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Effectiveness and safety of azvudine versus nirmatrelvir/ritonavir in hospitalized patients with COVID-19

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Abstract

Purpose To compare the effectiveness and safety of two antiviral drugs, azvudine and nirmatrelvir/ritonavir, in treating hospitalized patients with COVID-19.

Methods We conducted a retrospective analysis of patients who were admitted to the First Affiliated Hospital of Soochow University and diagnosed with SARS-CoV-2 infection between December 2022 and February 2023. These patients were treated with either azvudine or nirmatrelvir/ritonavir.

Results The study initially included a total of 1097 patients. After applying a 1:3 propensity score matching, we ultimately included 728 patients, comprising 521 recipients of azvudine and 207 recipients of nirmatrelvir/ritonavir. Among them, 463 patients (88.9%) in the azvudine group and 182 patients (87.9%) in the nirmatrelvir/ritonavir group achieved recovery and discharge, with no significant difference between the two groups ($P=0.816$). The median time of improvement was 5.5 days (3.3, 9.0) in the nirmatrelvir/ritonavir group and 5.0 days (4.0, 8.0) in the azvudine group, with no significant difference observed between the two groups ($P=0.732$). Furthermore, no significant differences were noted in terms of the time to fever resolution in patients with fever ($P=0.547$), the rates of usage of high-flow nasal cannula ($P=0.054$), non-invasive mechanical ventilation ($P=0.531$), and invasive mechanical ventilation ($P=0.667$), the duration of invasive mechanical ventilation usage ($P=0.732$), the rate of disease progression ($P=0.602$), and hospital length of stay ($P=0.884$). Regarding safety outcomes, there was a notable increase in the occurrence of myocardial injury in the nirmatrelvir/ritonavir group (13.5%) compared to the azvudine group (7.3%) ($P=0.012$). The two groups did not exhibit differences in the incidence of other adverse events.

Conclusion In hospitalized patients with COVID-19, the effectiveness of azvudine and nirmatrelvir/ritonavir was found to be comparable in various aspects, including the improved discharge rate, the improvement time, time to fever resolution, usage rates of high-flow nasal cannula, non-invasive mechanical ventilation, and invasive mechanical ventilation, rate of disease progression, time to discharge, and hospital length of stay. The occurrence of myocardial injury was higher in nirmatrelvir/ritonavir group compared to azvudine group, while no significant differences were observed in other adverse reactions.

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Keywords COVID-19, Azvudine, Nirmatrelvir/Ritonavir, Effectiveness, Safety

Effectiveness and safety of azvudine versus nirmatrelvir/ritonavir in hospitalized patients with COVID-19: a real-world retrospective cohort study.

Introduction

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has posed significant challenges to global healthcare systems since its outbreak in late 2019. Although Omicron strain has reduced pathogenicity, it features a shorter incubation period, higher transmissibility, and enhanced immune escape capabilities [1]. Effective antiviral treatments remain crucial to accelerating symptom resolution, reducing mortality, and alleviating healthcare burdens [2].

Currently, antiviral treatments for COVID-19 are mainly divided into four categories: small-molecule drugs, monoclonal antibodies, immunomodulators, and neutralizing antibodies [3–5]. Small-molecule drugs are most widely used. Their effectiveness is typically assessed through parameters such as viral load reduction, nucleic acid conversion time, hospital length of stay, disease progression, and mortality. Common adverse effects include gastrointestinal symptoms, neurological issues, and hepatic or renal dysfunction [6–12].

Azvudine and nirmatrelvir/ritonavir (trade name "Paxlovid") are two newly approved small-molecule drugs for COVID-19. Deng et al. [13] and Dian et al. [14] compared the all-cause mortality and composite risk of disease progression, demonstrating that azvudine exhibited superior effectiveness compared to nirmatrelvir/ritonavir. However, the safety of the two drugs was not evaluated in these studies. Furthermore, Wang et al. [15], Han et al. [16], and Wei et al. [17] also compared the two drugs in terms of all-cause mortality and composite outcomes of disease progression, concluding that the two antiviral drugs had similar clinical efficacy. Notably, Wei et al.'s study [17] revealed no significant differences between the two groups regarding adverse events such as gastrointestinal reactions, neurological symptoms, and impacts on liver and renal function. However, they did not investigate other potential safety concerns. Han et al. [16] used clinical improvement rates and median time to improvement as secondary endpoints of their study, while Su et al. [18] focused on the time to sustained clinical recovery and mortality rates in hospitalized patients as primary efficacy indicators to compare the efficacy and safety of the two drugs. However, these two studies only reported the effects on liver and renal function. Comprehensive comparative studies on the efficacy and adverse events of these two drugs are still lacking, especially regarding broader safety evaluations, which remain limited. Additionally, azvudine and nirmatrelvir/ritonavir are currently the most widely used oral antiviral drugs for COVID-19 in China. Therefore, this study focuses on comparing the efficacy and safety differences between azvudine and nirmatrelvir/ritonavir.

Our study aims to compare the effectiveness and safety of azvudine and nirmatrelvir/ritonavir. After baseline matching using propensity score matching (PSM), we compare the discharge rates, improvement time as well as safety outcomes such as liver and renal function, blood coagulation, and impact on the digestive system. The findings aim to further summarize experiences with antiviral treatment and provide clinical guidance for selecting more appropriate medicine.

Materials and methods

Study design

The retrospective analysis was conducted to evaluate the clinical application of two antiviral drugs. All data were collected from hospitalized patients diagnosed with COVID-19 who were treated with azvudine or nirmatrelvir/ritonavir at the First Affiliated Hospital of Soochow University between December 2022 and February 2023. Detailed information was obtained from electronic medical records, including the number of days required for the improvement of main symptoms, hospital length of stay, medication usage, type of respiratory support and their duration, and the proportion of disease progression. Additionally, laboratory test results obtained before and after treatment, along with other comorbid symptoms, were also collected. PSM was used to balance the baseline characteristics between the two groups, minimizing the impact of confounding factors, in order to compare the differences in efficacy and safety between the two drugs.

