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Effectiveness of azvudine versus nirmatrelvir/ritonavir for hospitalized patients with SARS-CoV-2 infection and pre-existing liver diseases

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Abstract

Background Azvudine and nirmatrelvir/ritonavir are recommended as priority treatments for SARS-CoV-2 infection in China, but their effectiveness and safety in patients with pre-existing chronic liver diseases remains unknown.

Methods We conducted a multicenter retrospective cohort study of hospitalized SARS-CoV-2 infected patients with chronic liver diseases in ten hospitals of Henan Province. Azvudine recipients were 2:1 propensity score matched with nirmatrelvir/ritonavir recipients. Efficacy and safety were evaluated by Kaplan–Meier analysis, multivariable Cox regression model, subgroup analysis, as well as sensitivity analyses.

Results Among 37606 hospitalized patients infected with SARS-CoV-2, 1355 azvudine recipients and 373 nirmatrelvir/ritonavir recipients met the inclusion criteria. Patients with azvudine treatment showed comparable effectiveness to nirmatrelvir/ritonavir with regard to both all-cause death ($P = 0.34$) and composite disease progression ($P = 0.32$), even after adjusting for other covariates (all-cause death: HR: 0.80, 95%CI: 0.574-1.128; composite disease progression: HR: 1.31, 95%CI: 0.999-1.723). Notably, compared with nirmatrelvir/ritonavir, azvudine showed better effectiveness for patients with a comorbidity of primary malignant tumor in reducing all-cause death. Four sensitivity analyses further confirmed the robustness.

Conclusions The effectiveness of azvudine may potentially comparable to nirmatrelvir/ritonavir in SARS-CoV-2 infected patients with pre-existing liver diseases with respect to all-cause death and composite disease progression, without serious safety concerns. Due to the existence of potential biases, further studies still need to evaluate the efficacy of these two drugs.

Trial registration The trial was retrospectively registered at ClinicalTrials.gov (CT.gov identifier: NCT06349655).

Keywords SARS-CoV-2, Azvudine, Paxlovid, Chronic liver disease, Effectiveness

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Background

The outbreak of coronavirus disease 2019 (COVID-19), a contagious respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), led to a substantial and profound impact on human health across numerous countries and regions. Up to now, the strains of SARS-CoV-2 continues to mutate and evolve, which show trends toward weaker virulence but higher infectiousness and still pose a great threat to human health, especially for those with pre-existing comorbidities [1, 2]. Evidence from the global outbreak showed that people with chronic liver diseases (CLD), such as hepatitis, cirrhosis, autoimmune hepatitis, nonalcoholic fatty liver disease (NAFLD), and metabolic-associated fatty liver disease (MAFLD) were the vulnerable population for SARS-CoV-2 infection and showed a higher risk for adverse clinical outcomes [3–5]. Given the immense CLD burden worldwide [6], appropriate and active treatments are needed urgently to prevent the disease progression, hospitalization and death of SARS-CoV-2 infected patients with pre-existing chronic liver diseases.

During the pandemic of COVID-19, nirmatrelvir/ritonavir (also known as Paxlovid) and azvudine were granted authorization or approval to fight against the SARS-CoV-2 infection as priority oral antiviral agents [7]. Paxlovid had been shown to reduce hospitalization or death among nonhospitalized patients with COVID-19 who were at high risk for progression to severe COVID-19 [8]. Insights from a single-center prospective cohort study showed that Paxlovid was associated with reduced hospitalization duration and elevated oxygen saturation levels at discharge in COVID-19 patients with pre-existing MAFLD [3]. Azvudine, the first Chinese oral anti-COVID-19 agent, was reported to exert its therapeutic potential against SARS-CoV-2 by inhibiting DNA- and RNA-dependent polymerases and suppressing virus replication [9]. Our previous randomized controlled trial also showed the effectiveness of azvudine in shortening nucleic acid negative conversion time in population with mild and moderate COVID-19 patients [10]. The efficacy of azvudine in treating COVID-19 was also confirmed in some real-world studies [11–13]. Recently, a real-world study revealed that azvudine therapy showed substantial clinical benefits in hospitalized patients with COVID-19 and pre-existing conditions compared with standard antiviral treatment [14]. However, the effectiveness and safety of azvudine versus Paxlovid in treating SARS-CoV-2 infected patients with pre-existing chronic liver disease remain unknown.

In this multi-center retrospective cohort study, we aimed to evaluate the clinical efficacy and safety of azvudine versus nirmatrelvir–ritonavir in hospitalized SARS-CoV-2 infected patients with pre-existing chronic liver diseases. We collected data from ten hospitals in Henan Province and the efficacy of the two antiviral agents was evaluated by comparing the outcomes of all-cause death and composite disease progression. The occurrence of adverse events was analyzed to evaluate their safety. So far, studies on the comparison of anti-COVID-19 drugs for SARS-CoV-2 infected patients with pre-existing comorbidities are still lack, and no direct evidence could be found on the anti-COVID-19 drug choice for patients with chronic liver diseases. This study may provide crucial insights into the choice of antiviral drugs for patients with SARS-CoV-2 infection and pre-existing chronic liver diseases.

Methods

Study design and patients

We performed a multi-center, retrospective cohort study comparing the effectiveness and safety of azvudine versus Paxlovid in hospitalized SARS-CoV-2 infected patients with pre-existing chronic liver diseases. Patients with SARS-CoV-2 infection were collected from ten hospitals in Henan Province during the period from December 5, 2022 to January 31, 2023. All data in this study were obtained from the electronic health records of the First Affiliated Hospital of Zhengzhou University, the First Affiliated Hospital of Henan University of Science and Technology, Henan Infectious Disease Hospital, Henan Provincial Chest Hospital, the Fifth People's Hospital of Anyang, Luoyang Central Hospital, Shangqiu Municipal Hospital, Nanyang Central Hospital, Fengqiu County People's Hospital, and Guangshan County People's Hospital. The study was approval by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (approval number: 2023-KY-0865-001).

