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Research Article
Effects of Azvudine on the Low-Risk Patients Infected with COVID-19 Omicron Variants: A Retrospective Case-Control Study

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Abstract

Background and Objective: Azvudine had been used in China to treat COVID-19 patients since 2022. However, there is few reports to analyze its efficacy. The aim of this study is to evaluate the efficacy and safety of Azvudine in treatment of the patients infected with COVID-19 Omicron variants. **Materials and Methods:** This study included the discharged patients after COVID-19 infection from October 17 to November 17, 2022, in Zhengzhou Central Hospital. The patients were divided into the symptomatic treatment group (ST) and the symptomatic treatment and oral Azvudine (STA) groups to evaluate the efficacy and safety of Azvudine. **Results:** A total 481 patients were included. The recovery time of patients did not correlate with oral Azvudine (beta = 1.920, p = 0.056) in a low-fit multiple linear regression with the data-available patients ($R^2 = 0.039$, F = 3.117, p = 0.027). No significant differences were found in the recovery time (12.12±2.83 vs 12.21±2.84, n = 33, p = 0.897) and symptomatic severity between the two groups after 1:1 matched. However, STA groups had a lower total viral load than the ST group after the final matching (28.03±4.72 vs 25.53±5.32, n = 33, p = 0.048). The 17 of 206 patients reported Azvudine-related adverse effects and stopped Azvudine. **Conclusion:** Azvudine had little effect on the low-risk patients with Omicron infection to improve recovery time and symptoms. However, it could slightly decrease total viral load during the first 5 days after administration while being relatively safe for oral use overall.

Key words: Azvudine, COVID-19, efficacy, symptomatic treatment, infection

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) has been a global pandemic since its initial identification in 2019[1,2]. On August 9, 2022, the National Health Commission of China conditionally approved Azvudine to treat COVID-19 patients with moderate symptoms[3,4]. The National Health Commission of China recommends oral Azvudine for treatment of COVID-19 infections in the Diagnosis and Treatment Program for Novel Coronavirus Pneumonia (Ninth edition). Originally developed to target reverse transcriptase to treat HIV infection[5]. Azvudine was reported to significantly shorten the mean times of the first nucleic acid negative conversion from 5.60 to 2.60 days for the patients infected by original COVID-19 variants in a pilot study (ChiCTR2000029853) with a very small sample size in the spring of 2020[6]. In December 2021, Zhang *et al.*[7] reported a randomized single-arm clinical trial of Azvudine that indicated it is effective and safe in treating COVID-19 infection. Yu and Chang[3] mentioned a phase III trial in a review on November 8, 2022 which indicated that Azvudine improved clinical symptoms by 40.43%, while placebo only improved them by 10.87%. However, all these trials were carried out on patients infected with alpha, beta, gamma or delta variants; not Omicron which was spreading internationally since its identification on November 9, 2021 in South Africa[8].

The COVID-19 virus has evolved into several dominant variants including Alpha, Beta, Gamma, Delta and currently Omicron BA 5.2 which is the dominant variant in China since November, 2022 and has caused millions of infections across the nation[9,10]. Omicron causes less severe disease than the previous variants of concern[11]. To date there is not enough evidence to support the efficacy of Azvudine in improving Omicron infection; however, it has been widely used to treat Omicron infection after China's zero-COVID policy was terminated on December 7th, 2022. There are few studies evaluating the effects of Azvudine on Omicron infection, thus this study aims to evaluate its efficacy using current available clinical data. We will also consider any potential side effects that may be associated with its use. Ultimately, our goal is to provide a comprehensive evaluation of the efficacy of Azvudine in treating COVID-19 infection.

MATERIALS AND METHODS

Study area: This study was carried out in October 17 to November 17, 2022, in Zhengzhou Central Hospital, Henan Province of China.

Patients: This study investigated the patients who were hospitalized in the quarantine facility of Zhengzhou Central Hospital due to infections of COVID-19 Omicron variants under COVID-zero policy in China.

Ethical consideration: It was approved by the Ethic Committee of Zhengzhou Central Hospital affiliated to Zhengzhou University with reference number 202301. An oral informed consent was obtained from the patients who took Azvudine in this study.

The patients who were discharged from October 17 to December 17, 2022 were collected for this study. The inclusion criteria for this study were that the RT-PCR results of COVID-19 (both ORF1ab and N gene) should be confirmed positive outside hospital and Ct value of COVID-19 RNA tests should be less than 40 (positive) for both ORF1ab and N gene within 2 days after admission. The patients were divided into two groups (Fig. 1): The symptomatic treatment group (ST) and the symptomatic treatment in combination with oral Azvudine group (STA, oral Azvudine tablets 5 mg daily).

Hospitalization procedures: Patients with a positive COVID-19 RNA test in China will be admitted to hospital for quarantine and therapy according to the zero-COVID policy before December 7, 2022. Upon admission, they will undergo RT-PCR for COVID-19 RNA test, whole blood count, blood chemistry test, COVID-19 serology status (lgG and lgM), EKG and Chest CT if necessary. Patients with Omicron infection typically present with fever, sore throat, myalgia, cough, sputum, abdominal distension, stomachache and diarrhea[12-14]. Treatments were based on symptoms and were divided into specific and non-specific treatments. Specific treatments target the symptoms directly such as acetaminophen or ibuprofen for fever while non-specific treatments usually involve traditional Chinese herbs (Table S1 and S2). Patients should only be transferred to ICU if they experience dyspnea with oxygen saturation below 90% under >5 L/min oxygen inhalation or hemodynamic instability. Discharge is possible when symptoms continue to improve and the Ct value of RT-PCR of both ORF1ab and N gene is more than 35 for consecutive two times with an interval time of at least 24 hrs. After discharge all patients are followed up by telephone within 1 month for further COVID-19 recovery, COVID-19 reinfection and satisfaction for hospitalization (Fig. 1)[13]. The satisfaction scale ranges from 0 to 100 scores; 0 meaning completely unsatisfied while 100 meaning absolutely satisfied. This satisfaction evaluation is important as it reflects how well the patient's symptoms were treated in a timely manner.

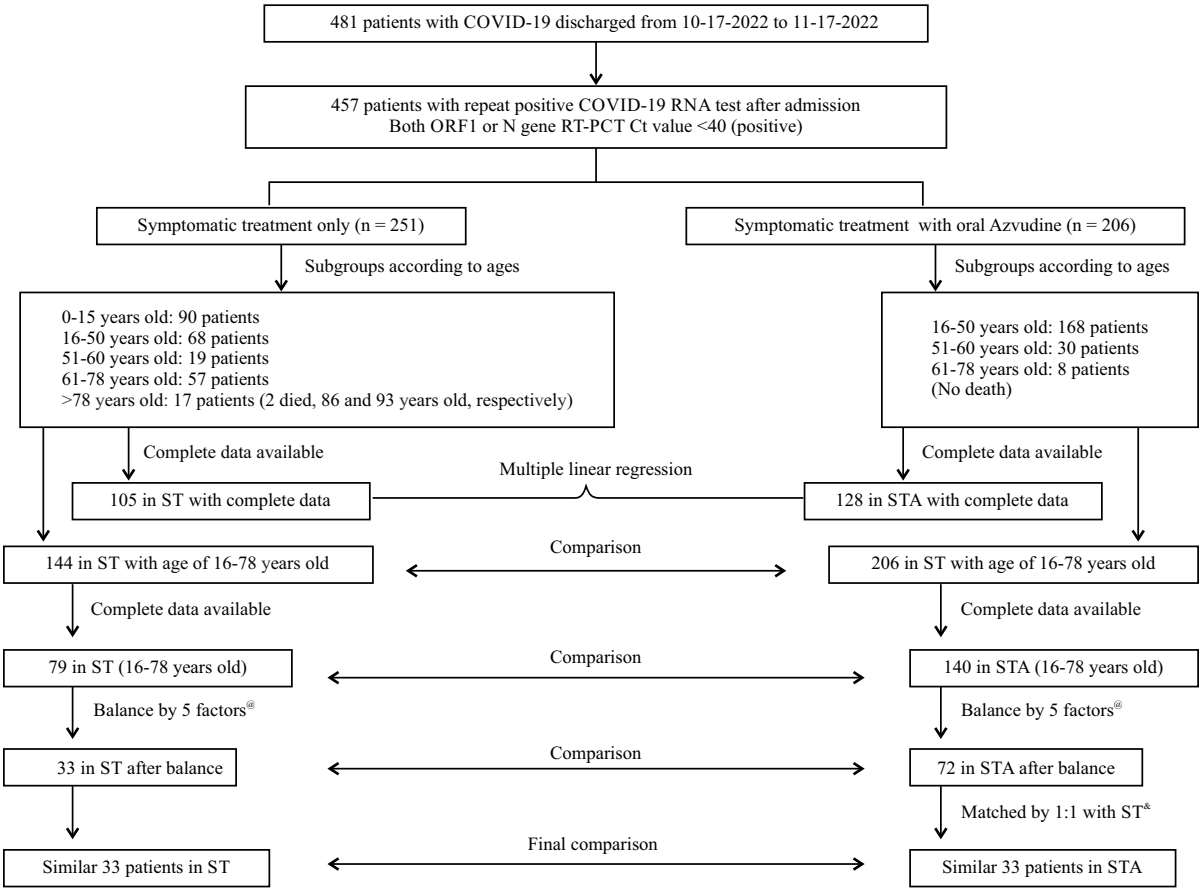

Fig. 1: Flow chart of the patients included in this study

@Five variables included age of 16-65 years old, ≤3 days from symptoms onset to admission, ≤3 days from symptoms onset to Azvudine administration[13], 2-3 doses vaccine, viral load 7-10 (log_{10} (copies/mL)) within 3 days after admission. Patents were matched by age (change within 3 years old), BMI (change within 2 kg/m^2), monocyte count (>1.5×10^9) and viral load (change within 3 (log_{10} (copies/mL)) after admission

