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CLINICAL TRIALS

Azvudine reduces the in-hospital mortality of COVID-19 patients: A retrospective cohort study

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KEY WORDS

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Abstract In our retrospective cohort study, we aim to explore whether Azvudine modifies the risk of death in COVID-19 patients. It was conducted on the medical records of patients, consecutively admitted for COVID-19 pneumonia to two hospitals in Chongqing, China. Based on Azvudine treatment exposure, the patients were divided into Azvudine group and non-Azvudine group. We used 1:2 ratio propensity score matching (PSM) in our study to adjust for confounding factors and differences between Azvudine and non-Azvudine groups. There were 1072 patients included in our original cohort. With 1:2 ratio PSM, the Azvudine group included 195 patients and non-Azvudine group included 390 patients. The results showed that Azvudine treatment was associated with improved in-hospital mortality in overall population (OR 0.375, 95% CI 0.225–0.623, $P < 0.001$), severe subgroup (OR 0.239, 95% CI 0.107–0.535, $P = 0.001$), critical subgroup (OR 0.091, 95% CI 0.011–0.769, $P = 0.028$) in matched cohort with univariate analysis. And there was a significantly lower in-hospital mortality in overall population (11% *vs.* 24%, $P < 0.001$), severe sub-group (10% *vs.* 32%, $P < 0.001$) and critical sub-group (5% *vs.* 34%, $P = 0.017$) in matched cohort. These results suggest Azvudine can reduce in-hospital mortality in overall COVID-19 patients, severe, and critical subgroup population.

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1. Introduction

As an emerging infectious disease, the COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1]. As of Feb 19, 2023, there were more than 757 million cases have been confirmed. And it has resulted more than 6 million deaths[2]. In recent years, to reduce the death of COVID-19 patients, human beings have tried their best to explore potential antiviral therapy of treating SARS-CoV-2 infections[3]. Azvudine was granted conditional authorization by the National Medical Products Administration to be used to treat COVID-19 on July 25, 2022. It was the first domestic oral antiviral agent which was approved in China. Azvudine is an RNA-dependent RNA polymerase (RdRp) inhibitor, which has potential value against SARS-CoV-2[4]. Since December 2022, Chongqing faced COVID-19 outbreak. The virus epidemic has posed unprecedented challenges to public health. Many patients with COVID-19 pneumonia required admission to hospital, and various treatments need to be adopted. some patients recovered and discharged from hospital, but there were still some non-survival patients. In this study, we collected information of patients admitted to hospital with COVID-19 pneumonia. We aimed to estimate whether Azvudine reduces the in-hospital mortality of the COVID-19 patients.

2. Methods

2.1. Patients and methods

Our retrospective cohort study was conducted on the medical records of 1320 patients, consecutively admitted for COVID-19 pneumonia to two Hospitals of Chongqing, China, from Dec 8, 2022 to Jan 20, 2023. For each patient, data including gender, age, clinical history (*e.g.*, comorbidities), complete blood cell count, C reactive protein (CRP), procalcitonin (PCT), D-dimer, imaging data, oxygenation index, and treatments were collected. Inclusion criteria: a) all the patients with a confirmed diagnosis of COVID-19 pneumonia were diagnosed by a positive SARS-CoV-2 Real Time-Polymerase Chain Reaction (RT-PCR) or positive SARS-CoV-2 antigen detection, or both, b) CT imaging findings met the standard of viral pneumonia. Exclusion criteria: a) age <18 years, b) other antiviral drugs (*e.g.*, Paxlovid) were used in addition to Azvudine. Some patients received Azvudine treatment after admitted to hospital and received other treatments following with doctors' judgement such as systemic corticosteroids, budesonide, supplemental oxygen, non-invasive mechanical ventilation (NIV), and invasive mechanical ventilation (IMV). At present, patients with COVID-19 were classified into four grades (mild, moderate, severe and critical) by "Diagnosis and Treatment Program for Novel Coronavirus Pneumonia (tenth Edition)" which published by the National Health Commission and National Administration of Traditional Chinese Medicine[5]. When we estimated the association between using Azvudine and in-hospital mortality of COVID-19 patients in overall and subgroups, these patients recruited into our study were divided into moderate, severe and critical sub-groups according to the above standard. The study was approved by the Research Ethics Commission of the Second Affiliated Hospital of Chongqing Medical University.

