Risk of severe case in COVID-19 patients and Azvudine: A Retrospective cohort study after exit from ‘zero-COVID’ policy

Lishan Li (850144863@qq.com)
The Fifth Affiliated Hospital of Sun Yat-sen University
Li Li (156318962@qq.com)
The Fifth Affiliated Hospital of Sun Yat-sen University
Lihua Ye (254241317@qq.com)
The Fifth Affiliated Hospital of Sun Yat-sen University
Baijie Lu (20160611@qq.com)
The Fifth Affiliated Hospital of Sun Yat-sen University
Jieling Wang (ling2005.hi@163.com)
The Fifth Affiliated Hospital of Sun Yat-sen University
Guanhua Wei (iznaug@163.com)
The Fifth Affiliated Hospital of Sun Yat-sen University
Zhuang Bian (bz232@163.com)
The Fifth Affiliated Hospital of Sun Yat-sen University

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Lishan Li, Li Li, Lihua Ye, Baijie Lu, Jieling Wang, Guanhua Wei, Zhuang Bian*

(Dr.) Zhuang Bian[1]*,MD Correspondence author
Professor and Head, Department of Medical Record Management,
The Fifth Affiliated Hospital of Sun Yat-sen University
Meihua East Road 52, Zhuhai, Guangdong, China 519000
Tel/Fax: 0086-756-2528388
Email: bz232@163.com

Dr. Lishan Li, MD First author
Department of Medical Record Management
The Fifth Affiliated Hospital of Sun Yat-sen University
Meihua East Road 52, Zhuhai, Guangdong, China 519000
Tel/Fax: 0086-756-2528675
Email: 850144863@qq.com

Running headline: Risk of severe case in COVID-19 patients and Azvudine

Abstract

Background: COVID-19 leaded to significant morbidity and mortality. To investigate contributing factors to severity and examine whether Azvudine can reduce mortality, we conducted a single-center, retrospective cohort study.

Method: 4201 COVID-19 patients discharged from our hospital were enrolled. Logistic regression analysis and ROC curve were used to investigate the role of comorbidities, laboratory parameters and clinical manifestation on progression of COVID-19. Propensity-score models conditional on baseline characteristics and Univariate Cox regression model were used to examine whether Azvudine can reduce the mortality of COVID-19.

Result: Age, male sex, cerebrovascular disease, chronic kidney disease, liver disease, tumor and chronic lung disease were associated with elevated risk of mortality and chronic kidney disease contributed the most risk. Uric acid showed a U-shape risk of severity. Both hyperuricemia and hypouricemia increased the risk of severity. D-dimer，NT-BNP, LDH and FT3 were the most sensitive and specific markers for the prediction of mortality. Poor appetite, consciousness deterioration, polypnea and persistent high fever were associated with elevated risk of severity. Compared with no antiviral group, Azvudine can reduce the COVID-19 mortality (hazard ratio 0.708(95% confidence interval 0.516 to 0.971), P=0.032. There was no significant difference in mortality reduction between Molnupiravir and Azvudine(P=0.486).

Conclusions: Among COVID-19 patients, age, male sex and comorbidities can affect progression of COVID-19. D-dimer，NT-BNP, LDH, FT3, UA, poor appetite, consciousness deterioration, polypnea and persistent high fever can help doctors predict severe illness. Azvudine is neck and neck with Molnupiravir in the mortality reduction among COIVD-19.

Key points: COVID-19; severity; mortality ;Azvudine

Introduction

The novel coronavirus disease (COVID-19) is a highly contagious disease caused by the SARS-CoV-2 virus, leading to significant morbidity and mortality. Until fall 2022, China maintained strict ‘zero-COVID’ policy. Starting from Dec. 7, nearly all interventions of ‘zero-COVID’ policy were removed given the high transmissibility of the Omicron variants BA.5 and BF.7 present in China. By the end of May 2023, it had caused two waves.

Here, we conducted a single-center, retrospective cohort study during the outbreak caused by Omicron. Comparing the peaks of these two waves, we infered that the population of COVID-19 survivors had immune protection against Omicron and high titer level of antibodies may be maintained for about 3-4 months (Fig 1). Accurately analyzing the clinical features of hospitalized patients is valuable strategies to handle large infection waves caused by Omicron variant.

RNA replicase, as the core component of viral transcription and replication, is highly conserved in viral variant species, and antiviral agents developed for this target are not susceptible to viral mutation. At present, RNA polymerase (RdRp) inhibitors recommended by Chinese guidelines include Molnupiravir and Azvudine. Molnupiravir use within five days of testing positive for SARS-CoV-2 has been shown to reduce the risk of mortality[1]. Several studies demonstrated that Azvudine could reduce the duration of virus clearance in COVID-19 patients[2]. Therefore, concerns arise about the clinical effectiveness of Azvudine versus Molnupiravir in COVID-19 patients.

Methods

Setting：Data were collected from The Fifth Affiliated Hospital of Sun Yat-sen University. Since the COVID-19 epidemic in 2019, the hospital had been the

only designated hospital in Zhuhai city under the "zero COVID-19" policy, and had rich experience in the treatment of severe COVID-19 patients. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee of the Fifth Affiliated Hospital of Sun Yat-sen University ([2023]K200-1). The study was registered on ClinicalTrials.gov. (NCT06006611). The informed consents from patients were not required.

Data sources：We extracted data from November 1, 2022 to May 31, 2023. Data domains used were inpatient diagnoses, inpatient pharmacy records, electronic case record and laboratory test results.

Cohort：Overall, 4201 patients were enrolled to study the role of clinical manifestation and underlying comorbidities on progression to severe COVID-19 case. The criterions of severe cases were based on the resting state, oxygen saturation ≤93% during air inhalation, (PaO2)/ (FiO2) ≤300mmHg, pulmonary imaging showing significant progress of > 50% within 24-48 hours, respiratory failure requiring mechanical ventilation, shock and other organ failure needing intensive care unit treatment. We conducted binary logistic regression analysis for the relative risk of comorbidities and clinical manifestation on progression of COVID-19 patients. Model likelihood ratio test was used to estimate whether the model is valid. Hosmer-Lemeshow test was used to estimate goodness of fit. ROC curve analysis was used to explore sensitivity and specificity of laboratory parameters for the prediction of mortality among COVID-19 patients.

In order to observe whether Azvudine can reduce the mortality of COVID-19 patients, patients with these conditions were excluded: 1) younger than 18 years; 2) received other antiviral agents; 3) received both Azvudine and Molnupiravir. Then 3945 participants were enrolled. First, patients were divided into Azvudine group and no antiviral group. The endpoint was all-cause death. Patients were observed from the date of admission until discharge or death, whichever came first. We used propensity-score models conditional on baseline characteristics, and the probability of receiving Azvudine was estimated in an approach of caliper matching without replacement, with a caliper width of 0.2. The baseline characteristics included age, sex, systemic steroid, mechanical ventilation and severity. The standard mean differences (SMDs) were used to assess the balance of each baseline characteristics between groups before and after propensity-score matching which less than 0.1 indicating covariate was balanced (Table2,3).

Univariate Cox regression model was used to estimate a hazard ratio (HR) with 95% confidence interval (CI) for the result between these two groups. Second, patients were divided into Azvudine group and Monotamivir group by the same method. All statistical analyses were conducted with SPSS version 22. P value less than 0.05 was statistically significant.

Result

Comorbidities

Compared with survival COVID-19, age was associated with elevated risk of progression to death (relative risk 1.042(95% confidence interval 1.031 to1.053); cerebrovascular disease (relative risk 1.362 (95% confidence interval 0.999 to1.856); chronic kidney disease (relative risk 4.083 (95% confidence interval 3.031 to 5.499); liver disease (relative risk 1.956 (95% confidence interval 1.363 to 2.806) ; tumor (relative risk 1.799 (95% confidence interval 1.303 to 2.484) and chronic lung disease (relative risk 1.320(95% confidence interval 0.929 to 1.876). Female had a lower risk of progression to death (relative risk 0.908 (95% confidence interval 0.676 to 1.218) (Fig 2). Furthermore, ROC curve analysis was used to explore sensitivity and specificity of age for the prediction of mortality among COVID-19 patients. The cutoff value of age was 66.5, sensitivity 0.721 and specificity 0.583(Fig 3).

Laboratory parameters

Accurate and rapid laboratory diagnosis of COVID-19 infection and its deterioration is one of the milestones of pandemic control. Comparing the diagnostic and prognostic accuracy of mainly used laboratory parameters (eosinophils, lymphocyte, uric acid (UA), aspartate transaminase (AST), D-dimer, creatine kinase (CK), NT-brain natriuretic peptide (NT-BNP), squamous cell carcinoma antigen (SCC), lactate dehydrogenase (LDH) and free triiodothyronine (FT3) of COVID-19 patients can assess the most appropriate biomarker used in severe patients. Our results revealed that the level of AST, D-dimer, CK, NT-BNP, SCC, LDH were significantly increased, while eosinophils, lymphocyte and FT3 were significantly decreased among severe COVID-19 patients when compared with non-severe ones (Fig 4). Binary logistic regression analysis was used to evaluate the role of UA on progression to severe COVID-19. Compared with <180umol/L group, 180-360μmol/L and 360-540μmol/L groups were associated with lower risk of severity (relative risk 0.551(95% confidence interval 0.414 to0.734), (relative

risk 0.807(95% confidence interval 0.599 to1.086). >540μmol/L group was associated with elevated risk of severity (relative risk 2.546(95% confidence interval 1.812 to3.577) (Fig 5). Furthermore, ROC curve analysis was used to explore sensitivity and specificity of laboratory data for the prediction of mortality among COVID-19 patients. Our results revealed that D-dimer ，NT-BNP, LDH and FT3 are the most sensitive and specific markers. Youden index was used to find cutoff value (Fig 6). The cutoff value of D-dimer was 1.025μg/ml, sensitivity 0.800 and specificity 0.670; NT-BNP was 449.500pg/ml, sensitivity 0.789 and specificity 0.680; LDH was 284.75U/L, sensitivity 0.648 and specificity 0.760; FT3 was 3.085 ρmol/L, sensitivity 0.670 and specificity 0.735.