Recovery time: The primary endpoint of this study was the recovery time, which was defined as the duration from the onset of symptoms to the consecutive second the Ct value of RT-PCR of both ORF1ab and N gene is more than 35 (Fig. 2a). Most patients infected with Omicron usually present with fever before a positive COVID-19 RNA result is obtained. However, some patients may have a positive COVID-19 RNA result before symptoms onset. In these cases, the recovery time will be calculated from the first positive COVID-19 RNA result to the consecutive second the Ct value of RT-PCR of both ORF1ab and N gene is more than 35. This method of calculating recovery time is less affected by the time between symptoms onset outside hospital and admission than days of hospital stay[15].

Symptomatic severity: The symptomatic severity was the second endpoint in this study. Common symptoms of Omicron in this infective wave of Zhengzhou included fever, cough, sore throat and gastroenterological symptoms (including abdominal distension, stomachache, nausea, vomiting, diarrhea and loss of appetite). These symptoms were evaluated every day according to the medications prescribed by physicians during hospitalizations. Symptomatic severity was scaled from 1-10 with 1 meaning normal condition and 10 meaning life threatening. Symptomatic severity was defined as 5 scores if a specific treatment was prescribed (Table S1). Symptomatic severity increased by 1 score if any kind of non-specific treatment or Chinese herb was prescribed (Table S2). Symptomatic severity increased by 1 to 5 if another specific treatment was administrated in addition to one specific treatment. However, symptomatic severity did not change if none-specific treatment was administrated in addition to specific treatment. The symptomatic severity decreased or increased by 1 score per day depending on whether the symptom improved or worsened the next day. The prescription usually contained 2 days doses.

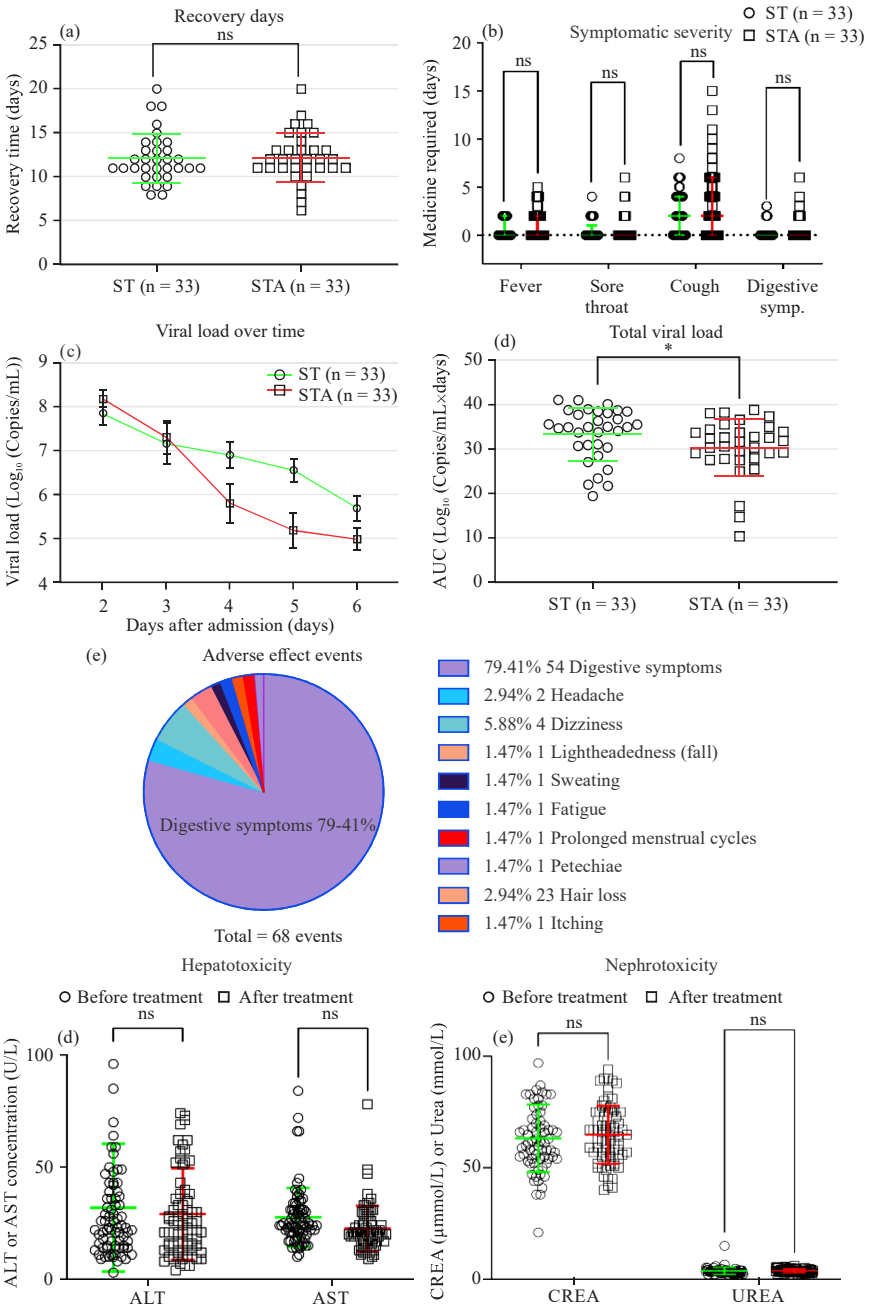

Fig. 2: Recovery time, total viral load and symptomatic severity in ST and STA groups after sample size matched by 1:1 and assessment of Azvudine-related adverse effects, (a) Recovery time of ST and STA groups after the patients' number were matched by the ratio of 1:1, (b) Symptomatic severities in ST and STA groups after the 1:1 match, (c) Changes of viral load over the time from the second day to the sixth day after admission or before oral Azvudine and after oral Azvudine for 5 days in the ST and STA groups after the 1:1 match (2.35±1.93 vs 3.20±1.85, p = 0.07), (d) Total viral load or AUC (area under curve) of ST and STA groups after the 1:1 match, (e) Parts of whole about the patients-reported Azvudine-related adverse effects, (f) Serum concentration of ALT and AST before and after oral Azvudine and (g) Serum concentration of creatinine and urea before and after oral Azvudine

(a) No significant difference was found between ST and STA groups (12.12±2.83 vs 12.21±2.83, p = 0.90), (b) There were no differences in fever, sore throat, cough and digestive symptoms between ST and STA groups (0(0, 2) vs 2(0, 3), p = 0.17 for fever), ((0(0, 1) vs 0(0, 4), p = 0.99) for sore throat), ((2(0, 4) vs 2(0, 6), p = 0.84) for cough) and ((0(0, 0) vs 0(0, 0), p>1) for digestive symptoms). The symptomatic severity was presented as median (25 and 75 percentile), (c-d) A significant difference was found between ST and STA groups (28.03±4.722 vs 25.53±5.324, p = 0.0482), (e-f) Differences in ALT and AST before and after oral Azvudine (31.99±28.49 vs 29.13±20.42 and 27.67±13.10 vs 22.63±10.2, p = 0.4787and p = 0.0090, respectively) and (g) There were no differences in creatinine and urea before and after oral Azvudine (63.25±15.17 vs 64.87±13.04 and 3.76±1.59 vs 3.84±0.84, p = 0.4962 and p = 0.7250, respectively)

The symptomatic severity was the cumulative days of symptomatic severity more than 4 scores during hospitalization. Therefore, symptomatic severity meant the cumulative days during which patients needed at least one specific or four kinds of non-specific medicines to alleviate their symptoms.

