Effects of leritrelvir for adults with mild-to-moderate coronavirus disease 2019: a multicenter real-world study

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Background: Real-world evidence for leritrelvir, a single-component 3C-like protease inhibitor, in adults with mild-to-moderate coronavirus disease 2019 (COVID-19) remains limited. We evaluated the association of early leritrelvir use with symptom resolution, negative viral-test conversion, and adverse events in routine clinical practice.

Methods: This prospective, multicenter, nonrandomized, open-label observational cohort study was conducted at 141 sites in China (mainland). Among 1,527 adults with mild-to-moderate COVID-19, 1,388 received leritrelvir (400 mg three times daily for 5 days) plus standard care and 139 received standard care alone. The primary endpoint was time to sustained resolution of 11 predefined symptoms. The key secondary

endpoint was time to negative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleic acid test (NAT) conversion. All participants contributed a primary time-to-event record. We estimated unadjusted and multivariable-adjusted Cox models and performed 1:1 propensity score (PS) matching (136 participants per group).

Results: For sustained symptom resolution, the unadjusted hazard ratio (HR) was 1.41 [95% confidence interval (CI): 1.18–1.68; P<0.001], the multivariable-adjusted HR was 1.66 (95% CI: 1.38–1.99; P<0.001), and the PS-matched HR was 1.81 (robust 95% CI: 1.43–2.29; P<0.001). In the matched cohort, median time to symptom resolution was 6 days with leritrelvir and 8 days with standard care alone. For negative NAT conversion, the corresponding HRs were 1.20 (95% CI: 1.01–1.43; P=0.04), 1.22 (95% CI: 1.01–1.47; P=0.04), and 1.47 (robust 95% CI: 1.21–1.79; P<0.001); matched medians were 3 and 4 days. Adverse events occurred in 22.41% and 19.42% of the unmatched groups, respectively.

Conclusions: In this prospective, multicenter, nonrandomized cohort, leritrelvir use was associated with earlier sustained symptom resolution and negative SARS-CoV-2 NAT conversion than standard care alone. Although the direction of association was consistent across multivariable-adjusted and PS-matched analyses, residual confounding, open-label symptom assessment, nonproportional hazards, incomplete follow-up, and the absence of severe-outcome events preclude causal, subgroup-specific, or severe-outcome conclusions.

Keywords: Leritrelvir; real-world study; coronavirus disease 2019 (COVID-19); Omicron variant

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Introduction

Coronavirus disease 2019 (COVID-19) has caused successive global waves and a substantial public-health burden (1,2). By June 2024, more than 775 million confirmed cases and 7 million deaths had been reported worldwide (3). Disease severity varies with viral lineage, viral burden, population immunity, and host factors such as comorbidities (4-6). Although most infections during the Omicron era were mild to moderate and could be managed outside hospital settings (7), high-risk patients remained vulnerable to progression. Early antiviral treatment may therefore remain clinically relevant, but its effectiveness in routine care requires careful evaluation of treatment selection and confounding.

Available antiviral therapies include molnupiravir, lopinavir/ritonavir, nirmatrelvir/ritonavir, remdesivir, VV116, and simnotrelvir (8-14). Ritonavir-containing regimens can create clinically important drug-drug interactions, particularly in patients receiving multiple long-term medications (9,15,16). Leritrelvir is a single-component inhibitor of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) 3C-like protease and does not require ritonavir coadministration. A multicenter, randomized, double-blind, placebo-controlled phase 3 trial involving 1,359 adults reported a shorter median time to sustained clinical recovery with leritrelvir than with placebo [251.02 *vs.* 271.33 hours; hazard ratio (HR) =1.20; P=0.0022] (17). That trial provided randomized evidence under placebo-controlled conditions, whereas comparative evidence against standard care in routine practice remained limited. We therefore conducted a prospective multicenter cohort study to evaluate associations between leritrelvir use and sustained symptom resolution, negative viral-test conversion, and adverse

Highlight box

Key findings

- In propensity score (PS)-matched analyses, leritrelvir use was associated with shorter times to sustained symptom resolution and negative severe acute respiratory syndrome coronavirus 2 nucleic acid test conversion than standard care alone. Multivariable-adjusted analyses were directionally consistent.

What is known and what is new?

- Randomized trials have evaluated leritrelvir in mild-to-moderate coronavirus disease 2019, but real-world evidence during later Omicron waves is limited.

- This prospective cohort reports unadjusted, multivariable-adjusted, and PS-matched associations.

What is the implication, and what should change now?

- The findings support further controlled evaluation of leritrelvir in routine-care populations. Residual confounding, open-label symptom assessment, nonproportional hazards, and exploratory subgroup analyses preclude a causal treatment recommendation from this study alone.

events in routine care. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-2026-2569/rc).

