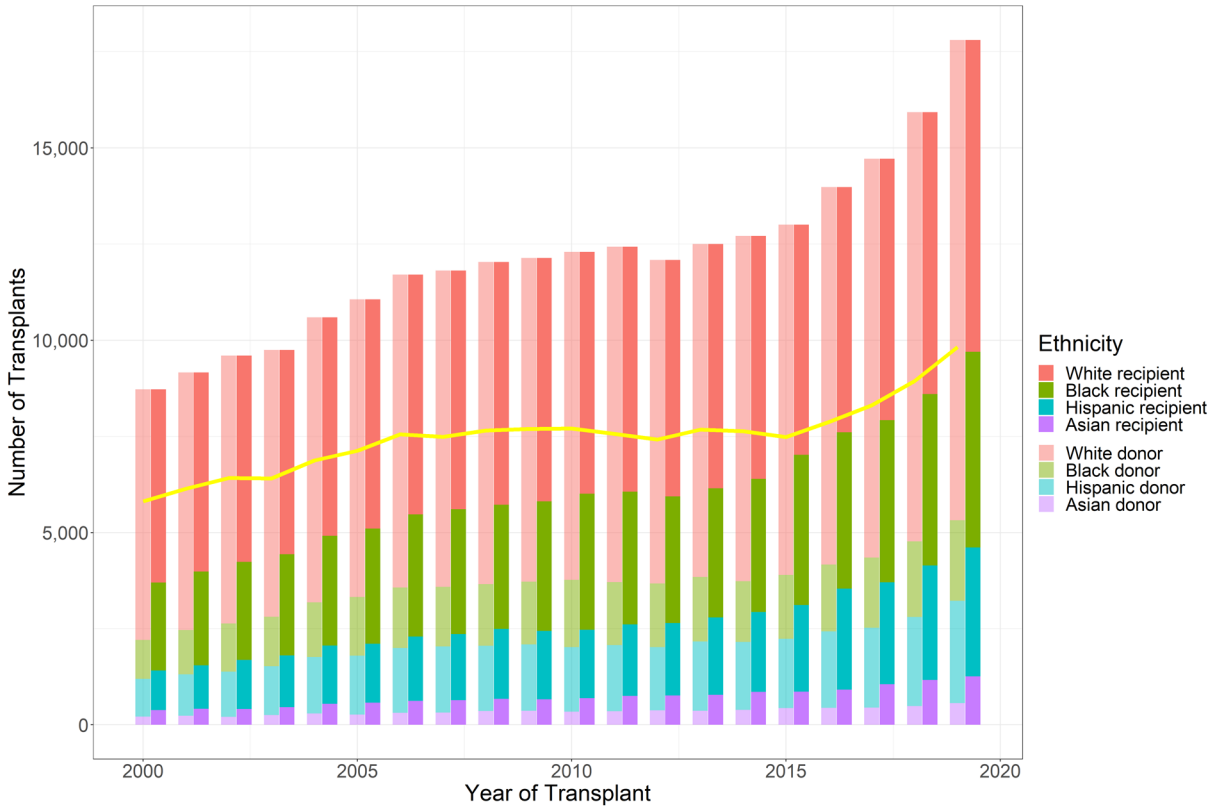

FIGURE 1
Number of kidney transplants performed during the study period, stratified by donor and recipient race (Caucasian, African American, Hispanic, and Asian). Line shows number of race-matched kidney transplants performed yearly (based on the UNOS database).

TABLE 1 Baseline characteristics stratified by donor-recipient race-matching.

	Race-matched (n = 149,600)	Race-unmatched (n = 94,437)	P-value
Recipient age, *n* (%)			
≥60	48,545 (32.4)	29,775 (31.5)	<0.001
Mean, (±SD)	51.59 (±13.71)	51.81 (±12.85)	<0.001
Recipient BMI, mean (±SD)	28.00 (±5.41)	28.08 (±5.42)	0.001
Recipient gender, male, *n* (%)	91,845 (61.4)	57,163 (60.5)	<0.001
Recipient ethnicity, *n* (%)			<0.001
Caucasian	107,351 (71.8)	16,295 (17.3)	
African America	20,741 (13.9)	46,869 (49.6)	
Hispanic	17,927 (12.0)	20,353 (21.6)	
Asian	3,581 (2.4)	10,920 (11.6)	
Cause of ESRD, *n* (%)			<0.001
Glomerular disease	30,888 (20.6)	15,593 (16.5)	
DM	38,889 (26.0)	28,428 (30.1)	
Hypertension	30,120 (20.1)	29,862 (31.6)	
Polycystic kidneys	18,824 (12.6)	6,015 (6.4)	
Other	30,879 (20.6)	14,539 (15.4)	
Recipient insurance, *n* (%)			<0.001
Public	84,688 (56.6)	71,121 (75.3)	
Private	64,902 (43.4)	23,311 (24.7)	
Recipient education level, *n* (%)			<0.001
College or graduate degree	74,182 (49.6)	40,283 (42.7)	
Pre-college	61,520 (41.1)	45,045 (47.7)	
Dialysis before KT, years, *n* (%)			<0.001
No	33,939 (22.7)	8,022 (8.5)	
Yes	114,685 (76.7)	85,952 (91.0)	
Days on waitlist, mean (±SD)	569.25 (±615.47)	909.24 (±784.06)	<0.001
Donor age, *n* (%)			
≥60	12,520 (8.4)	8,226 (8.7)	0.003
Mean (±SD)	40.63 (14.06)	39.55 (15.40)	<0.001
Donor BMI, mean (±SD)	27.22 (±5.73)	27.41 (±6.54)	<0.001
Donor gender, male, *n* (%)	74,119 (49.5)	54,953 (58.2)	<0.001
Donor ethnicity, *n* (%)			<0.001
Caucasian	107,351 (71.8)	64,281 (68.1)	
African American	20,741 (13.9)	10,848 (11.5)	
Hispanic	17,927 (12.0)	15,862 (16.8)	
Asian	3,581 (2.4)	3,446 (3.6)	
Donor type, *n* (%)			<0.001
Living donor	73,395 (49.1)	9,199 (9.7)	

(*continued*)

TABLE 1 Continued

	Race-matched ($n = 149,600$)	Race-unmatched ($n = 94,437$)	*P*-value
Deceased donor	76,205 (50.9)	85,238 (90.3)	
Deceased donor cause of death, *n* (%)			<0.001
Anoxia	19,897 (13.3)	24,819 (26.3)	
Cerebrovascular/Stroke	25,887 (17.3)	28,076 (29.7)	
Head trauma	28,081 (18.8)	29,613 (31.4)	
Other	2,340 (1.6)	2,730 (2.9)	
Period of transplantation, *n* (%)			<0.001
2000–2004	31,651 (21.2)	16,173 (17.1)	
2005–2009	37,517 (25.1)	21,236 (22.5)	
2010–2014	38,004 (25.4)	24,022 (25.4)	
2015–2019	42,428 (28.4)	33,006 (35.0)	
HLA mismatch, *n* (%)			<0.001
<3	37,558 (25.1)	310 (7.7)	
≥3	111,466 (74.5)	87,011 (92.1)	
Cold ischemic time, ≥12 h, *n* (%)	55,176 (36.9)	62,431 (66.1)	<0.001
Delayed graft function, *n* (%)	20,193 (13.5)	25,782 (27.3)	<0.001
Acute rejection, *n* (%)	12,318 (8.2)	9,214 (9.8)	<0.001

BMI, body mass index; ESRD, end-stage renal disease; DM, diabetes mellitus; KT, kidney transplant; HLA, human leukocyte antigen; SD, standard deviation.

the 20-year study period, with an upward trend over time, particular after 2015 (Figure 1).

Baseline characteristics

Differences in baseline characteristics were observed between race-matched ($n = 149,600$) and race-unmatched groups ($n = 94,437$). Specifically, recipients who received allografts from race-matched donors were younger (51.59 ± 13.71 vs. 51.81 ± 12.85, $P < 0.001$), presented with a lower BMI (28.00 ± 5.41 vs. 28.08 ± 5.42, $P = 0.001$), tended to be white (71.8%) and male (61.4% vs. 60.5%, $P < 0.001$), were less likely to have public insurance (56.6%) and dialysis prior to KT (76.7%), were more likely to get college or graduate degrees (49.6%), and spent an average of 340 days shorter on the waitlist than those receiving allografts from race-unmatched donors. The cause of ESRD was more likely to be DM ($n = 38,889$, 26.0%) in race-matched group, while it was to be hypertension ($n = 29,862$, 31.6%) in race-unmatched group.

Race-matched donors were older (40.63 ± 14.06 vs. 39.55 ± 15.40, $P < 0.001$), had a lower BMI (27.22 ± 5.73 vs. 27.41 ± 6.54, $P < 0.001$), tended to be female (50.5%), and were more likely to be living donors. In both groups, the highest racial proportion amongst donors was Caucasian (Table 1).

The number of transplant recipients showed an upward trend in both groups, with the highest number observed between 2015 and 2019. There were statistically significant differences between race-matched and unmatched-groups in terms of HLA mismatch (≥3), cold ischemic time (≥12 h), DGF, and acute rejection (Table 1).

Patient and graft survival

Race-matched recipients survived longer than unmatched recipients ($P < 0.001$) (Figure 2A) with similar result observed for graft survival ($P < 0.001$) (Figure 2B). Compared with race-unmatched patients, race-matched patients experienced a 14% and 21% reduction in the risk of unadjusted mortality and graft failure, respectively (HR 0.86, 95% CI: 0.84–0.87, $P < 0.001$ and HR 0.79, 95% CI: 0.78–0.80, $P < 0.001$) (Table 2). The cumulative 3-, 5-, and 10-year overall survival rates in patients receiving race-matched kidneys were 1.5%, 2.33%, and 4.02% respectively, higher than those in patients who received race-unmatched kidneys, whereas there was no significant difference in 1-year overall patient survival rates between race-matched and race-unmatched groups. Moreover, when examining patient survival at 1-, 3-, 5-, and 10-year within individual races, race-matched patients demonstrated a significant improvement compared to race-unmatched patients (Table 3). Race-matched patients demonstrated a significant improvement in individual-race and overall graft survival compared to race-unmatched patients (Table 4).

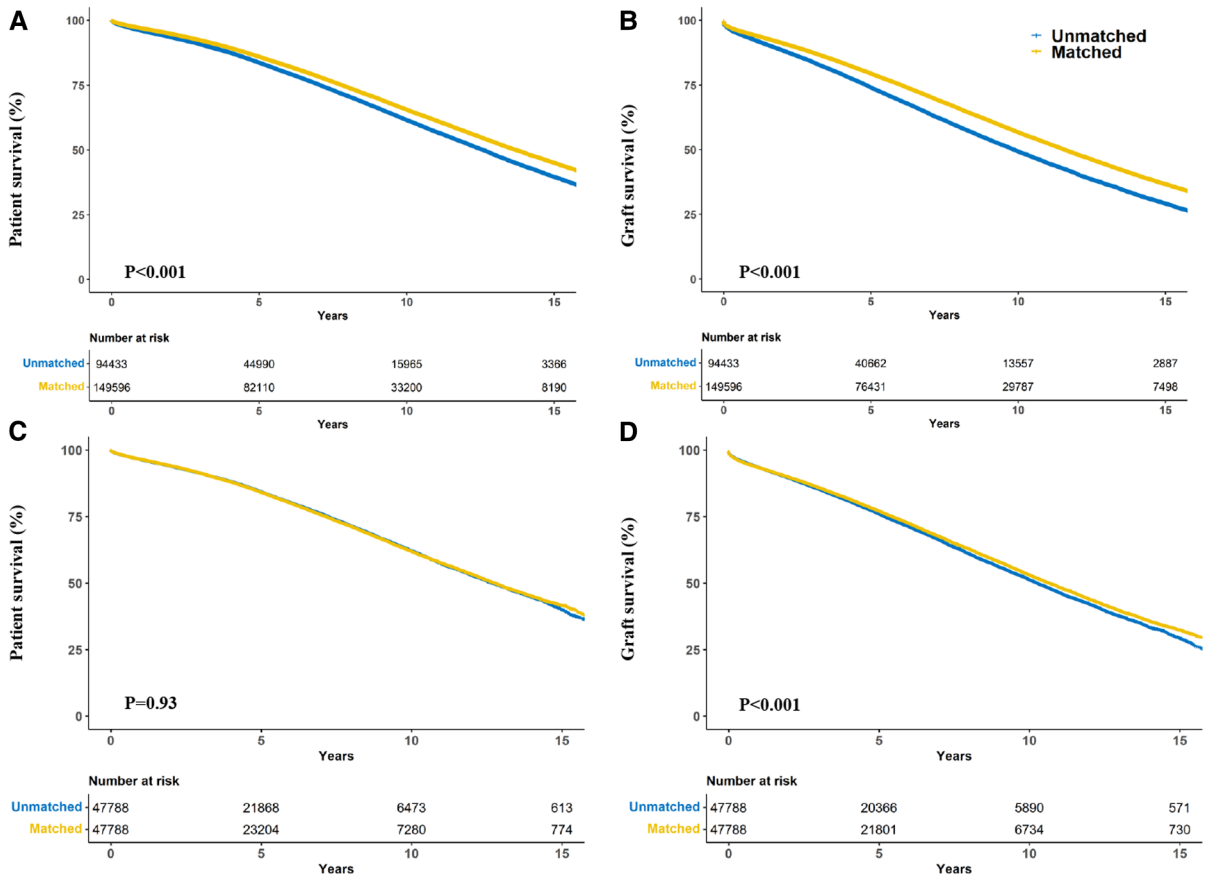

FIGURE 2
Crude kaplan–meier (A,B) and propensity score matching kaplan–meier (C,D) curves estimating patient (A,C) and graft (B,D) survival for kidney transplant recipients stratified according to donor-recipient race-matching vs. unmatching.

TABLE 2 Univariate cox regression model for mortality and graft loss.

	Mortality	*P*-value	Graft loss	*P*-value
Overall race-matched	0.86 (0.84–0.87)	<0.001	0.79 (0.78–0.80)	<0.001
LDKT race-matched	1.12 (1.06–1.20)	<0.001	1.01 (0.97–1.07)	0.565
DDKT race-matched	1.11 (1.09–1.14)	<0.001	0.97 (0.96–0.99)	0.001

LDKT, living donor kidney transplantation; DDKT, deceased donor kidney transplantation.

After propensity score-matching, no significant difference was found in patient survival ($P = 0.93$) (Figure 2C). Interestingly, race-matched patients continued to show longer graft survival after propensity score matching ($P < 0.001$) (Figure 2D).

Subgroup analysis

Notably, patients who received allografts from race-unmatched living donors demonstrated longer survival than those who received allografts from race-matched living donors in the unadjusted Kaplan–Meier curves ($P = 0.002$). A similar outcome was observed in patients who received allografts from deceased donors ($P < 0.001$) (Figure 3A). Compared to race-unmatched patients, race-matched patients who received allograft from living and deceased donors experienced a 12% and 11% increase in the risk of unadjusted mortality, respectively (HR 1.12, 95% CI: 1.06–1.20, $P < 0.001$ and HR 1.11, 95% CI: 1.09–1.14, $P < 0.001$) (Table 2). After propensity score-matching, race-matched LDKT patients had a longer

TABLE 3 Effect of race-matching on unadjusted kaplan–meier estimates of patient survival overall and stratified by race.

	1-year survival	3-year survival	5-year survival	10-year survival
Overall				
Matched	97.06% (96.97–97.15)	92.42% (92.28–92.56)	86.10% (85.90–86.29)	65.65% (65.32–65.99)
Unmatched	96.16% (96.04–96.28)	90.92% (90.72–91.11)	83.77% (83.50–84.04)	61.63% (61.17–62.09)
P-value	0.23	<0.001	<0.001	<0.001
Caucasian				
Matched	96.86% (96.75–96.96)	91.90% (91.73–92.08)	85.11% (84.87–85.35)	63.52% (63.13–63.92)
Unmatched	95.41% (95.09–95.74)	89.17% (88.67–89.68)	80.39% (79.71–81.09)	57.26% (56.21–58.33)
P-value	<0.001	<0.001	<0.001	<0.001
African American				
Matched	96.93% (96.69–97.16)	91.99% (91.60–92.38)	85.83% (85.30–86.37)	65.66% (64.76–66.57)
Unmatched	96.09% (95.91–96.27)	90.48% (90.19–90.76)	83.21% (82.82–83.60)	59.92% (59.26–60.59)
P-value	<0.001	<0.001	<0.001	<0.001
Hispanic				
Matched	98.15% (97.95–98.35)	95.33% (95.00–95.66)	91.17% (90.69–91.65)	77.08% (76.17–77.99)
Unmatched	96.45% (96.19–96.71)	92.12% (91.73–92.52)	85.57% (85.00–86.14)	64.44% (63.41–65.48)
P-value	<0.001	<0.001	<0.001	<0.001
Asian				
Matched	98.50% (98.10–98.90)	96.35% (95.70–96.99)	93.59% (92.69–94.50)	81.98% (80.16–83.84)
Unmatched	97.05% (96.72–97.37)	93.31% (92.81–93.82)	88.33% (87.63–89.04)	71.67% (70.41–72.96)
P-value	<0.001	<0.001	<0.001	<0.001

adjusted patient survival than unmatched control ($P = 0.047$) (Figure 4A); however, the opposite result was observed for DDKT patients ($P < 0.001$) (Figure 4D).

The survival of grafts received from race-matched deceased donors was longer than that of grafts from race-unmatched donors ($P < 0.001$) (Figure 3B), with a 3% decrease in the risk of unadjusted graft failure (HR 0.97, 95% CI: 0.96–0.99, $P < 0.001$) (Table 2). However, there was no significant difference in graft failure between race-matched and race-unmatched living donors ($P = 1$) (Figure 3B). After propensity score-matching, race-matched LDKT patients demonstrated longer adjusted graft survival than the unmatched control group ($P < 0.001$) (Figure 4B) and statistical differences still existed when deaths were censored ($P < 0.001$) (Figure 4C). However, there was no significant difference in graft survival between the race-matched and unmatched DDKT groups ($P = 0.64$) (Figure 4E). Interestingly, when deaths were censored, the survival difference between grafts received from race-matched and unmatched deceased donors was significant ($P = 0.018$) (Figure 4F).

Discussion

We used UNOS database between 2000 and 2019 to examine the effect of donor-recipient race-matching on post-KT outcomes. In our population-based cohort analysis of 244,037 patients, we observed that donor-recipient race-matching was associated with better prognosis for crude patient and graft survival, but with higher mortality when stratified by donor type. Here is an example of Simpson's paradox (13), which are the first to identify in KT. After propensity score-matching, donor-recipient race-matching was associated with a reduced risk of overall crude graft loss but not mortality. Race-matching resulted in longer patient, graft, and death-censored graft survival in LDKT and death-censored graft survival in DDKT. However, donor-recipient race-matching was associated with an increased risk of mortality in DDKT recipients. Therefore, it may be beneficial for patients to consider donor-recipient race-matching in clinical decision-making in KT.

Low rates of patient and graft survival in African Americans receiving KT were first identified in 1977 due to racial disparities (14). Although transplant medicine has made great progress in

TABLE 4 Effect of race-matching on unadjusted kaplan–meier estimates of graft survival overall and stratified by race.

