Efficacy and safety of Paxlovid in severe adult patients with SARS-Cov-2 infection: a multicenter randomized controlled study

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Summary

Background **Nirmatrelvir plus ritonavir (Paxlovid) reduced the risk of hospitalization or death by 89% in high-risk, ambulatory adults with COVID-19. We aimed at studying the efficacy and safety of Paxlovid in hospitalized adult patients with SARS-Cov-2 (Omicron BA.2.2 variant) infection and severe comorbidities.**

Methods **We conducted an open-label, multicenter, randomized controlled trial in which hospitalized adult patients with severe comorbidities were eligible and assigned in a 1:1 ratio to receive either 300 mg of nirmatrelvir plus**

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100 mg of ritonavir every 12 h for 5 days with standard treatment or only standard treatment. All-cause mortality on day 28, the duration of SARS-CoV-2 RNA clearance, and safety were evaluated.

Findings 264 patients (mean age, 70.35 years; 122 [46.21%] female) who met the criteria were enrolled at 5 sites in Shanghai from April 10 to May 19 in 2022. After randomization, a total of 132 patients were assigned to receive Paxlovid treatment plus standard treatment, and 132 patients were assigned to receive only standard treatment. The overall 28-day mortality was 4.92%, 8 patients died in the standard treatment group and 5 died in the Paxlovid plus standard treatment group. There was no significant difference in mortality from any cause at 28 days between the Paxlovid plus standard treatment group and the standard treatment group (absolute risk difference [ARD], 2.27; 95% CI −2.94 to 7.49, P = 0.39). There was no significant difference in the duration of SARS-CoV-2 RNA clearance among the two groups (mean days, 10 in Paxlovid plus standard treatment group and 10.50 in the standard treatment group; ARD, −0.62; 95% CI −2.29 to 1.05, P = 0.42). The incidence of adverse events that occurred during the treatment period was similar in the two groups (any adverse event, 10.61% with Paxlovid plus standard treatment vs. 7.58% with the standard, P = 0.39; serious adverse events, 4.55% vs. 3.788%, P = 0.76).

Interpretation Paxlovid showed no significant reduction in the risk of all-cause mortality on day 28 and the duration of SARS–CoV-2 RNA clearance in hospitalized adult COVID-19 patients with severe comorbidities.

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Keywords: Paxlovid; Efficacy; Safety; Severe; Comorbidities; SARS-CoV-2

Research in context

Evidence before this study

We searched PubMed on Aug 1, 2022, for articles that describe the Paxlovid treatment in patients with COVID-19 infection, using the search term "SARS-Cov2", "COVID-19", "Paxlovid" without any language restrictions. Paxlovid showed inconsistent therapeutic effects in different populations. The EPIC-HR trial showed that Paxlovid reduced hospitalization and 28-day mortality rates in ambulatory and unvaccinated COVID-19 patients. However, there was no evidence of the Paxlovid therapeutic effect on adult hospitalized COVID-19 patients with severe comorbidities. Moreover, most studies have been conducted in unvaccinated patients and pre-date the omicron variant. Therefore, data are particularly needed on the efficacy and safety of Paxlovid in adult hospitalized patients with SARS-Cov-2 (Omicron BA.2.2 variant) infection and severe comorbidities.

Added value of this study

To our knowledge, this was the first randomized trial on the efficacy and safety of Paxlovid treatment in hospitalized adult patients with SARS-Cov-2 infection (Omicron BA.2.2 variant) and severe comorbidities. This trial demonstrated that Paxlovid showed no significant reduction in the risk of all-cause mortality on day 28 and the duration of SARS-CoV-2 RNA clearance.

Implications of all the available evidence

Paxlovid treatment for COVID-19 patient with severe comorbidities showed no significant clinical benefits. Therefore, Paxlovid is not recommended for severe adult patients with SARS-Cov-2 infection. The development of safe, effective drugs to treat severe adult patients with SARS-Cov-2 infection remains crucial in preventing deaths of those suffering.

Introduction

With above 583 million confirmed cases and over 6.4 million of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) related deaths by 9 August 2022,[1] COVID-19 places tremendous burden to public health and economy system. Development of efficient vaccines enabled some control of the pandemic by limiting disease transmission and progression to death,[2] albeit variable vaccination coverage.[3–5] With the efforts of the government, the overall vaccination coverage exceeds 90% in Shanghai, however the coverage was remained low in older adults or patients with comorbidities.[6,7] Moreover, the currently dominant strain Omicron showed high transmissibility and immunologic escape.[8] Paxlovid combines nirmatrelvir and ritonavir.[9] Nirmatrelvir selectively and reversibly inhibits the main polyprotein protease (Mpo) of SARS-CoV-2, preventing the virus from making any functional proteins to replicate.[10] Ritonavir, an HIV-1 and HIV-2 protease inhibitor, irreversibly inhibits CYP3A, thereby increasing nirmatrelvir concentrations.[10,11] The EPIC-HR trial found in 2246 unvaccinated high-risk,

ambulatory COVID-19 patients, that, as compared to placebo, Paxlovid reduced hospitalization and 28-day mortality rates by 89.1% and 88.9%, respectively.[12] Paxlovid did not prevent low-risk and standard risk patients from progressing to severe COVID-19.[13,14] In a retrospective study of 180,351 patients with at least 1 comorbidity or condition associated with high risk for severe COVID-19, Paxlovid was associated with 46% risk reduction of disease progression.[15] No study has been published in hospitalized patients infected by SARS-CoV-2 (Omicron BA.2.2 variant) and studies published to date (the EPIC HR study) were with non-vaccinated patients. Our study aims to evaluate the efficacy and safety of Paxlovid in hospitalized adult patients with SARS-CoV-2 (Omicron BA.2.2 variant) infection and severe comorbidities.

