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Clinical outcomes among COVID-19 patients initiated on molnupiravir in Denmark – A national registry study

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Abstract

Background: Molnupiravir (MOV) is an orally bioavailable ribonucleoside with antiviral activity against all tested SARS-CoV-2 variants. We describe the demographic, clinical, and treatment characteristics of non-hospitalized Danish patients treated with MOV and their clinical outcomes following MOV initiation.
Method: Among all adults (>18 years) who received MOV between 16 December 2021 and 30 April 2022 in an outpatient setting in Denmark, we summarized their demographic and clinical characteristics at baseline and post-MOV outcomes using descriptive statistics. Outcomes were emergent hospitalization and all-cause mortality during the 28 days after MOV initiation. We estimated the odds ratios (OR) of outcomes by time from positive test to treatment using logistic regression.
Results: We identified 3691 MOV-treated patients, of whom 45.8% were male and mean age was 70.1 years. Most patients (76.2%) initiated MOV within 0–2 days after a positive SARS-CoV-2 test and 16.8% within 3–5 days. Over a 28-day period, rates for all-cause, respiratory- or COVID-19-related, and COVID-19-related hospitalization were 4.8%, 2.6% and 1.5%, respectively. All-cause mortality was 1.6%. Initiation of MOV 3–5 days after a positive SARS-CoV-2 test compared to 1–2 days was associated with an increased risk of all-cause (OR 1.85, 95% CI 1.29–2.67) and respiratory or COVID-19-related (OR 1.78, 95% CI 1.07–2.94) hospitalization, and all-cause mortality (OR 2.90, 95% CI 1.64–5.15).
Conclusion: MOV was primarily prescribed to vaccinated elderly persons with multiple comorbidities. The all-cause hospitalization and mortality rates in this population were low. Early initiation of MOV reduced the risk of hospitalization and death compared with late initiation.

Keywords

COVID-19, SARS-CoV-2, molnupiravir, mortality, hospitalization

Introduction

With more than 750 million confirmed cases and nearly seven million deaths globally, including 3.4 million confirmed cases and 8700 deaths in Denmark, the COVID-19 pandemic had overwhelmed healthcare systems around the world, and the admission of large numbers of patients to

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general wards and intensive care units (ICU) caused a significant drain on healthcare resources.[1] In most cases, infection with SARS- CoV-2 causes a mild respiratory disease that resolves without the need for intervention, but the elderly and those with underlying chronic medical conditions are at high risk of progression to severe disease that can result in hospitalization and/or death.[2] Vaccines have, to an extent, helped to curtail the spread of COVID-19, and reduced its associated morbidity and mortality.[3] However, possibly due to a waning efficacy of vaccines as well as emerging virus strains such as Omicron, the numbers of break-through infections in fully vaccinated individuals are high.[4] Therefore, there is still a need for effective oral antiviral drugs for treatment of early-stage COVID-19 in the outpatient setting to prevent progression to severe disease, hospitalization and/or death in high-risk patients.

Molnupiravir (MOV) is an orally bioavailable ribonucleoside with antiviral activity against all tested SARS-CoV-2 variants.[5] In the MOVe-OUT trial, early treatment of unvaccinated adults at high risk of progression to severe COVID-19 with MOV reduced the relative risk of hospitalization or death by 30%.[6] MOV is safe and the most common side effects are diarrhoea, nausea, and dizziness and no drug-drug-interaction has been identified.[7,8] In November 2021, the European Medicines Agency (EMA) issued advice on the use of MOV to support national authorities who may decide on possible early use of the medicine, which is currently not authorized in the EU. The Danish Medicine Agency approved MOV for pre-license use and on December 16th 2021 the Danish Health Authority recommended MOV to patients with a positive SARS-CoV-2 test, mild-to- moderate COVID-19, and a high risk of progression to severe COVID-19 (Table 1). Risk factors include (but are not limited to) severe lung disease, severe heart disease, chronic kidney failure and poorly regulated diabetes. The treatment must be started within 5 days of symptom onset.[9] At this time, MOV was the only available oral antiviral treatment for COVID-19, and the only available treatment for non-severe COVID-19 in patients without high-risk features such as haematological malignancies or other severe immunodepression.

With the increasing uptake of vaccines, antiviral treatment, and emergence of new variants, COVID-19 epidemiology continues to evolve quickly.[10] In addition, due to decisions of the healthcare authorities and practitioners, patient characteristics in real-world healthcare settings may not always reflect the specific inclusion/exclusion criteria of randomized controlled trials. Thus, it is important to understand the real-world use and clinical and societal benefits of MOV in preventing COVID-19 disease progression resulting in additional healthcare resources utilization, hospitalization, and death.

The aims of this nationwide real-world study are to describe the baseline demographic, clinical, and treatment characteristics of non-hospitalized Danish patients treated with MOV, and the clinical outcomes over a 28-day period following MOV initiation.

Table 1. The Danish Health Authorities recommendations for treatment with molnupiravir December 2021.

