Molnupiravir Use and Severe Covid-19 Outcomes During the Omicron Surge

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Abstract

Background

The oral antiviral molnupiravir is moderately effective in high-risk, unvaccinated non-hospitalized patients infected with early variants of SARS-CoV-2. Data regarding the effectiveness of molnupiravir against the B.1.1.529 (omicron) variant and in vaccinated populations are limited.

Methods

We obtained data for all members of Clalit Health Services, 40 years of age and older, eligible for molnupiravir therapy during the omicron surge. A Cox proportional-hazards regression model with time-dependent covariates was used to estimate the association between molnupiravir treatment and hospitalizations and deaths due to Covid-19, with adjustment for sociodemographic factors, coexisting conditions, and prior Covid-19 immunity status.

Results

A total of 19,868 participants met the eligibility criteria, of whom 1,069 (5%) received molnupiravir during the study period. In patients 65 years and above, the rate of hospitalizations related to Covid-19 in treated compared to untreated patients was 74.6 versus 127.6 per 100,000 person-days; adjusted hazard ratio (HR) 0.55 (95% CI, 0.34 to 0.88). The adjusted HR for death due to Covid-19 was 0.26 (95% CI, 0.10 to 0.73). Among patients aged 40 to 64, the hospitalizations rate in treated compared to untreated patients was 125.8 versus 49.1 per 100,000 person-days; adjusted HR 1.80 (95% CI, 0.86 to 3.77). The adjusted HR for death was 12.8 (95% CI, 3.41 to 48.2).

Conclusions

In a cohort of non-hospitalized, omicron-infected high-risk patients, molnupiravir therapy was associated with a significant reduction in hospitalizations and mortality due to Covid-19 in patients 65 years and above. However, no evidence of benefit was found in younger adults.

Background

Molnupiravir, an oral, antiviral prodrug, is active against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). The US Food and Drug Administration (FDA) issued on Dec 23, 2021, an Emergency Use Authorization (EUA) for molnupiravir for the treatment of mild to moderate Covid-19 in patients at a high risk of progression to severe Covid-19. However, the EUA was restricted by the FDA only to patients for whom alternative Covid-19 treatment options are not accessible or clinically appropriate (2).

Data supporting the approval of molnupiravir came from the MOVe-OUT randomized controlled trial (RCT) that evaluated molnupiravir in high-risk unvaccinated non-hospitalized adults. Molnupiravir reduced the rate of the primary endpoint, all-cause hospitalizations or death, by 30% (9.7% in the placebo arm vs. 6.8% in molnupiravir recipients) (1).

However, the effectiveness of molnupiravir in high-risk patients who are not eligible for other antiviral treatments, infected by the omicron variant, and in vaccinated populations is still limited (3–6). Therefore, our objective was to assess the real-world effectiveness of molnupiravir therapy in preventing severe Covid-19 outcomes in this patient population.

Methods

Study Design

This observational, retrospective cohort study was based on data obtained from the electronic medical records of Clalit Health Services (CHS), a large healthcare organization covering approximately 65% of the elderly Israeli population. The study period started on Jan 16, 2022, the first-day molnupiravir was administered to CHS patients, and ended on Mar 31, 2022, while the omicron variant (BA.1) was the dominant SARS-CoV-2 strain in Israel. The primary effectiveness endpoint was the rate of hospitalizations related to Covid – 19. The secondary outcome was death due to Covid-19. Patients were followed up for 35 days after the Covid-19 diagnosis. Safety outcomes were out of the scope of this study.

Study Population

The study population included all CHS members 40 years of age and above, diagnosed with Covid-19 as outpatients, estimated to be at high risk for progression to severe disease, and non-eligible for ritonavir-boosted nirmatrelvir therapy due to drug-drug interactions or impaired kidney function (7). High risk was defined according to a predictive risk score developed in CHS to evaluate the risk for severe Covid-19 in SARS-CoV-2 infected patients (8). Patients with a score of 2 points or more were considered high-risk. Patients residing in long-term care facilities, patients hospitalized before or on the same day of a positive SARS-CoV-2 test, and patients treated with ritonavir-boosted nirmatrelvir or monoclonal antibodies were all excluded from the study.

