**1 Association of nirmatrelvir/ritonavir treatment on upper respiratory SARS-**

**2 CoV-2 RT-PCR negative conversion rates among high-risk patients with**

**3 COVID-19**

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22  **Running title**: Time to SARS-CoV-2 negative conversion (38 characters)
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1  **Abstract**

2  **Background:** Acceleration of negative respiratory conversion of SARS-CoV-2 in

3  patients with coronavirus disease 2019 (COVID-19) might reduce viral transmission.

4  Nirmatrelvir/ritonavir is a new antiviral agent recently approved for treatment of

5  COVID-19 that has the potential to facilitate negative conversion.

6  **Methods:** A cohort of hospitalized adult patients with mild-to-moderate COVID-19

7  who had a high-risk for progression to severe disease were studied. These patients

8  presented with COVID-19 symptoms between March 5 and April 5, 2022. The time

9  from positive to negative upper respiratory RT-PCR conversion was assessed by

10  Kaplan-Meier plots and Cox proportional hazards regression with the adjustment for

11  patients baseline demographic and clinical characteristics.

12  **Results:** There were 258 patients treated with nirmatrelvir/ritonavir and 224 non-

13  treated patients who had mild-to-moderate COVID-19. The median (interquartile

14  range) time for patients who converted from positive to negative RT-PCR was 10

15  days (7-12 days) in patients treated ≤5 days after symptom onset and 17 days (12-21

16  days) in non-treated patients, respectively. The proportions of patients with a negative

17  conversion at day 15 were 89.7% and 42.0% in treated patients and non-treated

18  patients, corresponding to a hazard ratio of 4.33 (95% CI, 3.31-5.65). Adjustment for

19  baseline differences between the groups had little effect on the association. Subgroup

20  analysis on treated patients suggests that time to negative conversion did not vary

21  with the patients' baseline characteristics.

3

1    **Conclusion:** This cohort study of high-risk patients with mild-to-moderate COVID-

2    19 found an association between nirmatrelvir/ritonavir treatment and accelerated

3    negative RT-PCR respiratory SARS-CoV-2 conversion that might reduce the risk of

4    viral shedding and disease transmission.

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6    **Key words**: nirmatrelvir/ritonavir, SARS-CoV-2, COVID-19, negative conversion

7    rate, high-risk patients

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## 1 Introduction

2 Management of novel coronavirus disease 2019 (COVID-19) has mostly relied non-

3 pharmacologic and vaccination interventions [1, 2]. Neither of these provide relief of

4 disease for patients who have active COVID-19. Because there is a paucity of

5 effective antiviral agents, once a patient is infected with severe acute respiratory

6 syndrome coronavirus 2 (SARS-CoV-2), it runs its natural course with the patient at

7 risk for shedding virus and potentially infecting others from symptom onset or earlier

8 to 15 days depending on disease severity [3-6]. Antiviral agents are needed that can

9 actively treat SARS-CoV-2 infection to reduce the burden of the disease and also to

10 limit the spread of infection [7].

11 Recently, nirmatrelvir has been introduced as a treatment for COVID-19 [8].

12 Nirmatrelvir is a potent small molecule inhibitor that binds to the main protease

13 (Mpro, also known as 3CLpro) of SARS-CoV-2 [8], that is an important mediator of

14 viral replication [9]. The sequence of Mpro is highly conserved in coronaviruses [9],

15 such that nirmatrelvir has similar efficacy against wildtype SARS-CoV-2 and its

16 subsequent variants [10-12]. To maximize the therapeutic benefit of the nirmatrelvir,

17 the CYP3A inhibitor ritonavir is co-administered in a low dose (100 mg) to reduce

18 metabolism of nirmatrelvir [8, 13]. Co-administration of nirmatrelvir plus ritonavir

19 reduces hospitalization and death rates from COVID-19 when given in an outpatient

20 setting [14]. Little is known regarding nirmatrelvir/ritonavir treatment of COVID-19

21 and its ability to accelerate positive to negative conversion of upper respiratory

22 reverse transcriptase polymerase chain reaction (RT-PCR) testing that, in turn, would

5

1      suggest it might reduce viral transmission [15], which consequently leads to mitigated

2      pressures on the health care system and society.

