Oral Nirmatrelvir and Severe Covid-19 Outcomes During the Omicron Surge

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Research Article

Keywords:

Posted Date: June 1st, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1705061/v1

Abstract

Background

Nirmatrelvir, an inhibitor of the main protease of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has demonstrated a significant decrease in the risk of progression to severe disease in symptomatic high-risk patients infected with the B.1.617.2 (delta) variant of SARS-CoV-2. The effectiveness of nirmatrelvir against the B.1.1.529 variant (omicron) is unknown.

Methods

The study included all Clalit Health Services members, 40 years of age and older, with confirmed infection of SARS-CoV-2 during the omicron surge that were defined as high-risk for severe disease. A Cox proportional-hazards regression model with time-dependent covariates was used to estimate the association between nirmatrelvir treatment and hospitalizations and deaths due to Covid-19, with adjustment for individual sociodemographic factors, coexisting conditions, and prior Covid-19 immunity status.

Results

109,213 participants were eligible for nirmatrelvir therapy during the two-month study period. Among the 42,819 eligible patients aged 65 years and above, 2,504 were treated with nirmatrelvir. Hospitalizations due to Covid-19 occurred in 14 out of the treated and 762 of the untreated patients: adjusted HR 0.33 (95% CI, 0.19 to 0.55). Death due to Covid-19 occurred in 2 treated and 151 untreated patients; adjusted HR: 0.19 (95% CI, 0.05 to 0.76). Among the 66,394 eligible patients 40 to 64 years of age, 1,435 were treated with nirmatrelvir. Hospitalizations due to Covid-19 occurred in 9 treated and 334 untreated patients: adjusted HR 0.78 (95% CI, 0.40 to 1.53). Death due to Covid-19 occurred in 1 treated and 13 untreated patients; adjusted HR: 1.64 (95% CI, 0.40 to 12.95).

Conclusions

Nirmatrelvir therapy was associated with a 67% reduction in Covid-19 hospitalizations and an 81% reduction in Covid-19 mortality in patients 65 years and above. However, no significant benefit in avoidance of severe Covid-19 outcomes was shown in younger adults.

Background

The emergence of the fast-spreading B.1.1.529 (omicron) variant of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in late 2021 led to a global coronavirus disease 2019 (Covid-19) resurgence. By the end of December 2021, omicron was outcompeting the B.1.617.2 (delta) variant, and

by early January, omicron spread widely worldwide, even in communities with high levels of preexisting immunity (1).

The Food and Drug Administration (FDA) issued on December 22, 2021, an Emergency Use Authorization (EUA) for the oral antiviral nirmatrelvir for the treatment of mild to moderate Covid-19 in patients at a high risk of progression to severe disease (2). Nirmatrelvir treatment is provided for five consecutive days as soon as possible after a diagnosis of Covid-19 and within 5 days of symptom onset (3). The primary data supporting the FDA EUA came from the Evaluation of Protease Inhibition for Covid-19 in High-Risk Patients (EPIC-HR) randomized, double-blind, placebo-controlled trial that studied nirmatrelvir treatment in non-hospitalized, high-risk, symptomatic adults with Covid-19 (4). This trial was performed in a period when the delta variant was most likely responsible for the majority of infections (5). All participants in EPIC-HR were unvaccinated for Covid-19 and had not been previously confirmed infected with SARS-CoV-2. EPIC-HR demonstrated a relative risk reduction of 89% for hospitalization or death among those treated with nirmatrelvir. However, the effectiveness of nirmatrelvir against the omicron variant and in patients with prior Covid-19 immunity is unknown.

Therefore, our objective was to assess the effectiveness of nirmatrelvir therapy for preventing mortality and hospitalizations due to Covid-19 in high-risk patients during the omicron surge.

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 52% of the entire Israeli population and almost two-thirds of the older adults.

The study period started on January 9, 2022, the first day the drug was administered to CHS patients, and ended on March 10, 2022. During the study period, the omicron variant was the dominant strain in Israel (Fig. S1 in the Supplementary Appendix).