Inclusion and exclusion criteria

Inclusion criteria: Diagnosed with COVID-19 before or during hospitalization according to the diagnostic criteria of the "Diagnosis and treatment protocol for COVID-19 in China (trial version 10)" [19]; received only azvudine or nirmatrelvir/ritonavir monotherapy (without combination with other small-molecule antiviral drugs) during hospitalization; with complete medical records available for analysis.

Exclusion criteria: Age ≤ 18 years old; received azvudine or nirmatrelvir/ritonavir before admission; received both azvudine and nirmatrelvir/ritonavir sequentially or simultaneously; treatment duration<3 days; with severely incomplete medical records that could not be analyzed

(severely missing data is defined as missing more than 30% of the data in the patient's records).

Data collection

By reviewing the electronic inpatient medical records and laboratory systems, we collected clinical data of the enrolled subjects including gender, age, body mass index (BMI), comorbidities, symptoms at onset, classification of disease severity, types of antiviral drugs used and other concomitant treatments, type and duration of respiratory support, improvement time, adverse reactions, pre-and post-treatment laboratory test results, hospital length of stay, and final outcome (recovery, discharge against medical advice, or death). The classification of disease severity was based on the criteria outlined in the " Diagnosis and treatment protocol for COVID-19 in China (trial version 10)" [19], which categorized cases as mild, moderate, severe, or critical. The improvement time was defined as the days from medication initiation to either symptom resolution or hospital discharge, based on medical records.

Endpoints

The primary endpoints were the patients' final discharge rate with improvement and the improvement time. The improvement time was defined as follows: Objective indicators: Body temperature returning to normal and remaining stable for at least 24 h; respiratory rate ≤ 24/min; oxygen saturation ≥ 94% (without supplemental oxygen); and a reduction of ≥ 50% in inflammatory markers (e.g., C-reactive protein) from baseline. Subjective indicators: A comprehensive assessment by the attending physician, based on the "Diagnosis and treatment protocol for COVID-19 in China (trial version 10)," [19] confirming that the main symptoms, such as cough and sputum, chest tightness, nasal congestion, and muscle pain, had improved by ≥ 50%. The records were based on daily progress notes and laboratory results documented in the electronic medical record system.

Secondary endpoints included the days to fever resolution, usage rates of high-flow nasal cannula (HFNC), non-invasive mechanical ventilation (NIMV), and invasive mechanical ventilation (IMV), IMV duration, disease progression rate, and hospital length of stay.

Safety was assessed by monitoring adverse events occurring within 28 days of antiviral treatment, including diarrhea, nausea, vomiting, constipation, rash, oral ulcers, deep vein thrombosis, gastrointestinal bleeding, acute kidney injury, myocardial injury, abnormal liver function, and elevated D-dimer levels. Among them, acute kidney injury (AKI) was defined according to the criteria set forth in reference: an increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 μmol/L) within 48 h, or an increase to ≥ 1.5 times the baseline level within 7 days, or a urine output of < 0.5 mL/(kg·h) for more than 6 h [20]. Myocardial injury was defined as a rise in cardiac troponin levels following treatment, exceeding the upper limit of the normal range in comparison to the baseline [21]. Abnormal liver function was defined as an increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels above the upper limit of normal following treatment [22].

Statistical analysis

All statistical analyses were done with R version 4.2.3. Multiple imputation was used for data with missing values less than 30%. The missing data were imputed to create five complete datasets, which were then combined for analysis. Categorical variables were analyzed using the chi-square test or Fisher's exact test. For continuous variables, the Shapiro-Wilk normality test was employed for evaluation, and simultaneously, histograms and Q-Q plots were used to further assist in determining the distribution characteristics of the data. Near-normal continuous variables were described as mean ± standard deviation ($\bar{x} \pm s$) and compared using Student's t-test; non-normal continuous variables were described as median with interquartile range (IQR) and analyzed with the Mann-Whitney U-test. Based on previous literature and clinical experience [23], variables that might affect the treatment regimen and outcome were selected for PSM, including demographic characteristics (gender, age, BMI), various comorbid underlying diseases (cardiovascular and cerebrovascular diseases, diabetes mellitus, lung diseases, chronic kidney disease, chronic liver disease, rheumatic diseases, malignant tumors, immunosuppressive state), disease severity (mild/moderate/severe/critical), the time from the onset of symptoms to medication administration, and concomitant treatments (prone position [24], antibiotics, anticoagulant therapy, glucocorticoids). The 1:3 nearest neighbor matching method was adopted, with a caliper value of 0.03. The love plot showing the balance before and after matching (Fig. 1). Meanwhile, the Kaplan-Meier curve and the Cox proportional hazards regression model were used to analyze the differences between the two groups. A two-tailed alpha of 0.05 indicates a statistically significant level.

