

# ANALYSIS OF COVID-19 PATIENT OUTCOMES WITH MOLNUPIRAVIR TREATMENT AND THE ROLE OF RISK FACTORS: A SINGLE-CENTRE RETROSPECTIVE DESCRIPTIVE STUDY

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## SUMMARY

**Objective:** This study aims to describe the outcomes of COVID-19 patients treated with molnupiravir and to explore the associations with various risk factors.

**Methods:** We conducted a single-centre, descriptive, retrospective study without a comparison group.

**Results:** Out of 141 patients, 70 (49.7%) required follow-up outpatient care. In the subgroup of 66 (46.8%) hospitalized patients, 28 (19.9%) developed interstitial viral pneumonia, with 6 (4.3%) deaths. Unvaccinated patients had a higher incidence of pneumonia ( $p=0.020$ ), and obesity was a significant risk factor for both pneumonia ( $p=0.001$ ) and mortality ( $p=0.011$ ). Patients over 60 years ( $p=0.040$ ) and those with cardiovascular diseases ( $p=0.026$ ) also had increased pneumonia risk. Male sex was associated with a higher risk of death ( $p=0.020$ ).

**Conclusion:** Molnupiravir treatment was linked to reduced risks of hospitalization and death, particularly in high-risk patients. Vaccination provided additional protection, and obesity obstructive pulmonary disease and autoimmune diseases were significant risk factors for severe outcomes.

**Key words:** molnupiravir, COVID-19, treatment, Slovakia, risk factors, single, centre, study

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## INTRODUCTION

At the end of December 2019, the first cases of pneumonia of unknown aetiology progressing to acute respiratory insufficiency syndrome began to appear in the Chinese city of Wuhan (Hubei province). The Chinese Centre for Disease Control and Prevention (CDC) identified the causative agent of the disease in January 2020 as the new coronavirus SARS-CoV-2 causing the disease called COVID-19 (1). The high number of infected patients in a short period of time has necessitated, since the beginning of the pandemic, the discovery of effective medical treatment aimed mainly at stopping the replication of the virus and also preventing the progression to severe COVID-19 requiring hospitalization (2). The main goal of the study was to determine whether oral administration of molnupiravir is associated with a reduction in the risk of hospitalization and mortality in non-hospitalized patients who are at high risk of progression to severe disease from COVID-19 (viral pneumonia).

### Molnupiravir

The antiviral drug molnupiravir was originally developed to treat Venezuelan equine encephalitis and later, in the pre-pandemic period, entered preclinical studies with influenza.

Molnupiravir is an oral ribonucleoside analog, structurally similar to natural building block of RNA. After oral administration, it is converted intracellularly into its active form, N-hydroxycytidine triphosphate (NHC-TP). During viral RNA synthesis, NHC-TP is mistakenly incorporated into the viral RNA chain by the viral RNA polymerase, leading to errors and ultimately stopping the virus from replicating (3).

The effect of molnupiravir has been monitored in various clinical studies. An example is the MOVE-OUT study, which investigated the effect of this antiviral drug in a population of unvaccinated, high-risk patients infected with the delta variant of the coronavirus. Data from the MOVE-OUT phase 3 trial in nonhospitalized at-risk adults with COVID-19 demonstrated that molnupiravir, initiated within 5 days after symptom onset (800 mg twice daily for 5 days), significantly reduces the risk of hospitalization for any cause or death through day 29. The trial population was representative of real-world patients with one or more well-established risk factors for severe illness due to COVID-19 (4).

In contrast to the MOVE-OUT study, the later PANORAMIC study monitored the effect of molnupiravir (compared to standard – symptomatic treatment) in a group of at-risk, vaccinated patients infected with the Omicron variant. It found that molnupiravir did not reduce the already low number of hospitalizations and deaths

in this group, likely due to the protective effect of vaccination. However, the study did show that molnupiravir shortens the duration of clinical symptoms (from 15 to 9 days) and reduces the viral load, potentially decreasing the risk of further spread (5).

Currently, molnupiravir is one of the oral options in the treatment of COVID-19, which can be used especially in a specific group of risk patients, no later than 5 days after the onset of clinical symptoms, at a dose of 800 mg every 12 hours, for 5 days. Its administration is mainly indicated in high-risk patients who cannot receive other oral (nirmatrelvir + ritonavir) or parenteral (remdesivir) antivirals for any reason (drug interactions, severe renal or hepatic insufficiency, etc.).

This research is particularly relevant as it provides insights into the real-world application of molnupiravir, adding to the existing body of knowledge from controlled clinical trials. The findings aim to inform clinical decision-making, especially in the cases where alternative antiviral treatments may be limited or contraindicated.

