Is Azvudine Comparable to Nirmatrelvir-Ritonavir in Real-World Efficacy and Safety for Hospitalized COVID-19 Patients? A Retrospective Cohort Study

Qinqin Zhao[1#]· Bei Zheng[1#]· Bing Han[1]· Pinpin Feng[1]· Zhongni Xia[1]· Hong Jiang[1]· Yin Ying[1]· Jun Zhu[1]· Cheng Fei[2]· Junlei Xiang[3]· Lingli Shen[4]· Qiliang Luo[5]· Yinhuan Wu[6]· Ayiguzhali Wusiman[7]· Chuanwei Xin[1*]· Meiling Zhang[1*]· Gonghua Li[1*]· Xiang Li[8*]

[1]Department of Pharmacy, Tongde Hospital of Zhejiang Province, Hangzhou, 310012, China.

[2]Department of Pharmacy, The 72nd Group Army Hospital of PLA, Huzhou, 313000, China.

[3]Department of Pharmacy, Longquan People's Hospital, Longquan, 323700, China.

[4]Department of Pharmacy, Linping Hospital of Integrated Traditional Chinese and Western Medicine, Hangzhou, 311100, China.

[5]Department of Pharmacy, Zhaotong Mental Health Center, Zhaotong, 657000, China.

[6]Department of Pharmacy, Ruian Fifth People's Hospital, Ruian, 325200, China.

[7]Department of Pharmacy, Fourth People's Hospital of Aksu Region, Aksu, 843000, China.

[8]School of Basic Medical Sciences & Forensic Medicine, Hangzhou Medical College, Hangzhou, 311399, China.

#Equal contribution.

*Corresponding Author:

Chuanwei Xin, xcw373@163.com; Meiling Zhang, zml9998@163.com; Gonghua Li, ligonghua88@163.com. Department of Pharmacy, Tongde Hospital of Zhejiang Province, No. 234 Gucui Road, Xihu District, Hangzhou City, Zhejiang Province, 310012, China;

Xiang Li, leexiang@zju.edu.cn. School of Basic Medical Sciences and Forensic Medicine, Hangzhou Medical College, No. 8 Yikang Street, Lin'an District, Hangzhou City, Zhejiang Province, 311399, China.

Supplementary information

Table of Contents

Table S1 Severity of COVID-19 disease in accordance with the Chinese diagnosis and treatment protocol for COVID-19 infection (Version 10) 3
Table S2 Univariate and multivariate Cox regression analyses of all-cause 28-day mortality for the main cohort..... 4
Table S3 Univariate and multivariate Cox regression analyses of risk of 28-day progressing to critical condition for the main cohort 5
Table S4 Univariate and multivariate Cox regression analyses of proportion of 28-day nucleic acid negative conversion for main cohort 6
Table S5 Univariate and multivariate linear regression analyses of the first nucleic acid negative conversion time for the main cohort..... 7
Table S6 Univariate and multivariate linear regression analyses of the hospital length of stay for the main cohort study..... 8
Table S7 Baseline characteristics of study participants of the complete dataset with missing values removing according to oral antivirals (n=387) 9
Table S8 Associations between antivirals use and the efficacy outcomes in regression analysis for complete cohort (n=387) 10
Fig. S1 Forest plot for subgroup analyses of the efficacy of azvudine versus nirmatrelvir-ritonavir on all-cause 28-day mortality in patients with COVID-19 for main cohort 11
Fig. S2 Forest plot for subgroup analyses of the efficacy of azvudine versus nirmatrelvir-ritonavir on risk of progressing to critical condition within 28 days in patients with COVID-19 for main cohort..... 12
Fig. S3 Forest plot for subgroup analyses of the efficacy of azvudine versus nirmatrelvir-ritonavir on proportion of 28-day negative conversion of nucleic acid in patients with COVID-19 infection for main cohort 13
Fig. S4 Forest plot for subgroup analyses of the efficacy of azvudine versus nirmatrelvir-ritonavir on the first nucleic acid negative conversion time in patients with COVID-19 infection for main cohort 14
Fig. S5 Forest plot for subgroup analyses of the efficacy of azvudine versus nirmatrelvir-ritonavir on the hospital length of stay in patients with COVID-19 for main cohort..... 15

Table S1 Severity of COVID-19 disease in accordance with the Chinese diagnosis and treatment protocol for COVID-19 infection (Version 10)

Severity of COVID-19	Characteristics
Mild type	individuals who exhibit various symptoms of the disease, but do not experience shortness of breath, dyspnea or abnormal chest imaging
Moderate type	individuals exhibiting persistent high fever lasting more than three days, shortness of breath accompanied by a respiratory rate below 30 breaths/min, resting oxygen saturation levels measured by pulse oximetry above 93%, or chest imaging revealing the characteristic manifestations of COVID-19 pneumonia
Severe type	individuals exhibiting respiratory distress, with a respiratory rate of ⩾30 breaths/min, resting finger oxygen saturation ⩽93%, arterial partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FiO2) ⩽300 mm Hg, or imaging indicating lesion progression >50% within 24-48 hours
Critical type	individuals who experience respiratory failure requiring mechanical ventilation, develop shock, or suffer from multiple organ failures necessitating treatment in the intensive care unit (ICU)

