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MAJOR ARTICLE

Real Clinical Effectiveness of Molnupiravir Against 30-day Mortality Among 74 541 SARS-CoV-2–Positive Patients: A Nationwide Cohort Study From the Czech Republic

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Background. We examined the clinical effectiveness of molnupiravir in reducing deaths in a real-world cohort of adult patients with COVID-19 during the Omicron outbreak.

Methods. This was a population-wide retrospective cohort study in the Czech Republic. We analyzed all 74 541 patients with an officially registered diagnosis of SARS-CoV-2 infection between 1 January and 31 December 2022, aged 18 years or older, treated with molnupiravir. The primary outcome was 30-day all-cause mortality; the secondary outcome was 30-day COVID-19-related mortality. Hazard ratios (HRs) were estimated using stratified Cox regression and the Fine-Gray model.

Results. The use of molnupiravir in adult SARS-CoV-2 positive patients was associated with a lower risk of both 30-day all-cause mortality: adjusted HR 0.58 (95% confidence interval, 0.53–0.64; $P < .001$) and 30-day COVID-19–related mortality: adjusted HR 0.50 (95% confidence interval, 0.42–0.58; $P < .001$). The effect of molnupiravir was highly significant regardless of sex, Deyo-Charlson Comorbidity Index score, hospitalization status, COVID-19 vaccination status, and patients older than age 65 years.

Conclusions. In this cohort study, early initiation of molnupiravir was associated with a significant reduction in 30-day all-cause and COVID-19–related mortality in adult SARS-CoV-2 positive patients.

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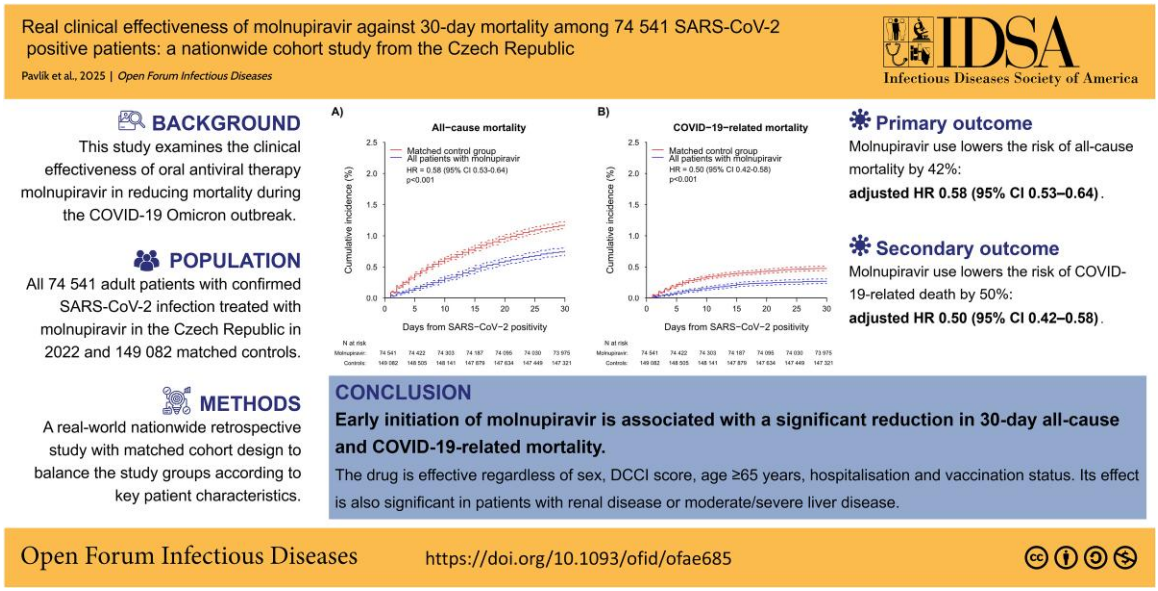
Graphical Abstract



This graphical abstract is also available at Tidbit: https://tidbitapp.io/tidbits/real-clinical-effectiveness-of-molnupiravir-against-30-day-mortality-among-74-541-sars-cov-2-positive-patients-a-nationwide-cohort-study-from-the-czech-republic

Keywords. 30-day all-cause mortality; COVID-19; COVID-19-related mortality; molnupiravir; SARS-CoV-2 infection.

Since the very beginning of the SARS-CoV-2 pandemic, a pressing need has arisen for effective protection and therapy to reduce the health burden. Vaccines have been shown to significantly reduce the number of COVID-19–related hospitalizations and deaths before and after the emergence of the SARS-CoV-2 Omicron (B.1.1.529) variant [1–3].

In addition, oral antiviral therapy (AVT), including molnupiravir (Lagevrio [Merck]) and nirmatrelvir plus ritonavir (Paxlovid [Pfizer]), has shown efficacy in reducing hospitalization rate and mortality in both randomized clinical trials (RCTs) of unvaccinated adult patients with COVID-19 [4, 5] and a meta-analysis [6]. Both oral antivirals have also shown effectiveness in reducing mortality risk and in-hospital disease progression in patients with COVID-19 in real-world settings [7–10]. However, some inconsistencies remain as not all RCTs have shown a benefit of molnupiravir against hospitalization and death [11].