To be eligible for inclusion in the study, participants should meet the criteria as follows: 1) adult hospitalized patients with pre-existing chronic liver diseases and positive RT-PCR for SARS-CoV-2 infection; 2) patients who were treated with either azvudine or Paxlovid after SARS-CoV-2 infection. We excluded participants who 1) were younger than 18 years; 2) received no antiviral drugs; 3) received other antiviral agents other than azvudine and Paxlovid; 4) received both azvudine and Paxlovid; 5) did not have chronic liver diseases.

The SARS-CoV-2 infection was diagnosed and classified according to the Diagnosis and Treatment Protocol for COVID-19 in China (Trial Version 10).

Data collection

All data required in the study were derived from electronic health records of the inpatient systems. The collected information included demographics, diagnoses, laboratory tests, prescription list, admission and

discharge records. The vital signs of the patients, respiratory rate and blood oxygen saturation were collected from the nursing records. The information on death was determined according to the discharge records. The information on vaccination status was obtained from Henan Provincial Center for Disease Control and Prevention.

Treatment exposure

During hospitalization, the administration of azvudine (5 mg once a day for less than 14 days) or Paxlovid (300 mg nirmatrelvir/100 mg ritonavir once per 12 hours for 5 days) to diagnosed SARS-CoV-2 infected patients with pre-existing chronic liver diseases was regarded as treatment exposure. All eligible patients were included either in the azvudine group or Paxlovid group according to their treatments. The baseline time range was defined as the period from the initial diagnosis to first dose.

Baseline covariates

The baseline covariates in this study included age, gender, body mass index (BMI), severity of COVID-19 at admission (mild, moderate and severe/critical), concomitant hormone therapy at admission (with or without), time from symptom onset to treatment exposure (within or beyond 5 days), medical history (diabetes, hypertension, cardio-cerebral diseases, chronic kidney diseases, and primary malignant tumors). Patients' laboratory test parameters at baseline time were also collected including neutrophil (Neut), lymphocyte (Lymph), glucose (Glu), high-density lipoprotein (HDL), low-density lipoprotein (LDL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (CREA), glomerular filtration rate (e-GFR), C–reactive protein (CRP), procalcitonin (PCT), prothrombin time (PT), activated partial thromboplastin time (APTT), cholesterol (CH), triglyceride (TG), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), albumin (ALB), and total bilirubin (TBIL). The classification of severity of COVID-19 referred to the Diagnosis and Treatment Protocol for COVID-19 in China (trial version 10) [7].

Outcomes

The primary outcome was all-cause death in COVID-19 patients with pre-existing chronic disease progression. Secondary outcome was a composite outcome of disease progression, including application of high-flow nasal cannula (HFNC) oxygen therapy, invasive or non-invasive mechanical ventilation, intensive care unit (ICU) admission, and all-cause death. The disease progression was defined that the disease progressed to a more severe stage. The outcomes were collected from the date of diagnosis to occurrence of outcome event, discharge date, or the date of death, whichever came first.

Safety evaluation

The safety of the drugs was evaluated by analyzing the occurrence of adverse events (AEs). Parameters on liver function (increased ALT, increased AST, increased ALP, increased GGT), kidney function (hyperuricemia, increased CREA), immunity (decreased lymphocyte count, increased lymphocyte count, increased neutrophil count), glucose/lipid metabolism (hypoglycemia, hypercholesteremia, and hypertriglyceridemia), anemia (decreased platelet-count, hemoglobin), and electrolyte (hypokalemia, hyperkalemia) were collected and assessed after azvudine and Paxlovid administration. AEs of grade 1, grade 2, and serious AEs greater than grade 3 were collected in this study. The grades of the AEs were determined according to the Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE 5.0).

Handling of Missing Data

We performed multiple imputation to fill up the missing data in this study. All incomplete variables demonstrated missing-at-random patterns with less than 30% missingness per parameter, meeting the threshold for multiple imputation implementation. We developed regression models (linear regression for continuous data, logistic regression for binary data) to iteratively generate 5 complete datasets via chained equations, sampling probabilistically from observed value distributions. Each imputed dataset underwent standardized analytic procedures, with final estimates combined via Rubin's pooling rules. This approach enhanced the plausibility of imputed values while mitigating systematic bias, thereby strengthening result validity against missing data uncertainty.

Statistical analysis

The propensity-score matching (PSM) by logistic regression was performed to balance the baseline covariates of the participants in azvudine and Paxlovid group. Multiple imputation was used to fill up the missing data, while the variable with more than 30% missing values was discarded. Kaplan–Meier method was used to estimate the cumulative hazards with the log-rank test during the follow-up period of 30 days. The hazard ratio (HR) for the outcome and its 95% confidence interval (CI) after adjusting for other cofounders were estimated with the use of the Cox proportional model. Subgroup analyses were performed at each level of the interested baseline covariates to assess the robustness of the results.

To assess the sensitivity of the primary and secondary outcome to possible biases, we repeated the analysis by filling up the missing data with mean value of the

available data. Then, we also repeated the analysis by using probabilistic model to perform propensity-score matching. In addition, we excluded patients who was discharged from the hospital within one day after drug treatment.

Continuous variables with normal distribution were presented as mean ± standard deviation (SD) and analyzed using t-test. Continuous variables without normal distribution were expressed as median (interquartile range, IQR) and analyzed using Mann-Whitney U test. Categorical variables were presented as absolute numbers (percentages) and analyzed by the Chi-square test. All statistical analyses were processed with R version 4.3.0. A two-sided $P < 0.05$ represent statistically significant.

Results

Study population

A total of 37606 hospitalized patients with SARS-CoV-2 infection were collected between December 5, 2022 and January 31, 2023. Of these, 1728 SARS-CoV-2 infected patients with pre-existing chronic liver diseases met the eligibility criteria and were included in the study. Propensity score matching was then performed to balance the baseline features between the two groups which result in a final enrollment of 674 recipients in azvudine group and 364 recipients in Paxlovid group (Fig. 1A). The baseline characteristics of the full analysis population before and after 2:1 matching of propensity score are presented in Table 1. After matching, all covariates at baseline received balance between the two groups, with the *P* value greater than 0.05 (Fig. 1B). The missing data in laboratory parameters was random and thus filled up with multiple imputation.

