AIDS Research and Therapy

BRIEF REPORT

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TheU-shape association between on-admission resting heart rate and 60-day all-cause mortality of AIDS inpatients in Fujian China: a retrospective cohort study

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Abstract

Background An elevated resting heart rate (RHR) is associated with poor outcomes in both healthy individuals and those with human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS). This study aimed to investigated the association between on admission resting heart rate (RHR) and 60-day mortality.

Methods This single-center retrospective cohort study evaluated the effect of RHR on the 60-day mortality of patient with AIDS in Southeast China. A total of 2188 patients with AIDS admitted for the first time between January 2016 and December 2021 were included. The RHR was categorized into tertiles. Disease progression was estimated using 60-day mortality rates. Cox proportional hazards regression models were used to evaluate the RHR with disease progression, and a two-piecewise Cox regression model was used to reveal the RHR effect at admission on 60-day mortality.

Results We observed a U-shape relationship between RHR and 60-day mortality. For a above 90 bpm, the 60-day mortality rose rapidly with a multivariable adjusted odds ratio (OR) of 1.032 (95% confidence interval [CI 1.016–1.048, $P < 0.001$). Below the threshold, 60 days mortality decreased as the RHR increased to 90 bpm with a multivariate-adjusted OR of 0.943 (95% CI 0.904–0.984, $P = 0.0065$).

Conclusions This study identified a U-shape relationship between RHR and 60-day mortality in HIV/AIDS patients. Further research is needed to characterize the role of RHR in the timely prevention of mortality in HIV/AIDS patients.

Keywords Resting heart rate, AIDS, Mortality, U-shape relationship

Background

Despite limitations in the number of available free antiretroviral drugs, China has successfully reduced the overall mortality of patients infected with human immunodeficiency virus (HIV) and/or acquired immune deficiency syndrome (AIDS) from 39.3 per 100 person-years in 2002 to 14.2 in 2014 [1]. However, according to the Chinese Center for Disease Control and Prevention Statistics, approximately 253,031 people in China lost their

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lives from AIDS-related causes in 2018 [2]. Mortality due to HIV or AIDS has placed a significant burden on health services and government finances globally.

Investigation regarding to the factors associated with mortality among patients with AIDS has been a primary area of interest for numerous scholars. The mortality rate of AIDS in the minority and male populations is higher than that in other Chinese populations. However, homosexual sex, antiretroviral therapy (ART), and increased CD4 test rates are associated with low mortality [3]. Patients with HIV/AIDS patients with high CD4 cell counts and late ART have a higher risk of an AIDS-related death [2]. However, there have been no significant differences in death outcomes among patients with different HIV-1 genotypes after ART [4].

In recent years, there has been a growing interest in exploring the prognostic impact of resting heart rate (RHR) on the life span of patients with or without cardiovascular disease. There is a negative correlation between RHR and life expectancy [5]. A greater RHR is associated with an increased risk of all-cause mortality [6]. However, there are limited articles discussing the association between RHR at admission and mortality in patients with AIDS.

The mechanisms underlying RHR and its relationship with clinical outcomes remain unclear. Many factors are believed to affect RHR, such as activation of the autonomic nervous system, subclinical inflammatory processes [7], and alcohol, caffeine, or heart failure in sinus rhythm [8]. It is noted that the shifting toward sympathetic dominance predisposes people with HIV or AIDS to an early and elevated risk of arrhythmias, cardiovascular events, and even accelerated HIV disease progression [9].

Therefore, we designed this retrospective cohort study based on the current state of this research. We investigated the association between RHR at admission and 60 days mortality rates of in patients with AIDS.

Methods

Study population

This retrospective cohort study included patients diagnosed with AIDS who were first time admitted to the Mengchao Hepatobiliary Hospital of Fujian Medical University, the largest treatment center for AIDS in Fujian province, from January 2016 to December 2021. HIV diagnosis was based on a confirmation report from the Fujian Provincial Center for Disease Control and Prevention. An AIDS diagnosis was based on Chinese Guidelines for Diagnosis and Treatment of Human Immunodeficiency Virus Infection/Acquired Immunodeficiency Syndrome (2021 edition). This study was conducted after the enrollment of subjects was completed in December 2021. We screened the subjects according to the guideline and excluded those who did not meet the diagnostic criteria. During the study period, all consecutively first admitted hospitalized patients with a diagnosis of AIDS were included in the study. Exclusion criteria included patients < 18 years of age or any of the following: none AIDS, no CD4 count, no admission RHR and infected with novel coronavirus. Individuals who die within 24 h after admission and, those whose deaths during the observation period were unrelated to the disease, such as suicide and car accidents were also excluded. After exclusions, 2188 patients constituted the study cohort (Fig. 1). All reports strengthened the reporting of observational studies in the epidemiology guidelines [10].

