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ORIGINAL RESEARCH

Real-World Effectiveness of Nirmatrelvir/Ritonavir in Hospitalized Older Adults with Severe Omicron COVID-19: A Retrospective Cohort Study from China

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Background: The real-world effectiveness of Nirmatrelvir/ritonavir (NMV/RTV) against the SARS-CoV-2 Omicron variant in older patients remains uncertain. We aimed to estimate the effectiveness in older patients aged 80 and above with severe COVID-19.

Methods: A retrospective study analyzed 263 COVID-19 patients aged 80 and above, admitted to the Department of Geriatrics at Jinling Hospital, affiliated with Nanjing University, between December 15, 2022, and January 15, 2023. Among them, 136 cases were non-severe, and 127 were severe. The severe cases were further categorized into a survival group (n=74) and a death group (n=53) based on 28-day mortality. Kaplan-Meier survival curves assessed 28-day survival, and Cox regression models identified factors influencing survival.

Results: Among the 127 severe cases, the death group had significantly higher rates of stroke history, renal impairment, endotracheal intubation, renal replacement therapy (RRT), bacterial infection, but significantly lower rates of NMV/RTV use and anticoagulation ($p<0.05$). Kaplan-Meier analysis indicated that NMV/RTV improved 28-day survival in severe older COVID-19 patients. Multivariate Cox regression identified NMV/RTV as a protective factor (adjusted hazard ratio [HR] 0.307, 95% confidence interval [*CI*] 0.152–0.620, $p=0.001$), while COPD (adjusted HR 2.993, 95% *CI* 1.563–5.731, $p=0.001$), stroke history (adjusted HR 3.871, 95% *CI* 1.953–7.671, $p<0.001$), and endotracheal intubation (adjusted HR 5.058, 95% *CI* 2.809–9.108, $p<0.001$) were significant risk factors for increased 28-day mortality.

Conclusion: NMV/RTV may improve the 28-day survival rate of older patients aged 80 and above with severe COVID-19.

Keywords: older adult, COVID-19, antiviral drugs, mortality

Background

Corona Virus Disease 2019 (COVID-19) is a global pandemic respiratory infectious disease. Since October 2022, the transmission advantage of sublineages such as BF.7, BQ.1, and BQ.1.1, which have stronger immune escape ability and higher transmissibility, has rapidly increased.[1] The pathogenicity of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron subvariants is significantly weakened compared to the prototype strain and other variant strains, and most infected individuals exhibit mild symptoms, with only 0.4% progressing to severe or critical illness.[2] Older patients are prone to progress to severe or critical conditions,[3] age is an independent risk factor affecting the prognosis of patients with COVID-19,[4] and are therefore a critical focus of clinical diagnosis and treatment. Effective antiviral therapy can shorten the infection course and promote recovery, and is an important approach for treating COVID-19.[2] Nirmatrelvir/ritonavir (NMV/RTV) is a co-packaged antiviral agent: NMV inhibits SARS-CoV-2 main protease (Mpro) by covalently binding to its catalytic site (Cys145), thereby blocking viral polyprotein processing, while RTV

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inhibits CYP3A4 to prolong nirmatrelvir's plasma half-life.[5] Notably, the main protease (Mpro) of Omicron subvariants, including BQ.1 and BF.7, remains highly conserved and has not exhibited significant resistance to NMV/RTV, suggesting preserved efficacy of NMV/RTV against these lineages.[6] NMV/RTV is recommended for adult patients with mild to moderate COVID-19 and high-risk factors for progression to severe disease, initiated within 5 days of symptom onset.[7]