2.2. Statistical analysis

The statistical analysis was performed with SPSS 26.0, the R package (version 4.2.2), and PSM plug-ins (version 3.0.4). For the parameters with a Gaussian distribution, Data were expressed as means±standard deviations (SD). It was considered statistically significant if P-values <0.05. To estimate the association between risk factors and in-hospital mortality, we used multivariable adjusted logistic regression models to analysis odds ratio (OR) and 95% confidence interval (95% CI). We used 1:2 ratio propensity score matching (PSM) in our study to adjust for confounding factors and differences between Azvudine and non-Azvudine groups.

3. Results

A total of 1320 patients with a diagnosis of COVID-19 pneumonia were evaluated. But following the exclusion criteria, only 1072 cases were included in our original cohort, and after PSM, matched cohort were divided into two groups: Azvudine group (195 cases) and non-Azvudine group (390 cases, Fig. 1).

The demographic and clinical characteristics of original cohort and matched cohort are shown in Table 1. In the original cohort, the mean age of the subjects in non-Azvudine group was higher than that in the Azvudine group (mean in years 71.5 *vs.* 66.7, $P = 0.005$). The frequency of systemic corticosteroids (53% *vs.* 33%, $P < 0.001$) was a significantly higher in the Azvudine group than non-Azvudine group, while the frequency of supplemental oxygen (55% *vs.* 65%, $P < 0.001$) was a significantly lower. After PSM, there were no significant differences in the mean age, gender, frequency of with diabetes, cardiovascular diseases, chronic pulmonary disease, chronic kidney disease, chronic liver disease, and the frequency of systemic corticosteroids and supplemental oxygen using between the two groups. More, in the matched cohort, there were no significant differences of the subgroup ratios in patients with Azvudine group and non-Azvudine group.

Our primary outcomes were the association of Azvudine treatment and in-hospital mortality. We analyzed it in overall and subgroups using logistic regression models (Table 2), The results showed that Azvudine treatment was associated with improved mortality in overall population in original cohort (OR 0.520, 95% CI 0.321−0.843, $P = 0.008$) and in matched cohort (OR 0.375, 95% CI 0.225−0.623, $P < 0.001$) with univariate analysis. These results were analogous in severe and critical subgroup in original cohort (OR 0.325, 95% CI 0.149−0.706, $P = 0.005$; OR 0.095, 95% CI 0.012−0.753, $P = 0.026$) and in matched cohort (OR 0.239, 95% CI 0.107−0.535, $P = 0.001$; OR 0.091, 95% CI 0.011−0.769, $P = 0.028$) with univariate analysis. However, Azvudine was not associated with improved mortality in moderate subgroup patients both in original cohort (OR 0.989, 95% CI 0.512−1.911, $P = 0.974$) and in matched cohort (OR 0.711, 95% CI 0.351−1.441, $P = 0.344$).

With multivariate analysis (Table 3), the results showed that Azvudine treatment was associated with improved mortality in overall population (OR 0.543, 95% CI 0.297−0.991, $P = 0.047$) and severe subgroup (OR 0.286, 95% CI 0.110−0.745, $P = 0.010$) in original cohort. In matched cohort, the results also showed that Azvudine treatment was associated with improved mortality in overall population (OR 0.210, 95% CI 0.108−0.408, $P < 0.001$), moderate subgroup (OR 0.294, 95% CI 0.112−0.774, $P = 0.013$) and severe subgroup (OR 0.130, 95% CI 0.044−0.381, $P < 0.001$).