Criteria for prescribing molnupiravir
1. Positive SARS-CoV-2 test (PCR or antigen)
2. Symptoms of COVID-19 with onset within 5 days
3. Belonging to one of the following groups
• 80 years or older who have received <3 vaccine doses
• 80 years or older with at least one risk factor regardless of vaccination status
• 65-75 years with at least one risk factor who have received <3 vaccine doses
• Non-vaccinated between 65 and 75 years
• Non-vaccinated between 50 and 64 years with at least one risk factor

Methods

Study design and population

The study is designed as a retrospective observational cohort study using de-identified patient level data from national public health registries in Denmark. The study population includes all individuals ≥18 years of age who received MOV in Denmark in the period 16 December 2021 to 30 April 2022 and who were not hospitalized at the time of MOV initiation. One of the criteria for prescription of MOV in Denmark was a current positive SARS-CoV-2 test. The date of MOV prescription redemption serves as the index event. Guidelines for when to initiate treatment is based on onset of symptoms. We do not have information on onset of symptoms and therefore use date of prescription redemptions as proxy for date of symptom onset. Because the registries do not capture whether or when a patient took their MOV medication, we assume that patients initiated MOV treatment the same day the MOV prescription was redeemed. The baseline period is the span 1-day to 24 months before the index event. Participants were retrospectively followed-up for 28 days after the index event. The study population consists of unique individuals. If a patient had more than one redemption, only the first redemption was included. Patients who were younger than 18 years old, died on the index date, had evidence of pregnancy in the 3 months prior to the index event (7 patients), or were treated with any antiviral medication for COVID-19 other than MOV in the 30 days before MOV initiation (27 patients) were excluded. To ensure that the population only consisted of non-hospitalized patients, patients who had a hospital contact (of any cause) on the day of the index event (245 patients) were also excluded.

Study data sources

The data for this study were extracted from multiple national registries, which contain individual-level health data linked to the unique identification numbers for all individuals living in Denmark. All inhabitants in Denmark are assigned a unique social security number (Central Person Register [CPR] number) at birth or immigration. All contacts with the health system, including drug prescription, are linked with the unique CPR number, and are captured in national public health registries. Patients' medication history was extracted from the Danish National Prescription Registry (DNPR), which records the Anatomical Therapeutic Chemical (ATC) codes and dates for all prescriptions redeemed from Danish pharmacies. Patients' medical, clinical, and hospital data were extracted from the Danish National Patient Registry (NPR), which records data using ICD-10 codes. COVID-19 vaccination history was extracted from the Danish Vaccination Registry (DVR). Data on a positive a SARS-CoV-2 tests were extracted from the COVID-19 surveillance registry. Any occurrence of death among the study population was identified from the Danish Civil Registration System (CRS). Demographic data, such as age, sex, civil status, and address, are also linked to CRS. Crosslinking the registries provided demographic characteristics, vaccination status, comorbidities, and concomitant medications, as well as hospitalization and mortality data.

Exposure

Adult patients (aged ≥18 years) treated with MOV in an outpatient setting. MOV treatment was defined by the first redeemed prescription for MOV identified through the Danish National Prescription Registry.

Outcomes

Primary outcomes were all-cause hospitalization, respiratory illness- or COVID-19-related hospitalization, COVID-19-related hospitalization, and all-cause mortality over a 28-day follow-up period after MOV initiation. Hospitalization was defined as inpatient admission that was emergent and lasting more than 24 hours to exclude planned contacts such as previously scheduled check-up visits. To control for potential misclassification of diagnosis, we specified two different COVID-19-related outcomes – one that includes hospitalizations due to COVID-19 and another that includes hospitalization due to COVID or other respiratory illnesses.

Covariates

Demographic covariates included age (continuous years, categorical age groups: 18–49, 50–59, 60–69, 70–79 and ≥80 years of age), sex (male, female, or unknown), and region of residence at index date. Clinical covariates included vaccination status at the index event and previous COVID-19 in the 180 days prior to the index event. Prevalence of comorbidities was based on diagnosis codes recorded during the baseline period, and comedications were based on redeemed prescription for ≥1 of the medications within 90 days prior to index event (see Table 2 for list of comorbidities and comedications).

Statistical analysis

Patients' demographic and clinical characteristics at baseline and post-MOV initiation were summarized using descriptive statistics of means and distribution across characteristics. We estimated the odds ratio and 95% confidence intervals (CI) of outcomes by time from positive test to treatment and vaccination status using logistic regression, controlling for age, gender, region of residence, comorbidities, and comedication. We did not control for previous infection due to too few cases. A p-value of <0.05 is considered statistically significant. Analyses were carried out in STATA 17.

Results

Baseline characteristics

After inclusion/exclusion criteria were applied, the study population consisted of 3691 MOV-treated patients. Table 3 show the characteristics for the full population and by time between positive SARS-CoV-2 test and initiation of treatment. In the full population 45.8% were male. Mean age was 70.1 years and 74.4% were 60 years of age or older. The majority (74.8%) had ≥2 comorbidities and 88.2% received comedication for concomitant conditions (Table 3). Only 5.5% were unvaccinated or partially vaccinated (0–1 vaccine dose) and 89.2% have received ≥3 vaccine doses (Table 3). Very few (1.4%) had SARS-CoV-2 infection within the last 180 days. The distributions between groups are similar for most characteristics. There is, however, indications that being fully vaccinated correlates with having treatment initiated quicker. These results are also significant when performing a logistic regression (Table 4).

Most patients (93%) initiated MOV within 5 days after a positive SARS-CoV-2 test: 76.2% within 2 days and 16.8% within 3–5 days (Table 3). Time from a positive SARS-CoV-2 test to MOV initiation was not different by age, sex, or burden of comorbidity (Table 4). Fully vaccinated patients were more likely to start treatment within both 2 (OR 1.41, 95% CI 1.109–1.802, $p = 0.005$) and 5 days (OR 1.61, 95% CI 1.103–2.357, $p = 0.014$) (Table 4).

Table 2. List of ICD-10 and ATC codes.