	1-year survival	3-year survival	5-year survival	10-year survival
Overall				
Matched	94.53% (94.41–94.64)	87.74% (87.56–87.91)	79.58% (79.35–79.81)	56.86% (56.52–57.21)
Unmatched	92.74% (92.58–92.91)	84.11% (83.86–84.36)	74.16% (73.84–74.48)	49.37% (48.91–49.84)
P-value	<0.001	<0.001	<0.001	<0.001
Caucasian				
Matched	94.43% (94.29–94.57)	87.94% (87.73–88.14)	79.81% (79.54–80.08)	56.72% (56.33–57.13)
Unmatched	92.07% (91.66–92.49)	83.53% (82.94–84.13)	73.51% (72.75–74.27)	49.98% (48.94–51.05)
P-value	<0.001	<0.001	<0.001	<0.001
African American				
Matched	93.00% (92.66–93.54)	82.77% (82.23–83.31)	72.42% (71.74–73.09)	48.41% (47.51–49.33)
Unmatched	91.98% (91.73–92.23)	81.79% (81.43–82.16)	70.74% (70.27–71.21)	44.38% (43.74–45.02)
P-value	<0.001	<0.001	<0.001	<0.001
Hispanic				
Matched	96.32% (96.04–96.60)	91.13% (90.69–91.58)	84.79% (84.18–85.39)	65.59% (64.58–66.61)
Unmatched	93.82% (93.49–94.15)	87.24% (86.75–87.73)	78.34% (77.67–79.01)	54.42% (53.37–55.49)
P-value	<0.001	<0.001	<0.001	<0.001
Asian				
Matched	97.28% (96.75–97.82)	93.98% (93.17–94.80)	90.01% (88.91–91.12)	72.94% (70.85–75.08)
Unmatched	95.03% (94.62–95.44)	89.36% (88.74–89.98)	82.83% (82.01–83.65)	62.21% (60.86–63.59)
P-value	<0.001	<0.001	<0.001	<0.001

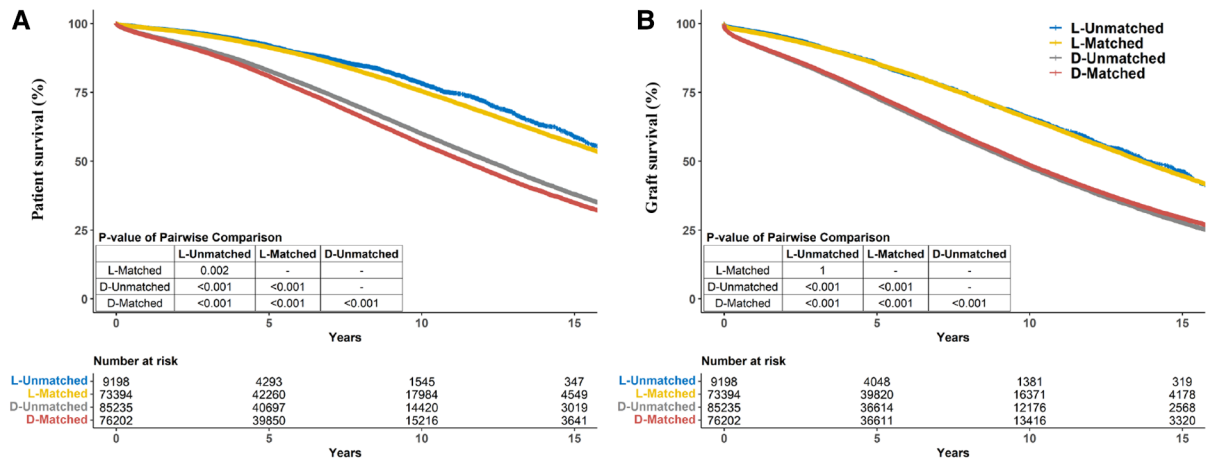

FIGURE 3
Crude kaplan–meier estimates of patient (A) and graft (B) survival for kidney transplant recipients stratified by living/deceased donor-recipient race-matched vs. unmatched groups.

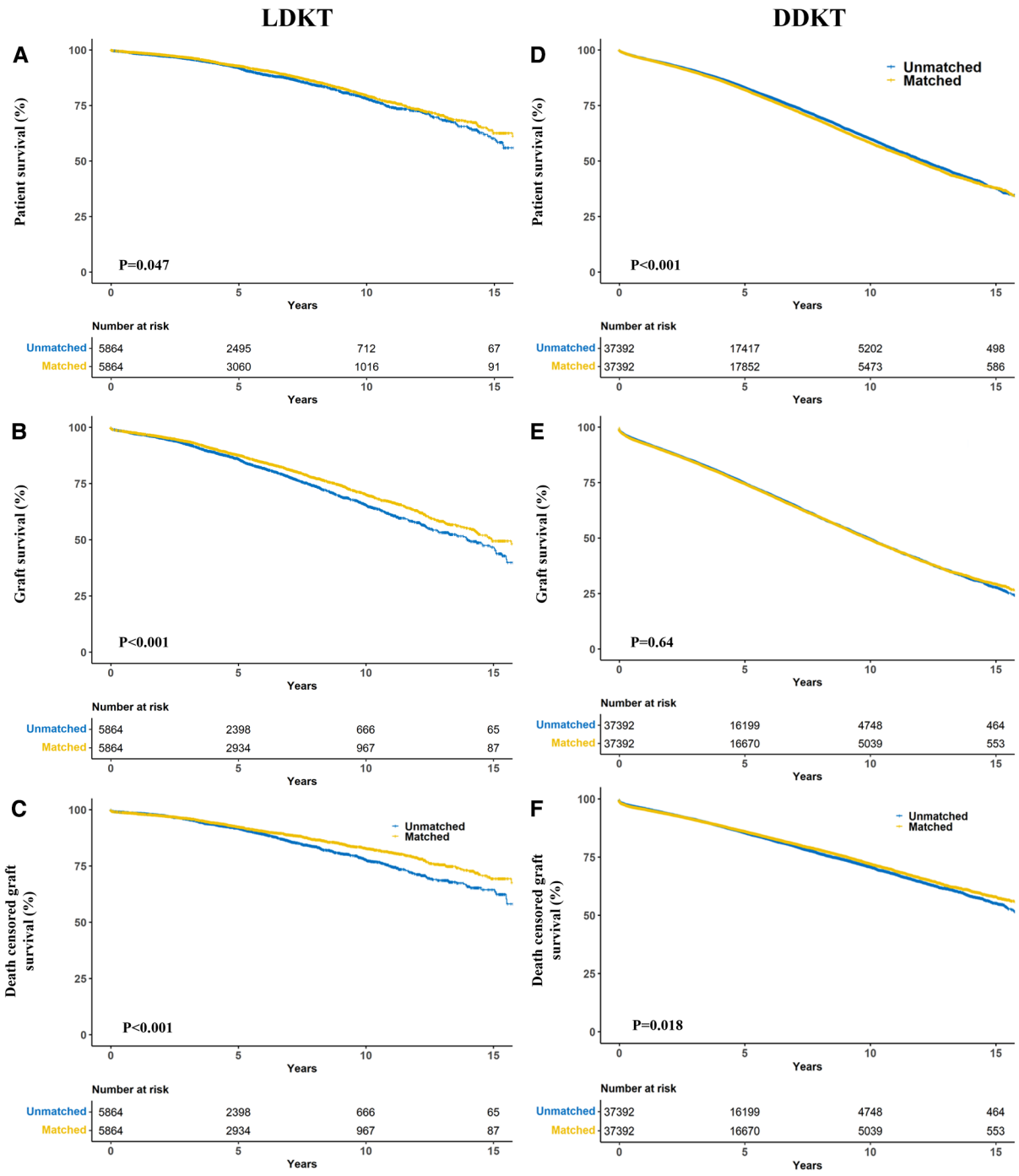

FIGURE 4
Propensity score matching kaplan–meier estimates of patient (A,B), graft (C,D) and death-censored (E,F) survival in living donor kidney transplant (A–C) and deceased donor kidney transplant (D–F) recipients stratified by donor-recipient race-matching.

terms of surgical techniques and immunosuppressant therapy over the past 50 years, racial disparities remain. Previous studies (12, 15–17) have shown that black patients have shorter graft survival and poorer graft function after KT. Despite inconsistent results, more recent studies (18, 19) have demonstrated that patient and graft survival among Asians and Hispanics are longer than among Caucasians. Moreover, non-African Americans experience longer patient survival than do African Americans (20, 21). Due to the disadvantages of socioeconomic status and other factors, less access to health care and specialists for African Americans may have contributed to these differences. In addition, previous researches (22, 23) have shown that the

immune response is more intense in African Americans, which increases the incidence of acute rejection and chronic allograft failure. Studies have confirmed that HLA matching affects survival after KT (24). Presumably, race-matched recipients are more likely to have similar HLA genes and experience fewer acute rejection events than unmatched recipients, which may result in longer patient and graft survival. In our study, the proportion of HLA mismatches (≥3) was higher in race-unmatched recipients, supporting this hypothesis.

Donor-recipient race-matching and post-transplant outcomes have been studied for lung (8), liver (9, 25), and heart (10, 26) transplantation, and the findings showed that the outcomes are more satisfactory if donors and recipients are race matched. Allen et al. (8) performed an analysis of 11,323 primary lung transplant patients from the UNOS dataset between 1997 and 2007 and found that race-matching was associated with a reduced risk of cumulative mortality. In the risk-adjusted model, donor-recipient race-matching reduced the cumulative mortality risk (HR 0.88, 95% CI: 0.80–0.96, $P = 0.006$). Silva et al. (9) retrospectively analyzed African Americans with hepatocellular carcinoma undergoing liver transplantation from 1994 to 2015 using the OPTN/UNOS database and observed that race-matched patients had a higher median overall survival than unmatched patients (135 vs. 78 months, $P = 0.007$). In multivariate analysis, the adjusted hazard ratio for race matching was shown to be 0.66 (95% CI: 0.49–0.88, $P = 0.004$). Kanter et al. (26) conducted a single-center analysis of 169 pediatric primary heart transplants and found that donor-recipient race mismatch showed a lower 5-year graft survival rate (72.3% vs. 48.9% for matched vs. unmatched, $P = 0.0032$). Donor-recipient race mismatching was a predictor of graft failure in the multivariable Cox proportional hazards regression model (HR 2.137, 95% CI: 1.054–4.335, $P = 0.0353$). They considered HLA mismatch as a possible confounder because the incidence of HLA crossmatch was higher for black recipients than for Caucasian recipients.

LeClaire et al. (11) conducted an analysis of solid organ (including heart, lung, liver, kidney, and pancreas) transplantations from the UNOS database and reported that patient survival in KT was not influenced by race-matching, but race-unmatched African Americans experienced shorter graft survival at all time points after controlling for potential confounders, which was inconsistent with our results. In our results, the crude patient and graft survival rates in race-matching were significantly higher than those in race-unmatching. The advantages of race-matching remain in reducing graft loss after propensity score-matching, although there is no significant difference in mortality. The discrepancy between that study and our results may be explained by differences in the control of confounders, with their study analyzing based on ethnicity and ours based on donor type.

We observed that this study presented longer overall crude patient survival in the race-matched group than in the unmatched controls. However, when stratified by donor type, we found the opposite in terms of patient survival, which was longer in the race-unmatched group. This can be explained by Simpson's paradox (1): there are more DDKT recipients in the unmatched group than in the race-matched group, whereas the reverse is true for LDKT recipients, and (2) patients receiving kidneys from living donors experience dramatically longer survival than those receiving kidneys from deceased donors. Simpson's paradox is not limited to race-matching and KT outcomes and has been observed in clinical trials (27), ecological studies (28) and other fields. The results of LDKT and DDKT separately support longer patient survival for race-matched patients, but opposite outcomes are achieved when these groups are combined. After adjusting for baseline confounders, race-matching was associated longer patient survival in LDKT but shorter patient survival in DDKT. Given the variation in clinical characteristics of patients (e.g., age, recipient race and cause of ESRD), Simpson's paradox may arise without adjusting for the possibility of some factors interacting. However, the cause of this discrepancy requires further investigation.

Since the successful practice of LDKT, over 35,000 LDKT procedures are performed each year in the world (29). According to available studies (30–32), living donors have apparent advantages over deceased donors in KT, as they offer longer long-term survival, especially with young donors. However, the number of DDKT cases is far greater than that of LDKT. Surprisingly, in the present study, we found that patient survival was shorter for race-matching than for unmatching in LDKT and DDKT, which may be caused by baseline differences. However, graft survival is longer in race-matched than unmatched transplant in DDKT. In contrast to DDKT, an advantage of race-matching for patient survival after adjustment was observed in LDKT. When deaths were rigorously censored, the advantages of race-matching in graft survival persisted in both the groups. Therefore, we believe that race-matching may be a protective factor in KT, especially for graft survival. Locke et al. (3) performed a retrospective study of the UNOS between 1993 and 2006 and found a 70% reduction in graft loss among African American recipients receiving race-matched kidneys from donation-after-cardiac-death (DCD). However, the allocation of DCD organs and post-transplant care has been improved dramatically in recent years and the applicability of that study is also limited by inadequate sample size. Pisavadia et al. (12) undertook a retrospective study of primary kidney-alone transplantation in adults, using UK Transplant Registry data between 2003 and 2015 and found no statistical differences in patient and graft survival by race-matching after stratification by LDKT and DDKT. The disparities between that study and ours may be due to the different compositions of the ethnic populations in the UK and the United States. Tahir et al. (33) performed a retrospective study comparing the outcomes of Black kidney transplant recipients in the United States and the UK and found that the outcomes of kidney transplants in Blacks differed between the two countries. Therefore, we believe that the differences in

racial effects between the two countries may lead to different outcomes.

Our study had several limitations. First, the study was limited by the methodology of the retrospective cohort, and we were unable to control for all potential confounders, with some important variables missing in our analysis due to the limitation of UNOS data collection. It must be noted that secondary outcomes data (e.g., rejection) in the UNOS dataset is not as complete as primary outcomes data (e.g., survival). Second, the populations of race-matched recipients are much larger for Caucasians than for African Americans, Hispanics, and Asians in KT. For example, there were 107,351 Caucasians recipients receiving matched kidneys, compared to only 20,741 African Americans, 17,927 Hispanics, and 3,581 Asians. Our conclusions may also be affected by the skewed racial distribution. Finally, the purpose of the study was not to identify the underlying mechanism associated with survival difference in donor-recipient race-matching and future studies should explore physiological mechanisms.

This analysis is a contemporary large-sample report on the prognosis of KT based on race-matching. Overall, the survival benefits for recipients improved slightly when the race of recipients was matched to that of donors. Moreover, our results identified that the confounding factors at baseline led to contorted crude conclusions in subgroups, which was reversed again to normal trends in the combined analysis due to Simpson's paradox caused by the LDKT/DDKT ratio. Given the lack of understanding of the mechanisms by which race-matching affects prognosis, this study will drive further scientific research on the immunology and genetics of race matching. However, when considering the clinical practice of KT, the impact of race-matching on patient outcomes was insufficient to affect organ transplant offers.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: Publicly available datasets were analyzed in this study. This data can be found here: https://optn.transplant.hrsa.gov/data/.

Author contributions

KL and YW: participated in research design and wrote the manuscript. KL: ran the statistical analysis. TS and QY: participated in the research design and the critical revision of the manuscript. WL, XH and XX: participated in the data analysis. SH, ZL and CL: participated in revising the article. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.1050416/full#supplementary-material.

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Age and metabolic syndrome are associated with unsatisfactory improvement in nocturia after holmium laser enucleation of the prostate

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Objective: To investigate the association between age, metabolic syndrome (MetS) and improvement in nocturia in patients with benign prostate hyperplasia (BPH) receiving holmium laser enucleation of the prostate (HoLEP).
Methods: The retrospective study was conducted on patients treated for BPH using HoLEP between January 2021 and May 2022. Lower urinary tract symptoms (LUTS) were measured before surgery and at 3 months postoperatively using the International Prostate Symptom Score (IPSS). The criteria of the Adult Treatment Panel III (ATP III) were adopted to diagnose the MetS. Unsatisfactory improvement in nocturia was defined as <50% reduction in nocturia from baseline on the IPSS.
Results: One hundred and seventy-five patients were eventually enrolled, with a median age of 69 years (IQR: 63/73). Unsatisfactory improvement in nocturia was reported in 95 patients (54%) after HoLEP. These patients were older (73; IQR: 67/79 vs. 66; IQR: 60/71, $P < 0.001$) and more likely to present with higher postoperative total (6; IQR: 4/9 vs. 3; IQR:2/5, $P < 0.001$), voiding (1; IQR: 0/3 vs. 1; IQR: 0/2, $P = 0.017$), and storage (4; IQR: 3/6 vs. 2; IQR: 1/4, $P < 0.001$) IPSS when compared to patients with satisfactory improvement in nocturia. Overall, 63 of 175 (36%) patients were diagnosed with MetS and of these, 44 (70%) reported unsatisfactory improvement in nocturia ($P = 0.002$) after HoLEP. Multivariate analysis revealed that age (OR = 1.117, 95% CI: 1.068–1.169, $P < 0.001$) and MetS (OR = 3.613, 95% CI: 1.727–7.562, $P = 0.001$) were independent risk factors for unsatisfactory improvement in nocturia after HoLEP.
Conclusion: Our findings suggest that increased age and MetS were associated with unsatisfactory improvement in nocturia in patients with BPH after HoLEP. Lifestyle management, including weight loss, may be of great importance in the improvement of nocturia.

KEYWORDS

benign prostate hyperplasia, lower urinary tract symptoms, nocturia, metabolic syndrome, holmium laser enucleation of the prostate

Introduction

Nocturia, defined as waking up at night once or more to empty the bladder, is one of the most troublesome and treatment-resistant lower urinary tract symptoms (LUTS) secondary to benign prostate hyperplasia (BPH) (1, 2). It has been shown that more frequent nocturnal episodes are associated with poorer quality of life. Among men aged >70 years, 29%–59.3% had two or more nocturnal episodes, and were strongly associated with BPH (3). More than two episodes of nocturia are considered to have negative physical and mental effects, such as falling at night, fractures, depression and inefficiency (4).

To complicate matters further, nocturia is a common symptom of complex systemic diseases, including diabetes, hypertension, congestive heart failure and sleep apnea (5). Medical management of nocturia is less effective than surgical treatment in achieving significant improvement (1). However, it has been shown that surgical treatments, such as transurethral resection of the prostate (TURP), are also inadequate for reducing the frequency of BPH-related nocturia (6). Risk stratification of nocturia improvement after surgical treatment would benefit standardized management and remains to be further investigated.

Age is believed to be an independent risk factor for nocturia in both men and women, although the underlying pathological mechanisms are incompletely understood (7). Metabolic syndrome (MetS), a complex disorder with increasing worldwide prevalence, has been described as a combination of several metabolic abnormalities, including central obesity, hypertension, insulin resistance and dyslipidemia (8). Notwithstanding their inconsistent findings, several studies have conformed the association of components of metabolic syndrome (obesity, hypertension and diabetes) (9, 10) and lifestyle (smoking, alcohol intake and physical activity) (5) with nocturia.

Holmium laser enucleation of the prostate (HoLEP) has become one of the most important procedures in the treatment of BPH. However, postoperative storage symptoms, especially nocturia, still often show unsatisfactory improvement. Hence, it is important to predict the postoperative improvement in nocturia to better counsel patients preoperatively. To our knowledge, no works have been conducted to evaluate the role of metabolic factors on the likelihood of nocturia improvement after HoLEP in Chinese patients. Therefore, we performed the study to evaluate the association between MetS, age and improvement in nocturia in patients with BPH after HoLEP.

Materials and methods

Study design and participants

Clinical data of patients with symptomatic BPH treated at our hospital were collected from January 2021 to May 2022. A total of 348 patients underwent HoLEP performed by a single surgeon, and 175 of the 348 (50%) patients were eventually included in the study. The Institutional Review Board of our institute approved this retrospective study, and informed consent was obtained from all patients, as this study was a *post-hoc* analysis of prospective data. All the patients met the indications for surgery. We excluded patients with a history of urethral surgery, bladder stone, bladder or prostate cancer, neurogenic bladder, recurrent urinary tract infection, and diuretic use.

Patient characteristics, such as age, body mass index (BMI), systolic and diastolic blood pressure (SBP/DBP), and waist circumference (WC), were collected. With patients standing, we measured the WC midway between the lowest rib and the iliac crest. Operative information including operative time and hemoglobin (Hb) level change, was also recorded. In addition, blood samples were drawn from patients for analysis of blood glucose, triglycerides (TG), high-density lipoprotein (HDL) cholesterol, and total prostate-specific antigen (PSA) after an overnight fast.