All-cause death

Within 30 days of follow-up, the primary analysis results showed no significant difference between azvudine and Paxlovid with respect to the cumulative hazards of all-cause death (P=0.34) (Fig. 2A). Of the 1038 patients receiving any treatment, the crude incidence rate of all-cause death was 10.94 per 1000 person-days in patients treated with azvudine vs. 12.74 per 1000 person-days in the Paxlovid group. Multivariate Cox regression analysis showed that the estimated hazard ratio in azvudine group was 0.80 (95% confidence interval [CI]: 0.574–1.128) compared to that of Paxlovid group after adjusting for other variables. No significant difference in effectiveness was observed between the two antiviral agents (P=0.208) (Fig. 2B).

Subgroup analyses of all-cause death indicated the similar effectiveness of the two drugs across most of the subgroups defined according to the gender, age, severity at admission, vaccination status, concomitant hormone therapy, antibiotics and the presence of comorbidities. Notably, compared to Paxlovid, a better protective effect of azvudine was observed in those with primary malignant tumor (HR: 0.21; 95% CI: 0.09–0.48) and in those who had more than 5 days from symptom onset to treatment exposure (HR: 0.50; 95% CI: 0.28–0.90) (Fig. 2C).

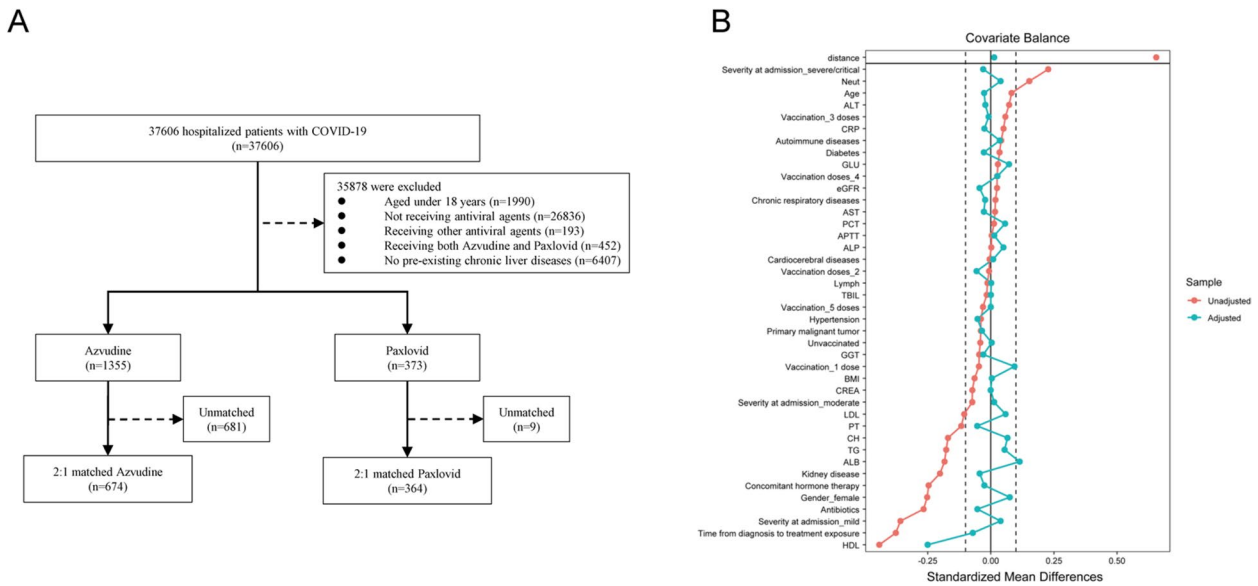


Fig. 1 The cohort flow diagram. **A** Study population flowchart showing the inclusion and exclusion of Azvudine recipients and Paxlovid recipients among hospitalized patients with COVID-19 and pre-existing chronic liver diseases during the study period. **B** Baseline characteristics of the study population before and after 2:1 propensity score matching

Table 1 Baseline characteristics of the study population before and after 2:1 propensity score matching

