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Original Article

Characteristics and outcomes of US Veterans at least 65 years of age at high risk of severe SARS-CoV-2 infection with or without receipt of oral antiviral agents☆

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SUMMARY

Objectives: Molnupiravir and nirmatrelvir/ritonavir each became available in the United States (US) through the Food and Drug Administration (FDA) emergency use authorization (EUA) in December 2021 after their respective initial prospective randomized controlled trials demonstrated efficacy for patients with mild-to-moderate SARS-CoV-2 active infection considered to be at high risk for progression of disease and hospitalization. Although sufficiently powered for this wide group, the mean age for patients in these studies was only 43 and 46 years of age, respectively. We sought to compare outcomes of US Veterans 65 years and older who received either of these oral antivirals to those who did not receive oral antivirals for mild-to-moderate SARS-CoV-2 active infection.

Methods: The current project was a retrospective, observational, nationwide propensity-matched analysis comparing outcomes of US Veterans 65 years and older who received either of these oral antivirals to US Veterans 65 years and older who did not receive oral antivirals for mild-to-moderate SARS-CoV-2 active infection.

Results: The composite primary outcome of admission or death within 30 days of diagnosis was reached less often in those receiving either molnupiravir or nirmatrelvir/ritonavir versus those that received no antiviral (65/1370 [4.75%] vs. 139/1370 [10.2%]; odds ratio 0.44, 95% confidence interval 0.32-0.60, $p<0.0001$). Baseline differences between Veterans selected for molnupiravir vs. nirmatrelvir/ritonavir therapy were noted, particularly in the number of concomitant medications with cautions or contraindications with nirmatrelvir/ritonavir.

Conclusions: Our findings support the use of molnupiravir or nirmatrelvir/ritonavir in patients 65 years of age and older. Patients with higher medication caution and contraindication burdens to nirmatrelvir/ritonavir are selected for molnupiravir therapy, which in the absence of a prospective head-to-head trial, may limit any efforts to compare the effectiveness of the two drugs.

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Introduction

Three years into the Covid-19 pandemic, as the end of 2022 approached, deaths attributed to the SARS-CoV-2 coronavirus stood at approximately 6.6 million people globally, including just over 1 million deaths in the United States (US).[1] In December of 2020, vaccines were developed that decreased chances of becoming infected and transmitting it to others, and decreased the severity of illness for those still becoming infected.[2]

For those patients presenting with mild-to-moderate active SARS-CoV-2 infection not requiring hospitalization, several sub-

☆ Summary: Patients 65 years of age and older had improved outcomes if given oral antiviral therapy for active SARS-CoV-2 infection. Molnupiravir is selected over nirmatrelvir/ritonavir in patients with multiple cautions or contraindications to nirmatrelvir/ritonavir, which may lead to baseline discrepancies when trying to compare groups receiving these therapies.

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groups have been identified as having a high risk for progression to serious disease and/or death.[3] By far, the most significant independent variable associated with progression to serious disease to date has been advancing age.[4,5] Through 2021, treatment options for these patients were limited to targeted monoclonal antibody infusions (e.g., casirivimab/imdevimab, bamlanivimab/etesevimab).[3] However, availability of these infusions, the staffing and resources necessary, and variant strains repeatedly becoming resistant to their effects, limited their usefulness.[3,6] Molnupiravir and nirmatrelvir/ritonavir were the first two oral antiviral agents to demonstrate reduced chances of hospitalization or death in this group of patients, and both of these drugs became available through US Food and Drug Administration (FDA) Emergency Use Authorization (EUA) process in early January 2022.[7,8] Although sufficient power was reached in these studies to demonstrate improvements in the intervention groups over the totality of conditions represented, arguably the most important predictor, advancing age past 65 years, was not well represented: the mean age for patients in these studies was only 43 and 46 years of age, respectively.[9,10]

The objective of this study was to characterize and compare clinical outcomes (risk of hospitalization and death within 30 days of Covid-19 diagnosis) of US Veterans 65 years of age prescribed molnupiravir or nirmatrelvir/ritonavir in the initial months of availability versus a propensity-matched set of Veterans that did not receive oral antivirals.

Methods

This study was conducted by collecting de-identified patient information from throughout the Veterans Health Administration (VHA). The VHA is the largest integrated healthcare system in the US, providing care in approximately 130 healthcare systems, serving approximately 9 million enrolled Veterans annually.[11] The VHA maintains the Corporate Data Warehouse (CDW), a central clinical and administrative database containing comprehensive electronic medical record system information. This data is available to VHA researchers, after obtaining authorization through a rigorous approval process, through a secure gateway in order to conduct research to optimize clinical practice and better serve our Veteran population.