Patients were eligible to be included in the study if they were diagnosed with Covid-19 by February 24, 2022. Patients' follow-up 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 hospitalization or death from any cause.

Study Outcomes

The primary outcome was hospitalizations due to Covid – 19. The secondary outcome was death due to Covid-19.

Study Population

The study population included all CHS members 40 years of age and above with confirmed SARS-CoV-2 infection, estimated to be at high risk for progression to severe Covid-19, and determined eligible for

nirmatrelvir therapy. High-risk participants were determined according to a score developed in CHS to evaluate the risk for severe Covid-19 in SARS-CoV-2 infected patients (Table S1). Eligibility to the antiviral therapy took into account also drug safety considerations, drug interactions, and contraindications as described in the nirmatrelvir FDA prescribing information (3). A nurse in each CHS district was responsible for delivering nirmatrelvir therapy to the patients' homes and verifying adherence to the treatment regimen. CHS policy was to initiate therapy in eligible patients as soon as possible after a positive SARS-CoV-2 test result to minimize the potential for hospitalizations in the high-risk population, as per FDA prescribing information (3)

Patients residing in long-term care facilities, patients hospitalized during the study period before a positive SARS-CoV-2 test result, and patients treated for Covid-19 during the study period with molnupiravir (the second oral antiviral available in Israel) were all excluded from the study.

The study population was divided into two groups, those who received nirmatrelvir therapy (treatment group) and those who had not (control group). All eligible participants were included in the study's control arm at the date of their positive SARS-CoV-2 test. Patients treated with nirmatrelvir were transferred to the treatment group when they received the initial dose.

The study was approved by the Community IRB and data utilization committees of Clalit Health Services. Due to the retrospective design, the study was exempt from obtaining informed consent from the patients. No financial or in-kind support was provided for the conduct of the study.

Data Sources and organization

We evaluated integrated patient-level data maintained by CHS from two primary sources: the primary-care operational and Covid-19 databases. The operational database includes sociodemographic data and comprehensive clinical information, such as coexisting chronic illnesses, history of community care visits, medications, and results of laboratory tests. The Covid-19 database includes PCR and state-regulated rapid antigen test results, vaccinations provided, and Covid-19-related hospitalizations and death. The Covid-19 database is updated daily from the central Covid-19 repository of the Israeli Ministry of Health. These same databases were used in the primary studies that evaluated the effectiveness of the BNT162b2 vaccine in real-world settings in Israel (6, 7). A description of the data repositories used in this study is provided in the Supplementary Appendix.

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 (ranging from 1 [lowest] to 10 [highest], as described in the Supplement).

The following clinical data were extracted: Covid-19 vaccination dates, PCR and state-regulated rapid antigen test dates and results, Covid-19 antiviral therapies, hospitalizations, and mortality. Data regarding the following 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 recent hospitalizations (in the last three years) from all causes. The eGFR lab test results were obtained as well.

All patients were classified into one of two categories according to their Covid-19 immune status; participants with no prior immunity (unvaccinated or vaccinated with only one mRNA vaccine dose and also with no previous documented SARS-CoV-2 infection) or participants that had already acquired prior immunity (vaccine-induced, infection-induced, or hybrid).

Statistical Analysis

Descriptive statistics were used to characterize the study participants. Since the independent variable (nirmatrelvir treatment) varied over time, univariate and multivariate survival analyses were performed with time-dependent covariates according to the study design. Participants were censored in cases of hospitalization or death from any cause or at the end of follow-up. Participants who received nirmatrelvir were censored from the control group on the day they received the antiviral therapy.

We used a multivariate Cox proportional-hazards regression model to estimate the association of all covariates and uptake of nirmatrelvir therapy. The association of nirmatrelvir and Covid-19 outcomes was estimated using a multivariate Cox proportional-hazards regression model with time-dependent covariates, adjusted for sociodemographic factors and coexisting illnesses. All covariates were tested for interactions with the variable of interest (nirmatrelvir treatment). A Kaplan–Meier analysis with a log-rank test was used for the univariate analysis. Comparison of the survival curves and Schoenfeld's global test were used to test the proportional hazards assumption for each dependent variable. Variables that met the testing criteria served as inputs for multivariate regression analysis.