Ethics statement

This study followed the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Mengchao Hepatobiliary Hospital of Fujian Medical University. Given the retrospective nature of the study and the use of anonymized patient data, the requirement for informed consent was waived.

General data collection and outcome assessment

This retrospective study collected data from 2016 to 2021. The baseline data included demographic information, vital signs measured at rest upon admission, laboratory test results obtained within 24 h of admission, and any complications recorded in the inpatient electronic medical records. The mortality data was extracted from the electronic medical records of hospitalized patients and supplemented with telephone follow-ups conducted 60 days after admission. The criteria for terminating follow-up included the completion of a

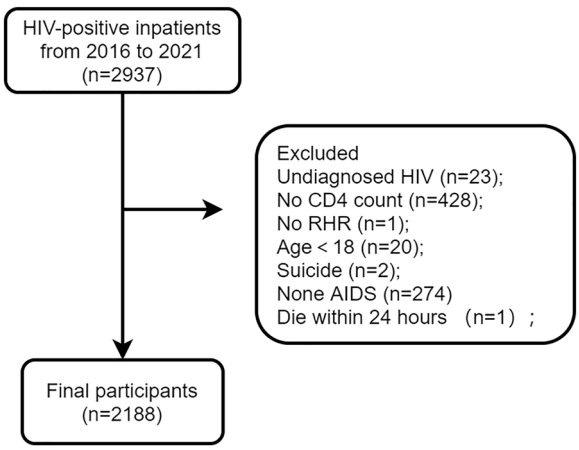

Fig. 1 Flowchart of study population with inclusion and exclusion criteria

60-day follow-up period, identification of events resulting in death as an endpoint, or the inability to maintain contact. To reduce bias, interviews were conducted with at least two or three family members. All laboratory data included measurements performed within the first 24 h of admission to reduce the probability that serum biomarker levels were affected by therapy.

Laboratory variables were assayed in local laboratories. Participant RHRs and blood pressure measurements were recorded using an non-invasive automated sphygmomanometer, which was conducted by a nurse with the participants lying in the supine position after been allowed to settle for 10 min at the time of hospital admission. The primary outcome measure was all-cause mortality within 60 days after hospital admission, excluding deaths unrelated to the underlying disease (such as suicide and motor vehicle accidents) and deaths occurring within 24 h of admission.

Statistical analysis

Data are expressed as mean (standard deviation) or median (interquartile rang) for continuous variables and percentages (%) for dichotomous variables. For baseline characteristics analysis, the statistical differences among tertile of RHR were tested using one-way ANOVA for continuous variables and chi-square test for categorical variables. Hazard ratios (HRs) and 95% confidence intervals (Cis) were calculated for 60-day mortality with RHR using Cox proportional hazards models. Both non-adjusted and multivariate-adjusted models were used. These potential confounders were chosen on the basis of previous scientific literature, or a more than 10% change in effect estimates. To further explore non-linearity, we also categorized RHR in tertile and examined the associations of tertile of RHR with 60-day mortality by using multivariate regression models Cox proportional hazards regression model with cubic spline functions and the smooth curve fitting were used to identify non-linear relationships between resting heart rate and 60-day mortality. If nonlinearity was detected, we firstly calculated the inflection point using recursive algorithm, and then constructed a two-piecewise Cox proportional-hazards regression model on both sides of the inflection point. The cumulative rates of death were compared using the Kaplan–Meier curves. Since the percentage of missing data was small (0%–6%), no imputation was performed. All analyses were performed using the statistical software packages R 3.3.2 (http://www.Rproject.org, The R Foundation, Vienna, Austria) and Free Statistics software version 1.1.