The EPIC-HR trial included high-risk adults (median age 46 years), with subgroup analyses showing consistent efficacy in participants aged ≥65 years, but data for those ≥80 years were not specifically reported.[8] The study by Weng et al[9] concluded that in elderly patients aged over 60 years, with a median age of 82 years, NMV/RTV treatment was associated with a significant reduction in shorter viral shedding time, reduced hospital stay duration compared to conventional therapy. Specific data for oldest-old populations remain limited. The incubation period of COVID-19 manifests as dry throat, sore throat, cough, and fever, patients typically do not seek medical attention during the early stages of the disease. Whereas a US cohort study found no mortality benefit when treatment was initiated beyond 5 days of symptom onset.[10] The efficacy of NMV/RTV in patients who have been diagnosed with COVID-19 for more than 5 days remains unclear. This knowledge gap is particularly critical for older adults ≥80 years, who constitute the highest-risk population but are underrepresented in prior studies. This study analyzed the relevant factors influencing the progression to severe COVID-19 infection in older patients aged 80 and above, examined the risk factors associated with the prognosis of severe patients, and investigated the role of NMV/RTV in treating severe COVID-19 infection in older patients.

Methods

The data supporting the findings of this study are available upon reasonable request from the corresponding author.

Study Population

Continuous collection of clinical data from patients aged 80 years or above with COVID-19 admitted to the Department of Geriatrics, Jinling Hospital, Nanjing University from December 15, 2022 to January 15, 2023. The participants included in this study all possess adequate medical coverage and insurance. In accordance with institutional protocols, hospitalized patients were subjected to daily nucleic acid testing during the COVID-19 pandemic. Community patients were regularly visited by their family doctors for nucleic acid testing, and those with symptoms were promptly tested for either nucleic acid or antigen, and admitted to hospital without delay.

All patients were aged ≥80 years and tested positive for the SARS-CoV-2 nucleic acid. The diagnosis and treatment were in accordance with the standards of the "Diagnosis and Treatment Protocol for COVID-19 (Version 10)" issued by the Joint Prevention and Control Mechanism of the State Council[7] and Diagnosis and Clinical Management of COVID-19 Infection in Adults: Operational Recommendations of Peking Union Medical College Hospital (2023).[11]

NMV/RTV Dosing Protocol: (1)Standard dose: Nirmatrelvir 300 mg (150 mg ×2) + ritonavir 100 mg twice daily for 5 days, (2) Reduced dose: For eGFR 30–60 mL/min/1.73m², nirmatrelvir reduced to 150 mg + ritonavir 100 mg twice daily. In patients with eGFR < 30 mL/min/1.73 m², a reduced dosing regimen was used only after obtaining informed consent. (3) Timing: Initiated within ≤5 days of symptom onset. With the patient's consent, the medication may be administered even if symptom onset has exceeded 5 days. Before initiation of NMV/RTV, all concurrent medications were reviewed by a clinical pharmacist to assess potential interactions. Adjustments such as temporary discontinuation, dose modification, or substitution with alternative medications were made accordingly.[12] Other treatments administered included oxygen supplementation, prone position ventilation, intravenous immunoglobulin (IVIG), corticosteroids, convalescent plasma, baricitinib, tocilizumab, and anticoagulant therapy.[7,11] Bacterial infection was defined as an infection that occurred during illness or hospitalization, with the following criteria: (1)The detection of pathogenic bacteria in sputum, bronchoscopy sputum, bronchoalveolar lavage, or blood culture samples. (2)The presence of purulent sputum, new pulmonary infiltrates on imaging, and elevated procalcitonin levels (≥0.5 ng/mL). Bacterial infection was confirmed by two pulmonology experts, and antibiotics were initiated or adjusted accordingly.

Patients were included if they were (a) confirmed diagnosis of COVID-19 infection; (b) age ≥ 80 years; (c) received standardized clinical management consistent with national and expert consensus guidelines.[7,11]

Patients were excluded if they (a)took other approved antiviral drugs for COVID-19, such as Azvudine, Molnupiravir, Amubarvimab/Romlusevimab Injection;[7] (2)took NMV/RTV but did not complete a 5-day course; (3)with incomplete clinical data or laboratory results; (4) were lost to follow-up or refused treatment (Figure 1).