Although RCTs are the gold standard for drug efficacy assessment, their findings may not apply to real-world populations because they usually focus on selected patients who differ from the real population in routine clinical practice [12]. An example is the PANORAMIC study [11], which included relatively younger and predominantly fully vaccinated patients. Evans et al. demonstrated that the PANORAMIC study results are not fully generalizable to the population level when they showed the effectiveness of molnupiravir against all-cause mortality in similarly aged and vaccinated patients at higher risk of hospitalization and death [13]. Other observational studies with molnupiravir focused primarily on elderly patients with comorbidities, showing effectiveness of molnupiravir in both vaccinated and unvaccinated hospitalized patients [9, 14], as well as vaccinated and unvaccinated ambulatory patients [7, 8, 15].

Of the 2 oral AVTs mentioned, the combination of nirmatrelvir plus ritonavir is far more widely used in patients with COVID-19 who are at high risk of hospitalization or progression to severe disease, because molnupiravir is not licensed for use in most European countries [16]. However, the combination of nirmatrelvir plus ritonavir has numerous drug interactions that contraindicate its use, particularly in patients with severe renal or hepatic impairment [17]. The contraindications to nirmatrelvir plus ritonavir mainly affect older patients with poorer health status, who are at the highest risk for a severe course of COVID-19. Therefore, it is important to evaluate the effectiveness of molnupiravir, particularly in real-world patients with comorbidities that may contraindicate the treatment with nirmatrelvir plus ritonavir. Such an evaluation is even more critical as many of these high-risk patients are not vaccinated [18, 19].

In this population-wide cohort study, we evaluated the association of molnupiravir use with the risk of death from any cause among all adult SARS-CoV-2 positive patients in the Czech Republic during the Omicron wave of the SARS-CoV-2 epidemic from January to December 2022.

METHODS

Study Design and Data Sources

We conducted a population-wide retrospective cohort study of all patients aged 18 years or older with confirmed SARS-CoV-2

infection who were treated with molnupiravir during the Omicron wave in the Czech Republic. The study period was from 1 January to 31 December 2022, with patient follow-up until 31 January 2023. During this period, the SARS-CoV-2 Omicron variant dominated in the Czech Republic, with the primary circulating strains changing from B.1.1.529 to BA.2, then to BA.4/BA.5, and finally to XBB/XBB.1.5 [20, 21].

We obtained population data on COVID-19 from the Czech National Information System of Infectious Diseases (ISID), which contains records of all individuals who tested positive for SARS-CoV-2 (defined as laboratory-confirmed positive real-time polymerase chain reaction test or positive rapid antigen test performed by a medical professional) in the Czech Republic since the beginning of the COVID-19 pandemic [22]. We analyzed information on demographic characteristics, dates of SARS-CoV-2 positivity, COVID-19 vaccination, patient's death from any cause, and selected procedures and drugs. The ISID database is operated by the Institute of Health Information and Statistics of the Czech Republic (IHIS). ISID data are routinely collected under Act No. 258/2000 Coll. on the Protection of Public Health and have previously been used for observational studies investigating the effectiveness of vaccination against COVID-19 at the population level [3, 23]. Information on patient deaths in ISID was verified against information on deaths and their cause available from the Death Certificate Information System [24].

Information on patients' comorbidities and hospitalizations was obtained from the National Register of Reimbursed Health Services (NRRHS), which contains data on all health services covered by Czech public health insurance [25]. We retrieved information on comorbidities defining the Deyo-Charlson Comorbidity Index (DCCI) including renal and liver diseases, which may represent potential contraindications to treatment with nirmatrelvir plus ritonavir. Comorbidities were determined based on International Classification of Diseases 10th Revision diagnoses. Supplementary Table 1 outlines the conditions covered by the DCCI score, their definitions, weights, and the principle of DCCI score calculation.

According to the clinical management guidelines for COVID-19 issued by the Czech Ministry of Health, patients were recommended to receive molnupiravir if they (1) were at risk of progression to severe disease (ie, meeting at least one of the following criteria: age ≥65 years; body mass index ≥35 kg/m^2; age ≥55 years and either arterial hypertension or body mass index ≥30 kg/m^2; chronic kidney disease 3–5, cirrhosis hepatitis; diabetes mellitus treated with oral antidiabetic drugs or insulin; primary or secondary immunodeficiency; chronic lung disease; thrombophilic disorder; neurological disorder affecting respiration; other serious health conditions contributing to the severity of COVID-19) (2), had mild symptoms (patient's clinical condition did not require hospitalization or therapeutic oxygen administration for COVID-19), and (3) were at an early stage of the disease (within 7 days of SARS-CoV-2 positivity) [26].

We excluded patients younger than age 18 years, reinfections within 2022 (defined in the Czech Republic as a new positive test result 60 days after a previous infection), invalid cases after validation from multiple data sources (mainly foreigners), patients who were prescribed molnupiravir 8 or more days after SARS-CoV-2 positivity, and those dead on or before the date of SARS-CoV-2 positivity. We also excluded patients who received other AVT available for treating SARS-CoV-2 infection (nirmatrelvir plus ritonavir, remdesivir).