Results

Study participant baseline characteristics

Figure 1 shows the number of eligible participants and the participants analyzed in this study; 2188 participants who met the inclusion and exclusion criteria between January 2016 and December 2021were included in the final analysis. The data from 2188 inpatients (mean age 45.3 ± 15.2 years; 1894 men, 294 women) were analyzed. A total of 110 patients died within 60 days after admission due to HIV-related mortality (80.9%) and HIV-unrelated mortality (19.09%). In addition, 1512(69.1%) patients were first confirmed and 1420 (64.9%) were first started on ART. The median CD4 count was 92.8 ± 131.4 cells/UL. The participants were divided into three groups based on their RHR at admission (< 80, 80–99, ≥ 100). Participants with higher RHR tended to be younger, lower CD4/CD8 count, and higher temperature ($P < 0.001$) (Table 1 and Fig. 1).

Association of RHR at admission with 60-day mortality

In the Kaplan–Meier curve, the highest 60-day mortality was observed in patients with RHR ≥ 100 bpm (log-rank test: $P = 0.0018$), (Fig. 2). Table 2 presents the association between RHR at admission and 60-day mortality using multiple Cox regression models. In the unadjusted model, a decline in mortality risk was observed initially at first, then followed by a subsequent rise as the RHR at admission of the groups increased. Individuals with a RHR at admission falling within the highest group, compared to those in the middle group, exhibited an approximate twofold elevation in the risk of mortality. (HR: 2.05; 95% CI 1.37–3.08; $P = 0.001$). Similar results were obtained in the model 3 adjusted for all covariates, including sex, age, CD4, CD8, temperature, first confirm, first ART, gastrointestinal bleeding, diabetes, hypertension, auricular fibrillation, electrolyte disturbance, body mass index, leukocyte, lymphocyte, albumin, total bilirubin(TBIL), alanine aminotransferase (ALT), aspartate transferase (AST), serum creatinine, and C-reactive protein (CRP) (HR: 2.02, 95% CI 1.3–3.12, $P = 0.002$).

Threshold effect analysis of RHR on 60-day mortality

The association between levels of RHR on a continuous scale and mortality risk was U-shape ($P_{nonlinearity} = 0.002$), (Fig. 3) after adjusting. By using a two-piecewise linear regression model, we found that the threshold RHR was 90 bpm (Table 3). Above the threshold, the 60-day mortality rose rapidly with a multivariable adjusted OR of 1.032 (95% CI 1.016–1.048, $P < 0.001$; Table 3, Fig. 3). Below the threshold, 60 days mortality decreased as the RHR increased to 90 bpm (HR:0.943, 95% CI 0.904–0.984, $P = 0.0065$); (Table 3).