Definition and grading of severity of COVID-19: Severe COVID-19 includes severe and critical cases. Severe cases are defined as meeting any of the following criteria: (1) dyspnea, respiratory rate ≥ 30 breaths/min; (2) oxygen saturation ≤ 93% at rest; (3) PaO2/FiO2 ≤ 300 mmHg (1 mmHg = 0.133 kPa); (4) radiographic progression of lung infiltrates > 50% within 24–48 hours. Critical cases are defined as meeting any of the following criteria: (1) respiratory failure requiring mechanical ventilation; (2) shock; (3) other organ failure requiring ICU care.

Clinical Data

Collect demographic and diagnostic data for all enrolled patients. Based on the severity of disease, patients were divided into non-severe and severe groups. Differences in general information, medical history, and treatment were recorded and compared between different disease classification groups.

We retrospectively analyzed patients' medical records to determine demographic, diagnostic, and clinical data. Comorbidities were verified by diagnosis records and corresponding ICD-9/ICD-10 diagnostic codes. Date of diagnosis, baseline characteristics, medical history, laboratory findings, disease severity, treatment regimen and duration, complications were all assessed. The presence of renal impairment was defined as an estimated glomerular filtration rate (GFR) <60 mL/min/1.73m2 by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for the Asian population.[13] In this study, the definition of a history of renal impairment did not include patients who had normal renal function in the past but developed acute kidney injury after COVID-19.

All patients underwent nutritional risk assessment when admission. The Mini Nutritional Assessment (MNA) was applied to assess nutritional risk in geriatric patients, with a score ≤23.5 indicating a risk of malnutrition.[14]

Statistical Analysis

Continuous variables presented as mean ± standard deviation or median (interquartile range) were compared using Student *t* test or Manne Whitney *U*-test as appropriate. Categorized variables presented as n (%) were compared using Pearson χ^2 test, continuous calibration χ^2 test or Fisher exact test. Kaplan-Meier method was used to draw the survival curve and calculate the survival rate, and Log rank test was used for comparison between groups. Cox regression covariate-adjusted incremental models were used to estimate effects for each covariate, with simultaneous adjustment for potential confounders in multivariable models. Proportional hazards assumptions and multicollinearity in the models

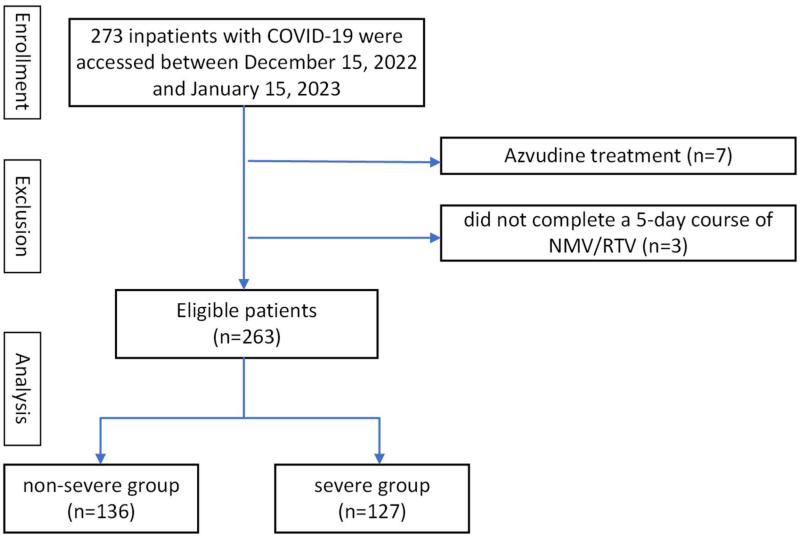

Figure 1 Flowchart of eligible inpatients.

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were verified. Variables with $p<0.1$ in univariate analysis were included in multivariate Cox proportional risk regression analysis in Survival model one. Survival model one included heart failure, chronic obstructive pulmonary disease (COPD), stroke history, renal impairment, endotracheal intubation, renal replacement therapy (RRT), use of NMV/RTV, anticoagulation, and bacterial infection. Survival model two included COPD, stroke history, endotracheal intubation, and use of NMV/RTV from the final Cox regression model using the backward Wald. Data were analyzed using SPSS24.0 (IBM Corp., Armonk, NY, USA) and R 4.2.2 (R Foundation, Vienna, Austria). A two-sided p value < 0.05 was considered to be statistically significant.