Methods

Trial design and oversight

This open-label, multicenter, randomized controlled trial was conducted on two parallel groups from April 10 to May 19, 2022, in five COVID-19-designated hospitals in Shanghai, China. The study was approved at Shanghai Jiao Tong University School of Medicine, Ruijin Hospital Ethics Committee, and ethic committee at each participating site (http://www.chictr.org.cn/, ChiCTR2200058477). Written informed consent was obtained prior to randomization from the patient or her/his legal representative. Details protocol of the trial is provided in Appendix 2.

Participants

Hospitalized patients were eligible if aged from 18 to 90 years old, had severe comorbidities, confirmed SARS-CoV-2 infection by positive of real-time PCR within the previous 48 h, duration from symptoms onset to hospital admission less than 5 days or the SARS-CoV-2 nucleic acid Ct value ≤ 25 by RT-PCR. The detailed eligibility criteria are provided in Appendix 2. The severity of COVID-19 was identified according to the Guidelines on the Diagnosis and Treatment of COVID-19 (Ninth Trial Edition).[16]

The inclusion exclusion criteria were as follows: Age >18 years and <90 years, admission within 48 h, and with severe comorbidities. The severe patients were defined as patients with severity comorbidities, SOFA or Charlson score ≥2. Severe comorbidities were defined as immunosuppressive disease or immunosuppressive status, chronic obstructive pulmonary disease, hypertension complicated with target organ injury, acute and chronic cardiac insufficiency, chronic renal insufficiency, etc. The detailed introduction of severity comorbidities was showed in Appendix 2. The exclusion criteria were as follows: history of active liver disease, patient is on dialysis or EGFR <45 mL/min/1.73 m^2 within the past six months, HIV infection, history of allergy to Paxlovid ingredients, etc. The details of exclusion criteria were showed in Appendix 2.

Randomization and blinding

Eligible patients were randomly assigned in a 1:1 ratio by a central randomization system to receive either nirmatrelvir plus ritonavir or standard treatment. Randomization was stratified by the severity of COVID-19, SOFA plus Charlson scores. Although this is an open label study, the treating physicians were blinded to the patient's grouping information unless it was considered necessary to know the treatment assignment of the patient by the management group and treating physicians.

Study interventions

In experimental arm, patients received Paxlovid at a dose of 300 mg nirmatrelvir [two tablets] + 100 mg ritonavir [one tablet], orally administered every 12 h for 5 days, in addition to standard treatment based on Guidelines on the Diagnosis and Treatment of COVID-19 (Ninth Trial Edition). In control arm, patients received only standard treatment. Standard care included antivirus, anticoagulant therapy, prone position ventilation, awake prone positioning, corticosteroid therapy, and nutrient support, etc. The detailed description was showed on Appendix 2.

Clinical and laboratory data

Data on demographic characteristics, the severity of illness, comorbidities, vaccination status, SOFA and Charlson scores, and other clinical and laboratory examinations were collected. Organ function, vital signs, nucleic acid test, and interventions (i.e., Human immunoglobulin for COVID-19, Corticosteroids, CRRT, ECMO, etc.) were recorded daily through day 28. Although each hospital has its nucleic acid testing policies, we recommended performing nucleic acid testing for each patient daily from nasopharyngeal swab. RT-PCR assays for SARS-CoV-2 were performed using the 2019-nCoV Nucleic acid detection kit (Biogerm, Shanghai, China). The kit detected the virus through the identification of 2 genetic markers named nucleocapsid (N) and open reading frame (ORF)1 ab gene. SARS-CoV-2 RNA clearance was defined as both negative for N and ORF1ab genes (Ct value ≥ 35 by real-time PCR) on two successive days outlined in the Guidelines on the Diagnosis and Treatment of COVID-19 (Ninth Trial Edition). Adverse events were assessed during the treatment duration.

Outcomes

The primary endpoint was 28-day all-cause mortality. Further exploratory analyses of the risk of death were assessed in subgroup participants based on the duration since symptoms onset to hospital admission, body mass index, Ct value of N and ORF1ab gene, and the total

number of comorbidities. The secondary endpoints for efficacy included in-hospital mortality, the proportion of progress to severe COVID-19 within 14 days, the proportion of acute exacerbation from the chronic disease within 14 days, SARS–CoV-2 RNA clearance within 7 days and 14 days, the duration of SARS–CoV-2 RNA clearance, length of hospital and ICU stay, and organ support days to 28 days. Primary outcome and secondary outcomes were also analyzed in patients who completed per-protocol treatment as sensitivity analyses. Safety endpoints were the occurrence of adverse events during or after the treatment period, as recorded by the investigators, and were coded according to the Medical Dictionary for Regulatory Activities (MedDRA), version 24.0. Further exploratory analyses of the SARS–CoV-2 RNA clearance were assessed in subgroup participants based on the severity of COVID-19 (mild, moderate), Charlson plus SOFA score (≥ 5, < 5), and the genes of N and ORF1ab.