Comorbidities		
Diagnosis	ICD-10	ATC
Cancer	C00-D48	
Chronic kidney disease	N00-N19	
Chronic lung disease	DJ40, DJ41, DJ42, DJ43, DJ44, DJ47, DJ60, DJ61, DJ62, DJ63, DJ64, DJ65, DJ66, DJ67, DJ684, DJ701, DJ703, DJ841, DJ920, DJ961, DJ982, DJ983	R03
Chronic liver disease	K70-76	
Diabetes mellitus type 1 and type 2	E10-11	A10A, A10B
Heart conditions	I00-I52	C
Mental health disorders limited to mood disorders including depression and schizophrenia spectrum disorders	F29-34	
Obstructive and central sleep apnoea	G47.3	
Tuberculosis	A15-A19	J04A
HIV	B20-B24, F02.4	J05AE, J05AF
Neurological conditions including dementia	G00-G99	N04-N06
Solid organ or blood stem cell transplant	Z94, BOQE5	
Substance abuse	F10-F17	N07BC except N07BC02
Primary thrombophilia: resistance of activated protein C (factor V Leiden mutation), antithrombin, protein C or protein S deficiency, prothrombin gene mutation*	D68.5	
Asthma	J45-J46	G03
Hypertension	I10-I15	
History of recurrent thromboembolic events	I74	
Immune deficiencies (except people with moderate to severe immune compromise due to a medical condition or receipt of immunosuppresive medications or treatments)	D80-D89	
Other diagnosis codes		
Diagnosis	ICD-10	ATC
Pregnant	Z340, Z348A, Z348B, Z358M	
Given birth	O80-O84	
COVID-19	B232A, B972A	
Respiratory	J0-J9	
Antiviral drugs		
Drug name	ICD-10	ATC
nirmatrelvir/ritonavir		J05AE03
remdesivir		J05AB16
monoclonal antibodies		J06BC, J06BD, L01F
casirivimab/imdevimab		J06BD07
sotrovimab		J06BD05
tixagevimab/cilgavimab2		J06BD03
Hydroxychloroquine3		P01BA02
Ivermectin3		P02CF01
Comedications		
Drug name	ICD-10	ATC
Amiodarone		C01BD01
Apalutamide		L02BB05
Apixaban		B01AF02
Bosentan		C02KX01

(continued)

Table 2. (continued)

Comorbidities	
Carbamazepine	N03AF01
Ciclosporin	L04AD01, S01XA18
Clopidogrel	B01AC04
Clozapine	N05AH02
Diazepam	N05BA01
Dihydroergotamine	N02CA01
Disopyramide	C01BA03
Dofetilide	C01BD04
Domperidone	A03FA03
Dronaderone	C01BD07
Enzalutamide	L02BB04
Eplerenone	C03DA04
Ergot derivatives	N02CA, G02AB02, G02CB
Ergoloid	C04AE01, N07CA52, C08CA
Ergometrine	G02AB03, G02AB01
Ergotamine	N02CA02, N02CA52, N02CA72
Enzalutamide	L02BB04
Everolimus	L01EG02, L04AA18
Flecainide	C01BC04
Glecaprevir/pibrentasvir	J05AP57
Ivabradine	C01EB17
Lomitapide	C10AX12
Llonafarnib	A16AX20
Lovastatin	C10AA02
Lurasidone	N05AE05
Lumateperone	N05AD10
Lumecaftor/ivacaftor	R07AX30
Meperidine (pethidine)	N02AB02
Mesylates	C04AE01
Mexilitine	C01BB02
Midazolam	N05CD08
Pimozide	N05AG02
Phenobarbital	N03AA02
Phenytoin	N03AB02
Primidone	N03AA03
Propafenone	C01BC03
Quinidine	C01BA01
Rifampin	J04AB02, J04AM02, J04AM05, J04AM06
Rifapentine	J04AB05
Riociguat	C02KX05
Rivaroxaban	B01AF01
Salmeterol	R03AC12, R03AK06
Sildenafil	G04BE03
Simvastatin	C10AA01, C10BA02
Tadalafil	G04BE08

(continued)

Table 2. (continued)

Comorbidities		
Tolvaptan		C03XA01
Vardenafil		G04BE09
Voclosporin		L04AD03
Analgesics		N02
Antiarrhytmics		C01B
Antibacterials		J01
Anticoagulants		B01
Anticonvulsants		N03
Antifungals		D01
Antipsychotics		N05A
Anxiolytics		N05B
Bronchodilators		R03
Calcium channel blockers		C08
Cancer drugs	C00-D48*	L01
Gastrointestinal agents		A
Antihypertensives		C02
Immunosuppressants		L04
HMG-CoA reductase inhibitors ("statins")		C10AA, C10BX03, C10BA

*Identified through cancer diagnosis instead of ATC, since most cancer drug treatment takes place at a hospital.

Outcomes

During the 28-day follow-up period, rates for all-cause, respiratory- or COVID-19-related, and COVID-19- related emergent hospitalization were 4.8%, 2.6%, and 1.5%, respectively. All-cause mortality rate was 1.6%.

Initiation of MOV 3–5 days after a positive a SARS-CoV-2 test compared to 1–2 days was associated with an increased odds of all-cause (OR 1.85 95% CI 1.29–2.66, $p = 0.001$), respiratory or COVID-19-related (OR 1.78, 95% CI 1.07–2.94, $p = 0.025$) emergent hospitalization, and all-cause mortality (OR 2.90, 95% CI 1.64–5.15, $p < 0.001$), but not COVID-19 related emergent (OR 1.82, 95% CI 0.97–3.42, $p = 0.064$) (Table 5). The ORs of outcomes for initiation of MOV later than 6 days compared to 1–2 days are not statistically significant. Relative to no or partial vaccination, being fully vaccinated significantly reduced the odds of all-cause (OR 0.59, 95% CI 0.37–0.96, $p = 0.032$), respiratory- or COVID-19-related (OR 0.44, 95% CI 0.24–0.81, $p = 0.009$) and COVID-19-related (OR 0.34, (5% CI 0.17–0.70, $p = 0.003$) emergent hospitalization, but not all-cause mortality (OR 0.56, 95% CI 0.23–1.33, $p = 0.185$) (Table 5).