Clinical manifestations

The main clinical manifestations of COVID-19 patients include fever, cough, sore throat, rhinobyon, running nose, diarrhea, muscle soreness, conjunctivitis, hyposmia and hypogeusia. In addition, we had observed that some COVID-19 patients felt weak, poor appetite, altered state of consciousness, somnipathy, weight loss and other manifestations. We reviewed the inpatient records and 2,312 patients with above symptoms who were clearly caused by COVID-19 were investigated (table1). Binary logistic regression analysis was used to evaluate the role of clinical manifestations on progression to severe COVID-19. Compared with non-severe COVID-19, consciousness deterioration was associated with elevated risk of progression to severe illness (relative risk 4.802 (95% confidence interval 3.4792 to 6.628); polypnea (relative risk 2.702 (95% confidence interval 2.158 to3.382); poor appetite (relative risk 1.536 (95% confidence interval 1.213 to 1.945); fever (relative risk 1.56 (95% confidence interval 1.208 to 2.013) and wek (relative risk 1.082 (95% confidence interval 0.848 to 1.380) (Fig 7).

We calculated the duration of fever from onset of COVID-19. 1287 cases recorded explicit fever duration. Binary logistic regression analysis was used to evaluate the role of fever duration on progression to severe COVID-19. Fever duration was associated with elevated risk of progression to severe illness (relative risk 1.07 (95% confidence interval 1.05 to 1.09) (Fig 8).

Antiviral agent

RNA polymerase (RdRp) inhibitors recommended by Chinese guidelines include Molnupiravir and Azvudine. Among 4201 hospitalized COVID-19

patients, 1112 Azvudine recipients, 111 Molnupiravir and 2722 no antiviral recipients were eligible for inclusion (Fig 9). Univariate Cox regression model was used to estimate whether Azvudine can reduce the mortality of COVID-19 illness. To assess the validity of the proportional hazard assumption, the assumption was assessed by log-minus-log-survival function and found to hold (Fig 10). Compared with no antiviral group, receiving Azvudine can reduce the mortality of COVID-19 illness (hazard ratio 0.708(95% confidence interval 0.516 to 0.971), P=0.032(Fig 11). Log-rank test was used to estimate the difference between Molnupiravir and Azvudine. There was no significant difference in mortality reduction between Molnupiravir and Azvudine(P=0.486) (Fig 12).

Discussion

Our study revealed that age, cerebrovascular disease, chronic kidney disease, liver disease, tumor and chronic lung disease were associated with elevated risk of COVID-19 mortality. Chronic kidney disease contributed the most risk. Adequate renal, liver and lung function are essential for host survival and adaptation to the rapidly changing internal environment. Age attribute to the decline in organ function and immunity[3]. Our result supported the idea that female was associated with reduced risk of COVID-19 mortality. Autoimmune disease, hypertension and cardiovascular diseases also showed a weak association with lower COVID-19 mortality although it did not reach a statistical significance. It seemed to be what we not expected.

The possible reasons given in these studies are as follows: (1) Angiotensin converting enzyme 2 (ACE2) is the receptor for the attachment and entry of SARS-CoV-2 into the host cells[4]. Lupus and certain types of malignancies can promote ACE2 expression and activity[5].(2)Several clinical and experimental data indicated that methotrexate has certain protective effects on SARS-CoV-2 infection via down regulating ACE2[6]; Tumor necrosis factor inhibitor (anti-TNF) use was associated with a reduced odds of hospitalization in patients with rheumatic disease.(OR 0.40, 95% CI 0.19 to 0.81)[7]; Hydroxychloroquine is known to increase the pH of endosomes, which inhibits membrane fusion, a required mechanism for viral entry into the cell[8]; For patients who have wild-type of ACE2 and TMPRSS2, a combination of camostat with hydroxychloroquine may have clinical benefit[9]; Although cytokine blockers and Janus kinases (Jak) inhibitors have raised theoretical concerns with regard to autoimmune disease therapy, it

should be noted that these agents are currently considered for clinical therapy of COVID-19 cases with hyperinflammation and ARDS[10]. These may help explain why autoimmune disease with underlying medicine showed a weak association with lower COVID-19 severity and mortality. (3) The administration of ACEI/ARB drugs had positive effect on reducing D-dimer and the number of people with fever[11]. ACEI/ARB therapy was not associated with increased risk of all-cause mortality or severe manifestations in patients with COVID-19[12]; Recent studies indicated that the use of statins lowered mortality by 42% in hospitalized patients with COVID-19 (HR = 0.58 with (0.43–0.8) 95% CI; p = 0.01). A[13] meta-analysis by Kow et al. including 8990 COVID-19 patients found statins reduce the risk of fatal or severe disease by 30%.These [13] results may be caused by the pleiotropic activity of statins, and recent studies suggested various mechanisms that may directly affect SARS-CoV-2 endocytosis (ACE2), replication (main protease and RNA polymerase) or indirect mechanisms unrelated to coronavirus infection, such as anti-inflammatory, anti-coagulant effects or endothelial function improvement[14]; Aspirin was associated with a small increase in the rate of being discharged alive within 28 days[15]. Therefore, we supported that autoimmune disease, hypertension and cardiovascular diseases themselves were associated with elevated risk of COVID-19 severity, but the underlying medicine could influence the risk. It required further study for us to clarify this issue.

Our findings provide evidence that markedly elevated D-dimer levels occurred in severe COVID-19 patients. FT3 serum levels are lower in patients with severe symptoms[16]. Whether thyroxine replacement therapy is beneficial to patients needs further research. Hyper-inflammation and cytokine storm may be linked to more severe disease. Neutrophilia, lymphopenia and high levels of LDH were common symptoms in severe COVID-19 disease[17]. Eosinophils release several cytokines involved in homeostasis maintenance and Th2-related inflammation. In the context of SARS-CoV-2 infection, emerging evidence indicates that eosinopenia seems to be an indicator of severity among patients with COVID-19, whereas an increased eosinophil count is associated with a better prognosis, including a lower incidence of severity and mortality[18]. SCC increased significantly in severe cases of COVID-19 as compared with mild cases. It was consistent with one study that severe SARS-CoV-2 infection may represent a marker of an undiagnosed lung cancer[19]. Low serum levels of uric acid are common and associate with disease severity and with progression to respiratory

failure requiring invasive mechanical ventilation. It might depend on antioxidant, endogenous modulator of innate immunity of uric acid which can inhibit the cytokine storm observed during COVID-19[20]. In our study, uric acid showed a U-shape risk on severity of COVID-19. The possible reasons are as follows: The evidences obtained by basic science suggest hyperuricemia can induce inflammation, endothelial dysfunction, proliferation of vascular smooth muscle cells, and activation of the renin-angiotensin system[21]. Therefore, we are inclined to support that both hyperuricemia and hypouricemia increase the risk of progression to severe COVID-19.

The clinical manifestation include cough, rhinobyon, sore throat, muscle soreness, dizziness, headache and somnipathy forebode upper respiratory tract infection (URTI). Diarrhea, nausea and vomiting forebode gastrointestinal symptoms. They are common symptoms in mild COVID-19. But, Poor appetite may result from edema of the mucosa of the digestive tract due to heart failure and it will make the body week and lack of energy to fight off viruses. Consciousness deteriorates forebode that the body is in a serious state of ischemia and hypoxia and the internal environment is disturbed. Polypnea forebodes failure of heart and lung function. In addition, with the extension of fever duration, the incidence of severe diseases will increase. We should pay more attention to these patients with poor appetite, consciousness deterioration, polypnea and persistent high fever.

Azvudine was recommended by Chinese health authorities for COVID-19 treatment. The mechanism is that Azvudine could be embedded during RNA synthesis of SARS-COV-2 and inhibits related polymerases, finally leading to RNA replication termination[2]. Azvudine is the most widely used antiviral against COVID-19 in China. After matching the baseline characteristics our study supported that Azvudine was effective in reducing the COVID-19 mortality compared with no antiviral group. Molnupiravir was recommended by Chinese health authorities for COVID-19 treatment as RNA polymerase inhibitors too. There is no significant difference between Azvudine and Molnupiravir in reducing COVID-19 mortality in our study.

Conclusion

Risk factors for severe COVID-19 include older age, male sex and pre-existing comorbidities .Underlying medicine may affect the risk. D-dimer, FT3, lymphopenia, LDH and SCC can help us predict COVID-19 severity. Uric acid showed a U-shape risk on COVID-19 severity. Poor appetite,

consciousness deterioration, polypnea and persistent high fever forebode severity. Azvudine was effective in reducing COVID-19 mortality and was not significantly different from Monotamivir.