Sample size

The sample size was calculated using trial simulations of the adaptive design rules. Epidemiological data have shown the mortality for hospitalized COVID-19 patients with underlying diseases can be as high as 30%. According to previous studies, Paxlovid reduced the risk of death by about 90% in patients with mild to moderate COVID-19. According to a more conservative calculation, Paxlovid reduced the risk of death by 50% in a population with mild to moderate COVID-19; that is, the mortality in the Paxlovid treated group was 15%. One hundred and eighteen patients had to be included in each treatment group, resulting in a power of 80% and $\alpha = 0.05$. Considering a drop-out rate of 10%, 132 patients had to be enrolled in each treatment group.

Statistical analysis

The main analysis was based on all the randomized patients according to the intent-to-treat principle. For the primary and secondary outcomes, we also performed a secondary analysis only including patients who completed per-protocol treatment of assignment. The definition of ITT and Per-protocol was shown in Appendix 2.

Shapiro–Wilk test was used to test for normal distribution. Quantitative data will be described using the mean and standard deviation if the data are normally distributed, or will be described using median and interquartile range. Qualitative data will be described as the number of cases and proportions. The independent Student t-test or the Wilcoxon-rank-sum test will be performed for comparison of quantitative data between groups according to the data distribution. The chi-square test, the exact probability method and the Cochran–Mantel–Haenszel (CMH) test will be used for the comparison of quantitative data between groups, where appropriate. The absolute differences and 95% confidence intervals in means or proportions for the outcome variables of interest between the two groups were calculated. Bonferroni correction for alpha was performed to adjust confidence intervals for both secondary outcomes and subgroup analyses. Non-inferiority tests were applied for both all-cause mortality on day 28 and the duration of SARS-CoV-2 RNA clearance in severe adult patients with SARS-CoV-2 infection. 10% effect from the standard treatment group as the non-inferiority margin. The survival time and the duration of SARS-CoV-2 clearance between the two groups were plotted using the Kaplan–Meier curve and were analyzed using the log-rank test. Generalized estimating equations were performed to evaluate the marginal effects and linear time interaction in the dynamics of Ct values between the Paxlovid plus standard treatment and the standard treatment. The link function for Generalized estimating equations was specified as "logit" for the dichotomized outcome. The working correlation structure in this GEE model was exchangeable. Cases are assumed to be dependent within subjects and independent between subjects. The correlation matrix that represents the within-subject dependencies was estimated. In addition, the mean structure is properly specified (all relevant variables are included, all irrelevant variables are excluded). Observations between clusters are not related (there is no higher level clustering mechanism). The working correlation/covariance matrix is "reasonably close" to the population structure. An independent working structure is reasonably close if ICC equal to 0.30 or less.[17] Normality of residuals is not assumed with GEE, although it does improve efficiency.

Statistical analysis was performed using SAS (version 9.4), R (version 4.1.3) and STATA (version 16.0) software for windows. The Kaplan–Meier curve was plotted using R. The Ct value dynamics of the N and ORF1ab gene was plotted using STATA. All other analysis was conducted by SAS. P value < 0.05 was considered statistically significant. A detailed statistical plan was available in Appendix 2.

Subgroup analysis

Prespecified subgroup analysis were performed for the primary outcome testing interactions for vaccination status (equal to or more than 2 doses and none or only 1 dose), the total patients were recruited in each centers (less than or equal to 50 and >50), sex, age (≤65 and >65 years), Charlson scores (≤2 and >2), SOFA scores (≤2 and >2), Charlson plus SOFA scores (≤5 and >5), and the severity of illness (mild and moderate). In prespecified subgroups, we estimated the odds ratio and their 95% confidence intervals was calculated using regression models that included an interaction term between the treatment assignment and the subgroup. Further exploratory analyses of the risk of death were assessed in subgroup participants based on the duration from symptoms onset to hospital admission, body mass index, the Ct value of N and ORF1ab gene, and the total

number of comorbidities (Supplementary Fig. S2). Bonferroni correction for alpha was performed to control type one error for subgroup analysis.

Role of study sponsor and funding sources

The trial is sponsored by department of critical care medicine of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine. The study was supported by National Natural Science Foundation of China (grant number: 82172152, 81873944). All the data were available to all the authors, who vouch for the accuracy and completeness of the data as well as the adherence to the trial.

Results

Patients

Of 290 patients screened, 264 patients who met the criteria for severe comorbidities of COVID-19 were enrolled at 5 sites from April 10 to May 19 in 2022. Of the recruited patients, a total of 132 patients were randomized and assigned to receive Paxlovid therapy plus standard treatment who had no known contraindication for Paxlovid, and 132 patients were randomized and eligible to receive standard treatment. 2 patients discontinued treatment in Paxlovid plus standard treatment group and 1 patient discontinued in the standard treatment group, 2 patients changed from the standard treatment group to Paxlovid treatment group (Fig. 1).

The characteristics of baseline were well balanced between two groups (Table 1). The mean (±SD) age of trial patients was 70.35 (±13.12) years, and 46.21% of the patients were female. The median duration from symptoms onset to hospital admission was 3 days. The proportion of patients who had received the vaccine (only SARS-CoV-2 inactivated vaccine) was 26.52%, and the most common comorbidity was cardiovascular disease (53.40%). There were 4 (3.03%) patients who received methylprednisolone therapy in each arm. There was no patient received remdesivir, Molnupiravir, Tociluzumab, Baricitinib and other antivirals in this study.