Results

The Baseline Demographic and Clinical Characteristics of the Study Population

After excluding 7 patients treated with azvudine and 3 patients who did not complete the 5-day NMV/RTV treatment course, a total of 263 older patients ≥80 years with COVID-19 were included in the study. The median age was 93 (91, 95) years old, with 241 (91.63%) males. Among them, 136 (51.71%) were classified as mild/moderate (non-severe group), and 127 (48.29%) were classified as severe/critical (severe group). Within 28 days follow up, 55 patients (20.91%) died. The non-severe group had lower age, lower proportions of atrial fibrillation, heart failure, renal impairment, dementia, and malnutrition risk than the severe group ($p<0.05$), while the prevalence of hypertension was higher ($p<0.05$). There were no significant differences in gender and community or hospital-acquired infection between the two groups ($p>0.05$), and there were no statistically significant differences in coronary heart disease, COPD, stroke, diabetes, and cancer history between the two groups ($p>0.05$). In terms of treatment, the severe group had higher proportions of NMV/RTV, anticoagulants, steroids and tocilizumab use ($p<0.05$), as well as a higher proportion of bacterial infection ($p<0.05$). The proportion of baricitinib use was higher in the severe group, but the difference was not statistically significant ($p=0.058$) (Table 1).

Table 1 Clinical Information Between Different Conditions in Older Patients Aged ≥80 years with COVID-19

Index	All Patients (n=263)	Non-severe Group (n=136)	Severe Group (n=127)	χ^2/Z	p value
Age[years, M (P25, P75)]	93(91,95)	92(89,94)	93(91,96)	3.287	0.001
Male[n, (%)]	241(91.63)	123(90.44)	118(92.91)	0.524	0.469
Hospital-acquired infection [n, (%)]	125(47.53)	64(47.06)	61(48.03)	0.025	0.875
Comorbidities					
Hypertension[n, (%)]	198(75.29)	111(81.62)	87(68.50)	6.070	0.014
Coronary heart disease[n, (%)]	186(70.72)	90(66.18)	96(75.59)	2.811	0.094
Atrial fibrillation[n, (%)]	53(20.15)	19(13.97)	34(26.77)	6.688	0.010
Heart failure[n, (%)]	67(25.48)	19(13.97)	48(37.80)	19.635	<0.001
COPD[n, (%)]	54(20.53)	24(17.65)	30(23.62)	1.437	0.231
Stroke[n, (%)]	35(13.31)	16(11.76)	19(14.96)	0.581	0.446
Diabetes[n, (%)]	104(39.54)	49(36.03)	55(43.31)	1.455	0.228
Renal impairment[n, (%)]	67(25.48)	24(17.65)	43(33.86)	9.091	0.003
Tumor[n, (%)]	46(17.49)	28(20.59)	18(14.17)	1.873	0.171
Dementia[n, (%)]	47(17.87)	17(12.50)	30(23.62)	5.535	0.019
Malnutrition risk[n, (%)]	186(70.72)	84(61.76)	102(80.31)	10.914	0.001
Treatment					
NMV/RTV[n, (%)]	71(27.00)	25(18.38)	46(36.22)	10.603	0.001
Anticoagulation[n, (%)]	148(56.27)	56(41.18)	92(72.44)	26.088	<0.001
Steroid[n, (%)]	104(39.54)	25(18.38)	79(62.20)	52.755	<0.001
Baricitinib[n, (%)]	8(3.04)	1(0.74)	7(5.51)	3.590	0.058
Tocilizumab[n, (%)]	5(1.90)	0(0)	5(3.94)		0.025
Bacterial infection[n, (%)]	138(52.47)	34(25.00)	104(81.89)	85.227	<0.001

Abbreviations: COVID-19, Coronavirus Disease 2019; COPD, Chronic Obstructive Pulmonary Disease; NMV/RTV, Nirmatrelvir/ritonavir.

