Journal of Clinical Pharmacology and Therapeutics

ISSN: 2766-8347

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

Objective: To evaluate the efficacy and safety of Azvudine in treatment of the patients infected with COVID-19 Omicron variants.

Methods: This study included the discharged patients after COVID-19 infection from October 17 to November 17 in 2022 in Zhengzhou Central Hospital. The patients were divided into two groups, 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 had no correlation with oral Azvudine (Beta=1.920, p=0.056) in a low-fit multiple linear regression with the data-available patients (R2=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 lower total viral load than ST group after the final matching (28.03 ± 4.72 *vs.* 25.53 ± 5.32, n=33, P=0.048). Seventeen 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.

Keywords: Azvudine; COVID-19; Efficacy; Symptomatic treatment; Infection

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. Bin et al. [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

Citation: Jin X, Chu Q, Wang J, Zhang C, Bing H, Sun L, et al. Effects of Azvudine on the Low-Risk Patients Infected with COVID-19 Omicron Variants: A Retrospective Case-Control Study. J Clin Pharmacol Ther. 2024;5(1):1049.

Publisher Name: Medtext Publications LLC

Manuscript compiled: Feb 12th, 2024

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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.

Methods

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. It was approved by the Ethic Committee of Zhengzhou Central Hospital affiliated to Zhengzhou University with reference number 202301. The patients who were discharged from October 17 to December 17, 2022 were collected for this study. The inclusion criteria for this study was 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 (Figure 1): the Symptomatic Treatment group (ST) and the symptomatic treatment in combination with oral Azvudine group (STA, oral Azvudine tablets 5 mg daily). An oral informed consent was obtained from the patients who took Azvudine in this study.

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. 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 hours. After discharge all patients are followed up by telephone within 1 month for further Covid-19 recovery, Covid-19 reinfection and satisfaction for hospitalization (Figure 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.

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. 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. Symptomatic severity increased by 1 score if any kind of non-specific treatment or Chinese herb was prescribed. 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. 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 two hours of collection. The ORF1ab and *N genes* of COVID-19 were targeted for amplification,

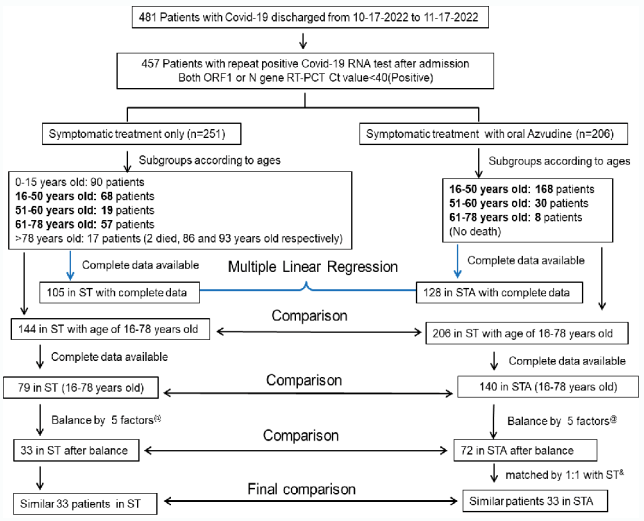

Figure 1: Flow chart of the patients included in this study. @ The five variables included age of 16-65 years old, ≤ 3 days from symptoms onset to admission, ≤ 3 days from symptoms onset to Azvudine administration [13], 2-3 doses vaccine, viral load 7-10 (log_{10}(Copies/ml)) within 3 days after admission. & The patents were matched by age (change within 3 years old), BIM (change within 2 kg/m^2), monocyte count (>1.5 × 10^9), and viral load (change within 3 (Log_{10} (Copies/ml)) after admission.

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

Characteristics and outcomes	ST (n=144)	STA (n=206)	*P*	Total (n=350)
Age (yrs)	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 doses	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)	0.826	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	(n=54) 1.87 ± 0.34	(n=102) 1.65 ± 0.50	0.0038**	(n=156)1.72 ± 0.462
3-5	(n=60) 3.37 ± 0.78	(n=84) 3.61 ± 0.712	0.0569	(n=144) 3.51 ± 0.75
>5	(n=30) 8.97 ± 4.33	(n=20) 7.75 ± 2.88	0.2762	(n=50) 8.48 ± 3.84
Viral load within 3 days (Log10(Copies/ml))	7.37 ± 2.00	8.31 ± 2.57	0.0003**	7.92 ± 2.39
Anti-Covid-19 lgG (S/CO)				
Available[Δ]	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 lgM(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
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	0.876	96.31 ± 7.69

Note: [Δ]median (25percentile, 75percentile), *P<0.05, **P<0.01. NA, not applicable

with a detection limit of Cycle Threshold (Ct) set to 40 (200 copies/ml). A Ct of ≥ 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). Ct ≥ 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 (Figure 2B and 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 ± 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 regressions were performed to assess the association between recovery time and clinical relevant factors. Categorical data was analyzed using Chi-Square (X^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. Twenty Four 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. 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-year-old female patient with senile dementia and myocardial ischemia who died of pneumonia, and a 93-year-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, only clinic relevant or a significant univariate relationship with the recovery time 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). 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 balanced from 16 to 78 years old (Figure 1 and Table 1). Secondly, only those with data-available were chosen from both groups. Thirdly, recovery-related variables were balanced according to reported clinic relevant variables (Figure 1) [13,18-22]. Lastly, the number of patients in each group was equalized (Figure 1 and Table 2) [23]. After these processes were completed no differences in recovery time between the two groups were found except for in total population size. 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) (Figure 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 (Figure 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 (Figure 2C and 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 (78.7%) of the adverse effects reported were digestive in nature, such as diarrhea, nausea, vomiting and constipation (Figure 2E). However, Omicron infection can also cause similar digestive symptoms and this study found no difference in severity between the