Methods

Study design

This prospective, multicenter, nonrandomized, open-label observational cohort study was conducted in a pragmatic real-world setting at 141 clinical sites in China from May 22, 2023, to May 4, 2024. Treatment was not randomly assigned and reflected routine clinical practice. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments and Good Clinical Practice. The protocol was approved by the Ethics Committee of The First Affiliated Hospital of Guangzhou Medical University (No. ES-2023-091-01), and all participants provided written informed consent before enrollment. The other participating institutions were informed of the study and completed the applicable local ethics review, filing, or institutional acceptance procedures before participation. The study was registered in the Chinese Clinical Trial Registry (ChiCTR2300077635).

Study participants

Eligible adults had a positive SARS-CoV-2 nucleic acid test (NAT) result and mild or moderate COVID-19 according to the Guidelines for the Diagnosis and Treatment of COVID-19 (10^{th} edition). Mild disease comprised upper-respiratory-tract symptoms such as sore throat, cough, or fever. Moderate disease comprised persistent high fever for more than 3 days and/or cough or dyspnea, with a respiratory rate <30 breaths/min and oxygen saturation >93% while breathing ambient air at rest; imaging-confirmed pneumonia was required. Exclusion criteria were receipt of another small-molecule antiviral, severe renal impairment (creatinine clearance <30 mL/min), psychiatric illness, coma or dysphagia, alanine aminotransferase or aspartate aminotransferase ≥10 times the upper limit of normal, uncontrolled human immunodeficiency virus type 1 infection, vaccination within 28 days, pregnancy or lactation, or participation in another clinical trial within 1 month.

Procedures

The study comprised screening, 5 days of treatment, and follow-up through day 28. Participants received standard care alone or standard care plus leritrelvir through a nonrandom treatment-selection process in routine care. Standard care followed the Diagnosis and Treatment Protocol for COVID-19 Patients (tentative 10^{th} edition) and could include supplemental oxygen, symptomatic treatment, and intravenous antibiotics when indicated, but excluded other small-molecule antivirals. Leritrelvir was administered orally at 0.4 g (two tablets) three times daily with meals for 5 days. Participants in both groups recorded the same predefined 11 symptoms in a diary: diarrhea, vomiting, nausea, dyspnea, sore throat, fever, chills, headache, myalgia, cough, and nasal congestion or rhinorrhea. Complete blood counts and liver and kidney function tests were obtained at the end of treatment and 5 days after treatment.

Study endpoints

The primary endpoint was time from treatment initiation to sustained resolution of all 11 predefined symptoms (sore throat, nasal congestion or rhinorrhea, diarrhea, vomiting, fever, nausea, chills, headache, myalgia, cough, and dyspnea). Secondary endpoints included mortality, progression to severe COVID-19, time to negative SARS-CoV-2 NAT conversion—defined as a cycle-threshold value ≥35 on two consecutive NATs more than 24 hours apart at scheduled assessments on days 2, 5, and 10—and time to the first negative NAT during follow-up. Safety endpoints included adverse-event type, incidence, severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0, duration, and investigator-assessed relationship to leritrelvir. Events that occurred or worsened between written consent and the final visit were recorded.

Statistical analysis

Sample size was calculated with PASS version 15.0 (NCSS, LLC, Kaysville, UT, USA). Assuming median times to symptom recovery of 7.17 days in the leritrelvir group and 9.83 days in the control group, a two-sided alpha of 0.05, 80% power, and a 10:1 allocation ratio, 1,110 and 111 participants were required, respectively. Allowing for 20% attrition yielded a target of 1,527 participants. The documented calculation did not include an allowance for residual confounding or loss of efficiency from subsequent 1:1 propensity score (PS) matching.

Baseline characteristics were summarized in unmatched and PS-matched cohorts. PSs were estimated by logistic regression using age, sex, vaccination history, inpatient status, clinical classification (which corresponded exactly to the grouped World Health Organization scale in the locked dataset), and eight chronic-condition indicators: cardiovascular or cerebrovascular disease, chronic lung disease, diabetes, immunosuppression, dialysis, liver disease, kidney disease, and cancer. Participants were matched 1:1 without replacement by nearest-neighbor matching with a caliper of 0.2 standard deviations of the PS. Covariate balance was evaluated using standardized mean differences (SMDs), with $|SMD| < 0.10$ considered desirable. The locked matched dataset contained 136 participants per group and valid matched-pair identifiers.

Time to sustained symptom resolution was summarized with Kaplan-Meier methods and compared using log-rank tests. Unadjusted Cox models were fitted in the unmatched cohort. Multivariable Cox models adjusted for age, sex, vaccination history, clinical classification, inpatient status, and the eight chronic-condition indicators listed above; the duplicate grouped World Health Organization (WHO)-scale variable was omitted to avoid exact collinearity. PS-matched Cox models used a robust sandwich variance clustered by matched pair. The proportional-hazards assumption was assessed with scaled Schoenfeld residuals and was not satisfied for the treatment group for either time-to-event endpoint. HRs are therefore interpreted as average relative event-rate summaries over follow-up rather than constant effects, and Kaplan-Meier medians and curves are emphasized. Subgroup analyses were post-hoc and exploratory. Treatment-by-subgroup interaction P values were estimated in the matched cohort, and no multiplicity adjustment was applied.