We used a matched cohort design to balance the study groups according to key patient characteristics. To adjust for potential immortal-time bias, we sequentially matched controls to molnupiravir-treated patients with respect to their time from SARS-CoV-2 positivity to initiation of molnupiravir, which is consistent with the procedure applied within the target trial emulation framework (Supplementary Figure 1). Thus, only an untreated patient who lived at least 4 days after his or her date of SARS-CoV-2 positivity could be matched to a treated patient who started molnupiravir 3 days after the date of SARS-CoV-2 positivity as a control. For treated patients, an index date was set as the date of molnupiravir treatment initiation. Untreated persons were assigned an index date that was the same number of days after the date of the positive SARS-CoV-2 test as the treatment date of the matched molnupiravir-treated patients. Each patient with confirmed SARS-CoV-2 infection who received molnupiravir was randomly matched to 2 control patients. The control group was selected from patients with confirmed SARS-CoV-2 infection who did not receive oral AVT during the observation period.

The director of the IHIS has granted that the retrospective analyses presented in this paper do not require ethical approval because the study data comes from the mandatory monitoring of infectious diseases and reimbursed healthcare in the Czech Republic. We followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline for cohort studies.

Outcomes

The primary outcome of our study was 30-day all-cause mortality calculated from the index date. The secondary outcome was 30-day COVID-19–related mortality. Each patient was followed up until death, outcome event, or end of the observational period (31 January 2023), whichever came first.

Statistical Analysis

The primary population for the analysis was defined as patients treated with molnupiravir from 1 January to 31 December 2022, and their respective controls matched at a 1:2 ratio. To define the control group of patients without AVT (molnupiravir, nirmatrelvir plus ritonavir, remdesivir), we used exact

matching without replacement in the retrospective cohort design, conditional on age categories (18–49, 50–64, 65+ years), sex, date of confirmed SARS-CoV-2 infection, hospitalization status (at the day of SARS-CoV-2 positivity), vaccination status (fully vaccinated patients were defined as those with at least 1 booster dose, ie, ≥ 3 vaccine doses), and categories of the DCCI.

We calculated cumulative incidences using the Aalen-Johansen method to estimate the probabilities of the specified outcomes within 30 days of SARS-CoV-2 positivity. In addition, hazard ratios (HRs) with 95% confidence intervals (CIs) for the primary outcome between molnupiravir users and their matched controls were estimated using multiple stratified Cox regression model. As the matching achieved an exact balance between the 2 study groups for sex, vaccination status, and hospitalization status, all 3 variables represented strata in the Cox model. However, using age and DCCI categories in the matching algorithm did not result in perfectly balanced groups by age and DCCI, so we included both variables in the Cox model to adjust the HR estimates. We assessed the proportional hazards assumption using Schoenfeld residuals against transformed time. The Fine-Gray model was employed for secondary outcome assessment with death from causes other than COVID-19 treated as competing risks. Patients without the event of interest were censored at 31 days from the index date. Statistical significance was set at $P < .05$.

To assess the robustness of our results, we performed 3 subgroup analyses. First, to explore potential differences in the effectiveness of molnupiravir across different demographic and clinical categories with different baseline risks of COVID-19–related death, we stratified the primary endpoint analysis by age, sex, DCCI, COVID-19 vaccination status, and hospitalization status. Second, to address the potential waning effect of molnupiravir treatment, we performed a subgroup analysis of both outcomes based on the number of days from SARS-CoV-2 positivity to molnupiravir treatment initiation. Third, to assess the effectiveness of molnupiravir in a high-risk patient population, we conducted a subgroup analysis in patients with renal disease or moderate or severe liver disease (International Classification of Diseases 10th Revision code definition is included in the Supplementary Table 1).

IBM SPSS Statistics software was used for data management. All statistical analyses were performed using the R software, version 4.2.2 (R Foundation).

RESULTS

Patients

We identified 1 595 127 adult patients with confirmed SARS-CoV-2 infection during the Omicron wave in the Czech Republic between 1 January 2022 and 31 December 2022 who were eligible for the analysis. In total, 74 541 patients (4.7%) received molnupiravir, while the remaining 1 520 586 patients without antiviral therapy form a set for the definition of control groups (Figure 1), of which 149 082 matched controls were identified (Supplementary Figure 1).

Comparison of demographic and clinical characteristics between the molnupiravir and the control groups before and after matching is shown in Table 1. Before matching, molnupiravir-treated patients were much older, more likely to be vaccinated, and more likely to have higher frequency of underlying comorbidities. After matching, all differences between the molnupiravir and control groups were balanced.

Primary and Secondary Outcomes

The cumulative incidences of both primary and secondary outcomes in all molnupiravir patients and their respective control group are shown in Figure 2.