Table 1 Baseline characteristics of the study participants

Variables	Total	RHR (bpm)			*p*
	n = 2188	< 80	80–99	≥ 100	
		n = 260	n = 1162	n = 766	
Sex, n (%)					
Male	1894 (86.6)	211 (81.2)	998 (85.9)	685 (89.4)	0.002
Female	294 (13.4)	49 (18.8)	164 (14.1)	81 (10.6)	
Age, Mean ± SD	45.3 ± 15.2	52.3 ± 14.9	46.5 ± 15.2	41.2 ± 14.0	< 0.001
CD4, Mean ± SD	92.8 ± 131.4	151.0 ± 178.1	97.4 ± 129.6	66.1 ± 106.1	< 0.001
CD8, Mean ± SD	560.4 ± 616.8	620.2 ± 668.8	600.3 ± 697.2	479.5 ± 433.8	< 0.001
First confirmed, n (%)					
No	659 (30.1)	84 (32.3)	334 (28.7)	241 (31.5)	0.422
Yes	1512 (69.1)	173 (66.5)	818 (70.4)	521 (68)	
N/A	17 (0.8)	3 (1.2)	10 (0.9)	4 (0.5)	
First ART, n (%)					
No	749 (34.2)	106 (40.8)	395 (34)	248 (32.4)	0.077
Yes	1420 (64.9)	151 (58.1)	755 (65)	514 (67.1)	
N/A	19 (0.9)	3 (1.2)	12 (1)	4 (0.5)	
60-day mortality, n (%)					
No	2078 (95.0)	245 (94.2)	1121 (96.5)	712 (93)	0.002
Yes	110 (5.0)	15 (5.8)	41 (3.5)	54 (7)	
Temperature, Mean ± SD	37.0 ± 0.8	36.7 ± 0.5	37.0 ± 0.8	37.2 ± 0.9	< 0.001
Impaired liver function, n (%)					
No	1590 (72.7)	196 (75.4)	795 (68.4)	599 (78.2)	< 0.001
Yes	598 (27.3)	64 (24.6)	367 (31.6)	167 (21.8)	
Lung infections, n (%)					
No	930 (42.5)	133 (51.2)	477 (41)	320 (41.8)	0.01
Yes	1258 (57.5)	127 (48.8)	685 (59)	446 (58.2)	
Cancer, n (%)					
No	2098 (95.9)	249 (95.8)	1108 (95.4)	741 (96.7)	0.325
Yes	90 (4.1)	11 (4.2)	54 (4.6)	25 (3.3)	
Tuberculosis, n (%)					
No	1818 (83.1)	230 (88.5)	931 (80.1)	657 (85.8)	< 0.001
Yes	370 (16.9)	30 (11.5)	231 (19.9)	109 (14.2)	
Cardiovascular disease, n (%)					
No	1988 (90.9)	227 (87.3)	1050 (90.4)	711 (92.8)	0.02
Yes	200 (9.1)	33 (12.7)	112 (9.6)	55 (7.2)	
Impaired renal function, n (%)					
No	2101 (96.0)	252 (96.9)	1114 (95.9)	735 (96)	0.729
Yes	87 (4.0)	8 (3.1)	48 (4.1)	31 (4)	
Gastrointestinal bleeding, n (%)					
No	2169 (99.1)	259 (99.6)	1156 (99.5)	754 (98.4)	0.05
Yes	19 (0.9)	1 (0.4)	6 (0.5)	12 (1.6)	
Diabetes, n (%)					
No	2051 (93.7)	245 (94.2)	1076 (92.6)	730 (95.3)	0.053
Yes	137 (6.3)	15 (5.8)	86 (7.4)	36 (4.7)	
Hypertension, n (%)					
No	1982 (90.6)	227 (87.3)	1043 (89.8)	712 (93)	0.01
Yes	206 (9.4)	33 (12.7)	119 (10.2)	54 (7)	
Auricular fibrillation, n (%)					
No	2166 (99.0)	256 (98.5)	1150 (99)	760 (99.2)	0.514
Yes	22 (1.0)	4 (1.5)	12 (1)	6 (0.8)	

Table 1 (continued)

Variables	Total	RHR (bpm)			*p*
	n = 2188	< 80	80–99	≥ 100	
		n = 260	n = 1162	n = 766	
Electrolyte disturbance, n (%)					
No	1299 (59.4)	173 (66.5)	633 (54.5)	493 (64.4)	< 0.001
Yes	889 (40.6)	87 (33.5)	529 (45.5)	273 (35.6)	

RHR resting heart rate

bpm beats per minute

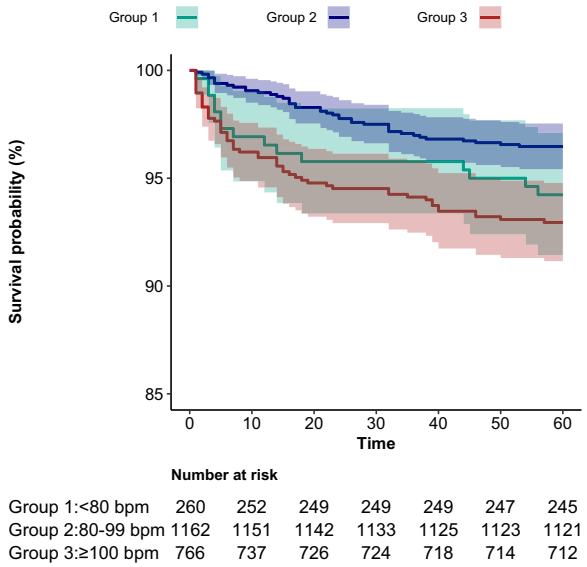

Fig. 2 Kaplan–Meier survival curves

Discussion

In this retrospective cohort of patients with AIDS admitted to the hospital, we reported the prognostic significance of the association between the RHR and admission and 60-day mortality. There was U-shape relationship between the RHR at admission and 60-day mortality after adjustments.