Data collected through the VINCI database consisted of all veterans 65 years and older who developed documented SARS-CoV-2 infection between January 1, 2022 and February 6, 2022. This timeframe was chosen to coincide with the first month of availability of molnupiravir or nirmatrelvir/ritonavir after US FDA Emergency Use Authorization and the omicron variant Covid-19 surge that began in the US in December 2021 before declining throughout the month of February 2022. Additionally, after the first week of February, there was evidence of an increased utilization of non-VHA pharmacies to distribute these oral antiviral agents to veterans, which may or may not be accurately reflected in VHA electronic medical records. Approximately 145,000 Veterans (of any age) were documented to have Covid-19 infection throughout the VHA during this timeframe.[12] Of these, patients that were 65 years or older at the time of diagnosis were included in the study if they had mild-to-moderate infection, defined as not requiring hospitalization admission or not dying within 24 h of Covid-19 diagnosis. An active SARS-CoV-2 infection diagnosis was considered valid with a corresponding ICD-10 diagnostic code entry for Covid-19 disease (U07.1) placed from 1/1/2022 to 2/6/2022, a VHA Covid database case date entry dated 1/1/2022 to 2/6/2022, and/or the prescription written date by a VA or community care provider. Patients were excluded if they were admitted or died within 24 h of Covid-19 diagnosis, or received targeted Covid-19 monoclonal antibody therapy or remdesivir therapy. Time zero was considered as the date and time of the reported results of a positive SARS-CoV-2 test, or in its absence, the date and time that the prescription was signed by the prescriber.

Data collection for Veterans 65 years and older in the study database was conducted to determine the following: (1) evidence of receipt of an oral antiviral (molnupiravir or nirmatrelvir) from 1/1/2022 to 2/6/2022; (2) baseline demographic data from the time of active SARS-Cov-2 infection to determine age, race, gender, weight, smoking status; (3) presence of ICD-10 code U07.1 from 1/1/2022 to 2/6/2022 to determine diagnosis of SARS-Cov-2 infection; (4) laboratory data or variables to assess organ dysfunction and characterize infection severity as outlined in FDA guidance when available; (5) all inpatient and outpatient encounter ICD-10 codes from 1/1/2018 to 2/6/2022 to determine patient comorbidities. Chronic comorbidities were defined by organ system (Supplementary Table S1) to produce a comprehensive list of a patient's comorbidities utilizing methods the authors have used in previous studies.[13]

All variables collected were assessed for their association, as univariate variables, with the use of either oral antiviral agent. Those univariate variables with a p value <0.1 were entered into a nominal multivariate logistic regression model to determine independent variables associated with the use of either oral antiviral agent, and the resultant probability formula calculated a propensity score for each patient. Each patient who received an oral antiviral (case) was matched to a patient who did not receive an oral antiviral (control) in a 1:1 ratio with the closest propensity score, stratified by VAMC site.

The resultant propensity case/control population was assessed with the following data collection for data points between 1/1/2022 and 3/8/2022 (30 days after last possible case date): hospitalization admission dates and discharge dates, ward location upon admission, discharge diagnostic ICD-10 codes associated with each admission, and date of death, if applicable.

The primary endpoint for the study was to compare the composite rate of any hospitalizations or death within 30 days of diagnosis in patients 65 years of age or older with Covid-19 who received oral antivirals versus the propensity-matched patients 65 years of age or older with Covid-19 who did not receive oral antivirals. Secondary endpoints consisted of the following: (1) overall comparative rates of any hospitalization within 30 days of diagnosis for both propensity-matched groups, (2) overall comparative rates of mortality within 30 days of diagnosis for both propensity-matched groups, (3) comparative rate of intensive care requirement associated with SARS-Cov-2 infection for patients who received oral antivirals versus propensity-matched patients who did not receive oral antivirals, and (4) subset analyses of primary and secondary outcomes by drug utilized and vaccination status. In addition, univariate analysis was conducted determine univariate variables associated with hospitalization or mortality, including the receipt of oral antivirals. Those univariate variables with a p value $<$ 0.10 were entered into a multivariate logistic regression model to determine the independent variables associated with hospitalization and mortality.

Inpatient admission was defined as related to SARS-CoV-2 infection if the primary admitting diagnosis or primary discharge diagnosis was specific for SARS-CoV-2 infection (ie, ICD10 code of U07.1) or related to SARS-CoV-2 infection (ie, non-specific respiratory disorder such as acute respiratory failure).