3      The First Hospital of Jilin University was granted emergency use approval for

4      nirmatrelvir/ritonavir to treat hospitalized COVID-19 patients [16-18]. Patients

5      treated at our facility undergo daily RT-PCR testing for SARS-CoV-2 to determine

6      when they no longer present a risk for airborne disease transmission.

7      Nirmatrelvir/ritonavir is usually administered in outpatient settings. The current study

8      capitalizes in the drug's use in inpatients in China and information obtained from

9      them while they are hospitalized to better understand how nirmatrelvir/ritonavir

10      affects the presence of SARS-CoV-2 in the upper respiratory tract. The purpose of the

11      current study is to determine if nirmatrelvir/ritonavir accelerates positive to negative

12      conversion of upper respiratory SARS-CoV-2 RT-PCR in hospitalized patients who

13      have mild-to-moderate COVID-19 and are at risk for severe disease.

14      **Methods**

15      **Ethical Review of the Study**

16      The study was approved by the Institutional Review Board of the First Hospital of

17      Jilin University and informed consent was achieved from all patients (No. AF-IRB-

18      032-06).

19      **Patients and Settings**

20      In China, all people who test positive for COVID-19 are referred to medical providers

21      for observation or treatment. This was a cohort study investigating a series of patients

22      referred for care to the First Hospital of Jilin University after contracting COVID-19.

1  The study coincided with a wave of Omicron variant infections occurring during this

2  time period in our region of China. This study focused on hospitalized patients older

3  than 18 years who had mild-to-moderate COVID-19 and had a high-risk for

4  developing severe disease.

5  Symptom severity was classified using the Diagnosis and Treatment Protocol for

6  COVID-19 (Trial Version 9) released by the China National Health Commission [23].

7  Mild COVID-19 refers to patients who have one or more mild symptoms including

8  fever, cough, sore throat, fatigue, muscle aches, or loss of smell, and there is no

9  concomitant pneumonia. Moderate COVID-19 was defined as patients having the

10  same types of symptoms as for mild disease but also have radiologic evidence of

11  pneumonia. High-risk was considered as age≥60, a history of diabetes, hypertension,

12  cardiovascular diseases, cerebral infarction, chronic liver or kidney diseases, cancers,

13  smoking, or obesity [19-22].

14  Patients with omicron-variant COVID-19 were referred to our facility beginning on

15  March 5, 2022. On March 24, 2022, nirmatrelvir/ritonavir became available at our

16  facility for the treatment of eligible patients who had COVID-19. Eligible patients

17  treated with nirmatrelvir/ritonavir were compared with similar patients treated at our

18  facility before the drug was available (Supplementary Figure 1). The study included

19  patients' whose symptom onset dates between March 5, 2022 to April 5, 2022. None

20  of them had prior COVID-19 infection. All patients were followed for RT-PCR

21  negative conversion for at least 15 days after symptom onset and 10 days after

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1 treatment initiation. All patients received standard medical care in accordance with

2 the diagnosis and treatment protocol for COVID-19 (i.e., Trial Version 9)[23].

3 **Patients Characteristics**

4 Patients' baseline characteristics were assessed and collected at the time of hospital

5 admission, including sex, age, clinical classification (i.e., symptom severity),

6 comorbidities, risk factors for progression to severe disease (defined above), and

7 vaccination. Days from symptom onset to hospitalization and to treatment were

8 calculated. Baseline specimens were collected from patients' upper respiratory tract

9 within 3 days after hospitalization by either nasopharyngeal or oropharyngeal swabs.