CHS policy was to initiate antiviral therapy in eligible patients as soon as possible after a positive SARS-CoV-2 test result. Each CHS geographical district was responsible for delivering molnupiravir therapy to the patient's homes and verifying adherence to the treatment regimen. The follow-up time of individual patients ended at the earliest of the following: 35 days from diagnosis of Covid-19; the end of the study period; or if censored earlier due to non-Covid-19 death.

The study was approved by the Community Institutional Review Board and the data utilization committee of Clalit Health Services. Due to the retrospective design, the study was exempt from obtaining informed

consent from the patients.

Data Sources and organization

We evaluated integrated patient-level data maintained by CHS from two primary sources: the primary-care operational database and the dedicated Covid-19 database. These same sources were used in the study that evaluated the effectiveness of ritonavir-boosted nirmatrelvir (8). For each participant in the study, the following sociodemographic data were extracted: age, sex, demographic group (general Jewish population, ultra-Orthodox Jewish population, or Arab population), and the score for socioeconomic status.

The following Covid-19 clinical data were extracted: vaccination dates, PCR and state-regulated rapid antigen test dates and results, antiviral therapies, hospitalizations, and mortality. Clinical risk factors for severe Covid-19 were also collected: immunosuppression, diabetes mellitus, asthma, hypertension, neurologic diseases, current cancer disease, chronic hepatic disease, chronic obstructive pulmonary disease, chronic kidney failure, chronic heart failure, obesity, history of stroke, history of or current smoking and all-cause hospitalizations in the last three years.

Subgroup Analysis by Immunity Status

All participants were classified into two categories of immunity status: participants who had acquired prior immunity (prior infection, vaccination, or both); or participants with no prior immunity (unvaccinated or vaccinated with only one vaccine dose that were not previously infected with SARS-CoV-2).

Statistical Analysis

Descriptive statistics were used to characterize the study participants. Since the independent variable (molnupiravir treatment) varied over time, univariate and multivariate survival analyses were performed with time-dependent covariates.

In order to avoid immortal time bias (9), we performed a time-dependent analysis in which a time-varying covariate was used to indicate the initiation of treatment for each treated patient. In this analysis, participants who received molnupiravir treatment were transferred from the 'untreated' risk set to the 'treated' risk set when treatment was initiated, modifying their treatment status from untreated to treated. For patients who did not receive treatment with molnupiravir, time zero was determined as the day of Covid-19 diagnosis. For patients who received treatment with molnupiravir, time zero corresponded to the time at which a patient began the treatment. Consequently, the follow-up of molnupiravir -treated patients started at the end of the immortal period.

The association of molnupiravir and Covid-19 outcomes was estimated using a multivariate Cox proportional-hazards regression model with time-dependent covariates, adjusted for sociodemographic and clinical risk factors. We applied two-step testing criteria for selecting covariates. First, a univariate Kaplan-Meier analysis with a log-rank test was applied to test the associations of each independent candidate variable with the time-dependent primary outcome. Then, a comparison of the survival curves

and Schoenfeld's global test was used to test the proportional hazards assumption for those variables. Variates that met these two testing criteria served as inputs for multivariate regression analysis. Another multivariate Cox proportional-hazards regression model was used to estimate the association of all covariates and uptake of molnupiravir therapy.

A sensitivity analysis assessed the effect size of molnupiravir treatment beginning on day 3 of follow-up by excluding patients hospitalized within 2 days after the start of follow-up in order to compare with the MOVe-OUT trial, in which patients were excluded if the need for hospitalization within 2 days after randomization was anticipated (1).

R statistical software version 3.5.0 (R Foundation) was used for the univariate and multivariate survival analysis with time-dependent covariates. SPSS software, version 26 (IBM), was utilized for all other statistical analyses.

Results

Study Population

A total of 1,166,404 CHS members were infected with SARS-CoV-2 during the study period (Fig. 1). Of them, 19,868 were eligible for molnupiravir therapy. 1,069 (5%) received at least one dose of molnupiravir. The mean age of the study participants was 69, with 68% of the participants aged 65 years and older and 28% female. The most common coexisting conditions were obesity, hypertension, and diabetes. 82% of participants had previous Covid-19 immunity, either by vaccination, prior SARS-CoV-2 infection, or hybrid immunity (Table 1).