Table S2 Univariate and multivariate Cox regression analyses of all-cause 28-day mortality for the main cohort

Factor	Crude		Model 1[a]		Model 2[b]		Model 3[c]	
	HR 95%CI	P value	HR 95%CI	P value	HR 95%CI	P value	HR 95%CI	P value
Antiviral								
Nirmatrelvir-ritonavir	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Azvudine	1.03 (0.45~2.35)	0.943	1.26 (0.54~2.96)	0.590	1.21 (0.51~2.87)	0.659	1.41 (0.56~3.56)	0.471
Age, Mean ± SD, yr	1.04 (1.00~1.09)	0.038	1.05 (1.00~1.09)	0.030	1.05 (1.01~1.09)	0.023	1.06 (1.01~1.11)	0.013
Sex, n (%)								
Male	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Female	0.53 (0.21~1.34)	0.180	0.91 (0.34~2.42)	0.853	0.84 (0.32~2.20)	0.717	0.80 (0.29~2.21)	0.673
BMI, Mean ± SD	1.30(1.18~1.43)	<0.001	1.26 (1.13~1.41)	<0.001	1.28 (1.14~1.43)	<0.001	1.31 (1.16~1.47)	<0.001
Severity of COVID-19, n (%)								
Mild-to-moderate	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Severe	8.82 (3.91~19.87)	<0.001	5.16 (2.12~12.53)	<0.001	4.84 (2.00~11.76)	<0.001	3.63 (1.42~9.3)	0.007
Smoking, n (%)	1.84 (0.55~6.18)	0.358						
Drinking, n (%)	0.76 (0.10~5.60)	0.775						
Diabetes, n (%)	1.81 (0.79~4.15)	0.158			1.88 (0.78~4.54)	0.16	1.71 (0.69~4.25)	0.247
Cardiovascular diseases, n (%)	1.16 (0.51~2.65)	0.726			0.80(0.33~1.90)	0.611	0.68 (0.27~1.71)	0.417
Chronic lung disease, n (%)	0.99 (0.34~2.91)	0.990			1.08 (0.34~3.39)	0.894	1.16 (0.37~3.63)	0.801
Tumor and immunosuppression, n (%)	1.48 (0.63~3.46)	0.366			2.03 (0.82~5.06)	0.128	2.20 (0.88~5.51)	0.093
LTM, Median (IQR), $\times 10^9$/L	0.69 (0.30~1.58)	0.377					0.70 (0.31~1.60)	0.400
D-dimer, Median (IQR), mg/L	1.08 (1.04~1.13)	<0.001					1.04 (0.99~1.10)	0.106
CRP, Median (IQR), mg/L	1.01 (1.00~1.01)	0.008					1.00 (1.00~1.01)	0.277

Abbreviation: HR, hazard ratio; IQR, interquartile range; LTM, lymphocyte count; CRP, C-reactive protein; BMI, body mass index

[a] Model 1 was adjusted for age, sex, BMI, and severity of COVID-19; [b] Model 2 was adjusted as model 1 plus diabetes, cardiovascular diseases, chronic lung disease, and tumor and immunosuppression; [c] Model 3 was adjusted as model 2 plus LTM, D-dimer, and CRP.

Table S3 Univariate and multivariate Cox regression analyses of risk of 28-day progressing to critical condition for the main cohort

Factor	Crude		Model 1[a]		Model 2[b]		Model 3[c]	
	HR 95%CI	P value	HR 95%CI	P value	HR 95%CI	P value	HR 95%CI	P value
Antiviral								
Nirmatrelvir-ritonavir	1（ref）		1（ref）		1（ref）		1（ref）	
Azvudine	1.19 (0.59~2.42)	0.624	1.42 (0.69~2.92)	0.337	1.42 (0.69~2.94)	0.341	1.67 (0.78~3.60)	0.189
Age, Mean ± SD, yr	1.05 (1.01~1.08)	0.011	1.05 (1.01~1.09)	0.010	1.05 (1.01~1.09)	0.009	1.06 (1.02~1.11)	0.003
Sex, n (%)								
Male	1（ref）		1（ref）		1（ref）		1（ref）	
Female	0.53 (0.24~1.17)	0.117	0.83 (0.36~1.90)	0.654	0.78 (0.34~1.78)	0.548	0.73 (0.31~1.74)	0.480
BMI, Mean ± SD	1.20 (1.10~1.32)	<0.001	1.15 (1.04~1.28)	0.007	1.16 (1.04~1.29)	0.006	1.18 (1.06~1.31)	0.002
Severity of COVID-19, n (%)								
Mild-to-moderate	1（ref）		1（ref）		1（ref）		1（ref）	
Severe	8.44 (4.19~16.99)	<0.001	5.72 (2.67~12.28)	<0.001	5.41 (2.51~11.67)	<0.001	4.58 (2.05~10.24)	<0.001
Smoking, n (%)	1.36 (0.41~4.46)	0.627						
Drinking, n (%)	0.56 (0.08~4.07)	0.525						
Diabetes, n (%)	1.61 (0.77~3.33)	0.202			1.56 (0.72~3.36)	0.261	1.64 (0.75~3.62)	0.219
Cardiovascular diseases, n (%)	1.34 (0.66~2.72)	0.411			0.99 (0.47~2.11)	0.984	0.88 (0.40~1.93)	0.753
Chronic lung disease, n (%)	1.15 (0.48~2.80)	0.751			1.11 (0.43~2.84)	0.830	1.14 (0.45~2.90)	0.782
Tumor and immunosuppression, n (%)	1.57 (0.76~3.26)	0.226			2.11 (0.96~4.62)	0.062	2.21 (1.00~4.88)	0.050
LTM, Median (IQR), $\times 10^9$/L	0.54 (0.25~1.18)	0.122					0.51 (0.23~1.16)	0.110
D-dimer, Median (IQR), mg/L	1.07 (1.02~1.12)	0.002					1.03 (0.98~1.08)	0.292
CRP, Median (IQR), mg/L	1.01 (1.00~1.01)	0.017					1.01 (1.00~1.01)	0.591