10 The specimens were tested by real-time fluorescence quantitative RT-PCR assay to

11 assess the presence of SARS-CoV-2 virus. The targets for the RT-PCR assay were

12 open reading frame 1ab (ORF) and nucleocapsid protein gene (N gene). The cycle

13 threshold (Ct) value (i.e., number of cycles that are needed to replicate the viral

14 nucleic acid to detectable level) was recorded for both targets. A lower cycle number

15 indicates a larger amount of viral RNA, implying high viral load [24]. Ct values less

16 than 35 for either ORF or N gene target was considered as a positive test for the

17 presence of SARS-CoV-2 virus.

18 **Intervention**

19 Patients in the treatment group received 300mg nirmatrelvir orally, together with

20 100mg ritonavir every 12 hours for 5 consecutive days (10 doses in total). All patients

21 in our facility received standard medical care that included bed rest, vital signs

22 monitoring, oxygen saturation measurement, routine blood chemistry and urine

1 analysis (by Sysmex XN and DIRUI FUS3000), biochemical indicators such as liver

2 and myocardial enzymes, and renal function (by BECKMAN COULTER AU5800),

3 coagulation parameters (by STA-R MAX), arterial blood gas analysis (GEM3500),

4 chest imaging (by Brilliance CT 64 Channel) and cytokine detection (by Roche-Cobas

5 8000 e801), and oxygen therapy if needed. Patients included in this analysis were not

6 treated with any other COVID-19 specific medications such remdesivir or monoclonal

7 antibodies.

**Primary Outcome**

9 The primary outcome was the time to conversion from a positive RT-PCR test for

10 upper respiratory SARS-CoV-2 to a negative test. Because we had limited

11 quantitative information about the positivity of pre-hospitalization COVID-19 testing

12 in our patients, the first test considered in this analysis was the one the patients had

13 within 3 days after they were hospitalized. China's COVID-19 diagnosis and

14 treatment protocol (i.e., Trial Version 9) [23, 25], consider RT-PCR tests as negative

15 if Ct values are more than or equal to 35 for both ORF and N SARS-CoV-2 genes for

16 2 consecutive RT-PCR tests having interval of more than 24 hours. All patients were

17 tested for conversion RT-PCR test through either nasopharyngeal or oropharyngeal

18 swabs on a daily basis beginning on day 3 of their hospitalization until conversion

19 was observed.

**Secondary Outcomes**

21 Secondary outcomes included the proportion of patients RT-PCR negative for

22 respiratory SARS-CoV-2 at 15 days following treatment initiation. Treatment side

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1 effects and subgroup analysis of the time to conversion to RT-PCR negative status for

2 SARS-CoV-2 were also examined. The specific subgroups analyses were based on

3 patients' sex, age, clinical classification, comorbidities and high-risk factors, baseline

4 Ct values, and vaccination history. Safety assessment regarding potential side effects

5 of the drug, such as diarrhea and gastric distress, were collected by health care

6 providers (physicians and nurses) through inquiry on a daily basis. Side effects

7 monitoring occurred from the initiation of the treatment until the patient was

8 discharged from the hospital.

9 **Surveillance**

10 A telephone survey was performed between June 20-26, 2022 to query the patients

11 about COVID-19 recurrence.

12 **Statistical Analysis**

13 Baseline characteristics were compared between patients treated and not treated with

14 nirmatrelvir/ritonavir using chi-square and Wilcoxon rank-sum tests. Outcomes were

15 assessed by Kaplan-Meier plots and Cox proportional hazards regression. Cox models

16 were created that adjusted for age and sex and also for all risk factors that were

17 different between the two groups. Logistic regression was utilized to investigate

18 associations between patient's baseline characteristics and side effects.

19 Analyses were conducted using Stata version 17.0 (StataCorp). All statistical tests

20 were two-sided and the statistical significance level was set to $P < .05$. This study

21 adhered to the Strengthening the Reporting of Observational Studies in Epidemiology

22 (STROBE) initiative guideline.