Table 1
Characteristics of the Participants at Baseline

Characteristic	All Participants (N = 19,868)	Molnupiravir treated (N = 1,069)	Untreated (N = 18,799)
Age, years			
Mean ± SD	69.1 ± 11.6	73.0 ± 11.0	68.9 ± 11.6
Distribution- no. (%)			
40–59 year	3,737 (19)	124 (12)	3,613 (19)
≥60yr	16,131 (81)	945 (88)	15,186 (81)
Female sex - no. (%)	5,646 (28)	360 (34)	5,286 (28)
Population sector- no. (%)			
General Jewish	16,177 (81)	963 (90)	15,214 (81)
Ultra-Orthodox Jewish	983 (5)	31 (3)	952 (5)
Arab	2,708 (14)	75 (7)	2,633 (14)
Socioeconomic status			
Mean ± SD	5.6 ± 1.9	6.0 ± 1.8	5.6 ± 1.9
Median (IQR)	6 (3–9)	6 (3–9)	6 (3–9)
Clinical risk factors - no. (%)			
Obesity	7,049 (36)	399 (37)	6650 (35)
Hypertension	12,211 (61)	782 (73)	11,429 (61)
Diabetes	8,113 (41)	505 (47)	7,608 (41)
Current or former smoking	5,838 (29)	281 (26)	5,557 (30)
Immunosuppression	3,381 (17)	279 (26)	3,102 (17)
Organ transplantation	466 (2)	75 (7)	391 (2)
Neurologic disease	4,018 (20)	233 (22)	3,785 (20)
Current cancer disease	2,284 (11)	201 (19)	2,083 (11)
Asthma	2,180 (11)	134 (13)	2,046 (11)
History of stroke	2,651 (13)	186 (17)	2,465 (13)
Chronic hepatic disease	1,374 (7)	98 (9)	1,276 (7)

Characteristic	All Participants (N = 19,868)	Molnupiravir treated (N = 1,069)	Untreated (N = 18,799)
Chronic obstructive pulmonary disease	1,981 (10)	173 (16)	1,808 (10)
Chronic heart failure	2,003 (10)	176 (16)	1827 (10)
Chronic kidney failure	2,507 (13)	248 (23)	2,259 (12)
Recent hospitalization	10,090 (51)	658 (62)	9,432 (50)
Covid-19 immune status - no. (%)			
No prior immunity	1,660 (8)	71 (7)	1,589 (8)
With prior immunity (overall)	18,208 (92)	998 (93)	17,210 (92)

Molnupiravir Uptake

The associations between patient characteristics and molnupiravir uptake are described in Table 2. The rate of molnupiravir use was notably higher in males, patients aged 65 years and above, and patients at a higher socioeconomic status. Uptake was also higher in patients with the following coexisting conditions: post-transplant, immunosuppression, chronic obstructive pulmonary disease, and cancer. The median time from a positive test to initiation of therapy was 2 days (range 1–5 days).

Table 2
Association between participant characteristics and molnupiravir uptake*

Variable	Adjusted Hazard Ratio (95% CI)
Age group	
40–64	Reference
≥65	1.55 (1.32–1.82)
Female Sex	0.71 (0.62–0.82)
Population sector	
General Jewish	Reference
Ultra-orthodox Jewish	0.90 (0.62–1.31)
Arab	0.78 (0.60–1.01)
Socio-Economic Status**	1.11 (1.07–1.15)
Clinical risk factors	
Obesity	1.11 (0.97–1.26)
Diabetes	1.12 (0.99–1.28)
Asthma	0.97 (0.80–1.17)
Hypertension	1.28 (1.10–1.49)
Current or former smoking	1.05 (0.91–1.22)
Immunosupression	1.25 (1.06–1.47)
Neurologic disease	1.07 ((0.92–1.24
Current cancer disease	1.53 (1.30–1.80)
Chronic hepatic disease	1.19 (0.97–1.47)
Chronic obstructive pulmonary disease	1.54 (1.28–1.84)
Chronic heart failure	1.23 (1.04–1.46)
Chronic kidney failure	1.37 (1.16–1.61)
History of stroke	1.08 (0.91–1.29)

***** The association between all covariates and nirmatrelvir uptake was estimated using a multivariate Cox proportional-hazards regression model. The higher the hazard ratio, the greater the association between the listed characteristic and nirmatrelvir uptake.