COVID-19 RNA test, viral load and total viral load: Real-Time Reverse Transcription-Polymerase Chain Reaction (RT-PCR) was used to detect COVID-19 RNA using a COVID-19 viral RNA detection kit (Mingde Biological Co. Ltd., Wuhan, China). The samples were collected from a combination of nasopharyngeal and oropharyngeal swabs by nurses wearing protective clothing. The samples were tested individually within 2 hrs of collection. The ORF1ab and N genes of COVID-19 were targeted for amplification, with a detection limit of cycle threshold (Ct) set to 40 (200 copies/mL). A Ct of $\geq$40 was defined as negative. A standard COVID-19 RNA (2000, 1000, 500 copies/mL) was used as a positive control in all experiments. Viral loads were calculated as the average of $\log_{10}$ (ORL1a/b Copies per milliliter) and $\log_{10}$ (N gene Copies per milliliter). The Ct$\geq$40 was directly recorded as viral loads of 2. The change in viral load between before oral Azvudine and five days after oral Azvudine administration was compared between the ST and STA groups. Azvudine was commonly administered on the second day after admission in this study, so the viral load on the second day after admission was considered as a baseline for both groups. The area under curve (AUC) from the baseline to the sixth day after admission (the fifth day after oral Azvudine) was defined as the total viral load (Fig. 2b-c). This comparison of viral load was chosen because viral load values for most patients were available from the second to sixth days[16]. The total viral load was used to assess total virus production or virus release after Omicron infection in this study.

Safety: All patients in this study had their adverse events and severity grade recorded. Grade II events were those that required treatment. To assess hepatotoxicity and nephrotoxicity, the serum concentrations of AST, ALT, urea and creatinine were compared before and after Azvudine administration.

Statistical analysis: The data was presented in a variety of ways. Continuous data was reported as the mean with standard deviation (Mean$\pm$SD) or median with interquartile range. Categorical variables were recorded as numbers and percentages. To analyze the continuous data, an independent t-test was used, while Wilcoxon Rank-Sum test was used to analyze skewed distribution data. Multiple linear regression was performed to assess the association between recovery time and clinically relevant factors. Categorical data was analyzed using Chi-Square (χ^2) test or Fisher's exact test and a p-value of less than 0.05 was considered statistically significant.

RESULTS

Patients collected: From October 17 to November 17, 2022, a total of 481 discharged patients were collected from Zhengzhou Central Hospital. As 24 patients were excluded due to negative COVID-19 RNA test results after admission. All patients received symptomatic treatment during hospitalization, with 251 receiving only symptomatic treatment in the ST group and 206 receiving symptomatic treatment plus oral Azvudine in the STA group (Table S3). Azvudine is typically used to treat healthy adults to avoid hepatotoxicity and reproductive toxicity. The ST group ranged in age from 0 to 93 years old, while the STA group ranged from 16 to 78 years old. Unfortunately, two patients died in the ST group; an 86 years old female patient with senile dementia and myocardial ischemia who died of pneumonia and a 93 years old male patient with COPD who died of septic shock. Neither of the two patients was admitted to ICU as their families refused further therapy. Fortunately, no patient died in the STA group. The rate of fever, cough, sore throat and digestive symptoms had no significant difference between the age-matched ST and STA groups before follow-up (Table 1). Additionally, there were no exacerbations or reinfections in either group before follow-up.

Recovery time: From the patients with available data of age, sex, BMI, vaccine dose, days of symptoms onset before admission, oral Azvudine, viral load at the admission, anti-COVID antibody, blood cell count, comorbidities and chest CT results (Table S4), only clinic relevant or a significant univariate relationship with the recovery time (Table S5) were chosen for multiple linear regression[17]. The low-fit multiple linear regression showed a significant difference from zero ($R^2 = 0.039$, $F = 3.117$, $df1 = 3$, $df2 = 229$, $p = 0.027$) (Table S6). The results suggested that oral Azvudine had no association with the recovery time (beta = 0.126, p = 0.056). To balance the heterogeneity between the two groups and compare their recovery times more accurately, similar patients were chosen from each group step by step. Firstly, the patients' age was

Table 1: Characteristics and outcomes of the patients aged 16-78 years old

Characteristics and outcomes	ST (n = 144)	STA (n = 206)	p-value	Total (n = 350)
Age (years)	50.38±19.37	37.51±12.51	<0.0001**	42.81±17.14
16-50	31.54±9.72 (n = 68)	33.09±8.87 (n = 168)	0.2397	32.64±9.13 (n = 236)
51-60	55.74±3.18 (n = 19)	55.00±3.01 (n = 30)	0.4175	55.29±3.06 (n = 49)
61-78	71.07±3.91 (n = 57)	64.88±5.46 (n = 8)	0.0002**	70.31±4.57 (n = 65)
Sex (M/F)	49/95	84/122	0.2193	133/217
BMI (kg/m²)				
Available	22.97±3.38 (n = 122)	24.32±3.78 (n = 177)	0.0018**	23.77±3.68 (n = 299)
Unavailable	(n = 22)	(n = 29)	0.7542	51
Vaccine				
0 dose	12/144 (8.3%)	4/206 (1.9%)	0.0015**	16
1 dose	6/144 (4.2%)	5/206 (2.4%)		11
2 doses	33/144 (22.9%)	32/206 (15.5%)		65
3 doses	71/144 (49.3%)	138/206 (66.0%)		209
Unavailable	22/144 (15.3%)	27/206 (13.1%)	0.5646	49
Symptoms onset before admission (days)	3.09±3.32	2.10±1.89	0.0004**	2.51±2.62 (n = 350)
<3	1.29±0.61 (n = 86)	1.31±0.57 (n = 146)	0.8260	1.30±0.58 (n = 232)
3-5	3.85±0.84 (n = 39)	3.44±0.66 (n = 54)	0.0118	3.61±0.77 (n = 93)
>5	9.68±4.67 (n = 19)	10.17±3.31 (n = 6)	0.8173	9.80±4.32 (n = 25)
Symptoms onset to oral Azvudine (days)	3.97±3.341	3.03±2.09	0.0014**	3.42±2.710 (n = 350)
<3	1.87±0.34 (n = 54)	1.65±0.50 (n = 102)	0.0038**	1.72±0.462 (n = 156)
3-5	3.37±0.78 (n = 60)	3.61±0.712 (n = 84)	0.0569	3.51±0.75 (n = 144)
>5	8.97±4.33 (n = 30)	7.75±2.88 (n = 20)	0.2762	8.48±3.84 (n = 50)
Viral load within 3 days (log_{10} (copies/mL))	7.37±2.00	8.31±2.57	0.0003**	7.92±2.39
Anti-COVID-19 IgG (S/CO)				
Available$^{\Delta}$	2.96 (0.51, 20.39) (n = 132)	4.11 (0.923, 14.41) (n = 187)	0.2876	3.88 (0.81, 16.71) (n = 319)
Unavailable	12 (8.3%)	19 (9.2%)	0.8498	31 (8.9%)
Anti-COVID-19 IgM (S/CO)				
Available	0.86±5.18 (n = 132)	0.35±2.07 (n = 187)	0.2256	0.56±3.69 (n = 319)
Unavailable	12 (8.3%)	19 (9.2%)	0.8498	31 (8.9%)
Comorbidities				
Diabetes mellitus	19/144 (13.2%)	8/206 (3.9%)	0.0002**	27
Cardiovascular disease	51/144 (35.4%)	29/206 (14.1%)	<0.0001**	80
Chronic kidney failure	0/144 (0)	1/206 (0.5%)	>0.9999	1
Chronic pulmonary conditions	4/144 (2.8%)	6/206 (2.9%)	>0.9999	10
CNS conditions	6/144 (4.2%)	2/206 (1.0%)	0.0688	8
Others	16/144 (11.1%)	12/206 (5.8%)	0.1077	28
Neutrophils (10^9/L)				
Available	3.33±1.99 (n = 143)	2.97±1.55 (n = 201)	0.0593	3.12±1.75 (n = 344)
Unavailable	1 (0.6%)	5 (2.4%)	0.4071	6 (1.7%)
Lymphocytes (10^9/L)				
Available	1.503±0.5876 (n = 143)	1.532±0.6906 (n = 201)	0.6872	1.52±0.649 (n = 344)
Unavailable	1 (0.6%)	5 (2.4%)	0.4071	6 (1.7%)
Monocytes (10^9/L)				
Available	0.32±0.15 (n = 143)	0.31±0.16 (n = 201)	0.4092	0.31±0.16 (n = 344)
Unavailable	1 (0.6%)	5 (2.4%)	0.4071	6 (1.7%)
D-dimers (mg/L)				
Available	0.60±2.09 (n = 122)	0.61±2.40 (n = 181)	0.9735	0.61±2.28 (n = 303)
Unavailable	22 (15.3%)	25 (12.1%)	0.4279	47 (13.4%)
CRP (mg/L)				
Available	10.85±16.82 (n = 141)	9.52±10.32 (n = 197)	0.3683	10.08±13.41 (n = 338)
Unavailable	3 (2.1%)	9 (4.4%)	0.3725	12 (3.4%)
Procalcitonin (PCT, ng/ml)				
Available	0.15±1.06 (n = 125)	0.05±0.067 (n = 182)	0.1902	0.09±0.68 (n = 307)
Unavailable	19 (13.2%)	24 (11.7%)	0.7413	43 (12.3%)
Chest CT results				
Non-acute abnormality	66/144 (45.8%)	128/206 (62.1%)	0.0276**	194 (55.4%)
Acute abnormality	38/144 (26.4%)	40/206 (19.4%)		78 (22.3%)
Unavailable	40/144 (27.8%)	38/206 (18.4%)	0.0499**	78 (22.3%)
Clinical outcomes				
ICU admission	0	0	NA	0
Death	0	0	NA	0