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. A two-sided P value of less than 0.05 was considered to indicate statistical significance in all analyses.

Results

Patient Population

A total of 109,213 participants met the study criteria. The assessment for eligibility is detailed in Figure 1. The mean age of the study participants was 60, with 39% of the participants aged 65 years and older and 60% female. The most common coexisting conditions were obesity, diabetes, and smoking. 78% of participants had previous Covid-19 immunity, either by vaccination, prior SARS-CoV-2 infection, or hybrid immunity (Table 1).

Nirmatrelvir Uptake

Of the entire population cohort, 3,939 participants (3.6%) received at least one dose of nirmatrelvir therapy during the study period. The association between patient characteristics and the nirmatrelvir uptake rate is described in Table S2. Uptake was notably higher in participants aged 65 years and above and among participants with a current cancer diagnosis. Uptake was significantly lower in participants with no prior Covid-19 immunity and within the Arab minority population.

Primary Outcome

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

Among the 66,394 patients aged 40 to 64, hospitalizations due to Covid-19 occurred in 343 patients (0.5%): 9 (0.6%) out of 1,435 treated patients and 334 (0.5%) out of 64,959 untreated patients; adjusted hazard ratio (HR) for hospitalization was 0.78 (95% confidence interval (CI), 0.40 to 1.53).

Among 42,819 patients 65 years of age and above, hospitalizations due to Covid-19 occurred in 776 patients (1.8%): 14 (0.6%) out of 2,504 treated patients and 762 (1.9%) out of 40,315 untreated patients; adjusted HR 0.33 (95% CI, 0.19 to 0.55) (Table 2). The cumulative hazard-ratio curves are shown in Figures 2a, 2b.

Across both age groups, lack of prior Covid-19 immunity and a previous hospitalization were variables most significantly associated with high rates of hospitalizations due to Covid-19. Immunosuppression was significantly associated with hospitalizations in the 40-64 age group.

Subgroup Analysis by Immunity Status

Among patients the 40-64 years of age, hospitalizations due to Covid-19 occurred in 182 of 20,531 patients (0.9%) without prior immunity and in 161 out of 45,863 (0.4%) with prior immunity. Among participants aged 65 years and above, hospitalizations due to Covid-19 occurred in 273 of 3,306 patients without prior immunity (8.3%) and in 503 of 39,513 patients with prior immunity (1.3%). The adjusted hazard ratios and absolute risk reductions of hospitalizations due to Covid-19 for nirmatrelvir therapy according to prior immunity status and age-group are presented in Table 3. Detailed Cox regression results are presented in tables S3, S4, S5, and S6.

Secondary Outcome

Among patients, 65 years of age and above, Covid-19 death occurred in 2 treated and 151 untreated patients; adjusted HR: 0.19 (95% CI, 0.05 to 0.76). Among patients 40 to 64 years of age, Covid-19 death occurred in 1 treated and 13 untreated patients; adjusted HR: 1.64 (95% CI), 0.40 to 12.95). Detailed Cox regression results are presented in tables S7 and S8.

Discussion

At the beginning of the omicron surge in January 2022, the Israeli authorities decided to set two lines of defense to protect the vulnerable and high-risk populations from severe Covid-19. The first line was approving a second-booster vaccine dose (8). The second was suggesting nirmatrelvir to patients at high risk for Covid-19 hospitalizations. Eligibility for nirmatrelvir was much broader than that was defined in the EPIC-HR registration trial (4), as it also included patients with prior immunity, which were the majority of high-risk patients in the Israeli population.

Treatment with nirmatrelvir is currently recommended by the United States National Institutes of Health (NIH) Covid-19 treatment guidelines as the first choice for antiviral therapy for non-hospitalized adults at high risk of disease progression (9). However, the NIH stated that there is currently a lack of data on the clinical efficacy of nirmatrelvir against the omicron variant of concern (10).