Time to negative SARS-CoV-2 NAT conversion was analyzed using the same unmatched, multivariable-adjusted, and PS-matched time-to-event framework. The

high-risk analyses used a separate 1:1 PS-matched cohort of 19 participants per group. High-risk status followed the classification recorded in the source dataset. Estimates from this small subgroup were post-hoc and exploratory.

Categorical safety outcomes were compared using the Chi-squared test or Fisher exact test, as appropriate. All tests were two-sided, and $P<0.05$ was considered statistically significant. Original figure production used SAS, and the revision analyses and figures were independently reproduced in R version 4.6.1 with the survival and MatchIt packages.

For the primary endpoint, the available analysis dataset contained a time and event/censoring indicator for all 1,527 participants: 1,512 had an observed sustained-resolution event and 15 were right-censored at day 28. We did not impute the 15 censored event times because doing so at or before day 28 would contradict observed censoring, whereas imputation beyond day 28 followed by administrative recensoring would not change the estimand. The available dataset did not contain subject-level day-28 completion/disposition indicators, dropout dates, or longitudinal symptom histories needed to define a valid multiple-imputation target or compare completers with non-completers by baseline characteristics; no pooled multiple-imputation estimate is therefore reported.

Results

Participant enrollment

Among 1,599 screened participants, 70 did not meet the eligibility criteria and 2 withdrew consent. The remaining 1,527 participants entered the cohort: 1,388 received leritrelvir and 139 received standard care alone (*Figure 1*). During follow-up, 297 participants in the leritrelvir group and 23 in the control group did not complete the day-28 assessment for the reasons shown in *Figure 1*; 1,091 and 116 participants, respectively, completed that assessment. All 1,527 participants nevertheless contributed a primary time-to-event record, comprising 1,512 observed events and 15 observations right-censored at day 28.

Because subject-level day-28 completion and disposition indicators linked to baseline covariates were absent from the available analysis dataset, baseline characteristics of completers and non-completers could not be reconstructed. Operational day-28 noncompletion and primary-endpoint censoring were therefore reported as distinct quantities.

Baseline characteristics for the unmatched and PS-matched cohorts are shown in *Table 1*. In the matched cohort, mild disease was present in 81.6% of the leritrelvir group and 83.1% of the control group; moderate disease was present in 18.4% and 16.9%, respectively. Residual imbalance remained for cardiovascular or cerebrovascular disease (SMD =0.104), diabetes (SMD =0.112), liver disease (SMD =0.175), and kidney disease (SMD =0.173), and was retained in the interpretation (Figure S1).

Primary endpoint

In the unmatched cohort, median time to sustained symptom resolution was 7 days in the leritrelvir group and 8 days in the control group [unadjusted HR =1.41; 95%