Comparison of Clinical Data and Treatment Between Different Clinical Outcomes in Severe Older Patients Aged ≥80 and Above with COVID-19

127 cases of severe/critical older patients with COVID-19 were included in this study. The clinical data and treatment of the death group (n=53) and the survival group (n=74) were compared. Age, the proportion of patients with stroke history, and renal impairment was higher in the death group than in the survival group ($p<0.05$). The proportion of patients comorbid heart failure was higher in the death group than in the survival group, but the difference was not statistically significant ($p=0.065$). There was no statistically significant difference in gender, community-acquired or hospital-acquired infection, hypertension, coronary heart disease, atrial fibrillation, COPD, diabetes, cancer history, dementia, and malnutrition risk between the two groups ($p>0.05$). In terms of treatment, the proportion of patients who underwent tracheal intubation, RRT, and anticoagulation was higher in the death group ($p<0.05$), and the proportion of patients with bacterial infection was higher in the death group ($p<0.05$). The proportion of patients taking NMV/RTV was lower in the death group ($p<0.05$). There was no significant difference in the time of NMV/RTV use, steroids use, baricitinib use, and tocilizumab use between the two groups ($p>0.05$) (Table 2).

Multivariate Cox Analysis of 28-Day Mortality Predictors in Older Patients Aged ≥80 years with Severe COVID-19 Infection

The Kaplan-Meier survival curve results showed that NMV/RTV treatment could improve the 28-day survival of older patients with severe COVID-19 (Log-rank 9.547, $p=0.002$) (Figure 2). The results of the multivariate Cox regression analysis showed

Table 2 Comparison of Clinical Characteristics Between the Survival Group and the Death Group

Index	All Patients (n=127)	Survival Group (n=74)	Death Group (n=53)	χ^2/Z	*p* value
Age[years, M (P25, P75)]	93(91,96)	93(91,96)	93(91.5,96)	3.287	0.001
Male[n, (%)]	118(92.91)	67(90.54)	51(96.23)	0.776	0.378
Hospital-acquired infection [n, (%)]	61(48.03)	39(52.70)	22(41.51)	1.550	0.213
Comorbidities					
Hypertension[n, (%)]	87(68.50)	52(70.27)	35(66.04)	0.256	0.613
Coronary heart disease[n, (%)]	92(72.44)	52(70.27)	40(75.47)	0.001	0.979
Atrial fibrillation[n, (%)]	34(26.77)	16(21.62)	18(33.96)	2.399	0.121
Heart failure[n, (%)]	48(37.80)	23(31.08)	25(47.17)	3.400	0.065
COPD[n, (%)]	30(23.62)	14(18.92)	16(30.19)	2.174	0.140
Stroke[n, (%)]	19(14.96)	6(8.11)	13(24.53)	6.545	0.011
Diabetes[n, (%)]	55(43.31)	33(44.59)	22(41.51)	0.120	0.729
Renal impairment[n, (%)]	43(33.86)	19(25.68)	24(45.28)	5.302	0.021
Tumor[n, (%)]	18(14.17)	11(14.86)	7(13.21)	0.070	0.792
Dementia[n, (%)]	30(23.62)	18(24.32)	12(22.64)	0.048	0.826
Malnutrition risk[n, (%)]	102(80.31)	58(78.38)	44(83.02)	0.421	0.517
Treatment					
Tracheal intubation	44(34.65)	10(13.51)	34(64.15)	31.972	<0.001
Renal replacement therapy	17(13.39)	5(6.76)	12(22.64)	6.721	0.010
NMV/RTV[n, (%)]	46(36.22)	35(47.30)	11(20.75)	9.418	0.002
Timing of NMV/RTV					0.713
≤5 day	14	10(13.51)	4(7.55)		
>5day	32	25(33.78)	7(13.21)		
Anticoagulation[n, (%)]	92(72.44)	59(79.73)	33(62.26)	4.719	0.030
Steroid[n, (%)]	79(62.20)	50(67.57)	29(54.72)	2.169	0.141
Baricitinib[n, (%)]	7(5.51)	6(8.11)	1(1.89)		0.237
Tocilizumab[n, (%)]	5(3.94)	3(4.05)	2(3.77)		0.999
Bacterial infection[n, (%)]	104(81.89)	55(74.32)	49(92.45)	6.843	0.009

Abbreviations: COVID-19, Coronavirus Disease 2019; COPD, Chronic Obstructive Pulmonary Disease; NMV/RTV, Nirmatrelvir/ritonavir.