For all tests and analyses except where specified, the *a priori* level of significance was set at $p \leq 0.05$. Categorical variables were assessed using Chi-square test and Fisher's exact test when appropriate. Continuous variables were assessed using the Mann-Whitney U test. Univariate and multivariate analyses were performed as described above. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. All statistical analyses were con-

Table 1
Baseline univariate variables associated with the receipt of an oral antiviral (molnupiravir or nirmatrelvir/ritonavir) from the propensity-matched cohort of patients 65 years of age or older.

Baseline variable*	Patients who received an oral antiviral (n=1370)	Patients who did not receive an oral antiviral (n=1370)	p-value
Age, mean years (SD)	74.4 (6.85)	74.4 (6.56)	0.55
Age ≥ 75 years	547 (39.9)	564 (41.2)	0.51
Gender (male)	1308 (95.5)	1324 (96.6)	0.12
Weight >100 kg	434 (33.8)	385 (30.1)	0.041
Race			0.57
White	1013 (74.0)	1042 (76.1)	
Black/African American	166 (12.1)	145 (10.6)	
Hispanic/Latino	52 (3.80)	49 (3.58)	
Other	139 (10.2)	134 (9.78)	
Vital sign abnormalities			
Any vitals obtained at time of prescription	725 (52.9)	709 (51.8)	0.54
Diastolic blood pressure <60 mmHg	40 (2.92)	38 (2.77)	0.82
Systolic blood pressure <90 mmHg	6 (0.44)	2 (0.15)	0.15
Respiratory rate >24 bpm	13 (0.95)	12 (0.88)	0.84
Temperature >100.4°F	25 (1.82)	30 (2.19)	0.50
Pulse >100 bpm	104 (7.59)	96 (7.01)	0.56
Laboratory abnormalities			
Leukocytosis (WBC >11,000)	28 (2.04)	29 (2.12)	0.89
Leukopenia (WBC <3,000)	11 (0.80)	13 (0.95)	0.68
Elevated serum creatinine >1.4 mg/dL	65 (4.74)	85 (6.20)	0.093
Precautions to receiving nirmatrelvir/ritonavir			
Single caution or contraindication	367 (26.8)	346 (25.3)	0.36
Single contraindication	127 (9.27)	117 (8.54)	0.50
Single caution	240 (17.5)	229 (16.7)	0.58
Multiple cautions or contraindications	753 (55.0)	780 (56.9)	0.30
Any caution or contraindication	1120 (81.8)	1126 (82.2)	0.77
Vaccination Status			
Received ≥ 1 vaccine dose	1097 (80.1)	1108 (80.9)	0.60
Received only 1 vaccine dose	31 (2.26)	30 (2.19)	0.86
Completed 1st vaccine series	1050 (76.6)	1064 (77.7)	0.52
Completed 1st vaccine booster	581 (42.4)	584 (42.6)	0.91
Comorbidities			
Respiratory	288 (21.0)	326 (23.8)	0.082
Renal/Urinary	463 (33.8)	453 (33.1)	0.69
Cardiovascular	663 (48.4)	694 (50.7)	0.24
Gastrointestinal	316 (23.1)	314 (22.9)	0.93
Hepatobiliary	54 (3.94)	51 (3.72)	0.77
Musculoskeletal	546 (39.8)	565 (41.2)	0.46
Neurological	390 (28.5)	407 (29.7)	0.47
Dermatological	174 (12.7)	186 (13.6)	0.50
Metabolic/Endocrine	681 (49.7)	682 (49.8)	0.97
Hematological	176 (12.8)	165 (12.0)	0.52
Immunologic/Rheumatic	112 (8.18)	124 (9.05)	0.41
Psychiatric	390 (28.5)	376 (27.4)	0.55
Neoplastic	268 (19.6)	248 (18.1)	0.33
Concomitant immunocompromising medication	175 (12.8)	180 (13.1)	0.78
Any tobacco use	59 (4.31)	55 (4.01)	0.70

* Data are presented number (percent) unless otherwise stated.

ducted using JMP Pro, version 12.0.1, SAS Institute, Cary, North Carolina.

Results

Within the study period, 135,287 patients within the VHA were diagnosed with active SARS-CoV-2 infection, and 49,017 patients were 65 years or older at the time of diagnosis. Inpatient admissions within 24 h excluded 5165 patients. Outpatient monoclonal antibody or remdesivir therapy excluded 436 patients. There were no exclusions due to death within 24 h. After all exclusions were applied, 43,416 patients were included in the study; 42,046 Veterans who did not receive oral antiviral prescriptions and 1370 Veterans that received oral antiviral prescriptions. Differences between the two groups were statistically significant for several baseline parameters (Supplementary Table S2), and these as well as other parameters with $p<0.10$ were included as univariate variables in the nominal multivariate logistic regression model that calculated the propensity scores (probability) of having an oral antiviral prescription dispensed. After propensity matching was conducted, 1370 patients not receiving oral antivirals were successfully matched to the 1370 patients who received either molnupiravir or nirmatrelvir/ritonavir. Supplementary Fig. 1 displays a propensity score histogram comparing groups pre- and post-matching. There were no statistically-significant differences in the baseline parameters between the two post-matched groups (Table 1), except for the proportion of patients with weight over 100 kg. Approximately ¾ in each group had completed the first SARS-CoV-2 vaccination series, and 42.5% had received the initial SARS-CoV-2 vaccination booster dose.