Then we analyzed how much can Azvudine reduce the in-hospital mortality in COVID 19 patients in overall population and

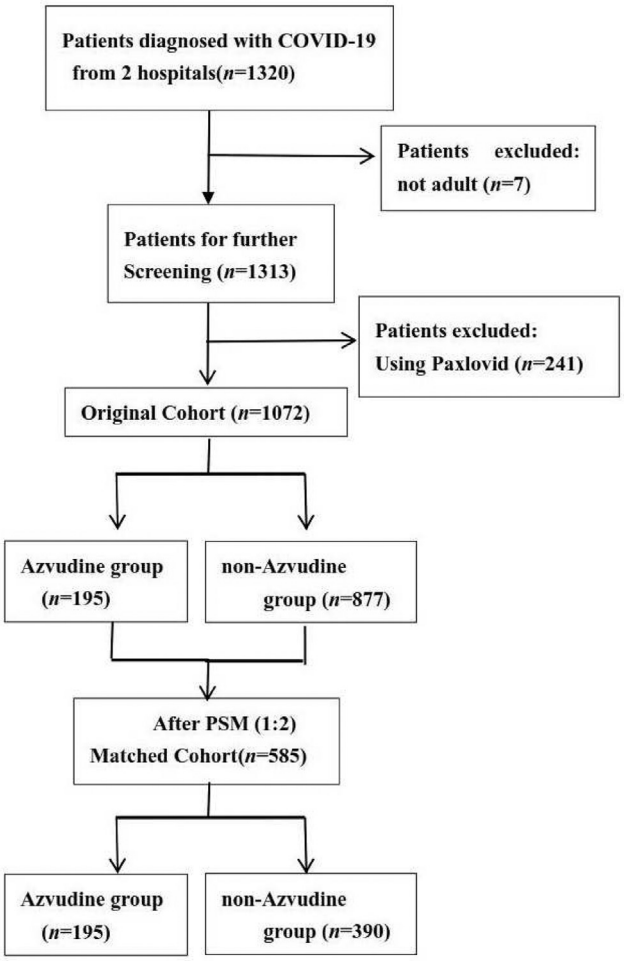

Figure 1 Flowchart of COVID-19 patient selection.

different clinical types (Fig. 2). Respectively, 8% and 13% lower in-hospital mortality were observed in Azvudine-treated patients in overall population in original cohort (11% *vs.* 19%, $P = 0.006$) and in matched cohort (11% *vs.* 24%, $P < 0.001$). While there was a significantly lower in-hospital mortality in critical sub-group (5% *vs.* 33%, $P = 0.006$) and severe sub-group (10% *vs.* 26%, $P = 0.002$) in original cohort. And in matched cohort, there was also a significantly lower in-hospital mortality similarly in critical sub-group (5% *vs.* 34%, $P = 0.017$) and severe sub-group (10% *vs.* 32%, $P < 0.001$). However, the results showed no significantly lower in-hospital mortality in moderate subgroup both in original cohort (13% *vs.* 13%, $P = 1.000$) and matched cohort (13% *vs.* 17%, $P = 0.395$).

In our study, in order to analyze the factors which may affected the effect of Azvudine, we conducted subgroup analysis on multiple factors in matched cohort (Table 4). The results showed that using Azvudine was associated with a significantly reduced risk of in-hospital mortality compared with no Azvudine treatment in the COVID-19 patients among the age older than 65 years (OR 0.305, 95% CI 0.172−0.539, $P < 0.001$), without diabetes (OR 0.277, 95% CI 0.137−0.560, $P < 0.001$), without chronic pulmonary disease (OR 0.390, 95% CI 0.224−0.677, $P = 0.001$), without chronic liver disease (OR 0.370, 95% CI 0.220−0.624, $P < 0.001$), with Cardiovascular diseases (OR 0.225, 95% CI 0.110−0.460, $P < 0.001$), without budesonide (OR 0.211, 95% CI 0.109−0.411, $P < 0.001$), and without IMV (OR 0.210, 95% CI 0.108−0.408, $P < 0.001$). And there was a significantly lower in-hospital mortality of the COVID-19 patients with Azvudine treatment than those without Azvudine treatment no mater they were male or female, with chronic kidney disease or not, or receiving systemic corticosteroids, supplemental oxygen and NIV or not.