LUTS/BPH assessment

Prostate volume (PV) was calculated using transrectal ultrasound, according to the ellipsoidal formula:

$$PV = \frac{\pi}{6} \times width \times height \times depth$$

We evaluated LUTS using the International Prostate Symptom Score (IPSS) questionnaire, which includes voiding and storage IPSS. Voids per night were assessed using IPSS item 7 (nocturia). Unsatisfactory improvement in nocturia was defined as <50% reduction in nocturnal episodes after HoLEP compared to baseline.

Mets definition

In this study, we applied the modified National Cholesterol Education Program/Adult Treatment Panel III (NCE/ATP III) to define MetS (11) as the presence of at least three of the following: (1) waist circumference ≥90 cm; (2) triglyceride level ≥1.7 mmol/L or taking drugs for hypertriglyceridemia; (3) HDL-cholesterol level <1.03 mmol/L or taking drug for low HDL-cholesterol; (4) fasting glucose ≥5.6 mmol/L or taking drugs for hyperglycemia; and (5) SBP ≥130 mmHg or DBP ≥85 mmHg or previously diagnosed hypertension.

Follow-up

All patients were asked to complete the IPSS questionnaire in the outpatient clinic after 3 months. Patients who could not

attend the outpatient clinic for follow-up were contacted *via* telephone to complete the IPSS questionnaire.

Statistical analysis

After evaluation, the data set showed a non-normal distribution. Differences between groups were compared using the Mann-Whitney test for continuous variables and Pearson's chi-square test for categorical variables. Risk factors of unsatisfactory improvement in nocturia (<50% reduction) after HoLEP were assessed using binary logistic regression. The statistically significant variables in the univariate analysis were included in the multivariate model. Multicollinearity occurs when two closely related variables (i.e., MetS and fasting blood glucose) appear in the same multivariable analysis model, leading to unreliable results. Considering the risk of multicollinearity, MetS components were excluded from the multivariate model.

Statistical analyses were performed with SPSS version 26.0. All P values were two-sided with $P < 0.05$ considered statistically significant.

TABLE 1 Characteristics of the analyzed population ($n = 175$).

	Overall
Age, year	69 (63/76)
BMI, kg/m^2	24.2 (22.3/26.2)
Smoking	77 (44%)
Alcohol	72 (41%)
Prostate volume, cc	62 (46/87)
Total PSA, ng/ml	3.37 (1.49/7.42)
Waist circumference ≥90 cm	109 (62%)
HDL <1.03 mmol/L or on drug treatment to reduced HDL-cholesterol	52 (30%)
Triglyceride ≥1.7 mmol/L or on drug treatment for elevated triglycerides	31 (18%)
Fasting glucose ≥5.6 mmol/L or on drug treatment for elevated glucose	58 (33%)
SBP ≥130 mmHg and/or DBP ≥85 mmHg or on antihypertensionsive drug treatment in a patient with history of hypertension	127 (73%)
MetS	63 (36%)
Preoperative IPSS	
Total	21 (17/27)
vIPSS	12 (10/16)
sIPSS	9 (7/12)
Nocturia	4 (3/5)
IPSS 3 mo	
Total	5 (3/7)
vIPSS	1 (0/3)
sIPSS	3 (2/5)
Nocturia	2 (1/3)
Nocturia improvement	80 (46%)

BMI, body mass index; PSA, prostate-specific antigen; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure; MetS, metabolic syndrome; IPSS, International Prostate Symptom Score; vIPSS, voiding International Prostate Symptom Score; sIPSS, storage International Prostate Symptom Score.

Results

The median age and BMI of the patients were 69 years and 24.2 kg/m^2, respectively. Overall, 77 (44%) men smoked and 72 (41%) men had a history of alcohol consumption. The median prostate volume and median PSA of all patients were 62 cc and 3.37 ng/ml, respectively. The median number of voids per night was 4 before the operation and 2 after the operation. A total 95 of 175 (54%) patients showed unsatisfactory improvement in nocturnal episodes after HoLEP (Table 1). Sixty-three of 175 (36%) patients were diagnosed with MetS, and of these 44 (70%) reported unsatisfactory improvement in nocturia. Moreover, elevated blood pressure (73%), elevated waist circumference (62%) and elevated blood glucose (58%) were the three most reported components of MetS. In addition, the highest and lowest probabilities of unsatisfactory improvement in nocturia were observed in patients with five and three components of MetS, 75% and 46% respectively (Figure 1).

Overall, patients with unsatisfactory improvement in nocturia were older (73; IQR: 67/79 vs. 66; IQR: 60/71, $P <$

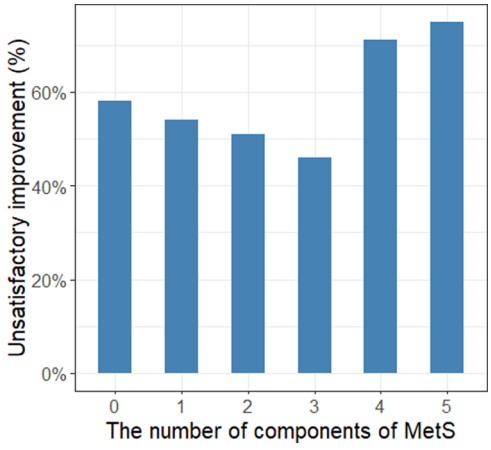

FIGURE 1
The association between the number of components of MetS and unsatisfactory improvement in nocturia.

0.001) and more likely to suffer from diabetes (26/95: 27% vs. 12/80: 15%, $P = 0.048$) and MetS (44/95: 46% vs. 19/80: 24%, $P = 0.002$) than show improvement in nocturia. These patients presented higher level of fasting glucose (5.06; IQR: 4.61/5.96 vs. 4.76; IQR: 4.48/5.20, $P = 0.001$), more MetS components (2; IQR: 1/3 vs. 2; IQR:1/2, $P = 0.011$), higher postoperative total (6; IQR: 4/9 vs. 3; IQR: 2/5, $P < 0.001$), voiding (1; IQR: 0/3 vs. 1; IQR: 0/2, $P = 0.017$), storage (4; IQR: 3/6 vs. 2; IQR: 1/4, $P < 0.001$) IPSS (Table 2). However, there were no significant differences between the groups in terms of BMI, hypertension, SBP, DBP, smoking, alcohol intake, WC, TG, HDL, operation time, Hb change, prostate volume, total PSA level or preoperative IPSS.

On crude logistic regression analysis, age (OR = 1.104; 95% CI: 1.058–1.151, $P < 0.001$), fasting glucose (OR = 1.468; 95% CI: 1.016–2.121, $P = 0.041$), and MetS (OR = 2.770; 95% CI: 1.440–5.327, $P = 0.002$) were predictors of unsatisfactory improvement in nocturia. Multivariate analysis revealed that age (OR = 1.117; 95% CI: 1.068–1.169, $P < 0.001$) and MetS (OR = 3.613; 95% CI: 1.727–7.562, $P = 0.001$) were independent risk factors for unsatisfactory improvement in nocturia after HoLEP (Table 3).

TABLE 2 Patient's characteristics according to the improvement or not in nocturia after HoLEP.

	Satisfactory improvement	Unsatisfactory improvement	*P*
Patients	80	95	
Age, year	66 (60/71)	73 (67/79)	<0.001
BMI, kg/m^2	24.3 (22.3/26.2)	24.2 (22.3/26.6)	0.690
Hypertension	33/80 (41%)	47/95 (49%)	0.277
SBP, mmHg	132 (125/137)	132 (126/140)	0.406
DBP, mmHg	76 (74/82)	76 (74/80)	0.930
Diabetes mellitus	12/80 (15%)	26/95 (27%)	0.048
Smoking	37/80 (46%)	40/95 (42%)	0.582
Alcohol	38/80 (48%)	34/95 (36%)	0.117
WC, cm	91 (87/96)	93 (87/97)	0.239
TG, mmol/L	1.00 (0.74/1.44)	1.09 (0.72/1.47)	0.654
HDL, mmol/L	1.21 (0.96/1.39)	1.17 (0.94/1.39)	0.509
Fasting glucose, mmol/L	4.76 (4.48/5.20)	5.06 (4.61/5.96)	0.001
Operation time, min	78 (60/100)	80 (60/100)	0.294
Hb change, g/L	9 (4/13)	7 (4/14)	0.724
MetS	19/80 (24%)	44/95 (46%)	0.002
No. MetS component	2 (1/2)	2 (1/3)	0.011
Prostate volume, cc	58 (43/82)	66 (47/89)	0.233
Total PSA, ng/ml	3.42 (1.57/8.72)	3.37 (1.40/6.90)	0.644
Preoperative IPSS			
Total	21 (17/27)	20 (16/27)	0.509
vIPSS	13 (10/16)	12 (10/15)	0.400
sIPSS	9 (7/12)	10 (6/12)	0.838
IPSS 3 mo			
Total	3 (2/5)	6 (4/9)	<0.001
vIPSS	1 (0/2)	1 (0/3)	0.017
sIPSS	2 (1/4)	4 (3/6)	<0.001

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; TG, triglycerides; HDL, high-density lipoprotein; MetS, metabolic syndrome; PSA, prostatespecific antigen; IPSS, International Prostate Symptom Score; vIPSS, voiding International Prostate Symptom Score; sIPSS, storage International Prostate Symptom Score.

Discussion

This study evaluated the association between MetS, age and improvement in nocturia after HoLEP in Chinese patients with BPH. In our study, 95 (54%) patients reported unsatisfactory improvement in nocturia episodes after HoLEP, and of these 44 (46%) reported MetS. Results from our study showed that age and MetS were independent risk factors for unsatisfactory improvement in nocturia, as assessed by IPSS item 7, after HoLEP. Nocturia, the most frequently observed storage symptom, is still considered to be the most treatment-resistant LUTS among patients undergoing treatment for BPH (12).

TABLE 3 Univariate and multivariate binary logistic regression to predict the risk of improvement in nocturia after HoLEP.

	Univariate odds ratio	*P*	Multivariate odds ratio	*P*
Age, year	1.104 (1.058–1.151)	<0.001	1.117 (1.068–1.169)	<0.001
BMI, kg/m^2	1.029 (0.927–1.142)	0.588		
Hypertension	1.395 (0.765–2.541)	0.277		
DM	2.135 (0.997–4.573)	0.051		
Smoking	0.845 (0.464–1.539)	0.582		
Alcohol	0.616 (0.336–1.130)	0.118		
WC, cm	1.026 (0.983–1.070)	0.239		
TG, mmol/L	1.417 (0.641–3.132)	0.389		
HDL, mmol/L	0.867 (0.326–2.304)	0.775		
Fasting glucose, mmol/L	1.468 (1.016–2.121)	0.041		
MetS	2.770 (1.440–5.327)	0.002	3.613 (1.727–7.562)	0.001
PV, cc	1.005 (0.997–1.012)	0.228		
PSA, ng/ml	1.000 (0.976–1.024)	0.999		

BMI, body mass index; DM, diabetes mellitus; WC, waist circumference; TG, triglycerides; HDL, high-density lipoprotein; MetS, metabolic syndrome; PV, prostate volume; PSA, prostate-specific antigen.

However, few studies have evaluated MetS and changes in nocturia in patients with BPH before and after surgery. Therefore, prospective studies are necessary to evaluate the impact of MetS and its components on the improvement of early long-term nocturia in patients with BPH.

Nocturia is an extremely common symptom that has been reported to be associated with a variety of comorbidities, including diabetes, obesity, coronary artery disease, depression and MetS (13). As people age, nocturnal episodes increases (5) and the prevalence of two or more voids per night can exceed 51% in men and 45% in women aged ≥60 years according to a 2019 study using the National Health and Nutrition Examination Survey (NHANS) (14). The potential causes are the loss of smooth muscle cells and the accumulation of collagen and fibrotic deposits in the aging bladder (15), leading to detrusor instability and deceased bladder capacity (16). When voiding ≥2 times per night, the elderly are at significantly increased risk of sleep disorders, falls, fractures, and daytime fatigue, leading to severe mortality (17).

Removal of bladder outlet obstruction promotes recovery of bladder function and alleviates associated symptoms such as nocturia. Wada et al. investigated the effects of TURP on nocturia and sleep disturbances in patients with LUTS/BPH. Their findings showed a significant improvement in nocturnal voids after surgical treatment, but nocturia showed the least improvement among items of the IPSS (18). Studies have reported a better nocturia response after TURP in patients with BPH compared with medications such as alpha-blockers, anticholinergics and desmopressin (19). Although TURP outcomes are better than medication, the nocturia response remains unsatisfactory after TURP.

Several studies have demonstrated that MetS and its components are associated with LUTS. Cosimo et al. conducted a retrospective study that showed that age, MetS, PV, and smoking were independent risk factors for the severity of nocturia (10). In addition, a separate study showed that PV, MetS, and smoking were associated with moderate/severe persistent nocturia after TURP in multivariate analysis (8). Regrettably, this study only described risk factors for the severity of postoperative nocturia. Considering the effect of preoperative nocturnal voids, we investigated the risk factors for unsatisfactory improvement (<50% reduction) in nocturia after HoLEP. In contrast to their findings, we found that age was associated with unsatisfactory improvement in nocturia after surgery.

Although the mechanism is not yet fully understood, several works have reported a positive correlation between obesity and nocturia. The Boston Area Community Health (BACH) survey reported that BMI > 30 increases the risk of nocturia (OR = 1.65, 95% CI: 1.29–2.11) (20). Similarly, other studies (21, 22) also reported that obesity is significantly associated with nocturia. Abdominal obesity may increase intra-abdominal pressure, leading to a reduction in bladder capacity, to consequent increase in nocturia (23). Additionally, a randomized clinical trial study reported an association between weight loss and improvement in nocturia, with a much lower incidence of nocturia in behavioral weight loss than in the control group over a 6-month period (24). In our study, a significant association between obesity and improvement in nocturia has not been reported.

Studies have reported that type 2 diabetes is closely related to nocturia (20, 25–27). Therefore, osmotic diuresis should not be ignored. Patients with diabetes have a higher incidence of nocturia than those without (27). Similarly, Fitzgerald et al. (20) reported a 1.67-fold increase in the risk of nocturia in patients with diabetes. Consistent with previous studies, our results showed that diabetes also affected nocturia improvement after HoLEP. An animal study (28) has shown that diabetes may affect bladder uroepithelial homeostasis and further contribute to bladder dysfunction. Hyperinsulinemia may lead to the activation of the sympathetic nervous system, and may be associated with increased prostatic smooth tone, leading to more severe LUTS (29).

In a Japanese study that included 728 patients with LUTS, multivariate analysis revealed that hypertension was significantly associated with nocturia (OR = 9.79, 95% CI: 6.53–14.9) (30). Moreover, blood pressure is significantly higher in elderly patients with nocturia than in those without (31). Hwang et al. reported that PV was relatively large in patients with poorly controlled blood pressure, which leads to increased functional bladder residual urine and consequently more nocturia (32). Additionally, sodium retention is an important mechanism leading to nocturnal polyuria in patients with hypertension, resulting in increased urine production.

However, a less clear association was observed between dyslipidemia and LUTS/nocturia. An overactive bladder and prostate enlargement, resulting in increased nocturnal voids, have been shown to occur in hyperlipidemic rats (33). A significant association between hypertriglyceridemia and nocturia (≥2 voids) was reported in a population-based epidemiological survey (34). However, an association between nocturia and dyslipidemia has not been found in other epidemiological studies (35).

It is well known that the prevalence of nocturia increases with age (3). In our study, age was an independent risk factor for unsatisfactory nocturia improvement after HoLEP. It is easy to understand that older men are more likely to develop bladder outlet obstruction, resulting in decreased functional capacity of bladder including impaired contraction strength and reduced storage function. Reduced bladder capacity (36) and overactive bladder (37) are also more common in the elderly. Older patients may have more comorbidities such as hypertension, diabetes and obesity, which contribute to nocturia. Therefore, eliminating the bladder outlet obstruction in these patients is an important intervention to reduce nocturia, but it alone is not sufficient.

This study had some limitations. First, there may have a selection bias because it was a retrospective study. This was a single-center study with a small sample size, which is less representative of the Chinese population. Second, considering the 24-h water intake, urine amount and nocturnal bladder capacity, the lack of frequency volume charts to evaluate nocturia is an important limitation of the present study. As in other studies (8, 10), we evaluated nocturia episodes using IPSS item 7, which may be inaccurate in the assessment of patients with more than five preoperative nocturia episodes. Moreover, the postoperative follow-up period was only 3 months, without long-term follow-up. Finally, we conducted this study in a Chinese patient cohort, and the findings may not be applicable to European or American populations.

In conclusion, our results suggest that age and MetS are significantly associated with unsatisfactory improvement in nocturia (<50% reduction) after HoLEP in the Chinese patients with BPH. It would be interesting for future studies to evaluate the effect of lifestyle on the improvement of nocturia after HoLEP in patients with BPH. Although the mechanism is not fully understood, counseling BPH patients with MetS about postoperative nocturia improvement is warranted.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of our Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

KL and YW participated in research design and wrote the manuscript. KL performed the statistical analysis. QY and TS participated in the research design and the critical revision of the manuscript. SH, ZL, and QM participated in the data analysis. WL, XX, CL and XH participated in revising the article. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Double pigtail tube drainage for large multiloculated pyogenic liver abscesses

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Background: This study aims to investigate the efficacy and safety of double pigtail tube drainage compared with single pigtail tube drainage for the treatment of multiloculated pyogenic liver abscesses greater than 5 cm.
Patients and Methods: This study retrospectively analyzed patients with pyogenic liver abscess admitted in the Affiliated Hospital of Chengde Medical College between May 2013 and May 2021. Patients with pyogenic liver abscess more than 5 cm in size, who underwent drainage of the abscess with either double pigtail or single pigtail tube, were included.
Results: A total of 97 patients with pyogenic liver abscesses larger than 5 cm were studied. These included 34 patients with double pigtail tube drainage and 63 patients with single pigtail tube drainage. The postoperative hospital stay (13.39 ± 4.21 days vs. 15.67 ± 7.50 days; $P = 0.045$), and time for removal of the catheter (17.23 ± 3.70 days vs. 24.11 ± 5.83 days; $P = 0.038$) were lower in the double pigtail tube group compared with the single pigtail tube group. The rate of reduction, in three days, of c-reactive protein levels was 26.61 ± 14.11 mg/L/day in the double pigtail tube group vs. 20.06 ± 11.74 mg/L/day in the single pigtail tube group ($P = 0.025$). The diameter of the abscess cavity at discharge was 3.1 ± 0.07 cm in the double pigtail tube group as compared with 3.7 ± 0.6 cm in the single pigtail tube group ($P = 0.047$). There was no bleeding in any of the patients despite abnormal coagulation profiles. There was no recurrence of abscess within six months of discharge and no death in the double pigtail tube group. Conclusion: Double pigtail tube drainage treatment in multiloculated pyogenic liver abscesses greater than 5 cm in size, is safe and effective.

KEYWORDS

pyogenic liver abscess, multiloculated pyogenic liver abscess, double pigtail tube drainage, percutaneous needle aspiration, percutaneous catheter drainage

Introduction

Pyogenic liver abscess (PLA) is a suppurative infection of the liver parenchyma. The incidence of PLA is high in Asian countries, The annual incidence of PLA in Taiwan was reported to increase from 11.15/100,000 population in 1996 to 17.59/100,000 population in 2004, showing an increasing trend (1). PLA is associated with significant in-hospital mortality which has ranged from 3%–20% in various reports (2–4). In recent decades, early diagnosis, effective antibiotic therapy and adequate drainage of pus have resulted in lower mortality, and the mortality rates having dropped to between 0.9 to 5.6% (5, 6).