Results

Patient characteristics

In the study, we finally identified 1097 hospitalized adults diagnosed with COVID-19 who met the inclusion and exclusion criteria. Among these, 855 were assigned to the azvudine group and 242 to the nirmatrelvir/ritonavir group. To balance the baseline characteristics, we employed a 1:3 PSM. The final analysis included 521 recipients of azvudine and 207 recipients of nirmatrelvir/ritonavir (Fig. 2). There were no significant differences

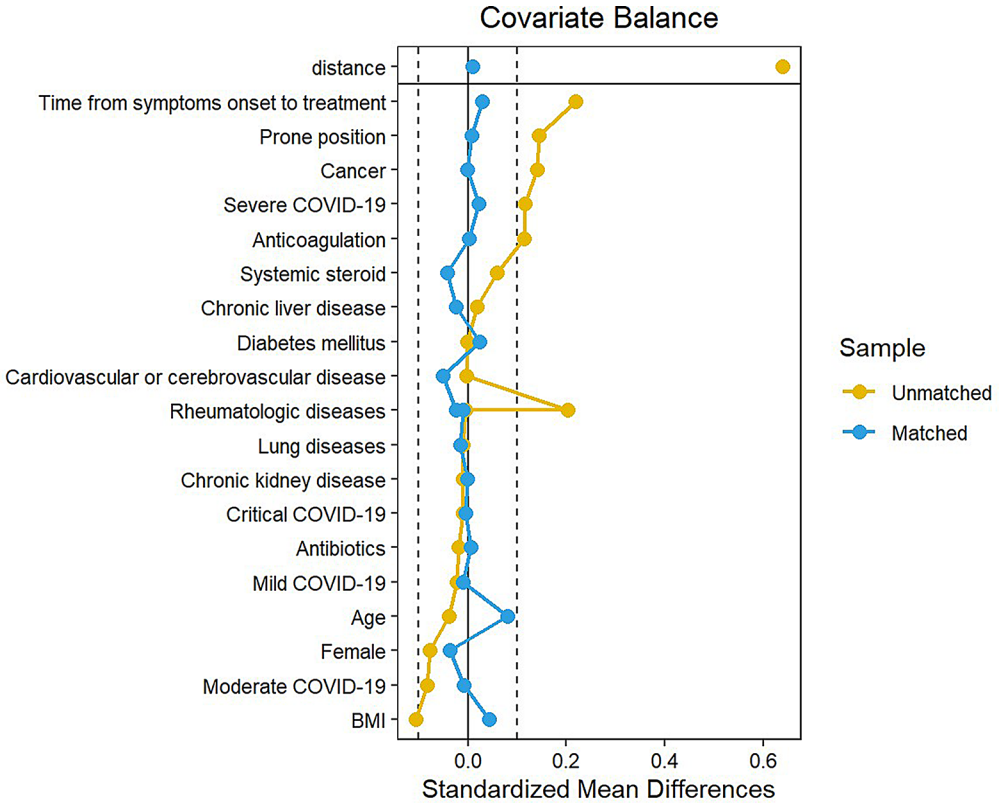

Fig. 1 The love plot illustrated the balance of covariates before and after 1:3 PSM between nirmatrelvir/ritonavir and azvudine

in baseline covariates between the two groups after propensity score matching, indicating covariate imbalance. Table 1 showed the baseline characteristics of patients before and after matching.

Flowchart of patient selection.

Effectiveness

Among 728 patients, 645 showed clinical improvement after antiviral treatment, with an overall improvement rate of 88.6%. The initial COVID-19-related symptoms in both groups primarily included cough and sputum, fever, and chest tightness. Moreover, some patients also experienced fatigue, loss of smell or taste, nasal congestion, runny nose, sore throat, muscle ache, and diarrhea. Among these symptoms, loss of smell or taste showed a statistically significant difference between the two groups ($P<0.001$) (Table 2). The median time from the onset of symptoms to hospital admission for antiviral treatment was eight days. Regarding the primary endpoints, 463 patients (88.9%) in the azvudine group and 182 patients (87.9%) in the nirmatrelvir/ritonavir group achieved recovery and discharge, with no significant difference between the two groups ($P=0.816$). Kaplan-Meier curves for discharge time as the primary outcome showed no significant difference in the cumulative discharge rate between the two groups. Cox regression analysis revealed a hazard ratio (HR) of 1.04 (95% CI: 0.88–1.24, $P=0.632$), indicating similar recovery and discharge rates between the two groups (Fig. 3). There was no significant difference between the two groups concerning the improvement time ($P=0.732$). The median improvement time was 5.0 (4.0, 8.0) days in the azvudine group and 5.5 (3.3, 9.0) days in the nirmatrelvir/ritonavir group (Table 3).

In addition, for the secondary endpoints, the rates of HFNC were 8.1% and 13.0% ($P=0.054$), the rates of NIMV were 4.8% and 6.3% ($P=0.531$), and the rates of IMV were 7.9% and 9.2% ($P=0.667$) in the azvudine and nirmatrelvir/ritonavir groups, respectively. The disease progression rates were 13.6% and 15.5% ($P=0.602$). The hospital length of stay was 13.0 days compared to the azvudine group and 12.0 days in the nirmatrelvir/ritonavir group ($P=0.884$), and the days to fever resolution for patients with fever at admission was 3.0 days in both groups ($P=0.547$). Among the 41 patients in the azvudine group who required IMV, the median duration of IMV was 17.0 days, compared to 12.0 days for the 19 patients in the nirmatrelvir/ritonavir group ($P=0.732$). None of these differences were statistically significant. After applying false discovery rate (FDR) correction to the secondary outcome measures, no significant differences were observed between the two groups for any of the outcomes, which was consistent with the original conclusion (Table 4).

Kaplan-Meier curves.