## MATERIALS AND METHODS

We conducted a single-centre, descriptive, retrospective study to analyse the treatment outcomes of high-risk outpatients with COVID-19 who received molnupiravir. A total of 141 patients with PCR-confirmed COVID-19 signed informed consent for inclusion in the study and for anonymous publication of the results (Table 1). All patients included in the study were initially examined at the infectious disease clinic in Košice, Slovakia, and

were prescribed the drug molnupiravir (fully covered by the health insurance company), which they used at home.

## Study Design

In the period from 1 January 2022 – 31 May 2022, we administered the antiviral drug molnupiravir on an outpatient basis to a total of 141 patients with PCR-confirmed SARS-CoV-2 infection. Ten patients were excluded from the study for not meeting the inclusion criteria (nine for developed viral pneumonia, and one woman for pregnancy). This period coincided with the prevalence of the Delta and Omicron variants of the coronavirus. Molnupiravir was the only available oral antiviral treatment option for high-risk, non-hospitalized COVID-19 patients in Slovakia at that time.

## Inclusion Criteria

Molnupiravir was prescribed to all non-hospitalized adults, who were examined at our infectious disease clinic with PCR-confirmed mild (temperature above 38.0°C, cough, sore throat, diarrhoea, no dyspnoea, no drop in oxygen saturation, normal findings on chest X-ray) or moderate (mild course symptoms + lower respiratory tract infection symptoms – not pneumonia, proven through physical methods or imaging methods, oxygen saturation  $\geq 94\%$ ) COVID-19, defined according to the Food and Drug Administration guidelines (6).

Other potential aetiologies of the disease, such as influenza and adenovirus, were excluded through PCR examination. All patients met the following criteria: they were within 5 days of symptom onset, had at least one risk factor for severe illness: age  $> 60$  years, active oncological disease, chronic kidney disease (eGFR  $< 30$  ml/min/1.73 m<sup>2</sup>), chronic obstructive pulmonary disease (COPD), obesity (BMI  $\geq 30$  kg/m<sup>2</sup>), severe heart disease, or diabetes mellitus, and showed no evidence of pneumonia on lung ultrasound (USG). The drug was administered in a standard dose of 800 mg every 12 hours per person, for a total of 5 days. Simultaneous administration of other symptomatic treatment was allowed – antipyretics, antiphlogistics, anticoagulants, vitamins, and immunomodulation (azoximer bromide).

## Exclusion Criteria

We excluded patients who had viral pneumonia confirmed by lung ultrasound or who required hospitalization for hypoxia due to pneumonia (oxygen saturation  $\leq 92\%$ ) because molnupiravir is an antiviral drug that blocks the replication of the virus in the early stages of the disease and is not indicated for the treatment of viral pneumonia. Additionally, we excluded pregnant and lactating women.

## Data Collection

The following parameters were monitored: age, sex, vaccination status, development of interstitial viral pneumonia verified by USG, return visits to the infectious diseases outpatient clinic due to deterioration of the clinical condition (fever, cough, dyspnoea, etc.), need for hospitalization for worsening of COVID-19 symptoms or other causes, death related to COVID-19, and death

**Table 1.** Baseline patient characteristics and selected underlying medical conditions or risk factors (N = 141)

Characteristics	n (%)
Age (years), mean	72
Sex	
Female	68 (48.23)
Male	73 (51.77)
Clinical symptoms of infection	
< 3 days	104 (73.76)
> 3 days	37 (26.24)
Vaccinated	
Yes	82 (58.16)
No	59 (41.86)
Medical condition or risk factor	
Age > 60	122 (86.52)
Obesity (BMI $> 30$ kg/m <sup>2</sup> )	66 (46.81)
Cardiovascular diseases	67 (47.52)
Diabetes mellitus	55 (39.01)
Active oncological diseases	39 (27.66)
Autoimmune diseases	19 (13.48)
Chronic obstructive pulmonary disease	5 (3.55)
Chronic renal insufficiency	29 (20.57)

from other causes. Specific attention was paid to identifying risk factors associated with the development of pneumonia and mortality among the treated patients.

## Statistical Analysis

Baseline characteristics of the cohort are presented as mean, frequency and percentage. The relative risk (RR) was calculated by comparing the incidence of each risk factor (e.g., age over 60 years, gender, obesity) in patients who developed viral pneumonia to the incidence of the same risk factor in patients who did not develop viral pneumonia. We used the openEpi software and the TwoByTwo table to calculate the odds ratio (OR) and Fisher's exact test to calculate the p-value of statistical significance. We considered p-values less than 0.05 as statistically significant.