4. Discussion

SARS-CoV-2 represents a rigorous challenge for health care systems throughout the world. It is a great difficult to accurately evaluate the severity of patients, and it is also a great difficult to provide effective and specific therapies to treat COVID-19[6,7]. As doctors, our aim is to provide high-quality care for the patients, and to reduce the mortality and accelerate recovery for patients. Recently, Sun et al.[8] pointed out in their study, Azvudine treatment was associated with significantly lower risks of composite disease progression outcome, but did not find a significant difference in all-cause death. Another study compared the antiviral effect of nirmatrelvir-ritonavir and azvudine[9].

In our retrospective cohort study, the association between Azvudine and in-hospital mortality of COVID-19 patients was comprehensively analyzed. Using logistic regression models, Azvudine treatment was associated with improved in-hospital mortality in overall population, severe and critical subgroup population both in original cohort and matched cohort. We found that using Azvudine can reduce the in-hospital mortality of overall COVID-19 patients from 19% to 11% in original cohort and from 24% to 11% in matched cohort. There was also a significantly reduced risk of in-hospital mortality in severe subgroup and critical subgroup before or after PSM. But Azvudine was not associated with improved mortality in moderate subgroup patients both in original cohort and matched cohort. We considered the reason for Azvudine did not significantly reduce the in-hospital mortality of moderate subgroup patients maybe was the in-hospital mortality of this subgroup itself was not high even without Azvudine treatment. It was difficult to achieve a significantly reduced risk of in-hospital mortality with Azvudine treatment. Another study about Azvudine-treated patients with mild or common COVID-19 infection showed this drug may shorten the nucleic acid negative conversion time[10]. The population and outcomes of this study were different from those of our study, but they can prove the effect of Azvudine better and more comprehensively together. Our study explores the effect of Azvudine on the in-hospital mortality in clinical real-world, and confirm the effects of Azvudine in Omicron infection.

Furthermore, we analyzed the association of using Azvudine and in-hospital mortality of COVID-19 patients in overall and subgroups with multivariable adjusted logistic regression models. We found that Azvudine treatment was associated with improved in-hospital mortality in overall (OR 0.210, $P < 0.001$), moderate subgroup (OR 0.294, $P = 0.013$) and severe subgroup population (OR 0.130, $P < 0.001$) in matched cohort, but not in critical subgroup population (OR 0.178, $P = 0.192$). These results may suggest that there are other factors that significantly affect the efficacy of Azvudine in the critical subgroup. Dian et al.[11] reported in their retrospective cohort study that Azvudine was associated with a significantly reduced risk of composite disease progression outcome. Deng et al.[12] also found Azvudine treatment showed effectiveness in hospitalized COVID-19 patients in terms of composite disease progression outcome by comparing with nirmatrelvir-ritonavir. They also believed that the effect of

Table 1 The demographic and clinical characteristics of COVID-19 patients with Azvudine treatment or not before and after PSM.