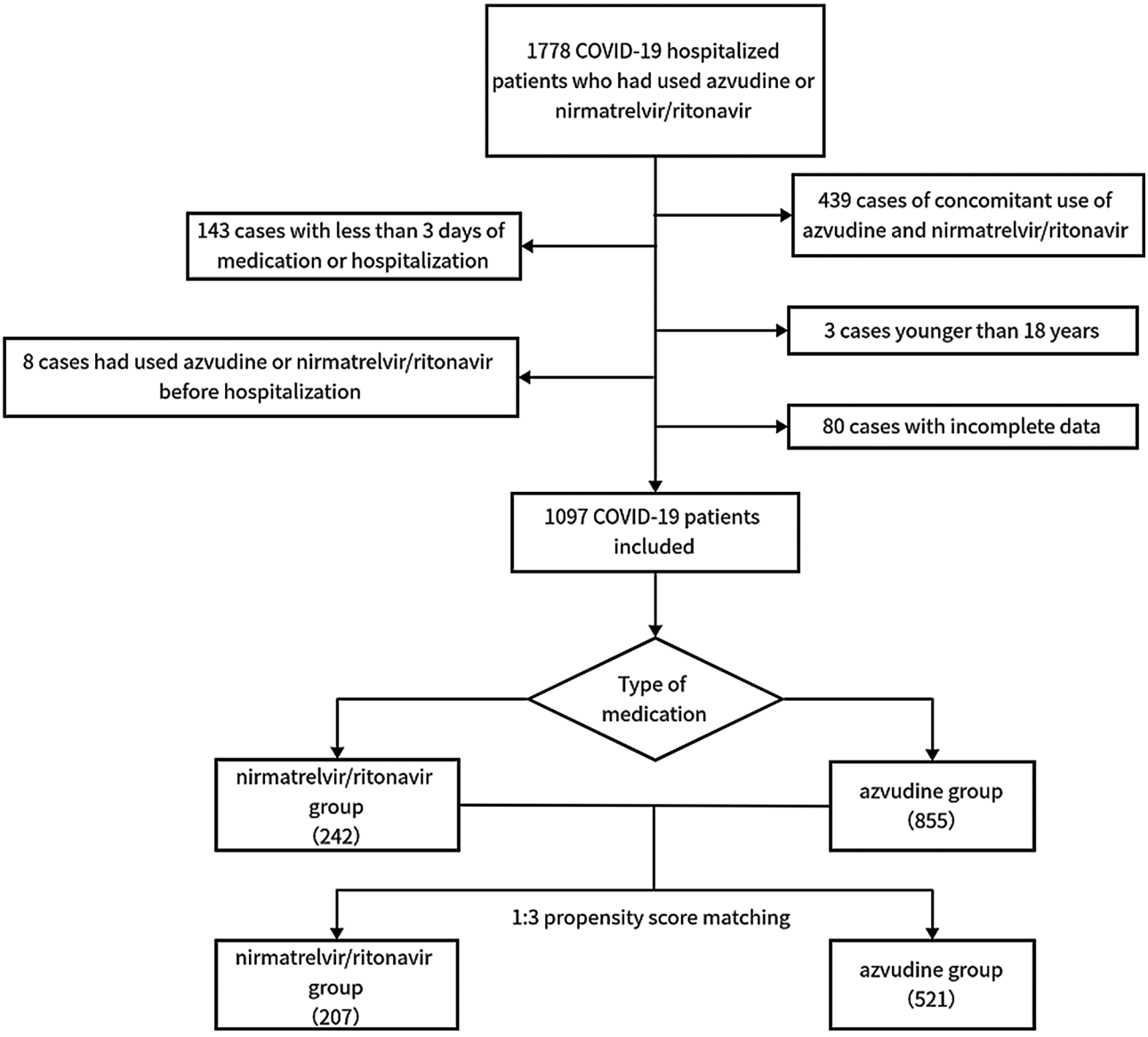

Fig. 2 After a 1:3 propensity score matching by baseline covariates with a caliper of 0.03, the analysis included 521 recipients of azvudine and 207 recipients of nirmatrelvir/ritonavir

Adverse reactions

In terms of safety outcomes, the most frequently observed adverse events in both groups were liver function abnormalities and elevated D-dimer levels. Additionally, a small number of patients also experienced myocardial injury, acute kidney injury, gastrointestinal bleeding, diarrhea, nausea and vomiting, constipation, erythra, oral ulcers, and deep vein thrombosis. Although, there was no significant difference in the overall incidence of adverse reactions between the two groups ($P = 0.062$), the total incidence of adverse events was slightly higher in the nirmatrelvir/ritonavir group (43.5%) compared to the azvudine group (35.7%). Regarding the incidence of individual adverse events, myocardial injury was reported in 7.3% of the azvudine group and 13.5% of the nirmatrelvir/ritonavir group, with a statistically significant difference between the two groups ($P = 0.012$). No statistically significant differences were observed between the two groups for other adverse reactions, including liver function abnormalities ($P = 0.185$), elevated D-dimer levels ($P = 0.991$), acute kidney injury ($P = 1.000$), gastrointestinal bleeding ($P = 0.683$), diarrhea ($P = 0.556$), nausea and vomiting ($P = 1.000$), constipation ($P = 1.000$), erythra ($P = 1.000$), oral ulcers ($P = 1.000$), and deep vein thrombosis ($P = 0.11$) (Table 5). A multivariate regression analysis was conducted to explore the influence of the following factors on the adverse reaction of myocardial injury, including age, gender, underlying