In recent decades, many researchers have focused on AIDS mortality. Although early combination ART has significant clinical benefits for people living with HIV, even with a CD4 count > 500 cells/μl [11], HIV currently ranks as the third highest cause of global mortality after cancer and cardiovascular diseases [12]. Among adults aged 25–49 years age, HIV is the second most common global disease burden [13].

Vital signs have been reported to be closely related to mortality due to HIV. It is believed that a respiratory rate > 20 breaths/min [12], systolic blood pressure < 90 mmHg, and systolic blood pressure > 140 mmHg at enrollment are associated with increased mortality [14]. However, systolic pressure and HIV infection are independent risk factors for mortality [15]. At the same

Table 2 Univariate Cox regression analysis of the 60-day mortality

Variable	N total	N event%	Mode1 1		Model 2		Model 3	
			HR95CI	*P* value	HR 95CI	*P* value	HR 95CI	*P* value
Ungrouped (bpm)	2188	110 (5)	1.03 (1.02 ~ 1.04)	< 0.001	1.03 (1.02 ~ 1.04)	< 0.001	1.02 (1.01 ~ 1.03)	< 0.001
Grouped (bpm)								
RHR (< 80)	260	15 (5.8)	1.66 (0.92 ~ 3)	0.093	1.99 (1.08 ~ 3.66)	0.028	2.38 (1.27 ~ 4.47)	0.007
RHR (80–99)	1162	41 (3.5)	1(Ref)		1(Ref)		1(Ref)	
RHR (≥ 100)	766	54 (7)	2.05 (1.37 ~ 3.08)	0.001	2.23 (1.46 ~ 3.39)	< 0.001	2.02 (1.3 ~ 3.12)	0.002
Trend test	2188	110 (5)		0.037		0.048		0.235

RHR resting heart rate

bpm beats per minute

Model 1: unadjusted

Model 2: adjusted for sex, age, CD4, CD8, temperature, first confirm, first ART, Gastrointestinal bleeding, diabetes, hypertension, Auricular fibrillation, electrolyte disturbance, BMI

Model 3: Adjusted for the variables in Model I plus leukocyte, lymphocyte, albumin, total bilirubin (TBIL), alanine aminotransferase (ALT), aspartate transferase (AST), serum creatinine, C-reactive protein (CRP)

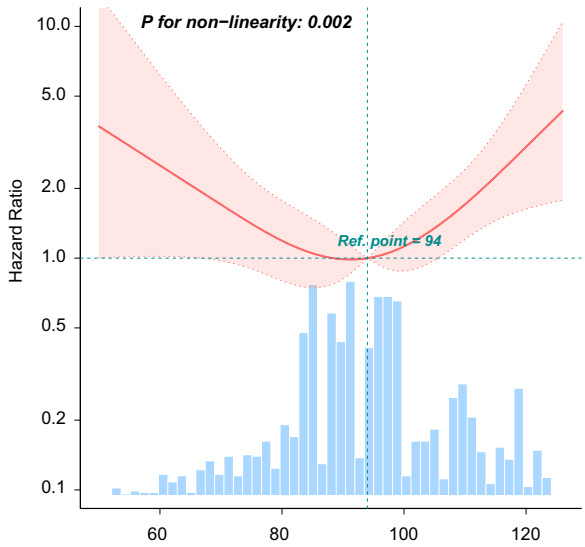

Fig. 3 U-shape relationship

Table 3 inflection point analysis of RHR on 60-days all-cause mortality

Outcome	HR (95%CI)	P-value
One—line linear regression model	1.02 (1.01 ~ 1.04)	< 0.001
Two-piecewise linear regression model		
RHR < 90 bpm	0.943 (0.904,0.984)	0.0065
RHR ≥ 90 bpm	1.032 (1.016,1.048)	< 0.001
P for log likelihood ratio test		< 0.001

Adjusted for the variables in sex, age, CD4, CD8, temperature, first confirm, first ART, Gastrointestinal bleeding, diabetes, hypertension, Auricular fibrillation, electrolyte disturbance, BMI, leukocyte, lymphocyte, albumin, total bilirubin (TBIL), alanine aminotransferase (ALT), aspartate transferase (AST), serum creatinine, C-reactive protein (CRP), procalcitonin (PCT)

time, the respiratory rate at admission is associated with both the frequency of monitoring and mortality [16]. Unfortunately, vital signs are currently poorly evaluated, leading to regular or accurate recordings [17].