Character	Original cohort			Matched cohort		
	Azvudine (n = 195)	non-Azvudine (n = 877)	P value	Azvudine (n = 195)	Non-Azvudine (n = 390)	P value
Age, years (mean ± SD)	66.7 ± 16.1	71.5 ± 14.5	$\mathbf{P = 0.005}$	67.8 ± 16.0	68.2 ± 16.6	$P = 0.737$
Gender, male	104 (53%)	528 (60%)	$P = 0.091$	104 (53%)	225 (58%)	$P = 0.332$
Diabetes	45 (23%)	242 (28%)	$P = 0.211$	45 (23%)	102 (26%)	$P = 0.479$
Cardiovascular diseases	87 (45%)	382 (44%)	$P = 0.811$	87 (45%)	143 (37%)	$P = 0.073$
Chronic pulmonary disease	30 (15%)	156 (18%)	$P = 0.465$	30 (15%)	68 (17%)	$P = 0.559$
Chronic kidney disease	21 (11%)	113 (13%)	$P = 0.474$	21 (11%)	49 (13%)	$P = 0.590$
Chronic liver disease	13 (7%)	48 (6%)	$P = 0.496$	13 (7%)	22 (6%)	$P = 0.712$
Clinical types						
Moderate subgroup	94 (48%)	512 (58%)	$\mathbf{P = 0.011}$	94 (48%)	205 (53%)	$P = 0.335$
Severe subgroup	79 (41%)	296 (34%)	$P = 0.081$	79 (41%)	153 (39%)	$P = 0.788$
Critical subgroup	22 (11%)	69 (8%)	$P = 0.154$	22 (11%)	32 (8%)	$P = 0.229$
Treatments in hospital						
Systemic corticosteroids	104 (53%)	283 (33%)	$\mathbf{P < 0.001}$	104 (53%)	193 (50%)	$P = 0.430$
Budesonide	36 (19%)	198 (23%)	$P = 0.215$	36 (19%)	98 (25%)	$P = 0.076$
Supplemental oxygen	107 (55%)	566 (65%)	$\mathbf{P = 0.011}$	107 (55%)	223 (57%)	$P = 0.597$
NIV	32 (16%)	178 (20%)	$P = 0.232$	32 (16%)	62 (16%)	$P = 0.905$
IMV	9 (5%)	67 (8%)	$P = 0.165$	9 (5%)	13 (3%)	$P = 0.491$
Outcomes						
Hospital stays, days (mean ± SD)	9.4 ± 6.4	8.5 ± 5.5	$P = 0.624$	9.4 ± 6.4	8.4 ± 5.2	$P = 0.345$

PSM (propensity score matching), NIV (non-invasive mechanical ventilation), IMV (invasive mechanical ventilation).
P value in bold indicates a statistical significant difference.

Table 2 Association of Azvudine treatment and in-hospital mortality of COVID-19 patients in different clinical subgroups with univariate analysis.

In-hospital mortality	Original cohort				In-hospital mortality	Matched cohort			
	OR	Lower.95	Upper.95	P-value		OR	Lower.95	Upper.95	P-value
Overall (n = 1072)	0.520	0.321	0.843	$\mathbf{P = 0.008}$	Overall (n = 585)	0.375	0.225	0.623	$\mathbf{P < 0.001}$
Moderate subgroup (n = 606)	0.989	0.512	1.911	$P = 0.974$	Moderate subgroup (n = 299)	0.711	0.351	1.441	$P = 0.344$
Severe subgroup (n = 376)	0.325	0.149	0.706	$\mathbf{P = 0.005}$	Severe subgroup (n = 232)	0.239	0.107	0.535	$\mathbf{P = 0.001}$
Critical subgroup (n = 91)	0.095	0.012	0.753	$\mathbf{P = 0.026}$	Critical subgroup (n = 54)	0.091	0.011	0.769	$\mathbf{P = 0.028}$

OR (odds ratio).
P value in bold indicates a statistical significant difference.

Azvudine was more obvious in some certain people. This is consistent with our study.

Finally, we conducted subgroup analysis on multiple factors in matched cohort, in order to analyze the factors which may affected the effect of Azvudine. We found that Azvudine treatment reduced the risk of in-hospital mortality among these certain COVID-19 patients, such as the age older than 65 years, without diabetes, chronic pulmonary disease and chronic liver disease, without budesonide and IMV treatment, with cardiovascular diseases. Whether the COVID-19 patients were male or female, with chronic kidney disease or not, and received systemic corticosteroids, supplemental oxygen and NIV, there was a significantly lower in-hospital mortality with Azvudine treatment than those without Azvudine treatment.

Table 3 Association of Azvudine treatment and in-hospital mortality of COVID-19 patients in different clinical subgroups with multivariate analysis.

