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Coronavirus Pandemic

Molnupiravir's real-world effectiveness in COVID-19 outpatients at high risk of severe disease: a single-center study

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Abstract

Introduction: The coronavirus disease 2019 (COVID-19) pandemic started in March 2020. Since then, there has been an urgent need for effective therapeutic methods to manage the disease. We aimed to assess the effectiveness of molnupiravir in reducing the need for hospitalization in at-risk, non-hospitalized COVID-19 patients.

Methodology: This was a single-center, non-randomized, observational retrospective study of non-hospitalized patients with confirmed COVID-19, treated at the Clinic for Infectious and Tropical Diseases, University Clinical Center in Belgrade, Serbia.

Results: The study was conducted between 15 December 2021 and 15 February 2022 and included 320 patients. Of these, 165 (51.6%) received treatment with molnupiravir. The study and control groups were similar in gender and age distribution. The study group had a higher proportion of vaccination (75.2% vs. 51%, $p < 0.001$). There was no statistically significant difference in presence of comorbidity within the groups. Majority of the patients who received molnupiravir did not require hospitalization; and this was statistically significant in comparison to control group (92.7 vs. 24.5%, $p < 0.001$). Oxygen supplementation was less frequently required in the study group compared to the control group (0.6% vs. 31%, $p < 0.001$). During the follow-up period of 12.12 ± 3.5 days, significantly less patients from the study group were admitted to the intensive care unit ($p < 0.001$). Molnupiravir significantly reduced the risk of hospitalization by 97.9% (HR 0.021; 95% CI 0.005-0.089; $p < 0.001$).

Conclusions: Molnupiravir is an effective therapy in preventing the development of severe forms of COVID-19 and hospitalization.

Key words: molnupiravir; COVID-19; therapy; hospitalization; comorbidities.

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Introduction

The World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19), caused by severe-acute-respiratory-syndrome-related-coronavirus-2 (SARS-CoV-2), a pandemic at the beginning of March 2020 [1]. The clinical appearance varied from mild to severe, and led to a substantial increase in morbidity and mortality worldwide. Many patients, especially the elderly and those with pre-existing illnesses (e.g., obesity, diabetes mellitus, and major heart problems), required hospitalization, and many died as a result of respiratory failure, shock, and multiple organ failure [2-4]. The genetic diversity of the virus presented an additional challenge; successive variants differed not only in infectivity and pathogenicity but also in antiviral medication effectiveness. There has been an urgent need for effective forms of therapy to reduce the global health burden since the outbreak.

Many clinical trials have shown that treatment should begin as soon as possible after the onset of symptoms and that it should ideally be readily available and easily administered by the patients themselves [5,6]. It takes time to develop a new medicine; therefore, researchers have focused their efforts on repurposing existing pharmaceuticals for new applications. Molnupiravir, an antiviral medication that was initially studied in preclinical studies with influenza, has risen to prominence during this time [7,8]. Molnupiravir is a polymerase inhibitor prodrug that acts as a synthetic nucleoside. It is orally administered, and it is used to treat COVID-19 because it facilitates therapy in the out-of-hospital setting [9,10]. Based on the phase two and three MOVe-OUT clinical study in non-hospitalized patients with SARS-CoV-2 infection, the Food and Drug Administration (FDA) approved molnupiravir for emergency use in the treatment of mild to moderate SARS-CoV-2 illness in

December 2021 [11]. This study showed that early treatment with molnupiravir reduces the risk of hospitalization or death in at-risk, unvaccinated adults with COVID-19 [11].

Our study aimed to assess the real-world effectiveness of molnupiravir in reducing the need for hospitalization in at-risk, non-hospitalized patients with confirmed COVID-19.