****** A hazard ratio of more than 1.00 indicates an association between a higher score for socioeconomic status and nirmatrelvir uptake.

Variable	Adjusted Hazard Ratio (95% CI)
Recent hospitalization	1.23 (1.08–1.40)
History of organ transplant	2.11 (1.57–2.85)
Chronic immunological disease	1.74 (1.02–2.99)
History of TIA	1.10 (0.86–1.39)
Covid-19 immune status	
With prior immunity	Reference
No prior immunity	0.95 (0.74–1.21)
Clalit Health Services District	
Haifa	reference
Jerusalem	1.28 (0.89–1.84)
Tel-Aviv	3.84 (2.95-5.00)
Dan- Petach-Tikva	0.98 (0.70–1.37)
Center	3.08 (2.39–3.97)
South	3.92 (3.03–5.07)
Sharon- Shomron	1.61 (1.22–2.13)
North	2.40 (1.81–3.19)
Eilat	0.00 (0.00-2.24E + 43)
***** The association between all covariates and nirmatrelvir uptake was estimated using a multivariate Cox proportional-hazards regression model. The higher the hazard ratio, the greater the association between the listed characteristic and nirmatrelvir uptake.	
****** A hazard ratio of more than 1.00 indicates an association between a higher score for socioeconomic status and nirmatrelvir uptake.	

Table 3
Association of confounding variables with Hospitalizations due to Covid-19, According to Age Group*

	Hazard Ratio (95% CI) for Hospitalizations due to Covid-19	
	Age 40–64	Age 65+
Molnupiravir treatment	**1.80 (0.86–3.77)**	**0.55 (0.34–0.88)**
Sex	1.43 (0.94–2.17)	0.93 (0.77–1.12)
Sociodemographic score	0.88 (0.79–0.99)	0.94 (0.89–0.98)
Recent Hospitalizations	2.72 (1.67–4.43)	2.60 (2.09–3.23)
Diabetes	1.71 (1.16–2.53)	1.28 (1.07–1.52)
Current cancer disease	1.81 (1.12–2.92)	1.75 (1.42–2.15)
CHF	**	2.19 (1.80–2.65)
COPD	**	1.43 (1.16–1.78)
CVA	**	1.69 (1.39–2.04)
No prior Immunity	2.60 (1.63–4.15)	**
Immunosuppression	3.71 (2.49–5.54)	**

*The association between nirmatrelvir therapy and hospitalizations due to Covid-19 was estimated using a multivariate Cox proportional-hazards regression model after adjusting for sociodemographic factors, coexisting illnesses, and Covid-19 immune status. Variables that met the testing criteria and were significantly associated with the outcome served as the inputs for the multivariate regression analysis.

** Parameters that did not pass the criteria for inclusion in the multivariate analysis.

Primary Outcome

Testing the interaction of molnupiravir treatment status with the other variables revealed a significant interaction with the age group (above or below 65). We, therefore, report all results separately for these two age groups.

Among the 13,569 patients 65 years of age and above, hospitalizations related to Covid-19 occurred in 18 treated patients (74.6 per 100,000 person-days) and in 513 untreated patients (127.6 per 100,000 person-days); adjusted hazard ration (HR) for hospitalization was 0.55 (95% confidence interval (CI), 0.34 to 0.88).

Among the 6,299 patients aged 40 to 64, hospitalizations related to Covid-19 occurred in in 8 treated patients (125.8 per 100,000 person-days) and 97 untreated patients (49.1 per 100,000 person-days), and adjusted HR for hospitalization was 1.80 (95% CI, 0.86 to 3.77). The cumulative hazard-ratio curves are shown in Figs. 2a, 2b.

Recent hospitalizations, active cancer, and diabetes were significantly associated with high rates of hospitalizations due to Covid-19 across both age groups. Chronic heart failure, active cancer disease, prior CVA and COPD were prominent risk factors in patients aged 65 years or older. In the younger age group, immunosuppression and lack of prior immunity were strongly associated with the risk of hospitalizations related to Covid-19.