Eighty-two percent of the patients in the study had at least one drug interaction contraindication or caution to nirmatrelvir/ritonavir, and over half had multiple contraindications or cautions. Patients receiving molnupiravir had a higher prevalence of multiple contraindications or cautions to nirmatrelvir/ritonavir as well as any caution or contraindication than patients receiving nirmatrelvir/ritonavir (Table 2). In addition, more patients receiving molnupiravir were receiving immunocompromising medications. In

Table 2
Baseline univariate variables associated with the receipt of either molnupiravir or nirmatrelvir/ritonavir from the propensity-matched cohort of patients 65 years of age or older.

Baseline variable*	Patients who received molnupiravir (n=557)	Patients who received nirmatrelvir/ritonavir (n=813)	p-value
Age, mean years (SD)	74.6 (6.89)	74.2 (6.82)	0.38
Age ≥ 75 years	228 (40.9)	319 (39.2)	0.53
Gender (male)	536 (96.2)	772 (95.0)	0.26
Weight >100 kg	194 (37.0)	240 (31.7)	0.047
Race			0.67
White	402 (72.2)	611 (75.2)	
Black/African American	72 (12.9)	94 (11.6)	
Hispanic/Latino	23 (4.13)	29 (3.57)	
Other	60 (10.8)	79 (9.72)	
Vital sign abnormalities			
Any vitals obtained at time of prescription	298 (53.5)	427 (52.5)	0.72
Diastolic blood pressure <60 mmHg	17 (3.05)	23 (2.83)	0.81
Systolic blood pressure <90 mmHg	3 (0.54)	3 (0.37)	0.64
Respiratory rate >24 bpm	6 (1.08)	7 (0.86)	0.69
Temperature >100.4°F	10 (1.80)	15 (1.85)	0.95
Pulse >100 bpm	37 (6.64)	67 (8.24)	0.27
Laboratory abnormalities			
Leukocytosis (WBC >11,000)	12 (2.15)	16 (1.97)	0.81
Leukopenia (WBC <3,000)	3 (0.54)	8 (0.98)	0.35
Elevated serum creatinine >1.4 mg/dL	0.27 (4.85)	38 (4.67)	0.88
Precautions to receiving nirmatrelvir/ritonavir			
Single caution or contraindication	122 (21.9)	245 (30.1)	0.0007
Single contraindication	44 (7.90)	83 (10.2)	0.14
Single caution	78 (14.0)	162 (19.9)	0.004
Multiple cautions or contraindications	362 (65.0)	391 (48.1)	<0.0001
Any caution or contraindication	484 (86.9)	636 (78.2)	<0.0001
Vaccination Status			
Received ≥ 1 vaccine dose	462 (82.9)	635 (78.1)	0.027
Received only 1 vaccine dose	9 (1.62)	22 (2.71)	0.027
Completed 1st vaccine series	449 (80.6)	601 (73.9)	0.0038
Completed 1st vaccine booster	255 (45.8)	326 (40.1)	0.037
Comorbidities			
Respiratory	113 (20.3)	175 (21.5)	0.58
Renal/Urinary	173 (31.1)	290 (35.7)	0.076
Cardiovascular	270 (48.5)	393 (48.3)	0.96
Gastrointestinal	115 (20.6)	201 (24.7)	0.078
Hepatobiliary	22 (3.95)	32 (3.94)	0.99
Musculoskeletal	222 (39.9)	324 (39.8)	0.99
Neurological	147 (26.4)	243 (29.9)	0.16
Dermatological	72 (12.9)	102 (12.6)	0.84
Metabolic/Endocrine	271 (48.6)	410 (50.4)	0.52
Hematological	74 (13.3)	102 (12.6)	0.69
Immunologic/Rheumatic	48 (8.62)	64 (7.87)	0.62
Psychiatric	156 (28.0)	234 (28.8)	0.75
Neoplastic	97 (17.4)	171 (21.0)	0.096
Concomitant immunocompromising medication	84 (15.1)	91 (11.2)	0.035
Any tobacco use	29 (5.21)	30 (3.69)	0.18

* Data are presented number (percent) unless otherwise stated.