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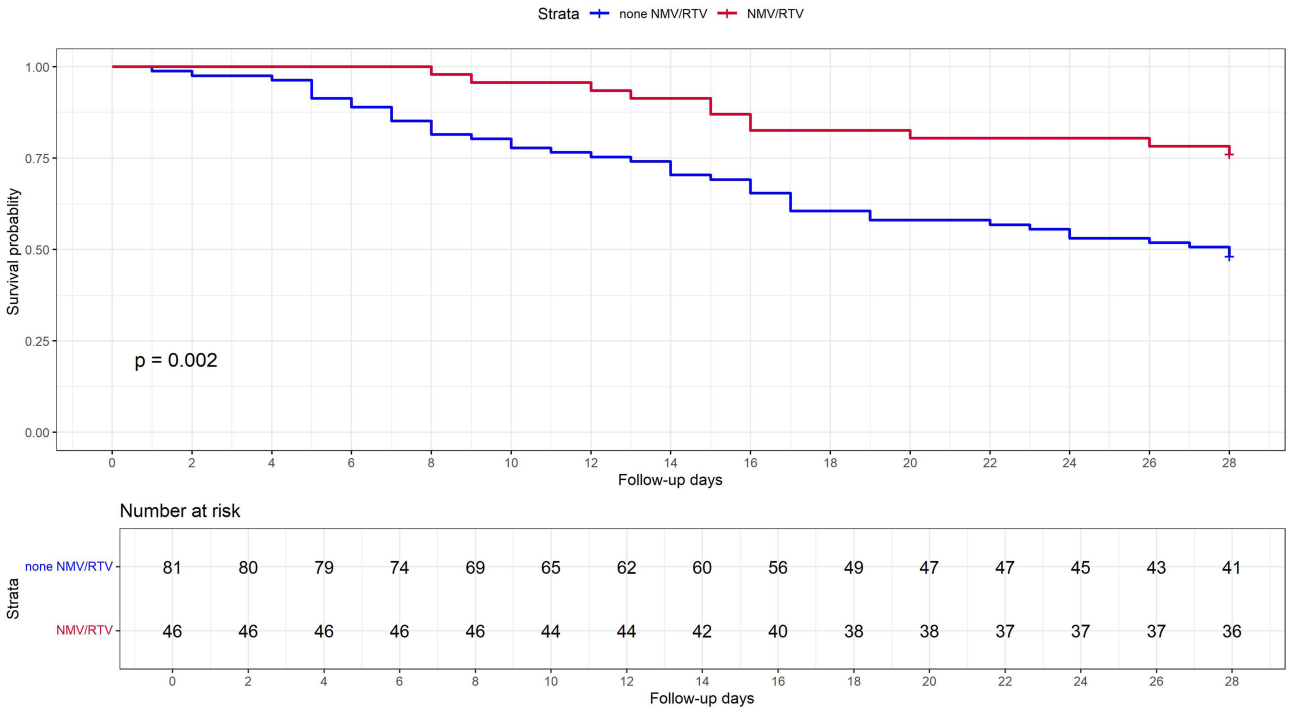

Figure 2 Kaplan-Meier survival curves of survival probability by patients treated with or without NMV/RTV.
Abbreviation: NMV/RTV, Nirmatrelvir/ritonavir.

that NMV/RTV treatment was an independent protective factor for 28-day mortality in older patients with severe/critical COVID-19 (adjusted hazard ratio [HR] 0.307, 95% confidence interval [*CI*] 0.152–0.620, p=0.001). COPD (adjusted HR 2.993, 95% CI 1.563, 5.731, p=0.001), stroke (adjusted HR=3.871, 95% CI 1.953, 7.671, p<0.001), and tracheal intubation (adjusted HR=5.058, 95% CI 2.809, 9.108, p<0.001) were independent risk factors for 28-day mortality in older patients with severe COVID-19. Details are shown in Table 3.