Results of the sensitivity analysis, which assessed the effect size of treatment from day 3 of follow-up onwards in patients 65 years or older, demonstrated a somewhat lower effect, with borderline significance, with an adjusted HR for hospitalizations related to Covid-19 of 0.62 (95% CI 0.38–1.01).

Subgroup Analysis by Immunity Status

The adjusted HR for hospitalizations due to Covid-19 in patients without prior immunity was 0.27 (95% CI: 0.07 to 1.09) for patients 65 years of age and above and was 2.01 (95% CI 0.43 to 9.37) among patients aged 40 to 64.

The adjusted HR for hospitalizations related to Covid-19 in patients with prior immunity was 0.62 (95% CI: 0.38–1.03) for patients 65 years of age and above and was 1.62 (95% CI: 0.70–3.80) among patients aged 40 to 64.

Secondary Outcome

In patients 65 years of age and above, death due to Covid-19 occurred in 4 of 845 treated and 137 of 12,724 untreated patients; adjusted HR: 0.26 (95% CI, 0.10 to 0.73).

Among patients aged 40 to 64, death due to Covid-19 occurred in 4 of 224 treated and 7 of 6,075 untreated patients; adjusted HR: 12.82 (95% CI, 3.41 to 48.17).

Discussion

Our study results indicate that molnupiravir was associated with lower Covid-19 hospitalization and mortality rates in patients aged 65 years or older. In participants aged 40–64, no benefit was observed for reducing the risk of Covid-19 hospitalization. Moreover, molnupiravir was associated with a significantly higher risk for mortality due to Covid-19. However, it should be noted that the number of death events was very low, and all four cases in the treatment group occurred in patients aged 60–64.

Compared to the MOVe-OUT trial that demonstrated a 31% reduction in the risk for Covid-19-related hospitalization or death in the entire population (with a borderline statistical significance) (1), our results demonstrate a higher effectiveness (45% effectiveness, 95%CI: 22%-66%) in patients aged 65 years or older and no benefit in younger patients. It should be noted that our study cohort included only patients who were not eligible for ritonavir-boosted nirmatrelvir therapy, per FDA registration (10).

Another study of the real-world effectiveness of molnupiravir from Hong Kong with a comparable population size also reported an interaction between the age group (above or below 65) and molnupiravir

treatment. Moreover, this study reported a significantly higher risk of hospitalization among younger patients and no benefit in older patients (11).

Molnupiravir therapy is recommended by the United States National Institutes of Health (NIH) guidelines only as a second-choice oral alternative when ritonavir-boosted nirmatrelvir use is clinically inappropriate. The prioritization of ritonavir-boosted nirmatrelvir over molnupiravir was established due to the relatively low clinical efficacy in Phase 3 RCTs, although the different antiviral options have not been directly compared (4). Molnupiravir's main advantage over ritonavir-boosted nirmatrelvir is that neither molnupiravir nor its active metabolites are inhibitors or inducers of major drug-metabolizing enzymes, and therefore no drug-drug interactions have been identified for this drug (10).

Several limitations of this study need to be considered. As in any retrospective cohort study, various confounders may have caused bias in the observed effectiveness. We attempted to overcome biases in risk for hospitalizations by adjusting for the variables known to affect severe Covid-19 outcomes. Nevertheless, some sources of residual confounding and selection bias may not have been measured or corrected adequately, such as differences in early diagnosis, disease severity, and differential access to molnupiravir therapy.

Our study observed that only a minority of patients who were high-risk but not eligible for nirmatrelvir therapy received molnupiravir. We do not know why the other eligible participants did not receive treatment, and there may be some selection mechanism that is not explained by the observed confounders; therefore, this remains our primary concern regarding residual bias.

Another limitation of our study is the relatively short data collection period, ending in February 2022, despite the elapsed time. As the Omicron wave surged in Israel, an extensive operation of medication delivery was conducted by Clalit. This operation included meticulous documentation throughout January and February 2022, which could not be maintained beyond that period. Therefore, we have limited the study period to avoid misclassifying treatment uptake.