Table 3
Primary and secondary outcomes between patients receiving an oral antiviral drug (molnupiravir or nirmatrelvir/ritonavir) versus patients not receiving an oral antiviral drug from the propensity-matched cohort of patients 65 years of age or older.

Outcomes	Patients who received an oral antiviral (n=1370)	Patients who did not receive an oral antiviral (n=1370)	Odds ratio (95% Confidence Interval)	p-value
Primary Outcome				
Admission or Death within 30 days	65 (4.75%)	139 (10.2%)	0.44 (0.32 to 0.60)	<0.0001
Secondary Outcome				
Admission within 30 days	61 (4.46%)	106 (7.74%)	0.56 (0.40-0.77)	0.0003
Death within 30 days	8 (0.58%)	43 (3.14%)	0.18 (0.08-0.39)	<0.0001

contrast, nirmatrelvir patients had lower vaccination rates and a higher incidence of a renal/urinary chronic comorbidity.

Table 3 summarizes the primary outcome and secondary outcomes between the two propensity-matched groups. The composite event of inpatient admission or death within 30 days was reached less often in patients receiving oral antiviral therapy versus those not receiving oral antiviral therapy (65/1370 [4.75%] vs 139/1370 [10.2%]; OR 0.44, 95% CI 0.32-0.60). Similarly, each event of inpatient admission and death within 30 days was reached less often in the oral antiviral group. There was no statistically-significant difference in the overall rate of intensive care unit admission in patients receiving oral antiviral therapy versus those not receiving oral antiviral therapy (6/1370 [0.44%] vs 14/1370 [1.02%]; p=0.07). Fig. 1 demonstrates the Kaplan–Meier time-to-event curves for each group for the composite primary outcome.

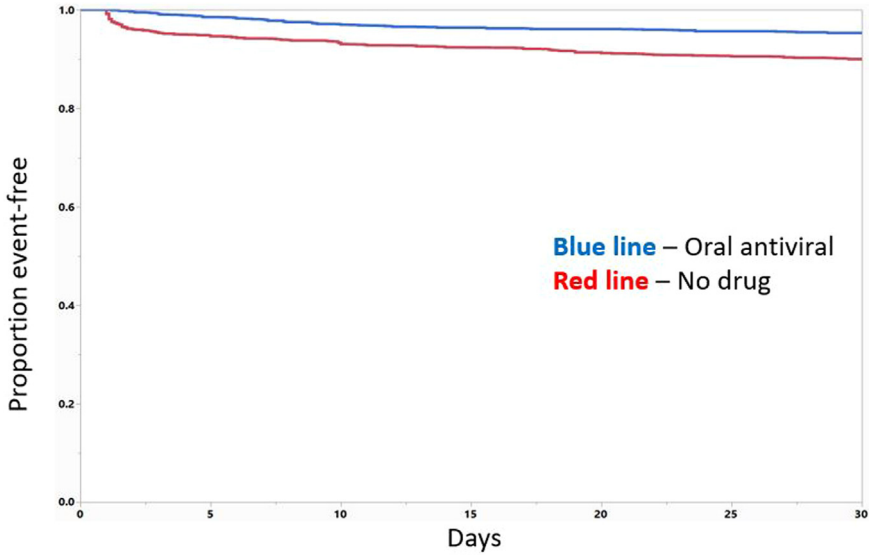

Fig. 1. Kaplan–Meier time-to-event curves between patients receiving an oral antiviral drug (molnupiravir or nirmatrelvir/ritonavir) versus patients not receiving an oral antiviral drug from the propensity-matched cohort of patients 65 years of age or older.