Methodology

In this single-center, non-randomized, observational retrospective study, we included data from the electronic medical database Heliant for non-hospitalized patients treated at the Clinic for Infectious and Tropical Diseases, University Clinical Center in Belgrade, Serbia [12]. We included patients treated between 15 December 2021, and 15 February 2022, which is considered the period of dominance of the Omicron SARS-CoV-2 variant in Serbia. The decision about the treatment regimen was taken entirely by the treating physician, concerning current knowledge and recommendations of the National Protocol of Serbia for COVID-19 [13]. All the patients were diagnosed with COVID-19 based on positive results of the real-time reverse transcriptase polymerase chain reaction (RT-PCR) or an antigen test from the nasopharyngeal swab specimen. All the patients were non-hospitalized adults aged ≥ 18 years, with mild or moderate COVID-19, and with associated risk factors for the development of severe illness from COVID-19 (age > 60 years; active cancer; chronic kidney disease; chronic obstructive pulmonary disease; obesity, defined by a body mass index (weight in kilograms divided by square of the height in meters) of 30; serious heart conditions [heart failure, coronary artery disease, or cardiomyopathies]; or diabetes mellitus). Mild or moderate illness was determined on the basis of definitions adapted based on WHO guidance [1]. According to the National Protocol of Serbia for COVID-19, molnupiravir may be used for the treatment of mild-to-moderate COVID-19 in people 18 years of age or older, who are at risk for progression to severe COVID-19, including hospitalization or death, and for whom other COVID-19 treatment options are not available [13]. Our study group included patients who started molnupiravir in the first 5 days after the onset of symptoms. Molnupiravir was administered orally twice daily at 800 mg for 5 days according to the National Protocol of Serbia for COVID-19 [13]. The control group included patients who did not take molnupiravir due to multiple reasons: the medicine was not available, they refused to take it, or they were diagnosed after the 5th day of their symptoms. Patients for the control group were collected simultaneously and in such a way that they corresponded to the clinical criteria for the use of molnupiravir and they had a similar distribution in terms of gender and age. Age, gender, symptoms with duration, risk factors (old age, active malignancy, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), obesity, a heart condition, diabetes mellitus, autoimmune disease), use of other non-antiviral medications against COVID-19, vaccination status reported by patients, and time since the last vaccination were all included in the baseline data. We included laboratory measurements taken during the first and last examinations, including C-reactive protein (CRP), white blood cells (WBC), platelets, d-dimer, aspartate transaminase (AST), and alanine transaminase (ALT). The primary effectiveness end point was the incidence of hospitalization for any cause (defined as 24 hours of acute care in a hospital or any similar facility). Patients were followed-up for 25 days or until the day of hospitalization. Moreover, the final outcome was analyzed using ordinal scale categories as follows: 0) unhospitalized; 1) hospitalized, requiring no oxygen supplementation but requiring medical care; 2) hospitalized, requiring oxygen supplementation via simple face mask; 3) hospitalized, on non-invasive ventilation with high-flow oxygen equipment; 4) hospitalized, on invasive mechanical ventilation.

Statistical analysis

Continuous variables with normal distribution of the data were presented as mean value ± standard deviation, while continuous heterogeneous variables were presented as median value (interquartile range 25th–75th percentile). The normal distribution of the data was checked using Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical variables were presented as the frequencies (percentage). Intergroup differences for continuous variables, were tested using two-sided t test if the distribution of the data was normal and Mann-Whitney's test if it wasn't, and the χ^2 or Fisher exact test was used to compare the distribution of categorical variables among groups. Univariate Cox regression model was used to identify the candidate predictors of hospitalization due to COVID-19. All the univariate predictors with statistical significance of $p < 0.05$ were included in the multivariate Cox regression analysis to identify independent predictors. A p value of < 0.05 defined statistical significance. The statistical analyses were performed using the IBM SPSS software v21.

Results

Our study group included 165 patients and the control group included 155 patients. Demographic and clinical characteristics with laboratory results of all the patients are summarized in Table 1. The study groups were similar in terms of gender and age. Most patients in both groups were aged over 60 years (62.4% in study group vs. 69.7% in control group). The study group had statistically significant more patients with heart diseases and active malignancy, while the control group had more chronic kidney patients and asthmatics. The vaccination status differed significantly between the

Table 1. Demographic and clinical characteristics of study and control group.