Primary outcome

In the intent-to-treat analysis, there were 8/132 deaths in the control arm and 5/132 in the Paxlovid arm on day 28 (ARD = 2.27, 95%CI: −2.94 to 7.49) (Table 2 and Fig. 2). There was no significant interaction for any of the predefined subgroups (Fig. 3). The primary outcome of per-protocol set was shown in Supplementary Table S5 and Fig. S1. In addition, non-inferiority test was preformed to evaluate the relationship between the Paxlovid in the all-cause mortality on day 28 and the duration of SARS-CoV-2 RNA clearance. After test, there were no statistically non-inferiority for all-cause mortality on day 28 (P = 0.14) and the duration of SARS-CoV-2 RNA clearance (P = 0.37), respectively.

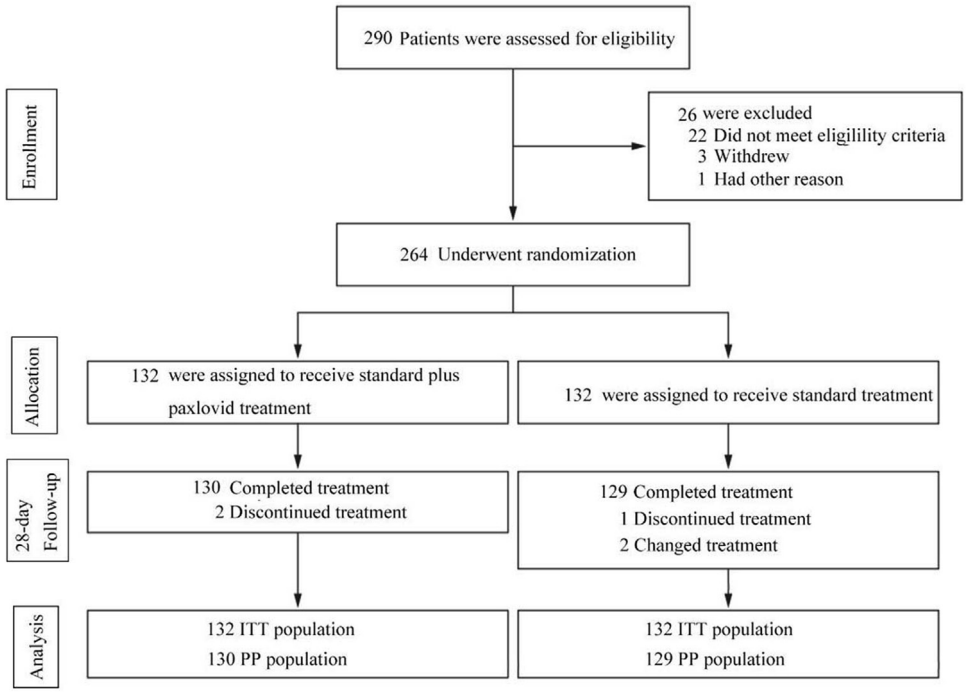

Fig. 1: **Randomization, treatment assignments, and follow-up. Patients were recruited from April 10 to May 19 in 2022. 5 sites in Shanghai, China.**

Characteristic	Standard treatment group (N = 132)	Standard treatment plus Paxlovid group (N = 132)	P value
Age (Mean ± SD) - yr	69.20 ± 14.43	71.50 ± 11.61	0.16
Sex - no. of patients (%)			0.81
Male	70 (53.03)	72 (54.55)	
Female	62 (46.97)	60 (45.45)	
Height (Mean ± SD) - cm	164.51 ± 11.31	165.63 ± 7.88	0.35
Weight (Mean ± SD) - kg	64.66 ± 12.01	63.24 ± 10.71	0.31
BMI	24.24 ± 7.72	23.02 ± 3.38	0.10
Duration since symptom onset			0.24
Median (range) - days	3 (2, 6)	3 (1, 5)	
Severity of COVID-19 - no. of patients (%)			>0.99
Mild	66 (50.00)	66 (50.00)	
Moderate	66 (50.00)	66 (50.00)	
Vaccination status - no. of patients (%)			0.12
None	93 (70.45)	101 (76.52)	
One dose	1 (0.76)	3 (2.27)	
Two doses	23 (17.42)	21 (15.91)	
Three doses	15 (11.36)	7 (5.30)	
Comorbidity - no. of patients (%)			
Diabetes	49 (37.12)	48 (36.36)	0.90
Cardiovascular disease	71 (53.79)	70 (53.03)	0.90
Cerebrovascular disease	26 (19.70)	38 (28.79)	0.08
Chronic pulmonary disease	25 (18.94)	28 (21.21)	0.64
Chronic liver disease	10 (7.58)	4 (3.03)	>0.99
Chronic kidney disease	4 (3.03)	7 (5.30)	0.36
Tumor	33 (25.00)	30 (22.73)	0.66
Hematological diseases	6 (4.55)	2 (1.52)	0.15
Immunosuppressive	0 (0.00)	1 (0.76)	>0.99
Rheumatic and autoimmune disease	2 (1.52)	3 (2.27)	>0.99
Others	35 (26.52)	26 (19.70)	0.19
Charlson score			0.99
Median (range)	3 (2, 4)	3 (2, 4)	
SOFA score			0.33
Median (range)	1 (0, 2)	1 (0, 2)	
Corticosteroids treatment - no. of patients (%)	4 (3.03)	4 (3.03)	>0.99

BMI: Body Mass Index; SOFA: Sequential Organ Failure Assessment.