Baseline characteristics	Before matching			After propensity score matching (2:1)		
	Azvudine (*n*=1355)	Paxlovid (*n*=373)	*P* value	Azvudine (*n*=674)	Paxlovid (*n*=364)	*P* value
Sociodemographic information						
Age, years (mean ± SD)	67.39 (14.43)	68.58 (14.45)	0.157	68.38 (13.80)	68.40 (14.50)	0.988
Gender, n(%)			<0.001			0.766
Male	886 (65.4)	284 (76.1)		504 (74.8)	276 (75.8)	
Female	469 (34.6)	89 (23.9)		170 (25.2)	88 (24.2)	
BMI, kg/m^2 (mean ± SD)	24.84 (4.06)	24.61 (3.56)	0.322	24.81 (4.09)	24.68 (3.55)	0.607
Severity at admission, n(%)			<0.001			0.824
Mild	163 (12.0)	17 (4.6)		28 (4.2)	17 (4.7)	
Moderate	805 (59.4)	208 (55.8)		390 (57.9)	204 (56.0)	
Severe**/critical**	387 (28.6)	148 (39.7)		256 (38.0)	143 (39.3)	
Vaccination status, n(%)			0.865			0.913
unvaccinated	440 (32.5)	114 (30.6)		216 (32.0)	111 (30.5)	
1 dose	71 (5.2)	16 (4.3)		26 (3.9)	16 (4.4)	
2 doses	192 (14.2)	52 (13.9)		88 (13.1)	52 (14.3)	
3 doses	640 (47.2)	187 (50.1)		339 (50.3)	181 (49.7)	
4 doses	11 (0.8)	4 (1.1)		5 (0.7)	4 (1.1)	
5 doses	1 (0.1)	0 (0.0)		0 (0.0)	0 (0.0)	
Concomitant hormone therapy, n(%)			<0.001			0.299
No	708 (52.3)	239 (64.1)		406 (60.2)	232 (63.7)	
Yes	647 (47.7)	134 (35.9)		268 (39.8)	132 (36.3)	
Antibiotics, n(%)			<0.001			0.223
No	614 (45.3)	218 (58.4)		359 (53.3)	209 (57.4)	
Yes	741 (54.7)	155 (41.6)		315 (46.7)	155 (42.6)	
Time from symptom onset to treatment exposure			<0.001			0.167
> 5 days	288 (21.3)	148 (39.7)		227 (33.7)	139 (38.2)	
0–5 days	1067 (78.7)	225 (60.3)		447 (66.3)	225 (61.8)	
Comorbidities, n(%)						
Diabetes	296 (21.8)	87 (23.3)	0.59	157 (23.3)	86 (23.6)	0.965
Hypertension	611 (45.1)	161 (43.2)	0.545	306 (45.4)	157 (43.1)	0.525
Cardio-cerebral diseases	457 (33.7)	125 (33.5)	0.987	226 (33.5)	123 (33.8)	0.987
Kidney diseases	528 (39.0)	111 (29.8)	0.001	217 (32.2)	111 (30.5)	0.622
Chronic respiratory diseases	248 (18.3)	71 (19.0)	0.805	128 (19.0)	69 (19.0)	1
Autoimmune diseases	60 (4.4)	20 (5.4)	0.535	32 (4.7)	20 (5.5)	0.706
Primary malignant tumors	177 (13.1)	44 (11.8)	0.575	79 (11.7)	43 (11.8)	1
Laboratory parameters, (mean ± SD)						
Neutrophil, $\times 10^9$/L	6.05 (4.05)	6.77 (4.73)	0.003	6.51 (4.11)	6.73 (4.74)	0.421
Lymphocyte, $\times 10^9$/L	1.01 (1.15)	0.99 (1.33)	0.801	0.99 (1.11)	1.00 (1.35)	0.842
Glucose, mmol/L	8.29 (4.08)	8.42 (4.42)	0.605	8.13 (3.80)	8.43 (4.44)	0.248
High-density lipoprotein, mmol/L	1.17 (2.35)	1.01 (0.36)	0.197	1.05 (1.54)	1.01 (0.36)	0.605
Low-density lipoprotein, mmol/L	2.28 (1.95)	2.18 (0.90)	0.361	2.14 (0.89)	2.17 (0.90)	0.558
Alanine aminotransferase, IU/L	56.96 (109.48)	64.31 (100.78)	0.244	62.32 (123.33)	65.21 (101.83)	0.702
Aspartate aminotransferase, IU/L	54.59 (83.16)	55.98 (81.72)	0.774	55.99 (90.09)	56.59 (82.56)	0.915
Creatinine, μmol/L	100.42 (174.70)	91.74 (118.69)	0.366	91.91 (99.81)	92.59 (120.01)	0.922
Glomerular filtration rate, ml/min	86.03 (54.58)	87.44 (56.29)	0.661	86.29 (60.29)	87.37 (56.93)	0.781
C–reactive protein, mg/L	55.73 (65.04)	59.09 (66.25)	0.379	60.35 (67.74)	59.56 (66.63)	0.857
Procalcitonin, ng/ml	1.29 (6.59)	1.38 (6.40)	0.828	1.29 (5.61)	1.39 (6.48)	0.791
Prothrombin time, s	18.00 (9.70)	16.59 (12.03)	0.019	17.41 (9.21)	16.67 (12.13)	0.27

Table 1 (continued)

Baseline characteristics	Before matching			After propensity score matching (2:1)		
	Azvudine (*n*=1355)	Paxlovid (*n*=373)	*P* value	Azvudine (*n*=674)	Paxlovid (*n*=364)	*P* value
Activated partial thromboplastin time, s	27.09 (11.69)	27.15 (15.37)	0.937	27.19 (11.02)	27.31 (15.48)	0.888
Cholesterol, mmol/L	3.93 (2.02)	3.74 (1.15)	0.074	3.75 (1.13)	3.74 (1.14)	0.979
Triglyceride, mmol/L	1.47 (2.22)	1.32 (0.83)	0.212	1.30 (0.77)	1.33 (0.83)	0.593
Alkaline phosphatase, IU/L	93.74 (72.74)	93.88 (64.60)	0.972	92.09 (70.90)	93.53 (63.79)	0.746
Gamma-glutamyl transpeptidase, IU/L	84.06 (194.79)	79.21 (105.88)	0.644	78.71 (96.60)	80.39 (106.89)	0.796
Albumin, g/L	34.28 (11.71)	32.82 (8.01)	0.023	32.59 (10.20)	32.91 (7.90)	0.6
Total bilirubin, umol/L	14.51 (16.92)	14.17 (21.45)	0.745	14.52 (15.35)	14.22 (21.70)	0.795