Gender	Patients on molnupiravir (N = 165, 51.6%)	Control group (N = 155, 48.4%)	*p* value
Male	80 (48.5%)	79 (51%)	0.657
Female	85 (51.5%)	76 (49%)	
Age (years)	64 ± 13	66 ± 16	0.297
Age ≥ 60 years	103 (62.4%)	108 (69.7%)	0.171
Risk factors			
Old age	100 (60.6%)	118 (76.1%)	< 0.001
Active malignancy	14 (8.5%)	2 (1.3%)	0.003
CKD	10 (0.6%)	60 (38.7%)	< 0.001
COPD	11 (6.7%)	6 (3.9%)	0.265
Obesity	0	1 (0.6%)	0.484
Heart condition	102 (61.8%)	21 (13.5%)	< 0.001
Obesity	0	1 (0.6%)	0.484
Diabetes	19 (11.5%)	21 (13.5%)	0.877
Autoimmune disease	7 (4.2%)	3 (1.9%)	0.236
Asthma	0	12 (7.7%)	< 0.001
Hypothyroidism	7 (4.2%)	14 (9%)	0.084
More than 1 risk factor	108 (65.5%)	101 (65.2%)	0.956
Duration of the symptoms (days) before 1st examination	2.8 ± 1.2	6.6 ± 3.4	< 0.001
Follow-up period (Min-Max)	12.12 ± 3.5 days (5-25)	4.59 ± 5.8 (0–25)	< 0.001
Vaccination			
Number of patients	124 (75.2%)	79 (51%)	<0.001
Number of doses of the vaccine	median 3 (1.5–3)	median 0.5 (0–3)	< 0.001
Vaccine type			
None	45 (27.3%)	76 (49%)	< 0.001
Pfizer	28 (17%)	6 (3.9%)	< 0.001
Sputnik V	26 (15.8%)	9 (5.8%)	0.004
Sinopharm	55 (33.3%)	51 (32.9%)	0.935
Other	1 (0.6%)	4 (2.6%)	0.202
Unknown	10 (6.1%)	9 (5.8%)	0.923
Non-antiviral medication before 1st examination			
Symptomatic	137 (83%)	63 (40.6%)	< 0.001
Antibiotic	15 (9.1%)	87 (56.1%)	< 0.001
Corticosteroids	7 (4.2%)	2 (1.3%)	0.175
CT	2 (1.2%)	0	0.499
Nolvadex	4 (2.4%)	0	0.123
Corticosteroids	7 (4.2%)	2 (1.3%)	0.175
Symptoms			
Cough	108 (65.5%)	124 (80%)	0.004
Sore throat	48 (29.1%)	0	< 0.001
Stuffy nose	19 (11.5%)	3 (1.9%)	0.001
Runny nose	33 (20.1%)	10 (6.5%)	< 0.001
Dyspnea	10 (6.1%)	59 (38.1%)	< 0.001
Muscle pain	37 (22.4%)	51 (32.9%)	0.036
Fatigue	105 (63.6%)	114 (73.5%)	0.057
High fever	137 (83%)	135 (87.1%)	0.309
Headache	36 (21.8%)	14 (9%)	0.002
Nausea	14 (8.5%)	25 (16.1%)	0.037
Vomiting	8 (4.8%)	12 (7.7%)	0.285
Diarrhea	8 (4.8%)	17 (11%)	0.042
Loss of the sense of taste	0	7 (4.5%)	0.006
Anosmia	0	7 (4.5%)	0.006
Laboratory results			
WBC at first examination (x 10^9)	median 6 (5.2–7.4)	median 5.85 (4.15–8.05)	0.074
WBC on the last examination (x 10^9)	7 ± 2.1	8.2 ± 3.7	0.006
Platelets at first examination (x 10^9)	median 206 (173–245)	median 212.5 (168–289)	0.930
Platelets on the last examination (x 10^9)	249.3 ± 72.8	269 ± 124.3	0.209
CRP at first examination (mg/L)	median 13 (4.5–23.8)	median 34.4 (8.9–60.4)	< 0.001
CRP on the last examination (mg/L)	median 3.4 (1.1–12.7)	median 9.1 (2.5–53.6)	< 0.001
D-dimer at first examination (mg/L)	median 0.48 (0.34–0.84)	median 0.6 (0.4–1.1)	< 0.001
D-dimer on the last examination (mg/L)	median 0.48 (0.3–0.82)	median 0.59 (0.34–0.91)	0.183
AST at first examination (U/L)	median 23 (19–31)	median 25 (21–40)	0.001
AST on the last examination (U/L)	median 22)16–28)	median 26 (19–35)	0.023
ALT at first examination (U/L)	median 33 (24–42)	median 32 (21–41)	0.450
ALT on the last examination (U/L)	median 32 (25–44)	median 38 (27–62)	0.496
Pneumonia	23 (13.9%)	116 (74.8%)	< 0.001

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CRP: C reactive protein; CT: chemotherapy; WBC: white blood cell.