Besides in-vitro studies in experimental models that have demonstrated potent inhibition of the omicron variant by nirmatrelvir (11-14), effectiveness data in real-life patients infected with omicron are still unavailable. Similarly, nirmatrelvir efficacy has only been demonstrated in patients without prior immunity, while in the real world, many of the individuals hospitalized with omicron have prior immunity by vaccinations or prior infections (15).

The findings from our current study suggest that during the omicron variant surge, Covid-19 hospitalizations rates were significantly lower in adults aged 65 years and above in nirmatrelvir treated participants, both in patients with and without prior Covid-19 immunity. The absolute benefit of therapy was substantially higher in patients without prior immunity. Covid-19 mortality rates were also 81% lower in nirmatrelvir treated participants of this age group. However, no significant benefit was shown in the younger cohort.

An observed difference in nirmatrelvir efficacy between patients older and younger than 65 was also demonstrated in the subgroup analysis of EPIC HR; The benefit from nirmatrelvir in participants younger than 65 was substantially less than in the older age group (a reduction of 13.93 percentage points relative to placebo in the $\geq$ 65-year group versus 4.35 in participants younger than 65).

The observed risk for hospitalizations due to Covid-19 in our study period (dominated by omicron) was significantly lower than what was reported in EPIC-HR during the delta wave, as expected (16). The risk in the 40-64 age group was ten-fold lower than in the comparable age group of EPIC-HR (0.5% vs. 5.1%). The baseline risk was low even in the subgroup without prior Covid-19 immunity (0.9%). The risk in the 65+ group was also significantly lower than the comparable EPIC-HR age group (1.8% vs.14.6%). However, within this higher age group, the subgroup without prior immunity had a much higher event rate in the non-treated patients (8.3%) and had a substantially higher absolute benefit (7.1 percentage points).

Our study has several strengths. First, the results are based on the integrated medical records system of CHS, with detailed demographic, clinical, and laboratory testing data, including data on coexisting conditions that could have significantly affected hospitalization rates and were therefore adjusted for in the statistical analysis. The second important strength is the large cohort of participants available for

analysis and the relevant large number of events to be analyzed, substantially higher than in the published randomized controlled trials.

Limitations

As in any retrospective cohort trial, confounding clinical and sociodemographic characteristics may have biased the observed effectiveness. We attempted to overcome these biases by adjusting for the variables known to affect Covid-19 hospitalizations. However, some sources of bias may not have been measured or corrected adequately.

Our study observed that only a minority of patients defined as high-risk patients and eligible for nirmatrelvir therapy received antiviral therapy. We do not know why controls did not receive treatment, and therefore, it is our main concern regarding residual bias. We also do not know the actual level of treatment adherence and, therefore, may be underestimating the effectiveness; if participants took less of the treatment, they are still included in the treatment group but did not benefit from the complete treatment course.

A major concern of potential unmeasured bias is the lack of data regarding the specific symptoms of the infected patients. Moreover, CHS policy was to administer therapy as soon as possible, even before the onset of symptoms, per FDA prescribing information (3). Patients with worse symptoms are presumably more likely to be offered and agree to receive therapy. This potential bias may underestimate the effectiveness of therapy. However, they may also be at a higher risk of hospitalization, overestimating effectiveness. Specifically, a substantial proportion of the observed effect occurs in the first two days of follow-up. As the hospitalizations in the clinical trial occurred mainly after the second day of follow-up, we cannot estimate whether the observed early effect results from residual bias or true early effectiveness.

Another limitation is the heterogeneity of degrees of immunity in the subgroup with prior immunity. This group included patients with infection-induced, vaccine-induced, and hybrid-induced immunity, disregarding any waning of such immunity over time. Nevertheless, our results in the subgroup of patients aged 65 and above without previous immunity are comparable to the results from EPIC-HR. Larger studies will be necessary to evaluate possible differences in nirmatrelvir effectiveness in these different subgroups.

A further limitation is the rate of SARS-CoV-2 infections and thus exposure to disease that changed during the study period. However, we assume that after adjustment for all covariates, including socioeconomic ones, these changes affected the treated and untreated populations similarly.

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 nirmatrelvir

administration in real-world settings.