Table 1: Continue

Characteristics and outcomes	ST (n = 144)	STA (n = 206)	p-value	Total (n = 350)
Recovery and discharge	144/144	206/206	>0.9999	350
Symptomatic treatment requirement				
Fever	33/144 (22.92%)	64/206 (31.07%)	0.1145	97/350 (27.71%)
Cough	79/144 (54.86%)	133/206 (64.56%)	0.0676	212/350 (60.57%)
Sore throat	33/144 (22.92%)	31/206 (15.05%)	0.0684	64/350 (18.29%)
Digestive symptoms	36/144 (25.00%)	37/206 (17.96%)	0.1411	73/350 (20.86%)
Follow up within 1 month				
Successful follow-up	122/144	175/206	>0.9999	297/350
Exacerbation	0	0	NA	0
COVID-19 reinfection	0	0	NA	0
Satisfaction for hospitalization	96.23±8.16	96.37±7.36	0.8760	96.31±7.69

[Δ]Median (25 and 75 percentile), *p<0.05, **p<0.01 and NA: Not applicable

Table 2: Demographic and clinical characteristics of the patients matched by 1:1 in the two groups

Characteristic	ST (n = 33)	STA (n = 33)	p-value	Total (n = 66)
Age (years)	32.03±13.48	32.67±12.54	0.8432	32.35±12.92
Sex (M/F)	13/20	10/23	0.6059	23/43
BMI (kg/m²)	22.85±4.15	22.17±3.45	0.4730	22.51±3.80
Vaccine				
2 doses	14 (42.4%)	9 (27.3%)	0.3015	23 (34.8%)
3 doses	19 (57.6%)	24 (72.7%)	NA	43 (65.2%)
Symptoms onset before admission ≤3 (days)	1.36±0.74	1.42±0.71	0.7355	1.39±0.72
Symptoms onset to Azvudine ≤3 (days)	2.27±0.57	2.18±0.72	0.5749	2.22±0.65
Viral load within 3 days (log_{10} (copies/mL))	8.55±0.63	8.48±0.87	0.7043	8.51±0.76
Anti-COVID-19 lgG (S/CO) [Δ]D	2.18 (0.68,12.06)	3.97 (0.92,14.74)	0.7008	3.74 (0.89,13.18)
Anti-COVID-19 lgM (S/CO)	0.23±0.75	0.15±0.24	0.5382	0.19±0.56
Comorbidities				
Diabetes mellitus	3 (9.1%)	1 (3.0%)	0.6132	4 (6.1%)
Cardiovascular disease	2 (6.1%)	4 (12.1%)	0.6724	6 (9.1%)
Chronic kidney failure	0 (0)	0 (0)	NA	0 (0)
Chronic pulmonary conditions	1 (3.0%)	0 (0)	>0.9999	1 (1.6%)
CNS conditions	0 (0)	1 (3.0%)	>0.9999	0 (0)
Others	1 (3.0%)	2 (6.1%)	>0.9999	3 (4.5%)
Neutrophils (10^9/L)	3.48±2.31	2.93±1.43	0.2574	3.20±1.9
Lymphocytes (10^9/L)	1.39±0.50	1.34±0.61	0.7198	1.36±0.55
Monocytes (10^9/L)	0.35±0.15	0.28±0.13	0.0549	0.32±0.14
D-dimers (mg/L)				
Available	0.37±0.64 (n = 31)	0.69±2.44 (n = 31)	0.4933	0.53±1.77 (n = 62)
Unavailable	2 (6.1%)	2 (6.1%)	>0.9999	4 (6.1%)
CRP (mg/L)	8.73±6.80	11.84±10.27	0.1511	10.28±8.78
Procalcitonin (PCT, ng/mL)				
Available	0.06±0.05 (n = 32)	0.07±0.15 (n = 32)	0.5528	0.06±0.11 (n = 64)
Unavailable	1 (3.0%)	1 (3.0%)	>0.9999	2 (3.0%)
Chest CT results				
None acute abnormality	28 (84.9%)	5 (15.2%)	0.3670	33 (50.0%)
Acute abnormality	24 (72.7%)	9 (2.7%)		33 (50.0%)
Clinical outcomes				
ICU admission	0	0	NA	0
Death	0	0	NA	0
Recovery and discharge	33	33	NA	66
Symptomatic treatment requirement				
Fever	9/33 (27.3%)	17/33 (51.5%)	0.0769	26/66 (39.4%)
Cough	20/33 (60.6%)	22/33 (66.7%)	0.7984	42/66 (63.6%)
Sore throat	8/33 (24.2%)	5/33 (15.2%)	0.5372	13/66 (19.7%)
Digestive symptoms	6/33 (18.2%)	7/33 (21.2%)	>0.9999	13/66 (19.7%)
Follow up within 1 month				
Successful follow-up	33/33	33/33	>0.9999	66/66
Exacerbation	0	0	NA	0
COVID-19 reinfection	0	0	NA	0
Satisfaction for hospitalization	94.85±15.03	97.88±5.45	0.2802	96.36±11.32

[Δ]Median (25 and 75 percentile), *p<0.05, **p<0.01 and NA: Not applicable

Table 3: A total of 47 from 206 patients with oral Azvudine reported Azvudine-related adverse effect events

Adverse effect	Grade I	Grade II	Grade III-V	Stop Azvudine	Treated
Digestive symptoms	52	2	0	12	1
Nausea	28	1	0	7	1
Vomiting	11	1	0	4	0
Diarrhea	11	0	0	1	0
Constipation	2	0	0	0	0
Headache	2	0	0	1	0
Dizziness	4	0	0	2	0
Lightheadedness (fall)	1	0	0	1	0
Hair loss	2	0	0	1	0
Sweating	1	0	0	0	0
Fatigue	1	0	0	0	0
Itching	1	0	0	0	0
Prolonged menstrual cycles	1	0	0	0	0
Petechiae	1	0	0	0	0
Total	66	2	0	17	1

balanced from 16 to 78 years old (Fig. 1 and Table 1). Secondly, only those with data-available were chosen from both groups (Table S7). Thirdly, recovery-related variables were balanced according to reported clinic relevant variables (Fig. 1, Table S8 and Fig. S1). Lastly, the number of patients in each group was equalized (Fig. 1 and Table 2). After these processes were completed no differences in recovery time between the two groups were found except for in total population size (Table S9). After final matching was done between them their respective recovery times were 12.12 ± 2.82 (n = 33) and 12.21 ± 2.84 (n = 33) for ST and STA groups, respectively (p = 0.8966) (Fig. 2a). The characteristics of these matched groups showed that they had an age range of 16-65 years old and had received 2-3 doses of vaccine with a low rate of comorbidities and abnormality in chest CT scans which suggested that they were at low risk for developing serious conditions. In fact, no deaths or ICU admissions were in either group after initial balance (Table 1).

Symptomatic severity: Patients admitted to the hospital typically experienced symptoms of fever, cough, sore throat and digestive issues. After 1:1-matching, there was no significant difference in the severity of symptoms between the two groups (Fig. 2b).

Total viral load: The results showed that the STA group had a lower total viral load than the ST group after 1:1 matching in the number of patients (Fig. 2c-d).

Patients-reported Azvudine-related adverse effects: A total of 47 out of 206 patients who were administered Azvudine reported Azvudine-related adverse effects, all of which belonged to Grade I or II events (Table 3). Of these patients, 17 stopped taking Azvudine by themselves and one required treatment for vomiting. The majority (79.41%) of the adverse effects reported were digestive in nature, such as diarrhea, nausea, vomiting and constipation (Fig. 2e). However, Omicron infection can also cause similar digestive symptoms and this study found no difference in severity between the ST and STA groups (Fig. 2b). This suggests that Omicron infection may have contributed to these adverse effects rather than Azvudine itself, indicating that Azvudine causes very mild adverse effects after administration.

No hepatotoxicity and nephrotoxicity were found after Azvudine administration: A total of 73 patients were tested for ALT and AST before and after administration of Azvudine. The results showed that there was no significant difference in ALT levels between before and after administration (Fig. 2f). However, the AST concentration was lower after oral Azvudine than before, which may be attributed to the recovery from COVID-19. Similarly, 71 patients were tested for creatinine and BUN before and after administration of Azvudine, with no significant differences observed between the two (Fig. 2g).