Table 1: **Demographic and clinical characteristics of the patients (full analysis population).**

Secondary outcomes

In the intent-to-treat analysis, the hospital mortality was in the control arm and the Paxlovid arm respectively (ARD = 3.03, 95%CI: –2.36 to 8.42). The rate of patients converted to severe COVID-19 within 14 days was 10.6%, and 14 patients converted to severe COVID-19 both in standard care and standard care plus Paxlovid group. The rate of patient acute exacerbation of chronic disease within 14 days was 12.88%, 15 patients with exacerbated chronic disease in the standard treatment group and 19 patients in the standard treatment plus Paxlovid group.

The median length of hospital stay was 13 days in both groups and the median length of ICU stay was 10.5 and 11.5 days in the standard treatment and the standard treatment plus Paxlovid group respectively. There was no significant difference in organ support between the two groups. Of all the recruited patients, 9.1% received non-invasive ventilation, 13 in the standard treatment group and 11 in the standard treatment plus Paxlovid group (ARD = –1.52, 95%CI: –8.45 to 5.42, P = 0.67). 6.1% received invasive mechanism ventilation, 6 in the standard care group and 10 in the Paxlovid group (ARD = 3.03, 95%CI: –2.71 to 8.78, P = 0.30). Moreover, the CRRT treatment was presented in 2 and 3 cases among standard treatment and Paxlovid groups respectively (ARD = 0.76, 95%CI: –2.53 to 4.04, P > 0.99). Artificial liver or plasma exchange was conducted in 2 patients only in the Paxlovid group (ARD = 1.52, 95%CI: –0.57 to 3.60, P = 0.48) (Table 2). The secondary outcomes of per-protocol set were shown in Supplementary Table S5.

Outcomes	Standard treatment group (N = 132)	Standard treatment plus Paxlovid group (N = 132)	Absolute Risk Difference (95% CI)	Adjusted confidence interval	P value
28-day mortality - no. of patients (%)	8 (6.06)	5 (3.79)	2.27 (−2.94, 7.49)	−5.35, 9.89	0.39
Hospital mortality - no. of patients (%)	9 (6.82)	5 (3.79)	3.03 (−2.36, 8.42)	−4.85, 10.91	0.27
Acute exacerbation of COVID-19 within 14 days - no. of patients (%)	5 (3.79)	3 (2.27)	1.52 (−2.62,5.65)	−4.53, 7.57	0.72
Acute exacerbation of chronic disease within 14 days - no. of patients (%)	15 (11.36)	19 (14.39)	3.03 (−5.04, 11.10)	−8.77, 14.83	0.46
Duration of SARS-CoV-2 RNA clearance on day 7 (%)	34 (25.76)	36 (27.27)	1.52 (−9.13, 12.16)	−14.05, 17.09	0.78
Duration of SARS-CoV-2 RNA clearance on day 14 (%)	98 (74.24)	103 (78.03)	3.79 (−6.49, 14.06)	−11.24, 18.82	0.47
Duration of SARS-CoV-2 RNA clearance - Median (range) - days	10.5 (7.00, 15.00)	10 (7.00, 14.00)	−0.62 (−2.29, 1.05)	−3.06, 1.82	0.42
Length of hospital stay - Median (range) - days	13 (10.00, 18.00)	13 (10.00, 17.00)	−0.38 (−2.09, 1.32)	−3.06, 1.82	0.80
Length of ICU - Median (range) - days	10.50 (8,00, 18.00)	11.50 (9.00, 17.00)	1.36 (−5.68, 8.34)	−8.86, 11.58	0.80
Noninvasive mechanical ventilation - no. of patients (%)	13 (9.850)	11 (8.330)	−1.52 (−8.45, 5.42)	−11.65, 8.61	0.67
Invasive mechanical ventilation - no. of patients (%)	6 (4.55)	10 (7.58)	3.03 (−2.71, 8.78)	−5.36, 11.42	0.30
CRRT - no. of patients (%)	2 (1.52)	3 (2.27)	0.76 (−2.53, 4.04)	−4.05, 5.57	>0.99
Artificial liver or plasma exchange - no. of patients (%)	0 (0.00)	2 (1.53)	1.52 (−0.57, 3.60)	−1.53, 4.57	0.48
ECMO - no. of patients (%)	0 (0.00)	0 (0.00)	0.00 (NA)	NA	>0.99

ICU: Intensive Care Unit; CRRT: Continuous Renal Replacement Therapy; ECMO: Extracorporeal Membrane Oxygenation.

Table 2: **Outcomes according to time since onset of hospitalization.**

SARS–CoV-2 RNA clearance

2153 nucleic acid testing was conducted in total. There were 1141 (53.04%) tests performed in the standard treatment group and 1101 (46.96%) in the Paxlovid plus standard treatment group. The mean (SD) number of tests was 8.85 (5.87) in the standard treatment group and 7.78 (4.81) in the Paxlovid plus standard treatment group.