SD standard deviation; *BMI* Body mass index

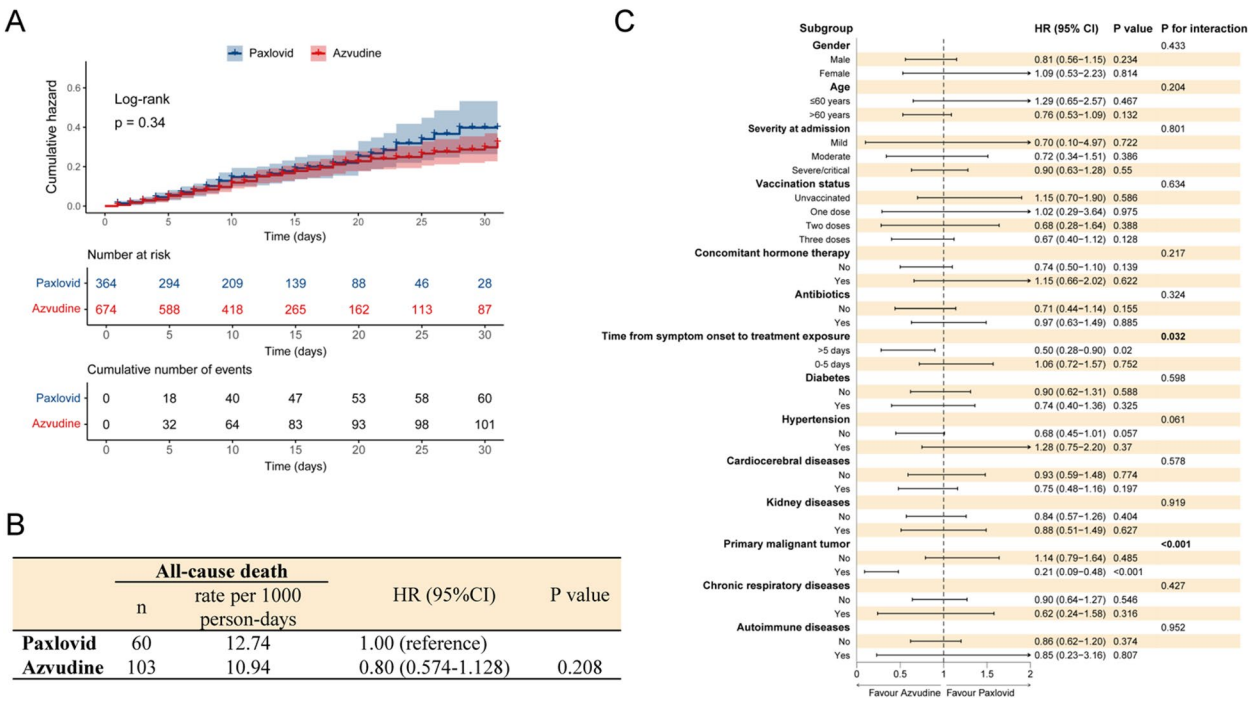


Fig. 2 The efficacy of Azvudine vs Paxlovid in reducing all-cause death. **A** Cumulative risk curve; **B** Incidence rate of all-cause death outcome with multivariate Cox regression analysis after adjusting for other confounding factors; **C** The effectiveness of Azvudine vs Paxlovid in reducing the risk of all-cause death by subgroups of selected baseline characteristics. HR: Hazard Ratio; 95%CI: 95% confidence interval

Four sensitivity analyses were then performed to identify the robustness of the all-cause death outcome. Firstly, we filled up the missing data with the mean value of the available data before performing propensity score matching (Table S1), both the Kaplan–Meier analysis (*P*=0.26) (Figure S1 A) and Cox regression results (HR: 0.77; 95% CI: 0.559–1.073, *P*=0.124) (Figure S2) showed no significant difference between the azvudine and Paxlovid group in reducing all-cause death. Secondly, we performed the propensity score matching using probabilistic method (Table S2), similar effectiveness of the two antiviral agents was observed (Kaplan–Meier: *P*=0.44; Cox regression: HR: 0.73; 95% CI: 0.525–1.018, *P*=0.064) (Figure S1B, Figure S2). Thirdly, we excluded patients who discharged within one day after drug treatment (Table S3), consistent with the previous results, no difference was observed in reducing all-cause death between the two drugs (Kaplan–Meier: *P*=0.47; Cox regression: HR: 0.81; 95% CI: 0.580–1.124, *P*=0.205) (Figure S1 C, Figure S2). Fourthly, to eliminate the effect of potential drug-drug interaction on the clinical outcomes, we excluded patients with a prescription of conflicting drugs either

with azvudine or Paxlovid. Similar results found that no difference was observed for all-cause death (log-rank *P* = 0.64; HR: 0.80, 95% CI: 0.556–1.163) between the two antiviral agents (Figure S1D, Figure S2). Sensitivity analyses confirmed the comparable effectiveness of azvudine to Paxlovid with respect to all-cause death in SARS-CoV-2 infected patients with pre-existing chronic liver diseases.

Composite disease progression

For the 30-day secondary outcome of composite disease progression, Kaplan–Meier analysis results showed no significant difference on the cumulative incidence rate of composite disease progression between azvudine and Paxlovid group (P=0.32) (Fig. 3A). The crude incidence rate of composite disease progression was 22.06 per 1000 person-days in azvudine group, which is comparable with that in the Paxlovid group (19.13 per 1000 person-days). According to multivariable Cox regression analysis, the hazard ratio for the incidence of composite disease progression (azvudine vs. Paxlovid) was 1.31 (95% CI, 0.999 to 1.723; *P*=0.051), which indicates that the effectiveness of azvudine was comparable to Paxlovid (Fig. 3B).

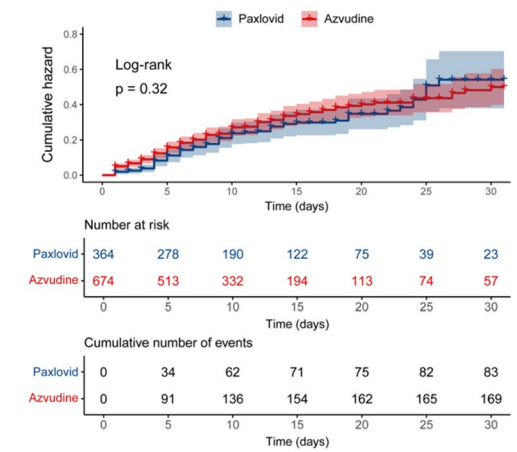
Subgroup analyses were then performed to estimate the treatment effects of the two drugs for fourteen subgroups of interest by fitting interaction models. Subgroup analyses of composite disease progression outcome did not detect significant interaction effect in all the interested subgroups except for primary malignant tumor (P for interaction = 0.02) (Fig. 3C).