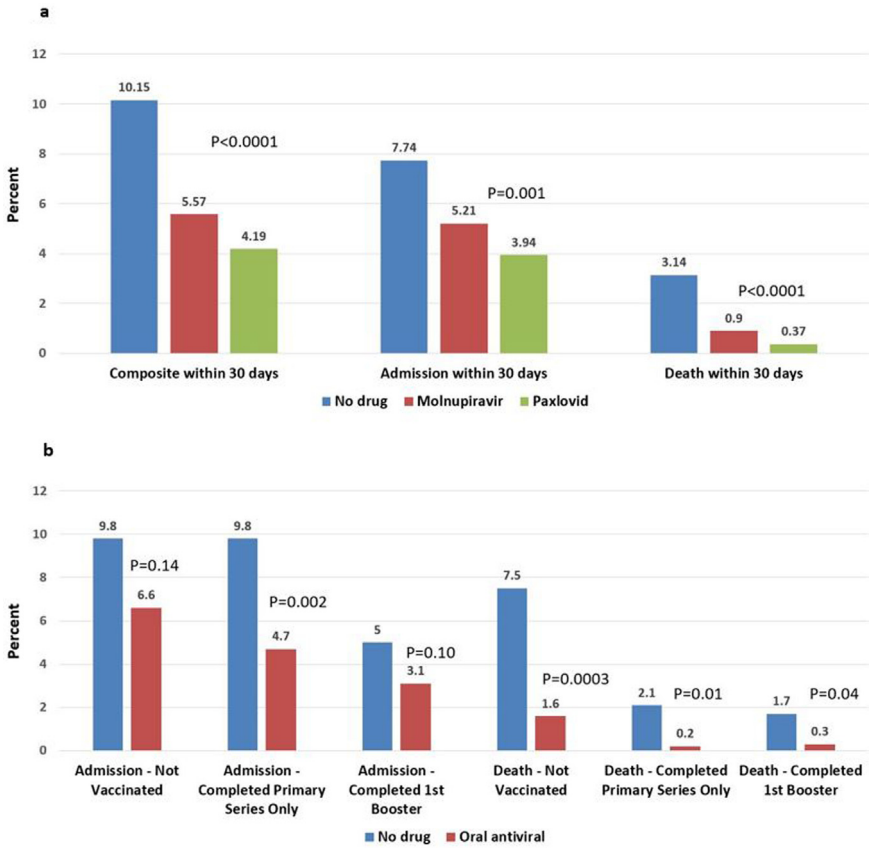

Fig. 2. Outcomes by drug (2a) and by vaccination status (2b) for patients 65 years of age or older.

For patients that required inpatient hospitalization within 30 days of SARS-CoV-2 infection diagnosis, admissions were related to SARS-CoV-2 infection in 85.8% (91/106) of hospitalizations in the group without oral antiviral therapy and 82.0% (50/61) in the group receiving oral antiviral therapy (p=0.51); the percentage in patients receiving molnupiravir was 79.3% (23/29) and in patients receiving nirmatrelvir/ritonavir was 84.4% (27/32). Ten of the 91 patients not receiving oral antivirals that had a SARS-CoV-2 infection-related hospitalization died within 30 days, versus 0 of 15 hospitalized unrelated to SARS-CoV-2 infection (p=0.35). Similarly, all 4 deaths in the hospitalized patients who received oral antiviral therapy were in patients whose hospitalization was related to SARS-CoV-2 infection (4/50 versus 0/11; p=0.99).

Fig. 2 demonstrates outcomes by drug (2a) and by vaccine status (2b). Patients who had completed their primary vaccination series had a statistically-significant improvement in inpatient admission rate if they received oral antivirals compared to those who had received oral antivirals. Receipt of oral antiviral agents was as-

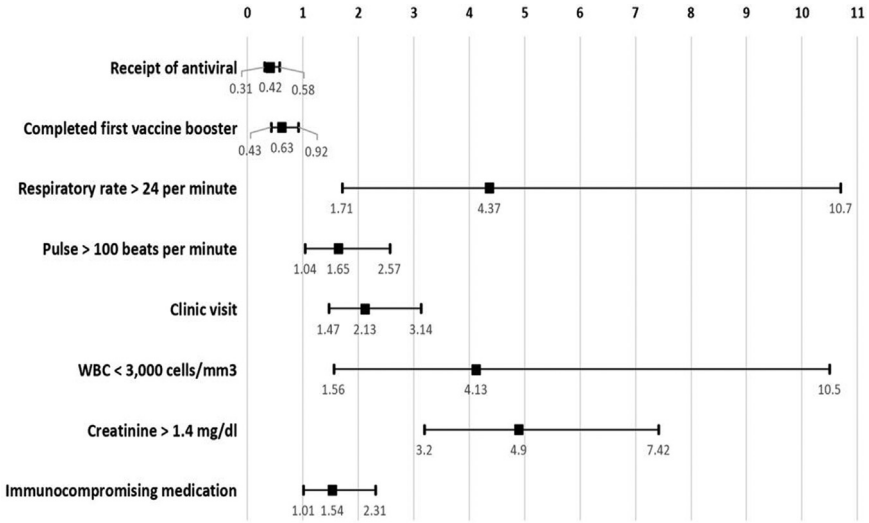

Fig. 3. Independent variables associated with the composite outcome of 30-day hospitalization or death. Data presented are odds ratio (middle value of each row) and 95% confidence intervals (first and last value of each row).

sociated with significantly lower death rates regardless of vaccination status.