Due to advances in imaging technology, percutaneous drainage has replaced open surgical drainage and is now the first-line treatment for PLA (7–9). No differences have been found in success rates with the use of percutaneous drainage in PLA whatever the location of the abscess or the size (10). Kulhari and Mandia (11) reported that percutaneous catheter drainage (PCD) was a better therapeutic option compared with percutaneous needle

aspiration (PNA), especially in the case of large liquefied abscesses. They reported that patients treated with PNA improved slowly, mainly due to the viscosity of the pus and its rapid re-accumulation in the abscess cavity. For larger PLA, a single drainage tube offered a better and faster drainage of pus and resulted in a reduction in the size of the abscess cavity (10, 12). Typically, percutaneous drainage is achieved by placing a single catheter in the dependent portion of an abscess. With a single catheter, complex abscesses with multiloculation, necrotic debris, and clots, can be challenging to adequately drain and resolve. A single catheter may not be adequate for drainage of such abscesses. In this study, we explored the safety and efficacy of double pigtail (DP) tube drainage in multiloculated PLA, more than 5 cm in size.

Patients and methods

This was a retrospective study conducted at the Affiliated Hospital of Chengde Medical College. The study protocol was approved by the Institutional Ethics Committee. The need for informed consent was waived because of the retrospective nature of the study.

The medical records of all patients admitted with a diagnosis of PLA, between May 2013 to May 2021 were reviewed. Inclusion criteria included: multiloculated abscess more than 5 cm in size on computerized tomography (CT) scan or magnetic resonance imaging (MRI) of the abdomen (**Figure 1**); aspiration of pus on ultrasound-guided percutaneous aspiration; patients who underwent percutaneous drainage of the abscess with either a single or double pigtail catheter. Patients with amebic abscesses and those with severe coagulopathy at admission were excluded. The doctor informed patients the possible risks and pain of the operation, and the patients chose to perform a single or double pigtail drainage catheters for treatment.

As per standard protocol, patients admitted with PLA were started on intravenous antibiotics. Treatment begun with parenteral third generation cephalosporins like cefoperazone sodium or with quinolones. In case the patient was not responding, the antibiotics were changed as per the sensitivity of the organism in the case of positive pus cultures or empirically to other drugs such as piperacillin tazobactam in the case of negative pus cultures. Intravenous antibiotics are given for 2–6 weeks depending on the response. In addition, the patients will be instructed to continue taking oral antibiotics for 2 weeks after discharge.

Two experienced physicians performed the operations. Percutaneous catheter drainage was done as follows: An 18-guage needle was inserted into the abscess cavity under ultrasound guidance and pus aspirated with a 20-ml syringe. A guidewire was inserted into the abscess cavity through the needle which was then removed. An or two 8F pigtail drainage catheters were then placed in the abscess cavity through the guidewire. The cavity was once flushed with 50–60 ml of normal saline every day thereafter.

Routine monitoring of the patient included: clinical status especially the body temperature and other vital signs, amount of pus drained, white blood cell count, serum calcitonin, c-reactive protein, and liver and renal function tests. Pus aspirated was sent for culture and sensitivity. An abdominal CT scan or MRI was done as indicated for evaluation of changes in the size of the abscess cavity and the presence of blood or pus (**Figures 2A–C**). A review liver CT scan was done before removal of the catheter.

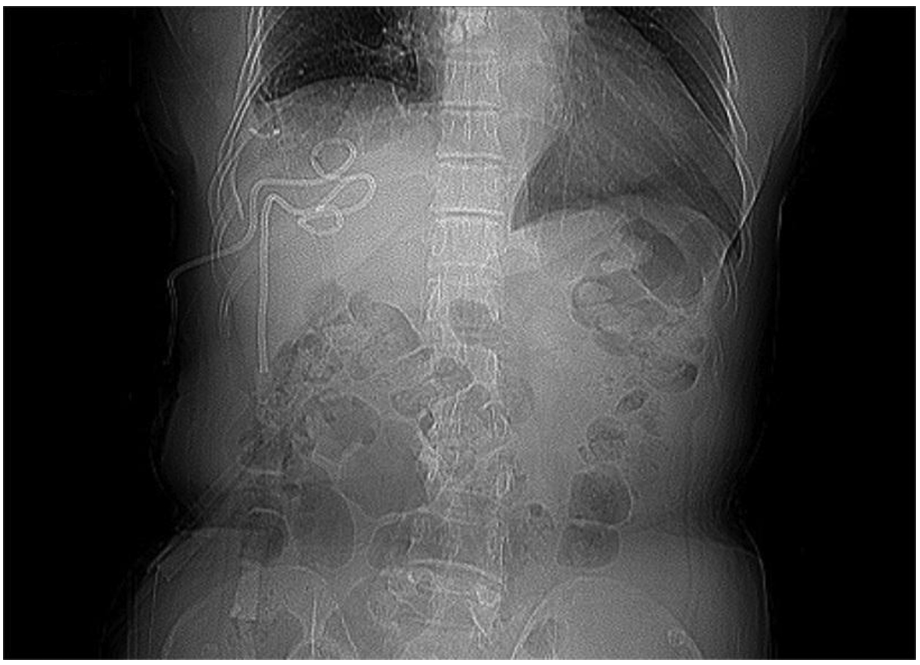

FIGURE 1
Preoperative abdominal CT suggested a large multiloculated pyogenic liver abscesses.

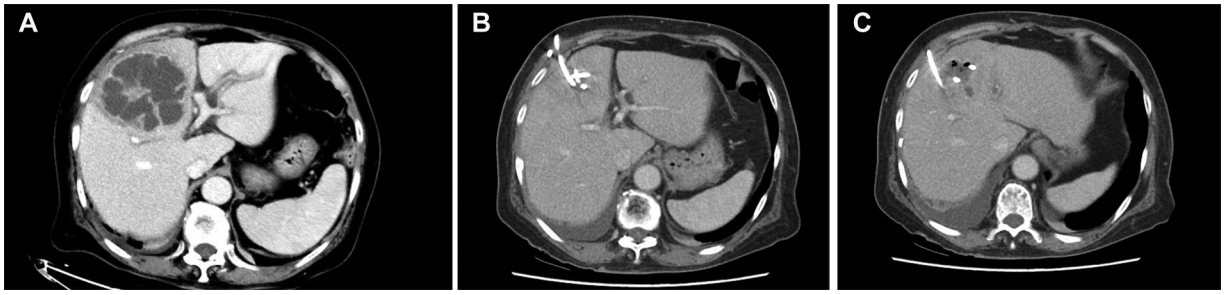

FIGURE 2
(A–C) two pigtail drainage catheters in the PLA and significant reduction of pyogenic liver abscess was observed on postoperative abdominal CT.

Data collected from the medical records included: demographic characteristics of patients, clinical features including presence of comorbidities, etiopathologic factors, laboratory and radiological findings, number, size and location of lesions, microbiological findings, details of treatment, treatment response, complications and mortality.

Statistical analysis

Categorical data were expressed as numbers and percentages. Continuous data were summarized as mean + standard deviation. Continuous variables were compared using the Student's *t*-test or Wilcoxon test as applicable. Categorical data were compared using the chi-square test or Fisher's exact test. Logistic regression analysis was used for analysis of risk factors for septic shock. Statistical analysis was done using the IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, NY, United States) A *P*-value <0.05 was taken as statistically significant.

Results

A total of 97 patients with PLA > 5 cm were treated with percutaneous drainage between May 2013 and May 2021. The baseline characteristics of patients who were treated with DP and single pigtail (SP) catheter drainage are summarized in Table 1. A majority of the patients in both groups were male. The right lobe of the liver was the most common location of the abscess. The two groups were comparable with respect to demographic characteristics, comorbid conditions and location and size of the liver abscess.

Table 2 summarizes the clinical symptoms, laboratory tests, and complications of patients in the two groups. Fever and abdominal pain were the most common presenting symptoms of patients in both groups. Invasive liver abscess syndrome was seen in four patients. There was no difference between the two groups with respect to symptoms, laboratory findings or complications.

The microbiological findings are shown in Table 3. Positive cultures (pus and/or blood culture) were seen in 83 of 97 patients (89.2%). Gram-negative bacilli (Klebsiella pneumoniae and Escherichia coli) were the most commonly isolated organisms (82%) with Klebsiella pneumoniae being the most common (76%).

TABLE 1 Baseline characteristics of patients in the two groups.

	Double pigtail catheter drainage (*n* = 34)	Single pigtail catheter drainage (*n* = 63)	*P*-value
Age mean ± SD (years)	58.94 ± 14.33	59.27 ± 14.87	0.904
Gender			
Male *n* (%)	22 (65%)	39 (62%)	0.482
Female *n* (%)	12 (35%)	24 (38%)	
Location of abscess			
Left lobe *n* (%)	10 (29%)	15 (24%)	0.792
Right lobe *n* (%)	22 (65%)	45 (71%)	0.794
Both lobes *n* (%)	2 (6%)	3 (5%)	0.685
Diameter of abscess (mm)	79.7 ± 19.5	81.4 ± 24.4	0.107
Containing gas *n* (%)	7 (21%)	11 (17%)	0.315
Concomitant disease			
Diabetes mellitus	14 (41%)	25 (40%)	0.528
Hypertension	9 (26%)	16 (25%)	0.546
Cholelithiasis	5 (15%)	11 (18%)	0.483
Malignancy	4 (12%)	7 (11%)	0.584
History of abdominal surgery	4 (12%)	9 (14%)	0.495

Table 4 summarizes the post-operative course in the two groups of patients. The postoperative hospital stay, the time for removal of the catheter and the abscess diameter at time of removal of catheter were significantly lower in the DP group compared with the SP group. The rate of reduction in c-reactive protein levels (measured over three days) was also more rapid in the DP group.

The risk factors for progression to septic shock were studied by univariate regression. Presence of gas in the abscess cavity and diabetes mellitus were further studied by multivariate regression. Only diabetes mellitus was found to be a significant independent

TABLE 2 Clinical symptoms, laboratory tests, and complications.

	Double pigtail catheter drainage ($n = 34$)	Single pigtail catheter drainage ($n = 63$)	*P*-value
Symptoms			
Fever *n* (%)	31 (91%)	58 (92%)	0.579
Abdominal pain *n* (%)	24 (71%)	39 (62%)	0.504
Generalized weakness *n* (%)	21 (62%)	37 (59%)	0.472
Cough *n* (%)	9 (6%)	21 (33%)	0.323
Nausea and vomiting *n* (%)	11 (32%)	19 (30%)	0.499
Laboratory results (mean ± SD)			
White blood cell count ($\times 10^9$/L)	15.31 ± 5.22	13.84 ± 4.53	0.158
Platelet count ($\times 10^9$/L)	26.91 ± 4.55	23.32 ± 5.83	0.659
C-reactive protein(mg/L)	134.19 ± 78.68	132.61 ± 69.26	0.709
Fibrinogen (mg/dl)	6.84 ± 1.58	6.42 ± 1.28	0.054
Alanine aminotransferase (U/L)	70.02 ± 46.23	74.52 ± 56.34	0.881
Total bilirubin (μmol/L)	25.83 ± 16.42	23.09 ± 14.58	0.447
Serum albumin (g/L)	27.09 ± 3.33	28.24 ± 4.48	0.112
Complications			
Pulmonary infection *n* (%)	13 (38%)	30 (48%)	0.273
Pleural effusion *n* (%)	25 (74%)	47 (75%)	0.546
Septic shock *n* (%)	4 (12%)	11 (17%)	0.335
ICU admission *n* (%)	1 (3%)	3 (5%)	0.562
Invasive liver abscess syndrome			
Endophthalmitis *n* (%)	1 (3%)	1 (2%)	0.654
Pulmonary abscess *n* (%)	1 (3%)	0	0.171
Subphrenic abscess *n* (%)	0	1 (2%)	0.351

ICU, Intensive Care Unit.

TABLE 3 Microbiological findings.

	Number of patients (total $n = 97$	Percentage (%)
Pus culture positive	77	79.4%
Blood culture positive	24	25%
Pus + blood culture positive	18	18.6%
Organisms		
Klebsiella pneumoniae	63	76%
Escherichia coli	5	6%
Streptococcus	5	6%
Enterococcus faecium	3	3.6%
Other bacteria	4	4.8%
Fungus	3	3.6%

TABLE 4 Comparison of the postoperative conditions between the two groups.

	Double pigtail catheter drainage ($n = 34$)	Single pigtail catheter drainage ($n = 63$)	*P*-value
Postoperative hospital stay (days)	13.39 ± 4.21	15.67 ± 7.50	0.045
Rate of reduction of c-reactive protein over 3 days (mg/l/day)	26.61 ± 14.11	20.06 ± 11.74	0.025
Complications			
Abdominal infection *n* (%)	0	1 (2%)	0.351
Postoperative fever and chill *n* (%)	22 (65%)	35 (56%)	0.398
Bleeding *n* (%)	0	0	
Recurrence of abscess within 6 months *n* (%)	0	1 (2%)	0.351
Time for removal of catheter (days)	17.23 ± 3.70	24.11 ± 5.83	0.038
Diameter of abscess at time of removal of catheter (cm)	3.1 ± 0.7	3.7 ± 0.6	0.047
Death in hospital *n* (%)	1 (3%)	2 (3%)	0.720

risk factor for septic shock. The results of the regression analysis are shown in Table 5.

Discussion

In recent years, antibiotic therapy along with PCD, rather than surgical drainage, has become the standard of care for PLAs (13, 14). PCD achieves the same cure rate as surgical drainage, but with less trauma, lower complication rates, and shorter hospital stay. Intravenous antibiotics are also the mainstay of treatment and are given for 2–6 weeks depending on the response.

TABLE 5 Risk factors for septic shock—univariate and multivariate analysis.

Variables	Univariate Analysis	*P*-value	Multivariate Analysis	*P*-value
	Odds Ratio (95% CI)		Odds Ratio (95% CI)	
Gas in abscess cavity	3.908 (1.227, 12.450)	0.021	2.877 (0.795, 10.407)	0.107
Diabetes mellitus	5.026 (1.468, 17.206)	0.010	5.203 (1.358, 19.935)	0.016
Gender	1.599 (0.527, 4.856)	0.407		
Age	1.013 (0.974, 1.053)	0.516		
C-reactive protein	1.044 (0.997, 10.12)	0.294		
Abscess size	0.999 (0.975, 1.024)	0.967		

In our study, the basic characteristics of the patients in the two groups were comparable. The mean age of presentation in our patients was around 59 years and more males than females were affected. Also, the right lobe of the liver was the most commonly affected. This is consistent with the findings in other studies. The incidence rate in men has been reported to be about 1.7 times higher than that in women, and the abscess was found more commonly in the right lobe of the liver (15, 16). Chan KS reported that the patients older than 65 would prolonged length of hospitalisation stay (17).

The common comorbid conditions seen in patients of liver abscess are diabetes mellitus, hypertension, malignant tumors, biliary stones, history of abdominal surgery, liver cirrhosis, and alcoholism (18). About 40% of patients in our study had diabetes and this is consistent with previous studies (19). Diabetes can lead to liver injury, abnormal bile secretion, and an increased chance of portal vein infection. It can also cause systemic metabolic impairment and reduced immunity, and weaken the ability of the liver to remove bacteria, thereby facilitating colonization of bacteria in the liver, leading to liver abscesses (1, 20, 21).

Studies have shown a higher proportion of use of carbapenem antibiotics in patients with liver abscesses complicated by diabetes. Poor glycemic control is associated with a higher rate of complications: difficulty in infection control, recurrence of abscess; and even death. Fifteen of our 97 patients also had septic shock. Multivariate analysis showed diabetes mellitus to be an independent risk factor for progression to septic shock in our patients. These observations suggest that PLA patients with diabetes may require more aggressive antibiotic therapy with carbapenem combinations (22, 23). Several population-based studies have shown that diabetes is a significant risk factor for PLA morbidity and mortality (14). Diabetes has been reported as an independent risk factor for mortality within six months in patients with PLA (24).

About 92% of our patients presented with fever and 55% with abdominal pain. Therefore, a diagnosis of liver abscess should be considered in patients presenting with persistent high fever and right upper abdominal pain. A total of 18 patients in our study demonstrated gas within their liver abscesses(18.6%), the result is similar to Chan KS'report (25). 72 had pleural effusion, and four had the invasive liver abscess syndrome. Zhang Jia et al. (26) reported a higher risk of pleural effusion and sepsis. Studies have also reported that the size of the abscess positively correlates with the severity of the disease. Larger PLAs are more prone to complications such as invasive liver abscess syndrome, pleural effusion, ascites, and abscess rupture. Also, the larger the PLA is, the longer the duration of hospitalization and the in-hospital mortality, independent of other risk factors (10, 27).

Du Zhao-Qing et al. found that pus cultures are more likely to be positive than blood cultures (14). This is consistent with the present study. All patients included in this study had a pus culture done. A majority of the patients also had blood cultures performed. As a result, we had a high rate of culture positivity (89.2%). Klebsiella pneumoniae was the commonest organism isolated (76%). Cultures are essential in guiding antibiotic therapy especially in immunocompromised patients. For patients with PLA without bacterial culture results, It is justified to treat them with empirical antibiotics targeted to K. pneumoniae (28).

Most PLA patients benefit from PCD, And there are fewer complications and adverse events, But PCD failures still occur (29). One patient in this study developed an inflow of pus into the abdominal cavity, Caused abdominal infection and acute peritonitis, It is considered because the abscess is located on the surface of the liver. Therefore, For abscesses located on the surface of the liver, It is recommended to puncture through more normal liver tissue. Avoid to puncture on the surface of the liver abscess. Patients of 58% with high fever and chills after PCD in this study, It is associated with inflammatory mediators in pus and bacterial entry into the blood. Although patients with liver abscesses generally have abnormal coagulation function, Bleeding complications after PCD treatment of liver abscess were relatively rare, all <1% (30). Many patients in this study performed 2 PCD procedures, No patients developed liver bleeding.

There are few reports on the study of double catheter drainage of PLAs and none comparing double catheter with single catheter drainage in PLAs (31). Double catheter drainage probably facilitates rapid emptying of the abscess cavity particularly in patients with large multiloculated lesions where a second drainage tube can be positioned in another part of the abscess. Rapid unobstructed emptying of the pus probably reduces the high bacterial load and inflammation, thereby decreasing the duration of hospitalization (32). In our study we observed a decrease in the time to removal of catheter and the duration of hospitalization in patients who had DP drainage compared with those treated with SP drainage. Besides, in patients with DP drainage, the time for reduction in the diameter of the abscess to half was shorter, the rate of decrease in c-reactive protein levels was more rapid (suggesting faster resolution of inflammation) and the size of the abscess at the time of catheter was smaller.

There is no consensus on the optimum time for removal of the percutaneous catheter. We opted to remove the catheter when the drainage through the unobstructed catheter was nil. Premature removal of the drain is not recommended, Although some studies have reported that the removal of drainage tubes with less than 10 ml of pus per day can be achieved a 90% successful treatment rate for larger liver abscesses (33). Carrying a drainage catheter increases the discomfort, However, there is still no study to confirm the safety and effectiveness of the early removal of drainage pipes. In that study, The average time for removal the catheter was 22 days. When remove the catheter, The mean diameter of the liver abscess was approximately 3.5 cm in these cases. All our patients were followed up for a minimum period of six months after discharge from the hospital, Only 1 case of patients hospitalized due to liver abscess recurrence.

Our study has certain limitations. Firstly, the study design was retrospective. Secondly, the number of patients was small. Thirdly A randomized controlled trial of double vs. single catheter drainage with an adequate sample size is necessary to establish whether double catheter drainage is superior or not to single catheter drainage in large PLAs. In this study, The 8F pigtail drainage catheters were applied in all patients. It was reported that the 10–12F catheters did not increase the risk of bleeding (28). We will try to use it in the future.

Conclusion

Double catheter drainage is a safe and effective technique for drainage of pus in multiloculated PLAs more than 5 cm in size.

