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Effectiveness and safety of molnupiravir among patients with mild to moderate COVID-19: A prospective, observational, cohort study

Serap Şimşek-Yavuz¹, Alpay Azap², Gülsüm Öztürk-Emiral³, Hüsna Çevik⁴, Rahmet Güner⁵, Müge Ayhan⁵, Belgin Coşkun⁶, Aysun Benli¹, Yeşim Tok⁷, Mustafa Önel⁸, İlker İnanç-Balkan⁹, Sezen Fansa⁹, Fatma Zehra Güneşer¹⁰, Mahir Kapmaz¹¹, Nilsun Altunal¹², Elif Selcen Beng¹³, Özlem Aydın¹⁴, Sezen Özge Özen¹, Seniha Başaran¹, Hasan Yağmur¹⁵, Meryem Çalışkan¹⁵, Melek-Nur Aslan¹⁶, Neslihan Uyar¹⁷, Burcu Atasoy Bozan¹⁸, Mihriban Aksoy¹⁹, Mehtap Aydın¹², Duygu Korkut Akyürek¹, Elif Mukime Sarıcaoğlu², Önder Ergönül¹¹, Sevim Meşe⁷, Füsün Can²⁰, Mert Ahmet Kuşkucu²⁰, Ali Ağaçfıdan⁸, Filiz Pehlivanoğlu¹⁸, Özlem Altuntaş-Aydın²¹, Alper Gündüz²¹.

1 Istanbul University, Istanbul Faculty of Medicine, Infectious Disease and Clinical Microbiology Department, Istanbul, Türkiye

2 Ankara University, Faculty of Medicine, Infectious Disease and Clinical Microbiology Department, Ankara, Türkiye

3 Ankara Yıldırım Beyazıt University, Faculty of Medicine, Public Health Department, Istanbul, Türkiye

4 Ankara University, Faculty of Medicine, Family Medicine Department, Ankara, Türkiye

5 Ankara Yıldırım Beyazıt University, Faculty of Medicine, Infectious Disease and Clinical Microbiology Department, Ankara, Türkiye

6 Ankara Bilkent City Hospital, Ankara , Türkiye

7 İzmir Katip Çelebi University, Faculty of Medicine, Medical Microbiology Department, İzmir, Türkiye

8 Istanbul University, Istanbul Faculty of Medicine, Medical Microbiology Department, Istanbul, Türkiye

9 Istanbul University Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Infectious Disease and Clinical

Microbiology Department, Istanbul, Türkiye

10 Ministry of Health, Beşiktaş District Health Center, Beşiktaş, İstanbul

11 Koç University Hospital, Infectious Disease and Clinical Microbiology Department, Istanbul, Türkiye

12 Ümraniye Research and Education Hospital, Infectious Disease and Clinical Microbiology Department, Ümraniye, İstanbul, Türkiye

13 Ministry of Health, Üsküdar District Health Center, Üsküdar, İstanbul, Türkiye

14 Ministry of Health, Ümraniye District Health Center, Ümraniye, İstanbul, Türkiye

15 Ministry of Health, Gölbaşı District Health Center, Gölbaşı, Ankara, Türkiye

16 Ministry of Health, Fatih District Health Center, Fatih, İstanbul, Türkiye

17 Ministry of Health, Kadıköy District Health Center, Kadıköy, İstanbul, Türkiye

18 Sultangazi Haseki Research and Education Hospital, Infectious Disease and Clinical Microbiology Department, Sultangazi, İstanbul

19 Ministry of Health, Sultangazi District Health Center, Sultangazi, İstanbul, Türkiye

11 Koç University, Faculty of Medicine, Infectious Disease and Clinical Microbiology Department, Istanbul, Türkiye

20 Koç University, Faculty of Medicine, Medical Microbiology Department, Istanbul, Türkiye

21 Çam Sakura Research and Education Hospital, Infectious Disease and Clinical Microbiology Department, İstanbul

Corresponding Author:

Serap Şimşek-Yavuz, serapsimsekyavuz@gmail.com, phone number: +905052696412

Address: Aziz Mahmut Hüdayi Mh., Tulumacılar Sk, İstanbul Apt, No 34/10, Üsküdar, İstanbul, Türkiye

ABSTRACT

Objectives: This study evaluates the effect of molnupiravir on clinical improvement, viral clearance and antibody responses of COVID-19 patients who previously developed immunity through vaccination or prior infection.

Methods: This multi-center, prospective, observational study included all mild adult COVID-19 cases for whom molnupiravir was recommended during the study period. The primary outcome was hospitalization, death or new oxygen need due to COVID-19 within 28 days of follow-up. The effects of molnupiravir on viral clearance, serum biochemical tests and SARS-CoV-2 antibody levels were also assessed.