groups; 75.2% patients in study group were fully vaccinated and 51% patients in control group were vaccinated. Among those who were vaccinated, in the study group, most of the patients received three doses of vaccine while in the control group most of the patients received one dose. The prevalence of symptoms was similar between groups, but the majority of patients in the control group complained of coughing (80%) and dyspnea (38%), whereas in the study group 65.5% complained of coughing and 6.1% of dyspnea. The duration of COVID-19 symptoms before their first examination was longer in the control group (6.6 days) compared to study group (2.8 days). During the follow-up period, the control group had a higher frequency of radiographically confirmed pneumonia (78.4%) than the study group (13.9%). Regarding laboratory analysis, there was a significant difference in WBC, CRP, and AST values among groups, including measurements at the first examination compared to the last ones. In the study group, 92.7% of patients did not require hospitalization, whereas 24.5% of patients in the control group did not require hospitalization. The majority of the patients in the control group (75.5%) needed hospitalization. During the 12.1 ± 3.5-day follow-up period, none of the study group patients were admitted to the intensive care unit, while 10.3% of the control group patients required this type of treatment (Table 2). In multivariate analysis molnupiravir was one of the independent predictors of hospitalization and reduced the possibility of hospitalization by 97.9%, while age and CRP were also independent predictors of hospitalization. An increase of one year in age, increased the possibility of hospitalization by 3.2%. An increase of CRP level by one unit, increased the possibility of hospitalization by 0.4% (Table 3).

Discussion

Our study used real-world data to demonstrate the effectiveness of molnupiravir against SARS-CoV-2 in outpatients who are at high risk of disease progression, in a single-center study. The analysis included 320 adult non-hospitalized patients who were being treated for COVID-19. Our results showed that molnupiravir reduced the risk of hospitalization (HR 0.021, 95% CI 0.005–0.089). Numerous studies on the effectiveness of molnupiravir have shown differences from our research results; while some favored its use, others did not show greater significance. Previous real-world effectiveness studies showed that molnupiravir use was associated with a lower risk of hospitalization in treated patients compared to non-recipients, including studies by Evans *et al.* (HR 0.49), Paraskevis *et al.* (OR 0.40), and Wai *et al*. (OR 0.72) [14–16]. In a study conducted among US veterans aged 65 years and older, molnupiravir was associated with a lower 30-day risk of hospitalization or death (RR 0.67, 95% CI 0.46–0.99), but the overall result between treated and untreated patients was similar [17]. The meta-analysis by Huang *et al*., which included six studies involving 89,480 patients (22,355 of whom received molnupiravir therapy and 67,125 received placebo therapy), indicated that the risk of mortality was reduced by 34% and the risk of the composite outcome of disease progression was reduced by 37% among patients who received molnupiravir [18]. On the other hand, Wong *et al*. reported that molnupiravir recipients in Hong Kong had a significantly lower risk of all-cause mortality than non-recipients (HR 0.76, 95% CI 0.61–0.95; $p = 0013$), but the risk of hospitalization was comparable to the control group (0.98 [CI 0.89-1.06]; $p = 058$) [19]. In another study by Yip *et al*. molnupiravir usage showed no statistically significant difference in reducing the risk for hospitalization versus the non-users [20]. In addition, the recently published 25,000 participant prospective, open-label study, PANORAMIC trial, found only a 1% risk of all-cause hospitalization, and concluded that molnupiravir did not reduce the frequency of COVID-19-associated hospitalizations or death among adults over 50 years of age or adults over 18 years with other risk factors, in the community [21].

Table 2. Assessment of clinical worsening in the study and control group.

	Patients on molnupiravir (N = 165, 51.6%)	Control group (N = 155, 48.4%)	*p* value
Clinical worsening			
No worsening	153 (92.7%)	38 (24.5%)	< 0.001
General care without oxygen supplementation	10 (6.1%)	38 (24.5%)	< 0.001
General care with oxygen supplementation	1 (0.6%)	48 (31%)	< 0.001
Semi-intensive care unit	1 (0.6%)	15 (9.7%)	< 0.001
Intensive care unit	0	16 (10.3%)	< 0.001
Follow-up in days (min–max)	8.92 ± 3.55 (5–15)	2.83 ± 4.95 (0–25)	< 0.001
Reason for clinical worsening			
None	153 (92.7%)	38 (24.5%)	< 0.001
COVID-19	12 (7.3%)	109 (70.3%)	< 0.001
Chronic illness	0	8 (5.2%)	0.003