Abbreviation: HR, hazard ratio; IQR, interquartile range; LTM, lymphocyte count; CRP, C-reactive protein; BMI, body mass index

[a] Model 1 was adjusted for age, sex, BMI, and severity of COVID-19; [b] Model 2 was adjusted as model 1 plus diabetes, cardiovascular diseases, chronic lung disease, and tumor and immunosuppression; [c] Model 3 was adjusted as model 2 plus LTM, D-dimer, and CRP.

Table S4 Univariate and multivariate Cox regression analyses of proportion of 28-day nucleic acid negative conversion for main cohort

Factor	Crude		Model 1[a]		Model 2[b]		Model 3[c]	
	HR 95%CI	P value	HR 95%CI	P value	HR 95%CI	P value	HR 95%CI	P value
Antiviral								
Nirmatrelvir-ritonavir	1（ref）		1（ref）		1（ref）		1（ref）	
Azvudine	0.93 (0.75~1.16)	0.516	0.93 (0.75~1.16)	0.524	0.88 (0.70~1.10)	0.252	0.87 (0.69~1.09)	0.220
Age, Mean ± SD, yr	0.99 (0.99~1.00)	0.121	0.99 (0.99~1.00)	0.127	0.99 (0.98~1.00)	0.122	0.99 (0.98~1.00)	0.238
Sex, n (%)								
Male	1（ref）		1（ref）		1（ref）		1（ref）	
Female	1.21 (0.98~1.50)	0.078	1.19 (0.96~1.48)	0.119	1.21 (0.97~1.50)	0.094	1.23 (0.99~1.54)	0.066
BMI, Mean ± SD	0.99 (0.95~1.02)	0.408	0.99 (0.96~1.03)	0.676	0.99 (0.95~1.02)	0.443	0.98 (0.95~1.02)	0.394
Severity of COVID-19, n (%)								
Mild-to-moderate	1（ref）		1（ref）		1（ref）		1（ref）	
Severe	0.76 (0.55~1.04)	0.085	0.80 (0.57~1.11)	0.174	0.83 (0.60~1.16)	0.280	0.88 (0.62~1.25)	0.489
Smoking, n (%)	0.93 (0.62~1.39)	0.712						
Drinking, n (%)	0.95 (0.60~1.51)	0.836						
Diabetes, n (%)	0.87 (0.68~1.12)	0.275			0.88 (0.68~1.14)	0.321	0.86 (0.66~1.12)	0.274
Cardiovascular diseases, n (%)	0.88 (0.70~1.10)	0.258			0.95 (0.74~1.21)	0.680	0.93 (0.73~1.19)	0.558
Chronic lung disease, n (%)	0.83 (0.63~1.11)	0.211			0.83 (0.62~1.12)	0.220	0.84 (0.63~1.13)	0.251
Tumor and immunosuppression, n (%)	0.82 (0.64~1.05)	0.122			0.72 (0.55~0.94)	0.016	0.72 (0.55~0.94)	0.017
LTM, Median (IQR), $\times 10^9$/L	1.03 (0.99~1.07)	0.177					1.03 (0.99~1.07)	0.182
D-dimer, Median (IQR), mg/L	0.97 (0.94~1.00)	0.027					0.97 (0.94~1.00)	0.050
CRP, Median (IQR), mg/L	0.999 (0.998~1.002)	0.924					1.001 (0.998~1.003)	0.562

Abbreviation: HR, hazard ratio; IQR, interquartile range; LTM, lymphocyte count; CRP, C-reactive protein; BMI, body mass index

[a] Model 1 was adjusted for age, sex, BMI, and severity of COVID-19; [b] Model 2 was adjusted as model 1 plus diabetes, cardiovascular diseases, chronic lung disease, and tumor and immunosuppression; [c] Model 3 was adjusted as model 2 plus LTM, D-dimer, and CRP.