In further data processing, we also used Lasso penalized logistic regression analysis to identify additional risk factors associated with the development of pneumonia and mortality in COVID-19 patients treated with molnupiravir. This approach was chosen for its ability to address issues of multicollinearity among variables and simplify the model by identifying the most significant risk factors. The use of Lasso penalized logistic regression allowed us to effectively narrow down the selection of variables and focus on the most important ones, thereby improving the model's accuracy and interpretability.

## RESULTS

### Participants

The group was nearly evenly divided between women (48.2%) and men (51.8%). The average PCR cycle threshold (Ct) value was 17.18, and the average age was 72 years. As shown in Figure 1, the majority of participants fell within the 70–80-year age range (51 patients), followed by the 60–70 years (35 patients) and 80–90 years (33 patients) old groups. Over half (58.2%) of the participants were fully vaccinated with three COVID-19 vaccine doses, while 41.8% were unvaccinated.

The majority (n=104, 73.8%) reported experiencing symptoms for less than 3 days, while the remaining 37 (26.2%) had symptoms for 4 or 5 days. Age over 60 years was the most common risk factor, affecting 122 (86.5%) of the participants. Due to limitations in laboratory testing, viral sequencing to identify

specific variants was not conducted. However, given the global epidemiological landscape during the study period, it is highly probable that the patients were infected with either the Delta or Omicron variant.

### Molnupiravir Treatment Outcomes

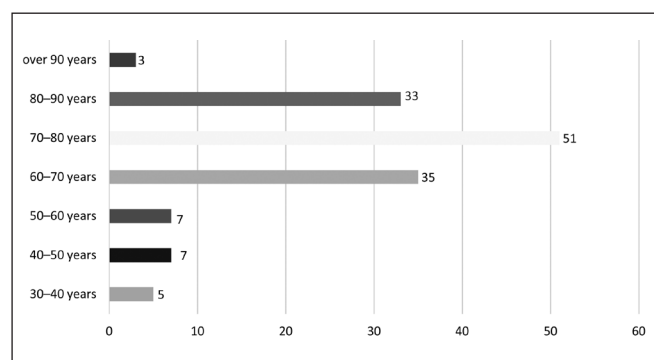
Following outpatient evaluation and treatment with molnupiravir (800 mg every 12 hours for 5 days), 70 (49.7%) patients required further follow-up at the outpatient clinic due to persistent symptoms, while 66 (46.8%) patients were hospitalized (Fig. 2). Of the hospitalized patients, 40 (60.6%) were admitted for worsening COVID-19 symptoms, and 26 (39.4%) were admitted for non-COVID-19 related reasons, often transfers from other medical departments (e.g., oncology) for isolation purposes. Importantly, none of these transferred patients developed pneumonia verified by lung ultrasound during hospitalization.

### Hospitalized Patients with Pneumonia

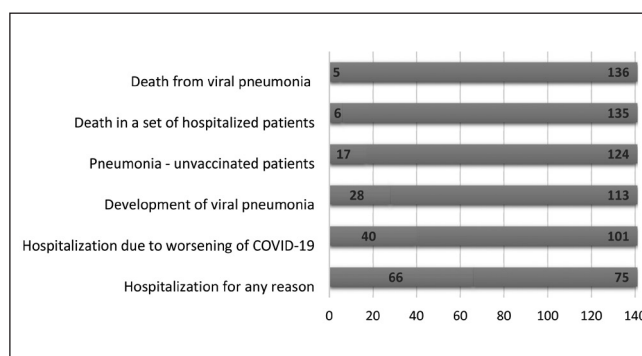
A total of 28 patients (42.4% of all hospitalized patients, 19.9% of the total study group) who were hospitalized for worsening COVID-19 symptoms developed interstitial viral pneumonia confirmed by lung ultrasound. The average age of these patients was 77.8 years, with 27 patients over 60 and only 1 patient under 60. All patients with viral pneumonia received the same treatment regimen immediately upon hospital admission: immunomodulators (dexamethasone 8 mg intravenously every 24 hours, baricitinib 4 mg orally every 24 hours), B, C and D vitamins, and other symptomatic treatment. Notably, none of these patients received parenteral antiviral remdesivir.