Table 1 Baseline characteristics of participants before and after PSM

Characteristics	Unmatched				Matched			
	Azvudine($n=855$)	Paxlovid($n=242$)	*P* value	SMD	Azvudine($n=521$)	Paxlovid($n=207$)	*P* value	SMD
Age(years), mean(SD)	68.68 ± 15.29	68.04 ± 16.23	0.585	0.040	69.27 ± 15.03	69.48 ± 16.01	0.870	0.014
Gender, n(%)			0.036	0.160			0.106	0.141
Male	488(57.1)	157(64.9)			312(59.9)	138(66.7)		
Female	367(42.9)	85(35.1)			209(40.1)	69(33.3)		
BMI(kg/m^2), mean(SD)	23.66 ± 3.55	23.29 ± 3.53	0.148	0.105	23.36 ± 3.64	23.56 ± 3.49	0.496	0.056
Comorbidities, n(%)								
Cardiovascular or cerebrovascular disease	511(59.8)	144(59.5)	1.000	0.005	312(59.9)	122(58.9)	0.880	0.019
Diabetes mellitus	220(25.7)	62(25.6)	1.000	0.003	126(24.2)	51(24.6)	0.974	0.011
Lung diseases	118(13.8)	31(12.8)	0.771	0.029	70(13.4)	29(14.0)	0.933	0.017
Chronic kidney disease	48(5.6)	11(4.5)	0.625	0.049	29(5.6)	8(3.9)	0.450	0.080
Chronic liver disease	26(3.0)	12(5.0)	0.215	0.098	24(4.6)	10(4.8)	1.000	0.011
Rheumatologic diseases	57(6.7)	15(6.2)	0.910	0.019	40(7.7)	15(7.2)	0.966	0.016
Malignant tumor	131(15.3)	71(29.3)	< 0.001	0.341	109(20.9)	53(25.6)	0.204	0.111
Long-term use of immunosuppressive drugs	126(14.7)	85(35.1)	< 0.001	0.485	105(20.2)	48(23.2)	0.420	0.074
Disease severity, n (%)			0.005	0.270			0.572	0.123
Mild	30(3.5)	3(1.2)			16(3.1)	3(1.4)		
Moderate	498(58.2)	121(50.0)			280(53.7)	109(52.7)		
Severe	300(35.1)	113(46.7)			210(40.3)	90(43.5)		
Critical	27(3.2)	5(2.1)			15(2.9)	5(2.4)		
Time from symptoms onset to treatment(d), median[IQR]	8.0[5.0,11.0]	8.0[5.0,15.0]	0.015	0.244	8.0[5.0,12.0]	8.0[4.0,14.0]	0.843	0.031
Co-medications, n(%)								
Prone position	272(31.8)	112(46.3)	< 0.001	0.300	201(38.6)	86(41.5)	0.513	0.061
Antibiotics	807(94.4)	224(92.6)	0.368	0.074	479(91.9)	194(93.7)	0.506	0.069
Anticoagulation	513(60.0)	173(71.5)	0.001	0.244	348(66.8)	149(72.0)	0.205	0.113
Systemic steroid	670(78.4)	204(84.3)	0.053	0.153	413(79.3)	171(82.6)	0.359	0.085

Table 2 The main symptoms of patients in two groups

Symptoms	Number of patients(*n*, %)	Azvudine(*n*, %)	Paxlovid(*n*, %)	*P* value
Cough and sputum	584(80.2)	420 (80.6)	164 (79.2)	0.748
Fever	521(71.6)	378 (72.6)	143 (69.1)	0.398
Chest tightness	401(55.1)	288 (55.3)	113 (54.6)	0.931
Fatigue	154(21.2)	102 (19.6)	52 (25.1)	0.121
Loss of smell or taste	101(13.9)	53 (10.2)	48 (23.2)	< 0.001
Muscle aches and pains	55(7.6)	41 (7.9)	14 (6.8)	0.723
Sore throat	53(7.3)	36 (6.9)	17 (8.2)	0.651
Diarrhea	23(3.2)	14 (2.7)	9 (4.3)	0.357
Nasal congestion	12(1.6)	10 (1.9)	2 (1.0)	0.556
Runny nose	12(1.6)	10 (1.9)	2 (1.0)	0.556

diseases (cardiovascular and cerebrovascular diseases, diabetes, chronic kidney disease, chronic liver disease, malignant tumors, rheumatic diseases, long - term use of immunosuppressive drugs), and the type of antiviral drugs. Among these factors, age (OR = 1.033, 95% CI [1.009, 1.058], $P = 0.006$), gender (OR = 0.378, 95% CI [0.190, 0.757], $P = 0.004$), cardiovascular and cerebrovascular diseases (OR = 1.986, 95% CI [1.038, 3.798], $P = 0.036$), chronic kidney disease (OR = 2.937, 95% CI [1.139, 7.563], $P = 0.023$), and the type of antiviral drugs received (OR = 1.957, 95% CI [1.131, 3.398], $P = 0.015$) were identified as influencing factors for myocardial injury (Fig. 4). After grouping patients with underlying conditions who experienced adverse reactions and those who did not, the results showed that in the azvudine group, the proportion of patients with chronic liver disease and rheumatic autoimmune diseases experiencing adverse reactions was significantly lower. In the nirmatrelvir/ritonavir group, the proportion of patients with malignancies experiencing adverse reactions was significantly lower, while the proportion of patients with cardiovascular or cerebrovascular diseases experiencing adverse reactions was significantly higher (Table 6a and 6b).