We found double catheter drainage to shorten hospitalization time, time to removal of catheter and time for reduction in the size of the abscess cavity. The rate of reduction in inflammatory parameters like c-reactive protein levels was also more rapid in these patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Our data were obtained with the consent of the Health Commission of the Affiliated Hospital of Chengde Medical College. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

JC contributed to the study conception and design. data collection and analysis were performed by YL. The first draft of the manuscript was written by JC and all authors commented on previous versions of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Waiting-List and early posttransplant prognosis among ethnoracial groups: Data from the organ procurement and transplantation network

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Background: Racial/ethnic disparity in waiting-list mortality among candidates listed for kidney transplantation (KT) in the United States remains unclear. We aimed to assess racial/ethnic disparity in waiting-list prognosis among patients listed for KT in the United States in the current era.

Methods: We compared waiting-list and early posttransplant in-hospital mortality or primary nonfunction (PNF) among adult (age ≥18 years) white, black, Hispanic, and Asian patients listed for only KT in the United States between July 1, 2004 and March 31, 2020.

Results: Of the 516,451 participants, 45.6%, 29.8%, 17.5%, and 7.1% were white, black, Hispanic, and Asian, respectively. Mortality on the 3-year waiting list (including patients who were removed for deterioration) was 23.2%, 16.6%, 16.2%, and 13.8% in white, black, Hispanic, and Asian patients, respectively. The cumulative incidence of posttransplant in-hospital death or PNF after KT was 3.3%, 2.5%, 2.4%, and 2.2% in black, white, Hispanic, and Asian patients,respectively. White candidates had the highest mortality risk on the waiting list or of becoming too sick for a transplant, while black (adjusted hazard ratio, [95% confidence interval, CI], 0.67 [0.66–0.68]), Hispanic (0.59 [0.58–0.60]), and Asian (0.54 [0.52–0.55]) candidates had a lower risk. Black KT recipients (odds ratio, [95% CI] 1.29 [1.21–1.38]) had a higher risk of PNF or death before discharge than white patients. After controlling confounders, black recipients (0.99 [0.92–1.07]) had a similar higher risk of posttransplant in-hospital mortality or PNF as white patients than Hispanic and Asian counterparts.

Conclusions: Despite having a better socioeconomic status and being allocated better kidneys, white patients had the worst prognosis during the waiting periods. Black recipients and white recipients have higher posttransplant in-hospital mortality or PNF.

KEYWORDS

kidney transplantation, waiting-list mortality, early posttransplant in-hospital mortality, kidney allocation system, primary nonfunction, racial/ethnic disparities

Abbreviations

aHR, adjusted hazard ratio; aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; CPRA, calculated panel-reactive antibody; ESRD, end-stage renal disease; KAS, Kidney Allocation System; KDPI, Kidney Donor Profile Index; KT, kidney transplantation; OPTN, Organ Procurement and Transplantation Network; PNF, primary nonfunction; HLA, human leukocyte antigen.

Introduction

Kidney transplantation (KT) is the best therapeutic option for the majority of patients with end-stage renal disease (ESRD) as it offers better quality of life and longer survival than other therapies (1, 2). Racial disparities are associated with lower socioeconomic status and longer transplant-waiting time (3, 4), which may affect the survival of patients on the waiting list and eventually contribute to worse graft and recipient survival in KT recipients (5, 6).

Previous studies have mainly focused on the racial disparities between whites and blacks in the long-term survival after transplantation of KT recipients; however, there is limited information on the racial disparities in the mortality rates of candidates awaiting KT. In the past 10 years, the proportion of Asian and Hispanic candidates in the United States has gradually increased, together with a decline in the proportion of white candidates (7). In the United States, the proportion of Asian and Hispanic patients on the waiting list increased from 7.5% and 17.7% in 2009 to 9.7% and 20.7% in 2019, respectively (7). However, only a few ethnoracially related KT studies have previously included Hispanic and Asian patients. Analysis of early posttransplant in-hospital mortality or primary nonfunction (PNF) may provide additional information on the prognosis of the waiting list, because sicker candidates tend to have a worse prognosis after KT. PNF, defined as failed function of the transplanted kidney, which necessitated continued maintenance dialysis (8) that occurred within 90 days post-KT, was included in the analysis.

The new Kidney Allocation System (KAS) implemented in 2014 increased the transplantation rates of highly sensitised individuals and reduced the known disparities in access to transplantation to some degree (9–11) whereas the relationship between KAS and waiting-list prognosis or early posttransplant prognosis remains unclear.

Kidney quality can be assessed using the Kidney Donor Profile Index (KDPI). Among kidney transplant recipients, a lower and higher KDPI are associated with longer and shorter predicted graft survival, respectively (12). Since the quality of the donated kidney can affect early posttransplant prognosis (12) we compared the differences in the changes in KDPI before and after KAS modification among races/ethnicities. The objectives of this study were to (a) compare baseline characteristics between white, black, Hispanic, and Asian patients listed for KT in the United States; (b) compare the waiting-list mortality* between these racial/ethnic groups; (c) compare early posttransplant in-hospital mortality or PNF between KT recipients across four groups; and (d) determine the role of KAS in the waiting list and early posttransplant prognoses.

Materials and methods

Study population

All adult patients (age ≥18 years) listed for only KT and no other organ transplants in the United States between July 1, 2004 and March 31, 2020 were identified in the Organ Procurement and Transplantation Network (OPTN) database, which includes data on all candidates awaiting KT in the United States. Individuals listed for multiorgan transplantation or removed on the day of enrollment (zero wait time) were excluded. The OPTN adult KT registration forms, which are completed by the transplantation centre clinicians, include details of the race/ethnicity of all recipients designated as white, black, Hispanic, or Asian. Due to their small number, patients belonging to other minorities were excluded from the study. The data reported here have been supplied by the UNOS as the contractor for OPTN. As the data was sourced from a public database, and study participants could not be identified directly or through linked identifiers, the study was exempted from ethics review.

Study design and definitions

Demographic and clinical variables were recorded at the time of listing, determining the waiting-list prognosis, or at the time of transplant for ascertaining early posttransplant prognosis. Baseline characteristics and prognosis were compared between white, black, Hispanic, and Asian patients who were listed for KT during the study period. The primary endpoint (denoted as waiting-list death*) was a composite of death while on the waiting list or becoming too ill to undergo transplantation (removal from the waiting list owing to clinical deterioration). The cumulative incidence of these two events is denoted as cumulative waiting-list mortality*. Patients who underwent KT or were removed from the waiting list (for recovery or other reasons) were censored. The secondary endpoint (denoted as PNF#) was early posttransplant in-hospital death or PNF in patients who underwent KT. For analysis of waiting-list prognosis, patients were followed-up from the time of listing until death, KT, removal from the list, or the day of the last observation (March 31,2021). Patients who received KT were followed-up either until discharge, in-hospital death, posttransplant failure for up to 90 days, or the last day of the study period(March 31, 2021), whichever was earlier. To assess whether the relationship between race/ethnicity and patients' prognosis was related to centre volume, we divided the listing centres into three categories according to the distribution of patients enrolled at each centre during the study period as follows: low-volume (<50th percentile), medium-volume (50th–90th percentile), and high-volume (>90th percentile) centres (13). None of the participants had missing data for the following variables: age, sex, race/ethnicity, body mass index (BMI), blood type, dialysis, and dates of listing, transplant, death, or removal from the waiting list. Candidates with missing data for other variables were excluded from the multivariate analysis.

Statistical analysis

Summary data are presented as the mean (standard deviation) or number (percentage). The differences between groups in baseline characteristics between ethnoracial groups were compared using the chi-square test or Student's *t*-test for categorical or continuous variables, respectively. The waiting list mortality* and PNF# of participants are presented in the Kaplan–Meier curve and further compared using the log-rank test. A univariate Cox proportional hazards model was developed first. Subsequently, a multivariate Cox

TABLE 1 Baseline characteristics of white, black, Hispanic and Asian patients listed for a kidney transplantation.

	White (23,5568)	Black (15,3932)	Hispanic (90,152)	Asian (36,799)	*p*
Age, years (mean (SD))	53.73 (13.27)	50.32 (12.48)	49.26 (13.37)	52.17 (13.03)	<0.001
Sex, Male, (%)	14,7902 (62.8)	90,441 (58.8)	56,438 (62.6)	21,608 (58.7)	<0.001
ABO (%)					<0.001
A	94,948 (40.3)	38,894 (25.3)	26,178 (29.0)	9,221 (25.1)	
B	25,944 (11.0)	31,316 (20.3)	8,769 (9.7)	10,676 (29.0)	
O	105,634 (44.8)	77,312 (50.2)	53,298 (59.1)	14,393 (39.1)	
AB	9,042 (3.8)	6,410 (4.2)	1,907 (2.1)	2,509 (6.8)	
BMI (mean (SD))	28.66 (5.62)	29.43 (5.78)	28.36 (5.24)	25.69 (4.78)	<0.001
Obese (BMI ≥30)	90,818 (38.6)	67,327 (43.7)	31,878 (35.4)	6,503 (17.7)	<0.001
History of diabetes (%)	84,762 (36.0)	66,273 (43.1)	46,086 (51.1)	16,041 (43.6)	<0.001
Private insurance (%)	120,412 (51.1)	54,500 (35.4)	31,069 (34.5)	18,685 (50.8)	<0.001
CPRA ≥30 (%)	49,256 (20.9)	41,723 (27.1)	19,165 (21.3)	7,664 (20.8)	<0.001
Working for income (%)	90,175 (38.3)	43,185 (28.1)	22,749 (25.2)	13,778 (37.4)	<0.001
College or graduate degree (%)	132,627 (56.3)	75,727 (49.2)	25,848 (28.7)	22,231 (60.4)	<0.001
Dialysis before registration (%)	138,629 (58.8)	124,317 (80.8)	72,688 (80.6)	25,301 (68.8)	<0.001
Centre volume (%)					<0.001
Low volume	31,965 (13.6)	16,809 (10.9)	10,056 (11.2)	3,702 (10.1)	
Medium volume	124,893 (53.0)	83,771 (54.4)	45,330 (50.3)	16,493 (44.8)	
High volume	78,710 (33.4)	53,352 (34.7)	34,766 (38.6)	16,604 (45.1)	
Cause of ESRD (%)					<0.001
Glomerular diseases	37,514 (15.9)	16,366 (10.6)	10,639 (11.8)	7,630 (20.7)	
Hypertensive nephrosclerosis	34,586 (14.7)	52,636 (34.2)	16,164 (17.9)	6,908 (18.8)	
DM	62,208 (26.4)	48,878 (31.8)	39,604 (43.9)	12,715 (34.6)	
Other	101,260 (43.0)	36,052 (23.4)	23,745 (26.3)	9,546 (25.9)	

SD, standard deviation; BMI, body mass index (calculated as weight in kilograms divided by height in metres squared); CPRA, calculated panel reactive antibody; ESRD, end-stage renal disease; DM, diabetes mellitus.

proportional hazards model was developed using backward stepwise selection, and all the variables in Table 1 were considered. A univariate logistic regression model was developed first, and a multivariate logistic regression model was then developed to evaluate racial/ethnic differences in PNF#. Segmental linear regression was used to ascertain the trend of waiting-list death* and PNF# before and after KAS. The KDPI of kidneys allocated to patients before and after KAS implementation was compared using the *t*-test. The distribution of the causes of death among waiting-listed candidates and recipients were compared using the chi-square test.

Data were analysed using R (version 3.6.2). All statistical tests were two-sided, and $P < 0.05$ was used to define statistical significance.

Results

During the study period, 553,369 patients in the United States were referred to transplant centres for only KT. Of these, 36,918 patients (6.7%) were excluded based on the predefined exclusion criteria (Figure 1). The remaining 516,451 patients were included in this analysis. Of these, 235,568 (45.6%) were white, 153,932 (29.8%) were black, 90,152 (17.5%) were Hispanic, and 36,799 (7.1%) were Asian (Figure 1).

Significantly ($P < 0.001$ for all), white patients were older than black, Hispanic, and Asian patients; were more likely to have type A blood (white 40.3% vs. black 25.3%, Hispanic 29.0%, and Asian 25.1%); have private insurance (51.1% vs. 35.4%, 34.5%, and 50.8%), and to work for income (38.3% vs. 28.1%, 25.2%, and 37.4%). Compared with black, Hispanic, and Asian patients, white patients were significantly ($P < 0.001$ for all) less likely to have a history of diabetes (white 36.0% vs. black 43.1%, Hispanic 51.1%, and Asian 43.6%) and dialysis before registration (58.8% vs. 80.8%, 80.6%, and 68.8%) or to register at a high-volume centre (33.4% vs. 34.7%, 38.6%, and 45.1%). White and Asian patients were less likely to have calculated panel-reactive antibody (CPRA) ≥ 30% than black and Hispanic patients (20.9% and 20.8% vs. 27.1% and 21.3%, respectively, $P < 0.001$). Black patients were more likely to be obese (43.7% vs. white 38.6%, Hispanic 35.4%, and Asian 17.7%) and were less likely to be diagnosed with glomerular diseases (10.6% vs. 15.9%, 11.8%, and 20.7%, $P < 0.001$), which is a cause of ESRD. Asian

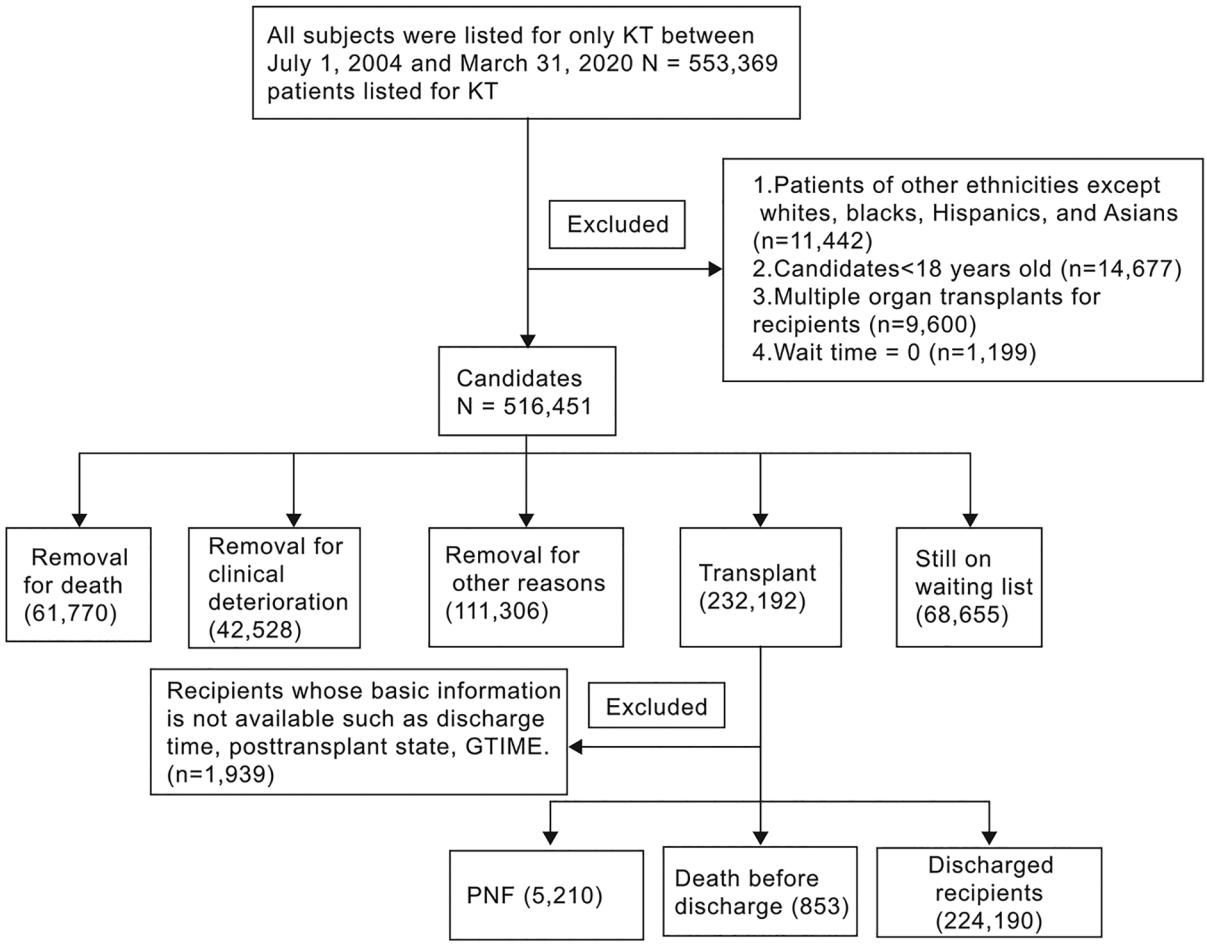

FIGURE 1
Flow diagram of the study participants. KT: kidney transplant; PNF: Primary nonfunction. Note: 1. GTIME, a variable derived from UNOS, indicates graft lifespan-kidney-days from transplant to failure/death/last follow-up; 2. Of the 853 deaths, 836 were simultaneously diagnosed with PNF.

patients were more likely to have a college or graduate degree (60.4% vs. white 56.3%, black 49.2%, and Hispanic 28.7%, $P < 0.001$; Table 1).

The same trend was observed in transplant recipients, except for centre volume and CPRA. Black recipients were significantly less likely ($P < 0.001$) to receive the transplant at a high-volume centre (32.2% vs. white 34.5%, Hispanic 37.0%, and Asian 41.7%), and white recipients were significantly less likely ($P < 0.001$) to have CPRA ≥30% (21.0% vs. black 26.4%, Hispanic 23.3%, and Asian 22.3%). The donor age for white recipients was higher than that of black, Hispanic, and Asian recipients. White recipients were significantly less likely ($P < 0.001$) to have race/ethnicity-mismatched KT (14.6% vs. black 70.8%, Hispanic 56.2%, and Asian 77.7%), cold ischaemic time ≥12 h (41.2% vs. 61.9%, 53.1%, and 52.0%), human leukocyte antigen (HLA) mismatch ≥3 (41.2% vs. 91.0%, 80.5%, and 88.2%). White recipients were significantly more likely to access kidneys donated by living donors (43.9% vs. black 16.8%, Hispanic 30.4%, and Asian 27.6%, $P < 0.001$; Table 2).

Waiting-List mortality

Overall, 104,298 (20.2%) patients reached the primary end point (61,770 [12.0%] died on the waiting list and 42,528 [8.2%] were removed due to clinical deterioration) during the study period. Ultimately, 20.0%, 21.1%, 20.2%, and 17.7% of white, black, Hispanic, and Asian candidates, respectively, on the KT waiting list died or were removed due to clinical deterioration. Moreover, 49.6%, 40.5%, 42.0%, and 40.8% of white, black, Hispanic, and Asian candidates, respectively, received KT (Figure 2). The median [IQR] waiting time for a KT was 11.5 [4.4–26.7], 19.7 [6.4–40.8], 16.6 [5.4–38.4], and 19.8 [7.2–41.9] months for white, black, Hispanic, and Asian candidates, respectively.

There was a significant difference in the cumulative waiting-list mortality* among the four groups. White patients had the highest risk of waiting-list mortality*, followed by black and Hispanic patients, while Asian patients had the lowest risk. The 3-year waiting-list mortality* of white, black, Hispanic, and Asian patients were 23.2%, 16.6%, 16.2%, and 13.8%, respectively (Figure 3).

In univariate Cox proportional hazards analysis, white candidates were at the highest risk of dying on the waiting list or becoming too sick for KT. After controlling for candidates' age, sex, blood type, BMI, history of diabetes, primary insurance, level of education, work state, dialysis time, CPRA, centre volume, causes of ESRD, and the implementation of KAS, white candidates still had the worst waiting-list prognosis, whereas black, Hispanic, and Asian candidates had a lower risk of poor prognosis (aHR [95% CI] 0.67 [0.66–0.68], 0.59 [0.58–0.60], and 0.54 [0.52–0.55]).

TABLE 2 Clinical characteristics at time of transplantation in kidney transplant recipients and donors, by race/ethnicity.