Table S5 Univariate and multivariate linear regression analyses of the first nucleic acid negative conversion time for the main cohort

Factor	Crude		Model 1[a]		Model 2[b]		Model 3[c]	
	β 95%CI	P value	β 95%CI	P value	β 95%CI	P value	β 95%CI	P value
Antiviral								
Nirmatrelvir-ritonavir	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Azvudine	1.89 (0.21~3.58)	0.029	2.06 (0.37~3.75)	0.018	2.39 (0.64~4.14)	0.008	2.53 (0.76~4.29)	0.005
Age, Mean ± SD, yr	0.05 (-0.02~0.11)	0.162	0.04 (-0.02~0.11)	0.190	0.03 (-0.04~0.10)	0.397	0.02 (-0.06~0.09)	0.648
Sex, n (%)								
Male	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Female	-1.04 (-2.72~0.63)	0.223	-1.29 (-2.97~0.39)	0.133	-1.19 (-2.87~0.49)	0.167	-1.35 (-3.04~0.35)	0.121
BMI, Mean ± SD	-0.16 (-0.43~0.11)	0.250	-0.16 (-0.44~0.12)	0.255	-0.13 (-0.42~0.15)	0.354	-0.12 (-0.40~0.16)	0.408
Severity of COVID-19, n (%)								
Mild-to-moderate	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Severe	0.47 (-2.04~2.98)	0.715	0.55 (-1.98~3.07)	0.671	0.41 (-2.13~2.96)	0.750	0.05 (-2.59~2.69)	0.969
Smoking, n (%)	0.38 (-2.82~3.59)	0.814						
Drinking, n (%)	0.88 (-2.71~4.47)	0.630						
Diabetes, n (%)	1.32 (-0.56~3.21)	0.170			0.85 (-1.13~2.83)	0.399	0.91 (-1.07~2.89)	0.369
Cardiovascular diseases, n (%)	1.08 (-0.64~2.80)	0.218			0.53 (-1.34~2.41)	0.576	0.74 (-1.14~2.62)	0.441
Chronic lung disease, n (%)	1.74 (-0.43~3.92)	0.117			1.77 (-0.46~4.01)	0.121	1.72 (-0.51~3.95)	0.132
Tumor and Immunosuppression, n (%)	0.43 (-1.47~2.34)	0.656			1.34 (-0.67~3.34)	0.192	1.27 (-0.74~3.27)	0.216
LTM, Median (IQR), $\times 10^9$/L	-0.17 (-0.55~0.21)	0.380					-0.14 (-0.53~0.24)	0.469
D-dimer, Median (IQR), mg/L	0.25 (0.02~0.48)	0.036					0.28 (0.03~0.52)	0.027
CRP, Median (IQR), mg/L	0.00 (-0.02~0.01)	0.583					0.00 (-0.02~0.01)	0.605

Abbreviation: IQR, interquartile range; LTM, lymphocyte count; CRP, C-reactive protein; BMI, body mass index

[a] Model 1 was adjusted for age, sex, BMI, and severity of COVID-19; [b] Model 2 was adjusted as model 1 plus diabetes, cardiovascular diseases, chronic lung disease, and tumor and immunosuppression; [c] Model 3 was adjusted as model 2 plus LTM, D-dimer, and CRP.

Table S6 Univariate and multivariate linear regression analyses of the hospital length of stay for the main cohort study

Factor	Crude		Model 1[a]		Model 2[b]		Model 3[c]	
	β 95%CI	P value	β 95%CI	P value	β 95%CI	P value	β 95%CI	P value
Antiviral								
Nirmatrelvir-ritonavir	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Azvudine	-1.43 (-3.35~0.48)	0.143	-1.24 (-3.12~0.65)	0.201	-0.85 (-2.81~1.11)	0.396	-0.95 (-2.93~1.04)	0.350
Age, Mean ± SD, yr	0.15 (0.08~0.22)	<0.001	0.14 (0.07~0.22)	<0.001	0.13 (0.05~0.21)	0.002	0.13 (0.05~0.21)	0.002
Sex, n (%)								
Male	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Female	-0.22 (-2.13~1.70)	0.825	-0.31 (-2.21~1.58)	0.745	-0.23 (-2.13~1.66)	0.809	-0.34 (-2.27~1.59)	0.727
BMI, Mean ± SD	-0.25 (-0.56~0.05)	0.106	-0.15 (-0.46~0.16)	0.331	-0.12 (-0.43~0.19)	0.451	-0.12 (-0.43~0.20)	0.474
Severity of COVID-19, n (%)								
Mild-to-moderate	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Severe	0.30 (-2.52~3.11)	0.836	0.37 (-2.43~3.17)	0.798	0.27 (-2.55~3.10)	0.849	0.49 (-2.54~3.51)	0.752
Smoking, n (%)	-0.50 (-4.08~3.09)	0.786						
Drinking, n (%)	-0.47 (-4.50~3.56)	0.819						
Diabetes, n (%)	1.91 (-0.21~4.04)	0.079			0.75 (-1.47~2.98)	0.506	0.68 (-1.55~2.92)	0.550
Cardiovascular and cerebrovascular diseases, n (%)	2.07 (0.12~4.02)	0.038			0.70 (-1.40~2.80)	0.513	0.70 (-1.42~2.81)	0.517
Chronic lung disease, n (%)	2.71 (0.20~5.21)	0.035			1.82 (-0.72~4.36)	0.160	1.80 (-0.75~4.35)	0.168
Tumor and Immunosuppression, n (%)	0.66 (-1.48~2.79)	0.545			1.41 (-0.81~3.64)	0.214	1.49 (-0.76~3.74)	0.196
LTM, Median (IQR), $\times 10^9$/L	-0.12 (-0.54~0.30)	0.590					-0.13 (-0.55~0.29)	0.550
D-dimer, Median (IQR), mg/L	0.20 (-0.11~0.50)	0.210					0.05 (-0.28~0.37)	0.784
CRP, Median (IQR), mg/L	-0.01 (-0.02~0.01)	0.537					-0.01 (-0.03~0.01)	0.337