In-hospital mortality	Original cohort				In-hospital mortality	Matched cohort			
	OR	Lower.95	Upper.95	P-value		OR	Lower.95	Upper.95	P-value
Overall (n = 1072)	0.543	0.297	0.991	$\mathbf{P = 0.047}$	Overall (n = 585)	0.210	0.108	0.408	$\mathbf{P < 0.001}$
Moderate subgroup (n = 606)	0.961	0.418	2.212	$P = 0.962$	Moderate subgroup (n = 299)	0.294	0.112	0.774	$\mathbf{P = 0.013}$
Severe subgroup (n = 376)	0.286	0.110	0.745	$\mathbf{P = 0.010}$	Severe subgroup (n = 232)	0.130	0.044	0.381	$\mathbf{P < 0.001}$
Critical subgroup (n = 91)	0.291	0.007	11.794	$P = 0.514$	Critical subgroup (n = 54)	0.178	0.013	2.377	$P = 0.192$

OR (odds ratio). Variables in logistic regression model: Azvudine, systemic corticosteroids, budesonide, supplemental oxygen, NIV, IMV, age, gender, diabetes, cardiovascular diseases, chronic pulmonary disease, chronic kidney disease, chronic liver disease.
P value in bold indicates a statistical significant difference.

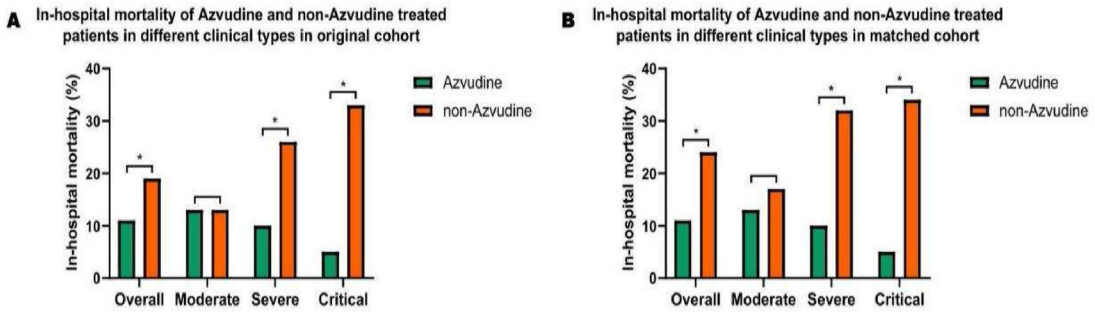

Figure 2 The rate of in-hospital mortality between Azvudine and non-Azvudine groups (*$P < 0.05$). (A) The in-hospital mortarlity of Azvudine and non-Azvudine treated patiens in different clinical types in original cohort. (B) The in-hospital mortality of Azvudin and non-Azvudine treated patients in different clincal types in matched cohort.

From age aspect, Dian et al.[11] pointed out that their results support the use of Azvudine in those under 65 years of age according to compare with paxlovid. This is different from our study. More researches have been needed to confirm it.

Previous research found that independent risk factors associated with higher mortality included high fraction of inspired oxygen (FiO_2)[13,14], and high positive end-expiratory pressure[15,16] in COVID-19 patients. Chang et al.[17] considered that the major correlation with ICU mortality was IMV in a systematic review and meta-analysis. From our study, the effect of Azvudine was even more obvious in patients without IMV treatment. This suggests that IMV treatment may affect the therapeutic effect of Azvudine.

About NIV, some studies did not affirm HFNC and NIV increased or decreased the risk of death[18,19]. Meanwhile, Nair et al.[18] pointed out that using NIV to the patient of COVID-19 pneumonia should carefully monitor to avoid delaying in endotracheal intubation. But other study pointed out that the use of NIV had proven helpful when the global pandemic of COVID-19[20,21]. Our study has been proved that the effect of Azvudine on reduction of in-hospital mortality will not be significantly affected by using NIV, supplemental oxygen and systemic corticosteroids or not in COVID-19 pneumonia patients.