In our study, considering that the groups were very similar in terms of demographic data, and the sole notable difference was in the number of vaccinated individuals, there was a reason to suspect that vaccination had an impact on the more favorable course of the disease of those who were treated. However, that doubt is dispelled by the fact that the Omicron variant diverged immunologically from the earlier variants on the basis of which the vaccine was developed and with which patients may have previously come into contact [22,23]. We believe that prior immune status could not have had a significant impact on the efficacy of an antiviral drug devoid of immunomodulatory activity. Our patients taking molnupiravir had a milder clinical course of disease and a lower frequency of pneumonia, but they were examined earlier and started therapy on

Table 3. Univariate and multivariate Cox regression analysis of risk factors for hospitalisation in COVID-19 non-hospitalised patients.

	Univariate analysis					Multivariate analysis		
	B	*p* value	HR	95% CI		*p* value	HR	95% CI
				lower	upper			lower upper
Gender: Male	**-0.244**	**0.167**	**0.783**	**0.553–1.108**				
Age (years)	0.023	0.001	1.023	1.010–1.037		0.022	1.032	1.005–1.059
Age > 60 years	0.537	0.008	1.711	1.147–2.553		0.665	1.225	0.489–3.067
Duration of the symptoms (days)	0.175	< 0.001	1.191	1.144–1.241		0.118	1.063	0.985–1.148
Risk factors								
Without	/	/	/	/				
Old age	1.609	< 0.001	4.996	3.387–7.369		0.137	0.504	0.205–1.243
Active malignancy	-0.957	0.102	0.384	0.122–1.207				
CKD	0.263	0.794	1.301	0.182–9.315				
COPD	-0.748	0.143	0.473	0.174–1.286				
Obesity	-3.005	0.734	0.050	/				
Heart condition	-1.767	< 0.001	0.171	0.096–0.304		0.674	1.328	0.354–4.981
Diabetes	0.139	0.615	1.149	0.669–1.971				
Autoimmune disease	-1.499	0.136	0.223	0.031–1.599				
More than 1 risk factor	0.110	0.560	1.116	0.772–1.613				
Vaccinated patients	-0.764	< 0.001	0.466	0.329–0.659		0.461	1.821	0.370–8.954
Time from the vaccination to the symptoms onset (days)	-0.136	0.001	0.873	0.804–0.949		0.240	0.894	0.742–1.078
Number of vaccine doses	-0.309	< 0.001	0.734	0.646–0.833		0.579	0.854	0.489–1.491
Vaccine type								
None	0.725	< 0.001	2.065	1.460-2.919				
Pfizer	-1.696	0.001	0.183	0.067–0.505		0.598	0.709	0.197–2.550
Sputnik V	-0.561	0.105	0.571	0.289–1.125				
Sinopharm	-0.106	0.579	0.900	0.619–1.308				
Other	0.193	0.787	1.213	0.299–4.913				
Unknown	0.007	0.987	1.007	0.470–2.158				
Non-antiviral medication before 1st examination								
Symptomatic	-0.888	< 0.001	0.411	0.290–0.584		0.405	0.503	0.100–2.536
Antibiotic	0.998	< 0.001	2.712	1.912–3.847		0.245	0.384	0.077–1.926
Corticosteroids	-0.340	0.561	0.712	0.226–2.240				
CT	-3.016	0.495	0.049	/				
Nolvadex	-3.031	0.325	0.048	/				
Cough	1.218	< 0.001	3.382	1.941–5.892		0.311	1.496	0.686–3.262
Sore throat	-2.071	< 0.001	0.067	0.017–0.727		0.945	/	/
Stuffy nose	-1.324	0.024	0.266	0.085–0.937		0.241	3.607	0.423–30.766
Runny nose	-1.305	0.002	0.271	0.119–0.616		0.813	0.833	0.184–3.775
Dyspnea	1.431	< 0.001	4.183	2.920–5.992		0.699	1.121	0.629–1.997
Muscle pain	0.137	0.478	1.147	0.785–1.676				
Fatigue	0.493	0.017	1.637	1.093–2.454		0.744	0.900	0.479–1.692
High fever	0.704	0.025	2.023	1.090–3.753		0.544	1.347	0.515–3.524
Headache	-0.468	0.089	0626	0.365–1.073				
Nausea	0.523	0.026	1.687	1.065–2.674		0.596	1.196	0.617–2.319
Vomiting	0.123	0.724	1.130	0.573–2.231				
Diarrhea	0.366	0.212	1.441	0.812–2.559				
Loss of the sense of taste	0.099	0.868	1.104	0.345–3.531				
Anosmia	0.096	0.872	1.101	0.344–3.520				
Pneumonia	-0.281	0.010	0.755	0.611–0.934		0.106	1.703	0.893–3.250
WBC at first examination ($\times 10^9$)	0.052	0.001	1.053	1.022–1.085		0.884	1.003	0.960–1.048
WBC on the last examination ($\times 10^9$)	0.139	< 0.001	1.149	1.066–1.238				
Platelets at first examination ($\times 10^9$)	0	0.779	1.00	0.998–1.003				
Platelets on the last examination ($\times 10^9$)	-0.001	0.591	0.999	0.996–1.002				
CRP at first examination (mg/L)	0.009	< 0.001	1.009	1.007–1.011		0.029	1.004	1.000–1.007
CRP on the last examination (mg/L)	0.012	< 0.001	1.012	1.010–1.015				
D-dimer at first examination (mg/L)	0.076	0.001	1.079	1.033–1.126		0.708	0.985	0.909–1.067
D-dimer on the last examination (mg/L)	0.021	0.006	1.021	1.006–1.036				
AST at first examination (U/L)	0.014	< 0.001	1.014	1.008–1.020		0.252	1.007	0.995–1.020
AST on the last examination (U/L)	0.018	< 0.001	1.018	1.012–1.024				
ALT at first examination (U/L)	0.007	0.028	1.007	1.001–1.13		0.953	1.000	0.989–1.012
ALT on the last examination (U/L)	0.005	0.119	1.005	0.999–1.012				
Molnupiravir	-3.127	< 0.001	0.044	0.024–0.081		< 0.001	0.021	0.005–0.089