1 **Results**

2 **Patient Demographic and Clinical Characteristics**

3 There were 296 eligible patients treated with nirmatrelvir/ritonavir. Of these 38 (13%)

4 were excluded from the analysis because treatment was discontinued early. Early

5 termination of treatment was usually due to the side effects of dysgeusia and gastric

6 discomfort. The final analytic sample for the treatment group included 258 patients

7 treated with nirmatrelvir/ritonavir who were compared to a control group of 224

8 untreated patients. The median (interquartile range) age was 56 (45-66) years, 282

9 (58.5%) were men, 435 (90.3%) were classified as mild cases, 391 (81.1%) had

10 received as least one dose of SARS-CoV-2 vaccine. All the patients had received

11 inactivated vaccine (SINOVAC), with 374 of 391 (95.7%) patients having 2 or 3

12 doses administered. For the 364 (93.1%) vaccinated patients who had available

13 information about the last dose date, the median (interquartile range) time from last

14 dose to symptom onset was 209 (125-240) days. The most common baseline

15 comorbidities were age 60 years and above (188 [39.0%]), hypertension (172

16 [35.7%]), diabetes (92 [19.1%]), and current smoking (84 [17.4%]); 203 (42.1%)

17 patients had more than one risk factor. Table 1 shows the baseline characteristics

18 between patients treated with or without nirmatrelvir/ritonavir. Patients in the

19 treatment group were on average 4 years younger and had 1 fewer day of delay

20 between symptom onset and hospitalization. They were more likely to smoke but less

21 likely to have diabetes or hypertension than non-treated patients**.**

22

**Primary Outcome: Time to Negative Conversion**

Patients treated with nirmatrelvir/ritonavir within 5 days after symptom onset showed more rapid conversion from positive to negative upper respiratory SARS-CoV-2 RT-PCR testing compared with non-treated patients (median [interquartile range] time: 10 [7-12] days vs. 17 days (12-21 days) days). This difference was not observed for patients whose nirmatrelvir/ritonavir treatment was initiated more than 5 days after symptom onset (Figure 1). The median (interquartile range) time from treatment initiation to negative upper respiratory RT-PCR conversion among all patients in the treatment group was 3 days (6-9 days).

**Secondary Outcomes**

At day 15, 89.7% of patients treated with nirmatrelvir/ritonavir within 5 days of symptom onset had their upper respiratory RT-PCR convert from positive to negative. This day 15 conversion occurred 42.0% of non-treated patients. Of the patients who initiated nirmatrelvir/ritonavir 5 days after symptom onset, 51.8% converted (Table2). Adjustment for baseline differences between the groups had little effect on the hazard ratio for the effect of nirmatrelvir/ritonavir treatment. The hazard ratio for the day 15 conversion rate for patients treated within 5 days of symptom onset was substantially higher (hazard ratio, 4.33; 95% confidence interval, 3.31-5.65) compared with non-treated patients, with the hazard ratio little affected by the adjustment for baseline characteristics (Table 2).

Subgroup analysis of time to negative conversion of RT-PCR testing in patients receiving nirmatrelvir/ritonavir showed no statistically significant association with a

1    patient's sex, age, clinical classification, baseline comorbidities, risk factors, and

2    vaccination history both in the minimally and adjusted models (Supplementary Table

3    1 and Supplementary Figure 2). Patients having lower Ct values before the treatment

4    (e.g., larger viral load), were associated with a lower rate of negative RT-PCR

5    conversion within 10 days after the treatment.

6    Among patients treated with nirmatrelvir/ritonavir, 103 (39.9%) patients experienced

7    at least one side effect. The most common side effects were dysgeusia (94 [36.4%])

8    and diarrhea (14 [5.4%]). Subgroup analysis also showed that elderly patients (i.e.,

9    age≥60) were less likely to report side effects, particularly for dysgeusia (odds ratio

10   [OR], 0.48; 95% CI, 0.26-0.87) (Supplementary Table 2). There was a statistically

11   significant greater risk of experiencing any side effect, in particular dysgeusia in

12   patients who were current smokers, had baseline N gene and ORF Ct values below 30,

13   or were vaccinated for SARS-CoV-2; patients in these subgroups were statistically

14   significantly younger than those in the reference group.