Conclusions

Nirmatrelvir therapy was associated with a significant reduction in Covid-19 hospitalizations and mortality rates in adults aged 65 and higher during the omicron variant surge. Although this study is observational, we believe that its findings and the observed potential for avoiding severe Covid-19 could assist decision-makers in prioritizing the currently constrained supplies to those in whom nirmatrelvir was shown to be substantially effective.

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Tables

Table 1: Characteristics of the Participants at Baseline

Characteristic	All Participants (N=109,213)
Age	
Mean ± SD - yr	59.9 ± 12.8
Distribution- no. (%)	
40-64 yr	66,394 (61)
≥65 yr	42,819 (39)
Female sex - no. (%)	65,699 (60)
Population sector- no. (%)	
General Jewish	81,865 (75)
Ultra-Orthodox Jewish	6,350 (6)
Arab	20,998 (19)
Median score for socioeconomic status, Median (IQR)	5 (2)
Clinical risk factors - no. (%)	
Obesity	37,757 (35)
Hypertension	37,132 (34)
Diabetes	28,656 (26)
Current or former smoking	26,640 (24)
Immunosuppression	10,816 (10)
Neurologic disease	9,254 (9)
Current cancer disease	7,621 (7)
Asthma	6,440 (6)
History of stroke	5,687 (5)
Chronic hepatic disease	4,853 (4)
Chronic obstructive pulmonary disease	3,494 (3)
Chronic heart failure	3,176 (3)
Chronic kidney failure	1,470 (1)
Recent hospitalization	31,814 (29)
Covid-19 immune status - no. (%)	
No prior immunity	23,837 (22)
With prior immunity	85,376 (78)

Table 2: Association between Hospitalizations due to Covid-19 and Demographic and Clinical Variables, According to Age Group*

Variable	Hazard Ratio for Hospitalization Due to Covid-19 (95% CI)	
	40-64 Yr of Age (N=66,394)	≥65 Yr of Age (N=42,819)
Nirmatrelvir therapy	0.78 (0.40-1.53)	0.33 (0.19-0.55)
Male Sex	1.55 (1.25-1.92)	1.62 (1.40-1.87)
Score for socioeconomic status	NA	0.89 (0.86-0.93)
No prior immunity	6.20 (4.92-7.81)	5.81 (4.98-6.78)
Clinical risk factors		
Recent hospitalization	3.11 (2.47-3.91)	2.10 (1.80-2.45)
Obesity	1.28 (1.02-1.60)	NA
Diabetes	1.34 (1.04-1.72)	1.36 (1.18-1.57)
Immunosuppression	2.91 (2.24-3.79)	NA
Chronic hepatic disease	1.72 (1.20-2.44)	NA
Neurologic disease	1.73 (1.24-2.40)	1.59 (1.34-1.88)
Chronic heart failure	2.57 (1.72-3.83)	1.48 (1.20-1.82)
Chronic obstructive pulmonary disease	NA	1.75 (1.42-2.17)
History of stroke	1.86 (1.28-2.72)	1.39 (1.16-1.66)
Chronic kidney failure	NA	1.80 (1.35-2.40)

*The association between nirmatrelvir therapy and hospitalizations due to Covid-19 was estimated utilizing a multivariate Cox proportional-hazards regression model after adjustment 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.

Table 3: Rates and Hazard Ratios for Hospitalizations due to Covid-19, Subgroup Analysis According to Immunity Status

Variable	Hazard Ratio for Hospitalization (95% CI)		Absolute Benefit - Percentage Points (95% CI)	
	40-64 Yr of age	≥65 Yr of Age	40-64 Yr of age	≥65 Yr of age
All patients	0.78 (0.40-1.53)	0.33 (0.19-0.55)	0.11 (-0.27-0.33)	1.21 (0.82-1.47)
No prior immunity	0.21 (0.03-1.53)	0.14 (0.04-0.57)	0.70 (-0.47-0.86)	7.10 (3.55-7.93)
With prior immunity	1.18 (0.57-2.41)	0.40 (0.23-0.71)	-0.06 (-0.49-0.15)	0.76 (0.37-0.98)