Declaration

Authors' contributions

All authors participated in the design of the study. Zhuang Bian performed the statistical analysis. Lishan Li was the major contributor in writing the manuscript. All authors read and approved the final manuscript.

Funding

Not applicable

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available due to limitations of ethical approval involving the patient data and anonymity but are available from the corresponding author on reasonable request.

Ethical approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee of the Fifth Affiliated Hospital of Sun Yat-sen University ([2023] K171-1).

Informed consent waiver with Institutional Ethics Committee of the Fifth Affiliated Hospital of Sun Yat-sen University.

Consent to publication

Not applicable

Competing interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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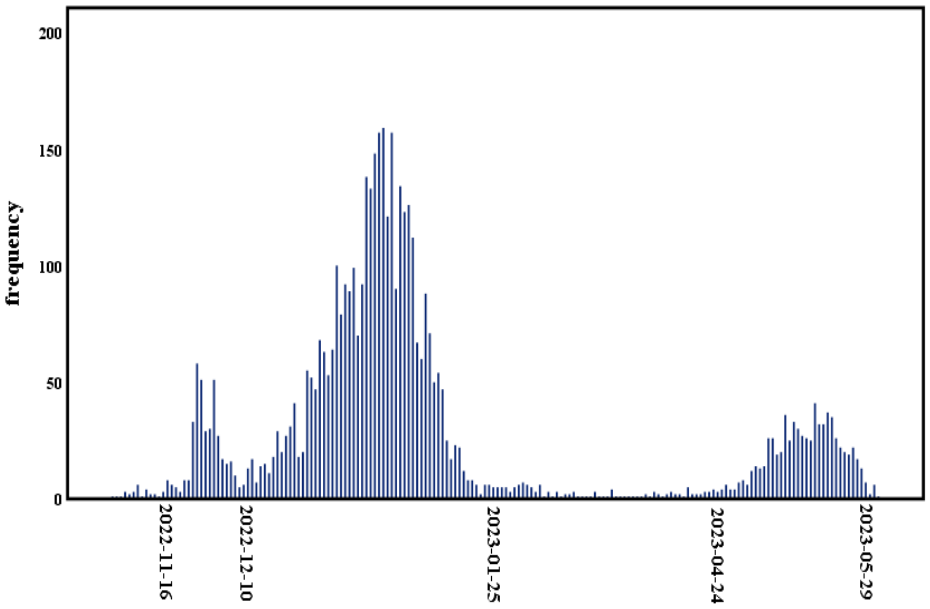


Fig 1. As the ‘zero-COVID’ policy was removed, the number of COVID-19 patients admitted to our hospital began to rise in late December 2022; It began to rise again in late April 2023 and peaked in mid-May.

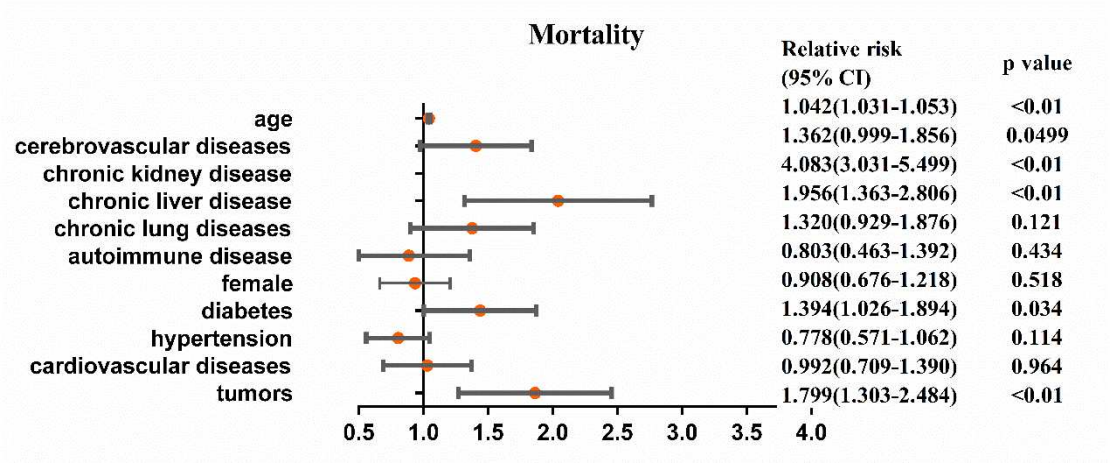


Fig 2. Relative risk of underlying comorbidities on mortality of COVID-19 illness.

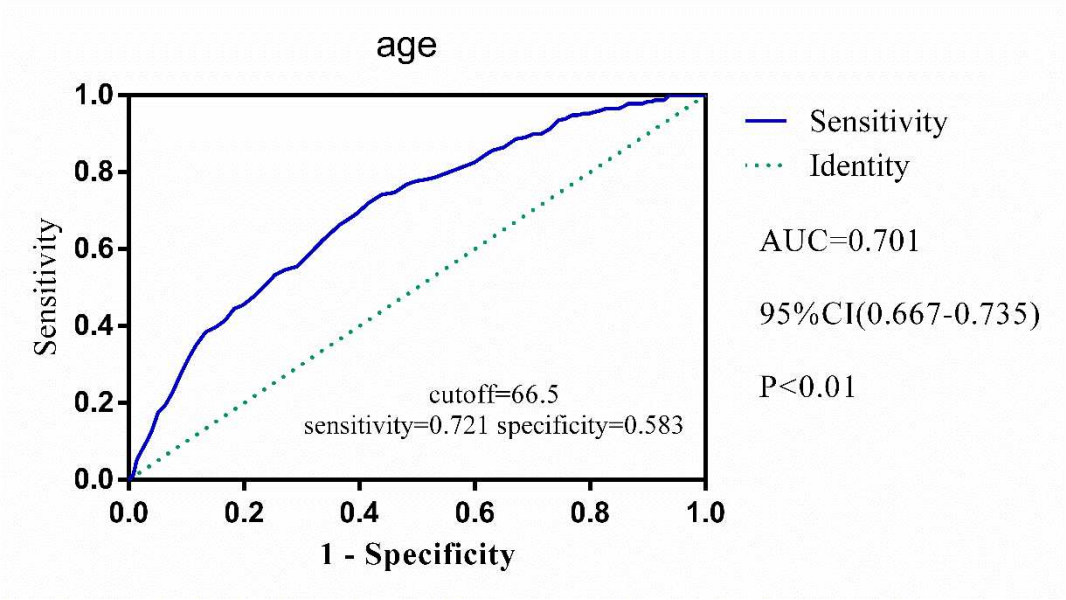
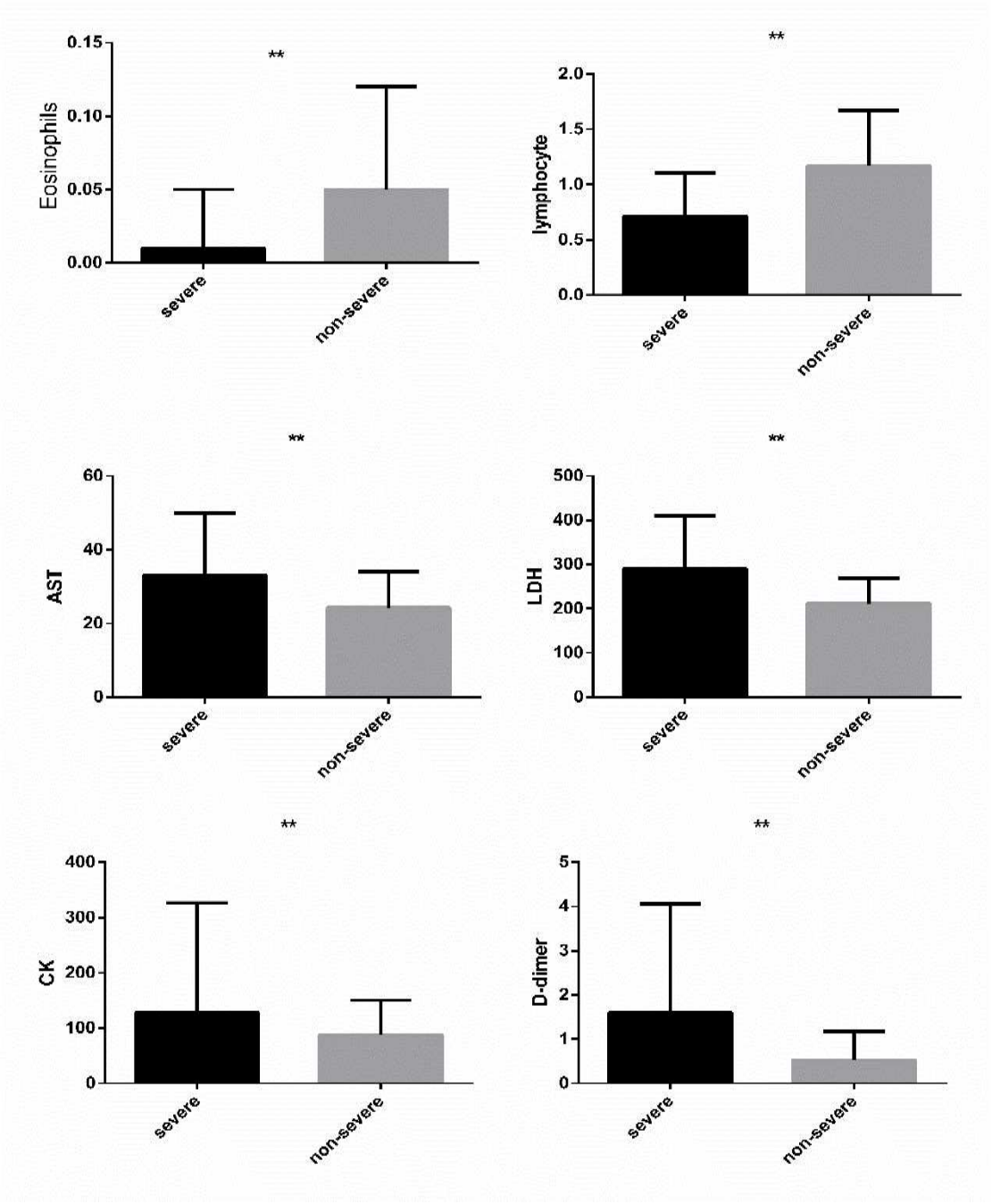


Fig 3. ROC curve of age for the prediction of mortality among COVID-19 patients.