15   **Surveillance**

16   COVID-19 recurrence occurred in 2 patients in the treatment group and in 3 patients

17   in the control group (Supplementary Table 3).

18

19   **Discussion**

20   In this observational cohort study of patients with mild-to-moderate COVID-19 and at

21   high-risk for progression to severe disease, nirmatrelvir/ritonavir was associated with

22   more rapid conversion from positive to negative respiratory SARS-CoV-2 RT-PCR

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1   status as compared with non-treated patients. The median time for RT-PCR negative

2   conversion was 7 days earlier in patients receiving the treatment within 5 days after

3   symptom onset compared with non-treated patients. Timing of drug administration

4   relative to symptom onset was an important predictor of positive to negative RT-PCR

5   conversion. Patients who received treatment more than 5 days after symptom onset

6   failed to accelerate RT-PCR negative conversion as compared with the non-treated

7   patients.

8   The subgroup analysis of time to negative conversion since treatment initiation within

9   the treatment group demonstrated several interesting phenomena. The rate at which

10  RT-PCR conversion became negative was not affected by age, sex, clinical

11  classification, types of comorbidities, or vaccination history. As such,

12  nirmatrelvir/ritonavir should be recommended as treatment for patients with

13  irrespective of baseline characteristics because aside from accelerating their recovery

14  from COVID-19, they will cease shedding virus sooner and reduce the risk of disease

15  transmission [26]. Although medication discontinuation was fairly common because

16  of dysgeusia and gastrointestinal side effects, there were no serious adverse effects

17  attributable to nirmatrelvir/ritonavir.

18  Our findings extend results from a phase II/III randomized controlled trial (RCT),

19  showing that the co-administration of nirmatrelvir/ritonavir, significantly reduced the

20  risk of progression to severe COVID-19 for non-hospitalized adults with risk factors

21  for the development of severe disease [27]. Our study shows that this medication can

22  accelerate the time to negative conversion and, therefore, potentially shorten the

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1    duration that patient's shed virus. The previous RCT studied unvaccinated and non-

2    hospitalized adults of all races [27]. Our study focused on hospitalized, high-risk

3    Asian adult patients, most of whom were vaccinated. The focus of our investigation

4    was to better understand nirmatrelvir/ritonavir's effect on positive to negative upper

5    respiratory conversion rates as a proxy for when it is safe to end isolation intending to

6    limit COVID-19 disease transmission.

7    Our investigation was of a community sample, and might be more generalizable than

8    the RCT results. However, a consequence of the observational nature of our study was

9    having differences between the treatment and control groups that included age, days

10    from symptom onset to hospitalization, and the incidence of diabetes and

11    hypertension. Multivariable Cox regression modeling was used to adjust these

12    potential confounding factors suggesting that they did not affect the time to negative

13    SARS-CoV-2 RT-PCR conversion.

14    Rapid mutation of SARS-CoV-2 results in frequent alterations of the spike protein

15    that may attenuate vaccine and neutralizing antibody treatment effectiveness [28, 29].

16    Nirmatrelvir targets the conserved coronavirus $M^{pro}$ enzyme enabling it to remain

17    effective against COVID-19 variants including Omicron [8, 10, 30]. Co-

18    administration of nirmatrelvir plus ritonavir increases the potency and results in

19    improved safety against COVID-19 compared with other currently available antiviral

20    drugs [31, 32].

21    COVID-19 patients can experience recurrence (rebound) following treatment with

22    nirmatrelvir/ritonavir. In this phenomenon, viral load increases after an initial

15

1  decrease that occurred after anti-viral treatment.[33, 34] In this study, we found 2

2  patients in the treatment group and 3 patients in the control group that experienced

3  viral rebound. The average time for COVID-19 RT-PCR tests to convert to positive

4  after being negative was 7.0 and 10.6 days in the two groups, respectively. There were

5  no symptoms associated with these rebound episodes.