Heart rate variability is considered to serve as an indicator of the overall physiological well-being of the human body and the RHR of healthy adults fluctuates between 50 and 90 bpm from day to night [18, 19]. Changes in the RHR can indicate acute infection, cardiovascular disease, cancer, gastrointestinal bleeding, pulmonary embolism, and use of antiviral drugs [19]. Vital signs, including heart rate, temperature, and respiratory and blood pressure, are the simplest and cheapest to monitor, and may also be the most important in hospitals. they also provide almost complete body function information and helps to assess general physical health [20].

An elevated RHR is associated with poor outcomes for both healthy individuals and patients with cardiovascular diseases [21, 22]. A higher RHR during young adulthood is associated with a greater risk of incident hypertension in middle-aged black men, white men, and white women [23]. For populations with obesity, RHR monitoring can be used as a noninvasive clinical indicator of increased risk of inflammation and cardiovascular disease [24]. A lower RHR, irrespective of treatment, was associated with a better prognosis only in patients with sinus rhythm [8]. An increased RHR is a significant predictor of all-cause mortality in patients with ambulatory heart failure receiving optimal medical therapy and is also an increased risk trend with older age [25]. We found a similar result; when the RHR was more than 90 bpm, a higher RHR was positively linked to 60-day mortality from HIV/AIDS. However, Gutierrez-Martinez et al. found a U-shaped relationship between RHR and cancer mortality, with inflection points at 60 and 80 bpm [26]. Yao et al. revealed a J-shaped association between mean heart rate and 30-day mortality in ischemic stroke with atrial fibrillation and an inflection point at approximately 80 bpm [27].

Our study has several strengths. First, the continuous collection of patients between 2016 and 2021 avoided selection bias. Second, RHR at admission is affected by many factors, including music, emotion, drugs, age, cardiovascular diseases, infection [28, 29]. Therefore, several synergistic factors were considered. The synergy factor laboratory data included leukocyte, lymphocyte, hemoglobin, platelet, albumin, TBIL, ALT, AST, Na, serum creatinine, triglycerides, CRP, PCT, CD4, and CD8 levels. Age, sex, complications, initial diagnosis, and temperature were included in our study. Finally, we focused on the RHR, which is the easiest and cheapest measurement to obtain and is easy for clinicians to use.

This study has a few limitations. First, retrospective research allows for the analysis of association rather than causality, and we could not adjust for all factors linked RHR at admission and 60-day mortality. Therefore, second the effects of the residual confounding factors could not be eliminated. Third, all the patients were Chinese; thus, our findings may not apply to other ethnicities. Finally, we focused on inpatients and the results may not extend to outpatients with HIV infections.

Conclusion

In this retrospective cohort study, we found a nonlinear association between RHR at admission and 60-day mortality in patients with HIV/AIDS, and an increase in the 60-day mortality with the increase in RHR when the RHR was > 90 bpm. These observations are similar to those in patients with ischemic stroke, cancer, or cardiovascular disease. However, further studies are needed to assess this effect.

Abbreviations

AIDS	Acquired immune deficiency syndrome
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
AST	Aspartate transferase
CI	Confidence interval
CRP	C-reactive protein
HIV	Human immunodeficiency virus
HR	Hazard ratio
RHR	Resting heart rate
TBIL	Total bilirubin

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Patient consent
Due toGiven the retrospective nature of the study and the use of anonymized patient data, the requirement for informed consent was waived.

Author contributions
R.H. and Y.L. conducted data analysis and wrote the manuscript. L.H. and R.H. designed the study and reviewed the manuscript. L.C. and Y.Y. conducted data collection and interpretation J.W. and H.Z. reviewed the data. All authors read and approved the final manuscript.

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Data availability of data and materials
The raw data required to reproduce these findings cannot be shared with the data from an ongoing study. The study is still ongoing, and therefore, the data presented in this paper cannot be shared at this timelf necessary, some or all data used during the study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Medical Ethics Committee of Mengchao Hepatobiliary Hospital of Fujian Medical University (2022-017-01).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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