Sex, number of comorbidities, and comedication were not significantly associated with the risk of all-cause, respiratory-, or COVID-19-related hospitalization or all-cause mortality. There were no differences in outcomes among the five Danish Regions (Table 5).

As a sub analysis, we examined the outcomes of fully vaccinated patients (≥3 vaccinations per Danish standards) separately. Since 89.2 % of the population is fully vaccinated the results are very similar to those of the full population. Initiation of MOV 3–5 days after a positive SARS-CoV-2 test compared to 1–2 days had higher odds of all-cause (OR 2.05 95% CI 1.4–3.01, $p < 0.001$), respiratory or COVID-19-related (OR 2.04, 95% CI 1.12–3.47, $p = 0.009$) and COVID-19 related (OR 2.12 95% CI 1.07–4.23, $p = 0.033$) emergent hospitalization, and all-cause mortality (OR 2.93, 95% CI 1.61–5.35, $p < 0.001$). Of note, time between MOV initiation and COVID-19-related emergent hospitalization was significant in the fully vaccinated population but not in the full population. The ORs for initiation of MOV later than 6 days compared to 1–2 days remains not statistically significant.

As a second sub analysis, we examined the population of patients with concomitant cancer. 15.1 % of the MOV-treated population had concomitant cancer. Patients with cancer had a higher risk of all cause hospitalization compared to patients without cancer (6.8% vs 4.7%, p-value: 0.035). There were no significant differences between cancer and non-cancer patients with regards to COVID-19-related, COVID-19-related or respiratory-related hospitalizations, and death. Additionally, we found no significant difference in outcome comparing initiation of MOV at 1–2 days to initiation at 3–5 days for patients with cancer (Table 5).

Discussion

In December 2021, the Danish Medicines Agency approved MOV for pre-license use. To reduce the number of

Table 3. Patient characteristics at the time of MOV initiation.

	Total population	0–2 days between test and treatment	3–5 days between test and treatment	5+ days between test and treatment
Patient Characteristics	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Age Groups				
18–49	486 (13.2%)	344 (12.2%)	104 (16.7%)	38 (14.7%)
50–59	460 (12.5%)	349 (12.4%)	77 (12.4%)	34 (13.2%)
60–69	600 (16.3%)	455 (16.2%)	104 (16.7%)	41 (15.9%)
70–79	820 (22.2%)	659 (23.4%)	105 (16.9%)	56 (21.7%)
80+	1325 (35.9%)	1005 (35.6%)	231 (37.2%)	89 (34.5%)
Sex				
Female	2001 (54.2%)	1508 (53.6%)	358 (57.6%)	135 (52.3%)
Male	1690 (45.8%)	1304 (46.4%)	263 (42.4%)	123 (47.7%)
Region				
North Denmark Region	528 (14.3%)	396 (14.1%)	82 (13.2%)	50 (19.4%)
Central Denmark Region	917 (24.9%)	725 (25.8%)	136 (21.9%)	56 (21.7%)
Region of Southern Regioner	895 (24.3%)	693 (24.7%)	153 (24.6%)	49 (19%)
Capital Region of Denmark	942 (25.6%)	688 (24.5%)	175 (28.2%)	79 (30.6%)
Region Zealand	404 (11%)	305 (10.9%)	75 (12.1%)	24 (9.3%)
Number of comorbidities				
0	202 (5.5%)	156 (5.5%)	29 (4.7%)	17 (6.6%)
1	729 (19.8%)	550 (19.6%)	128 (20.6%)	51 (19.8%)
2	1178 (31.9%)	902 (32.1%)	201 (32.4%)	75 (29.1%)
3	924 (25.0%)	693 (24.6%)	160 (25.8%)	71 (27.3%)
4	470 (12.7%)	362 (12.9%)	74 (11.9%)	34 (13.2%)
5+	188 (5.1%)	149 (5.3%)	29 (4.7%)	10 (3.9%)
Receiving comedication				
	3256 (88.2%)	2491 (88.6%)	538 (86.6%)	227 (88%)
Number of vaccines received				
0–1	196 (5.3%)	138 (4.9%)	41 (6.6%)	17 (6.6%)
2	201 (5.4%)	137 (4.9%)	41 (6.6%)	23 (8.9%)
3+	3294 (89.2%)	2537 (90.2%)	539 (86.8%)	218 (84.5%)
More than 180 days since last infection or no previous infection				
	3641 (98.6%)			
N	3691	2812	621	258

*Days since last infection can only be reported for the total population due discretionary considerations.

COVID-19-related hospitalizations and deaths, the Danish Health Authorities recommended that MOV be offered to patients with mild-to-moderate COVID-19 with symptoms for ≤5 days and an increased risk of progression to severe disease[9] (Table 1). During the study period, MOV was the only available oral antiviral treatment for COVID-19 in Denmark and could be prescribed by both general physicians and hospital doctors. The treatment was tax-funded and free of charge for the patients.

The MOVe-OUT trial was carried out in an unvaccinated population during the period of Delta variant predominance.[6,10] Given the dynamic nature of the COVID-19 pandemic, with emergence of new variants of concern, and, implementation of COVID-19 vaccine programs, there is considerable uncertainty about whether the clinical benefit of treatments observed in clinical trials are realized in the real world in Denmark and the rest of the world. Therefore, in this nationwide real-world study, we aimed to describe the baseline demographic, clinical, and treatment characteristics of non-hospitalized Danish patients treated with MOV and their clinical outcomes over a 28-day period following a redeemed prescription of MOV.

Our study population consist of MOV treated, predominantly vaccinated, elderly patients with multiple comorbidities likely infected with the Omicron variant. The population characteristics show that not all MOV prescriptions were in accordance with the recommendations from the Danish Health Authority (Table 1). 13% of the population were younger than 50 years of age and not all patients had a positive SARS-CoV-2 test registered.