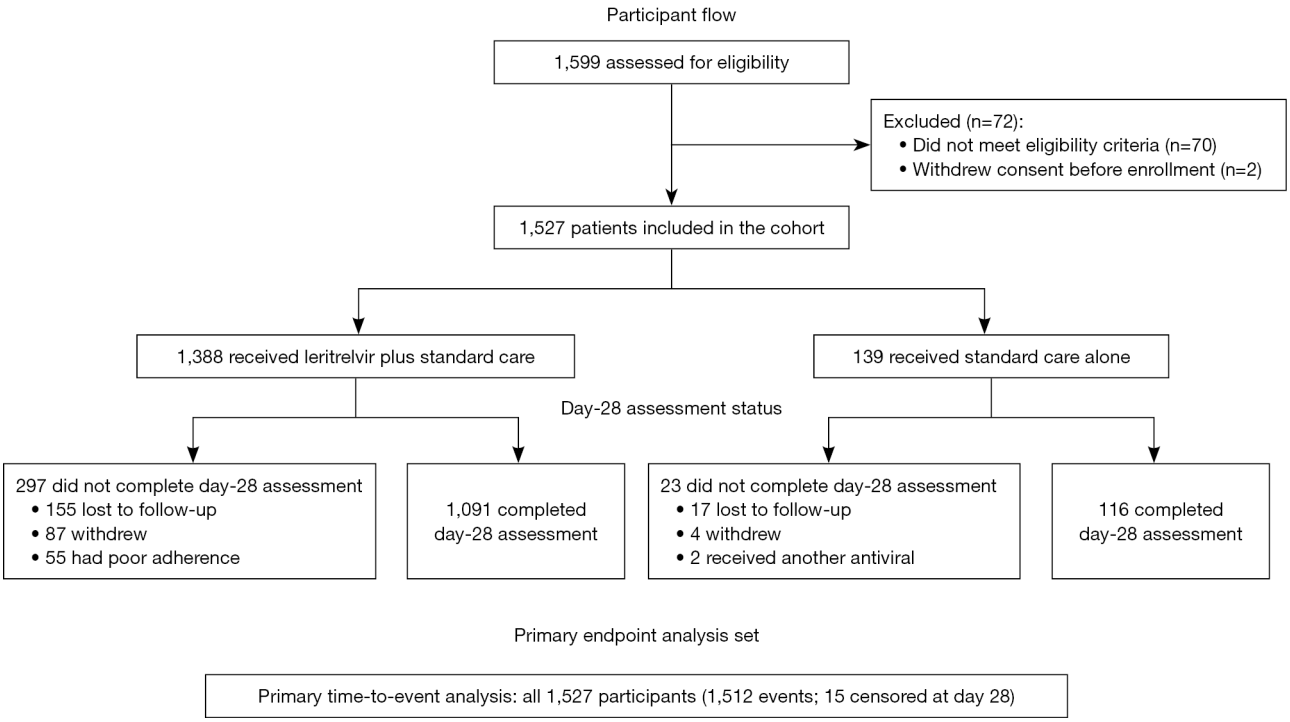


Figure 1 Participant disposition and primary analysis set. The cohort included 1,527 participants. Treatment-group boxes show observed exposure. Day-28 assessment completion and noncompletion are displayed separately from the primary time-to-event analysis set. The primary time-to-event analysis included all 1,527 participants (1,512 events and 15 observations censored at day 28).

confidence interval (CI): 1.18–1.68; P<0.001]. The multivariable-adjusted HR was 1.66 (95% CI: 1.38–1.99; P<0.001). In the PS-matched cohort, medians were 6 and 8 days, respectively (HR =1.81; pair-cluster robust 95% CI: 1.43–2.29; P<0.001) (*Figure 2*, *Table 2*). In the separate high-risk matched cohort, medians were 6 and 8 days (HR =1.92; pair-cluster robust 95% CI: 1.06–3.48; Cox P=0.03; log-rank P=0.04) (Figure S2). Post-hoc subgroup estimates are shown in *Figure 3*; interaction P values were 0.72 for sex, 0.54 for age, 0.76 for clinical classification, 0.62 for inpatient status, and 0.63 for the Methods-aligned chronic-disease composite. None indicated statistically detectable heterogeneity.

Secondary endpoints

No deaths or progression to severe COVID-19 were reported. In the unmatched cohort, median time to negative SARS-CoV-2 NAT conversion was 3 days in the leritrelvir group and 4 days in the control group (unadjusted HR =1.20; 95% CI: 1.01–1.43; Cox P=0.04; log-rank P=0.01). The multivariable-adjusted HR was 1.22 (95% CI: 1.01–1.47; P=0.04). In the PS-matched cohort, medians were 3 and 4 days (HR =1.47; pair-cluster robust 95% CI: 1.21–1.79; P<0.001) (*Figure 4*, *Table 2*). In the separate high-risk matched cohort, the association was not statistically significant (3 *vs.* 4 days; HR =1.03; pair-cluster robust 95% CI: 0.55–1.91; Cox P=0.93; log-rank P=0.91) (Figure S2).

Table 1 Demographic and clinical characteristics of the unmatched and PS-matched populations

Baseline characteristics	Unmatched				PS-matched			
	Control group (n=139)	Leritrelvir group (n=1,388)	P value	SMD	Control group (n=136)	Leritrelvir group (n=136)	P value	SMD
Age (years)	35.14±14.54	51.72±20.69	<0.001	0.927	35.06±14.65	35.07±15.29	>0.99	<0.001
Sex			0.003	0.268			>0.99	<0.001
Female	87 (62.6)	686 (49.4)			85 (62.5)	85 (62.5)		
Male	52 (37.4)	702 (50.6)			51 (37.5)	51 (37.5)		
Ethnicity			0.25	0.095			0.79	0.032
Han Chinese	131 (94.2)	1,336 (96.3)			128 (94.1)	129 (94.9)		
Others	8 (5.8)	52 (3.7)			8 (5.9)	7 (5.1)		
Vaccination history of COVID-19			0.006	0.287			0.52	0.078
Yes	133 (95.7)	1,220 (87.9)			130 (95.6)	132 (97.1)		
No	6 (4.3)	168 (12.1)			6 (4.4)	4 (2.9)		
History of substance abuse			0.65	0.054			NE	<0.001
Yes	0 (0.0)	2 (0.1)			0 (0.0)	0 (0.0)		
No	139 (100.0)	1,386 (99.9)			136 (100.0)	136 (100.0)		
History of drug allergy			0.25	0.109			0.79	0.032
Yes	8 (5.8)	119 (8.6)			8 (5.9)	7 (5.1)		
No	131 (94.2)	1,269 (91.4)			128 (94.1)	129 (94.9)		
Inpatient			<0.001	1.16			>0.99	<0.001
Yes	7 (5.0)	691 (49.8)			7 (5.1)	7 (5.1)		
No	132 (95.0)	697 (50.2)			129 (94.9)	129 (94.9)		
Mild or moderate			<0.001	0.444			0.75	0.039
Mild	113 (81.3)	857 (61.7)			113 (83.1)	111 (81.6)		
Moderate	26 (18.7)	531 (38.3)			23 (16.9)	25 (18.4)		
WHO scale score			<0.001	0.444			0.75	0.039
1–3 points	113 (81.3)	857 (61.7)			113 (83.1)	111 (81.6)		
4–5 points	26 (18.7)	531 (38.3)			23 (16.9)	25 (18.4)		
Chronic diseases								
Cardiovascular and cerebrovascular diseases (including hypertension)	8 (5.8)	393 (28.3)	<0.001	0.629	8 (5.9)	5 (3.7)	0.39	0.104
Chronic lung disease	2 (1.4)	193 (13.9)	<0.001	0.482	2 (1.5)	1 (0.7)	0.56	0.07
Diabetes	7 (5.0)	134 (9.7)	0.07	0.178	7 (5.1)	4 (2.9)	0.36	0.112
Immunosuppressive state	1 (0.7)	21 (1.5)	0.45	0.076	1 (0.7)	1 (0.7)	>0.99	<0.001
Dialysis	0 (0.0)	1 (0.1)	0.75	0.038	0 (0.0)	0 (0.0)	NE	<0.001
Liver disease	6 (4.3)	110 (7.9)	0.13	0.151	6 (4.4)	2 (1.5)	0.15	0.175