The cumulative incidence rates of 30-day all-cause mortality were 0.76% (95% CI, 0.70–0.82) in patients treated with molnupiravir and 1.18% (95% CI, 1.13–1.24) in matched controls, with an absolute risk difference of −0.42% points (Table 2, Figure 2*A*). Molnupiravir use was associated with a significantly lower risk of all-cause mortality: adjusted HR 0.58 (95% CI, 0.53–0.64; $P < .001$).

For the secondary outcome of COVID-19–related mortality, adjusted for death from other causes as competing risks, molnupiravir use was associated with a significantly lower risk of COVID-19–related death: the cumulative incidence rates were 0.28% (95% CI, 0.24–0.31) in molnupiravir patients and 0.48% (95% CI, 0.44–0.51) in the control group; the absolute risk difference was −0.20% points (Table 2, Figure 2*B*). The adjusted HR was 0.50 (95% CI, 0.42–0.58; $P < .001$).

Subgroup Analyses

In subgroup analyses, we found no significant interaction between molnupiravir treatment and vaccination status for either outcome, suggesting no reduction in the effectiveness of molnupiravir with respect to vaccination (Table 2). The cumulative incidences of both primary and secondary outcomes according to vaccination status in molnupiravir patients and their respective control group are shown in Figure 3.

Molnupiravir-treated patients also had a lower risk of both all-cause and COVID-19–related mortality compared with their matched controls regardless of sex, DCCI score, and hospitalization status (Table 2). For sex and hospitalization status, however, we saw significantly different levels of molnupiravir effectiveness, with greater risk reduction in both all-cause and COVID-19–related mortality among women and hospitalized patients.

We observed a different effect of molnupiravir against both outcomes across patient age groups; namely, no significant benefit of molnupiravir in patients aged ≤ 64 years but a highly significant effect in patients aged 65 years and above (Table 2).

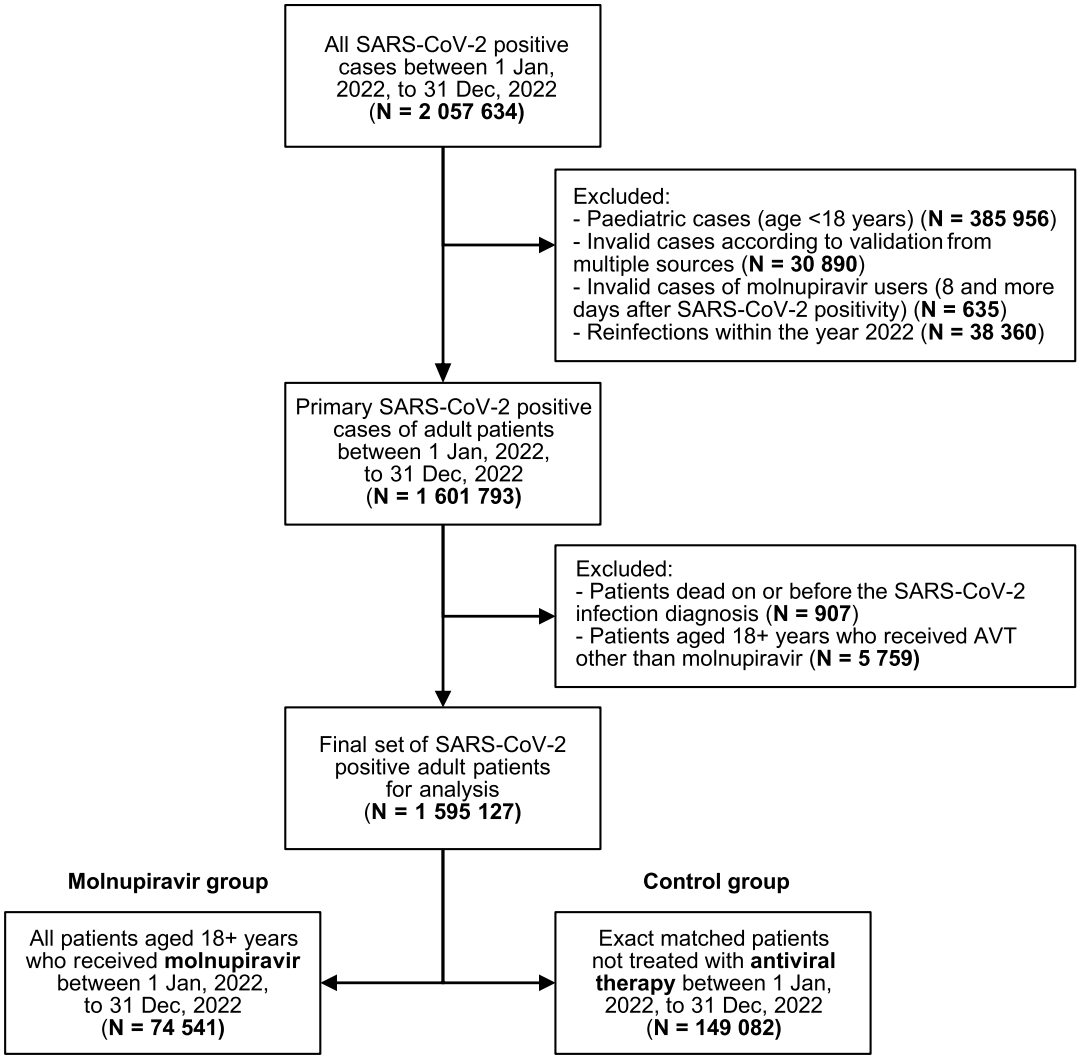


Figure 1. Study flow diagram and definition of patient subsets according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