### Deaths

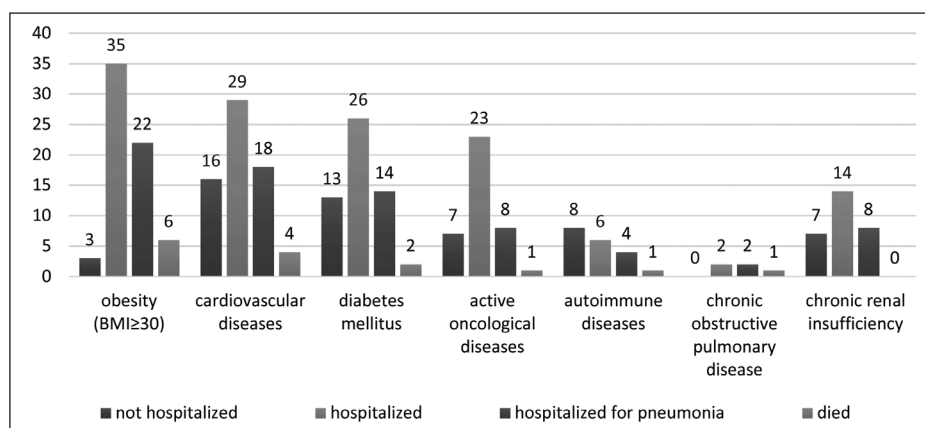
Six patients in the study group died (all men), representing 4.26% of the total group and 9.09% of hospitalized patients. Five deaths were attributed to interstitial viral pneumonia. One patient with colon cancer did not develop pneumonia and died from the underlying cancer. The average age of deceased patients was 75 years, with 3 (50%) vaccinated and 3 (50%) unvaccinated. Two deceased patients had severe pre-existing lung disease (small cell carcinoma and chronic obstructive pulmonary disease in terminal stage – according to the GOLD classification, stage D) (7).



**Fig. 1.** Age distribution of patients in the monitored group (N=141).



**Fig. 2.** Division of patients into individual groups.



**Fig. 3.** Distribution of comorbidities in the study group.

### Comorbidities and Risk Factors

The aim of this analysis is to determine how different patient factors affect the outcomes within the treatment group (Table 2).

Age over 60 years was the most common risk factor for molnupiravir administration, affecting 126 (89.36%) of the patients. Among these patients, 31 (24.8%) individuals had no other identified comorbidities or obesity.

The analysis of hospitalized patients revealed that obesity was the most prevalent comorbidity ( $n=35$ , 53.03%), followed by cardiovascular diseases (chronic heart failure and ischaemic heart disease ( $n=29$ , 43.94%), diabetes mellitus ( $n=26$ , 39.39%), active oncological disease ( $n=23$ , 34.85%), and chronic renal insufficiency ( $n=14$ , 21.21%). These findings are illustrated in Figure 3.

A similar distribution of comorbidities was observed among patients hospitalized for viral pneumonia (Fig. 3). Obesity was again the most frequent comorbidity ( $n=22$ , 78.57%), followed by cardiovascular diseases ( $n=18$ , 64.29%), diabetes mellitus ( $n=14$ , 50.00%), chronic renal insufficiency ( $n=8$ , 28.57%), and active oncological disease ( $n=8$ , 28.57%).

All deceased patients had obesity as a comorbidity ( $n=6$ , 100.00%). Additionally, four had cardiovascular diseases (66.67%), and two had diabetes mellitus (33.34%).

The majority of patients hospitalized for pneumonia had three of the observed comorbidities ( $n=8$ , 28.57%) (Fig. 3). The most common combination was obesity, diabetes, and cardiovascular disease ( $n=5$ ). Three patients had a combination of diabetes, obesity, and chronic renal insufficiency; 7 (25.00%) patients had two comorbidities (obesity and cardiovascular diseases), and 6 (21.43%) patients had one comorbidity.

Fisher's exact test revealed that obesity (BMI over 30 kg/m<sup>2</sup>) was the strongest risk factor associated with both developing viral pneumonia ( $p=0.001$ , relative risk (RR) = 4.16, odds ratio (OR) = 5.75) and death ( $p=0.011$ , RR=68.27, OR = 75) in hospitalized patients treated with molnupiravir. Importantly, none of the other monitored risk factors were statistically significantly associated with an increased risk of death from viral pneumonia. Patients older than 60 years ( $p=0.040$ , RR=4.23, OR=5.12) and those with cardiovascular diseases ( $p=0.026$ , RR=1.98, OR=2.35) had a statistically significantly higher risk of developing viral pneumonia. Diabetes mellitus, active oncological disease, autoimmune disease, and chronic renal insufficiency were not associated with a statistically significant increase in pneumonia risk. Unvaccinated patients ( $p=0.020$ , RR=2.15, OR=2.59) had a statistically significantly higher risk of developing viral