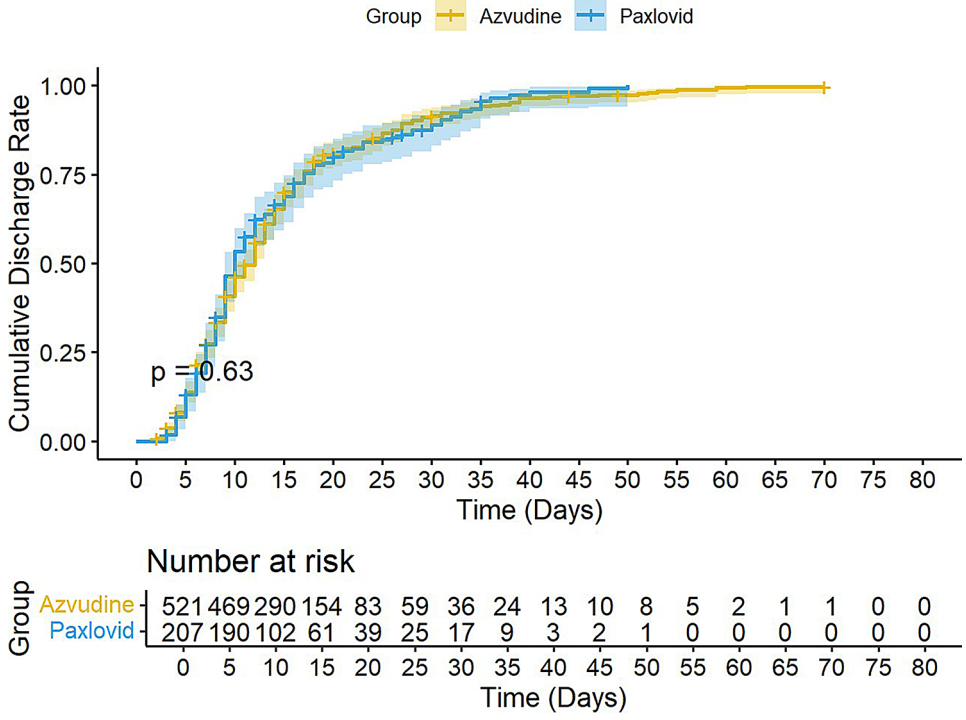

Fig. 3 Kaplan-Meier curves for discharge time showed no significant difference in the cumulative discharge rate between the two groups

Table 3 Primary endpoints of the efficacy of two groups

	Azvudine($n=521$)	Paxlovid($n=207$)	*P* value
Discharge rate with improvement(n, %)	463(88.9)	182(87.9)	0.816
Improvement time [IQR]	5.0 [4.0, 8.0]	5.5 [3.3, 9.0]	0.732

Discussion

Since the spread of COVID-19 in late 2019, it has posed a significant threat to global health and life safety. Early and appropriate application of antiviral agents have been shown to effectively shorten the duration required for viral clearance, mitigate damage induced by high viral loads, improve patient outcomes, and significantly lower the rates of severe disease and mortality [25].

The mechanism of small-molecule antiviral drugs primarily involves the inhibition of viral replication within cells [26]. These drugs typically exhibit conservative targets and high stability, offering cost-effective solutions with the advantage of oral administration, which greatly enhance convenience. Azvudine is an orally administered small-molecule antiviral drug developed in China, which functions as a novel dual-targeted inhibitor of nucleoside auxiliary proteins and reverse transcriptase. Its metabolites specifically target the RNA-dependent RNA polymerase (RdRp) of SARS-CoV-2, inhibiting viral RNA synthesis and effectively preventing viral replication [27, 28]. Nirmatrelvir is an inhibitor of the main protease Mpro (also known as 3CLpro) of SARS-CoV-2, disrupting the processing of polyprotein precursors, and thereby inhibiting viral replication. Ritonavir is an HIV-1

Table 4 Secondary endpoints of the efficacy of two groups

	Azvudine($n=521$)	Paxlovid($n=207$)	*P* value	FDR *P*
HFNC (n, %)	42(8.1)	27(13.0)	0.054	0.483
NIMV (n, %)	25(4.8)	13(6.3)	0.531	0.884
IMV (n, %)	41(7.9)	19(9.2)	0.667	0.884
Disease progression (n, %)	71(13.6)	32(15.5)	0.602	0.884
Hospital length of stay (d), median[IQR]	13.0[8.0,19.0]	12.0[9.0,19.5]	0.884	0.884
Time to fever resolution (d), median[IQR]	127	59		
	3.0[2.0,5.0]	3.0[1.0,6.0]	0.547	0.884
Duration of IMV (d), median[IQR]	41	19		
	17.0[8.0,24.0]	12.0[8.5,21.0]	0.732	0.884

HFNC, high-flow nasal cannula; NIMV, non-invasive mechanical ventilation; IMV, invasive mechanical ventilation; IQR, interquartile ranges; FDR, false discovery rate

Table 5 Comparison of the incidence of adverse reactions after medication between two groups

	Azvudine($n=521$)	Paxlovid($n=207$)	*P* value
Shock	51 (9.8)	24 (11.6)	0.557
Acute kidney injury	15 (2.9)	6 (2.9)	1.000
Deep vein thrombosis	5 (1.0)	6 (2.9)	0.110
Gastrointestinal bleeding	13 (2.5)	7 (3.4)	0.683
Diarrhea	13 (2.5)	3 (1.4)	0.556
Nausea and vomiting	1 (0.2)	0 (0.0)	1.000
Oral ulcers	1 (0.2)	0 (0.0)	1.000
Constipation	1 (0.2)	0 (0.0)	1.000
Erythra	1 (0.2)	0 (0.0)	1.000
Myocardial injury	38 (7.3)	28 (13.5)	0.012
Liver function abnormalities	78 (15.0)	40 (19.3)	0.185
Elevated D-dimer levels	61 (11.7)	25 (12.1)	0.991
Total adverse reactions	186 (35.7)	90 (43.5)	0.062

protease inhibitor and CYP3A inhibitor, and it increases the plasma concentration of nirmatrelvir by preventing CYP3A-mediated metabolism. The combination of these two drugs effectively inhibits viral replication [7, 29].