Figures

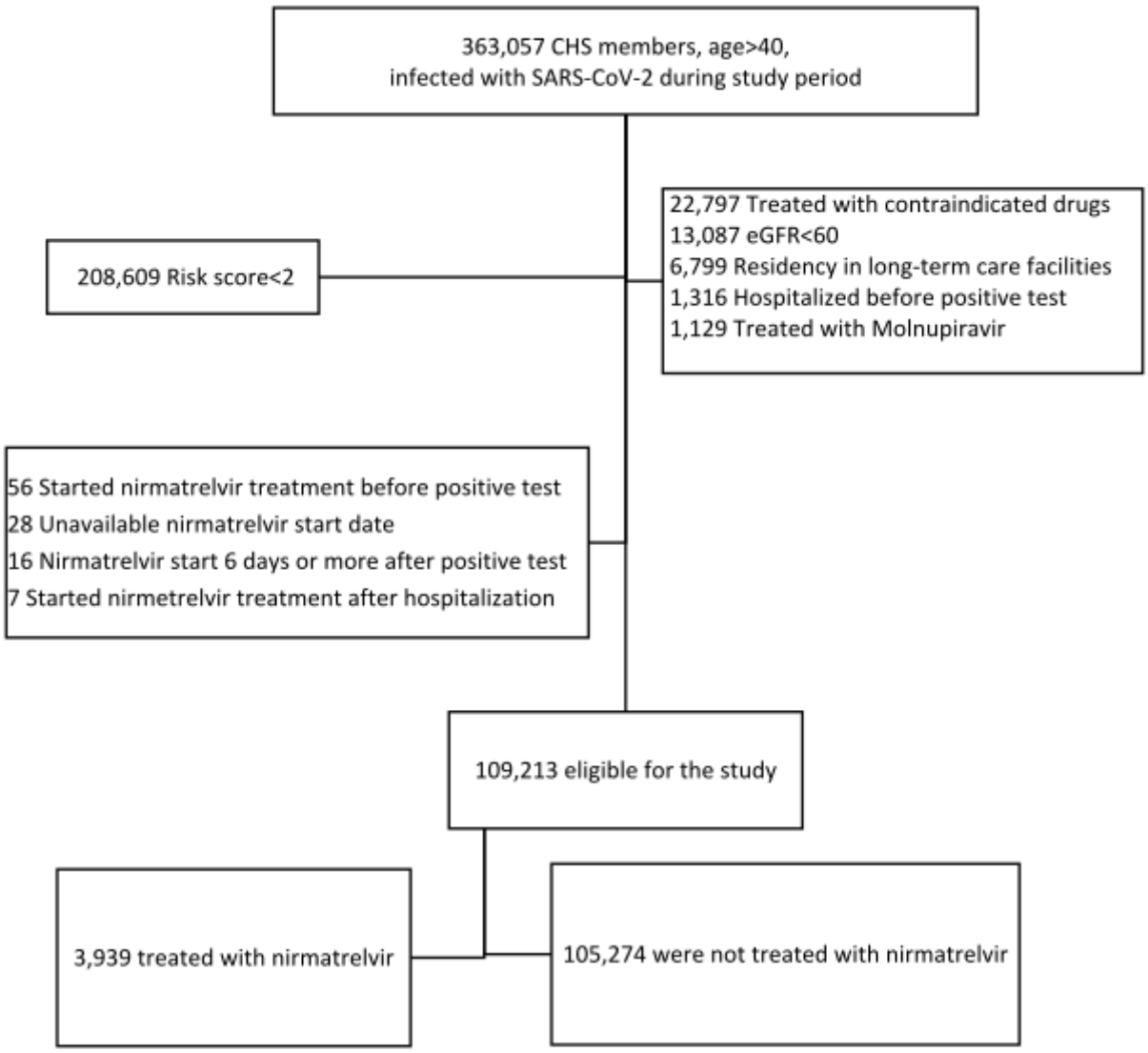
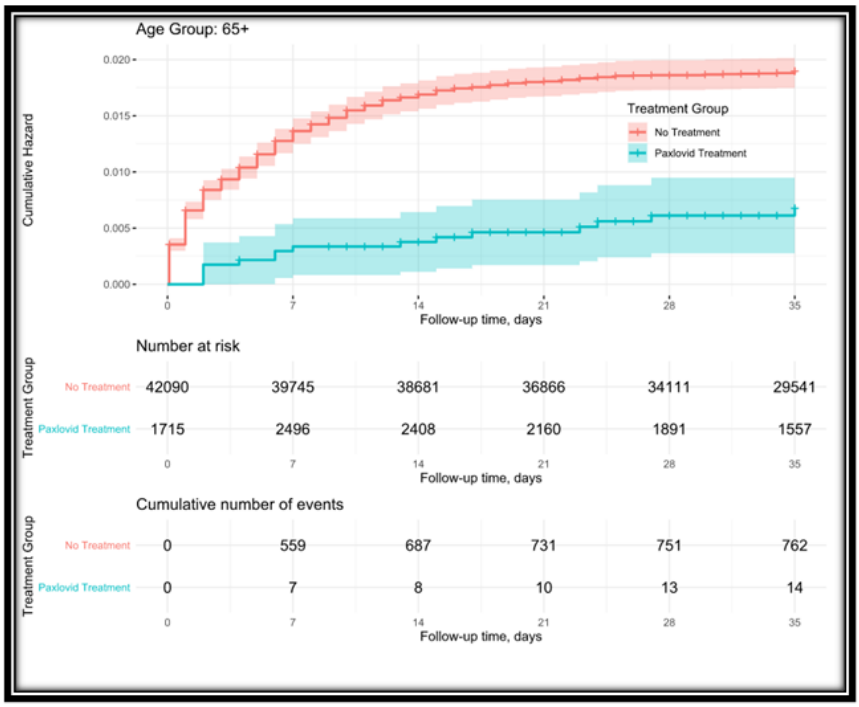