In the analysis based on the number of days from SARS-CoV-2 positivity to molnupiravir initiation, we found a similar risk reduction in all-cause mortality and COVID-19–related mortality in patients who started molnupiravir 0–1 days after SARS-CoV-2 positivity and patients who started molnupiravir 2–3 days after SARS-CoV-2 positivity as in the whole study cohort (Supplementary Figure 2A-D). On the other hand, we observed no significant benefit of molnupiravir in patients who started molnupiravir 4–7 days after SARS-CoV-2 positivity (Supplementary Figure 2E-H).

Patients with renal disease or moderate or severe liver disease had about 3 times higher all-cause mortality rate than the overall cohort: the cumulative incidence rates of all-cause mortality were 2.30% (95% CI, 1.98–2.62) in molnupiravir-treated patients and 3.96% (95% CI, 3.61–4.30) in matched controls, with an absolute risk difference of −1.66% points (Supplementary Figure 3). Also, in these patients, molnupiravir showed a significant reduction in the risk of both all-cause and COVID-19–related mortality: adjusted HR 0.58 (95% CI, 0.49–0.68; $P < .001$) and 0.46 (95% CI, 0.35–0.62; $P < .001$), respectively.

DISCUSSION

In this retrospective cohort study of adult SARS-CoV-2 positive patients during the Omicron wave of the SARS-CoV-2 epidemic, early initiation of molnupiravir was associated with a significant reduction in both 30-day all-cause mortality and COVID-19–related mortality in adult patients with an officially reported SARS-CoV-2 positivity. In addition, molnupiravir was effective regardless of sex, DCCI score, age in patients older than age 65 years, hospitalization status, and COVID-19 vaccination status.

Our study has several strengths. To our knowledge, this study includes the largest population-based molnupiravir-treated

Table 1. Demographic and Clinical Characteristics of the Analyzed Cohort of Patients

Clinical Characteristics	Patients Without AVT Eligible for the Definition of Control Group (N = 1 520 586)		All Patients Treated With Molnupiravir (N = 74 541)		Matched Control Group of Patients Without AVT (N = 149 082)		Pre-match SMD	Post-match SMD
	Mean	SD	Mean	SD	Mean	SD		
Age (y)	45.2	15.8	68.7	12.6	67.1	12.9	1.65	0.12
	N	%	N	%	N	%	…	…
Age categories (y)								
≤64	1 329 935	87.5%	22 286	29.9%	44 572	29.9%	…	…
65–79	149 896	9.9%	39 162	52.5%	84 779	56.9%	1.44	0.13
80+	40 755	2.7%	13 093	17.6%	19 731	13.2%	…	…
Sex								
Women	828 434	54.5%	42 725	57.3%	85 450	57.3%	0.06	0
Men	692 152	45.5%	31 816	42.7%	63 632	42.7%	…	…
DCCI score								
0–4	1 457 066	95.8%	58 098	77.9%	121 005	81.2%	…	…
5–6	40 157	2.6%	10 283	13.8%	18 185	12.2%	0.55	0.08
7+	23 363	1.5%	6 160	8.3%	9 892	6.6%	…	…
Vaccination status								
Without booster dose (0–2 doses)	1 085 525	71.4%	20 128	27.0%	40 256	27.0%	0.99	0
At least one booster dose (3 + doses)[a]	435 061	28.6%	54 413	73.0%	108 826	73.0%	…	…
Hospital status								
Outpatient	1 470 876	96.7%	70 879	95.1%	141 758	95.1%	0.08	0
Inpatient	49 710	3.3%	3 662	4.9%	7 324	4.9%	…	…
Comorbidities								
Diabetes	151 755	10.0%	26 788	35.9%	47 310	31.7%	0.65	0.09
Chronic lung disease	224 345	14.8%	21 321	28.6%	38 213	25.6%	0.34	0.07
Cancer	77 896	5.1%	15 456	20.7%	28 133	18.9%	0.48	0.05
Cerebrovascular disease	70 959	4.7%	12 653	17.0%	24 459	16.4%	0.40	0.02
Heart failure	39 496	2.6%	9 041	12.1%	13 994	9.4%	0.37	0.09
Renal disease	34 653	2.3%	8 084	10.8%	11 788	7.9%	0.35	0.10
Mild liver disease	80 817	5.3%	7 647	10.3%	15 058	10.1%	0.19	0.01
Moderate or severe liver disease	2 603	0.2%	392	0.5%	695	0.5%	0.06	0.01

Abbreviations: AVT, antiviral therapy; SD, standard deviation; SMD, standardized mean difference.

[a]At least 30 days since the first booster dose.