Abbreviation: IQR, interquartile range; LTM, lymphocyte count; CRP, C-reactive protein; BMI, body mass index; [a] Model 1 was adjusted for age, sex, BMI, and severity of COVID-19 before antivirals; [b] Model 2 was adjusted as model 1 plus diabetes, cardiovascular diseases, chronic lung disease, and tumor and immunosuppression; [c] Model 3 was adjusted as model 2 plus LTM, D-dimer, and CRP.

Table S7 Baseline characteristics of study participants of the complete dataset with missing values removing according to oral antivirals (n=387)

Characteristic	Total (n = 387)	Nirmatrelvir-ritonavir (n = 241)	Azvudine (n = 146)	*P* value[a]
Age, Mean ± SD, yr	76.69 ± 12.83	76.89 ± 13.45	76.36 ± 11.79	0.691
Sex, n (%)				0.200
Male	241 (62.27)	156 (64.73)	85 (58.22)	
Female	146 (37.73)	85 (35.27)	61 (41.78)	
BMI, Mean ± SD[b]	22.86 ± 3.18	22.89 ± 3.27	22.81 ± 3.04	0.812
Severity of COVID-19 before antivirals, n (%)				0.822
Mild-to-moderate	332 (85.79)	206 (85.48)	126 (86.30)	
Severe	55 (14.21)	35 (14.52)	20 (13.70)	
Smoking, n (%)	30 (7.75)	17 (7.05)	13 (8.90)	0.509
Drinking, n (%)	22 (5.68)	12 (4.98)	10 (6.85)	0.441
Diabetes, n (%)	101 (26.10)	58 (24.07)	43 (29.45)	0.242
Cardiovascular disease, n (%)	132 (34.11)	79 (32.78)	53 (36.30)	0.479
Chronic lung disease, n (%)	62 (16.02)	49 (20.33)	13 (8.90)	0.003
Tumor and immunosuppression, n (%)	102 (26.36)	79 (32.78)	23 (15.75)	< 0.001
LTM, Median (IQR), $\times 10^9$/L	0.80 (0.50, 1.20)	0.80 (0.50, 1.10)	1.00 (0.70, 1.30)	< 0.001
D-dimer, Median (IQR), mg/L	0.92 (0.52, 1.89)	0.96 (0.55, 2.05)	0.87 (0.49, 1.56)	0.090
CRP, Median (IQR), mg/L	29.00 (9.04, 68.60)	37.60 (12.50, 77.30)	19.60 (5.12, 52.70)	< 0.001

Abbreviation: IQR, interquartile range; LTM, lymphocyte count; CRP, C-reactive protein; BMI, body mass index.

[a] P value was based on Student's t-test, Mann-Whitney U test, χ^2 tests, or Fisher's exact, as appropriate.

[b] BMI was calculated as weight in kilograms divided by height in meters squared.

Table S8 Associations between antivirals use and the efficacy outcomes in regression analysis for complete cohort (n=387)

Outcomes[a]	Nirmatrelvir-ritonavir (n =241)	Azvudine (n = 146)	Crude		Model 1[b]		Model 2[c]		Model 3[d]	
			HR 95%CI or β 95%CI	P value	HR 95%CI or β 95%CI	P value	HR 95%CI or β 95%CI	P value	HR 95%CI or β 95%CI	P value
All-cause 28-day mortality, n (%)	9 (3.73)	8 (5.48)	1.46 (0.56~3.77)	0.440	1.55 (0.59~4.05)	0.376	1.56 (0.58~4.17)	0.379	1.77 (0.61~5.13)	0.294
Risk of 28-day progressing to critical condition, n (%)	12 (4.98)	12 (8.22)	1.66 (0.75~3.70)	0.213	1.87 (0.83~4.20)	0.131	1.98 (0.86~4.53)	0.106	2.31 (0.97~5.51)	0.058
Proportion of 28-day negative conversion of nucleic acid, n (%)	198 (82.16)	124 (84.93)	0.88 (0.70~1.10)	0.248	0.88 (0.70~1.10)	0.247	0.81 (0.64~1.02)	0.070	0.81 (0.64~1.02)	0.072
The first nucleic acid negative conversion time, Median (IQR), days[e]	14.00 (10.00, 20.25)	16.00 (12.00, 21.00)	2.08 (0.35~3.82)	0.019	2.20 (0.45~3.94)	0.014	2.59 (0.80~4.39)	0.005	2.60 (0.78~4.42)	0.005
Hospital length of stay, Median (IQR), days[f]	13.00 (9.00, 23.00)	15.00 (10.00, 20.00)	-1.43 (-3.35~0.48)	0.143	-1.24 (-3.12~0.65)	0.201	-0.85 (-2.81~1.11)	0.396	-0.95 (-2.93~1.04)	0.350

Abbreviation: HR, hazard ratio; IQR, interquartile range

[a]was measured by azvudine vs nirmatrelvir-ritonavir

[b]Model 1 was adjusted for age, sex, BMI, and severity of COVID-19 before antivirals.