DISCUSSION

This study evaluated the efficacy and safety of Azvudine in clinical treatment of COVID-19 in China since August 9, 2022. Although several papers report that Azvudine improved the recovery of COVID-19 infection, current results didn't find that positive efficacy[6,18-26]. Current results indicated that Azvudine had no effect on improving the recovery time and symptomatic severity in low-risk patients. However, it was found to slightly decrease the total viral load during hospitalization. Additionally, Azvudine exhibited very mild adverse effects without hepatotoxicity or nephrotoxicity after administration.

The results of this study suggested that Azvudine may not influence the recovery time in low-risk patients after Omicron infection. However, the sample size of 33 in each group may not have been large enough to detect the effect of Azvudine on the recovery time. To address this, sample size was estimated according to the data from a clinical trial in China (ChiCTR2000029853)[6]. In that trial, it was reported that Azvudine shortened the mean time of the first nucleic acid negative conversion from 9.8 to 2.5 days with a 7.3 day difference in treatment of patients with early infection of COVID-19. The sample size was calculated to be at least 8 patients in each group to detect the effects of Azvudine if parameters were set as alpha = 0.05, Z alpha = 1.96, power = 80%, Z beta = 0.84, expected SD = 3 days and accepted effect size = 3 days[27]. Therefore, the sample size of 33 in each group in this study is sufficient to detect 3-day effects of Azvudine in improving the recovery time after Omicron infection. However, it may not have enough power to detect any effects on improvement of total viral load and symptomatic severity.

The mild virulence of the current COVID-19 dominant variant, Omicron BA 5.2, may be the cause of our negative results. Several papers reported that Azvudine had effects on improving COVID-19 infection during the pandemic of COVID-19 alpha, beta and delta variants[28]. However, Omicron is different from these variants as it causes less disease but spreads more rapidly[13]. The patients in this study were infected by Omicron BA 5.2 during the COVID-zero policy of China[29]. Therefore, Azvudine may have effects on the alpha, beta or delta variants but have no effects on Omicron variants since Omicron only replicates limitedly in the upper respiratory tract and not all over the body like alpha, beta and delta variants.

Azvudine was only approved in August, 2022 and so it was given to young adults with caution due to potential adverse effects. This bias administration of Azvudine in patients aged 16-60 with moderate symptoms and without serious comorbidity may have contributed to the negative results of this study. Similarly, Paxlovid, an effective anti-COVID medicine, also showed little effect on patients under 60 years old[30]. Additionally, our study didn't have the capacity to detect the efficacy of Azvudine using mortality rate as a measure. Mortality rate or ICU admission rate may be more appropriate metrics for evaluating the efficacy of Azvudine in seriously ill patients with Omicron infection.

Although Azvudine may have decreased the total viral load during hospitalization, the reduction appears to be very slight and there was no significant difference in the viral load before and after oral Azvudine between the two groups. This retrospective study had a small sample size, so the advantages of administering Azvudine should be re-evaluated.

This study had several weaknesses. Firstly, it was a retrospective study, which means it could not confirm the efficacy of Azvudine on COVID-19 infection. The patients who consented to take Azvudine may have had higher confidence in their health or milder symptoms than those who did not take Azvudine, leading to a selection bias that could mask the effects of Azvudine on Omicron infection. Secondly, the recovery time was only a limited endpoint for evaluating the efficacy of Azvudine, as a comprehensive evaluation should include mortality rate, progressive rate to serious situation or ICU admission rate. Unfortunately, there were no deaths or ICU admissions in either group after initial balance.

CONCLUSION

Azvudine had limited effects on low-risk patients with Omicron infection in terms of accelerating recovery and alleviating symptoms. However, it was observed that Azvudine could slightly reduce the total viral load within 5 days of its administration. Oral Azvudine is relatively safe for treating COVID-19 and it should be targeted towards high-risk patients with Omicron infection in order to conserve resources during this pandemic.

SIGNIFICANCE STATEMENT

The aim of this study was to evaluate the efficacy and safety of Azvudine in treatment of the patients infected with COVID-19 Omicron variants. This study included the discharged patients after COVID-19 infection in Zhengzhou Central Hospital. No significant differences were found in the recovery time and symptomatic severity between the two groups (symptomatic treatment group (ST) and symptomatic treatment and oral Azvudine (STA) groups) after 1:1 matched. Azvudine had little effect on the low-risk patients with Omicron infection to improve recovery time and symptoms. Azvudine should be targeted towards high-risk patients with Omicron infection to conserve resources during this pandemic.

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Table S1: Medicines used to treat specific symptoms

Specific symptom	Chinese name of medicine	English name of medicine
Fever	酚麻美敏片	Compound dextromethorphan hydrobromide tablets
	对乙酰氨基酚片	Paracetamol tablets
	布洛芬混悬液布洛芬缓释胶囊	Ibuprofen
	小儿氨酚黄那敏颗粒(四川)	Child paracetamol and amantadine hydrochloride capsules
	复方氨酚烷胺胶囊	Compound paracetamol and amantadine hydrochloride capsules
Digestive symptoms	双歧杆菌四联活菌片	Bifidobacterium tetravaccine tablets
	枯草杆菌二联活菌颗粒	*Bacillus subtilis*
	多潘立酮片	Domperidone tablets
	甲氧氯普胺片	Metoclopramide
	健胃消食片	Jianweixiaoshi for digestion tablets
	枸橼酸莫沙必利片	Mosapride citrate tablets
	马来酸曲美布汀分散片	Trimebutine maleate tablets
	泮托拉唑钠肠溶片	Pantoprazole sodium enteric-coated tablets
	注射用泮托拉唑钠(泮立苏)	Pantoprazole sodium for injection
	奥美拉唑肠溶胶囊(罗欣恩康)	Omeprazole enteric-coated capsules
	铝碳酸镁咀嚼片	Calcium carbonate chewing tablets
	乳果糖口服溶液	Lactulose solution
	麻仁润肠丸(小蜜丸)	Maren runchang pill for constipation
	蒙脱石散	Montmorillonite powder for diarrhea
	盐酸小檗碱片	Berberine hydrochloride tablets for diarrhea
	盐酸洛哌丁胺胶囊	Loperamide hydrochloride capsules
Cough	急支糖浆	Cough syrup
	盐酸氨溴索口服溶液	Ambroxol hydrochloride oral solution
	肺力咳合剂	Feilike mixture for cough
	吸入用乙酰半胱氨酸溶液	N-Acetylcysteine for inhalation
	盐酸二氧丙嗪片	Dioxopromethazine hydrochloride
	盐酸氨溴索注射液	Ambroxol hydrochloride injection
	吸入用复方异丙托溴铵溶液	Compound ipratropium bromide solution
	吸入用布地奈德混悬液(普米克令舒)	Budesonide suspension
Sore throat	甘桔冰梅片	Ganju bingmei tablets for sore throat
	开喉剑喷雾剂	Open throat sword spray for sore throat

Table S2: Medicines used to treat non-specific symptoms

Chinese name	English name
莲花清瘟颗粒	Lianhuaqingwen
人参败毒散	Ren shen bai du san
清肺排毒汤	Clean lung paidu decoction
银翘散	*Lonicerae* and *Forsythiae* powder
抗病毒口服液	Kangbingdu oral solutio
小柴胡颗粒	Xiaochaihu granule
蒲地蓝消炎口服液	Pudilan xiaoyan decoction
板蓝根颗粒	Banlangen granule
康复新液	Kangfuxin liquid
痰热清胶囊	Tanreqing capsules
金振口服液	Jinzhen mixture
三拗汤	Sanaotang
宣肺败毒颗粒	Xuanfeiqing granules
四磨汤口服液	Simotang oral solution
保和丸	Baohewan
香砂六君子汤	Xiangsha liujunzi decoction
桉柠蒎肠溶软胶囊	Anningpai enteric-coated capsules

Table S3: Characteristics and outcomes of the total patients included in this study