Table 4. The correlation between covariates and treatment initiation.

	Treatment initiated within 2 days			Treatment initiated within 5 days		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age						
18–49	RC	RC	RC	RC	RC	RC
50–59	1.257	[0.937;1.687]	0.127	1.015	[0.622;1.655]	0.953
60–69	1.217	[0.918;1.613]	0.172	1.081	[0.670;1.746]	0.749
70–79	1.567	[1.190;2.065]	0.001	1.062	[0.673;1.676]	0.796
80+	1.189	[0.929;1.522]	0.168	1.056	[0.693;1.608]	0.801
Gender						
Female	0.939	[0.804;1.097]	0.427	1.117	[0.864;1.445]	0.399
Region						
North Denmark Region	RC	RC	RC	RC	RC	RC
Central Denmark Region	1.279	[0.991;1.650]	0.058	1.601	[1.074;2.388]	0.021
Region of Southern Regioner	1.159	[0.900;1.494]	0.253	1.822	[1.207;2.749]	0.004
Capital Region of Denmark	0.931	[0.727;1.191]	0.567	1.173	[0.806;1.707]	0.404
Region Zealand	1.058	[0.781;1.432]	0.717	1.751	[1.053;2.913]	0.031
Number of comorbidities						
0	RC	RC	RC	RC	RC	RC
1	0.774	[0.525;1.145]	0.2	1.154	[0.626;2.127]	0.646
2	0.782	[0.530;1.155]	0.216	1.252	[0.681;2.302]	0.47
3	0.707	[0.473;1.057]	0.091	1.016	[0.543;1.900]	0.96
4	0.782	[0.507;1.205]	0.265	1.067	[0.541;2.102]	0.852
5+	0.865	[0.515;1.453]	0.585	1.45	[0.610;3.448]	0.401
Relevant comedication						
Receiver of comedication	1.102	[0.850;1.427]	0.464	0.903	[0.579;1.410]	0.654
Vaccination status						
Fully vaccinated	1.414	[1.109;1.802]	0.005	1.612	[1.103;2.357]	0.014
Observations	3,686			3,686		

*RC: Reference category.
*- : Omitted due to too little variation.
*The number of observations vary due to a few individuals not having information about what region they live in and categories being omitted due to too little variation.

However, home-tests are not in the registries, and the few patients without a positive SARS-CoV-2 test visible in the registries are assumed to have a positive home-test.[11,12]

We found that the rates of all-cause (4.8%), respiratory- or COVID-19-related (2.6%), and COVID-19 related (1.5%) emergent hospitalization and all-cause mortality (1.6%) were low. However, hospitalization rates increased with age among people with COVID-19, and were 2.9% for people aged 65–79 and 10.7% for people aged 80+ according to national surveillance data, which both are significantly higher than the estimates from our study.[13] MOV treatment, high vaccine coverage, predominant infection with the Omicron variant or a combination of these factors may explain low overall hospitalization rates. However, data on the background population during the study period cannot be directly compared with the results from our MOV-treated study population. Among other things we restricted the study population to people not hospitalized immediately before or at the time of a positive test, whereas the reported statistics include them. Therefore, it cannot be concluded whether MOV treatment contributed to the low hospitalization and death rates seen in the study population. In a sub analysis, we found that patients with cancer had a higher risk of all-cause hospitalization, but not respiratory- or COVID-19-related, and COVID-19 related emergent hospitalization and all-cause mortality compared to patients with no cancer. A study examining hospitalization rates and mortality among MOV-treated patients with haematological malignancies found substantially higher rates of hospitalization (20 %) and mortality (4 %) in the 28 days after breakthrough COVID-19 diagnosis during the same time period as our study.[14] This could potentially be explained by the higher vaccination rates in our population, as only half of the participants in the other study had received a booster. Of note, early treatment with MOV was associated with reduced risk of hospitalization and death, indicating that initiation of MOV within 1–2 days of a positive SARS-CoV-2 test influences the clinical outcome

Table 5. The effect of time of treatment initiation on health outcomes.