Table 3 Univariate and Multivariate Analysis of Risk Factors for Prognosis of Severe Older Patients Aged ≥80 years with COVID-19

	Univariate Analysis		Multivariate Analysis			
			Model 1		Model 2	
	HR (95% CI)	*p* Value	Adjusted HR (95% CI)	*p* value	Adjusted HR (95% CI)	*p* Value
Heart failure	1.674(0.976,2.872)	0.061	1.292(0.674,2.476)	0.440		
COPD	1.743(0.969,3.135)	0.063	2.831(1.463,5.476)	0.002	2.993(1.563,5.731)	0.001
Stroke	2.631(1.401,4.941)	0.003	4.218(1.976,9.003)	<0.001	3.871(1.953,7.671)	<0.001
Renal impairment	1.826(1.062,3.138)	0.029	1.244(0.612,2.528)	0.546		
Tracheal intubation	4.991(2.824,8.820)	<0.001	4.025(2.088,7.759)	<0.001	5.058(2.809,9.108)	<0.001
RRT	2.155(1.131,4.104)	0.020	1.140(0.510,2.546)	0.750		
NMV/RTV	0.369(0.190,0.717)	0.003	0.359(0.171,0.753)	0.007	0.307(0.152,0.620)	0.001
Anticoagulation	0.491(0.282,0.857)	0.012	0.667(0.359,1.240)	0.201		
Bacterial infection	3.142(1.132,8.175)	0.028	1.355(0.449,4.083)	0.590		

Abbreviations: COVID-19, Coronavirus Disease 2019; COPD, Chronic Obstructive Pulmonary Disease; RRT, renal replacement therapy; NMV/RTV, Nirmatrelvir/ritonavir.

Discussion

This study showed that the use of NMV/RTV, anticoagulants, steroids, and tocilizumab was more common in severe cases compared to non-severe cases. Among the severe cases, the NMV/RTV treatment was associated with improved short-term survival rates in older patients aged ≥80 years with severe COVID-19.

COVID-19 is clinically classified as mild, moderate, severe, and critical by the "Diagnosis and Treatment Protocol for COVID-19 (Version 10)".[7] Patients with severe and critical conditions progress more rapidly, and severe complications such as multiple organ failure, sepsis, and shock can endanger life. The clinical prognosis of severe and critical patients is worse than that of mild and moderate patients. Early recognition of severe and critical patients and timely intervention is a key task in the treatment of COVID-19.

Older patients often suffer from multiple chronic conditions. This study revealed that multiple comorbid diseases are associated with the progression to severe condition in older patients with COVID-19. There were statistically significant differences in comorbid diseases (atrial fibrillation, heart failure, renal impairment, dementia, and malnutrition risk) between the non-severe and severe groups, which is consistent with other research results.[15,16] Older patients with comorbidities may experience severe lung function impairment and other organ dysfunction, necessitating timely hospitalization and treatment. The indications, drug selection, and timing of antiviral therapy have received widespread attention in COVID-19 management. The virus titer is highest during the initial stages of infection, and the treatment's efficacy is greatest when administered early.[17] However, the findings of this real-world study suggest that the proportion of older patients receiving NMV/RTV treatment was relatively low, with only 27% patients being treated, and the proportion was even lower among those with mild to moderate symptoms. The proportion of patients taking NMV/RTV was higher for severe/critical patients. Further analysis revealed that among severe/critical patients, 14 out of 46 took NMV/RTV within 5 days of diagnosis, while 32 out of 46 took NMV/RTV after 5 days.