Characteristics	ST (n = 251)	STA (n = 206)	p-value	Total (n = 457)
Age (years)	37.32±28.31	37.51±12.51	0.782	37.20±22.35
Sex (M/F)	95/156	84/122	0.5637	179/278
BMI (kg/m²)				
Available	21.58±4.23 (n = 211)	24.32±3.78 (n = 177)	<0.0001	22.83±4.25 (n = 388)
Unavailable	40 (15.9%)	29 14.1%	0.6020	69 (15.1%)
Vaccine				
0 dose	41 (16.3%)	4 (1.9%)	<0.0001	45 (9.8%)
1 dose	7 (2.8%)	5 (2.4%)		12 (2.6%)
2 doses	87 (34.7%)	32 (15.5%)		119 (26.0%)
3 doses	79 (31.5%)	138 (67.0%)		217 (47.5%)
Unavailable	37 (14.7%)	27 (13.1%)	0.6851	64 (14.0%)
Symptoms onset before Admission (days)	2.76±2.86	2.10±1.89	0.0045**	2.46±2.49
<3	1.31±0.62 (n = 161)	1.31±0.57 (n = 146)	0.9728	1.31±0.60 (n = 307)
3-5	3.75±0.84 (n = 63)	3.44±0.66 (n = 54)	0.0356*	3.61±0.78 (n = 117)
>5	9.11±4.18 (n = 27)	10.17±3.31 (n = 6)	0.5682	9.30±0.78 (n = 33)
Symptoms onset to oral Azvudine (days)	NA	3.03±2.09	NA	3.03±2.09
<3	NA	1.65±0.50 (n = 102)	NA	1.65±0.50 (n = 102)
3-5	NA	3.61±0.712 (n = 84)	NA	3.61±0.712 (n = 84)
>5	NA	7.75±2.88 (n = 20)	NA	7.75±2.88 (n = 20)
Viral load within 3 days (log_{10} (copies/mL))	7.25±2.21	8.31±2.57	<0.0001	7.73±2.44
Anti-COVID-19 IgG (S/CO)				
Available$^{\Delta}$	2.75 (0.64, 19.33) n = 196	4.11 (0.92, 14.41) (n = 187)	0.0245	3.56 (0.81, 16.40) (n = 383)
Unavailable	55 (21.9%)	19 (9.2%)	0.0003	74 (16.2%)
Anti-COVID-19 IgM (S/CO)				
Available	0.22±4.69 (n = 196)	0.35±2.07 (n = 187)	0.2190	0.58±3.66 (n = 383)
Unavailable	55 (21.9%)	19 (9.2%)	0.0003	74 (16.2%)
Comorbidities				
Diabetes mellitus	25 (10.0%)	8 (3.9%)	0.0171	33 (7.2%)
Cardiovascular disease				
Chronic kidney failure	0 (0%)	1 (0.5%)	0.4508	1 (0.2%)
Chronic pulmonary conditions	8 (3.2%)	6 (2.9%)	>0.9999	14 (0.3%)
CNS conditions	8 (3.2%)	2 (1.0%)	0.1966	10 (2.2%)
Others	21 (8.4%)	12 (5.8%)	0.3648	33 (7.2%)
Neutrophils (10^9/L)				
Available	3.05±1.81 (n = 225)	2.97±1.55 (n = 201)	0.6218	3.01±1.69 (n = 426)
Unavailable	26 (10.3%)	5 (2.4%)	0.0006	31 (15.0%)
Lymphocytes (10^9/L)				
Available	1.84±1.13 (n = 225)	1.53±0.69 (n = 201)	0.0008	1.70±0.96 (n = 426)
Unavailable	26 (10.3%)	5 (2.4%)	0.0006	31 (15.0%)
Monocytes (10^9/L)				
Available	0.313±0.15 (n = 225)	0.31±0.16 (n = 201)	0.6424	0.31±0.15 (n = 426)
Unavailable	26 (10.3%)	5 (2.4%)	0.0006	31 (15.0%)
D-dimers (mg/L)				
Available	0.60±1.77 (n = 186)	0.61±2.40 (n = 181)	0.9369	0.60±2.11 (n = 367)
Unavailable	65 (25.9%)	25 (12.1%)	0.0002	90 (19.69%)
CRP (mg/L)				
Available	10.71±16.82 (n = 218)	9.522±10.32 (n = 197)	0.3936	10.14±14.11 (n = 415)
Unavailable	33 (13.1%)	9 (4.3%)	0.0011	42 (9.2%)
Procalcitonin (PCT, ng/mL)				
Available	0.13±0.86 (n = 194)	0.05±0.07 (n = 182)	0.2052	0.09±0.62 (n = 376)
Unavailable	57 (22.7%)	24 (11.7%)	0.0021	81 (17.7%)
Chest CT results				
Non-acute abnormality	97 (38.6%)	128 (62.1%)	0.0462	225 (49.2%)
Acute abnormality	51 (20.3%)	40 (19.4%)		91 (19.9%)
Unavailable	103 (41.0%)	38 (18.4%)	<0.0001	141 (30.9%)
Clinical outcomes				
ICU admission	0	0	NA	0
Death	2	0	0.5038	2
Recovery and discharge	249	206	1	457*

Table S3: Continue

Characteristics	ST (n = 251)	STA (n = 206)	p-value	Total (n = 457)
Symptomatic treatment requirement				
Fever	61/251 (24.3%)	64/206 (31.07%)	0.1144	125/457 (%)
Cough	137/251 (54.6%)	133/206 (64.56%)	0.0354*	270/457 (%)
Sore throat	37/251 (14.7%)	31/206 (15.05%)	>0.9999	68/457 (%)
Digestive symptoms	58/251 (23.1%)	37/206 (17.96%)	0.2029	95/457 (%)
Follow up within 1 month				
Successful follow-up	214/251	175/206	1	389/457
Exacerbation	0	0	1	0
COVID-19 reinfection	0	0	1	0
Satisfaction for hospitalization	9.6±0.9	9.6±0.7	0.8544	9.6±0.8

*Two patients died during hospitalization

Table S4: Characteristics of the data-available patients for multiple linear regression

Characteristics	ST (n = 105)	STA (n = 128)	p-value	Total (n = 233)
Age (years)	42.87±25.97	35.88±12.18	0.0074**	39.03±19.89
Sex (M/F)	43/62	59/69	0.5071	102/131
BMI (kg/m²)	22.34±4.31	24.11±3.82	0.0010**	23.31±4.13
Vaccine				
0 dose	10 (9.5%)	4 (3.1%)	<0.0001****	14 (6.0%)
1 dose	3 (2.9%)	5 (3.9%)		8 (3.4%)
2 doses	48 (45.7%)	25 (19.5%)		73 (31.3%)
3 doses	44 (41.9%)	94 (73.4%)		138 (59.2%)
Symptoms onset before admission (days)	2.53±2.14	1.77±1.05	0.0004***	2.11±1.67
<3	1.34±0.589 (n = 68)	1.28±0.55 (n = 99)	0.5368	1.31±0.57 (n = 167)
3-5	3.90±0.92 (n = 30)	3.41±0.568 (n = 29)	0.0184*	3.66±0.80 (n = 59)
>5	8.29±2.63 (n = 7)	0 (0.0%)	NA	8.29±2.63 (n = 7)
Symptoms onset to oral Azvudine (days)	3.53±2.14	2.85±1.34	0.0033**	3.16±1.77
<3	1.90±0.30 (n = 41)	1.74±0.44 (n = 61)	0.0403*	1.80±0.40 (n = 102
3-5	3.52±0.69 (n = 46)	3.53±0.63 (n = 58)	0.9218	3.53±0.65 (n = 104
>5	7.28±2.27 (n = 18)	6.00±0.00 (n = 9)	0.1070	6.85±1.94 (n = 27)
Viral load within 3 days (log_{10} (copies/mL))	7.38±1.79	8.66±2.42	<0.0001****	8.08±2.25
Anti-COVID-19 lgG (S/CO)[Δ]	2.64 (0.61, 11.00)	3.59 (0.88, 13.02)	0.5122	3.44 (0.68, 12.06)
Anti-COVID-19 lgM(S/CO)	0.85±5.72	0.24±1.14	0.2415	0.52±3.93
Comorbidities				
Diabetes mellitus	11 (10.5%)	5 (3.9%)	0.0671	16 (6.9%)
Cardiovascular disease	25 (23.8%)	16 (12.5%)	0.0150*	41 (17.6%)
Chronic kidney failure	0 (0)	0 (0%)	NA	0 (0%)
Chronic pulmonary conditions	5 (4.8%)	3 (2.3%)	0.4728	8 (3.4%)
CNS conditions	4 (3.8%)	2 (1.6%)	0.4131	6 (2.6%)
Others	8 (7.6%)	9 (7.0%)	1	17 (7.3%)
Neutrophils (10^9/L)	3.16±1.79	3.01±1.52	0.5062	3.08±1.65
Lymphocytes (10^9/L)	1.64±0.81	1.54±0.65	0.3170	1.59±0.73
Monocytes (10^9/L)	0.32±0.15	0.30±0.15	0.3780	0.31±0.15
D-dimers (mg/L)	0.42±0.63	0.68±2.78	0.3474	0.57±2.10
CRP (mg/L)	10.54±16.18	9.94±11.27	0.7393	10.21±13.67
Procalcitonin (PCT, ng/mL)	0.17±1.15	0.05±0.08	0.2586	0.10±0.78
Chest CT results				
Non-acute abnormality	71 (67.6%)	100 (78.1%)	0.0758	171 (73.4%)
Acute abnormality	34 (32.4%)	28 (21.9%)		62 (26.6%)
Clinical outcomes				
ICU admission	0	0	1	0
Death	0	0	1	0
Recovery and discharge	105	128	1	233
Symptomatic treatment requirement				
Fever	26/105 (24.7%)	48/128 (37.5%)	0.0475*	74/233 (31.7%)
Cough	70/105 (66.7%)	82/128 (64.1%)	0.7823	152/233 (65.2%)
Sore throat	18/105 (17.1%)	26/128 (20.3%)	0.6150	44/233 (18.9%)
Digestive symptoms	26/105 (24.7%)	21/128 (16.4%)	0.1399	47/233 (20.2%)
Follow up within 1 month				
Successful follow-up	105/105	128/128	1	233/233
Exacerbation	0	0	1	0
COVID-19 reinfection	0	0	1	0
Satisfaction for hospitalization	9.8±1.0	9.7±0.7	0.8325	9.7±0.8