Table 1 *(continued)*

Table 1 *(continued)*

Baseline characteristics	Unmatched				PS-matched			
	Control group (n=139)	Leritrelvir group (n=1,388)	P value	SMD	Control group (n=136)	Leritrelvir group (n=136)	P value	SMD
Kidney disease	2 (1.4)	63 (4.5)	0.08	0.183	2 (1.5)	0 (0.0)	0.16	0.173
Cancer	2 (1.4)	84 (6.1)	0.03	0.245	2 (1.5)	1 (0.7)	0.56	0.07

Data are presented as mean ± SD or n (%). Absolute SMD values <0.10 were considered desirable. Residual post-match SMDs were 0.104 for cardiovascular or cerebrovascular disease, 0.112 for diabetes, 0.175 for liver disease, and 0.173 for kidney disease. COVID-19, coronavirus disease 2019; NE, not estimable; PS, propensity score; SD, standard deviation; SMD, standardized mean difference; WHO, World Health Organization.

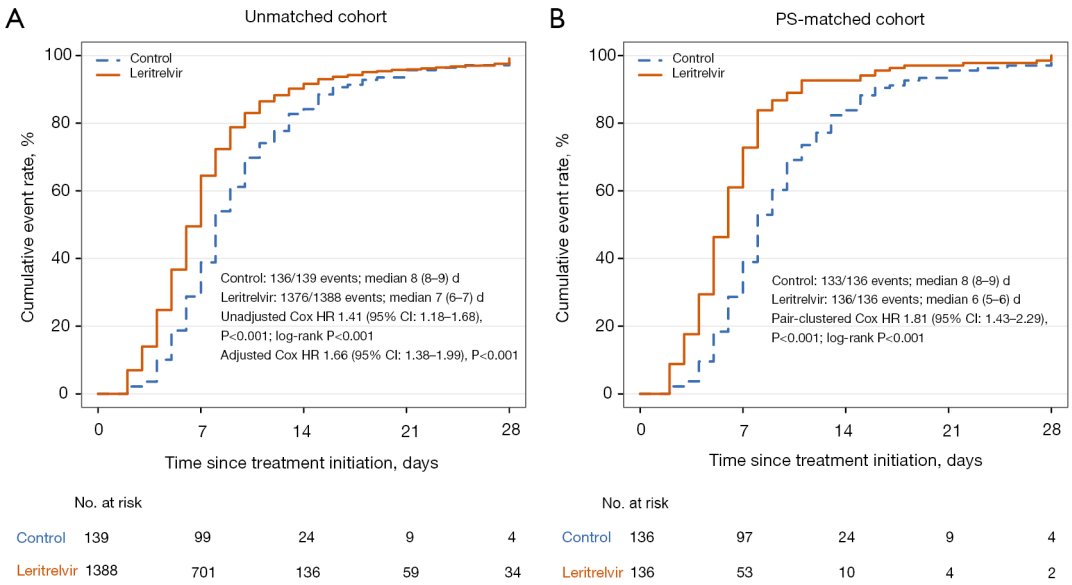


Figure 2 Time to sustained symptom resolution. Cumulative event curves for time to sustained symptom resolution. (A) The unmatched cohort: the unadjusted Cox estimate was HR =1.41 (95% CI: 1.18–1.68), and the multivariable-adjusted estimate was HR =1.66 (95% CI: 1.38–1.99). (B) The 1:1 PS-matched cohort: the pair-clustered Cox estimate was HR =1.81 (95% CI: 1.43–2.29). Numbers at risk are shown below each panel. Because the proportional-hazards assumption was not supported for treatment, HRs are interpreted as average event-rate summaries over follow-up. CI, confidence interval; d, days; HR, hazard ratio; No., number; PS, propensity score.

Safety

In the unmatched cohort, adverse events were recorded in 311 of 1,388 participants (22.41%) in the leritrelvir group and 27 of 139 participants (19.42%) in the standard-care group (*Table 3*). The most frequently recorded events were neutrophil count decreased, alanine aminotransferase increased, hyperuricemia, aspartate aminotransferase increased, diarrhea, and fatigue. In the PS-matched cohort, adverse-event incidence was 19.12% and 19.85%, respectively (P=0.88). The two historical

treatment-related summary categories and grade-specific counts are not presented because they could not be reproducibly derived from the available safety-event file.