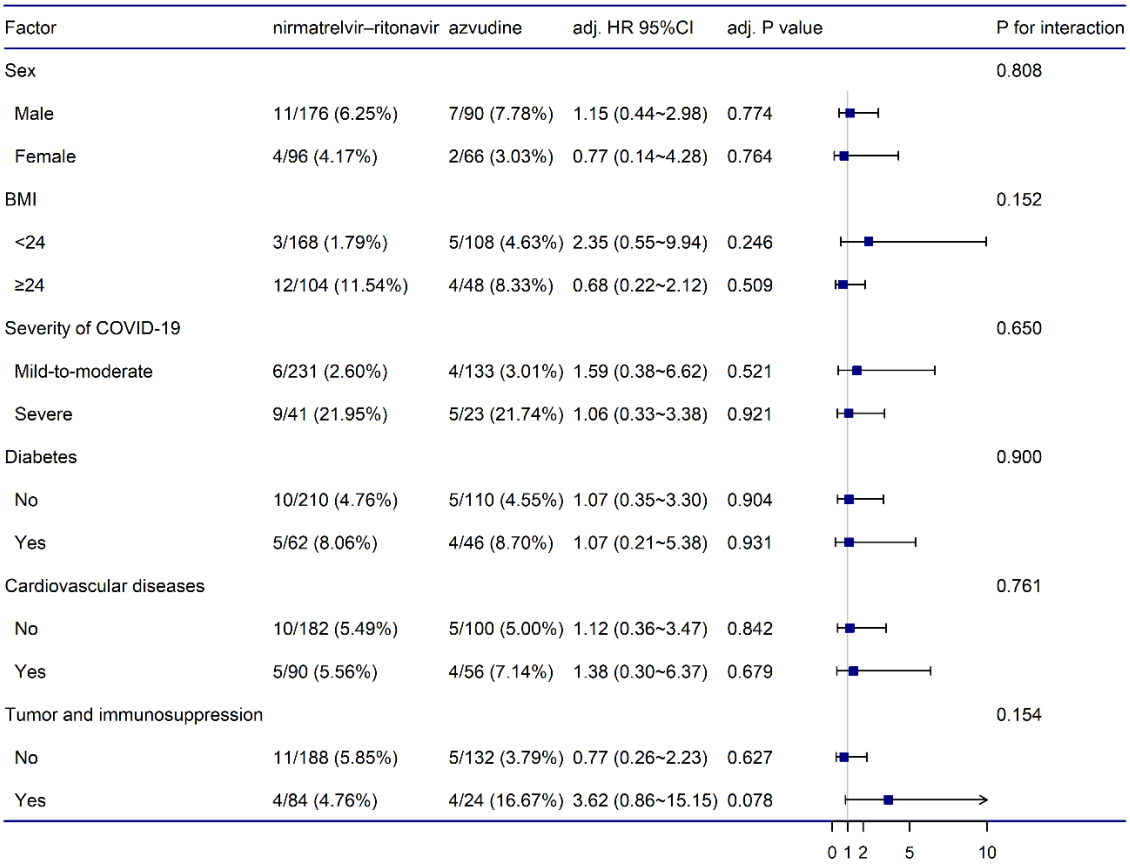
[c]Model 2 was adjusted as model 1 plus diabetes, cardiovascular diseases, chronic lung disease, and tumor and immunosuppression.

[d]Model 3 was adjusted as model 2 plus LTM, D-dimer, and CRP.

[e] patients who died or lost before the nucleic acid turned negative were further excluded