Sensitivity analyses with four different methods were then further identified the robustness of the results. By filling up the missing data with the mean value of the available data before performing propensity score matching (Table S1), or performing propensity score matching using probabilistic method (Table S2), or excluding patients discharged within one day after drug treatment (Table S3), or excluding patients taking potential conflicting drugs, all of these results showed no significant difference between the azvudine and Paxlovid treatment in reducing the risk of composite disease progression with a P value of 0.89 (Figure S3 A, Figure S4), 0.36 (Figure S3B, Figure S4), 0.69 (Figure S3 C, Figure S4), 0.42 (Figure S3D, Figure S4), respectively.

Safety

To evaluate the safety of azvudine and Paxlovid, we collected key biochemical parameters associated with liver function, kidney function, blood glucose and lipid, immune cells, anemia, and electrolyte. Regarding adverse

A



B

	Composite disease progression		HR (95%CI)	P value
	n	rate per 1000 person-days		
Paxlovid	83	19.13	1.00 (reference)	
Azvudine	169	22.06	1.31 (0.999-1.723)	0.051

C

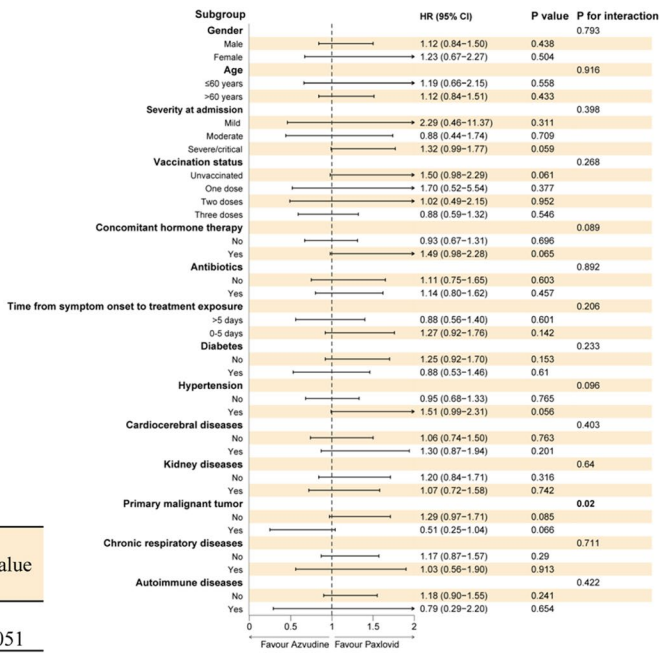


Fig. 3 The efficacy of Azvudine vs Paxlovid in reducing composite disease progression. **A** Cumulative risk curve; **B** Incidence rate of composite disease progression outcome with multivariate Cox regression analysis after adjusting for other confounding factors; **C** The effectiveness of Azvudine vs Paxlovid in reducing the risk of composite disease progression by subgroups of selected baseline characteristics. HR: Hazard Ratio; 95%CI: 95% confidence interval

events of grade 1, the occurrence of increased ALT, and increased AST showed a relatively lower risk in azvudine group compared with Paxlovid group. In addition, the occurrence of increased ALP decreased in azvudine group for adverse events of grade 2. However, no significant difference existed between the two groups in adverse events of grade greater than 3 (Table 2).

We then further evaluated the liver function in both azvudine and Paxlovid groups by observing the dynamic changes of ALT, AST, GGT, and TBIL within 15 days after drug treatment. The results showed that ALT levels were above the normal range in both groups, with significant differences at some time points (Fig. 4A). AST levels revealed a trend of gradual decrease either in azvudine and Paxlovid group (Fig. 4B). The GGT levels of the patients in both groups were both above normal, of which azvudine treatment group showed a slow recovery rate. Nevertheless, no significant difference was observed between the two groups except for at 12 days point (Fig. 4C). TBIL levels were within the normal range between the two groups, and there was basically no significant difference (Fig. 4D). In general, among adults with SARS-CoV-2 infection and pre-existing chronic liver diseases, the occurrence of adverse events of azvudine and Paxlovid was comparable and within limits of acceptability.

Discussion

In this retrospective cohort study of hospitalized patients with SARS-CoV-2 infection and pre-existing chronic liver disease, we found a noninferiority of azvudine to Paxlovid with respect to the all-cause death and composite disease progression. According to the subgroup analysis, the point estimates of HRs for other comorbidities of primary malignant tumor increase to the right of 1, suggesting the higher risk of Paxlovid and the favor of azvudine on patients with COVID-19 and pre-existing chronic liver diseases in reducing all-cause death. To our knowledge, this is the first multicenter cohort study to compare the efficacy and safety of azvudine with Paxlovid in hospitalized patients with COVID-19 and pre-existing chronic liver disease.

As for the SARS-CoV-2 infected patients with chronic liver diseases, Paxlovid was reported to be associated with reduced hospitalization duration and elevated oxygen saturation levels at discharge [3]. A retrospective study also confirmed that Paxlovid contributed to lowering the risk of all-cause emergency department visits, hospitalization, or mortality in non-hospitalized COVID-19 patients with nonalcoholic fatty liver disease [15]. However, the high cost of Paxlovid limited its widespread promotion and application. In this study, similar efficacy was observed between azvudine and Paxlovid in either all-cause death or composite disease progression, highlighting the clinical benefits of azvudine in the patients with SARS-CoV-2 infection and pre-existing chronic liver diseases.

The efficacy of antiviral agents may vary according to the patient characteristics, vaccination status, severity of COVID-19, concomitant hormone therapy, antibiotics, and comorbidities. According to the subgroup analysis in this study, we interestingly found that the administration of azvudine provided better clinical benefits for patients with comorbidities of primary malignant tumor compared with Paxlovid in reducing both all-cause death and composite disease progression. The immune system is known to play a vital role in fighting against SARS-CoV-2 and killing cancer cells, whereas individuals with chronic liver diseases and tumor showed a poor immune function [16, 17]. Paxlovid is a protease inhibitor drug combination which performed antiviral effects by targeting the main protease of the novel coronavirus 3CL protease and inhibiting viral replication [18]. Different to Paxlovid, azvudine is a nucleoside analog that inhibits RNA-dependent RNA polymerases (RdRps). Besides inhibition of viral replication, azvudine was found to concentrate in the thymus with its active form after oral administration and thus protect the immune function of the thymus [19, 20]. The activation of the immune system further promotes the elimination of the virus, which enhanced the efficiency of azvudine in treating hospitalized SARS-CoV-2 infected patients with pre-existing chronic liver diseases and malignant tumor. This might provide a reasonable explanation for the priority of azvudine for patients with primary malignant tumor.