6  **Strength and Limitations**

7  Patients in this clinical observational study were isolated and managed using standard

8  treatment protocols, facilitating more efficient comparisons between treatment groups

9  as well as acquisition of high quality and complete data capture. Being observational,

10  the results are generalizable to actual clinical practice. This study has some

11  limitations. First, it is an observational study on investigating a series of patients who

12  received medical care for COVID-19 at our facility. Because of its demonstrated

13  efficacy, when nirmatrelvir/ritonavir became available, all eligible patients treated at

14  our facility received the medication precluding having a concurrent control group to

15  study. Second, there were imbalances between the two groups, but these had little

16  effect on the outcomes following statistical adjustment. Third, the test for COVID-19

17  was mainly based on RT-PCR and corresponding Ct values. RT-PCR may

18  overestimate active viral replication and shedding, picking up inactive viral fragments

19  as compared with antigen tests which are likely better at capturing active disease[35].

20  Fourth, because we did not perform cell-based assays or disease transmission studies,

21  the present study cannot demonstrate a patients' infectivity or actual transmission of

22  COVID-19 to other patients.

16

**Conclusion**

Nirmatrelvir/ritonavir can shorten the time of RT-PCR conversion for high-risk

SARS-CoV-2 infected adults suggesting that this treatment may reduce the risk of

viral shedding and disease transmission.

**Notes:**

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Table 1. Demographic and clinical characteristics of patients treated with and without nirmatrelvir/ritonavir.

| Characteristics | Patients No. (%) | | |
| --- | --- | --- | --- |
| | Treated with Nirmatrelvir/ritonavir (n=258) | Non-treated (n=224) | P value[a] |
| Age, years | | | |
| Median (IQR) | 54 (41-66) | 58 (50-67) | 0.01 |
| Sex | | | |
| Women | 104 (40.3%) | 96 (42.9%) | 0.57 |
| Men | 154 (59.7%) | 128 (57.1%) | |
| Days from symptom onset to hospitalization | | | |
| Median (IQR) | 2 (1-3) | 3 (2-5) | <0.00 |
| Clinical classification | | | |
| Mild | 231 (89.5%) | 204 (91.1%) | 0.57 |
| Moderate | 27 (10.5%) | 20 (8.9%) | |
| No. of comorbidities and risk factors | | | |
| 1 | 160 (62.0%) | 119 (53.1%) | 0.08 |
| 2 | 73 (28.3%) | 71 (31.7%) | |
| ≥3 | 25 (9.7%) | 34 (15.2%) | |
| Diabetes | | | |
| No | 220 (85.3%) | 170 (75.9%) | 0.01 |
| Yes | 38 (14.7%) | 54 (24.1%) | |
| Hypertension | | | |
| No | 181 (70.2%) | 129 (57.6%) | <0.01 |
| Yes | 77 (29.8%) | 95 (42.4%) | |
| Smoking | | | |
| No | 197 (76.4%) | 201 (89.7%) | <0.00 |
| Yes | 61 (23.6%) | 23 (10.3%) | |
| Age≥60 | | | |
| No | 164 (63.6%) | 130 (58.0%) | 0.21 |
| Yes | 94 (36.4%) | 94 (42.0%) | |
| Baseline N gene Ct value | | | |
| ≥30 | 66 (25.6%) | 67 (29.9%) | 0.29 |
| <30 | 192 (74.4%) | 157 (70.1%) | |
| Baseline ORF Ct value | | | |
| ≥30 | 82 (31.8%) | 84 (37.5%) | 0.19 |
| <30 | 176 (68.2%) | 140 (62.5%) | |

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| | | | |
|---|---|---|---|
| Vaccination | | | |
| No | 50 (19.4%) | 41 (18.3%) | 0.76 |
| Yes | 208 (80.6%) | 183 (81.7%) | |
| No. of vaccination | | | |
| 1 | 8 (3.9%) | 9 (4.9%) | |
| 2 | 139 (66.8%) | 134 (73.2%) | 0.23 |
| 3 | 61 (29.3%) | 40 (21.9%) | |

Abbreviations: Ct, cycle threshold; IQR, interquartile range; SD, standard deviation.