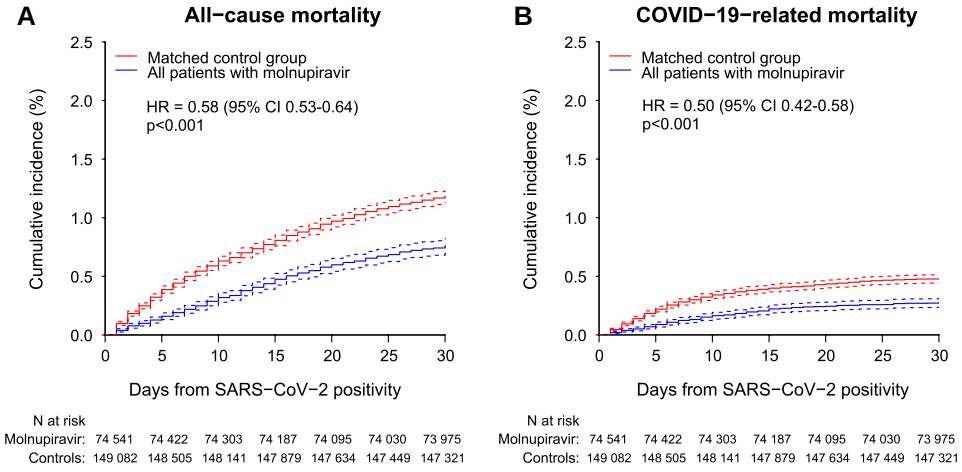


Figure 2. Cumulative incidence plots: All-cause mortality (*A*) and COVID-19–related mortality (*B*) for all molnupiravir patients versus their matched controls.

Table 2. Subgroup Analyses of all-cause Mortality and COVID-19–related Mortality in Molnupiravir Patients vs Respective Matched Control Group Without Antiviral Therapy

	All-cause Mortality						COVID-19–related Mortality					
	All Patients Treated With Molnupiravir (N = 74 541)		Matched Control Group of Patients Without Antiviral Therapy (N = 149 082)				All Patients Treated With Molnupiravir (N = 74 541)		Matched Control Group of Patients Without Antiviral Therapy (N = 149 082)			
Population Groups	Number of Deaths	Cumulative Incidence[b] (%)	Number of Deaths	Cumulative Incidence[b] (%)	Adjusted HR[a] (95% CI)	*P* Value for Interaction	Number of COVID-19–related Deaths	Cumulative Incidence[b] (%)	Number of COVID-19–related Deaths	Cumulative Incidence[b] (%)	Adjusted HR[a] (95% CI)	*P* Value for Interaction
Overall	566	0.76%	1761	1.18%	0.58 (0.53–0.64)	…	205	0.28%	714	0.48%	0.50 (0.42–0.58)	…
Age												
≤ 64	45	0.20%	78	0.17%	1.11 (0.77–1.60)	.003	14	0.06%	23	0.05%	1.14 (0.59–2.21)	.051
65–79	194	0.50%	649	0.77%	0.60 (0.51–0.70)	.35	69	0.18%	256	0.30%	0.56 (0.43–0.73)	.15
80+	327	2.50%	1034	5.24%	0.54 (0.48–0.62)		122	0.93%	435	2.20%	0.44 (0.36–0.53)	
Sex												
Women	233	0.55%	866	1.01%	0.50 (0.43–0.58)		81	0.19%	325	0.38%	0.44 (0.35–0.57)	
Men	333	1.04%	895	1.41%	0.67 (0.59–0.75)	.004	124	0.39%	389	0.61%	0.53 (0.43–0.65)	.28
DCCI score												
0–4	268	0.46%	855	0.71%	0.60 (0.52–0.69)		95	0.16%	341	0.28%	0.49 (0.39–0.62)	
5–6	158	1.54%	463	2.55%	0.62 (0.52–0.74)	.74	55	0.53%	174	1.09%	0.47 (0.35–0.63)	.80
7+	140	2.27%	443	4.48%	0.53 (0.44–0.64)	.25	55	0.89%	199	1.76%	0.54 (0.40–0.73)	.51
Vaccination status												
Without booster dose (0–2 doses)	242	1.20%	740	1.84%	0.59 (0.51–0.68)		95	0.47%	347	0.86%	0.46 (0.37–0.58)	
At least 1 booster dose (3+ doses)[c]	324	0.60%	1 021	0.94%	0.58 (0.51–0.66)	.91	110	0.20%	367	0.34%	0.52 (0.42–0.64)	.48
Hospital status												
Outpatient	278	0.39%	739	0.52%	0.66 (0.58–0.76)	.015	103	0.15%	267	0.19%	0.69 (0.55–0.87)	.006
Inpatient	288	7.86%	1022	13.95%	0.53 (0.46–0.60)		102	2.79%	447	6.10%	0.44 (0.36–0.55)	

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]HRs lower than 1 or greater than 1 indicate that molnupiravir-treated patients had a lower or higher risk of the outcome than the matched control group.

[b]At 30 days from start of molnupiravir treatment.

[c]At least 30 days since the first booster dose.