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

Age (yrs)	32.03 ± 13.48	32.67 ± 12.54	0.8432	32.35 ± 12.92
Sex (M/F)	13/20	23-Oct	0.6059	23/43
BMI(kg/m²)	22.85 ± 4.15	22.17 ± 3.45	0.473	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%)		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)^{D}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 (10⁹/L)	3.48 ± 2.31	2.93 ± 1.43	0.2574	3.20 ± 1.9
Lymphocytes (10⁹/L)	1.39 ± 0.50	1.34 ± 0.61	0.7198	1.36 ± 0.55
Monocytes (10⁹/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%))	0.367	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

Note:$^{\Delta}$median (25percentile, 75percentile), *P<0.05, **P<0.01. NA, not applicable

ST and STA groups (Figure 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 (Figure 2 F). 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 (Figure 2 G).

Discussion

This study evaluated the efficacy and safety of Azvudine in clinical treatment of Covid-19 in China since August 9, 2022. The 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 have an effect on 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, we estimated our sample size 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, Zalpha=1.96, power=80%, Zbeta=0.84, expected SD=3days, accepted effect size=3 days [24]. Therefore, the sample size

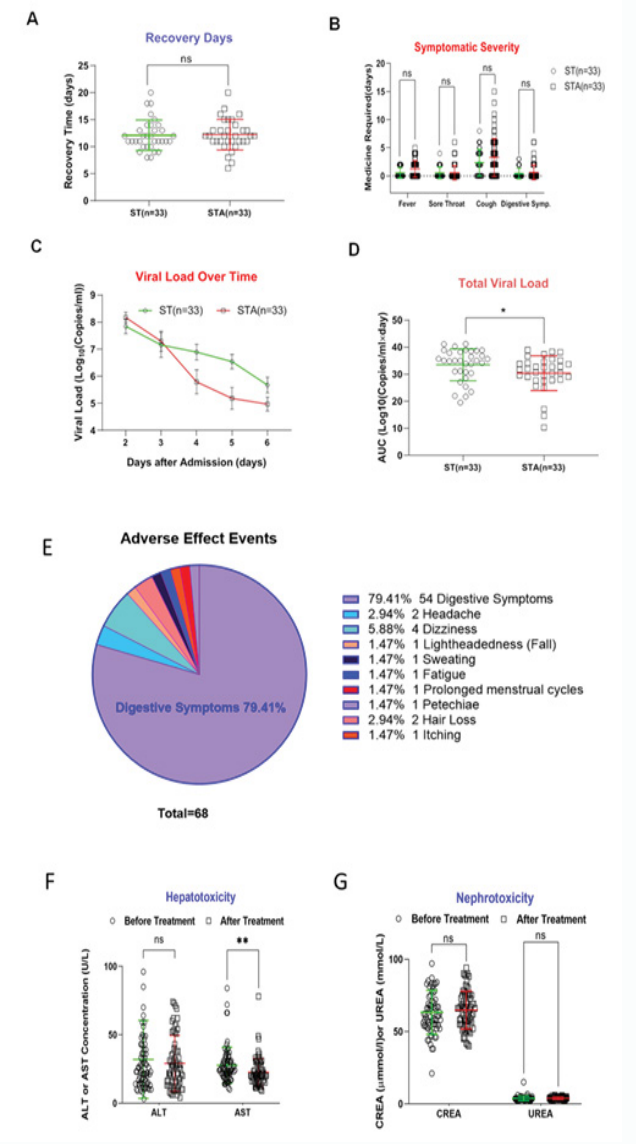

Figure 2: The recovery time, total viral load and symptomatic severity in ST and STA groups after sample size matched by 1:1 and Assessment of Azvudine-related adverse effects. (A). the recovery time of ST and STA groups after the patients number were matched by the ratio of 1:1. No significant difference was found between ST and STA groups (12.12 ± 2.83 *vs.* 12.21 ± 2.83, p=0.8966). (B). the symptomatic severities in ST and STA groups after the 1:1 match. 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=0.1717 for fever), ((0(0, 1) *vs.* 0(0,4), p=0.9902) for sore throat), ((2(0,4) *vs.* 2(0,6), p=0.8432) 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). The 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=0.0748). (D). The total viral load or AUC (area under curve) of ST and STA groups after the 1:1 match. A significant difference was found between ST and STA groups (28.03 ± 4.722 vs. 25.53 ± 5.324, p=0.0482). (E). Parts of Whole about the Patients-reported Azvudine-related adverse effects. (F). Serum concentration of ALT and AST before and after oral Azvudine. The 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=0.4787 and p=0.0090 respectively). (G). Serum concentration of Creatinine and Urea before and after oral Azvudine. 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).

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 [25]. 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 [26]. 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 [27]. Additionally, this study may not have had the capacity to detect the efficacy of Azvudine using recovery time 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.

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Table 3: A total of 47 from 206 Patients with oral Azvudine reported Azvudine-related Adverse Effect Events.

Adverse Effects	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

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