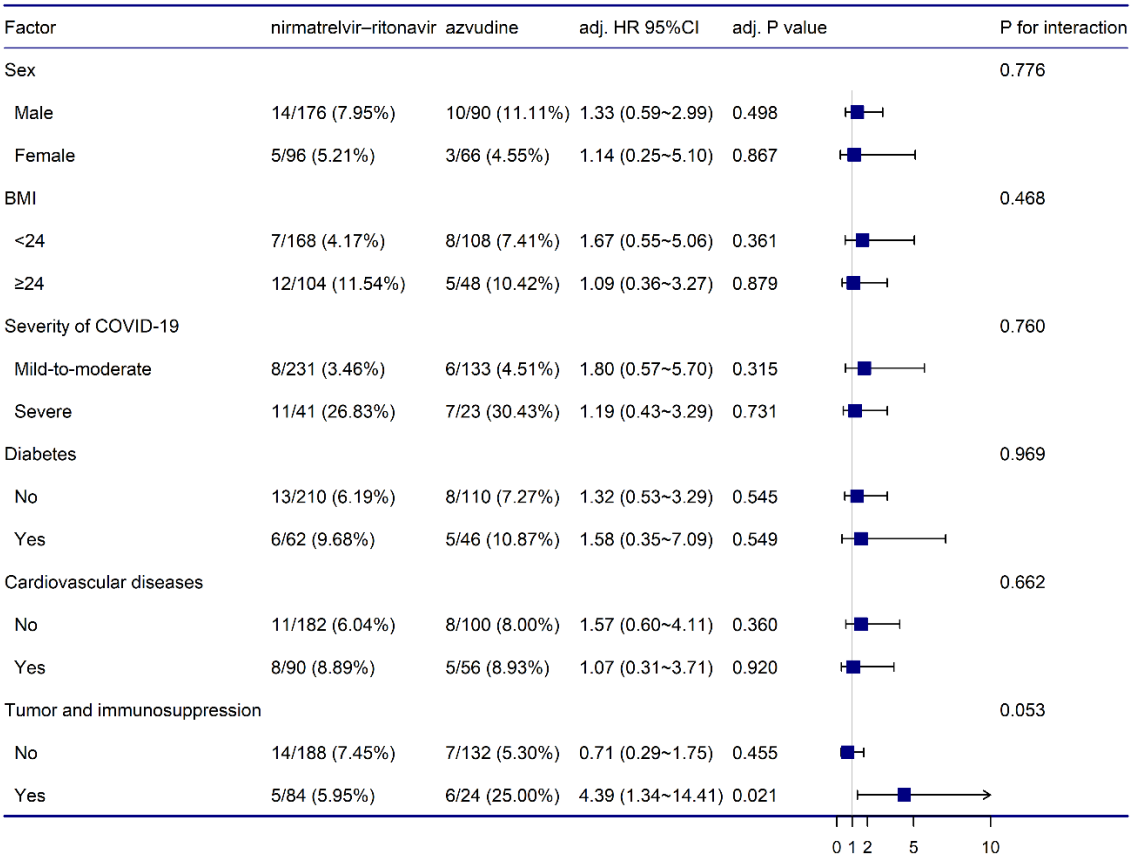
[f] patients who died during hospitalization were further excluded

Fig. S1 Forest plot for subgroup analyses of the efficacy of azvudine versus nirmatrelvir-ritonavir on all-cause 28-day mortality in patients with COVID-19 for main cohort



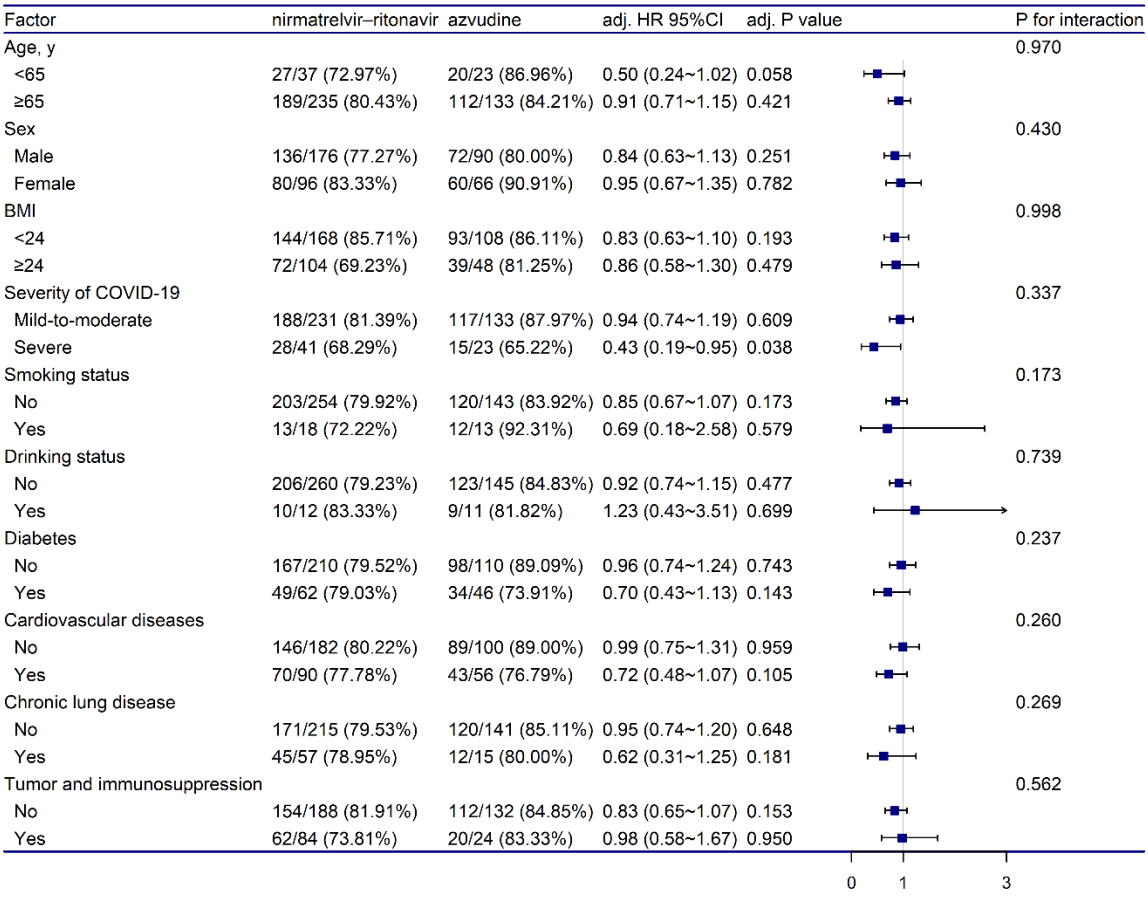
Hazard ratios are plotted as squares, the horizontal lines represent 95% confidence intervals.