As is known, the choice of antiviral agents is a comprehension decision according to the treatment efficacy, the cost-effectiveness, and safety. Existing evidence pointed that antiviral agents may possibly increase the burden of liver and kidney, as well as cause liver and kidney disorders. Therefore, particular attention should be paid to the changes of liver function of patients after drug treatment in patients with COVID-19 and pre-existing chronic liver diseases. According to previous randomized clinical studies, azvudine treatment could be well tolerated by patients, with no significant change of hepatic and renal functions in azvudine group compared with the normal treatment group [9, 10, 21]. The dynamic changes of ALT, AST, GGT and TBIL observed in this study confirmed a slightly better safety of azvudine relative to Paxlovid in alleviating the injury of liver function. Fewer serious adverse events provided favorable support for the safety of the two antiviral drugs.

There are some limitations in our study. Firstly, there exists non-randomized treatment selection arising from the retrospective design of the study though some

Table 2 Incidence of adverse events of the study population receiving Azvudine or Paxlovid treatment

Adverse events (N, %)	Available data[a]		Grade 1[b]			Grade 2[b]			Grade ≥ 3[b]		
	Azvudine (674)	Paxlovid (364)	Azvudine n (%)	Paxlovid n (%)	*P* value	Azvudine n (%)	Paxlovid n (%)	*P* value	Azvudine n (%)	Paxlovid n (%)	*P* value
ALT increased	423	250	103 (24%)	86 (34%)	0.005	22 (5.2%)	20 (8.0%)	0.15	18 (4.3%)	13 (5.2%)	0.6
AST increased	433	254	78 (18%)	62 (24%)	0.045	20 (4.6%)	10 (3.9%)	0.7	23 (5.3%)	12 (4.7%)	0.7
ALP increased	421	250	39 (9.3%)	24 (9.6%)	0.9	1 (0.2%)	5 (2.0%)	0.029	0 (0%)	1 (0.4%)	0.4
GGT increased	339	242	50 (15%)	48 (20%)	0.11	15 (4.4%)	13 (5.4%)	0.6	3 (0.9%)	7 (2.9%)	0.10
CREA increased	433	247	20 (4.6%)	13 (5.3%)	0.7	24 (5.5%)	12 (4.9%)	0.7	14 (3.2%)	5 (2.0%)	0.4
Hyperuricemia	377	243	42 (11%)	11 (4.5%)	0.004	0	0	NA	0	0	NA
Hypokalemia	467	279	55 (12%)	43 (15%)	0.2	55 (12%)	43 (15%)	0.2	56 (12%)	29 (10%)	0.5
Hyperkalemia	467	279	24 (5.1%)	11 (3.9%)	0.5	23 (4.9%)	11 (3.9%)	0.5	9 (1.9%)	1 (0.4%)	0.10
Hypoglycemia	149	13	38 (26%)	4 (31%)	0.7	0	0	NA	0	0	NA
Hypercholesteremia	107	43	6 (5.6%)	7 (16%)	0.052	1 (0.9%)	0 (0%)	>0.9	0	0	NA
Hypertriglyceridemia	90	40	14 (16%)	10 (25%)	0.2	1 (1.1%)	1 (2.5%)	0.5	1 (1.1%)	0 (0%)	>0.9
Lymphocyte count decreased	570	296	24 (4.2%)	14 (4.7%)	0.7	56 (9.8%)	26 (8.8%)	0.6	153 (27%)	94 (32%)	0.13
Lymphocyte count increased	570	296	6 (1.1%)	4 (1.4%)	0.7	9 (1.6%)	3 (1.0%)	0.8	0 (0%)	2 (0.7%)	0.12
Neutrophil count increased	377	248	6 (1.6%)	4 (1.6%)	>0.9	7 (1.9%)	3 (1.2%)	0.7	7 (1.9%)	3 (1.2%)	0.7
Platelets-count decreased	437	255	26 (5.9%)	18 (7.1%)	0.6	13 (3.0%)	13 (5.1%)	0.2	31 (7.1%)	22 (8.6%)	0.5
Hemoglobin decreased	389	252	66 (17%)	41 (16%)	0.8	41 (11%)	26 (10%)	>0.9	51 (13%)	34 (13%)	0.9

ALT alanine aminotransferase; *AST* aspartate aminotransferase; *ALP* alkaline phosphatase; *GGT* gamma-glutamyl transpeptidase; *CREA* creatinine

[a] Number of patients who completed the follow-up of data collection for this clinical parameter

[b] The grades of adverse events were defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0