Anyway, this study has several limitations. First, it is a retrospective study based on data mainly collected from medical records for clinical purposes. This was a real-life database. We could not assess the effect of other important variables. Second, the severity of the comorbidities could not be evaluated carefully because of no enough information in medical records. So that we couldn't get rid of their impact on mortality of patients with COVID-19 pneumonia. Third, we mainly concerned about the impact of Azvudine on mortality, while had not strictly ruled out the role of antibiotics and traditional Chinese medicine. Moreover,

Table 4 Association of Azvudine treatment and in-hospital mortality of COVID-19 patients with each subgroup analysis.

In-hospital mortality	Matched cohort			
	OR	Lower.95	Upper.95	*P*-value
Older than 65 years	0.305	0.172	0.539	**$P < 0.001$**
Under 65 years	0.608	0.163	2.274	$P = 0.460$
Male	0.406	0.219	0.753	**$P = 0.004$**
Female	0.331	0.132	0.831	**$P = 0.018$**
With diabetes	0.593	0.269	1.309	$P = 0.196$
Without diabetes	0.277	0.137	0.560	**$P < 0.001$**
With cardiovascular diseases	0.225	0.110	0.460	**$P < 0.001$**
Without cardiovascular diseases	0.544	0.261	1.135	$P = 0.105$
With chronic pulmonary disease	0.309	0.083	1.143	$P = 0.078$
Without chronic pulmonary disease	0.390	0.224	0.677	**$P = 0.001$**
With chronic kidney disease	0.140	0.029	0.670	**$P = 0.014$**
Without chronic kidney disease	0.442	0.257	0.760	**$P = 0.003$**
With chronic liver disease	0.528	0.049	5.678	$P = 0.598$
Without chronic liver disease	0.370	0.220	0.624	**$P < 0.001$**
Treatments received in hospital				
With systemic corticosteroids	0.253	0.103	0.618	**$P = 0.003$**
Without systemic corticosteroids	0.457	0.243	0.860	**$P = 0.015$**
With budesonide	1.599	0.660	3.874	$P = 0.298$
Without budesonide	0.211	0.109	0.411	**$P < 0.001$**
With supplemental oxygen	0.435	0.246	0.768	**$P = 0.004$**
Without supplemental oxygen	0.162	0.037	0.706	**$P = 0.015$**
With NIV	0.160	0.062	0.412	**$P < 0.001$**
Without NIV	0.432	0.223	0.835	**$P = 0.013$**
With IMV	0.800	0.131	4.874	$P = 0.809$
Without IMV	0.301	0.169	0.538	**$P < 0.001$**

P value in bold indicates a statistical significant difference.

the patients in our study were all admitted to hospital and suffered from COVID-19 pneumonia, but a large number of mild subgroup patients were excluded, which made this study unable to evaluate the efficacy of Azvudine in mild patients. Although this study has several limitations, it still provides good evidence for accurate estimation the role of Azvudine in patients with COVID-19 pneumonia.

In conclusion, in this study, we find that Azvudine can reduce the in-hospital mortality of overall COVID-19 patients, severe and critical subgroup population. This effect is even more obvious in patients with the age older than 65 years, without diabetes, chronic pulmonary disease and chronic liver disease, with cardiovascular diseases, and not receiving IMV treatment. There were no differences of Azvudine treatment in reducing in-hospital mortality among the patients with different gender, with or without chronic kidney disease, receiving systemic corticosteroids, supplemental oxygen and NIV or not. This found distinguishes the beneficial group, and could be the evidence to guide the treatment of COVID-19 with Azvudine.

Ethic statement

The study was approved by the Ethics Commission of the Second Affiliated Hospital of Chongqing Medical University, and written informed consent was not required for this retrospective study.

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Author contributions

Kaican Zong and Shiying Li conceived and designed the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors collected the data and had full access to all of the data in the study. All authors critically revised the manuscript for important intellectual content and gave final approval for the version to be published.

Conflicts of interest

The authors have declared no conflict of interest.

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