Eosinophils
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0.00
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severe
non-severe
lymphocyte
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severe
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AST
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severe
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LDH
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severe
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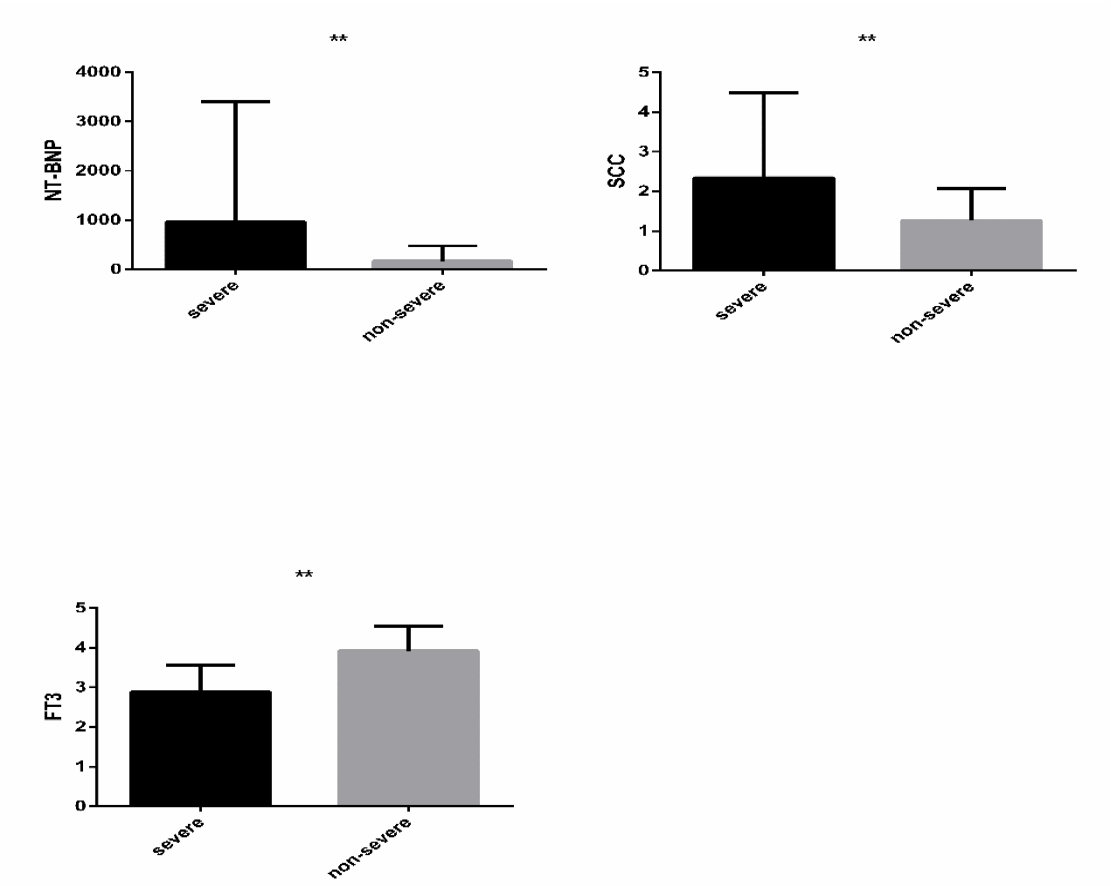


Fig 4. The Mann-Whitney U test for the laboratory data between severe and non-severe groups.** P<0.01

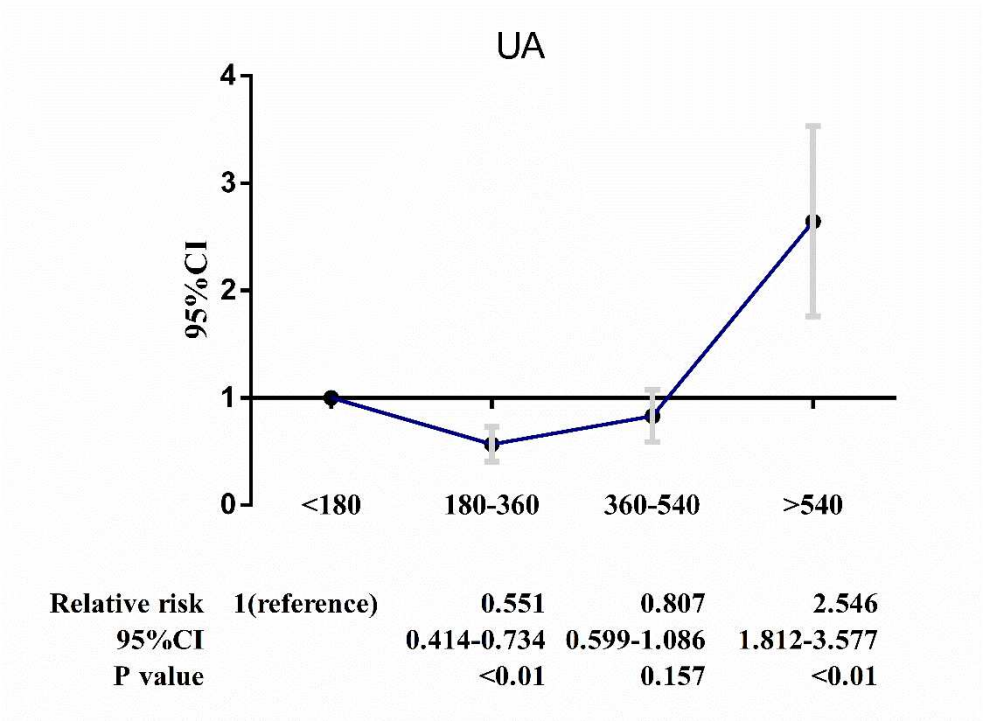
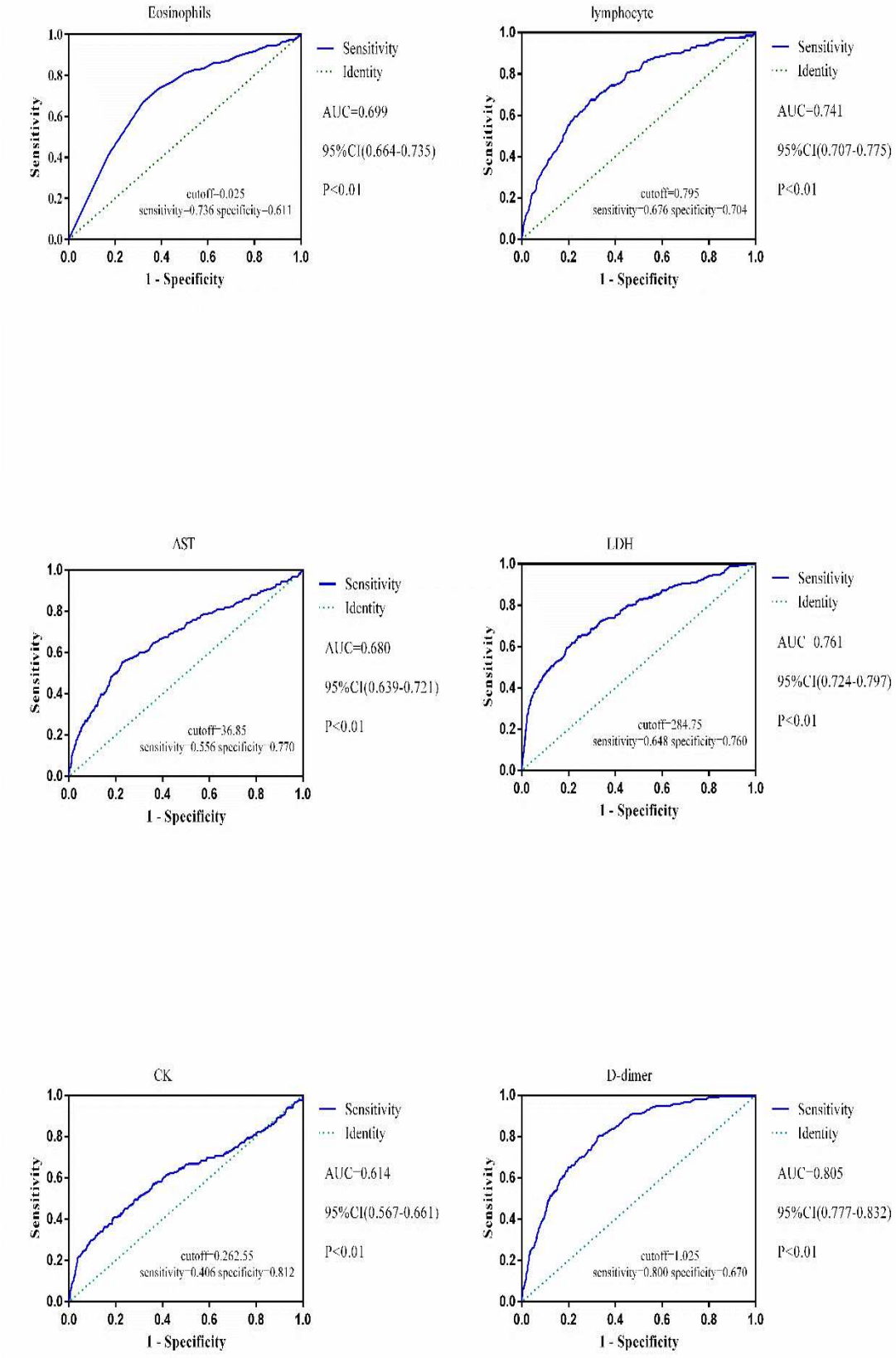