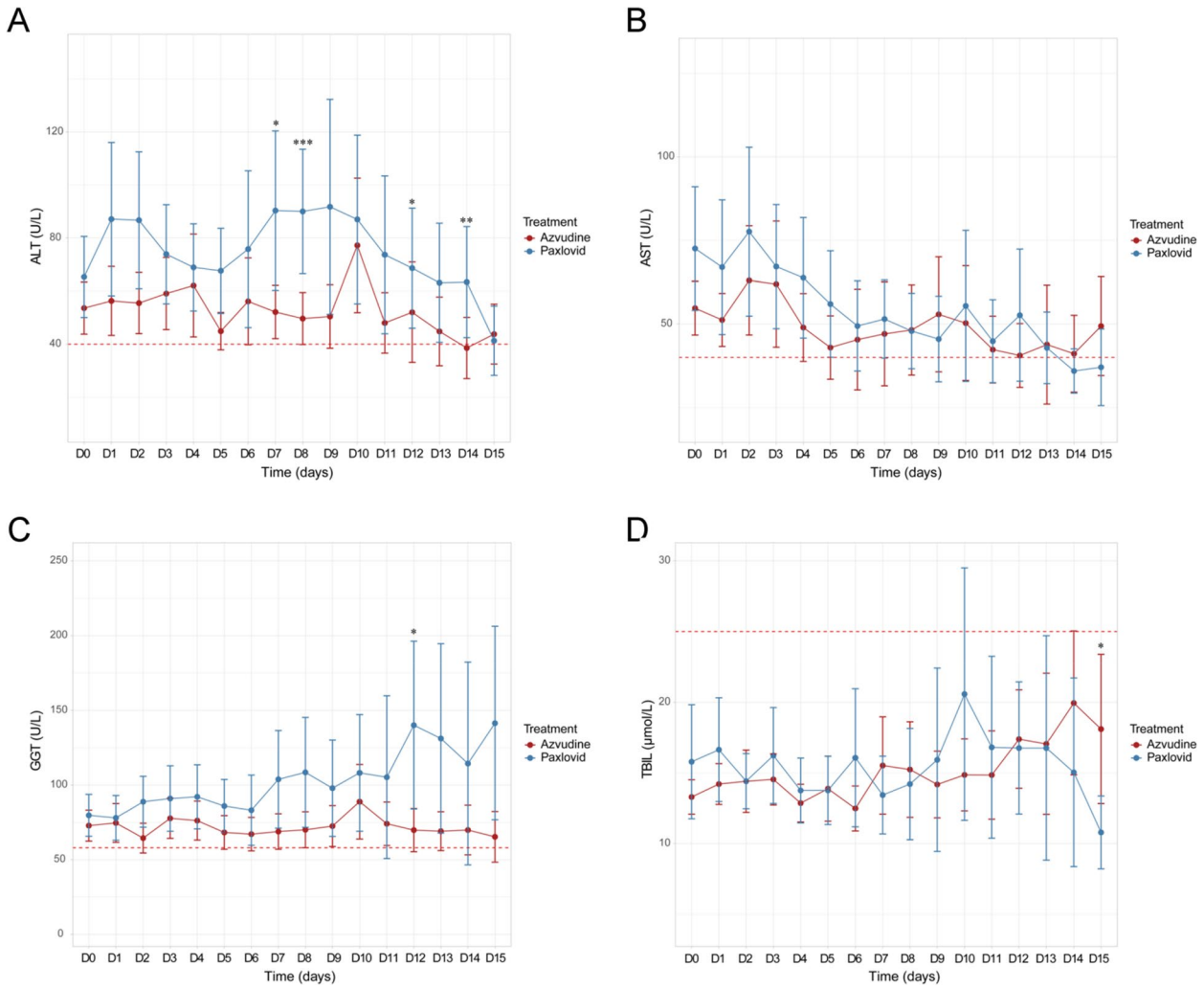


Fig. 4 The dynamic changes of liver function within 15 days after treating with Azvudine or Paxlovid. Dynamic changes in (**A**) ALT, (**B**) AST, (**C**) GGT, and (**D**) TBIL. ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; TBIL, total bilirubine. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

potential confounding factors are balanced. Our real-world research included a number of patients from ten hospitals in different regions, which may to some extent enhance the reliability of the results. Secondly, the enrollment of severe/critical patients beyond guideline reference may also introduce some selection bias, but the utilization of propensity score matching may help balance the baseline characteristics between the two groups and minimize this bias. Thirdly, the included cohort can only be considered to be representative in Henan province, and studies on the efficacy of azvudine and Paxlovid in different regions and ethnicities should be carried out. Fourthly, the real-world drug choice may be influenced by a variety of factors, such as availability of drugs, clinician preferences, cost-effectiveness, affordability of patients. Fifthly, treatment duration is an important factor affecting clinical outcomes but there lacked related information on specific treatment duration in this study. All of these factors may affect the clinical outcomes, but the bias is difficult to address in retrospective studies. Further randomized controlled trials with larger samples are still needed to confirm the efficacy of azvudine versus Paxlovid.

Conclusions

In this multicenter retrospective study, azvudine showed a similar all-cause death outcome and composite disease outcome with Paxlovid in patients with SARS-CoV-2 infection and pre-existing chronic liver disease, with few serious adverse events. For patients

with comorbidity of primary malignant tumor, azvudine was superior to Paxlovid in reducing all-cause death. Our findings are expected to provide a reference for the selection and prioritization of antiviral drugs in SARS-CoV-2 infected patients with pre-existing chronic liver disease. Given the potential for biases, further studies remain necessary to assess the therapeutic effects of these two antiviral agents.

Abbreviations

COVID-19	Coronavirus disease 2019
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
CLD	Chronic liver diseases
NAFLD	Nonalcoholic fatty liver disease
MAFLD	Metabolic-associated fatty liver disease
BMI	Body mass index
PSM	Propensity score matching
HR	Hazard ratio
CI	Confidence interval

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12985-025-02771-1.

Supplementary Material 1.

Acknowledgements
Not applicable.

Ethics statement
This study has been granted approval from the Institutional Review Board from The First Affiliated Hospital of Zhengzhou University (2023-KY-0865-001). The trial has been registered with ClinicalTrials.gov (NCT06349655).

Authors' contributions
G.S. and F. G. contributed equally to this work. H. L. and Z. R. conceived and designed the study; Z. R., L. W., G. L., G. L., G. Q., S. Z., H. L., S. L. and D. Z. managed the patients; G. S., F. G., M. Y., L. W., N. H. and G. Q. collected the data; M. Y. analyzed the data; G. S. and F. G. wrote the manuscript. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study has been granted approval from the Institutional Review Board from The First Affiliated Hospital of Zhengzhou University (2023-KY-0865-001). The retrospective cohort study employing anonymized data did not require individual informed consent.

Consent for publication
The retrospective cohort study employing anonymized data did not require individual informed consent.

Competing interests
The authors declare no competing interests.

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