	White (116,085)	Black (61,766)	Hispanic (37,518)	Asian (14,884)
Recipient				
Age, years (mean (SD))	53.29 (13.74)	51.13 (12.55)	48.91 (13.85)	52.12 (13.47)
Sex, Male, (%)	72,148 (62.2)	36,783 (59.6)	23,072 (61.5)	8,403 (56.5)
Obese (BMI ≥30)	41,043 (35.4)	25,073 (40.6)	11,873 (31.6)	2,177 (14.6)
History of diabetes (%)	33,081 (28.5)	22,585 (36.6)	14,822 (39.5)	4,997 (33.6)
Private insurance (%)	50,705 (43.7)	13,881 (22.5)	10,584 (28.2)	5,509 (37.0)
CPRA ≥30 (%)	24,383 (21.0)	16,284 (26.4)	8,752 (23.3)	3,317 (22.3)
Working for income (%)	44,039 (37.9)	15,564 (25.2)	9,580 (25.5)	5,021 (33.7)
College or graduate degree (%)	67,145 (57.8)	31,179 (50.5)	11,432 (30.5)	9,072 (61.0)
Dialysis before registration (%)	65,655 (56.6)	50,565 (81.9)	30,057 (80.1)	10,327 (69.4)
Center volume *N* (%)				
Low volume	13,447 (11.6)	7,175 (11.6)	4,542 (12.1)	1,510 (10.1)
Medium volume	62,580 (53.9)	34,720 (56.2)	19,093 (50.9)	7,170 (48.2)
High volume	40,058 (34.5)	19,871 (32.2)	13,883 (37.0)	6,204 (41.7)
Cause of ESRD (%)				
Glomerular diseases	23,076 (19.9)	8,303 (13.4)	6,260 (16.7)	4,105 (27.6)
Hypertensive nephrosclerosis	17,597 (15.2)	23,036 (37.3)	7,921 (21.1)	3,077 (20.7)
DM	24,701 (21.3)	17,252 (27.9)	12,834 (34.2)	3,964 (26.6)
Donor				
Age (mean (SD))	41.48 (14.54)	38.79 (14.95)	38.32 (14.87)	39.66 (16.46)
Obese (BMI ≥30)	31,208 (26.9)	19,276 (31.2)	11,005 (29.3)	3,641 (24.5)
Cold ischaemic time ≥12 h	47,835 (41.2)	38,264 (61.9)	19,921 (53.1)	7,739 (52.0)
Sex mismatch = Yes (%)	58,012 (50.0)	29,451 (47.7)	18,504 (49.3)	7,487 (50.3)
Race/ethnicity mismatch = Yes (%)	16,906 (14.6)	43,751 (70.8)	21,082 (56.2)	11,565 (77.7)
ABO incomparable = Yes (%)	1,157 (1.0)	825 (1.3)	350 (0.9)	323 (2.2)
HLA mismatch ≥3 (%)	89,335 (77.0)	56,219 (91.0)	30,185 (80.5)	13,130 (88.2)
Donor type = Living (%)	51,005 (43.9)	10,401 (16.8)	11,416 (30.4)	4,102 (27.6)
Deceased donor cause of death (%)				
Anoxia	22,560 (34.7)	18,118 (35.3)	8,939 (34.2)	3,926 (36.4)
Cerebrovascular/stroke	18,906 (29.1)	14,916 (29.0)	7,629 (29.2)	3,262 (30.3)
Head trauma	21,532 (33.1)	16,753 (32.6)	8,710 (33.4)	3,182 (29.5)

SD, standard deviation; BMI, body mass index (calculated as weight in kilograms divided by height in metres squared); CPRA, calculated panel reactive antibody; ESRD, end-stage renal disease; DM, diabetes mellitus; HLA, human leukocyte antigen.

Moreover, the implementation of KAS, BMI ≥30, possessing private insurance, and registration in a higher volume centre were associated with lower probability of waiting-list death*(aHR [95% CI] 0.93 [0.92–0.95], 0.87 [0.85–0.88], 0.85 [0.84–0.86], and 0.90 [0.88–0.92], respectively), whereas older age (patients ≥60 years), diabetes, and dialysis before KT registration were associated with higher probability of waiting-list death* (aHR [95% CI] 2.94 [2.86–3.02], 1.74 [1.70–1.77], and 1.69 [1.66–1.72], respectively). Employed patients were 29% less likely to die on the waiting list compared with unemployed patients (95% CI 0.70–0.72) (Figure 4).

Posttransplant in-hospital mortality or PNF

Among 230,253 participants who received a KT and whose discharge status was known, 224,190 (97.4%) were discharged from the hospital without PNF; 5,210 (2.3%) recipients suffered from PNF before hospital discharge; and 853 (0.4%) died (including 836 recipients who were diagnosed with PNF before death) in the hospital. The cumulative incidence of PNF[#] after KT was 3.3%, 2.5%, 2.4%, and 2.2% in black, white, Hispanic, and Asian recipients, respectively ($P < 0.001$; Figure 5).

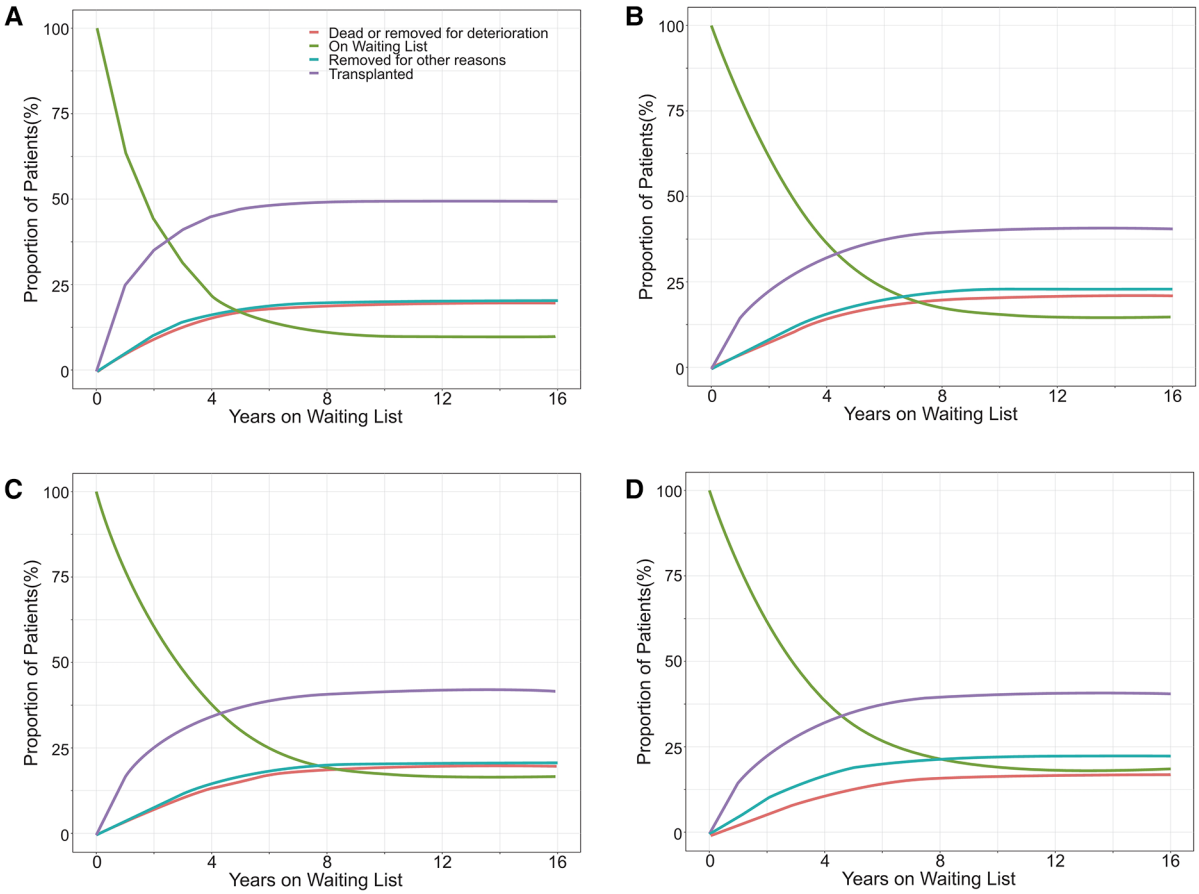

FIGURE 2
The proportion of outcomes for white (A), black (B), Hispanic (C), and Asian (D) patients listed for a kidney transplant in the United States.

In univariate logistic regression analysis, compared to white recipients, black recipients (OR [95% CI] 1.29 [1.21–1.38]) had the highest risk of PNF[#], whereas Hispanic, and Asian patients had similar risks (OR [95% CI] 0.95 [0.88–1.03], and 0.90 [0.79–1.02], respectively). After controlling for recipients' age, BMI, history of diabetes, primary insurance, education level, work state, dialysis time, CPRA, centre volume, the implementation of KAS, and causes of ESRD, donors' age, cold ischaemic time, BMI, cause of death, race/ethnicity mismatch, and sex mismatch between recipients and donors, the risk in black recipients was similar to that of white recipients (aOR 0.99, 95% CI 0.92–1.07), that is, the worst overall posttransplant prognosis. With regard to the recipients' characteristics, most variables had a similar relationship with PNF[#] as did the characteristics of candidates on the waiting-list death*, although some factors, such as obesity (BMI ≥30) and higher education level (college or graduate degree), had the opposite relationship (associated with higher probability of PNF[#] aOR [95% CI] 1.19 [1.12–1.26] and 1.07 [1.01–1.13], respectively). Notably, CPRA was not associated with PNF[#] (1.06 [0.99–1.13]). With regard to donor characteristics, older age (age ≥60 years), obesity, cold ischaemic time ≥12 h, race/ethnicity mismatch, and ABO mismatch were associated with higher probability of PNF[#] (1.51 [1.37–1.66], 1.16 [1.09–1.23], 1.30 [1.21–1.40], 1.11 [1.04–1.19], and 1.62 [1.29–2.01], respectively; Figure 6).

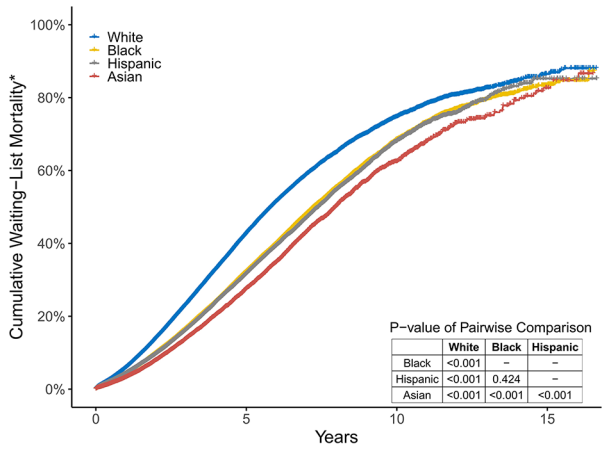

FIGURE 3
The cumulative percentage of those who died or became too sick for a transplant in the four groups. These two endpoints are simply referred to as Wait-List mortality*.

Role of KAS

The number of deaths (including patients who were removed for deterioration) among white, black, Hispanic, and Asian patients

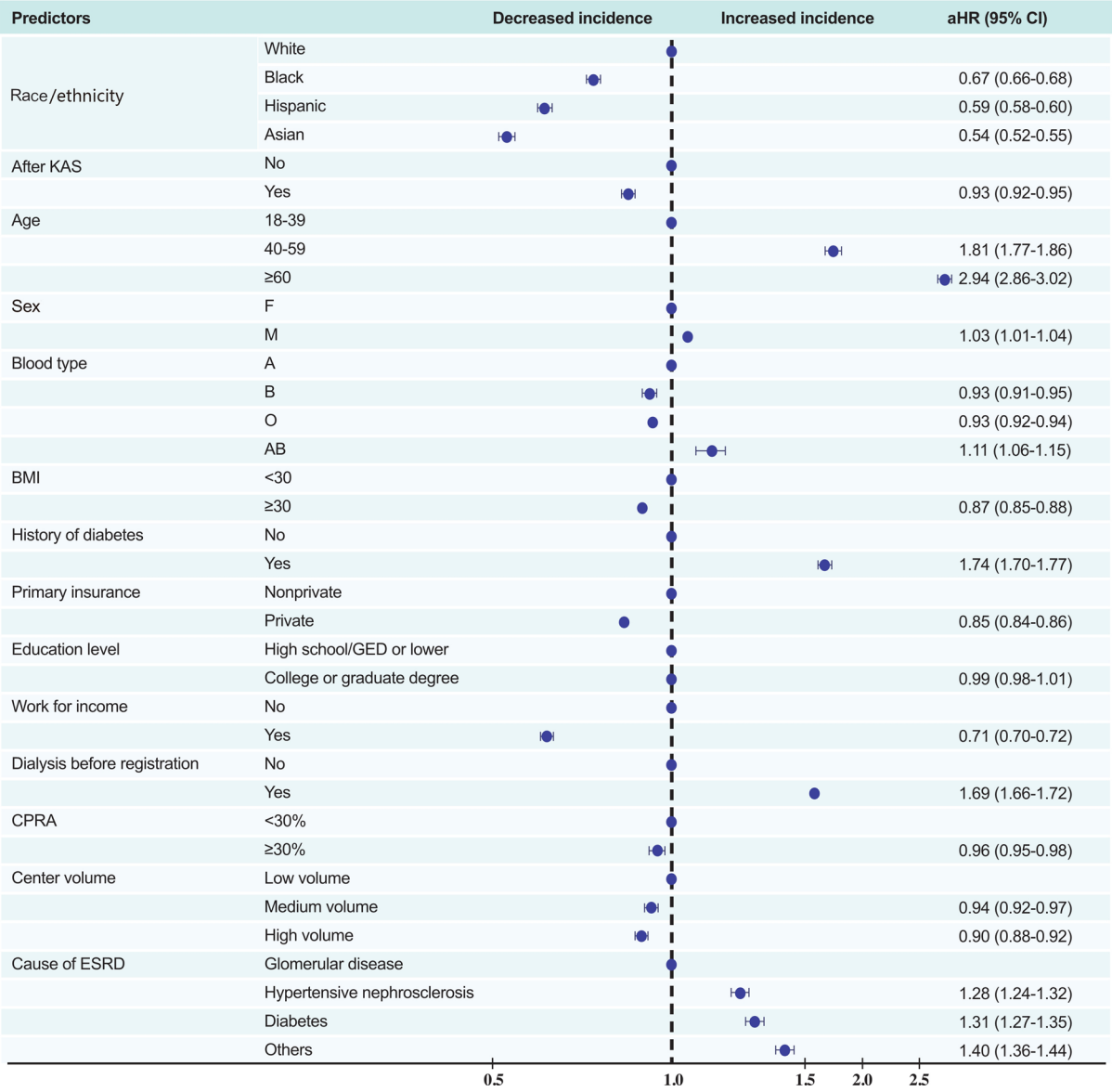

FIGURE 4
Multivariate predictors of waiting-list death or removal from the list owing to clinical deterioration. KAS, Kidney Allocation System BMI, body mass index (calculated as weight in kilograms divided by height in metres squared); CPRA, calculated panel reactive antibody; ESRD, end-stage renal disease; DM, diabetes mellitus.

increased yearly between 2005 and 2010, but slowed down thereafter until 2015. After the implementation of KAS in December 2014, the number of deaths per year for white, black, Hispanic, and Asian patients on the waiting list decreased (Figure 7B). The number of PNF[#] in KT recipients increased yearly between 2005 and 2010 in white, black, Hispanic, and Asian patients; and, between 2010 and 2015, was moderate in Hispanic and Asian patients, but showed a downward trend in white and black patients. After the implementation of KAS in December 2014, the number of PNF[#] in white and black patients showed an upward trend again, which further slowed in Hispanic patients, whereas it maintained the original upward trend in Asian patients (Figure 7D).

The mean KDPI of kidneys allocated to white (0.43 ± 0.27 vs. 0.45 ± 0.26) and Hispanic patients (0.42 ± 0.27 vs. 0.44 ± 0.26) increased significantly after KAS implementation but decreased significantly for black (0.46 ± 0.27 vs. 0.45 ± 0.25) and Asian (0.49 ± 0.27 vs. 0.47 ± 0.27) patients ($P < 0.001$ for all, Table 3).

Causes of waiting-list and posttransplant in-hospital deaths

The primary causes of death among these four groups are summarised in Table 4. Deaths due to cardiovascular or cerebrovascular causes (14.2%), infection (4.3%), others/unknown (40.8%), and clinical deterioration (41.1%) were the four major contributors for removal from the waiting list. Death due to other reasons includes miscellaneous causes, cancer, renal failure, haemorrhage, trauma, and other factors. Cardiovascular or cerebrovascular disease is the leading cause of death, and it appears

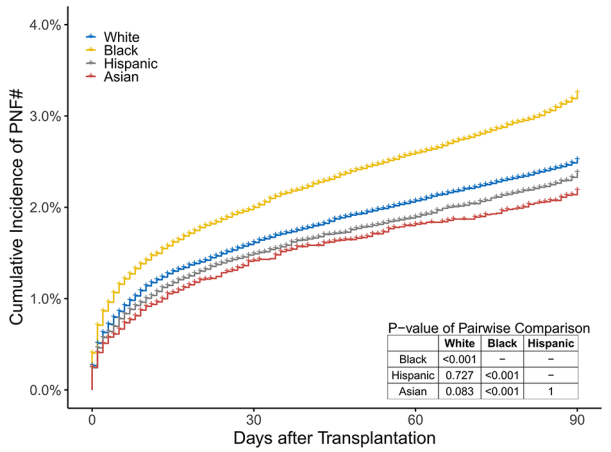

FIGURE 5
The cumulative percentage of recipients who died or suffered from PNF before discharge in the 4 groups. These two endpoints are simply referred to as PNF[#].

to be a more frequent cause of waiting-list death* among Asians (16.7%) compared with white (13.3%), black (14.0%), or Hispanic (16.0%) patients ($P < 0.001$). Among recipients who died before discharge, cardiovascular or cerebrovascular death (40.3%), infection (16.4%), and other reasons/unknown (43.3%) were the main causes. As the leading cause of death, cardiovascular or cerebrovascular death occurred less frequently among Hispanic (34.4%) than in white (40.6%), black (42.6%), or Asian (40.3%) KT recipients. Infection was a more frequent cause among Asian (19.4%) than in white (19.0%), black (12.5%), or Hispanic (15.2%) KT recipients, but the differences in distribution of cause of death did not reach statistical significance ($P = 0.202$, Table 4).

Discussion

We investigated the relationship between race/ethnicity (white, Hispanic, black, and Asian) and the prognosis of candidates and recipients in this study, which included 516,451 patients waiting for KT between July 1, 2004 and March 31, 2020, whose data were recorded in the OPTN database. Furthermore, we explored the relationship between KAS and the prognosis of candidates and recipients. This study had four major findings. First white patients with KT were older, more likely to have private insurance, and less likely to have a history of diabetes. Second, white patients were at the highest risk of dying on the waiting list or becoming too sick for KT, whereas Asian patients had the lowest risk. Third, black recipients had the highest risk of PNF[#]; however, after controlling for some confounding factors, black recipients had a similar risk as white recipients but with a higher risk of PNF[#] than their Hispanic and Asian counterparts. Finally, the implementation of KAS were associated with lower risk of waiting-list mortality* but were associated with higher risk of PNF[#] in white and black KT recipients.

Our study found that despite the higher prevalence of comorbidities, barriers to private healthcare, and lower socioeconomic status, racial minorities have a survival advantage compared to white KT candidates. This finding supports previous studies on the effects of racial differences in survival among patients undergoing dialysis (14–19), which showed that black or Hispanic patients survive longer than their white counterparts, indicating a survival paradox (20, 21). Our findings are consistent with the results of these studies, probably because approximately 76.3% of the candidates listed for KT in our study were also on dialysis.

Possible explanations include the higher rates of discontinuation of dialysis therapy, which may account for the lower survival rates of white candidates. Agunbiade et al. (22) found that white patients tended to have an earlier desire to quit dialysis, which may account for their higher mortality. Our findings also indicate that advanced age is a critical risk factor for waiting-list death*, and white candidates were significantly older than candidates of other races/ethnicities (Table 1). Moreover, this survival paradox may partly be subjected to referral bias. Severely ill minority patients with ESRD may be less likely to be offered, elect to initiate dialysis (15), or be referred for KT (4) than their white counterparts. For example, in the United States, the black population accounts for 12%, but represents 36% of the ESRD population. In this analysis, however, they made up only 29% of the OPTN database (23).