Fig 5. Relative risk of UA on severity of COVID-19 illness.


Eosinophils
Sensitivity
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AUC=0.699
95%CI(0.664-0.735)
P<0.01
cutoff=0.025
sensitivity=0.736 specificity=0.611
lymphocyte
Sensitivity
Identity
AUC=0.741
95%CI(0.707-0.775)
P<0.01
cutoff=0.795
sensitivity=0.676 specificity=0.704
AST
Sensitivity
Identity
AUC=0.680
95%CI(0.639-0.721)
P<0.01
cutoff=36.85
sensitivity=0.556 specificity=0.770
LDH
Sensitivity
Identity
AUC=0.761
95%CI(0.724-0.797)
P<0.01
cutoff=284.75
sensitivity=0.648 specificity=0.760
CK
Sensitivity
Identity
AUC=0.614
95%CI(0.567-0.661)
P<0.01
cutoff=0.262.55
sensitivity=0.406 specificity=0.812
D-dimer
Sensitivity
Identity
AUC=0.805
95%CI(0.777-0.832)
P<0.01
cutoff=1.025
sensitivity=0.800 specificity=0.670
Sensitivity
1 - Specificity

507

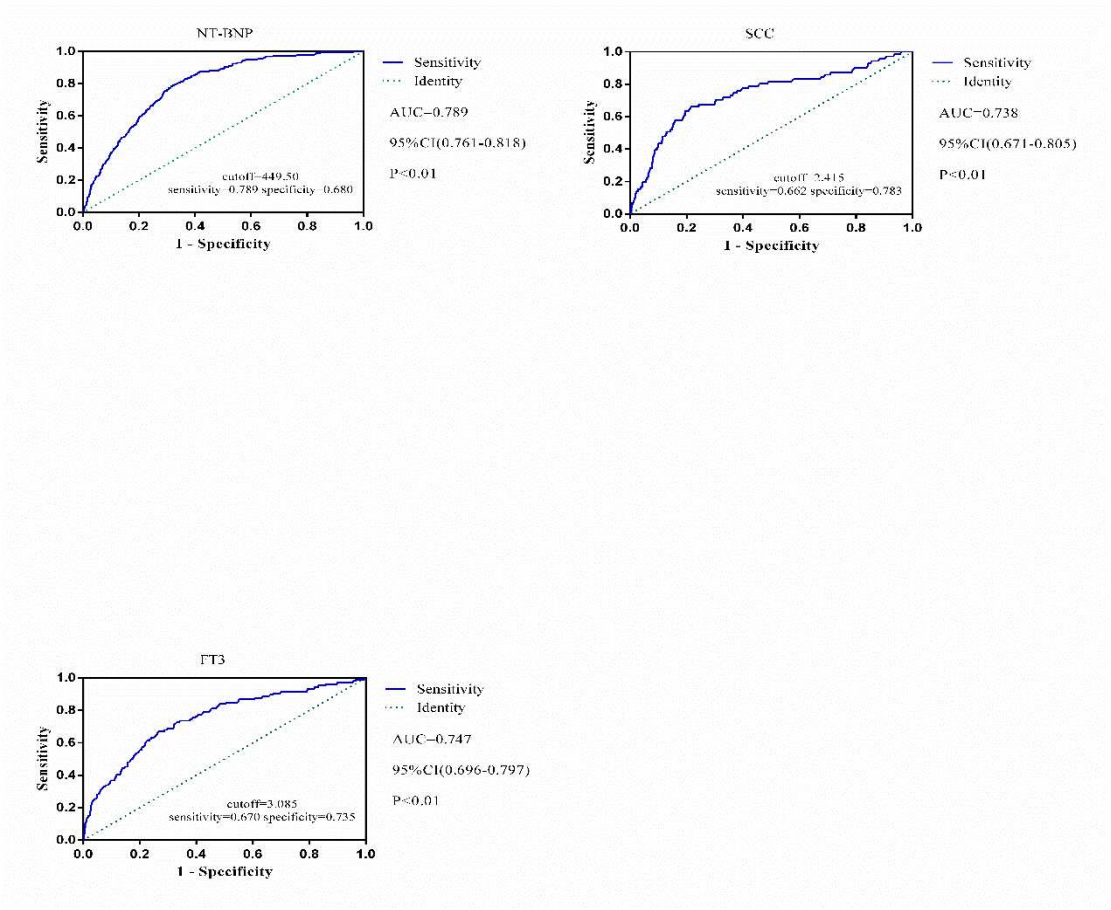


Fig 6. ROC curve of the laboratory data for the prediction of mortality among COVID-19 patients.

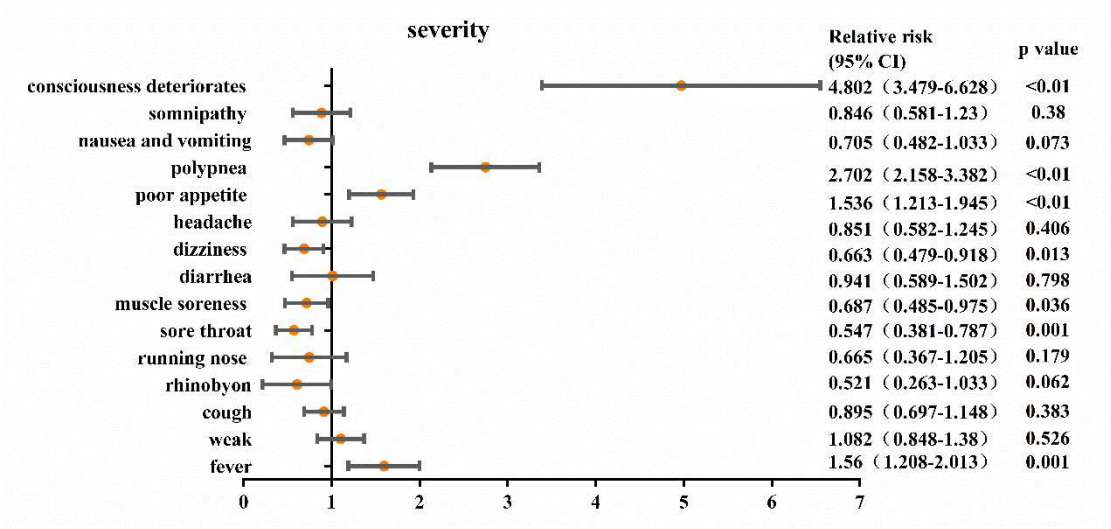


Fig 7. Relative risk of clinical manifestations on progression to severe COVID-19 illness.

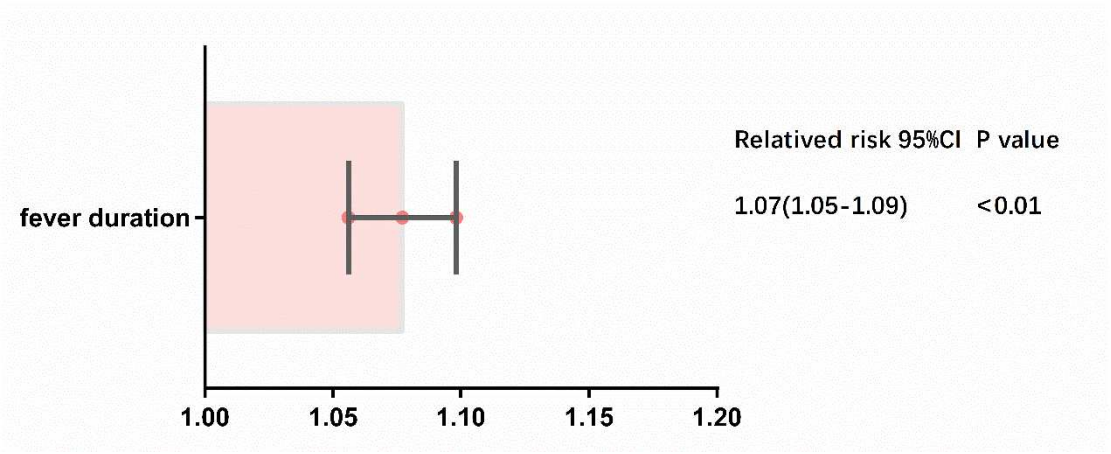


Fig 8. Relative risk of fever duration on progression to severe COVID-19 illness.