**Table 2.** Risk factors associated with development of pneumonia and death of patients in the study group

Selected risk factors	Development of pneumonia				Death			
	p-value	RR	OR	95% CI	p-value	RR	OR	95% CI
Obesity	<b>0.001</b>	4.17	5.75	2.16–15.32	<b>0.011</b>	68.27	75.00	1.32–undefined
Diabetes mellitus	0.132	1.56	1.76	0.66–4.69	0.565	0.78	0.77	0.068–5.63
Cardiovascular diseases	<b>0.026</b>	1.98	2.35	0.88–6.26	0.294	2.21	2.27	0.31–25.92
Active oncological diseases	0.537	1.05	1.05	0.39–2.80	0.468	0.52	0.51	0.01052–4.8
Autoimmune diseases	0.548	1.07	1.09	0.41–2.90	0.587	1.28	1.30	0.05774–4.514
COPD	0.258	2.09	2.82	1.06–7.51	0.198	5.44	6.36	0.02606–12.6
Chronic renal insufficiency	0.180	1.55	1.75	0.66–4.66	0.592	0.32	0.681	0.01281–5.354
Male gender	0.567	0.985	0.981	0.37–2.61	<b>0.020</b>	55.97	60.90	1.074–undefined
Absence of vaccination	<b>0.020</b>	2.15	2.59	0.97–6.90	0.494	1.39	1.41	0.1817–10.9
Age over 60 years	<b>0.040</b>	4.21	5.12	1.92–13.64	0.440	9.39	9.83	0.1677–undefined

COPD – chronic obstructive pulmonary disease; RR – risk ratio; OR – odds ratio; CI – confidence interval for OR; p-values were calculated by Fisher's exact test. Numbers in bold indicate statistically significant values.



**Table 3.** OR values for risk factors according to Lasso penalized logistic regression

Selected risk factors	Development of pneumonia OR	Death OR
Age over 60	1	1
Obesity	1	1
Cardiovascular diseases	1	1
Diabetes mellitus	1	1
Absence of vaccination	1	1
Male gender	1	1
Active oncological diseases	1	1
Autoimmune diseases	1	1.840
Chronic obstructive PD	1	2.207
Chronic renal insufficiency	16.583	1

PD – pulmonary disease

pneumonia compared to vaccinated patients. Male gender was associated with a significantly higher risk of death ( $p=0.020$ ,  $RR=55.97$ ,  $OR=60.90$ ).

From the results of the Lasso penalized regression (Table 3), it is evident that most risk factors have OR values close to 1, indicating a low impact on the prediction of pneumonia and death. Significant OR values were observed for chronic kidney failure ( $OR=16.58$ ) in predicting pneumonia and for chronic obstructive pulmonary disease ( $OR=2.21$ ), and autoimmune diseases ( $OR=1.84$ ) in predicting death. These results highlight that using Lasso regression can bring attention to additional risk factors that may be important for further patient management.

## DISCUSSION

Molnupiravir is currently one of the oral antiviral treatment alternatives for COVID-19, used selectively in patients with mild to moderate disease who are at high risk of progression to severe conditions. It is an oral ribonucleoside analog with a broad spectrum of antiviral activity (8–10).

As part of this research, we administered molnupiravir to 141 patients with PCR-verified COVID-19 who had various risk factors, including age over 60 years, active oncological disease, chronic kidney disease, COPD, obesity, severe heart disease (heart failure, coronary artery disease, or cardiomyopathy), or diabetes mellitus. During the research period, molnupiravir was the only available oral antiviral agent in Slovakia for outpatient treatment of mild to moderate COVID-19 in high-risk patients. Treatment was initiated in all patients within 5 days of symptom onset, the period during which the highest clinical benefit is expected.

Out of the 141 monitored patients, 40 (28.37%) experienced a worsening of their condition requiring hospitalization. Additionally, 28 patients (19.86%) developed viral pneumonia, verified by lung ultrasound, and 6 patients (4.26%) died. According to the results of the MOVE-OUT trial, administration of molnupiravir (at a dose of 800 mg every 12 hours) to at-risk patients with mild or moderate COVID-19 led to a reduction in the risk of hospitalization or death.

Our results also show that the administration of molnupiravir could reduce the risk of developing pneumonia and death in at-risk patients in the study population. However, the reported associations between patient characteristics and outcomes are based on subgroup analyses within a single-arm study.

Furthermore, outpatient antiviral treatment helped reduce the burden on the healthcare system during the observed pandemic period (11). Several studies have shown that treatment with molnupiravir is associated with a significant reduction in the risk of hospitalization and mortality in non-hospitalized patients at high risk of COVID-19 progression. Additionally, not taking molnupiravir was identified as an independent risk factor for the worsening of COVID-19 (12–14).