In addition to the survival paradox that may be caused by racial differences, the obesity paradox was detected in our study: that is, obesity is a protective factor for waiting-list death*. In the general population, obesity is associated with an increased cardiovascular risk and decreased survival (24). In patients with ESRD, however, an 'obesity paradox' has been consistently reported (24–26), namely, a higher BMI is paradoxically associated with better survival (24). The relatively better nutritional status of ESRD patients with high BMI may be responsible for the reduced mortality. Notably, the improved survival associated with obesity was in the adjusted analysis, and that the covariates included diabetes, which is typically associated with obesity in adults.

Given that sicker patients on the KT waiting list may also have a poor perioperative prognosis, we analysed PNF[#] for additional insights into waiting-list prognosis. We found that black recipients had the highest risk of PNF[#]. However, after controlling for confounding factors, both black and white recipients had the worst early postoperative prognosis compared with their Hispanic and Asian counterparts. This finding is similar to the prognosis of candidates; that is, although white patients are significantly better off than racial minority patients in terms of medical and socioeconomic factors, the early posttransplant prognosis is still the worst. However, unlike the candidates' prognosis, the early posttransplant prognosis of black recipients was significantly worse than that of their white counterparts before adjusting for confounders. Presumably, despite the similar baseline characteristics of recipients and candidates, white patients were allocated better kidneys than black patients. For example, kidneys allocated to racial minority patients tend to have characteristics such as longer ischaemia times and higher racial mismatch rates, which are detrimental to the early posttransplant prognosis of KT recipients.

Our study demonstrates that the implementation of KAS was associated with the number of deaths among candidates on the waiting list. Taber et al. (27) reported that KAS implementation led to significant changes in recipient demographics, increasing the proportion of African Americans, Hispanics, and those with more

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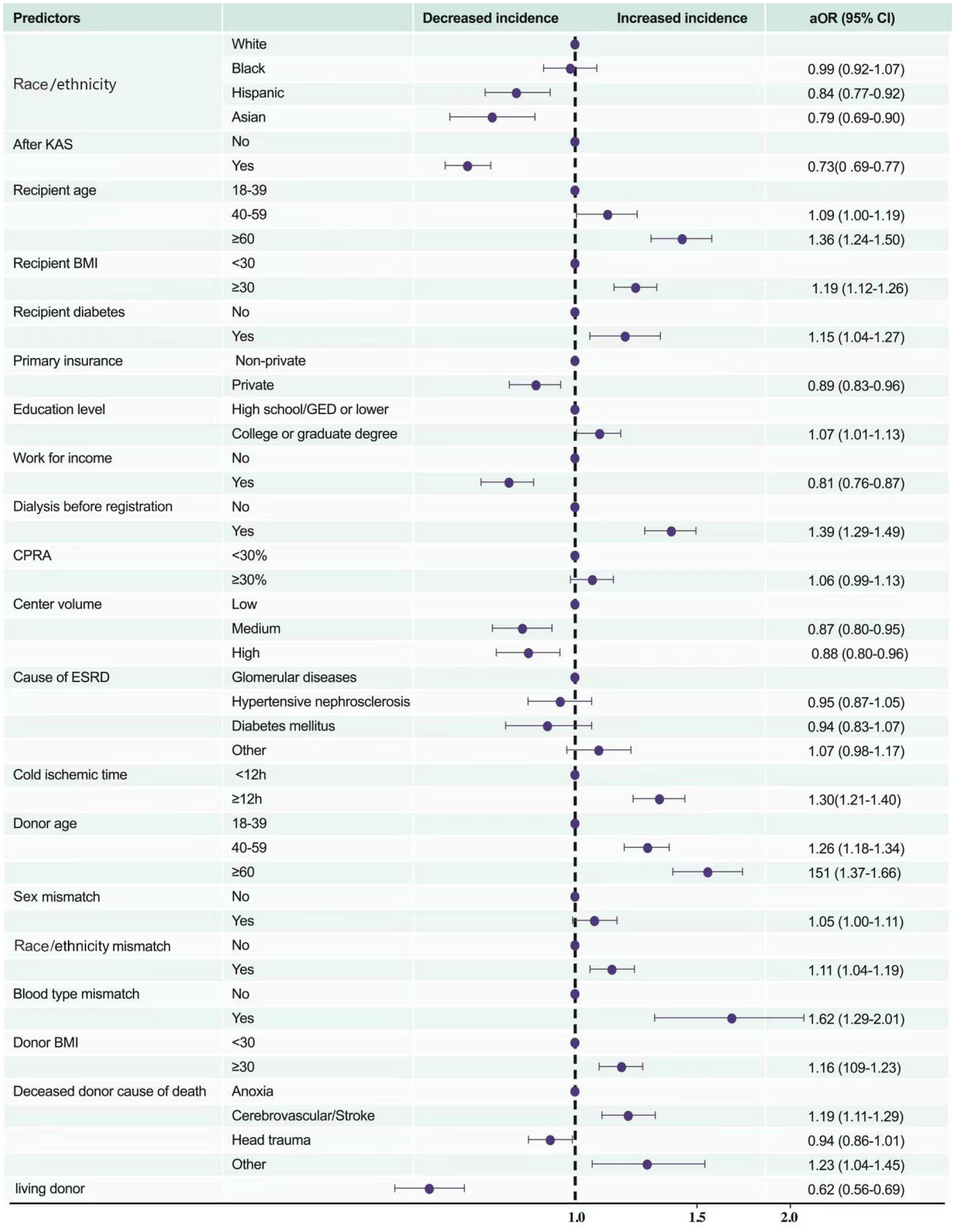

FIGURE 6
Multivariate predictors of posttransplant in-hospital death or PNF. KAS, Kidney Allocation System BMI, body mass index (calculated as weight in kilograms divided by height in metres squared); CPRA, calculated panel reactive antibody; ESRD, end-stage renal disease; DM, diabetes mellitus; PNF, primary nonfunction.

comorbid conditions. Furthermore, although sensitisation status is associated with higher death (28, 29), KAS has increased the likelihood that highly sensitised recipients (CPRA 99%–100%) would receive transplants (30). Therefore, the proportion of patients on the waiting list with high mortality will be reduced. The results of these studies support our findings.

However, few studies have reported the relationship between KAS implementation and PNF in recipients. Our study found that KAS was

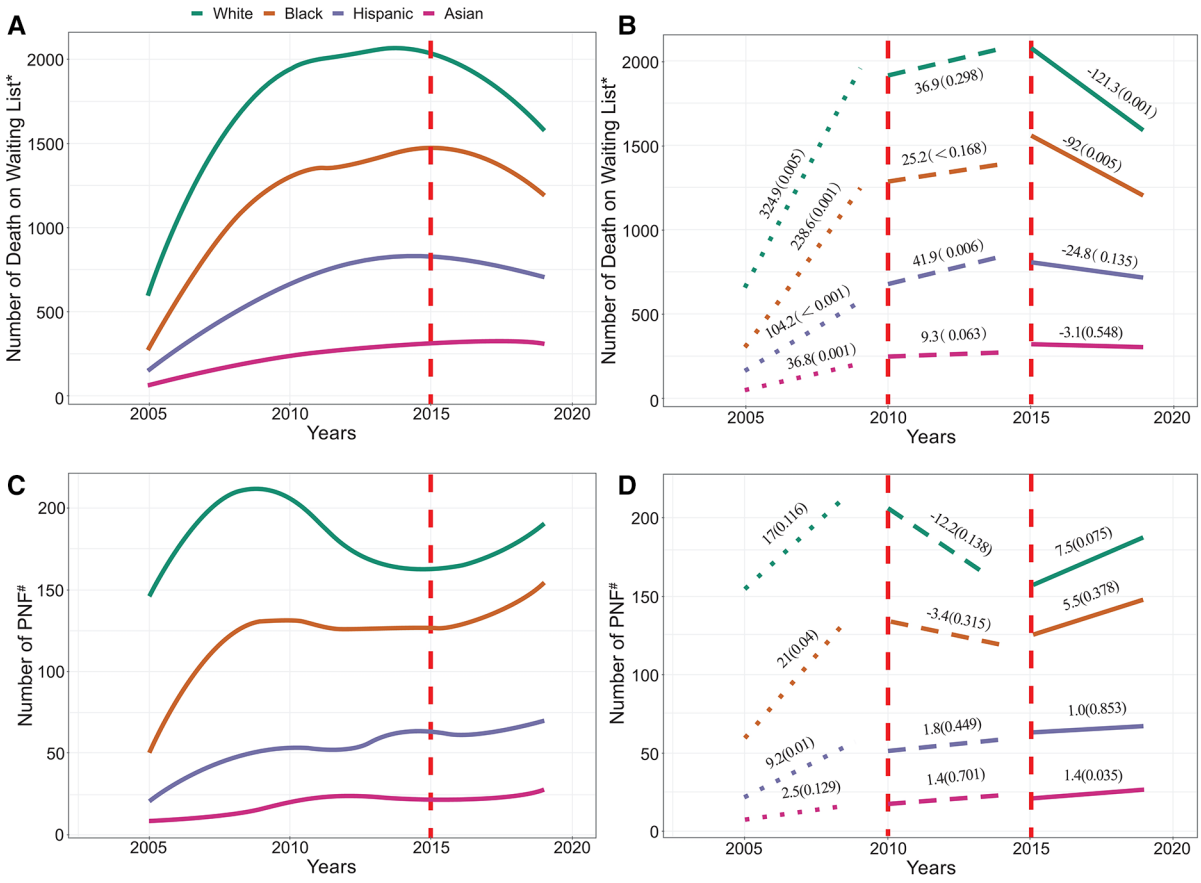

FIGURE 7
(A) illustrates the number of patients who died on the waiting list, and (B) depict its trend. (C) illustrates the number of recipients with PNF or who died posttransplant, and (D) depict its trend. *Includes patients who were removed from the list due to deterioration. #Includes patients who died posttransplant. The vertical line in the figure indicates the start time of KAS.

associated with increasing number of early posttransplant deaths or PNF in white and black recipients, but not in Hispanic and Asian recipients (Figure 7). However, the reasons for the different relationship between KAS and posttransplant PNF or death in recipients of different race/ethnicity require further investigation.

The strength of this study lies in its large sample size of 516,451 participants. In addition, the study included a diverse racial/ethnic group of patients, including whites, blacks, Hispanics, and Asians. However, this study had some limitations. First, as the database had only limited patient-level information, we could not control for unmeasured confounders, which could be residual confounding factors. For instance, the methods and drugs used to treat terminally ill patients on waiting lists among different races/ethnicities may vary, but data are not available. Second, we were limited in our ability to exclude candidates who were multi-registered, which may have contributed to a potential bias. However, given that this phenomenon occurs across all racial/ethnic groups, it should not have a substantial effect on the results. Third, smaller racial/ethnic groups were excluded as the number of patients was substantially small and heterogeneous to make meaningful conclusions. Fourth, the OPTN database classifies patients as white, black, Hispanic, Asian, American Indian/Alaska Native and others, however, Hispanic/Latino refers to ethnicity only. Thus the "Hispanic" category in the current study may include patients of white race and black race, which means that any conclusions about the Hispanic category are not independent of race differences. Finally, the analysis used United States data and the background provided is United States-centric and does not encompass the broader issues of racial/ethnic intersection in transplantation globally.

In conclusion, race/ethnicity was associated with the prognosis of candidates listed for KT and the early posttransplant prognosis of KT recipients. Despite having better socioeconomic status and allocated better kidneys, white patients have the worst prognosis during the waiting period. Black recipients and white recipients have higher posttransplant in-hospital mortality or PNF. KAS implementation was associated with improved waiting-list survival across all four

TABLE 3 KDPI of kidneys allocated to patients of different races/ethnicities before and after KAS implementation.

KDPI	Before KAS	After KAS	*p*
White (mean (SD))	0.43 (0.27)	0.45 (0.26)	<0.001
Black (mean (SD))	0.46 (0.27)	0.45 (0.25)	<0.001
Hispanic (mean (SD))	0.42 (0.27)	0.44 (0.26)	<0.001
Asian (mean (SD))	0.49 (0.27)	0.47 (0.27)	<0.001

KDPI, Kidney Donor Profile Index; KAS, Kidney Allocation System; SD, standard deviation.

TABLE 4 Distribution of causes of waiting-list death* and posttransplant in-hospital death.

	White	Black	Hispanic	Asian	Total	*p*
Waiting-List death* (%)						<0.001
Cardiovascular or cerebrovascular	6,246 (13.3)	4,547 (14.0)	2,906 (16.0)	1,087 (16.7)	14,786 (14.2)	
Infection	2,017 (4.3)	1,219 (3.7)	946 (5.2)	267 (4.1)	4,449 (4.3)	
Others/unknown	19,521 (41.5)	13,492 (41.4)	6,846 (37.7)	2,676 (41.1)	42,535 (40.8)	
Removal (deteriorated)	19,275 (41.0)	13,298 (40.8)	7,476 (41.1)	2,479 (38.1)	42,828 (41.1)	
Posttransplant in-hospital death (%)						0.202
Cardiovascular or cerebrovascular	163 (40.6)	113 (42.6)	43 (34.4)	25 (40.3)	344 (40.3)	
Infection	76 (19.0)	33 (12.5)	19 (15.2)	12 (19.4)	140 (16.4)	
Others/unknown	162 (40.4)	119 (44.9)	63 (50.4)	25 (40.3)	369 (43.3)	

*Includes patients who were removed from the list due to deterioration.

races/ethnicities but impaired early posttransplant prognosis for white and black recipients.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://optn.transplant.hrsa.gov/data/request-data/.

Author contributions

TS and QY participated in the research design, drafted the first draft of the paper, and oversaw data analysis and performance of the study. YYW and KKL participated in the research design, writing of the paper, and revised all drafts of the paper. CL, XWH and WHL participated in the research design and data analysis. XZX and ABP participated in revising the article and supervising data analysis. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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The optimal dose of oxycodone in PCIA after laparoscopic surgery for gastrointestinal cancer in elderly patients: A randomized controlled trial

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Objective: To explore the optimal bolus dose of oxycodone for patient controlled intravenous analgesia (PCIA) without background dose in elderly patients after laparoscopic surgery for gastrointestinal cancer.
Methods: In this prospective, randomized, double-blind, parallel-controlled study, we recruited patients aged 65 years or older. They underwent laparoscopic resection for gastrointestinal cancer and received PCIA after surgery. Eligible patients were randomly divided into 0.01, 0.02, or 0.03 mg/kg group according to the bolus dose of oxycodone in PCIA. The primary outcome was VAS scores of pain on mobilization at 48 h after surgery. Secondary endpoints included the VAS scores of rest pain, the total and effective numbers of press in PCIA, cumulative dose of oxycodone used in PCIA, the incidence of nausea, vomiting and dizziness, as well as patients' satisfaction at 48 h after surgery.
Results: A total of 166 patients were recruited and randomly assigned to receive a bolus dose of 0.01 mg/kg ($n = 55$), 0.02 mg/kg ($n = 56$) or 0.03 mg/kg ($n = 55$) of oxycodone in PCIA. The VAS scores of pain on mobilization, the total and effective numbers of press in PCIA in 0.02 mg/kg group and 0.03 mg/kg group were lower than those in 0.01 mg/kg group ($P < 0.05$). Cumulative dose of oxycodone used in PCIA and patients' satisfaction in 0.02 and 0.03 mg/kg groups were more than those in 0.01 mg/kg group ($P < 0.01$). The incidence of dizziness in 0.01 and 0.02 mg/kg groups was lower than that in 0.03 mg/kg group ($P < 0.01$). There were no significant differences in VAS scores of rest pain, the incidence of nausea and vomiting among three groups ($P > 0.05$).
Conclusion: For elderly patients undergoing laparoscopic surgery for gastrointestinal cancer, 0.02 mg/kg bolus dose of oxycodone in PCIA without background infusion may be a better choice.

KEYWORDS
gastrointestinal cancer, laparoscopic surgery, postoperative pain, oxycodone, patient controlled intravenous analgesia

Introduction

Gastrointestinal cancer is a common malignant tumor, and its prevalence and mortality increase with age, affecting millions of people around the world (1). Laparoscopic-assisted minimally invasive resection is the first-line treatment for the disease (2), offering the advantages of minimizing skin incision and reducing postoperative pain compared to

open surgery (3). Nevertheless, postoperative pain, especially visceral pain, remains an important issue for patients undergoing laparoscopic surgery for gastrointestinal cancer (4).

PCIA based on μ-opioid receptor agonist, is widely used to relieve acute postoperative pain. Although PCIA has been applied, some patients still experienced visceral pain following abdominal surgery (5). Considering κ-opioid receptor has been found to be involved in visceral pain (6), it is possible that both μ and κ-opioid receptors agonist, such as oxycodone, may provide more effective analgesia than pure μ-opioid receptor agonist in patients following laparoscopic surgery for gastrointestinal cancer (4, 7). However, oxycodone in PCIA may cause serious side effects, including respiratory depression, apnea, bradycardia, hypotension, or even death (8). Especially elderly patients, their sensitivity to opioids is significantly increased. The demand for opioids in the elderly is lower, but the side effects are greater (9). Therefore, the dose adjustment of oxycodone in PCIA has become a challenge for elderly patients. Considering that oxycodone has an action time of more than 4 h (8), continuous background infusion may lead to overdose or obscure the actual needs of patients, especially in elderly patients (10, 11). We thought bolus dose and no background dose infusion of oxycodone in PCIA allowed elderly patients to achieve self-controlled analgesia, provided better titration and reduced side effects. Thus, we tried to explore the optimal bolus dose of oxycodone in PCIA without background infusion in elderly patients after laparoscopic surgery for gastrointestinal cancer.

To the best of our knowledge, there is little evidence regarding optimal dose of oxycodone in PCIA to elderly patients. In this prospective, randomized, double-blind study, we compared the analgesic efficacy, adverse events and patients' satisfaction of oxycodone with different bolus doses in PCIA without background infusion among elderly patients who underwent laparoscopic surgery for gastrointestinal cancer.

Methods

Study design

This single-center, double-blinded, randomized control trial has been performed in the third Xiangya hospital of Central South University. The trial protocols were approved by the Ethics Committee of the third Xiangya hospital of Central South University (batch number: R16001) and registered at http://www.chictr.org.cn (ChiCTR-IPR-15006814, principal investigator: QL) before implementation. Written informed consent was obtained from all participants.

Participants and recruitment

From July 2017 to September 2022, elderly patients who underwent elective laparoscopic surgery for gastrointestinal cancer in our hospital were assessed for eligibility on admission. Eligibility criteria were as follows: ≥65 years old; American Society of Anesthesiologists (ASA) physical status I–III; scheduled for elective laparoscopic surgery for gastrointestinal cancer and PCIA treatment. Written informed consent was obtained from each patient. Exclusion criteria were: (1) patients were reluctant to join the trial; (2) chronic pain before participating in the study; (3) long-term use of analgesics or other pain-related drugs, alcohol dependence; (4) patients with multiple comorbidities, including severe abnormal liver and kidney function, severe cardiovascular or cerebrovascular disease, psychiatric disorders; (5) allergy to oxycodone and its antagonist.

Sample size

PASS software (version 15, NCSS, United States) was used for sample size calculation. We used the following settings to calculate it: $\alpha = 0.05$, the test power $1\text{-}\beta = 0.8$, two sided, and three groups allocation were equal. In the preliminary experiment, 60 elderly patients who underwent laparoscopic surgery for gastrointestinal cancer were enrolled. According to different bolus doses of oxycodone in PCIA, the above patients were randomly divided into 0.01, 0.02 or 0.03 mg/kg group, with 20 patients in each group. The VAS scores of pain on mobilization at 48 h after surgery in 0.01, 0.02 and 0.03 mg/kg group were 35.52 ± 13.02, 32.92 ± 11.05 and 28.65 ± 12.62, respectively. According to the results of the above preliminary experiment, we calculated that 50 patients were needed for each of three groups. Taking a 20% dropout rate into consideration, we needed to recruit 63 patients per group.