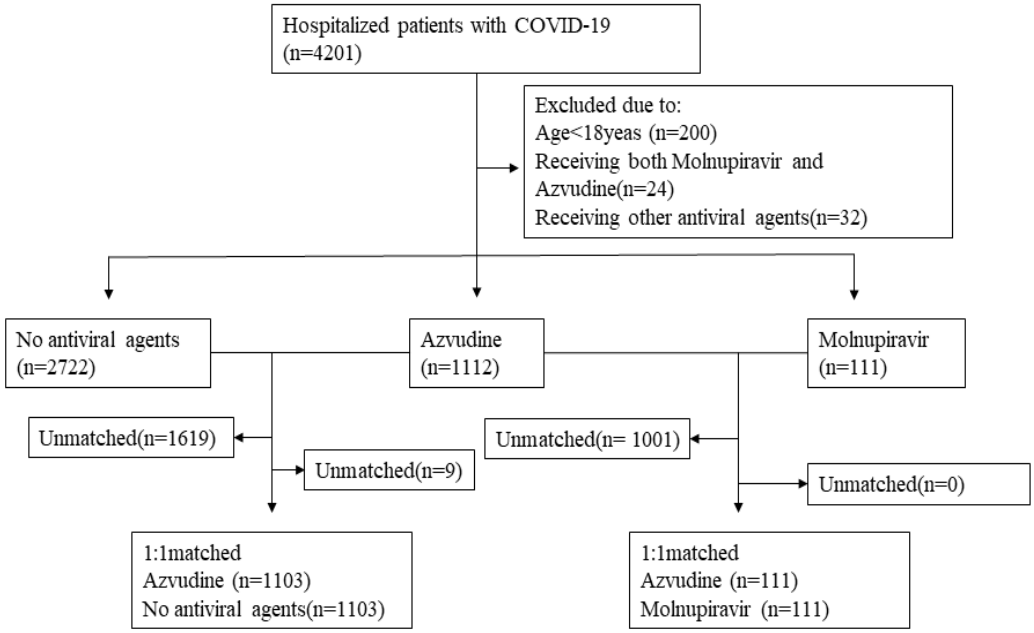


Fig 9. Flow chart showed the inclusion and exclusion of COVID-19 hospitalized patients during the study period.

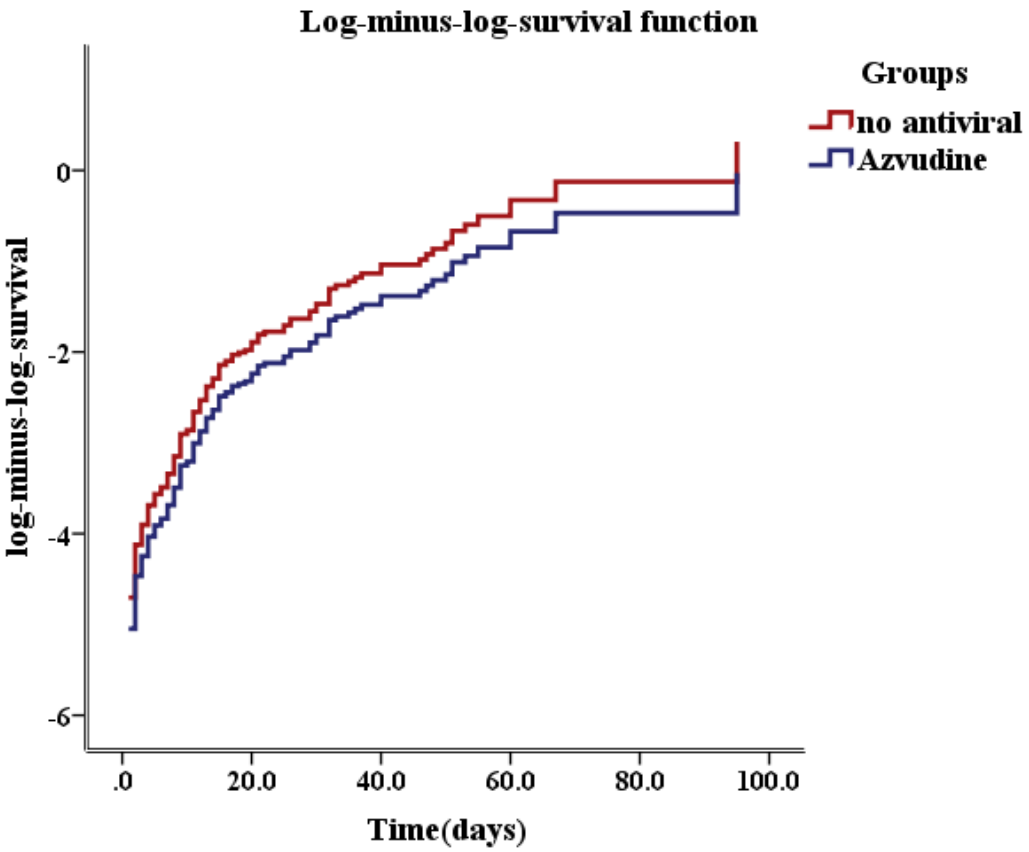
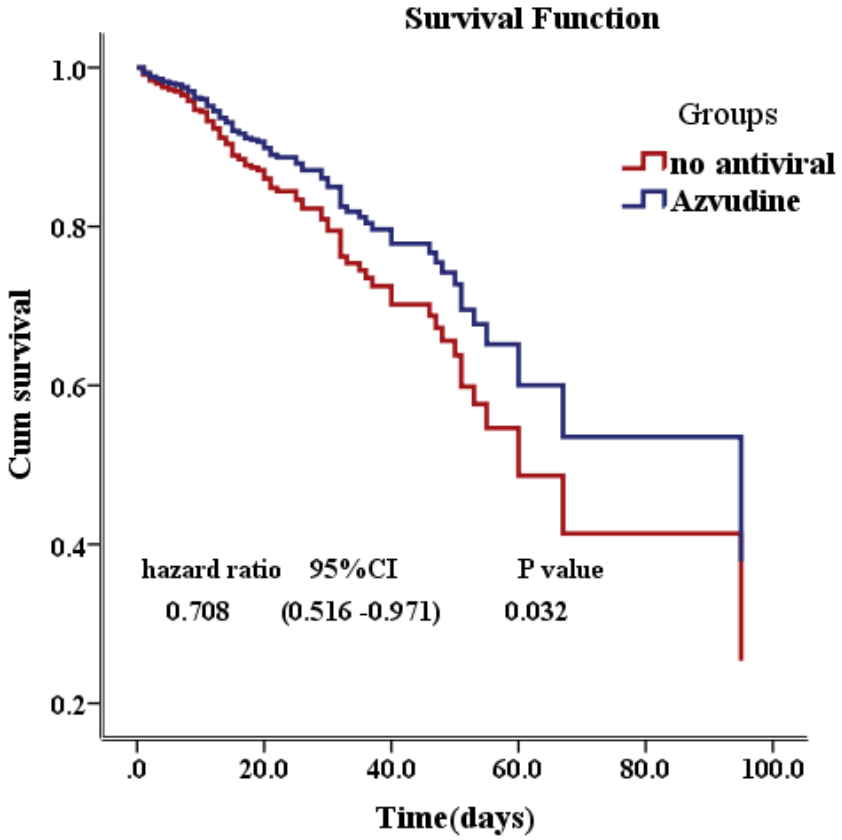


Fig 10. Log-minus-log-survival function between Azvudine and no antiviral groups.