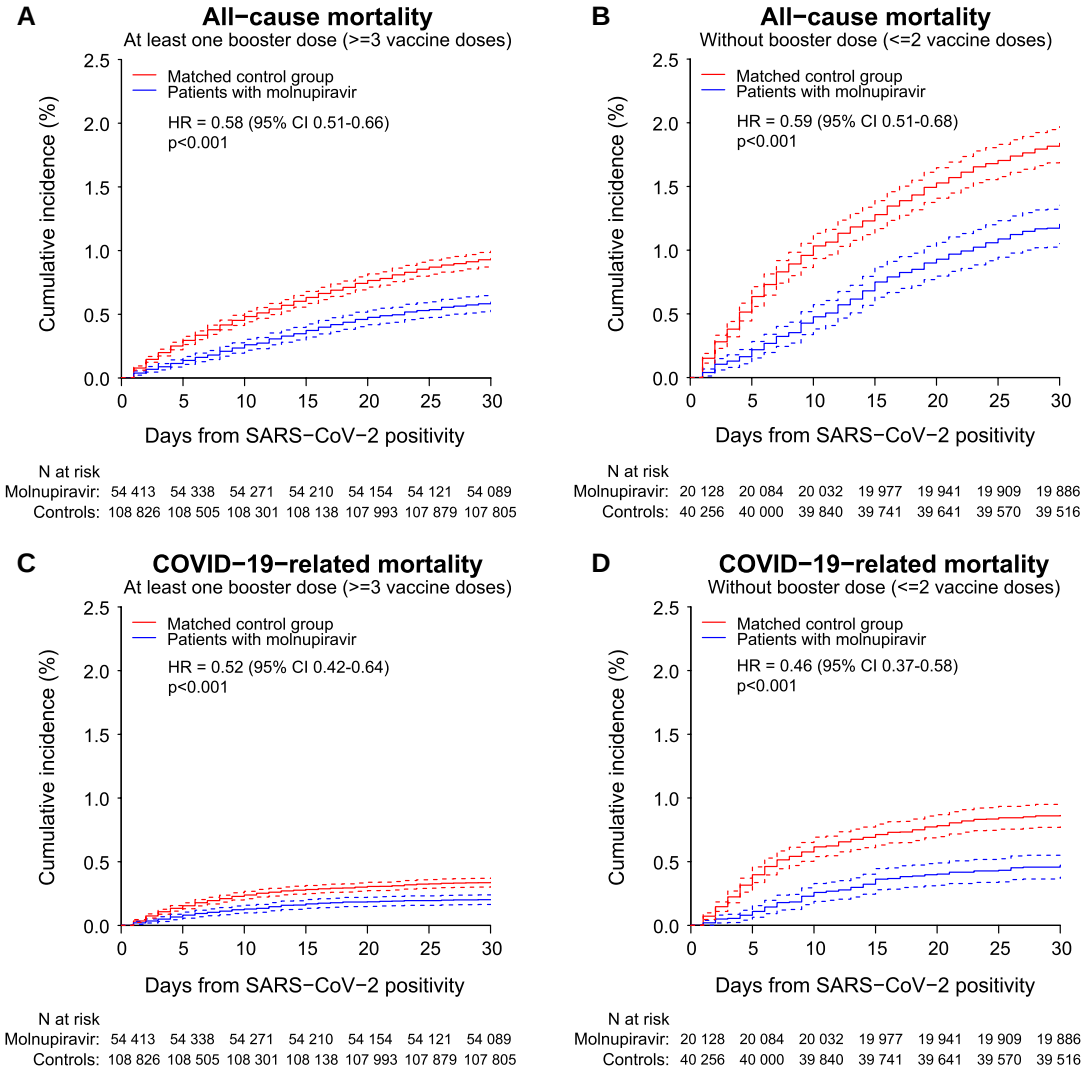


Figure 3. Cumulative incidence plots: all-cause mortality (*A, B*) and COVID-19–related mortality (*C, D*) for molnupiravir patients versus their matched controls according to vaccination status.

patients analyzed to date. Moreover, our study was conducted in a single healthcare system. We used data from the national healthcare databases of the IHIS with 100% coverage of the Czech population to collect information on diagnosis codes, drug prescription records, COVID-19 history, vaccination records, hospitalization records, and death records. In addition, data on primary and secondary outcomes were validated against additional data sources. These data allowed us to estimate the risk of death and COVID-19–related mortality in a clinically meaningful way.

Two relevant RCTs were conducted to assess the risk reduction of hospitalization or death in nonhospitalized adult patients with COVID-19 treated with molnupiravir. However, their results remain inconsistent. First, the landmark phase 3 MOVe-OUT trial reported that molnupiravir, when initiated within 5 days of symptom onset, significantly reduced the risk of all-cause hospitalization or death up to day 29 in unvaccinated patients with COVID-19 (HR 0.11 for death vs 0.58 in our study for all molnupiravir patients) [4]. Second, the PANORAMIC study showed that molnupiravir use was not associated with a lower risk of death in vaccinated, nonhospitalized patients [11], raising questions about the real-world effectiveness of molnupiravir in the Omicron era.