Table 2 Unadjusted, multivariable-adjusted, and PS-matched time-to-event estimates

Endpoint	Analysis	HR (95% CI)	P value	Notes
Sustained symptom resolution	Unmatched Cox	1.41 (1.18–1.68)	<0.001	Unadjusted
	Multivariable Cox	1.66 (1.38–1.99)	<0.001	Adjusted for age, sex, vaccination, clinical classification, inpatient status, and eight chronic-condition indicators
	1:1 PS-matched Cox	1.81 (1.43–2.29)	<0.001	Pair-cluster robust standard error
Negative NAT conversion	Unmatched Cox	1.20 (1.01–1.43)	0.04	Unadjusted
	Multivariable Cox	1.22 (1.01–1.47)	0.04	Same adjustment set
	1:1 PS-matched Cox	1.47 (1.21–1.79)	<0.001	Pair-cluster robust standard error

The proportional-hazards assumption was not satisfied for the treatment group in either endpoint; HRs are therefore interpreted as average relative event-rate summaries over follow-up, with Kaplan-Meier medians and curves emphasized. CI, confidence interval; HR, hazard ratio; NAT, nucleic acid test; PS, propensity score.

Discussion

In this prospective nonrandomized cohort, leritrelvir use was associated with shorter times to sustained symptom resolution and negative SARS-CoV-2 NAT conversion than standard care alone. The direction of association was consistent across unadjusted, multivariable-adjusted, and PS-matched analyses. Effect magnitudes differed across analyses, indicating sensitivity to baseline composition. Because proportional hazards were not supported, the HRs summarize average relative event rates over follow-up and should be interpreted alongside Kaplan-Meier medians and curves. No deaths or progression to severe COVID-19 were observed, so the study cannot establish an effect on severe outcomes. The study was conducted during an Omicron-dominant period that included EG.5 and JN.1 subvariants (18-27).

In the separate high-risk PS-matched cohort, leritrelvir use was associated with faster sustained symptom resolution, whereas negative NAT conversion did not differ statistically between groups. These analyses included only 19 participants per group and were exploratory. The main matched-cohort subgroup interaction tests did not show statistically detectable heterogeneity, but their limited precision and absence of multiplicity adjustment preclude claims of differential treatment association.

Leritrelvir is administered without ritonavir, thereby avoiding the addition of ritonavir as a pharmacokinetic booster and potentially simplifying management of drug-drug interactions in patients receiving susceptible concomitant medications (28-34). However, neither the published phase 3 trial nor the present cohort directly compared clinical drug-drug interaction outcomes with a ritonavir-containing antiviral. This potential management advantage therefore requires evaluation in appropriately controlled comparative studies.

This study extends trial evidence by examining leritrelvir in a large multicenter cohort during routine care. The published randomized, double-blind, placebo-controlled phase 3 trial reported a 20.31-hour shorter median time to sustained