Fig. S2 Forest plot for subgroup analyses of the efficacy of azvudine versus nirmatrelvir-ritonavir on risk of progressing to critical condition within 28 days in patients with COVID-19 for main cohort



Hazard ratios are plotted as squares, the horizontal lines represent 95% confidence intervals.

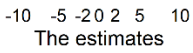
Fig. S3 Forest plot for subgroup analyses of the efficacy of azvudine versus nirmatrelvir-ritonavir on proportion of 28-day negative conversion of nucleic acid in patients with COVID-19 infection for main cohort



Hazard ratios are plotted as squares, the horizontal lines represent 95% confidence intervals.

Fig. S4 Forest plot for subgroup analyses of the efficacy of azvudine versus nirmatrelvir-ritonavir on the first nucleic acid negative conversion time in patients with COVID-19 infection for main cohort

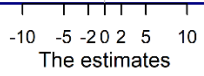
Factor	nirmatrelvir–ritonavir	azvudine	adj. β 95%CI	adj. P value	P for interaction
Age, y					0.908
<65	33	22	4.87 (0.19~9.55)	0.047	
≥65	220	123	2.14 (0.22~4.06)	0.030	
Sex					0.059
Male	161	82	3.24 (0.83~5.66)	0.009	
Female	92	63	1.08 (-1.42~3.57)	0.399	
BMI					0.470
<24	163	101	2.16 (0.03~4.30)	0.048	
≥24	90	44	3.55 (0.42~6.69)	0.028	
Severity of COVID-19					0.280
Mild-to-moderate	222	128	1.83 (-0.05~3.71)	0.058	
Severe	31	17	6.38 (1.46~11.29)	0.015	
Smoking status					0.276
No	237	133	2.50 (0.69~4.31)	0.007	
Yes	16	12	2.37 (-5.59~10.33)	0.567	
Drinking status					0.572
No	242	134	2.41 (0.60~4.23)	0.009	
Yes	11	11	-4.28 (-11.60~3.04)	0.274	
Diabetes					0.270
No	196	103	1.89 (0.020~3.76)	0.049	
Yes	57	42	3.92 (-0.48~8.32)	0.084	
Cardiovascular diseases					0.118
No	168	94	1.30 (-0.75~3.34)	0.216	
Yes	85	51	3.76 (0.38~7.14)	0.031	
Chronic lung disease					0.186
No	200	131	1.78 (-0.07~3.63)	0.060	
Yes	53	14	5.04 (-0.35~10.43)	0.072	
Tumor and immunosuppression					0.562
No	176	125	2.68 (0.78~4.59)	0.006	
Yes	77	20	1.52 (-2.93~5.97)	0.505	



Estimated β is plotted as squares, the horizontal lines represent 95% confidence intervals.

Fig. S5 Forest plot for subgroup analyses of the efficacy of azvudine versus nirmatrelvir-ritonavir on the hospital length of stay in patients with COVID-19 for main cohort

Factor	nirmatrelvir–ritonavir	azvudine	adj. β 95%CI	adj. P value	P for interaction
Age, y					0.906
<65	34	23	0.88 (-4.39~6.15)	0.744	
≥65	223	124	-1.41 (-3.58~0.77)	0.205	
Sex					0.297
Male	165	83	-0.20 (-2.74~2.35)	0.879	
Female	92	64	-2.77 (-5.96~0.42)	0.091	
BMI					0.408
<24	165	103	-1.94 (-4.36~0.49)	0.118	
≥24	92	44	0.64 (-2.91~4.19)	0.725	
Severity of COVID-19					0.567
Mild-to-moderate	225	129	-1.17 (-3.31~0.97)	0.286	
Severe	32	18	-0.47 (-5.60~4.66)	0.858	
Smoking status					0.462
No	241	135	-1.02 (-3.09~1.06)	0.338	
Yes	16	12	-0.60 (-8.07~6.87)	0.877	
Drinking status					0.834
No	246	136	-1.46 (-3.45~0.52)	0.150	
Yes	11	11	-1.99 (-9.61~5.63)	0.615	
Diabetes					0.677
No	200	105	-1.21 (-3.43~1.01)	0.287	
Yes	57	42	-0.74 (-5.15~3.68)	0.745	
Cardiovascular diseases					0.976
No	172	95	-0.72 (-3.12~1.69)	0.560	
Yes	85	52	-1.82 (-5.41~1.76)	0.321	
Chronic lung disease					0.691
No	204	132	-1.44 (-3.49~0.61)	0.169	
Yes	53	15	-0.77 (-7.61~6.07)	0.825	
Tumor and immunosuppression					0.527
No	177	127	-1.36 (-3.55~0.83)	0.225	
Yes	80	20	1.11 (-3.55~5.78)	0.641	



Estimated β is plotted as squares, the horizontal lines represent 95% confidence intervals.