Our study is not directly comparable with either of these studies. In the first case, our results cannot be adequately compared with respect to the SARS-CoV-2 variant. In the MOVe-OUT trial, most participants were infected with the Delta variant; in contrast, our cohort includes predominantly patients infected with the Omicron variant with a generally different (lower) case fatality rate [27]. In the latter case, our results may differ substantially because of the different age structure, the proportion of high-risk patients, and the

vaccination status of the patients. In the PANORAMIC trial, molnupiravir-treated patients were, on average, aged 56.7 years (with only 6% older than 75 years), and 95% received at least 3 doses of COVID-19 vaccine, as reported by Butler and colleagues. Our study includes much older patients (mean age 68.7 years, 35% older than 75 years), of whom only 73% are fully vaccinated. Supplementary Tables 2 and 3 summarize the key differences between our study and the PANORAMIC and the MOVe-OUT trials, respectively.

In contrast to both studies, we focus primarily on death as the ultimate endpoint (without combining it with hospitalizations) in a nonselective population of SARS-CoV-2–confirmed patients, including both inpatient and outpatient cases. In addition, our nationwide real-world study provides robust results supported by sufficient sample size to assess the effectiveness of molnupiravir even for low-incidence endpoints and clinically relevant patient subgroups.

Several observational and trial emulation studies have evaluated the effectiveness of molnupiravir against mortality during the Omicron wave [7–10, 14, 28–30]. The first 7 studies reported that molnupiravir reduced all-cause mortality in both outpatient [7, 8, 10, 28] and inpatient [9, 14, 29] settings. In addition, the 10th study by Lui et al. showed that molnupiravir was associated with a lower mortality risk in patients with COVID-19 and type 2 diabetes [30]. The HRs for all-cause mortality reported in these studies ranged from 0.23 (95% CI, 0.16–0.34) to 0.76 (0.95% CI, 0.61–0.95) for the outpatient use of molnupiravir and from 0.23 (95% CI, 0.18–0.30) to 0.87 (0.95% CI, 0.81–0.93) for inpatient use.

To supplement their findings, our population-based study demonstrates the efficacy of molnupiravir in a nonselective population with a high proportion of old and other high-risk patients, who were excluded from some of the previous studies [7, 9, 14]. This is particularly appealing in the European population, including the Czech population, whose aging and obesity significantly increase the risk of chronic diseases, and which has been so severely affected by the COVID-19 pandemic in the past [31]. Furthermore, our analysis highlights the need for early initiation of molnupiravir treatment. Although we observed a significant reduction in all-cause and COVID-19-related mortality in patients who started molnupiravir within 3 days of SARS-CoV-2 positivity, no significant effect against death was seen in those who started treatment 4 or more days after testing positive.

Limitations

Nevertheless, this study has several limitations. First, it is not an RCT; therefore, bias from the study's observational nature might have affected our results. We attempted to minimize confounding biases by (1) performing a population-based analysis using sequential exact matching of the study groups according to patient's sex, age category, DCCI score, vaccination status, and hospitalization status and (2) adjusting our HR estimates for age and DCCI score, for which it was not possible to ensure complete balance between the study groups. Second, although the ISID database had population-wide coverage and records on all patients with confirmed SARS-CoV-2 infection in the Czech Republic were analyzed, we cannot rule out a self-ascertainment bias. Some patients with SARS-CoV-2 infection may not have been reported in the database because of deliberate refusal of testing or, to a lesser extent, suboptimal laboratory results [32]. Third, our study does not include individuals who exclusively used at-home testing. Based on US data, the percentage of individuals with confirmed SARS-CoV-2 infection who used only at-home testing was reported to be approximately 10%–20% during the Omicron era [33, 34]. However, these patients were younger and less likely to develop severe course of COVID-19 [33]. We believe that these patients do not represent a significant source of bias for our study because, as younger patients had a lower risk of severe COVID-19, they would not be included in our control group. Fourth, the NRRHS administrative data are used primarily for billing purposes and thus may not contain data on all health conditions of the patients analyzed. Therefore, another limitation of our study is the limited record of potential comorbidities of individual patients, as the NRRHS data may not contain information on diseases that are not being treated in the patient. Fifth, indication bias in prescribing molnupiravir could not be excluded. In addition, that molnupiravir was available throughout the whole study period and nirmatrelvir plus ritonavir only from June 2022 might play a role. However, our study did not aim to compare the effect of the two oral antiviral therapies.

CONCLUSION

In this retrospective cohort study using population-based data from the Czech Republic during the Omicron era of the COVID-19 pandemic, the early administration of molnupiravir was associated with reduced risk of both all-cause and COVID-19–related mortality among all adult SARS-CoV-2–positive patients. The effect of molnupiravir was highly significant regardless of sex, DCCI score, hospitalization status, COVID-19 vaccination status, and patients older than age 65 years.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. T.P., J.J., and L.D. designed the study, performed the data analysis, and wrote the first draft. J.J. and O.Š. processed the data from the database. M.K.V., P.D., V.Č., P.Š., and V.V. interpreted the results

and co/wrote the manuscript. All authors have read, edited, and approved the final manuscript.

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