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Number at risk

No antiviral-	1103	142	35	4	0
Azvudine-	1103	186	43	7	0
	0	20	40	60	80

Time (Days)

529 Fig 11. Cumulative survival between Azvudine and no antiviral groups.

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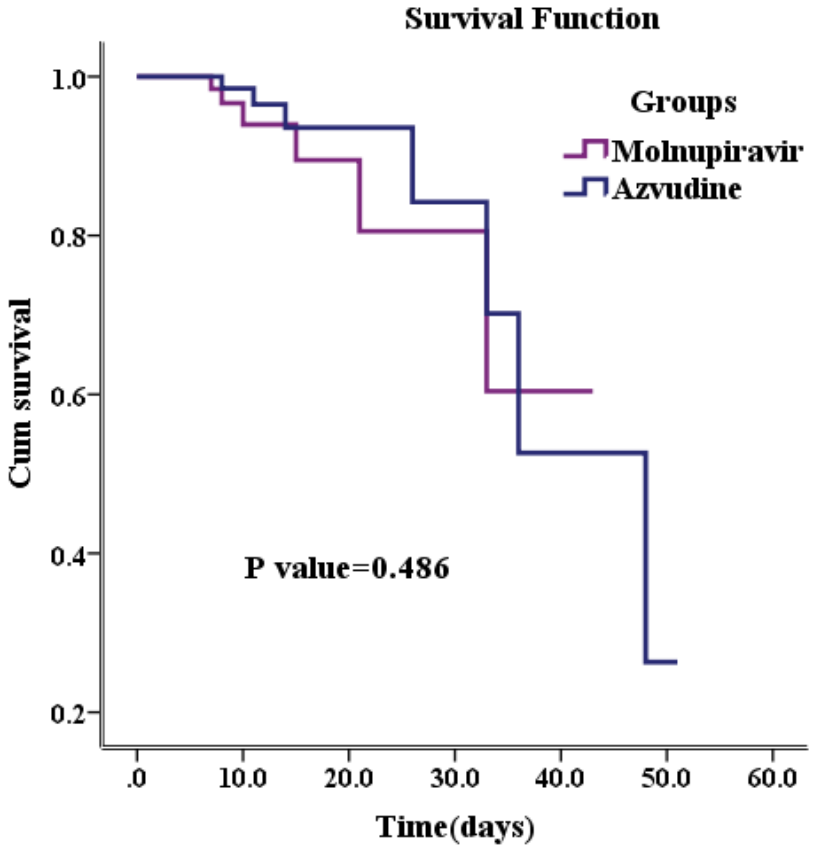

Number at risk					
Molnupiravir -	111	43	11	4	0
Azvudine-	111	60	18	6	0
	0	10	20	30	40

Fig 12. Cumulative survival between Azvudine and Molnupiravir groups.

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clinical manifestation	Overall cohort	Severe group	Non-severe group	P value
fever	1652（71.5）	354（76.0）	1298（70.3）	0.016
period of fever>5days	625(48.6)	166(60.6)	459(45.3)	<0.01
weak	783 (33.9)	159（34.1）	624（33.8）	0.897
cough	1641(71)	322（69.1）	1319（71.5）	0.317
hyposmia	24(1.0)	5（1.1）	19(1.0)	0.934
hypogeusia	30(1.3)	7（1.5）	23(1.2)	0.662
rhinobyon	186(8)	14（3）	172（9.3）	<0.01
running nose	202(8.7)	20（4.3）	182（9.9）	<0.01
sore throat	382(16.5)	41（8.8）	341（18.5）	<0.01
muscle soreness	371(16.0)	49（10.5）	322（17.4）	<0.01
diarrhea	140(6.1)	28（6）	112（6.1）	0.962
dizziness	413(17.9)	59（12.7）	354（19.5）	0.001
headache	291(12.6)	41（8.8）	250（13.5）	0.006
poor appetite	824(35.6)	205（44）	619（33.5）	<0.01
polypnea	808(34.9)	239（51.3）	569（30.8）	<0.01
nausea and vomiting	256(11.1)	41（8.8）	215（11.6）	0.08
somnipathy	233(10.1)	46（9.9）	187（10.1）	0.868

consciousness deteriorates	205(8.9)	100（21.5）	105（5.7）	<0.01
weight loss	32(1.4)	4（0.9）	28（1.5）	0.277

Table1. The proportion of clinical manifestations among COVID-19 patients, Pearson Chi-square test was used to evaluate the differences.

Baseline characteristics	Before matching			After 1:1 propensity matching		
	Azvudine (n=1112)	No antiviral agent(n=2721)	SMD	Azvudine (n=1103)	No antiviral agent(n=1103)	SMD
Age, n (%)			0.261			0.004
＜65	458(41.2)	1470(54)		458(41.5)	456(41.3)	
⩾65	654(58.8)	1251(46)		645(58.5)	647(58.7)	
Sex, n (%)			0.037			0.031
Men	638(57.4)	1512(55.6)		635(57.6)	618(56.0)	
Women	474(42.6)	1209(44.4)		468(42.4)	485(44.0)	
Systemic steroid, n (%)	62(5.6)	74(2.7)	0.124	53(4.8)	51(4.6)	0.008
Mechanical ventilation n (%)	118(10.6)	181(6.7)	0.129	117(10.6)	117(10.6)	0.000
Severity, n (%)	253（22.8）	440（16.2）	0.157	252（22.8）	254（23.0）	0.004

Table 2. Baseline characteristics of Azvudine and no antiviral groups before and after 1:1 propensity score-matching.

Baseline characteristics	Before matching			After 1:1 propensity matching		
	Azvudine(n=1112)	Molnupiravir(n=111)	SMD	Azvudine(n=111)	Molnupiravir (n=111)	SMD
Age, n (%)			0.060			0.037
<65	458(41.2)	49(44.1)		51(45.9)	49(44.1)	
⩾65	654(58.8)	62(55.9)		60(54.1)	62(55.9)	
Sex, n (%)			0.151			0.018
Men	638(57.4)	72(64.9)		71(64.0)	72(64.9)	
Women	474(42.6)	39(35.1)		40(36.0)	39(35.1)	
Systemic steroid, n (%)	62(5.6)	11(9.9)	0.189	13(11.7)	11(9.9)	0.078
Mechanical ventilation n (%)	118(10.6)	13(11.7)	0.036	15(13.5)	13(11.7)	0.058

Severity, n (%)	253（22.8）	22（19.8）	0.070	27(24.3)	22(19.8)	0.107

Table 3. Baseline characteristics of Azvudine and Molnupiravir groups before and after 1:1 propensity score-matching.