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CRP: C reactive protein; CT: chemotherapy; WBC: white blood cell.

time. Based on data on follow-up time until hospitalization, regardless of the favorable course of most treated patients, they should be followed for at least 15 days after starting treatment, and those who are not receiving therapy should be followed for up to 25 days.

Our study had some inherent limitations due to its real-world and single-center observational nature, which might lead to bias. The main limitation of our study was the short duration of treatment as well as the small sample size. This limitation was overcome by the fact that the groups of patients proved to be similar in terms of gender and age, and this result came about by chance, without an a priori desire for matching. Our data provide significant support for expanding the base, and a multicenter, national study is being planned. Another potential limitation was the lack of data on viral subvariants.

Conclusions

The results of our study showed that, the use of molnupiravir further reduced the risk for hospitalization, with the effect being more pronounced in highly vulnerable populations. Thus, its use in high-risk populations is strongly indicated to reduce the burden of disease and unfavorable outcomes.

Authors' contributions

Conceptualization, GI, TN, SM, KN; methodology, GI, SG; validation, AB, SG; formal analysis, GI; investigation, GI, TN, SM, KN; resources, GI, TN, SM, KN; data curation, IG, BA, SG; writing—original draft preparation, GI, TN, SM, KN, VA, NN, MI; writing—review and editing, GI, BA, SG; visualization, GI; supervision, SG; project administration, GI. All authors have read and agreed to the published version of the manuscript.