NMV/RTV is a Pfizer-developed oral antiviral drug for the treatment of mild to moderate COVID-19 in patients aged 12 years or older with a body weight of at least 40 kg, who are at high risk of progressing to severe illness within 5 days of symptom onset. On December 22, 2021, the FDA issued an emergency use authorization for NMV/RTV, making it the first FDA-authorized oral antiviral drug for the treatment of COVID-19.[18] Approved for sale in China through special approval on February 12th, 2022,[19] and has been included in the medical insurance payment. NMV/RTV is mainly used in China for early treatment of high-risk populations, advanced age and multiple chronic diseases are high-risk factors. In COVID-19 patients with concurrent chronic cardiovascular disease, the direct damage to the cardiovascular system and the cardio-pulmonary interaction can lead to increased difficulty in treatment. COVID-19 infection is associated with increased risk of adverse cardiovascular outcomes.[20] It is necessary to adjust the dosage of chronic disease medications with narrow therapeutic index or replace them with similar drugs that have relatively small drug-drug interactions (DDI) effects, or suspend the "forced drugs" for at least 8 days after NMV/RTV administration. In this regard, older patients with multimorbidities will face complex management of polypharmacy. In clinical practice, particular attention should be paid to the rational use of NMV/RTV in older population with multimorbidities. If chronic disease medications are currently essential to the patient's clinical condition and there is no possibility of adjusting the dosage or replacing or stopping the drug for at least 8 days, the decision to replace NMV/RTV with other antiviral treatment regimens should be made after a thorough consideration of the benefits and risks. Some older people, due to their chronic disease management needs and concerns about NMV/RTV, did not consider taking NMV/RTV therapy in the early stages of the disease when their symptoms were mild.

For older patients aged 80 and above with COVID-19 whose disease duration exceeds 5 days, there is currently a lack of relevant clinical studies to determine whether antiviral treatment remains beneficial. Some studies suggest that the detection of low-level nucleic acid in the body of such patients does not necessarily indicate the presence of live and infectious SARS-CoV-2,[21] thereby questioning the necessity and value of continued antiviral therapy. However, in cases where high viral loads are still detectable, antiviral treatment may aid in terminating the persistent viral carriage. In this study, an analysis of 46 severe or critically ill patients treated with NMV/RTV found that there was no correlation between short-term prognosis of COVID-19 and the timing of medication intake, whether taken within 5 days or 5 days later. This may be related to the slow clearance and delayed shedding of the virus in older patients,[22] which can cause prolonged and persistent infection. It is suggested that older patients with a COVID-19 disease course of more than 5 days can consider a rescue treatment with NMV/RTV.

In conclusion, this study found that heart failure, renal impairment, and dementia history are risk factors for older COVID-19 patients aged 80 and above to progress to severe illness. NMV/RTV can improve short-term prognosis in older patients with severe COVID-19.

This study has several limitations. Firstly, as a single-center retrospective study with a predominantly male population, it may be subject to selection bias and limited generalizability. Secondly, the sample size is relatively small, which may increase the risk of overfitting in multivariate models. Additionally, there is a lack of clinical data on survival and long-term outcomes of discharged patients, making it difficult to assess the impact of the above factors on the long-term prognosis of patients with COVID-19. Although we attempted to adjust for many confounding factors, other unmeasured or unknown confounding factors, such as vaccination status, Omicron subvariants, and frailty, may also have played a role. Therefore, the results of this study should be interpreted with caution, and further clarification through large-scale clinical studies with external validation is necessary.

Conclusion

This study found that NMV/RTV can improve short-term prognosis in older patients with severe COVID-19. Delayed initiation of NMV/RTV in older patients (≥80 years) with severe or critical COVID-19 may still confer survival benefits.

Abbreviations

COVID-19, Coronavirus disease 19; NMV/RTV, Nirmatrelvir/ritonavir; RRT, renal replacement therapy; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2; COPD, chronic obstructive pulmonary disease; PaO2/FiO2, Persistent arterial partial pressure of oxygen/fraction of inspired oxygen; GFR, glomerular filtration rate; ACE2, Angiotensin-converting enzyme 2.

Human and Animal Rights

All cohorts included in the analysis were conducted according to the Declaration of Helsinki.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethics Approval and Consent to Participate

The study was approved by the Institutional Review Board of Jinling Hospital (2017NZGKJ-079). In addition, this study was performed in accordance with the ethical principles of the Declaration of Helsinki.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts.

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