[a] *P* value by Person's chi-square and Wilcoxon rank-sum tests.

Table 2. Comparison of negative conversion between patients treated with and without nirmatrelvir/ritonavir.

| Patients | Total | No. (%) with a negative conversion [a] | Negative conversion ≤ 15 days after symptom onset [a] | |
| --- | --- | --- | --- | --- |
| | | | Model 1 [b] HR (95% CI) | Model 2 [c] HR (95% CI) |
| Without treatment | 224 | 94 (42.0%) | Reference | Reference |
| Treated with Nirmatrelvir/ritonavir ≤5 days | 175 | 157 (89.7%) | 4.33 (3.31-5.65) | 4.85 (3.56-6.61) |
| Treated with Nirmatrelvir/ritonavir >5 days | 83 | 43 (51.8%) | 1.29 (0.90-1.86) | 1.47 (1.02-2.13) |

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] All patients were followed from symptom onset to negative conversion or day 15, whichever was earliest.

[b] Model 1: adjusted for patient's age and sex.

[c] Model 2: adjusted for all patient's baseline characteristics shown in Table 1.

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1   Figure 1. Comparison of conversion from positive to negative SARS-CoV-2 RT-PCR testing
2   between patients treated with and without nirmatrelvir/ritonavir.
3
4   Legend: Kaplan-Meier plot for the proportion of patients converted from positive SARS-
5   CoV-2 RT-PCR to negative, all patients were followed for at least 15 days since symptom
6   onset. The median (interquartile range) time for positive to negative RT-PCR conversion was
7   17 days (12-21 days) in non-treated patients, 10 days (7-12 days) in patients treated with
8   nirmatrelvir/ritonavir ≤5 days after symptom onset, and 15 days (11-21 days) in patients
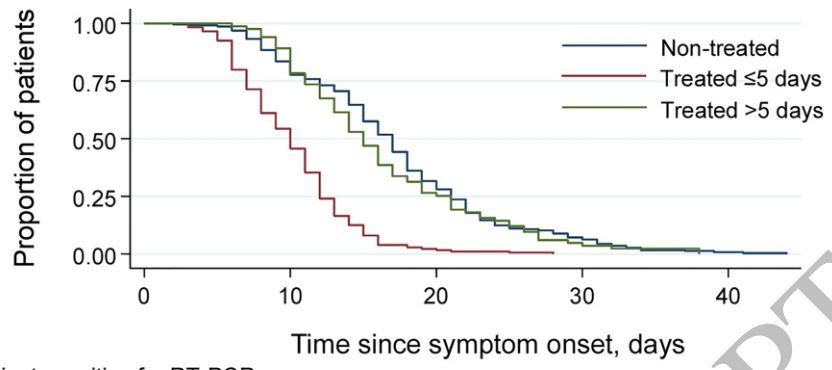9   treated > 5 days after symptom onset, respectively.
10
11   Abbreviations: polymerase chain reaction to negative (RT-PCR); severe acute respiratory
12   syndrome coronavirus 2 (SARS-CoV-2).
13

Number of patients positive for RT-PCR

| | | | | | |
|---|---|---|---|---|---|
| Non-treated | 224 | 187 | 71 | 16 | 2 |
| Treated ≤5 days after symptom onset | 175 | 95 | 4 | 0 | 0 |
| Treated >5 days after symptom onset | 83 | 74 | 22 | 4 | 0 |

1

2                                         **Figure 1**

3                                **147x66 mm ( x  DPI)**