	Emergent hospitalization lasting more than 24 hours – all cause			Emergent hospitalization lasting more than 24 hours – COVID related			Emergent hospitalization lasting more than 24 hours – respiratory or COVID related			Deceased		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Days between test and treatment initiation												
0-2	RC	RC	RC	RC	RC	RC	RC	RC	RC	RC	RC	RC
3-5	1,852	[1,287; 2,664]	0,001	1,818	[0,967; 3,419]	0,064	1,777	[1,073; 2,943]	0,025	2,903	[1,637; 5,146]	0,000
6+	1,067	[0,485; 2,349]	0,872	0,488	[0,066; 3,616]	0,483	0,873	[0,267; 2,854]	0,823	2,281	[0,778; 6,687]	0,133
No test	5,487	[3,176; 9,479]	0,000	5,508	[2,345; 12,939]	0,000	4,356	[2,065; 9,187]	0,000	2,389	[0,705; 8,090]	0,162
Age												
18–49	RC	RC	RC	RC	RC	RC	RC	RC	RC	RC	RC	RC
50–59	0,830	[0,380; 1,816]	0,641	0,567	[0,138; 2,328]	0,431	0,514	[0,152; 1,738]	0,284	-	-	-
60–69	1,677	[0,873; 3,223]	0,121	1,393	[0,467; 4,153]	0,552	1,517	[0,617; 3,730]	0,364	3,883	[0,441; 34,198]	0,222
70–79	1,949	[1,043; 3,642]	0,037	1,883	[0,682; 5,201]	0,222	2,403	[1,045; 5,528]	0,039	6,934	[0,859; 55,948]	0,069
80+	2,062	[1,135; 3,744]	0,018	1,998	[0,762; 5,237]	0,159	1,822	[0,806; 4,118]	0,149	15,204	[2,023; 114,273]	0,008
Gender												
Female	0,790	[0,582; 1,071]	0,129	1,052	[0,614; 1,800]	0,854	1,092	[0,713; 1,673]	0,686	0,710	[0,419; 1,204]	0,204
Region												
North Denmark Region	RC	RC	RC	RC	RC	RC	RC	RC	RC	RC	RC	RC
Central Denmark Region	0,771	[0,475; 1,253]	0,295	1,260	[0,555; 2,862]	0,581	0,772	[0,406; 1,468]	0,430	1,056	[0,473; 2,355]	0,894
Region of Southern Regioner	0,770	[0,476; 1,246]	0,288	0,503	[0,191; 1,326]	0,165	0,551	[0,279; 1,090]	0,087	1,057	[0,477; 2,342]	0,892
Capital Region of Denmark	0,840	[0,523; 1,350]	0,471	0,792	[0,328; 1,915]	0,605	0,695	[0,364; 1,329]	0,271	0,758	[0,321; 1,787]	0,527
Region Zealand	0,912	[0,517; 1,606]	0,749	1,515	[0,610; 3,761]	0,371	1,079	[0,529; 2,202]	0,834	0,501	[0,135; 1,859]	0,301
Number of comorbidities												
0	RC	RC	RC	RC	RC	RC	RC	RC	RC	RC	RC	RC
1	1,418	[0,520; 3,868]	0,495	2,766	[0,333; 22,981]	0,346	3,570	[0,451; 28,253]	0,228	1,925	[0,238; 15,540]	0,539
2	1,025	[0,372; 2,820]	0,962	1,775	[0,206; 15,276]	0,601	2,345	[0,292; 18,812]	0,422	1,079	[0,132; 8,808]	0,944
3	1,858	[0,676; 5,105]	0,230	4,289	[0,511; 36,004]	0,180	4,195	[0,526; 33,484]	0,176	1,318	[0,159; 10,932]	0,798
4	2,683	[0,955; 7,538]	0,061	6,625	[0,767; 57,195]	0,086	6,405	[0,789; 51,971]	0,082	0,871	[0,093; 8,203]	0,904
5+	2,768	[0,904; 8,477]	0,075	4,556	[0,446; 46,566]	0,201	5,175	[0,580; 46,169]	0,141	1,116	[0,091; 13,651]	0,932

(continued)

Table 5. (continued)

	Emergent hospitalization lasting more than 24 hours – all cause			Emergent hospitalization lasting more than 24 hours – COVID related			Emergent hospitalization lasting more than 24 hours – respiratory or COVID related			Deceased		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Relevant comedication												
Receiver of comedication	1,266	[0,668; 2,399]	0,470	0,953	[0,337; 2,691]	0,927	1,578	[0,594; 4,195]	0,360	3,251	[0,741; 14,258]	0,118
Vaccination status												
Fully vaccinated	0,591	[0,365; 0,957]	0,032	0,343	[0,168; 0,703]	0,003	0,437	[0,236; 0,810]	0,009	0,548	[0,225; 1,333]	0,185
Observations	3.686			3.686			3.686			3.226		

of COVID-19. Viral replication is highest in the initial stage of the infection, so treatment with MOV has the best effect during this period.[7] An observational study from Australia suggests that treatment with MOV within 1 day of diagnosis provided the greatest benefit.[15] No benefit in reducing the risk of hospitalization was seen if treatment was initiated two or more days after diagnosis and for death four or more days after diagnosis.[15] However, since we cannot control for confounding factors, such as disease severity at the time of MOV initiation, we cannot conclude whether the difference in outcomes are caused by earlier initiation of treatment or that patients initiating treatment earlier were less likely to have severe symptoms. In our study being vaccinated significantly reduced the risk of being hospitalized, but not all-cause mortality. This is, however, most likely due to 95% of our population being fully vaccinated and a very low event rate of all-cause mortality. Previous studies have shown that vaccines are effective at preventing COVID-19 related death.[16] In our sub analysis, consisting of individuals with ≥3 vaccines, initiation of MOV within 3-5 days of a positive SARS-CoV-2 test compared to 1–2 days had higher risks of hospitalization and all-cause mortality; odds ratios for all outcomes were higher compared to the full population. However, based on this analysis we cannot determine whether this is because early initiation of MOV treatment is more effective if patients have received a third booster vaccine dose or if there are other differences between the groups such as disease progression or symptoms.

Observational studies from Hong Kong and Israel have suggested that treatment with MOV is associated with reduced risk of hospitalization and death in patients over 65 years of age.[17,18] PANORAMIC is the largest study including over 25,000 participants who were randomized to MOV plus usual care or only usual care. The study population was young (mean age 56.6 years) and 94% had received at least three doses of COVID-19 vaccines. Early treatment with MOV did not reduce the low risk (1%) of the composite outcome of hospitalization or death, but MOV reduced time to recovery and reduced viral load.[19] A meta-analysis including six studies during the Omicron wave found that MOV only had clinical effectiveness on disease progression and all-cause mortality in patients with low vaccine coverage. However, MOV was associated with faster reduction in viral load than placebo.[20] A recent systematic review and meta-analysis including nine randomized clinical trials concluded that MOV has no effect on mortality and likely no effect on hospitalization and death in a predominantly immunized population of COVID-19 patients and its effect on symptom resolution is uncertain.[21] In accordance, an observational study from Israel found that only older and inadequately vaccinated patients had clinical benefit of treatment with MOV.[22]