The proportions of participants with a negative conversion on days 7 and 14 from hospital admission were 25.76% and 74.24% in the standard treatment group and 27.27% and 78.03% in the Paxlovid plus standard treatment group respectively (Table 2). The medians (interquartile range) time from admission to negative conversion was 10.5 (7, 15) days in the standard treatment group and 10 (7, 14) days in the Paxlovid plus standard treatment group, there was no difference in the duration of SARS-Cov-2 nucleic acid converted to negative between the standard treatment and the standard

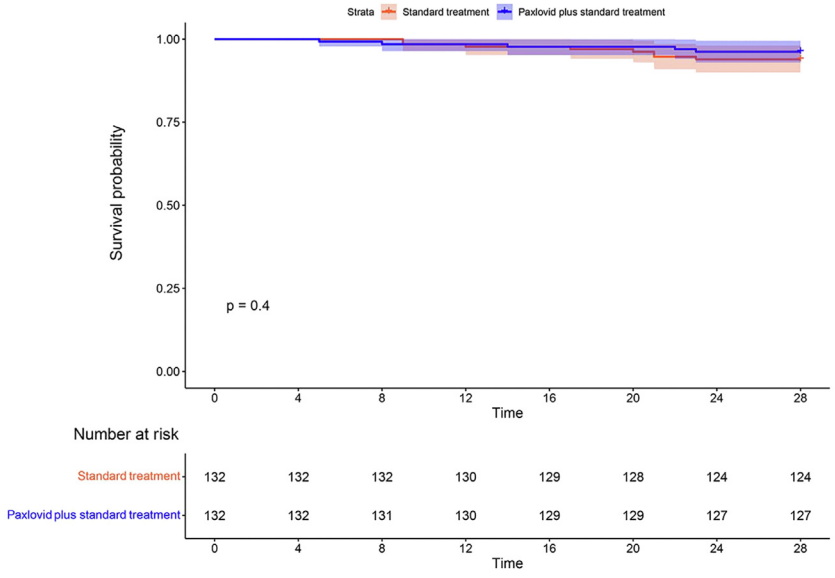

Fig. 2: **Efficacy of Nirmatrelvir plus Ritonavir (NMV-r) in preventing 28-day mortality from any cause in severe adult patients with COVID-19 infection (Intention-to-treat cohort).** The cumulative percentage was estimated for each group with use of the Kaplan–Meier method with 95% confidence intervals (I bars).

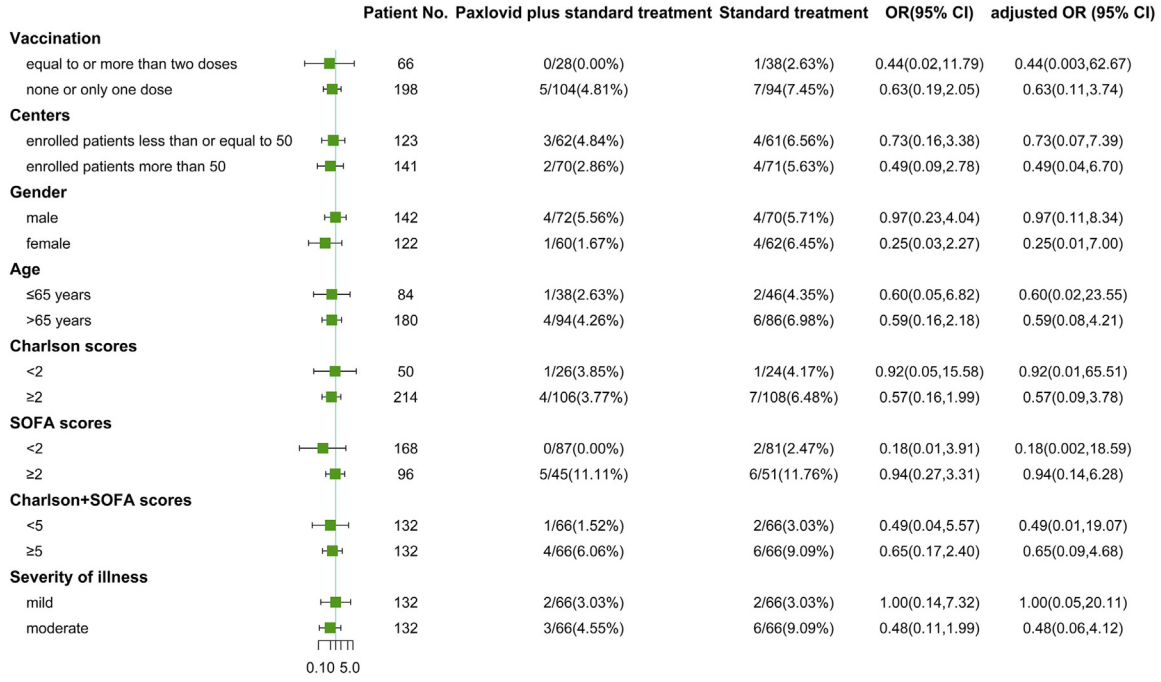

***Fig.* 3: Efficacy of Nirmatrelvir plus Ritonavir (NMV-r) on 28-day mortality from any cause in severe adult patients with COVID-19 infection, according to subgroup.** Shown are data for the primary end point in key subgroups of each group. It showed subgroup analysis of the differences in patients treated with Paxlovid plus standard treatment or only standard treatment who had COVID-19–related death from any cause through day 28, Odds ratios are plotted as squares, the horizontal lines represent 95% confidence intervals.

treatment plus the Paxlovid group (ARD = –0.62: 95%CI -2.29 to 1.05, P = 0.42) (Table 2). According to the Kaplan–Meier plot (Fig. 4A), there was no significant difference in SARS–CoV-2 RNA clearance from admission to day 28 (P = 0.34). The Ct value dynamics of the N and ORF1ab gene showed that there was no significant difference in standard treatment group and Paxlovid plus standard treatment group (Fig. 4B and C; 4B, β = 0.18 (SE, 0.84), P = 0.83; 4C, β = 1.13 (SE, 1.24), P = 0.33). The explored analysis of Ct value dynamics of the N and ORF1ab gene in subgroup patients were shown in Supplementary Fig. S3 and S4.