Previous studies have confirmed the efficacy of either azvudine or nirmatrelvir/ritonavir in reducing SARS-CoV-2 viral load, improving patient outcomes, and causing only mild adverse effects [9–12, 30, 31]. Current research on the efficacy and safety of these two drugs primarily focused on endpoints such as time to viral clearance, hospital length of stay, ICU admission rates, mortality rates, composite outcomes of disease progression, and impacts on liver and kidney function. In head-to-head comparisons of the efficacy and safety of these two antiviral drugs, studies by Deng et al. [13] and Dian et al. [14] suggested that azvudine recipients had lower crude incidence rates of composite disease progression outcome, while all-cause death, ICU admission rates, and IMV rates were similar between the two groups. Conversely, studies by Wang et al. [15] and Han et al. [16] indicated no significant differences in efficacy between azvudine and nirmatrelvir/ritonavir in terms of all-cause death and composite disease progression outcome. Our study was conducted during an outbreak predominantly

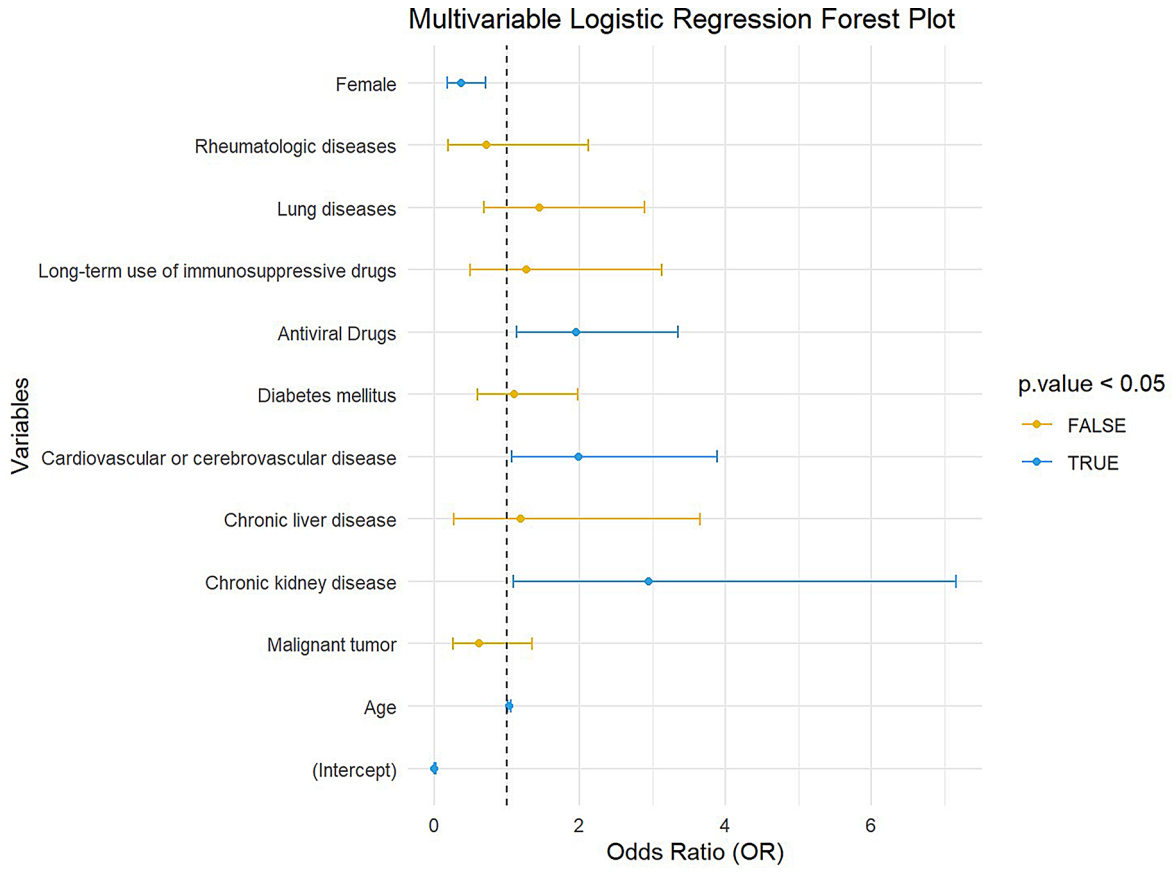

Fig. 4 Impact of covariates on myocardial injury

Table 6 (**a**). Distribution of patients with and without adverse reactions in the azvudine group. (**b**). Distribution of patients with and without adverse reactions in the nirmatrelvir/ritonavir group

Underlying comorbidities (*n*,%)	Adverse reaction group (*n* = 186)	No adverse reaction group (*n* = 335)	*P* value
Cardiovascular or cerebrovascular disease	119 (64.0)	193 (57.6)	0.184
Diabetes mellitus	42 (22.6)	84 (25.1)	0.596
Lung diseases	25 (13.4)	45 (13.4)	1.000
Chronic kidney disease	11 (5.9)	18 (5.4)	0.953
Chronic liver disease	3 (1.6)	21 (6.3)	0.027
Rheumatologic diseases	7 (3.8)	33 (9.9)	0.020
Malignant tumor	36 (19.4)	69 (20.6)	0.822
Long-term use of immunosuppressive drugs	35 (18.8)	74 (22.1)	0.443
Underlying comorbidities (n,%)	**Adverse reaction group (*n* = 90)**	**No adverse reaction group (*n* = 117)**	***P* value**
Cardiovascular or cerebrovascular disease	66 (73.3)	56 (47.9)	< 0.001
Diabetes mellitus	23 (25.6)	28 (23.9)	0.916
Lung diseases	16 (17.8)	13 (11.1)	0.243
Chronic kidney disease	3 (3.3)	5 (4.3)	1.000
Chronic liver disease	5 (5.6)	5 (4.3)	0.921
Rheumatologic diseases	9 (10.0)	6 (5.1)	0.285
Malignant tumor	12 (13.3)	36 (30.8)	0.005
Long-term use of immunosuppressive drugs	17 (18.9)	36 (30.8)	0.075

driven by the Omicron variant. Based on the discharge criteria outlined in the " Diagnosis and treatment protocol for COVID-19 in China (trial version 10)" [19], we employed the discharge rate (based on clinical improvement) and the improvement time as the primary endpoints to compare the efficacy between azvudine and nirmatrelvir/ritonavir, in addition to the endpoints observed in the studies mentioned above. We also assessed several secondary efficacy endpoints for a more comprehensive comparison of the efficacy of the two drugs, including the time to fever resolution, the usage rates of HFNC, NIMV and IMV, the duration of IMV, the rate of disease progression, and the hospital length of stay. Similar to the studies of Su et al. [18], our results showed that azvudine and nirmatrelvir/ritonavir had comparable efficacy in terms of the improvement time. However, it was noteworthy that their study had a smaller sample size and concentrated solely on liver and kidney function as adverse events. In contrast, our research provides a more comprehensive comparison supported by a larger sample size. In conclusion, our research demonstrates that the efficacy of azvudine is comparable to that of nirmatrelvir/ritonavir, aligning with the findings of a recent systematic review and meta-analysis [32].