Table S5: Correlation of the recovery time with the variables in the 233 data-available patients

Variable	r	95%CI	p-value
Sex (1,0; M/F)	0.003298	-0.1290-0.1355	0.9601
Age (years)	0.07810	-0.05474-0.2082	0.2350
Symptoms onset before admission (days)	0.09419	-0.03857-0.2237	0.1518
Azvudine (0,1; no/yes)	0.1562	0.02440-0.2826	0.0170*
Symptoms onset to oral Azvudine (days)	0.1017	-0.03102-0.2308	0.1217
BMI (kg/m^2)	0.01454	-0.1180-0.1465	0.8253
Vaccine doses (0, 1, 2, 3)	-0.0006793	-0.1329-0.1316	0.9918
Diabetes mellitus (0,1; no/yes)	0.03565	-0.09709-0.1671	0.5882
Cardiovascular disease (0,1; no/yes)	0.07524	-0.05761-0.2055	0.2527
Chronic pulmonary conditions (0,1; no/yes)	0.01410	-0.1184-0.1461	0.8305
CNS conditions (0,1; no/yes)	0.005064	-0.1273-0.1372	0.9387
Others (0,1; no/yes)	0.1082	-0.02444-0.2371	0.0995
Chest CT ((0,1; non-acute abnormality/acute abnormality)	0.06861	-0.06425-0.1991	0.2970
NEUT (10^9/L)	0.008336	-0.1241-0.1405	0.8993
LYMPH (10^9/L)	-0.1326	-0.2603-0.0002780	0.0432*
MONO (10^9/L)	-0.04262	-0.1739-0.09017	0.5174
D-dimer (mg/L)	0.09320	-0.03957-0.2227	0.1562
CRP (mg/L)	-0.04211	-0.1734-0.09067	0.5224
Procalcitonin (PCT, ng/mL)	-0.08272	-0.2127-0.05010	0.2084
IgG (S/CO)	-0.1436	-0.2708-0.01159	0.0284*
IgM (S/CO)	-0.1933	-0.3174-0.06261	0.0031**
Viral load within 3 days (log_{10} (copies/mL))	0.08483	-0.04798-0.2147	0.1970

Table S6: Multiple linear regression (the recovery time over oral Azvudine, lymphocytes, anti-COVID-19 IgG, but IgM was eliminated because of multicollinearity with IgG)

Multiple linear regression, $R^2 = 0.039$, $F = 3.117$, $df1 = 3$, $df2 = 229$, $p = 0.027$

	Unstandardized coefficients		Standardized coefficient			Collinearity statistics	
Variable	B	Standard error	Beta	T	p-value	Tolerance	VIP
Constant	12.328	0.733	NA	16.830	<0.001	NA	NA
Oral Azvudine	0.804	0.0419	0.126	1.920	0.056	0.977	1.023
Lymphocyte count	-0.196	0.295	-0.045	-0.663	0.508	0.931	1.074
IgG	-0.136	0.063	-0.146	-2.175	0.031	0.926	1.080

Table S7: Demographic and clinical characteristics of the patients with complete data available and within 16-78 years old

Characteristics	ST (n = 79)	STA (n = 140)	p-value	Total (n = 219)
Age (years)	48.23±20.57	36.10±12.21	<0.0001**	40.47±16.75
Sex (M/F)	27/52	64/76	0.1165	91/128
BMI (kg/m^2)	22.93±3.44	24.10±3.74	0.0232*	23.67±3.67
Vaccine				
Unvaccinated	8 (10.1%)	4 (2.8%)	0.0083**	12 (5.4%)
1 dose	3 (3.7%)	5 (3.5%)		8 (3.6%)
2 doses	25 (31.6%)	26 (18.5%)		51 (23.2%)
3 doses	43 (54.4%)	105 (75.0%)		148 (67.5%)
Symptoms onset before admission (days)	2.44±2.10	1.78±1.06	0.0023**	2.01±1.54
<3	1.26±0.56 (n = 51)	1.28±0.56 (n = 107)	0.7903	1.27±0.56 (n = 158)
3-5	3.83±0.89 (n = 23)	3.36±0.55 (n = 33)	0.0194*	3.55±0.74 (n = 56)
>5	8.20±2.68 (n = 5)	0 (n = 0)	NA	8.20±2.68 (n = 5)
Symptoms onset to oral Azvudine (days)	3.30±2.09 (n = 79)	2.79±1.34 (n = 140)	0.0287*	2.98±1.66 (n = 219)
<3	1.91±0.28 (n = 35)	1.69±0.50 (n = 68)	0.0158*	1.77±0.45 (n = 103)
3-5	3.31±0.74 (n = 32)	3.52±0.619 (n = 63)	0.1440	3.45±0.66 (n = 95)
>5	7.333±2.309 (n = 12)	6.00±0 (n = 9)	0.1015	6.76±1.84 (n = 21)
Viral load within 3 days (log_{10} (copies/mL))	7.69±1.77	8.64±2.40	0.0023**	8.30±2.24
Anti-COVID-19 IgG (S/CO)$^{\Delta}$	3.88 (0.48, 19.31)	3.87 (0.91, 13.02)	0.1859	3.88 (0.71, 13.51)
Anti-COVID-19 IgM (S/CO)	1.17±6.64	0.23±1.09	0.1014	0.57±4.09
Comorbidities				
Diabetes mellitus	8 (10.1%)	5 (3.6%)	0.0714	13 (5.5%)
Cardiovascular disease	21 (26.6%)	18 (12.9%)	0.0046**	39 (17.8%)
Chronic kidney failure	0	0	NA	0 (0%)

Table S7: Continue

Characteristics	ST (n = 79)	STA (n = 140)	p-value	Total (n = 219)
Chronic pulmonary conditions	2 (2.5%)	3 (2.1%)	>0.9999	5 (2.3%)
CNS Conditions	2 (2.5%)	2 (1.4%)	0.6208	4 (1.8%)
Others	8 (10.1%)	9 (6.4%)	0.4306	17 (7.8%)
Neutrophils (10^9/L)	3.57±2.16	2.99±1.50	0.0201	3.20±1.79
Lymphocytes (10^9/L)	1.49±0.63	1.52±0.66	0.7620	1.51±0.65
Monocytes (10^9/L)	0.34±0.17	0.30±0.15	0.0533	0.32±0.16
D-dimers (mg/L)				
Available	0.65±2.64 (n = 75)	0.67±2.71 (n = 135)	0.9563	0.66±2.68 (n = 210)
Unavailable	4 (5.0%)	5 (3.6%)	0.7256	9 (4.1%)
CRP (mg/L)				
Available	9.71±11.50 (n = 78)	10.05±11.10 (n = 136)	0.8278	9.75±10.68 (n = 214)
Unavailable	1 (1.3%)	4 (2.9%)	0.6561	5 (2.3%)
Procalcitonin (PCT, ng/mL)				
Available	0.21±1.36 (n = 76)	0.05±0.08 (n = 135)	0.1810	0.11±0.82 (n = 211)
Unavailable	3 (3.8%)	5 (3.6%)	>0.9999	8 (3.7%)
CT results				
None acute abnormality	52 (65.8%)	107 (76.4%)	0.1144	159 (72.6%)
Acute abnormality	27 (34.2%)	33 (23.6%)		60 (27.4%)
Clinical outcomes				
ICU admission	0	0	1	0
Death	0	0	1	0
Recovery and discharge	79	140	1	219
Symptomatic treatment requirement				
Fever	19/79 (24.1%)	52/140 (37.1%)	0.0517	71/219 (32.4%)
Cough	47/79 (59.5%)	91/140 (65.0%)	0.4670	138/219 (63.0%)
Sore throat	18/79 (22.8%)	28/140 (20.0%)	0.7300	46/219 (21.0%)
Digestive symptoms	21/79 (26.6%)	24/140 (17.1%)	0.1173	45/219 (20.5%)
Follow up within 1 month				
Successful follow-up	79/79	140/140	1	219/219
Exacerbation	0	0	1	0
COVID-19 reinfection	0	0	1	0
Satisfaction for hospitalization	9.6±1.1	9.7±0.7	0.3291	9.7±0.8