The results of the study show that among patients taking molnupiravir, the unvaccinated have a significantly higher risk of developing viral pneumonia ( $p=0.020$ ,  $RR=2.15$ ,  $OR=2.59$ ) compared to vaccinated patients. According to Xie et al., molnupiravir is particularly effective in unvaccinated patients, reducing the risk of progression to a severe condition. Unvaccinated patients clearly benefit from the antiviral treatment (15). However, unvaccinated patients taking molnupiravir do not have a statistically significantly higher risk of death ( $p=0.494$ ,  $RR=1.39$ ,  $OR=1.41$ ).

We found that obesity is the most significant risk factor for the development of viral pneumonia ( $p=0.001$ ) and a risk factor for death from viral pneumonia ( $p=0.011$ ) in patients taking molnupiravir. Obese patients have a 4.17-fold higher risk of developing pneumonia and a 68.27-fold higher risk of dying from viral pneumonia despite taking molnupiravir.

Our results, therefore, show that no statistically significant difference in mortality was observed in patients taking molnupiravir, except in those with obesity among the monitored risk factors.

Similar conclusions were reached by Sawadogo et al., Simonnet et al., and Tamara and Tahapary, who demonstrated that obesity increases the risk of hospitalization, development of pneumonia, and death in connection with COVID-19 (16–18).

As we have shown, cardiovascular diseases are another significant risk factor for developing pneumonia ( $p=0.026$ ,  $RR=1.98$ ,  $OR=2.35$ ). Patients with cardiovascular diseases have almost twice the risk of developing viral pneumonia. However, unlike obesity, cardiovascular disease is not associated with a higher risk of death.

A meta-analysis by Silverio et al. suggests that older age and diabetes are associated with a higher risk of in-hospital mortality in patients infected with SARS-CoV-2. Conversely, male sex, hypertension, and smoking did not independently correlate with fatal outcomes (19). Similarly, Cheng et al. reported that older age, diabetes mellitus, and chronic respiratory diseases were independent risk factors for hospitalization and mortality. These results demonstrate that molnupiravir has important clinical benefits beyond the reduction in hospitalization or death for patients with multiple comorbidities (20).

In our study, we did not confirm by Fisher exact test that the other observed comorbidities (diabetes mellitus, chronic kidney disease, autoimmune diseases, and chronic obstructive pulmonary disease) are associated with a statistically significant higher risk of developing pneumonia or death.

However, for COPD, the risk of developing viral pneumonia is more than doubled and the risk of death is more than five-fold, but

these differences are not statistically significant, likely due to the low number of patients with COPD in the study ( $p=0.258$ ). This statement was subsequently confirmed when using Lasso penalized regression, other risk factors were highlighted. Significant OR values were observed in COPD ( $OR=2.207$ ) as a predictor of death and also in chronic renal failure ( $OR=16.583$ ) as a predictor of the development of pneumonia.

These findings provide insight into how observed risk factors influence the outcomes of molnupiravir treatment but do not establish causality between the treatment and improved outcomes.

Arbel et al. highlight the benefits of molnupiravir treatment, particularly in older, unvaccinated patients and in women compared to men. In a cohort of non-hospitalized, Omicron-infected, high-risk patients, molnupiravir therapy was associated with a significant reduction in hospitalizations and mortality due to COVID-19 in older patients, with no evidence of benefit found in younger adults. Our results indicate that age over 60 years is a risk factor for the development of viral pneumonia in the studied cohort. These patients had a more than two-fold higher risk of developing pneumonia ( $p=0.040$ ,  $RR=4.21$ ,  $OR=5.12$ ), but did not have a statistically significant higher risk of death. Consistent with Arbel et al., we found gender differences, male gender was a significant risk factor for death ( $p=0.020$ ,  $RR=55.97$ ,  $OR=60.90$ ) (21).

The mortality rate in our monitored group of patients was 4.26%. Weil et al. and Kimata et al. report an all-cause mortality rate of about 1% in patients treated with molnupiravir. We attribute the observed difference in mortality mainly to the smaller number of patients in our study cohort (22, 23).

This study has several limitations. As a descriptive retrospective study, its results cannot be directly compared with those from randomized controlled trials. The study was designed as a single-arm study due to difficulties in defining a suitable comparison group and was conducted in only one healthcare facility. This could lead to differences in the patient population compared to other regions and variations in data collection, which precludes the ability to calculate the reduced risk specifically attributable to molnupiravir compared to standard care or no treatment. Therefore, it is necessary to conduct further randomized controlled trials in the future, especially to determine the comparative effectiveness of molnupiravir compared to standard care or other treatments.