In clinical trials with unvaccinated adults at high risk of progression to severe COVID-19, early treatment with nirmatrelvir/ritonavir (NMV/r) or remdesivir reduced the relative risk of hospitalization or death by 89% and 87%, respectively.[23,24] In addition, the neutralizing monoclonal antibodies (nMAb) casirivimab and imdevimab and sotrovimab have been used for treatment of early COVID-19.[24] Remdesivir and nMAb can only be administered intravenously and NMV/r has a high potential for drug-drug-interactions.[8] Further, the emergence of new SARS-CoV-2 variants, including the Omicron variant, have been found to evade neutralization by nMAb.[25] In a recent retrospective cohort study from Wales, it was shown that prompt outpatient treatment of high-risk patients with COVID-19 with MOV, NMV/r, or sotrovimab was associated with a significant reduction in hospitalization and death within 28 days of infection. No difference in effectiveness between treatments were observed. The rates of hospitalization or death were 4.1% among treated and 10.9% among untreated. The study was conducted in the same period as our study when Omicron was the dominant

variant and 95.6% of participants were vaccinated.[26] The hospitalization rate in the treated group is comparable with our findings in MOV-treated patients. Mutoh et al. compared the effectiveness of MOV and NMV/r in a real-world community during the surge of the Omicron BA.5 subvariant in Japan. COVID-19 related hospitalization (2.8% and 3.5%, respectively) and death (0.4% and 3.5%, respectively) did not differ significantly between the MOV and NMV/r groups.[27] The mean age of the high-risk participants was 71.7 years and 71.7% had received at least three COVID-19 vaccine doses. The low hospitalization and death rates are comparable with our findings. Most patients receiving MOV are older and have comorbidities or comedications that made them otherwise ineligible for treatment with NMV/r.[8] This treatment selection bias could result in a pool of eligible participants with very high risk for hospitalization and death, thus masking the effectiveness of MOV treatment.

The strength of this study is the nationwide design and the very high quality of the Danish national registries, which captures health information on all residents in Denmark. This makes it possible to obtain demographic and health information on all individuals with a redeemed MOV prescription. By identifying the entire population of patients with redeemed MOV prescriptions we have eliminated some of the possible selection bias. However, when looking at the outcomes for different rates of initiating treatment, there is a possibility of unobserved confounding factors. The results in Table 3 does show that, with the exception of vaccination status and living in the Central Denmark Region, there are no differences in the observable characteristics between patients whose treatment was initiated within 2 days, 5 days or later than 5 days. But there could be difference in unobservable confounding factors such as difference in disease progression and symptoms. Since medical conditions will be identified based on existing records, coding inaccuracies may lead to misclassification bias. However, this misclassification will be non-differential since this would be the case for the entire population. In addition, we cannot ascertain based on the registry data that patients perfectly adhere to the MOV regimen or took MOV at all after being prescribed the medication. However, because only redeemed prescriptions are recorded in the Danish National Prescription Registry, it is likely that most of the study participants were exposed to MOV.

The limitations are that there is no comparison group. Further, the high vaccine coverage and predominance of infection with the Omicron variant during our study period could result in lower hospitalization or death rates compared to infection with other previous variants of concern. Moreover, because there is currently no reliable distinction between COVID-19-related and non-COVID-19-related deaths, we used all-cause mortality as the outcome. This definition could also result in the underestimation of MOV effectiveness due to its lack of specificity. In addition, the lack of availability of some risk factor information (obesity, smoking, physical activity, etc.) could limit the full characterization of MOV-treated patients in Denmark.

Since 27 February 2023, the Danish Health Authorities no longer recommend MOV for treatment of early COVID-19 in high-risk patients based on EMA recommending that a marketing authorization should not be granted.[28] In consequence, the MOV European Union application for marketing authorization for treatment of COVID-19 in adult was withdrawn on 23 June 2023. According to the WHO living guideline for COVID-19 drugs, NMV/r is the preferred drug, but MOV is conditionally recommended for patients with non-severe COVID-19 at highest risk of hospitalization.[29]

Conclusion

In Denmark, in the period December 2021 to April 2022 when Omicron was the predominant variant, MOV was primarily prescribed to predominantly vaccinated older patients with multiple comorbidities in accordance with the guidelines from the Danish health authorities. The all-cause hospitalization and mortality rate during 28 days of follow-up were low in this population. In most cases, treatment was initiated within 5 days after a positive test. Initiation of MOV within 2 days after a positive test reduced the risk of all-cause hospitalization and death. This indicates that even in a population of immunized elderly high-risk patients infected with Omicron prompt initiation of treatment with MOV may have a beneficial effect on the clinical course of COVID-19.

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Ethical statement

Ethical approval

This study will not require patient informed consent or patient IRB/EC review.