Table S8: Demographic and clinical characteristics of the patients after balance in 5 variables

Characteristics	ST (n = 33)	STA (n = 72)	p-value	Total (n = 105)
Age (years)	32.03±13.48	36.03±12.46	0.1401	34.77±12.86
Sex (M/F)	20/13	41/31	0.8321	61/44
BMI (kg/m^2)	22.85±4.15	23.96±3.57	0.1656	23.61±3.78
Vaccine >2 doses	33	72	1	105
Viral load within 3 days	8.55±0.63	8.35±0.80	0.2120	8.41±0.76
Symptoms onset before admission ≤3 (day)	1.36±0.74	1.40±0.71	0.7956	1.39±0.71
Symptoms onset to oral Azvudine ≤3 (days)	2.27±0.57	2.11±0.76	0.2802	2.16±0.71
Anti-COVID-19 IgG (S/CO)$^{\Delta}$	2.18 (0.68,12.06)	3.52 (0.92,9.77)	0.1954	3.49 (0.91,11.11)
Anti-COVID-19 IgM (S/CO)	0.23±0.75	0.14±0.22	0.3158	0.17±0.46
Comorbidities				
Diabetes mellitus	3 (9.09%)	4 (5.56%)	0.6754	7 (6.67%)
Cardiovascular disease	2 (6.06%)	8 (11.11%)	0.4998	10 (9.52%)
Chronic kidney failure	0	0	1	0
Chronic pulmonary conditions	1 (3.03%)	0	0.3173	1 (0.95%)
CNS conditions	0	1 (1.39%)	>0.9999	1 (0.95%)
Others	1 (3.03%)	6 (8.33%)	0.4288	7 (6.67%)
Neutrophils (10^9/L)	3.48±2.31	3.09±1.51	0.3078	3.21±1.80
Lymphocytes (10^9/L)	1.39±0.50	1.36±0.62	0.7976	1.37±0.59
Monocytes (10^9/L)	0.35±0.15	0.29±0.13	0.0491*	0.31±0.14
D-dimers (mg/L)				
Available	0.37±0.64	0.56±1.73	0.5743	0.50±1.47
Unavailable	2 (6.06%)	5 (6.94%)	>0.9999	7 (6.67%)
CRP (mg/L)				
Available	8.73±6.80	11.52±13.39	0.2614	10.63±11.75
Unavailable	0	1 (1.39%)	>0.9999	1 (0.95%)

Table S8: Continue

Characteristics	ST (n = 33)	STA (n = 72)	p-value	Total (n = 105)
Procalcitonin (PCT, ng/mL)				
Available	0.06±0.05	0.06±0.10	0.9282	0.06±0.09
Unavailable	1 (3.0%)	5 (6.9%)	0.6625	6 (5.7%)
CT results				
Non-acute abnormality	28 (84.9%)	53 (73.6%)	0.3164	81 (77.1%)
Acute abnormality	5 (15.2%)	19 (26.4%)		24 (22.9%)
Clinical outcomes				
ICU admission	0	0	1	0
Death	0	0	1	0
Recovery and discharge	33	72	1	105
Symptomatic treatment requirement				
Fever	9/33 (27.3%)	34/72 (47.2%)	0.0586	43105 (41.0/%)
Cough	20/33 (60.6%)	48/72 (66.7%)	0.6605	68/105 (64.8%)
Sore throat	8/33 (24.2%)	14/72 (19.4%)	0.6106	22/105 (21.0%)
Digestive symptoms	6/33 (18.2%)	17/72 (23.6%)	0.6179	23/105 (21.9%)
Follow up within 1 month				
Successful follow-up	33/33	72/72	1	105/105
Exacerbation	0	0	1	0
COVID-19 reinfection	0	0	1	0
Satisfaction for hospitalization	9.5±1.5	9.7±0.6	0.2191	9.7±1.0

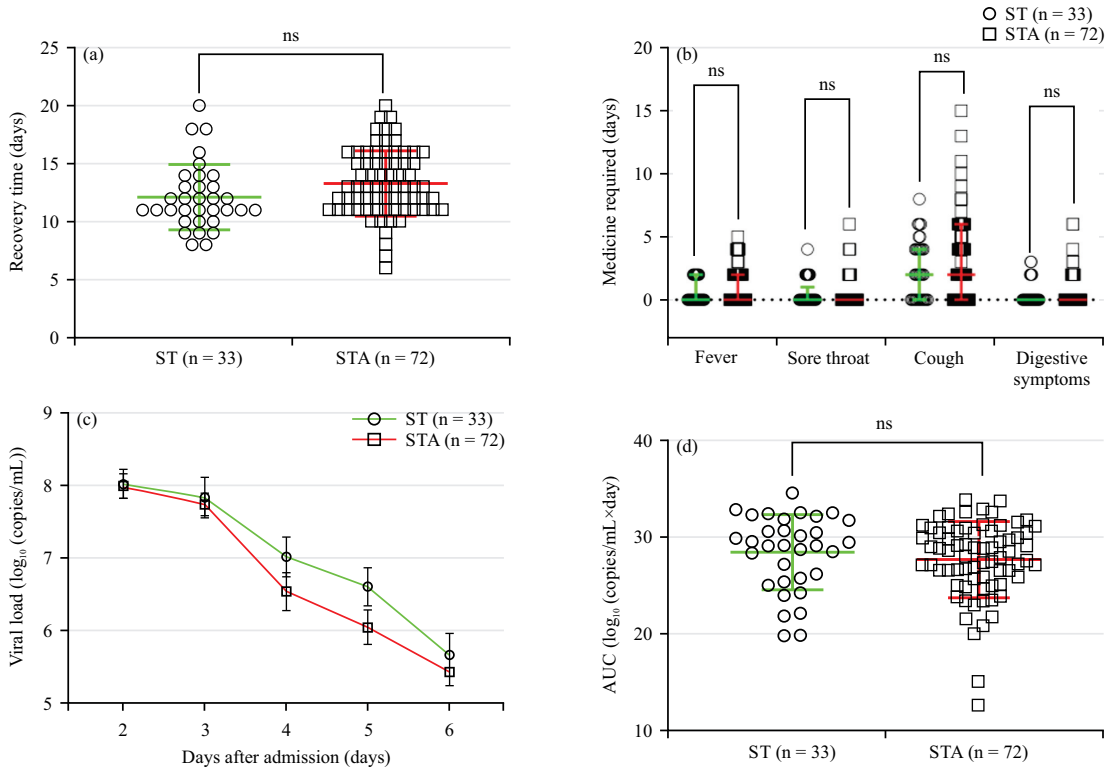

Fig. S1(a-d): Recovery time, total viral load and symptomatic severity after balance of 5 variables, (a) Recovery days, (b) Symptomatic severity, (c) Viral load over time and (d) Total viral load

(a) Recovery time of ST and STA groups after the patients were further chosen by the age of 16-65 years, less than 3 days from symptoms onset to admission, less than 3 days from symptoms onset to Azvudine administration, more than 2 doses vaccine, viral load 7-10 (log_{10} (copies/mL)) within 3 days after admission. No significant difference was found in the recovery time between ST and STA groups, (12.12±2.83 vs 13.31±2.85, p = 0.0502), (b) Symptomatic severity in ST and STA groups after balance. There were no differences in fever, sore throat, cough and digestive symptoms between ST and STA groups (0(0,2) vs. 0(0,2), p = 0.3287 for fever),0(0,1) vs. 0(0,0), p>0.9999 for sore throat, 2(0,4) vs. 2(0,6), p = 0.7463 for cough) and (0(0,0) vs. 0(0,0), p>0.9999 for digestive symptoms). The symptomatic severity was presented as median (25 percentile, 75 percentile), (c) There was no statistically significant difference in the changes in viral load between pre- and post-oral Azvudine administration between the two groups (2.35±1.92 vs. 2.57±2.06, p = 0.6195) and (d) Total viral load or AUC of ST and STA groups after the balance of partial variables. No significant difference was found between ST and STA groups, (46.27± 13.25 vs.50.04 ± 17.91, p = 0.2829). n = 33 in ST group, n = 72 in STA group

Table S9: Comparison of the recovery time between ST and STA groups

	ST	STA	p-value
Total population	12.26±3.40 (n = 249*)	13.22±3.01 (n = 206)	0.0016
Age matched (16-78 years)	12.62±3.46 (n = 144)	13.22±3.01 (n = 206)	0.0827
Complete data available matched	12.65±3.50 (n = 79)	13.50±2.89 (n = 140)	0.0529
Partial factors matched	12.12± 2.83 (n = 33)	13.31±2.85 (n = 72)	0.0502
1:1 matched	12.12±2.83 (n = 33)	12.21± 2.83 (n = 33)	0.8966

*Two patients died during hospitalization in ST group in total population