Risk factors, which are variables that affect both the exposure (in this case, molnupiravir treatment) and the outcome (such as the development of pneumonia or mortality), can distort the real association between the treatment and outcomes. Additionally, findings from subgroup analyses may not be generalizable to the entire population, and establishing temporal relationships in retrospective studies is challenging. Therefore, these analyses demonstrate associations but do not establish causality. Small sample sizes within subgroups reduce statistical power and increase the likelihood of errors, while multiple comparisons increase the risk of finding statistically significant associations by chance.

Another limitation is that we did not monitor changes in viral load after molnupiravir administration, despite its known effect on reducing viral load. Additionally, the study took place when the Delta variant of the coronavirus was predominant in Slovakia, which could be considered a disadvantage. However, several studies have shown that molnupiravir maintains antiviral effectiveness against various SARS-CoV-2 variants, including

B.1.1.529 (Omicron), B.1.1.7 (Alpha), B.1.351 (Beta), B.1.617.2 (Delta), and P.1 (Gamma). Molnupiravir may prevent the selection of drug-resistant variants and could be effective against current virus variants (24, 25).

We acknowledge that molnupiravir is not currently the preferred treatment for COVID-19 in patients with mild to moderate disease. Nevertheless, we assert its potential therapeutic value, particularly in cases where oral treatments such as nirmatrelvir/ritonavir are contraindicated or when administering parenteral antivirals like remdesivir is impractical due to constraints on healthcare facility resources.

## CONCLUSION

This real-world study supports the findings of previous research, indicating that molnupiravir treatment is associated with a reduced risk of hospitalization and mortality in non-hospitalized, high-risk COVID-19 patients. However, molnupiravir should be considered primarily for patients who cannot use other oral antivirals like nirmatrelvir/ritonavir or parenteral treatments like remdesivir due to contraindications such as drug interactions or severe renal or hepatic insufficiency.

The study highlights obesity as a significant risk factor for both developing viral pneumonia and mortality in patients treated with molnupiravir. Specifically, obesity increased the risk of pneumonia by 4.17 times and mortality by 68.27 times. Additionally, unvaccinated patients had a significantly higher risk of developing viral pneumonia compared to vaccinated individuals, underscoring the importance of vaccination in this patient population.

While this study provides valuable insights, its findings are limited by its single-centre, retrospective design and the lack of a control group. Therefore, further randomized controlled trials are necessary to compare the effectiveness of molnupiravir with standard care or other antiviral treatments, and to confirm these observations in broader patient populations.

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## Conflicts of Interest

None declared

## REFERENCES

1. Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. *Nat Rev Microbiol*. 2021 Mar;19(3):141-54.
2. Yuan Y, Jiao B, Qu L, Yang D, Liu R. The development of COVID-19 treatment. *Front Immunol*. 2023;14:1125246. doi: 10.3389/fimmu.2023.1125246.
3. Maas BM, Strizki J, Miller RR, Kumar S, Brown M, Johnson MG, et al. Molnupiravir: mechanism of action, clinical, and translational science. *Clin Transl Sci*. 2024 Feb;17(2):e13732. doi: 10.1111/cts.13732.
4. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, et al. Molnupiravir for oral treatment of covid-19 in nonhospitalized patients. *N Engl J Med*. 2022 Feb 10;386(6):509-20.
5. Butler CC, Hobbs FDR, Gbinigie OA, Rahman NM, Hayward G, Richards DB, et al. Molnupiravir plus usual care versus usual care alone as