Previous studies have demonstrated that the common adverse reactions associated with azvudine included abnormalities in liver function, dizziness, with occasional occurrences of rash, elevated blood glucose, and decreased lymphocyte counts [33]. With regard to nirmatrelvir/ritonavir, the most frequently reported adverse reactions were taste disturbances and diarrhea, while other common reactions included dyspepsia, dry mouth, bitter taste, gastroesophageal reflux, myalgia, dizziness, and elevated liver enzymes [34, 35]. The majority of these adverse reactions for both drugs were mild and generally did not necessitate intervention or only required symptomatic treatment. This study collected data on adverse reactions occurring within 28 days after medication based on historical medical records and laboratory results. Diarrhea emerged as the predominant symptom observed in both groups, while symptoms such as dry mouth and dizziness were not reported, likely due to their subjective nature, mild severity, and incomplete documentation in medical records. As for objective indicators, both groups primarily exhibited abnormal liver function, elevated D-dimer levels, and increased troponin levels. However, no cases necessitated discontinuation of medication due to excessive abnormalities in these indicators. Among the adverse events, only the incidence of myocardial injury showed a significant difference between the two groups ($P = 0.012$), indicating that the safety profiles of the two drugs were comparable in most instances. A few reports have documented cases of sinus tachycardia induced by azvudine [36], as well as myocardial injury, bradycardia, syncope, and sinus arrest associated with nirmatrelvir/ritonavir [37–39]. Nevertheless, no existing literature currently compares the myocardial injury between these two antiviral drugs or explores the underlying mechanisms. Studies have suggested that ritonavir inhibits CYP450 enzymes, leading to increased bioavailability of drugs that prolong the QT interval [40]. Consequently, the notable variation in myocardial injury events may be related to the pharmacokinetic and pharmacodynamic properties of nirmatrelvir/ritonavir. Furthermore, adverse reaction rates were significantly lower among azvudine-treated patients with chronic liver disease or rheumatic autoimmune disorders, and among nirmatrelvir/ritonavir-treated patients with malignancies. This result may be related to stricter medication monitoring or differences in drug metabolism in these patient categories. However, due to the small number of patients with these comorbidities experiencing adverse reactions, the robustness of the results may require further validation. Additionally, in the nirmatrelvir/ritonavir group, patients with cardiovascular or cerebrovascular diseases were at a heightened risk for adverse reactions following the administration of antiviral medications. This increased risk may be linked to underlying

pathological conditions, drug interactions, and the direct effects of SARS-CoV-2 on the cardiovascular system [41–44]. These findings underscore the necessity for clinicians to exercise heightened vigilance when prescribing antiviral drugs to patients with cardiovascular comorbidities.

Limitations

First, the cohort consisted of hospitalized patients during the period of the COVID-19 outbreak (December 2022 to March 2023). In accordance with the " Diagnosis and treatment protocol for COVID-19 in China (trial version 10)" [19] in China, the criterion of nucleic acid negativity was no longer utilized for discharge. As a result, we lack data on the time to nucleic acid negativity following antiviral treatment, and we also lack data on cases of secondary infections. Second, as a retrospective study, all data were collected from electronic medical records, which might have introduced selection and information biases. Although baseline differences were minimized by balancing the cohorts through propensity score matching, residual confounding factors that could influence the results cannot be excluded. Third, the number of cases in the nirmatrelvir/ritonavir group was relatively smaller compared to the azvudine group, which might have affected the statistical power of the study. Finally, as a single-center study, the external validity of the results requires further verification through multi-center studies.

Conclusions

In conclusion, this study demonstrated that azvudine and nirmatrelvir/ritonavir exhibited comparable efficacy in discharge rate and the improvement time. Both groups also showed similar outcomes in terms of time to fever resolution, usage rates of HFNC, NIMV and IMV, duration of IMV, rate of disease progression, and hospital length of stay. The overall safety of both antiviral drugs was generally favorable, with adverse effects primarily related to liver function abnormalities and elevated D-dimer levels. Notably a higher incidence of myocardial injury was observed in the nirmatrelvir/ritonavir group compared to the azvudine group. In clinical practice, physicians should select the appropriate antiviral treatment based on the specific condition of each patient to optimize therapeutic outcomes and minimize adverse reactions.

Abbreviations

AKI	Acute kidney injury
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
COVID-19	The coronavirus disease 2019
FDR	False discovery rate
HFNC	High-flow nasal cannula
IMV	Invasive mechanical ventilation
NIMV	Non-invasive mechanical ventilation
PSM	Propensity score matching
RdRp	RNA-dependent RNA polymerase
SARS-CoV-2	The severe acute respiratory syndrome coronavirus 2

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Author contributions

J.M and L.D contributed to the conception of the study; R.L, Y.Y and J.F.Z made the data collection; J.Y analyzed the clinical data and wrote this article; W.L helped perform the analysis with constructive discussions. All authors read and approved the final manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This was a retrospective analysis study. The Ethics Committee of The First Affiliated Hospital of Soochow University approved the study. The requirement for informed consent was waived by the Ethics Committee of The First Affiliated Hospital of Soochow University because of the retrospective nature of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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