Figure 1

Assessment for Eligibility



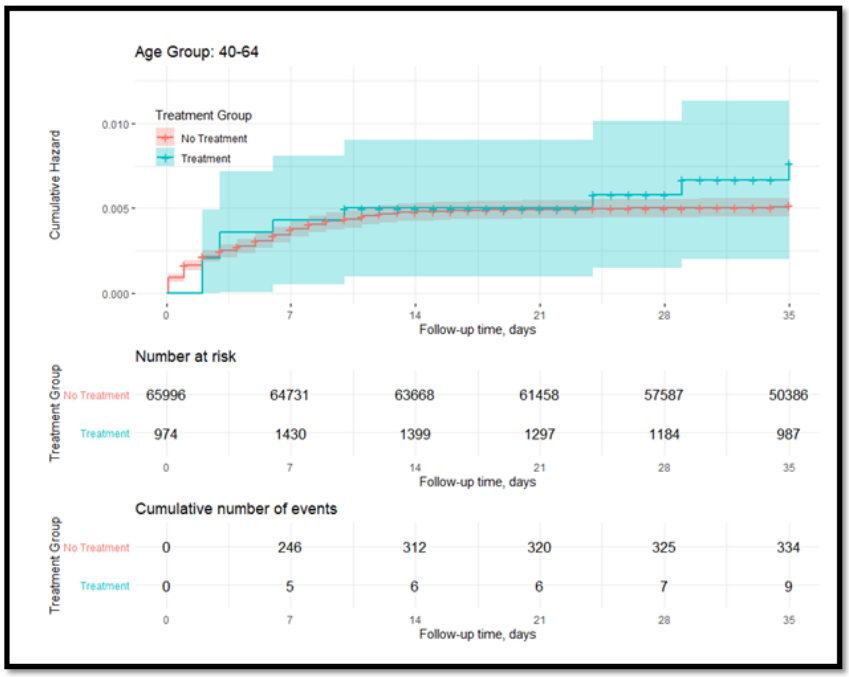


Figure 2

Cumulative Hazard Ratio for Hospitalizations Due to Covid-19

Supplementary Files

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- SupplementaryMaterialPaxlovidHosptanddeathV1.docx