- early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial. *Lancet*. 2023 Jan 28;401(10373):281-93.
6. U. S. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for LAGEVRIO™ (molnupiravir) capsules [Internet]. White Oak: FDA; 2023 [cited 2024 Nov 29]. Available from: <https://www.fda.gov/media/155054/download>.
  7. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. *Am J Respir Crit Care Med*. 2017;195(5):557-82.
  8. Kabinger F, Stiller C, Schmitzová J, Dienemann C, Kocic G, Hillen HS, et al. Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis. *Nat Struct Mol Biol*. 2021;28:740-6.
  9. Vicenti I, Zazzi M, Saladini F. SARS-CoV-2 RNA-dependent RNA polymerase as a therapeutic target for COVID-19. *Expert Opin Ther Pat*. 2021;31(4):325-37.
  10. Paymode DJ, Vasudevan N, Ahmad S, Kadam AL, Cardoso FSP, Burns JM, et al. Toward a practical, two-step process for molnupiravir: direct hydroxylation of cytidine followed by selective esterification. *Org Process Res Dev*. 2021;25(8):1822-30.
  11. Fischer W, Eron JJ, Holman W, Cohen MS, Fang L, Szewczyk LJ, et al. Molnupiravir, an oral antiviral treatment for COVID-19. *medRxiv* [Preprint]. 2021 Jun 17:2021.06.17.21258639. doi: 10.1101/2021.06.17.21258639.
  12. Caraco Y, Crofoot GE, Moncada PA, Galustyan AN, Musungaie DB, Payne B, et al. Phase 2/3 trial of molnupiravir for treatment of covid-19 in nonhospitalized adults. *NEJM Evid*. 2022 Feb;1(2):EVIDoa2100043. doi: 10.1056/EVIDoa2100043.
  13. Suzuki Y, Shibata Y, Minemura H, Nikaido T, Tanino Y, Fukuhara A, et al. Real-world clinical outcomes of treatment with molnupiravir for patients with mild-to-moderate coronavirus disease 2019 during the Omicron variant pandemic. *Clin Exp Med*. 2023 Oct;23(6):2715-23.
  14. Wong CKH, Au ICH, Lau KTK, Cowling BJ, Leung GM. Real-world effectiveness of early molnupiravir or nirmatrelvir-ritonavir in hospitalised patients with COVID-19 without supplemental oxygen requirement on admission during Hong Kong's omicron BA.2 wave: a retrospective cohort study. *Lancet Infect Dis*. 2022 Dec;22(12):1681-93.
  15. Xie Y, Bowe B, Al-Aly Z. Molnupiravir and risk of hospital admission or death in adults with COVID-19: emulation of a randomized target trial using electronic health records. *BMJ*. 2023 Mar 7:380:e072705. doi: 10.1136/bmj-2022-072705.
  16. Sawadogo W, Tsegaye M, Gizaw A, Adera T. Overweight and obesity as risk factors for COVID-19-associated hospitalisations and death: systematic review and meta-analysis. *BMJ Nutr Prev Health*. 2022;5(1):10-8.
  17. Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. *Obesity*. 2020;28(7):1195-9.
  18. Tamara A, Tahapary DL. Obesity as a predictor for a poor prognosis of COVID-19: a systematic review. *Diabetes Metab Syndr*. 2020 Jul-Aug;14(4):655-9.
  19. Silverio A, Di Maio M, Citro R, Esposito L, Iuliano G, Bellino M, et al. Cardiovascular risk factors and mortality in hospitalized patients with COVID-19: systematic review and meta-analysis of 45 studies and 18,300 patients. *BMC Cardiovasc Disord*. 2021 Jan 7;21(1):23. doi: 10.1186/s12872-020-01816-3.
  20. Cheng SL, Wang PH, Chang CY, Wang HH, Wang CJ, Chiu KM. The benefits of molnupiravir treatment in healthcare facilities patients with COVID-19. *Drug Des Devel Ther*. 2023 Jan 19;17:87-92.
  21. Arbel R, Wolff Sagy Y, Battat E, Lavie G, Sergienko R, Friger M, et al. Molnupiravir use and severe COVID-19 outcomes during the omicron surge. *Res Sq* [Preprint]. 2022 Sep 29:rs.3.rs-2115769. doi: 10.21203/rs.3.rs-2115769/v1.
  22. Weil C, Bergroth T, Eisenberg A, Whiteside YO, Caraco Y, Tene L, et al. Real-world utilization of molnupiravir during the COVID-19 omicron surge in Israel. *Epidemiologia*. 2023;4(3):309-21.
  23. Kimata M, Watanabe A, Yanagida Y, Kinoshita D, Maekawa S. Safety and effectiveness of molnupiravir (LAGEVRIO®) capsules in Japanese patients with COVID-19: interim report of post-marketing surveillance in Japan. *Infect Dis Ther*. 2023 Apr;12(4):1119-36.
  24. Ohashi H, Hishiki T, Akazawa D, Kim KS, Woo J, Shionoya K, et al. Different efficacies of neutralizing antibodies and antiviral drugs on SARS-CoV-2 Omicron subvariants, BA.1 and BA.2. *Antiviral Res*. 2022 Sep;205:105372. doi: 10.1016/j.antiviral.2022.105372.
  25. Rosenke K, Okumura A, Lewis MC, Feldmann F, Meade-White K, Bohler WF, et al. Molnupiravir (MK-4482) is efficacious against Omicron and other SARS-CoV-2 variants in the Syrian hamster COVID-19 model. *bioRxiv* [Preprint]. 2022 Feb 23:2022.02.22.481491. doi: 10.1101/2022.02.22.481491.

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