References

1. WHO (nd) Coronavirus (COVID-19) dashboard. Available: https://covid19.who.int/. Accessed: 25 June 25, 2023.
2. Ko JY, Danielson ML, Town M, Derado G, Greenlund KJ, Kirley PD, Alden NB, Yousey-Hindes K, Anderson EJ, Ryan PA, Kim S, Lynfield R, Torres SM, Barney GR, Bennett NM, Sutton M, Talbot HK, Hill M, Hall AJ, Fry AM, Garg S, Kim L, COVID-NET Surveillance Team (2021). Risk factors for coronavirus disease 2019 (COVID-19)-associated hospitalization: COVID-19-associated hospitalization surveillance network and behavioral risk factor surveillance system. Clin Infect Dis 72: e695-e703. doi: 10.1093/cid/ciaa1419.
3. Stokes EK, Zambrano LD, Anderson KN, Marder EP, Raz KM, El Burai Felix S, Tie Y, Fullerton KE (2020) Coronavirus disease 2019 case surveillance-United States, January 22-May 30, 2020. Morb Mortal Wkly Rep MMWR 69: 759-765. doi: 10.15585/mmwr.mm6924e2.
4. Kompaniyets L, Goodman AB, Belay B, Freedman DS, Sucosky MS, Lange SJ, Gundlapalli AV, Boehmer TK, Blanck H (2021) Body mass index and risk for COVID-19-related hospitalization, intensive care unit admission, invasive mechanical ventilation, and death-United States, March-December 2020. Morb Mortal Wkly Rep MMWR 70: 355-361. doi: 10.15585/mmwr.mm7010e4.
5. Arribas JR, Bhagani S, Lobo SM, Khaertynova I, Mateu L, Fishchuk R, Park WY, Hussein K, Kim SW, Ghosn J, Brown ML, Zhang Y, Gao W, Assaid C, Grobler JA, Strizki J, Vesnesky M, Paschke A, Butterton JR, De Anda C (2022) Randomized trial of molnupiravir or placebo in patients hospitalized with COVID-19. NEJM Evid 1: EVIDoa2100044. doi: 10.1056/EVIDoa2100044.
6. Cohen MS, Wohl DA, Fischer WA, Smith DM, Eron JJ (2021) Outpatient treatment of severe acute respiratory syndrome coronavirus 2 infection to prevent coronavirus disease 2019 progression. Clin Infect Dis 73: 1717-1721. doi: 10.1093/cid/ciab494.
7. Painter GR, Natchus MG, Cohen O, Holman W, Painter WP (2021) Developing a direct acting, orally available antiviral agent in a pandemic: the evolution of molnupiravir as a potential treatment for COVID-19. Curr Opin Virol 50: 17-22. doi: 10.1016/j.coviro.2021.06.003.
8. Sinha S, Kumarasamy N, Suram VK, Chary SS, Naik S, Singh VB, Jain MK, Suthar CP, Borthakur S, Sawardekar V, Sk N, Reddy N, Talluri L, Thakur P, Reddy M, Panapakam M, Vattipalli R (2022). Efficacy and safety of molnupiravir in mild COVID-19 patients in India. Cureus 14: e31508. doi: 10.7759/cureus.31508.
9. Abdelnabi R, Foo CS, De Jonghe S, Maes P, Weynand B, Neyts J (2021) Molnupiravir inhibits replication of the emerging SARS-CoV-2 variants of concern in a hamster infection model. J Infect Dis 224: 749-753. doi: 10.1093/infdis/jiab361.
10. Gordon CJ, Tchesnokov EP, Schinazi RF, Götte M (2021) Molnupiravir promotes SARS-CoV-2 mutagenesis via the RNA template. J Biol Chem 297: 100770. doi: 10.1016/j.jbc.2021.100770.
11. Jayk Bernal A, Gomes Da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, Martín-Quirós A, Caraco Y, Williams-Diaz A, Brown ML, Du J, Pedley A, Assaid C, Strizki J, Grobler JA, Shamsuddin HH, Tipping R, Wan H, Paschke A, Butterton JR, Johnson MG, De Anda C, MOVe-OUT Study Group (2022) Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients. N Engl J Med 386: 509-520. doi: 10.1056/NEJMoa2116044.
12. Heliant Health (2021) Healthcare information system. Available: https://heliant.rs/our-products/health/?lang=en. Accessed: 25 June 25, 2023.
13. Pelemis M, Stevanovic G, Turkulov V, Vucinic V, Matijasevic J, Milosevic B, Milosevic I, Gajovic O, Ladjevic N, Vrbic M, Barac B, Udovicic I, Jankovic R, Mikic D, Antic D, Mujovic N, Djordjevic M, Korac M, Ranin J, Bukarica Lj, Dragovic G (2022) National protocol of the Republic of Serbia for the treatment of COVID-19 infection, Version 13. IOPHOS - Batut: Home. Org.Rs. Available: https://batut.org.rs/index.php?lang=2. Accessed: 12 September 2023. [Article in Serbian].
14. Evans A, Qi C, Adebayo JO, Underwood J, Coulson J, Bailey R, Lyons R, Edwards A, Cooper A, John G, Akbari A (2023)