Laboratory test and vital signs data

There was no significant difference in laboratory test and vital signs data on the first day or the seventh day since admission between the two groups except total bilirubin and direct bilirubin on day 7, and the detailed data was shown in Supplementary Tables S1–S4.

Safety

The total number of adverse events during the treatment period was similar in the Paxlovid group and the standard treatment care group (17 in the Paxlovid group and 13 in the standard treatment group) as shown in Table 3. No death was to be related to the trial regimen considered by the investigators. Adverse events were similar in the Paxlovid group compared to the standard treatment group (14 VS 10). Likewise, serious adverse events were similar among the two groups (6 VS 5). Seven events were considered to be related to drug interventions, of which 5 occurred in the Paxlovid group and 2 in the standard treatment group. 4 patients discontinued drug interventions because of adverse events. Detailed adverse events during the treatment period were shown in Supplementary Table S6.

Discussion

Paxlovid treatment did not reduce 28-day mortality in COVID-19 patients with severe comorbidities. Paxlovid treatment did not modify SARS–CoV-2 RNA clearance, and did not increase the risk of adverse events.

The omicron variant of SARS-CoV-2 rapidly appeared in Shanghai, China. In just two months, 650,783 cases have been confirmed, including 588,262 asymptomatic cases according to the Shanghai Municipal Health Commission and resulting in about 600 deaths, especially in patients with comorbidities.[18] The genomes in Shanghai were the SARS-CoV-2 BA.2.2 variant.[7] To our knowledge, this is the first study that evaluated the efficacy and safety of Paxlovid therapy in severe hospitalized patients with the omicron variant infection.

There are several differences between this study and EPIC-HR study that may explain the discrepancies in

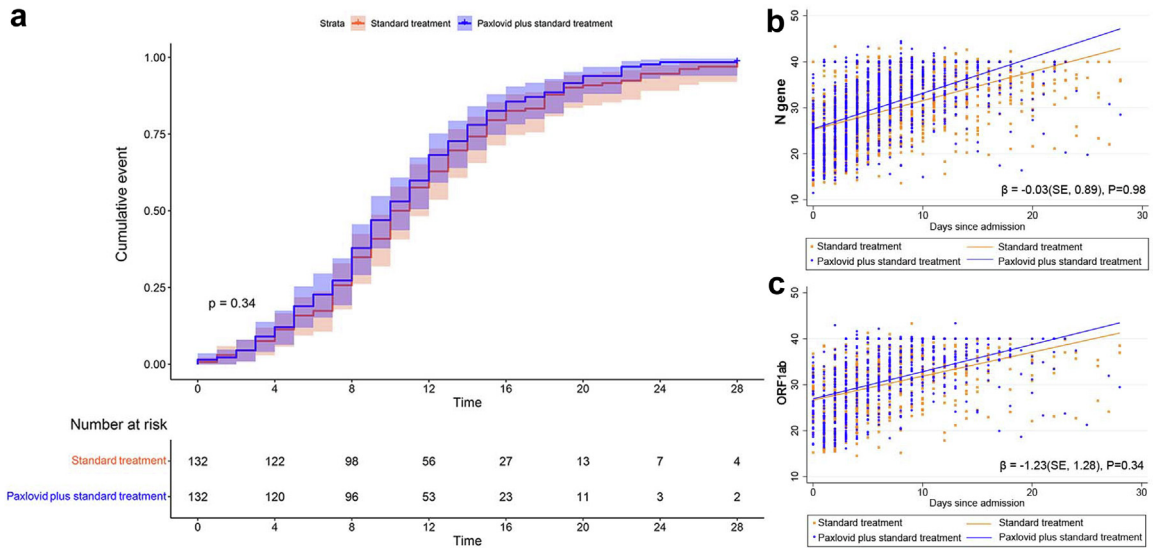

Fig. 4: **The cumulative percentage of patients with SARS–CoV-2 RNA clearance (a) and the cycle threshold value of N (b) and ORF1ab (c) genes from upper respiratory tract**. Proportion of Negative Conversion in the Paxlovid plus standard treatment and the standard treatment group (A), the cumulative percentage was estimated for each treatment group with use of the Kaplan–Meier method. Scatterplots for dynamics of cycle threshold values between Paxlovid plus standard treatment and standard treatment patients for the ORF1ab gene (B) and N gene (C). Beta value represents a slope of decline. There was no significant difference in the ORF1ab gene (β = 0.183 [SE, 0.84]; P = 0.83) and N gene (β = 1.125 [SE, 1.244]; P = 0.33) between the 2 groups. More scatterplots figures were shown in Supplementary Fig. S3 and S4.