Eighteen univariate variables met criteria to be included in the multivariate nominal logistic regression analysis to determine independent variables associated with the composite outcome of inpatient admission or death within 30 days; only one of these variables was a chronic comorbidity (cardiovascular). Fig. 3 demonstrates the baseline variables found to be independently associated with the composite outcome, which included the protective parameters of receiving an antiviral (OR 0.42, 95% CI 0.31-0.58) and receiving the initial vaccine booster (OR 0.63, 95% CI 0.43-0.92).

Discussion

In late December 2021, the US FDA issued emergency use authorizations for nirmatrelvir/ritonavir and molnupiravir after review of the two respective industry-sponsored Phase 2/3 randomized controlled trials that initially established adequate safety and efficacy in non-vaccinated patients with mild to moderate SARS-CoV-2 infection at high risk for progression to severe disease.[7,8] In the nirmatrelvir/ritonavir trial, fewer patients receiving the nirmatrelvir/ritonavir up to 5 days after symptom onset reached the composite outcome of either requiring hospitalization or death within 30 days versus patients receiving placebo (0.77% {8/1039} vs. 6.31% {66/1046}; RRR=87.8%, $p<0.001$).[10] There were no deaths in the nirmatrelvir/ritonavir arm and 12 overall deaths in the placebo arm. Interim results halfway through the similar Phase 3 trial for molnupiravir demonstrated patients receiving molnupiravir either required hospitalization or died compared to patients receiving placebo (7.3% {28/385} vs. 14.1% {53/377}; RRR=48.2%, $p=0.001$). However, the benefit favoring molnupiravir appeared to close in the second half of the trial: the total combined effect for patients receiving molnupiravir with either hospitalization or death compared to patients receiving placebo declined to a relative risk reduction of 29.9% (6.8% {48 of 709} vs. 9.7% {68 of 699}; $p<0.05$).[9] Deaths occurred for one patient in the molnupiravir group compared to 9 patients in the placebo group. Both molnupiravir and nirmatrelvir/ritonavir were generally well-tolerated in the trials, but safety concerns remain; molnupiravir is not recommended for use in women of child-bearing potential and nirmatrelvir/ritonavir has a multitude of clinically-significant drug interactions.[14,15]

Several questions were left unanswered by the two trials. Given the exclusion of vaccinated individuals, no data were available to determine if these drugs would provide benefit in this population. Throughout 2021, patients of advanced age were prioritized to receive covid vaccination; indeed, individuals 65 and over who completed the initial covid vaccination series achieved rates of over 90% in the US by the end of December 2021.[16] Perhaps as a result, the two oral antiviral trials did not include large numbers of patients 65 and older. Only 158 (11.1%) of the 1433 patients enrolled in the molnupiravir trial were 65 years or older, and only 268 (12.8%) of the 2085 patients in the nirmatrelvir/ritonavir trial were 65 years or older. Disparate results were seen for this population; while little to no benefit was seen in older individuals receiving molnupiravir, a larger benefit was suggested in the nirmatrelvir/ritonavir trial.[9,10]

To date, there has been only one subsequent large randomized controlled trial preprint reported.[17] This study was an open-label trial involving around 25,000 vaccinated patients with a mean age of 57 years who received either molnupiravir or usual care. Baseline analysis showed very low incidences of chronic comorbidities in both groups. The primary outcome was composite hospitalization or death at 28 days, which was reached in a very small proportion of patients in each group: 0.8% versus 0.8%. There are a few observational studies available evaluating either nirmatrelvir/ritonavir or molnupiravir compared to usual care, but these studies are also challenged by varying primary outcomes, low incidences of primary outcome events, or low numbers of individuals included at least 65 years or older.[18–24] The largest of these projects was from Shah and colleagues at the US Centers for Disease Control and Prevention.[24] Administrative database review limited to nirmatrelvir/ritonavir patients examining effect of treatment on subsequent need of hospitalization demonstrated a a 51% lower hospitalization rate within 30 days after diagnosis than those who were not prescribed nirmatrelvir/ritonavir. The extent of benefit appeared to be similar for patients 65 years of age and older. Benefit was also demonstrated regardless of vaccination status. Mortality data were not presented. The authors note several limitations, some of which are similar to those of the current study. Two studies from China combined patients receiving either nirmatrelvir/ritonavir or molnupiravir and compared outcomes to those receiving usual care (similar to our current study). While each drug appeared to provide benefit to either hospitalization or death, no data was available specific to advanced age.