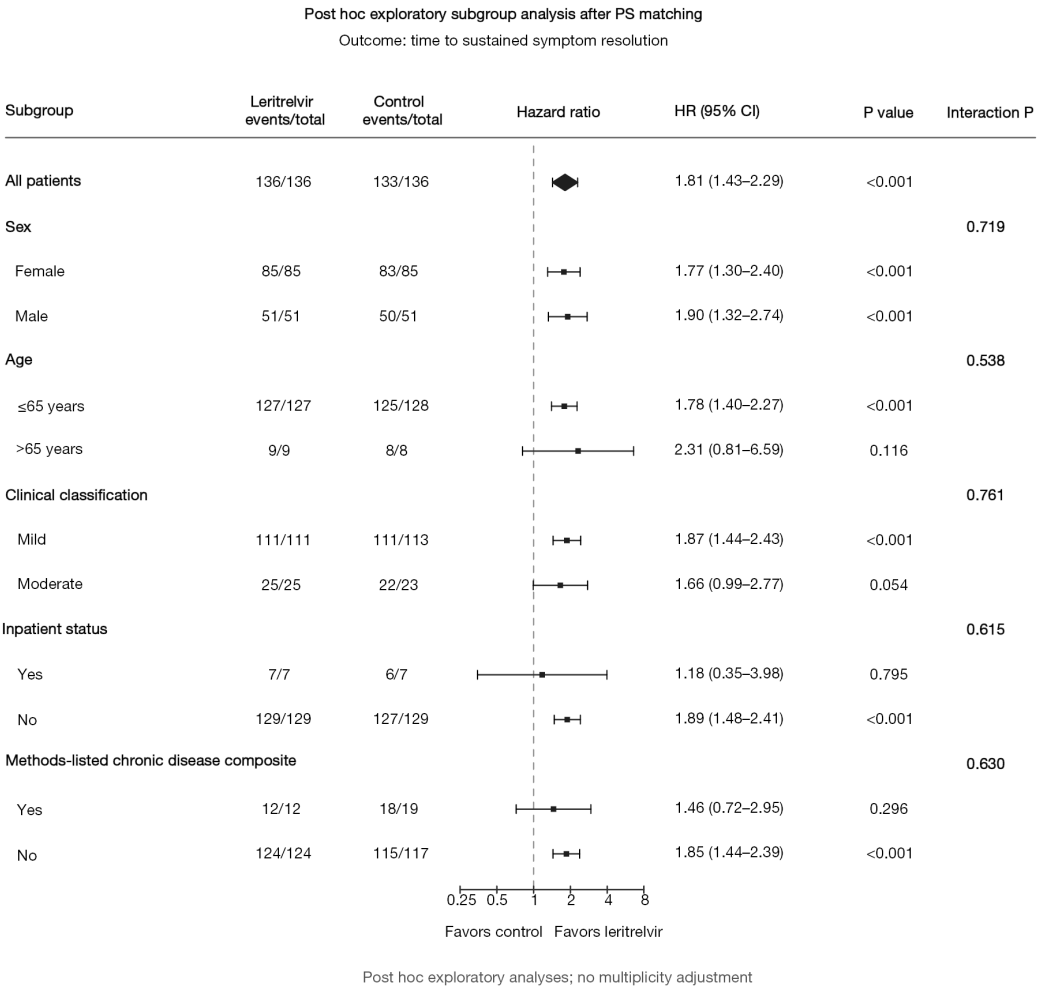


Figure 3 Post-hoc exploratory subgroup analysis after PS matching. Post-hoc exploratory subgroup analysis after PS matching. HRs for sustained symptom resolution are shown with 95% CIs. P values in the body of the forest plot are within-level pair-clustered Cox tests. Interaction P values are treatment-by-subgroup terms from pair-clustered Cox models. The chronic-disease composite is positive for any recorded cardiovascular or cerebrovascular disease, chronic lung disease, diabetes, immunosuppressive condition, dialysis, liver disease, kidney disease, or cancer, consistent with the variables listed in the "Methods" section. No multiplicity adjustment was applied. CI, confidence interval; HR, hazard ratio; PS, propensity score.

clinical recovery with leritrelvir than with placebo (251.02 *vs.* 271.33 hours; HR =1.20; P=0.0022) (17). In the subgroup in which the interval from the first positive NAT result to randomization was no more than 72 hours, the median between-group difference was 33.90 hours. On day 4, the reduction from baseline in viral load was 0.82 $\log_{10}$ copies/mL greater with leritrelvir than with placebo. The direction of the symptom findings was therefore consistent between the randomized trial and the present cohort. However, the estimates are not interchangeable because the studies differed in design, comparator, population, endpoint timing, and statistical model. The phase 3 viral-load endpoint and the present time-to-negative-NAT endpoint are also distinct virologic measures. Because neither study observed death or progression to severe COVID-19,