It should be noted that the evaluation of adverse events and safety data reports was beyond the scope of this study. Future studies will be needed to assess the short- and long-term safety of molnupiravir administration in real-world settings.

Conclusion

In a real-world cohort of non-hospitalized, high-risk patients with Covid-19 from omicron, molnupiravir therapy was associated with a significant reduction in hospitalizations and mortality due to Covid-19 in patients 65 years and above. However, no evidence of benefit was found in younger adults.

Declarations

Statement of sources of support:

This work did not receive any financial or in-kind support.

Conflicts of Interest

All authors report no Conflicts of interest

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Figures

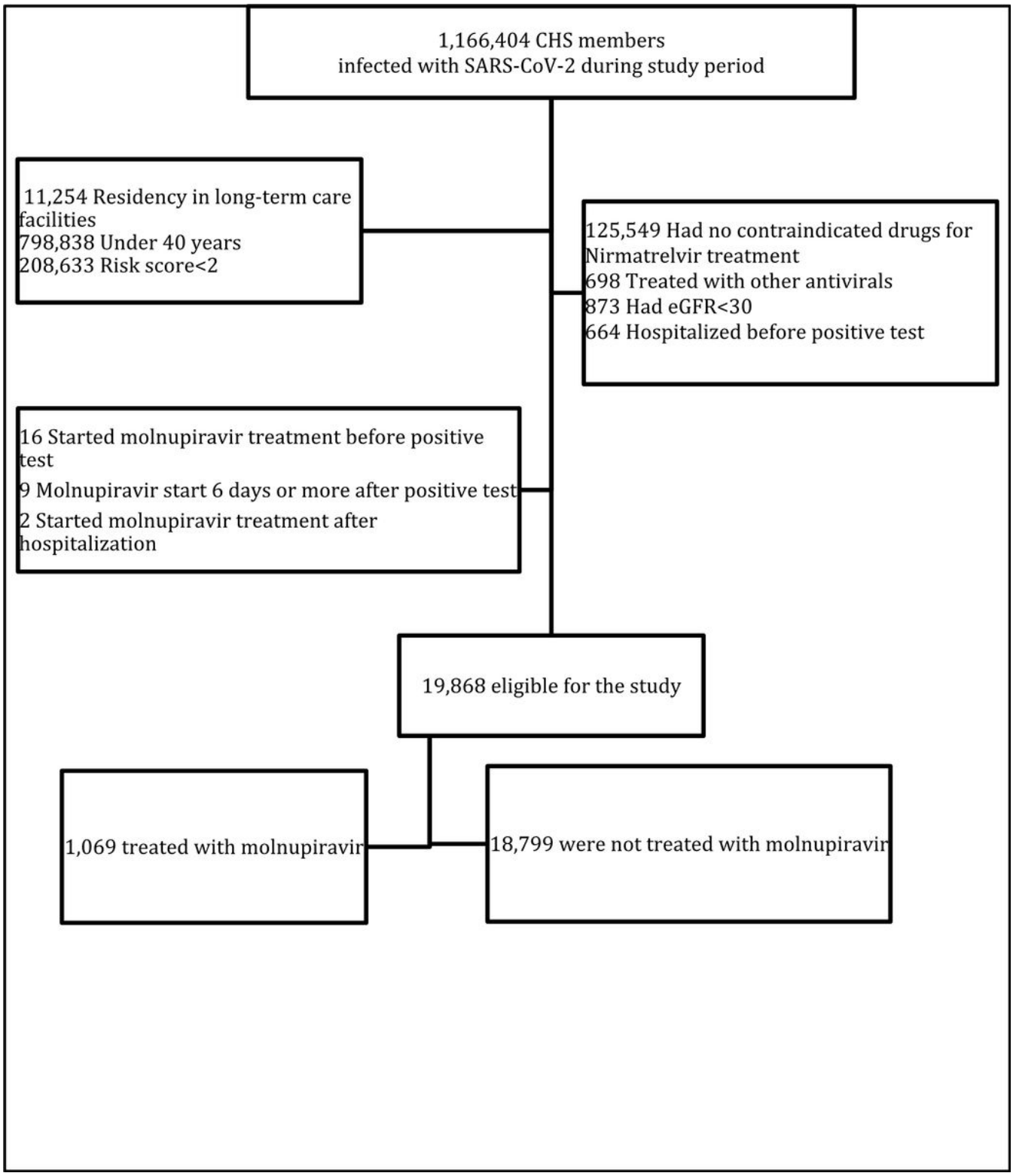

Figure 1

Assessment for Eligibility

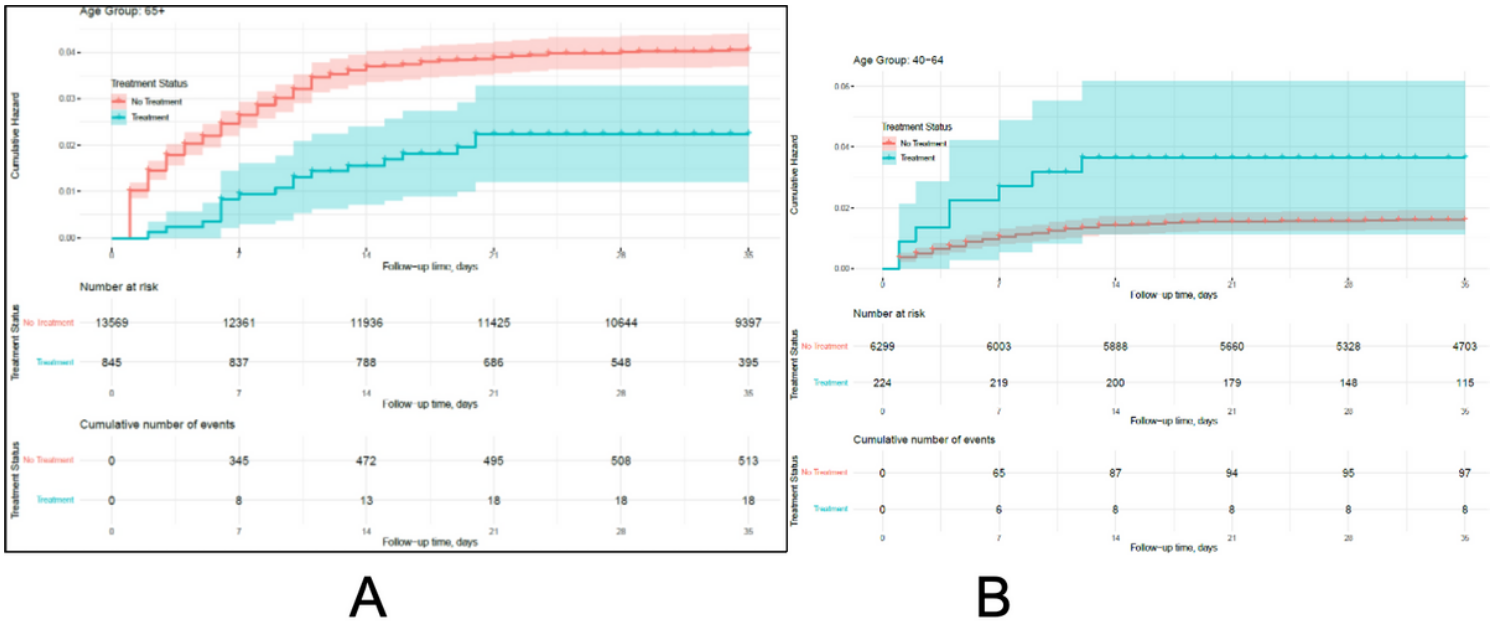

Figure 2

a: Cumulative Hazard Ratio for Hospitalizations Due to Covid-19*, ages 65 years or older

* Time zero in the 'No treatment' panel corresponds to the time at which each patient was diagnosed with Covid-19. Time zero in the 'treatment' panel corresponds to the time at which a patient receiving molnupiravir initiated the treatment.

b: Cumulative Hazard Ratio for Hospitalizations Due to Covid-19*, ages 40-64 years

* Time zero in the 'No treatment' panel corresponds to the time at which each patient was diagnosed with Covid-19. Time zero in the 'treatment' panel corresponds to the time at which a patient receiving molnupiravir initiated the treatment.