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Figures

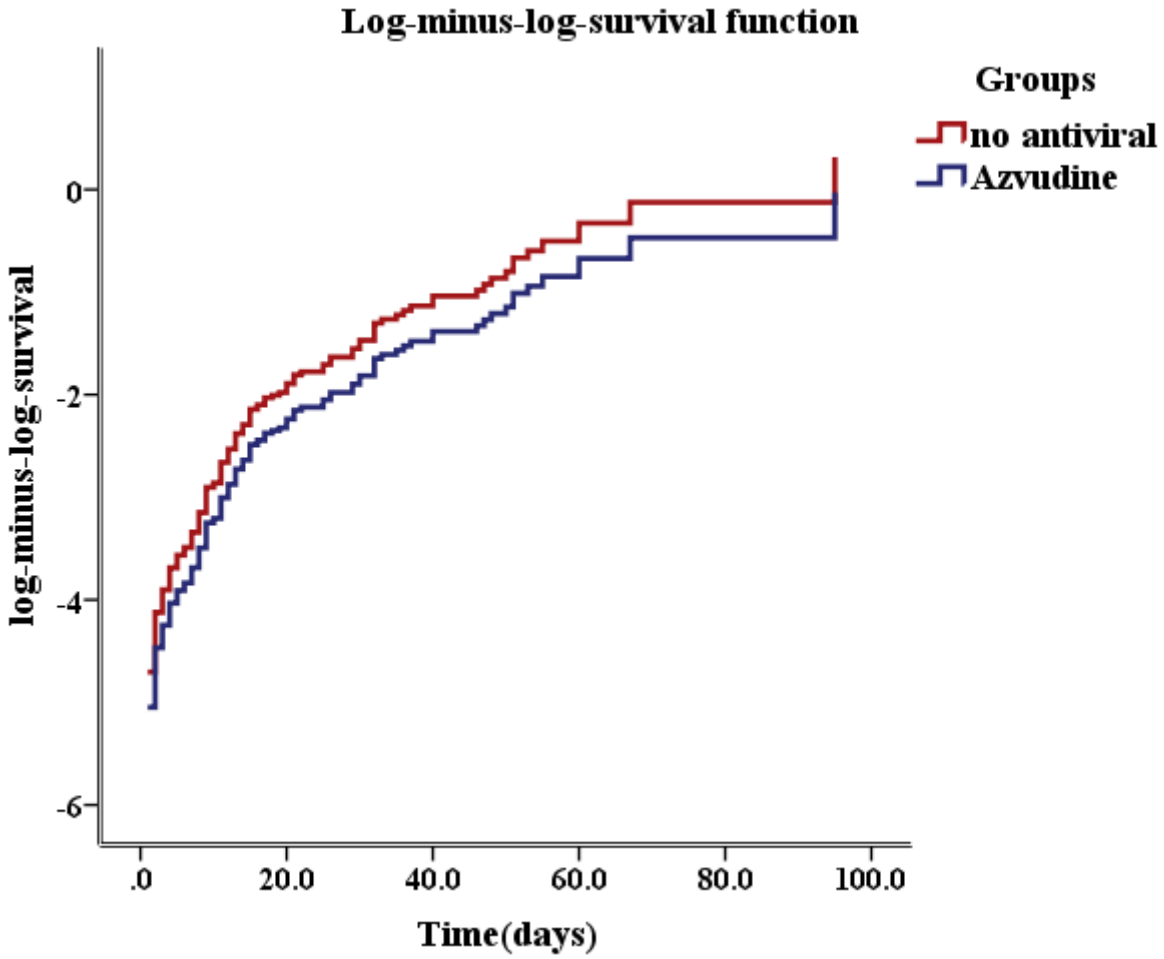

Figure 1

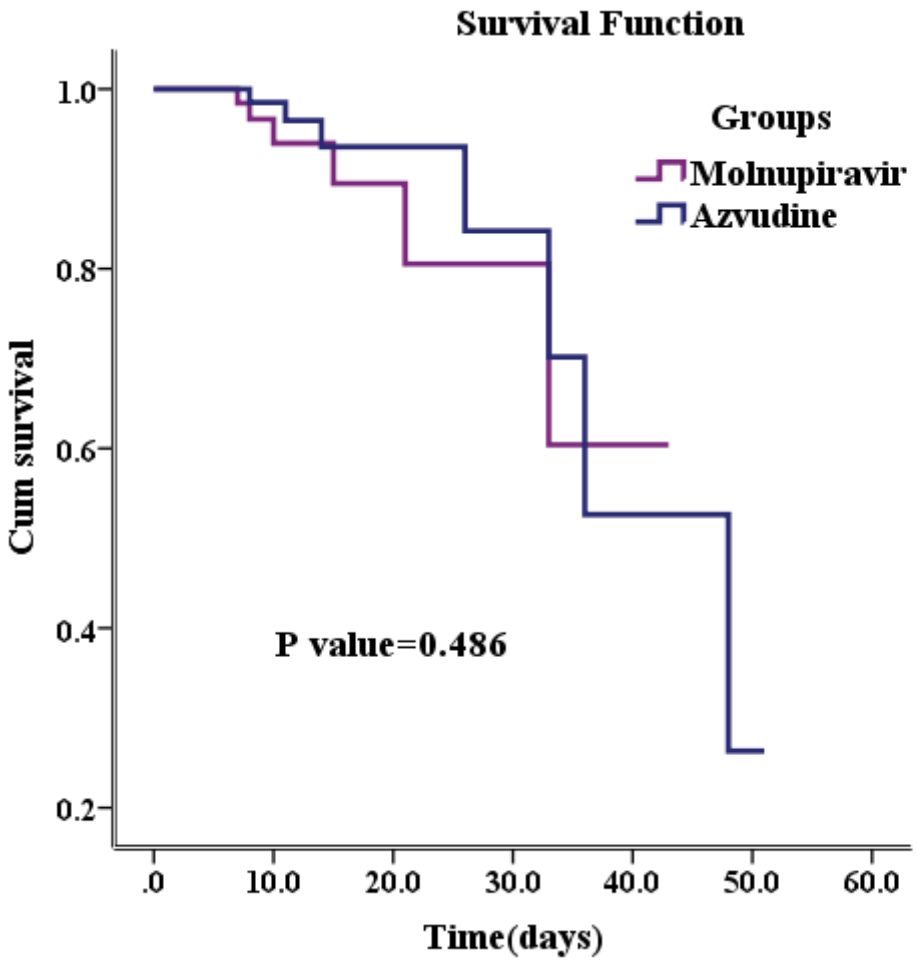

Figure 2

Figure 3

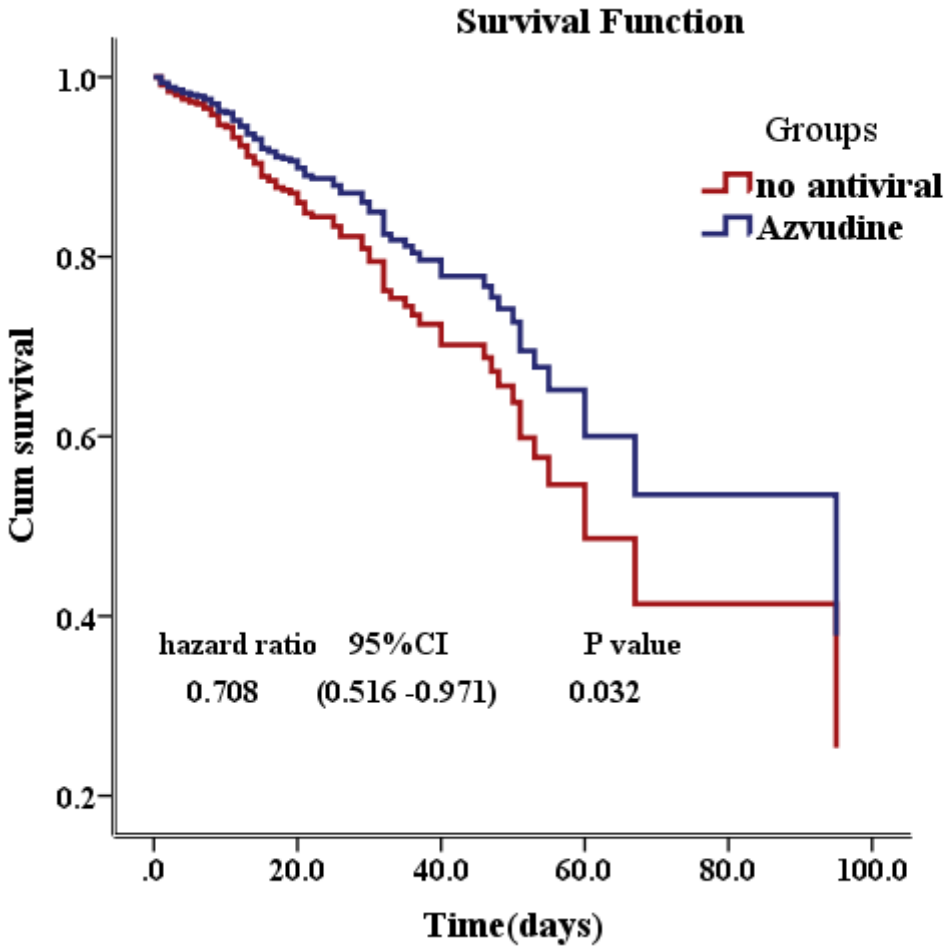

Figure 4

Figure 5

Figure 6

Figure 7

Figure 8

Figure 9

Figure 10

Figure 11

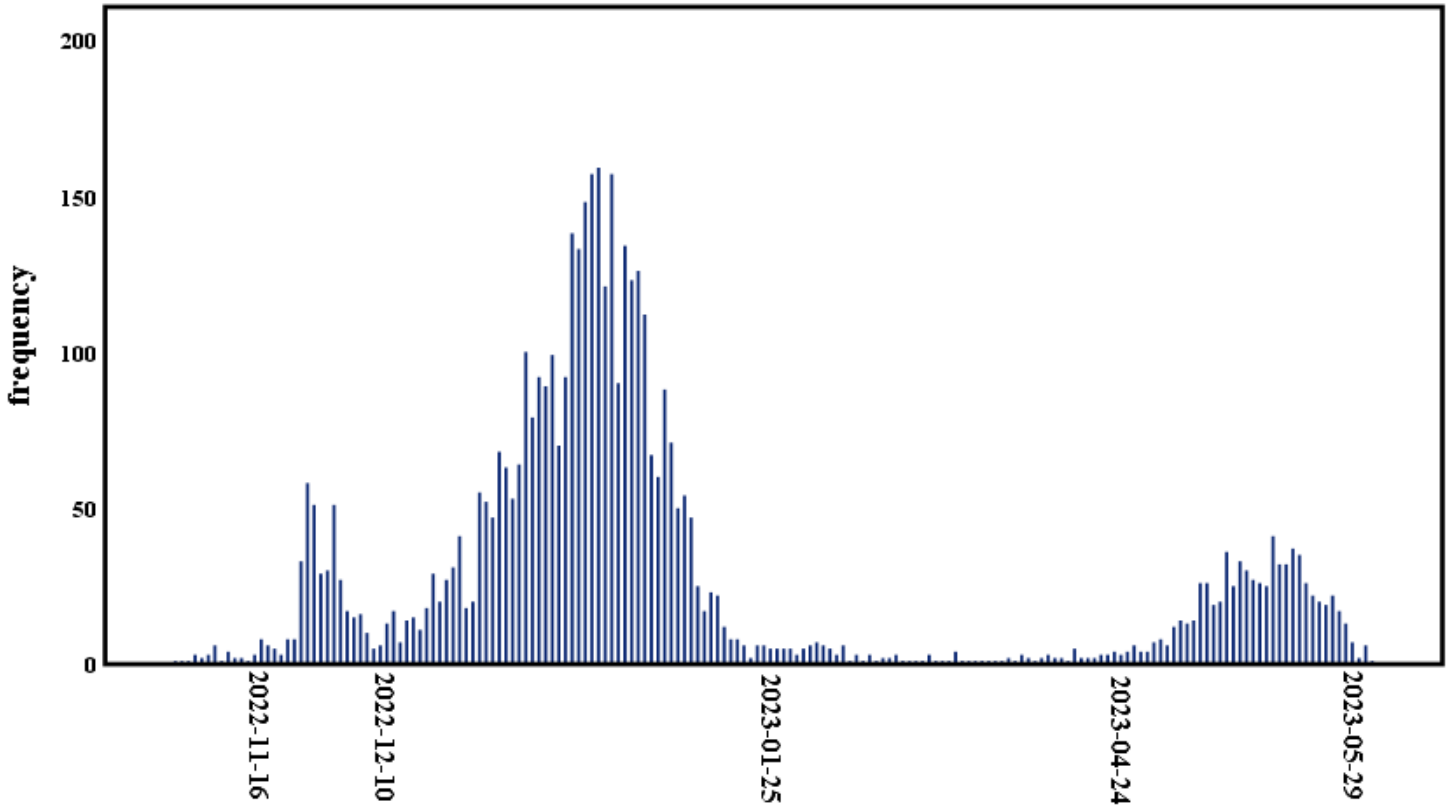

Figure 12

Figure 13

Figure 14

Supplementary Files

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- table.docx