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References

1. Grant MC, Geoghegan L, Arbyn M, *et al.* The prevalence of symptoms in 24,410 adults infected by the novel coronavirus (SARS-CoV-2; COVID-19): a systematic review and meta-analysis of 148 studies from 9 countries. *PLoS One* 2020; **15**: e0234765.
2. Ko JY, Danielson ML, Town M, *et al.* RiskFactors for Coronavirus Diseases 2019 (COVID-19)-associated hospitalization: COVID-19-associated hospitalization surveillance network and behavioral risk factor surveillance system. *Clin Infect Dis* 2021; **72**: e695–e703.
3. Sharma K, Koirala A, Nicolopoulos K, *et al.* Vaccines for COVID-19: where do we stand in 2021? *Paediatr Respir Rev* 2021; **39**: 22–31.
4. Lipsitch M, Krammer F, Regev-Yochay G, *et al.* SARS-CoV-2 breakthrough infections in vaccinated individuals: measurement, causes and impact. *Nat Rev Immunol* 2022; **22**(1): 57–65.
5. Teli D, Balar P, Patel K, *et al.* Molnupiravir: a versatile prodrug against SARS-CoV-2 Variants. *Matabolites* 2023; **13**: 309.
6. Jayk BA, Gomes da SMM, Musungaie DB; Group MO-OS. Molnupiravir for oral treatment of covid-19 in nonhospitalized patients. *N Engl J Med* 2022; **386**: 509–520.
7. Tiang F, Feng Q, Chen Z. Efficacy and safety of molnupiravir treatment for COVID-19: a systematic review and meta-analysis of randomized controlled trials. *Internatinal Journal of Antimicrobial Agents* 2023; **2**: 5.
8. Larsen CS. Assessing the proportion of the Danish population at risk of clinically signidicant drug-drug interactions with new oral antivirals for early treatment of COVID-19. *Int J Infect Dis* 2022; **122**: 599–601.
9. Danish Health Authority. Præparatanmeldelse Lagevrio (molnupiravir). 2021. Available at: https://www.sst.dk/-/media/Udgivelser/2021/Corona/Tabletbehandling/Praeparatanmeldelse-Lagevrio.ashx?sc_lang=da&hash=5958AF0A0FE94663F9DE08C0FBDC6EE3 (accessed 6 June 2023).
10. He D, Cowling BJ, Ali ST, *et al.* Rapid global spread of variants of concern of SARS-CoV-2. *IJID Regions* 2023; **7**: 63–65.
11. European Centre for Disease Control. *The European Respiratory Virus Surveillance Summary*. 2023. Available at: https://www.ecdc.europa.eu/en/covid-19/country-overviews (accessed 11 June 2023).
12. Nyberg T, Ferguson NM, Nash SG, *et al.* Comparative analysis of the risk of hospitalization and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. Lancet 2022, 399; 1303-1312A living WHO guideline on drugs for COVID-19. *BMJ* 2020; **370**: m3379.
13. Statens Serum Institut. Historiske Covid-19 opgørelser. 2023. Available at: https://www.ssi.dk/sygdomme-beredskab-og-forskning/sygdomsovervaagning/c/historiske-covid-19-opgoerelser (accessed 14 August 2023).
14. Bołkun Ł, Pula B, Kołkowska-Leśniak A. Molnupiravir is effective in patients with haematological malignancies. *Int J Cancer* 2023; **153**(6): 1251–1256.
15. The Conversation. Paxlovid is Australia's first-line COVID antiviral but Lagevrio also prevents severe disease in over-70s. 2022. Available at: https://theconversation.com/paxlovid-is-australias-first-line-covid-antiviral-but-lagevrio-also-prevents-severe-disease-in-over-70s-195349 (accessed 11 June 2023).
16. Brnic S, Buric B, Marcec R. Likic: the relationship between vaccine acceptance and COVID-19 mortality in Europe: a Cross-Country analysis of public opinion and Epidemiological data. *Vaccine X* 2023; **15**: 100391.
17. Wong CKH, Au ICH, Lau KTK, *et al.* Real-world effectiveness of early molnupiravir or nirmatrelvir-ritonavir in hospitalised patients with COVID-19 without supplmental oxygen requirement on admission during Hong Kong's omicron BA.2 wave: a retrospective study. *Lancet Infect Dis* 2022; **22**: 1681–1693.
18. Arbel R, Sagy YW, Battat E, *et al.* Molnupiravir and severe COVID-19 outcome during the omicron surge. *Research Square* 2022; **29**: 2.
19. Butler CC, Hobbs FDR, Gbingie, *et al.* Molnupiravir plus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomized controlled trial. *Lancet* 2023; **401**: 281–293.
20. Huang C, Lu T-L, Lin L. Real-world clinical outcomes of molnupiravir for the treatment of mild to moderate COVID-19 in adult patients during the dominance of the Omicron variant: a meta-analysis. *Antibiotics* 2023; **12**: 393.
21. Malin JJ, Weibel S, Gruell H, *et al.* Efficacy and safety of molnupiravir for the the treatment of SARS-CoV-2 infection: a systematic review and metaanlysis.
22. Najjar-Debbiny R, Gronich N, Weber G, *et al.* Effectiveness of Molnupiravir in high-risk patients: a propensity score matched analysis. *Clin Infect Dis* 2023; **76**(3): 453–460.
23. Hammond J, Leister-Tebbe H, Gardner A, *et al.* Oral nimatrelvir for high-risk, nonhospitalized adults with COVID-19. *N Engl J Med* 2022; **3863**: 1397–1408.

24. Gottlieb RL, Vaca CE, Paredes R, *et al.* Early Remdesivir to prevent progression to severe COVID-19 in outpatients. *N Engl J Med* 2022; **386**(4): 305–315.
25. Evans A, Qi C, Adebayo JO. Real-world effectiveness of molnupiravir, nirmatrelvir-ritonavir, and sotrovimab on preventing hospital admission among higher-risk patients with COVID-19 in Wales: a retrospective cohort study. *J Infect* 2023; **86**: 352–360.
26. Cox M, Peacock TP, Harvey WT, *et al.* SARS-CoV-2 variant evasion of monoclonal antibodies based on in vitro studies. *Nat Rev Microbiol* 2023; **21**: 112–124.
27. Mutoh Y, Umemura T, Nishikawa, *et al.* Real-world experience og the comparative effectiveness and safety of molnupiravir and nirmatrelvir/ritonavir in high-risk patients with COVID-19 in a community setting. *Viruses* 2023; **15**: 811.
28. The Danish Health Authority. Sundheds-styrelsen anbefaler ikke længere Lagevrio til behandling af covid-19. 2023. Available at: https://www.sst.dk/da/nyheder/2023/sundhedsstyrelsen-anbefaler-ikke-laengere-lagevrio-til-behandling-af-covid19 (accessed 12 June 2023).
29. Argawal A., *et al.* A living WHO guideline on drugs for COVID-19. *BMJ*. 2020; **370**: m3379.