Molnupiravir patients tended to have a higher incidence of renal disease in one study, and in the other study these patients were older and less likely to be vaccinated.[25,26] Similarly, a small observational study attempted to directly compare outcomes of patients treated with molnupiravir versus those treated with nirmatrelvir/ritonavir.[27] There were only a handful of primary outcome events such that no difference could be determined, however molnupiravir patients were older, had more chronic heart disease, and had a greater proportion with at least 2 comorbidities compared to nirmatrelvir/ritonavir patients at baseline.

Our study directly examines the effectiveness of receiving one of these two antiviral drugs in patients 65 years and older with mild-to-moderate SARS-CoV-2 infection versus usual care. Benefit of oral antiviral therapy was clearly evident in the primary and secondary outcomes, regardless of vaccination status. This study is the first to demonstrate the substantial proportion of individuals 65 years of age and older with mild-to-moderate SARS-CoV-2 infection receiving one (~80%) or more (>50%) drugs with serious drug interaction precautions or contraindications to nirmatrelvir/ritonavir. While the study achieved a robust propensity match between two large sample sizes and demonstrated clear benefit in preventing hospitalization or death, limitations exist that deserve comment. Among these are the standard limitations of a non-randomized, observational retrospective study using a clinical administrative database. One possible limitation was that some control group patients may have been included despite having symptoms longer than the 5 days allowed to receive either drug. However, in our study timeframe where for every eligible person with mild-to-moderate infection receiving drug around 40 did not, lack of availability was the overwhelming driver to not receive drug. If patients with long durations of mild-to-moderate symptoms were included in the control group, outcomes would tend to favor the control group. Another potential bias could have been introduced where providers chose not to prescribe an oral antiviral drug to some patients when their symptoms were very mild (favoring the control group). However, despite these possibilities, a rigorous multivariate nominal logistic regression-derived, propensity-matching methodology seemed to successfully produce two very comparable groups. This assumes that all variables potentially influencing outcomes were appropriately taken into account in our analysis; certain variables may have been overlooked. We used statistical inference rather than standardized mean difference to determine which univariate variables should be included into multivariate analysis to produce the propensity score calculation primarily due to the *a priori* effect size expectation of the patient group receiving oral antivirals and the sole use of dichotomous univariate variables. Some may prefer that SMD be used to determine univariate variables to undergo propensity score calculations, however in examining SMD of all univariate variables, only 3 were included within the 17 univariate variables included in multivariate analysis, and these 3 variables did not affect the final model. As with most of the other observational data available, tolerability and safety of molnupiravir or nirmatrelvir/ritonavir was not assessed adequately in our study. Similarly, adherence to the 5- day courses given was not evaluated. These observational studies can suffer from immortal time bias, particularly if the “clock” starts at different times between groups. However, the current study used date and time of diagnosis for both groups as the starting point, and any patient with hospitalization or death occurring within 24 h of the starting point was excluded from the study. It is important in these observational studies to assess the possibility that some individuals in the “usual care” control group did not actually receive one of these two antivirals (or any other pharmaceutical interventions such as monoclonal antibody therapy or outpatient remdesivir therapy) outside of the sources within study database. In our study, to minimize this possibility we limited our analysis to the very first few weeks that these agents were available; in general, during this time the VHA system was likely the only avenue US Veterans had to obtain one of these two agents. As these drugs became more available in the community after the first week of February 2022, it was no longer feasible to assume that a Veteran might not have been able to receive one of the drugs from non-VHA community pharmacies. In addition, Veterans receiving monoclonal antibody therapy or outpatient remdesivir therapy were excluded. The outcomes of the study favoring Veterans receiving drug from VA facilities suggests that these methods worked well in minimizing control group errors. As with many studies conducted within the US VHA system, the study comprised of a small female population. Bajema and colleagues recently reported their VHA study investigating potential disparities in access to antiviral therapy during the first two months of 2022 found rates of oral antiviral treatment consistent with our results in the similar timeframe.[28] Our pre-matched analysis found similar disparities of receipt of oral antiviral therapy among black/African American and Hispanic/Latino populations compared to the White population (Supplementary Table S2), however these disparities were no longer present in our post-matched groups. Finally, the study period took place within the time that SARS-CoV-2 BA.1 omicron variant became predominant within the US population; extrapolation of the study results could be limited with different variants.

Conclusion

This observational study directly evaluated the use of molnupiravir or nirmatrelvir/ritonavir in patients 65 years of age and older with mild-to-moderate SARS-CoV-2 infection and found that the use of either of these two antiviral drugs was associated with lower hospitalization or death through 30 days, regardless of vaccination status. Patients with medication cautions and contraindications to nirmatrelvir/ritonavir were more often given molnupiravir therapy. In the absence of a prospective head-to-head trial, any efforts to directly compare the effectiveness of the two drugs may be limited.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2023.01.018.

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