their results. Firstly, Paxlovid was administered much earlier in the EPIC-HR study than in our study. Paxlovid was given within 5 days from symptoms onset in EPIC-HR study, whereas Paxlovid was given within 5 days from symptoms onset or a Ct value ≤ 25 of N and ORF1ab genes by real-time PCR in our study. Secondly, EPIC-HR patients were not vaccinated for COVID-19 compared to 26.52% in our study. Although Omicron was characteristic of immunologic escape, the vaccine still showed an important protective effect on COVID-19.[8] The vaccination coverage was exceeded 90% in Shanghai, however, the vaccination coverage was remaining low in adults with comorbidities and old people.[6,7] Moreover, only 4.97% of the patients who died with or from SARS-Cov-2 infection were received vaccination.[7]

Vaccines have significantly reduced the number of disease-related hospitalizations and deaths from SARS-CoV-2.[3–5,15] Thirdly, the dominant strain in the EPIC-HR trial was the B.1.617.2 (Delta), whereas the wild spread strain was the BA.2.2 variant (Omicron) in our study. The Omicron showed lower hospitalizations and deaths which might also attenuate the effect of Paxlovid treatment.[8] A similar result was also shown in a retrospective study in which Omicron strain was the dominant variant (approximately 95%), and the magnitude of risk reduction in patients who received Paxlovid treatment was smaller compared to the EPIC-HR trial.[15] Finally, Paxlovid showed different therapeutic effects in different populations. The EPIC-SR study enrolled patients who are at standard risk for developing severe COVID-19, and the results showed

Adverse Event Category	Standard treatment plus Paxlovid group (N = 132)	Standard treatment group (N = 132)	P value
Total number of adverse events[a] - no. of patients (%)	17 (12.90)	13 (9.80)	0.44
Patients with adverse events[a] - no. of patients (%)			
Any adverse event	14 (10.6)	10 (7.6)	0.39
Serious adverse event	6 (4.5)	5 (3.8)	0.76
Event considered to be related to drug interventions	5 (3.8)	2 (1.5)	0.25
Discontinued drug interventions because of adverse events	4 (3.0)	0 (0)	0.04
Had dose reduction or temporary discontinuation owing to adverse event	1 (0.8)	1 (0.8)	>0.99

[a]Adverse events were defined as newly developed adverse events or progression of prior existed conditions.

Table 3: **Summary of adverse events, serious adverse events, and adverse events leading to discontinuation during the treatment period.**

no significant reduction in the risk of hospitalization or death. The EPIC-PEP study evaluated the effect of Paxlovid in post-exposure prophylactic showed no significant preventive effect in adults who had been exposed to the virus through household contact. Non-hospitalized COVID-19 patients with at least one condition at high risk of progression to severe COVID-19 were recruited in the EPIC-HR study. However, we enrolled patients with severe comorbidities or SOFA scores ≥2 or Charlson scores ≥2 which often means the patients were more severity, and probably had a higher mortality.[19–21]

There was no significant difference in the duration of SARS–CoV-2 RNA clearance. Patients were older and more severe in our study compared to EPIC-HR study. Elderly patients often had a high proportion of comorbidities and were likely to show low immune function.[22,23] Although Paxlovid inhibited the 3CL protease inhibitor of SARS-CoV-2 preventing the replication of the virus, however, it was difficult to clear the virus through their low immunity in severe adult patients with COVID-19.[24]

Limitations

This study has several limitations. First, it was an open-label trial due to time constraints of producing a placebo in a pandemic scenario with an urgent need for reliable and randomized data. However, the treating physicians were blinded to the patient's grouping information unless it was considered necessary to know the treatment assignment of the patient by the management group and treating physicians. Therefore, clinician and patient awareness of the study assignment likely had minimal effect on the primary outcome. Second, a small number of patients stopped or did not complete treatment for various reasons. Third, our study was only conducted in China, whether it can be extended to other countries is uncertain. Fourth, the mortality was lower than expected and the confidence interval was wider in the subgroup analysis. Fifth, As the virus variation, the mortality decreases, the mortality in our study was lower than expectation. However, this trial represents the largest randomized data on Paxlovid in this population to our knowledge. Sixth, we did not conclude neither superiority nor non-inferiority for Paxlovid. Therefore, the results of our main prespecified outcomes our study may have a risk of being underpowered.

Conclusion

The results of our study did not show additional benefits of all-cause mortality on day 28 and the duration of SARS–CoV-2 RNA clearance with Paxlovid therapy to the standard care in the adult hospitalized patients with SARS-Cov-2 (Omicron BA.2.2 variant) infection and severe comorbidities. The trial may provide initial evidence for the benefit–risk profile of Paxlovid in the patients and larger sample size are warranted in the further.

Contributors

QZ (Qiang Zhao), RZ, Annane D, JQ, and DC conceived and designed the study and took responsibility for the integrity of the data and the accuracy of the data analysis. JL, XP, and SZ drafted the manuscript. XG and YY provided trial design consultation and professional guidance. ML, KM, CF, and YiL were responsible for the clinical trials in each sub-center. XY did the statistical analysis. XD, YW, LQ, ZX, ZG, QZ (Quanhong Zhou), XZ, YL, TQ, ZW, SH, LZ, TW, YL, YH, WL, HD, YC, and YX collected the data. All the authors critically revised the manuscript for important intellectual content and gave final approval for the version to be published. All the authors had full access to all of the data in the study. All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data sharing statement

The individual-level data used in this study are sensitive and cannot be publicly shared. After approval of a proposal by the investigator, data can be shared through a secure online platform after signing a data access agreement.

Declaration of interests

All other authors declare no competing interests.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100694.

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