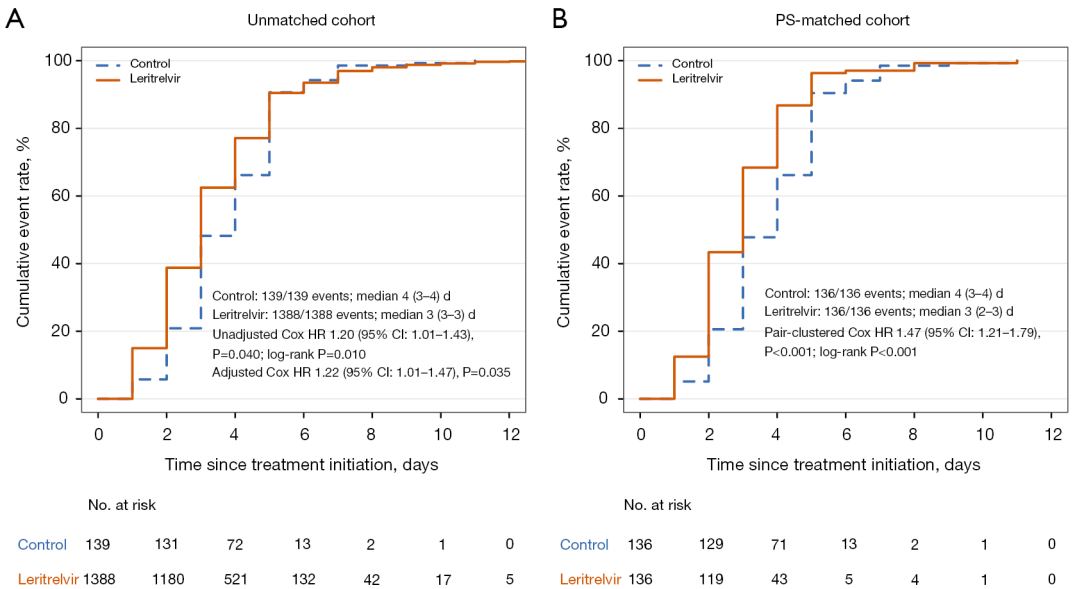


Figure 4 Time to negative conversion of NAT results. Cumulative event curves for time to negative SARS-CoV-2 NAT conversion. (A) The unmatched cohort: the unadjusted Cox estimate was HR =1.20 (95% CI: 1.01–1.43), and the multivariable-adjusted estimate was HR =1.22 (95% CI: 1.01–1.47). (B) The 1:1 PS-matched cohort: the pair-clustered Cox estimate was HR =1.47 (95% CI: 1.21–1.79). Numbers at risk are shown below each panel. Because the proportional-hazards assumption was not supported for treatment, HRs are interpreted as average event-rate summaries over follow-up. CI, confidence interval; d, days; HR, hazard ratio; NAT, nucleic acid test; No., number; PS, propensity score; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

neither establishes a reduction in severe disease or mortality. Presenting unadjusted, multivariable-adjusted, and PS-matched estimates makes the influence of measured baseline differences more transparent. Nevertheless, the observational design means that the present results are estimates of association and do not establish treatment superiority.

Table 3 Adverse events

Adverse event	Leritrelvir group (n=1,388)	Standard-care group (n=139)
Any adverse event	311 (22.41)	27 (19.42)
Neutrophil count decreased	77 (5.55)	14 (10.07)
Alanine aminotransferase increased	70 (5.04)	1 (0.72)
Hyperuricemia	54 (3.89)	9 (6.47)
Aspartate aminotransferase increased	48 (3.46)	1 (0.72)
Diarrhea	17 (1.22)	1 (0.72)
Fatigue	17 (1.22)	0

Data are presented as n (%). Any adverse event denotes at least one recorded event. Events that occurred or worsened from written consent through the final visit were recorded. Participants could contribute more than one specific event. The supplied event file supported participant-level counts for any adverse event and the six specific events shown, but did not include the event-date, treatment-period, or grade-derivation fields needed to report the historical treatment-related categories or grade-specific columns reproducibly.

This study has several limitations. First, treatment allocation was nonrandom and the groups were markedly unequal in size and baseline risk. Confounding by indication and selection bias are major limitations because measured and unmeasured factors may have influenced both treatment choice and outcomes. Although multivariable adjustment and PS matching addressed measured covariates, residual imbalance remained in several chronic disease covariates after PS matching and may have introduced residual confounding. Second, the primary endpoint was a participant-reported 11-symptom composite in an open-label study. Use of the same symptom definition and diaries in both groups standardized capture but did not eliminate reporting or assessment bias. Third, although all 1,527 participants had primary time and status records, 320 did not complete the day-28 assessment. Subject-level disposition indicators, dropout dates, and longitudinal symptom histories were unavailable in the analysis dataset, so differential attrition by baseline characteristics and the requested pooled multiple-imputation sensitivity analysis could not be reconstructed. Informative follow-up therefore remains possible. Fourth, proportional-hazards assumptions were violated; Cox HRs should therefore be interpreted as average summaries and not constant effects. Fifth, subgroup analyses were post-hoc, involved multiple comparisons, and had limited precision; no interaction test supported disease-specific treatment-effect heterogeneity. Sixth, the documented sample-size calculation did not account for matching losses or residual confounding. Finally, low severe-outcome event rates, absence of a direct active-antiviral comparator, and limited follow-up precluded conclusions about severe disease, death, recurrence, or viral rebound; generalizability beyond the enrolled population and circulating variants is uncertain. Accordingly, this prospective observational cohort cannot provide confirmatory evidence equivalent to a randomized controlled trial. Its findings should be interpreted cautiously and should not, on their own, determine clinical treatment recommendations.

Conclusions

In this prospective multicenter nonrandomized cohort, leritrelvir use was associated with earlier sustained symptom resolution and negative SARS-CoV-2 NAT conversion than standard care alone. The direction of association remained consistent after multivariable adjustment and PS matching, although effect estimates varied across analyses. Residual confounding, open-label symptom assessment, nonproportional hazards, incomplete follow-up, and the absence of severe-outcome events limit inference. These findings do not establish treatment superiority, subgroup-specific efficacy, or a reduction in severe COVID-19 or mortality.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-2026-2569/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-2026-2569/coif). N.S.Z. serves as the Editor-in-Chief of *Journal of Thoracic Disease*. J.X.H. serves as the unpaid Executive Editor-in-Chief of *Journal of Thoracic Disease* from December 2024 to November 2029. All authors report that this study has received financial support and study drugs from Guangdong Raynovent Co., Ltd. (Guangdong, China), and support from the National Natural Science Foundation of China (No. 82670033 to L.L.C.) and the National Key Research and Development Program (No. 2021YFC0864500 to N.S.Z.). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are 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. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments and Good Clinical Practice. The protocol was approved by the Ethics Committee of The First Affiliated Hospital of Guangzhou Medical University (No. ES-2023-091-01), and all participants provided written informed consent before enrollment. The other participating institutions were informed of the study and completed the applicable local ethics review, filing, or institutional acceptance procedures before participation.

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