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 86: 352-360. doi: 10.1016/j.jinf.2023.02.012.
15. Paraskevis D, Gkova M, Mellou K, Gerolymatos G, Psalida P, Gkolfinopoulou K, Kostaki EG, Loukides S, Kotanidou A, Skoutelis A, Thiraios E, Saroglou G, Zografopoulos D, Mossialos E, Zaoutis T, Gaga M, Tsiodras S, Antoniadou A (2023) Real-world effectiveness of molnupiravir and nirmatrelvir/ritonavir as treatment for COVID-19 in patients at high risk. J Infect Dis 228: 1667-1674. doi: 10.1093/infdis/jiad324.
16. Wai AK-C, Chan CY, Cheung AW-L, Wang K, Chan SC-L, Lee TT-L, Luk LY-F, Yip ET-F, Ho JW-K, Tsui OW-K, Cheung KW-Y, Lee S, Tong C, Yamamoto T, Rainer TH, Wong EL-Y (2023) Association of molnupiravir and nirmatrelvir-ritonavir with preventable mortality, hospital admissions and related avoidable healthcare system cost among high-risk patients with mild to moderate COVID-19. Lancet Reg Health West Pac 30: 100602. doi: 10.1016/j.lanwpc.2022.100602.
17. Bajema KL, Berry K, Streja E, Rajeevan N, Li Y, Yan L, Cunningham F, Hynes DM, Rowneki M, Bohnert A, Boyko EJ, Iwashyna TJ, Maciejewski ML, Osborne TF, Viglianti EM, Aslan M, Huang GD, Ioannou GN (2023) Effectiveness of COVID-19 treatment with nirmatrelvir-ritonavir or molnupiravir among US veterans: target trial emulation studies with one-month and six-month outcomes. Ann Intern Med 176: 807-816. doi: 10.7326/M22-3565.
18. Huang C, Lu T-L, Lin L (2023) 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 12: 393. doi: 10.3390/antibiotics12020393.
19. Wong CKH, Au ICH, Lau KTK, Lau EHY, Cowling BJ, Leung GM (2022). Real-world effectiveness of molnupiravir and nirmatrelvir plus ritonavir against mortality, hospitalisation, and in-hospital outcomes among community-dwelling, ambulatory patients with confirmed SARS-CoV-2 infection during the omicron wave in Hong Kong: an observational study. Lancet 400: 1213-1222. doi: 10.1016/S0140-6736(22)01586-0.
20. Yip TC-F, Lui GC-Y, Lai MS-M, Wong VW-S, Tse Y-K, Ma BH-M, Hui E, Leung MKW, Chan HL-Y, Hui DS-C, Wong GL-H (2023) Impact of the use of oral antiviral agents on the risk of hospitalization in community coronavirus disease 2019 patients (COVID-19). Clin Infect Dis 76: e26-e33. doi: 10.1093/cid/ciac687.
21. Butler CC, Hobbs FDR, Gbinigie OA, Rahman NM, Hayward G, Richards DB, Dorward J, Lowe DM, Standing JF, Breuer J, Khoo S, Petrou S, Hood K, Nguyen-Van-Tam JS, Patel MG, Saville BR, Marion J, Ogburn E, Allen J, Rutter H, Francis N, Thomas NPB, Evans P, Dobson M, Madden TA, Holmes J, Harris V, Png ME, Lown M, van Hecke O, Detry MA, Saunders CT, Fitzgerald M, Berry NS, Mwandigha L, Galal U, Mort S, Jani BD, Hart ND, Ahmed H, Butler D, McKenna M, Chalk J, Lavallee L, Hadley E, Cureton L, Benysek M, Andersson M, Coates M, Barrett S, Bateman C, Davies JC, Raymundo-Wood I, Ustianowski A, Carson-Stevens A, Yu LM, Little P (2023) 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 401: 281-293. doi: 10.1016/S0140-6736(22)02597-1.
22. Flisiak R, Zarębska-Michaluk D, Rogalska M, Kryńska JA, Kowalska J, Dutkiewicz E, Dobrowolska K, Jaroszewicz J, Moniuszko-Malinowska A, Rorat M, Podlasin R, Tronina O, Rzymski P (2022) Real-world experience with molnupiravir during the period of SARS-CoV-2 Omicron variant dominance. Pharmacol Rep 74: 1279-1285. doi: 10.1007/s43440-022-00408-6.
23. De Gier B, Huiberts AJ, Hoeve CE, Den Hartog G, Van Werkhoven H, Van Binnendijk R, Hahné SJM, De Melker HE, Van Den Hof S, Knol MJ (2023) Effects of COVID-19 vaccination and previous infection on Omicron SARS-CoV-2 infection and relation with serology. Nat Commun 14: 4793. doi: 10.1038/s41467-023-40195-z.

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