Randomization and blinding

The enrolled patients were randomized to three groups by a biostatistician not involved in this trial using a computer program in a ratio of 1:1:1. Patients' numbers were entered into SPSS 20.0 software (SPSS Inc., Chicago, United States) to generate a randomization scheme. Eligible patients were randomly assigned to 0.01, 0.02 or 0.03 mg/kg group. They received 0.01, 0.02, or 0.03 mg/kg bolus doses of oxycodone in PCIA in the absence of background infusion, respectively. Different doses of oxycodone in PCIA were prepared by a nurse who did not participate in the study. Neither researchers nor patients knew the group assignment.

Anesthesia and PCIA protocol

The standardized and uniform anesthesia protocol was adopted in all groups. Premedication was not given to each patient. After patients were transported to the operating room, they were monitored pulse oximetry, electrocardiogram, heart rate, arterial blood pressure and arterial blood gas analysis. All patients' anesthesia induction was performed with 0.04 mg/kg midazolam, 0.15 mg/kg cisatracurium besilate, 0.2 mg/kg etomidate, and 5 μg/kg fentanyl. After successful tracheal intubation, mechanical ventilation was performed. End-tidal $PaCO_2$ was monitored and

maintained between 35 and 45 mmHg. Fraction of inspired oxygen (FiO_2) was set to 0.5. Anesthesia was maintained with a combination of intravenous and inhaled anesthesia according to the bispectral index (Bis EEG VISTA Covidien, America) and hemodynamics: inhalation of 1%–2% sevoflurane, intravenous infusion of propofol (4–6 mg/kg/h), remifentanil (5–15 μg/kg/h) and cisatracurium besilate (0.1–0.15 mg/kg/h) through micropumps. An intravenous bolus of 3 μg/kg fentanyl was used before skin incision. The anesthesiologist then decided to give fentanyl (1 μg/kg each time) according to the vital signs, but the maximum dose of any patients should not exceed 12 μg/kg to prevent the residual effects of fentanyl after surgery. 8 mg of ondansetron hydrochloride was administered intravenously to prevent postoperative nausea and vomiting before skin closure. 0.5% ropivacaine was used for local infiltration anesthesia in the wound after skin suture for wound analgesia. All patients' surgeries were performed by two identical surgeons.

After surgery, patients were sent to the post-anesthesia care unit (PACU) for recovery. When the patient recovered breathing, neostigmine was used to antagonize muscle relaxation. The trachea was extubated when the patients were awake. Then we evaluated and recorded pain severity by VAS. If the patients felt moderate or severe pain (VAS 40–100), they were given 20 μg of fentanyl intravenously. Reassessed their pain 5 min later. If they still felt moderate or severe pain, intravenous bolus of 20 μg fentanyl was continued until their VAS was ≤30. PCIA was started when they perceived slight pain (VAS 10–30). We ensured that PCIA commenced at the same and mild pain level. The electronic-controlled analgesic pump (Renxian Medical, Jiangsu Province, China) contained 40 mg oxycodone in 0.9% normal saline for a total volume of 160 ml, and was programmed to no background infusion, PCIA dose of 0.01, 0.02 or 0.03 mg/kg bolus of oxycodone solution, with a lockout period of 5 min. All patients were told how to use the analgesic pump. PCIA was continued for 48 h after surgery. No other rescue drugs, except oxycodone, were used during the 48 h postoperatively.

Outcome measurements

Demographic and clinical data, including patients' age, gender, height, weight, ASA physical status, cancer's type and stage, preoperative anxiety and depression scores, duration of surgery, and medical history were collected before surgery.

The primary outcome was the VAS scores of pain on mobilization at 48 h after surgery. The secondary outcomes included the VAS scores of rest pain, the total and effective numbers of press in PCIA, cumulative dose of oxycodone used in PCIA, adverse events (nausea, vomiting, and dizziness) and patients' satisfaction within 48 h after surgery.

Statistical analysis

SPSS 20.0 statistical software (SPSS Inc., Chicago, IL, United States) was used for statistical analysis. The Kolmogorov-Smirnov test was used to evaluate if the continuous variables followed a normal distribution. Normally distributed continuous variables were expressed as mean ± standard deviation (SD). Barlett's test was employed to determine the variance homogeneity. One-way analysis of variance (ANOVA) was used to compare the three groups of continuous variables with normal distribution and homogeneous variance. If the differences were significant, the Student-Newman-Keuls q test was further used to compare the differences between pairwise groups. Numbers and/or percentages were used to describe the count data. The χ^2 test was used to evaluate whether the count data exhibited significant differences among the three groups. A P value < 0.05 was considered statistically significant. Multiple comparisons of the count data (0.01 mg/kg group to 0.02 mg/kg group, 0.01 mg/kg group to 0.03 mg/kg group, 0.02 mg/kg group to 0.03 mg/kg group) were done for significant results, and the α lever was set at 0.017, following Bonferroni adjustment.

Results

Demographic data and clinical characteristics

A total of 189 patients who underwent laparoscopic surgery for gastrointestinal cancer were evaluated for eligibility before enrollment. Of these patients, nine patients declined to participate. Seven patients' surgery type was converted to open surgery. Seven patients received a secondary surgery. Finally, 166 patients were enrolled in this study. After informed consent was obtained, eligible patients were prospectively randomized into 0.01 mg/kg group ($n = 55$), 0.02 mg/kg group ($n = 56$), or 0.03 mg/kg group ($n = 55$) (Figure 1). Their demographic and clinical characteristics were shown in Table 1. There were no significant differences in age, gender, height, weight, ASA physical status, stage of cancer, type of cancer, preoperative anxiety and depression, and duration of surgery among three groups (all $P > 0.05$).

Analgesic effect and usage amount of oxycodone in PCIA

The VAS scores of pain on mobilization were significantly different among three groups at 48 h after surgery ($P < 0.01$). 0.02 mg/kg group and 0.03 mg/kg group had a lower scores of pain on mobilization than 0.01 mg/kg group ($P < 0.05$, respectively), but there was no significant difference between 0.02 mg/kg group and 0.03 mg/kg group ($P > 0.05$). There was no significant difference in VAS scores of rest pain at 48 h after surgery among three groups ($P = 0.27$).

During the first 48 h postoperatively, the total and effective numbers of press in PCIA among three groups were significantly different ($P < 0.01$, respectively). The total and effective numbers of press in 0.02 mg/kg group and 0.03 mg/kg group were both less than those in 0.01 mg/kg group ($P < 0.05$, respectively). There was no significant difference in total and effective numbers of press between 0.02 mg/kg group and 0.03 mg/kg group ($P > 0.05$).

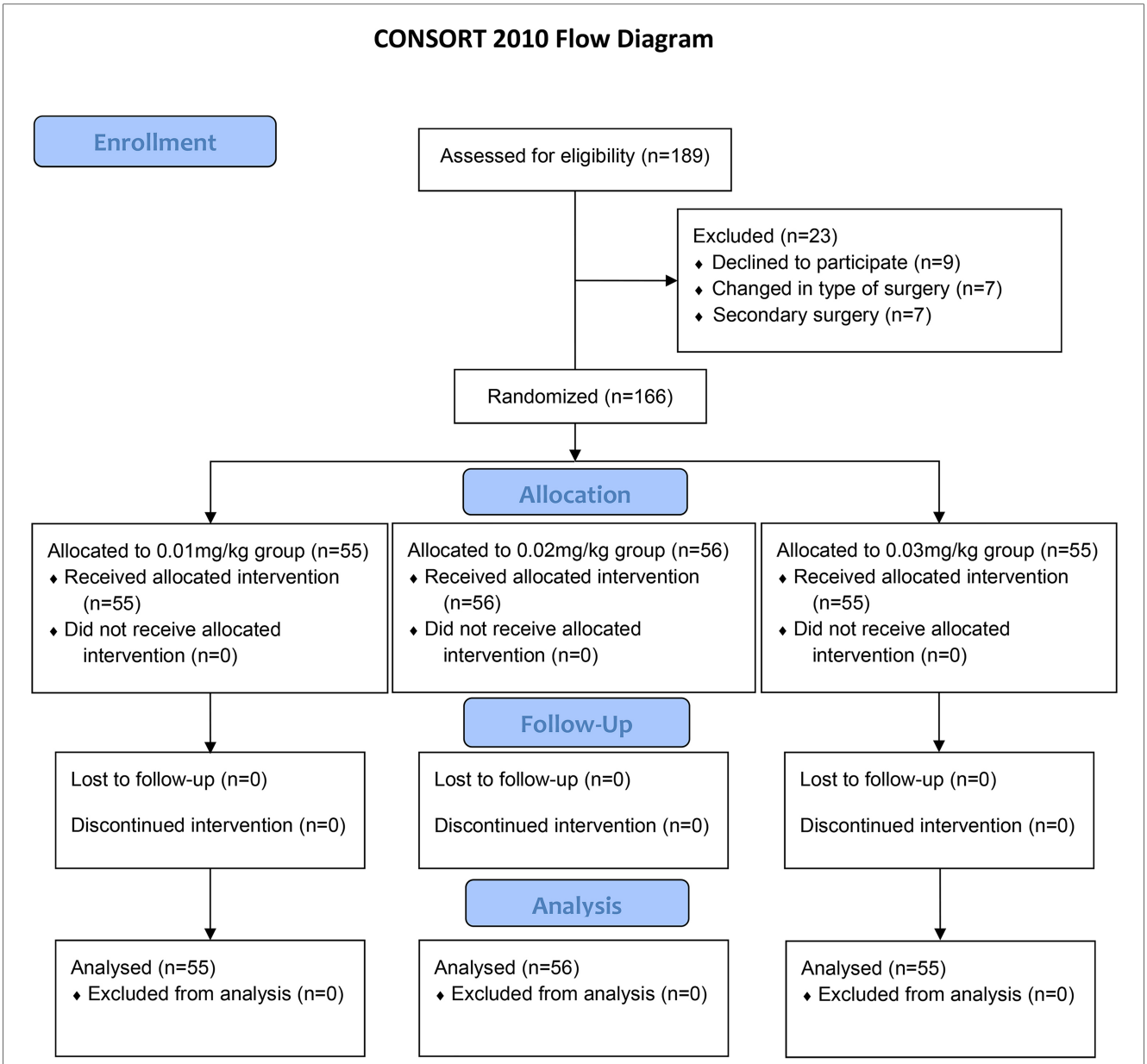

FIGURE 1
Consolidated standards of reporting trials (CONSORT) flow diagram of patients' distribution.

Cumulative dose of oxycodone used in PCIA was significantly different among three groups within 48 h after surgery ($P < 0.01$). The dosage of oxycodone used in 0.02 mg/kg group and 0.03 mg/kg groups was significantly more than that in 0.01 mg/kg group ($P < 0.05$, respectively). There was no significant difference in dosage of oxycodone between 0.02 mg/kg group and 0.03 mg/kg group ($P > 0.05$) (Table 2).

Adverse events

There was no significant difference in the incidence of nausea and vomiting among three groups during the first 48 h after surgery ($P > 0.05$, respectively). The incidence of dizziness in 0.01 mg/kg group and 0.02 mg/kg group was lower than that in 0.03 mg/kg group ($P < 0.01$, respectively). None of the patients had respiratory depression (Table 2).

Patients' satisfaction

In addition, there was significant difference in patients' satisfaction within 48 h postoperatively among three groups ($P < 0.01$). Satisfaction of patients in 0.02 mg/kg group and 0.03 mg/kg group was significantly higher than that in 0.01 mg/kg group ($P < 0.01$, respectively). There was no significant difference in patients' satisfaction between 0.02 mg/kg group and 0.03 mg/kg group ($P > 0.05$) (Table 2).

TABLE 1 Demographic and clinical data of the patients.

	0.01 mg/kg group	0.02 mg/kg group	0.03 mg/kg group	*P* value
Age, years	72.55 ± 5.91	72.41 ± 4.57	70.78 ± 4.02	0.11
Gender, male/female	31/24	33/23	39/16	0.24
Height, cm	160.10 ± 6.97	161.10 ± 7.73	163.20 ± 8.23	0.10
Weight, kg	56.70 ± 10.07	57.72 ± 9.52	59.23 ± 9.91	0.40
ASA physical status I/II/III, *n*	3/15/37	5/23/28	4/21/30	0.45
Stage of cancer I/II/III, *n*	4/41/10	5/37/14	4/43/8	0.67
Type of cancer (stomach/colon/rectal), *n*	7/24/24	10/25/21	9/26/20	0.91
Preoperative anxiety scores	24.45 ± 4.37	25.39 ± 5.39	24.51 ± 4.85	0.53
Preoperative depression scores	25.55 ± 5.88	26.68 ± 7.07	24.87 ± 4.12	0.26
Duration of surgery, hours	3.85 ± 1.26	4.09 ± 1.48	4.06 ± 1.47	0.63

Data are presented as the mean ± standard deviation (SD) or count (percentage). ASA, American Society of Anesthesiologists.

Discussion

We conducted this prospective, randomized controlled study to compare the analgesic and adverse effects of varying doses of oxycodone in PCIA following laparoscopic surgery for gastrointestinal cancer in elderly patients. According to the results of this study, 0.02 mg/kg group and 0.03 mg/kg groups showed better analgesic effect and patients' satisfaction than 0.01 mg/kg group. In addition, the incidence of dizziness in 0.02 mg/kg group was lower than that in 0.03 mg/kg group during the first 48 h after surgery. Thus, 0.02 mg/kg bolus dose of oxycodone in PCIA would be a better choice after laparoscopic surgery for gastrointestinal cancer in elderly patients.

Visceral pain is a large contributor of postoperative pain in patients with laparoscopic surgery for gastrointestinal cancer (4, 12, 13). κ-opioid receptor plays an important role in the mediation of visceral pain (6). Oxycodone, a dual agonist of μ and κ receptors (14), has been shown to provide effective analgesia for acute postoperative pain (15, 16), especially visceral pain. However, the safe and effective dose of oxycodone in PCIA following laparoscopic surgery for gastrointestinal cancer in elderly patients has not been determined. As we know, oxycodone is a long-acting analgesic, no background dose infusion in PCIA can reduce side effects in elderly patients. Therefore, we compared three different bolus doses of oxycodone, including 0.01, 0.02 and 0.03 mg/kg, expecting to find an optimal dose in PCIA without background infusion after laparoscopic surgery for gastrointestinal cancer in elderly patients.

VAS, the numbers of press and the satisfaction rate were used to assess the analgesic effect. VAS is a commonly used tool of pain intensity during the assessment of postoperative pain, including the pain at rest and on mobilization (17, 18). In our study, there was no significant difference in VAS scores of rest pain, but the VAS scores of pain on mobilization were significantly different among three groups at 48 h after surgery. 0.02 and 0.03 mg/kg groups had a lower pain scores on mobilization than 0.01 mg/kg group, which indicated that the pain on mobilization was not well controlled in 0.01 mg/kg group. The total and effective numbers of press in PCIA were significantly different during the first 48 h postoperatively among three groups. The total number and effective number of press in 0.02 mg/kg group and 0.03 mg/kg group were both significantly less than those in 0.01 mg/kg group. In 0.01 mg/kg group, the total number of press was about 33 times within 48 h after operation, which further indicated that the badly analgesic effect in 0.01 mg/kg group. And we also found that there was no significant difference of the VAS scores of pain on mobilization at 48 h after surgery between 0.02 mg/kg group and 0.03 mg/kg group, that is, 0.02 mg/kg of oxycodone

TABLE 2 Primary outcome and secondary outcomes among three groups.

	0.01 mg/kg group (*n* = 55)	0.02 mg/kg group (*n* = 56)	0.03 mg/kg group (*n* = 55)	*P* value
Primary outcome				
Scores of pain on mobilization	36.00 ± 13.14	30.30 ± 10.15	28.73 ± 12.77	<0.01
Secondary outcomes				
Resting pain scores	13.27 ± 12.92	16.25 ± 13.01	12.73 ± 10.79	0.27
Total numbers of press, *n*	32.91 ± 24.00	20.16 ± 14.10	15.95 ± 10.66	<0.01
Effective numbers of press, *n*	23.11 ± 15.89	16.68 ± 10.53	13.44 ± 8.29	<0.01
Amount of oxycodone used in PCIA(mg)	12.72 ± 8.38	19.16 ± 11.44	22.07 ± 12.47	<0.01
Postoperative nausea, [*n*(%)]	8 (14.5%)	8 (14.3%)	10 (18.2%)	0.82
Postoperative vomiting, [*n*(%)]	3 (5.5%)	1 (1.8%)	3 (5.5%)	0.54
Postoperative dizziness, [*n*(%)]	2 (3.6%)	1 (1.8%)	13 (23.6%)	<0.01
Patients' satisfaction				<0.01
Very satisfied, *n*(%)	12 (21.8%)	18 (32.1%)	19 (34.5%)	
Satisfied, *n*(%)	25 (45.5%)	35 (62.5%)	33 (60.0%)	
Neutral, *n*(%)	12 (21.8%)	3 (5.4%)	3 (5.5%)	
Dissatisfied, *n*(%)	6 (10.9%)	0 (0%)	0 (0%)	
Very dissatisfied, *n*(%)	0 (0%)	0 (0%)	0 (0%)	

Data are presented as mean ± standard deviation (SD) or count (percentage). PCIA, patient controlled intravenous analgesia.

could provide the same analgesic effect as 0.03 mg/kg of oxycodone.

Previous studies have shown that the adverse effects of oxycodone included nausea, vomiting, and dizziness (19–21). There was no significant difference in the incidence of postoperative nausea and vomiting among three groups in our study. However, the incidence of dizziness in 0.01 mg/kg group and 0.02 mg/kg group was lower than that in 0.03 mg/kg group during the first 48 h after surgery, which may be related to less dosage of oxycodone in 0.01 mg/kg group and 0.02 mg/kg group.

In addition, the satisfaction rate of patients in 0.02 mg/kg group and 0.03 mg/kg group was significantly higher than that in 0.01 mg/kg group. Although 0.01 mg/kg group had the lowest incidence of dizziness, it has a poor analgesic effect and a high number of press. The press number in 0.01 mg/kg group was close to once every 1.5 h, seriously affected the rest of patients and reduced the satisfaction rate of patients. Although 0.3 mg/kg group suffered highest incidence of dizziness, the degree of dizziness was slight and had little effect on the activity of the patients, which only occured when the patients got up. After the patients rested in bed for several minutes, dizziness relieved spontaneously. These patients in the 0.03 mg/kg group were satisfied with the good analgesic effect. There was no significant difference in patients' satisfaction rate between 0.02 mg/kg group and 0.03 mg/kg group.

There are some limitations of this study. First, this was a single-center investigation. Second, we didn't perform a multidimensional pain assessment in this study. Finally, whether postoperative analgesia with oxycodone without background infusion is suitable for all gastrointestinal surgical procedures (e.g., non-laparoscopic gastrointestinal procedures) needs to be further studied.

In summary, 0.02 mg/kg of oxycodone could provide the same analgesic effect and satisfaction as 0.03 mg/kg of oxycodone, but the incidence of dizziness was lower than that in the 0.03 mg/kg group. Therefore, 0.02 mg/kg bolus dose of oxycodone in PCIA without background infusion may be a better choice after laparoscopic surgery for gastrointestinal cancer in elderly patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The ethical approval for the study was issued by the Ethical Committee of the third Xiangya hospital of Central South University. The ethics approval number was R16001. Informed consent was obtained from all patients when they agree to comply with our research plan. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Corresponding authors, FZ and QL, are responsible for the concept and protocol development. YZ and XH are responsible for manuscript writing and will be cofirst authors. HC is responsible for sample size calculation and statistical analyses. HS, WX and ZP are responsible for recruitment of patients. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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