Results: A total of 844 patients (402 molnupiravir, 442 no molnupiravir) were included. The mean age was 66, 75% of them were vaccinated. The primary outcome occurred in 8 patients, with no significant difference between propensity score-matched groups. Molnupiravir showed no effect on clinical improvement. Viral clearance was higher in the molnupiravir group on day 3, but higher in the untreated group by day 10. Serum SARS-CoV-2 antibody levels on day 28 were lower in the molnupiravir group.

Conclusions The effectiveness of molnupiravir in reducing hospitalization and death may be insufficient in previously immune COVID-19 patients. Additionally, molnupiravir may reduce day-28 serum SARS-CoV-2 antibody level.

Keywords: COVID-19, treatment, molnupiravir, nosocomial COVID-19, viral load, SARS-CoV-2 spike antibody

Introduction

Molnupiravir, an RNA dependent RNA polymerase inhibitor, is the first agent that was shown to reduce the rate of death and hospitalization due to COVID-19 significantly in an adequate phase-3 clinical trial [1]. Therefore, in many countries, molnupiravir has been given emergency use approvals for the treatment of COVID-19. Nirmatrelvir/ritonavir and remdesivir were later shown to be more effective than molnupiravir, as a result molnupiravir was included in the guidelines as an alternative treatment option for COVID-19. However, as nirmatrelvir/r has many drug interactions and remdesivir requires iv administration, molnupiravir is still widely used in the treatment of COVID-19 world-wide [2-4]. In the later stages of the pandemic, the number of people who developed immunity against the disease through exposure or vaccination increased, therefore deaths and hospitalizations from COVID-19 decreased significantly.

It is not known whether the already low efficacy of molnupiravir on COVID-19 related hospitalization/death continues in groups that have become immune through vaccination or disease, or whether it accelerates clinical or laboratory recovery or viral clearance at this stage of the Pandemic. In addition, since it is a drug that has been widely used only for four years, long-term adverse effects have not been established, and its effect on the host's specific antibody response to SARS-CoV-2 is not defined.

This study examined the effects of molnupiravir treatment on clinical outcomes, nasopharyngeal viral loads, serum antibody levels and blood test results of COVID-19 patients in a real-world setting.

Materials and Methods

This multi-center, prospective, observational cohort study included all eligible mild adult COVID-19 cases who were followed up in the study centers. Patients were recruited from healthcare institutions in two cities in Türkiye. These included six primary care centres and six tertiary care hospitals in Istanbul, and one primary care centre and two tertiary care hospitals in Ankara from 29.03.2022 to 29.09.2023. During the early and late phases of the study, Omicron B.A.2.75 and XBB.1 were the circulating variants in Türkiye, respectively (Nextstrain; <https://nextstrain.org/ncov/open/global/6m>).

Patients were eligible if they had symptom onset within 5 days, had at least one risk factor for severe COVID-19 (age ≥ 65 years, age ≥ 18 years with ≥ 1 comorbidity, immunosuppression, or body mass index ≥ 30 kg/m²), had a positive nasopharyngeal SARS-CoV-2 PCR test within the previous 48 hours, and were recommended molnupiravir by the attending physician, regardless of whether they accepted or declined treatment.

Molnupiravir was administered orally at a dose of 800 mg twice daily for a total of 5 days. As molnupiravir was the only available antiviral agent at that time in the country, patients in the non-molnupiravir group did not receive any antiviral treatment for SARS-CoV-2 and were managed with symptomatic and supportive care alone. Only patients who received at least 80% of the prescribed treatment were included in the analyses.

Patients diagnosed with COVID-19, both as outpatient or while hospitalized for other reasons, were included in the study. Nosocomial COVID-19 was defined as the onset of symptoms and a positive SARS-CoV-2 test occurring after hospital day seven following

admission and no known exposures or risk factors before hospitalization. Infections in outpatients and cases in which symptoms and/or SARS-CoV-2 test positivity developed within the first 7 days of hospitalization following admission were considered community-acquired COVID-19 [5].

After getting the information about the history including previous COVID-19 episodes, the comorbidities, details of medications and COVID-19 vaccinations, and the physical examination findings on the first day, participants were followed up through telephone call daily in the first 5 days, then on day 10, 14 and 28 and 3rd and 6th month of the study. The “WHO ordinal clinical severity scale” [6] was used to evaluate the clinical conditions of the patients at baseline and on the study days of 3, 5, 7, 10, 14, 28 and 3rd and 6th month of the study. While primary outcome was hospitalization or new oxygen need or death due to COVID-19 at 28th day of the study, same outcomes on 3rd and 6th month, admission to ICU or ventilator support in the first 28 days were recorded as secondary outcomes.

Nosocomial and community acquired COVID-19 cases were also compared. Household transmission was defined as the development of COVID-19-compatible symptoms or a positive SARS-CoV-2 test among household members of the index case on days 3, 5, 7, 10, 14, and 28 days after the diagnosis.

Nasopharyngeal SARS-CoV-2 viral load, serum SARS-CoV-2 antibody level, acute phase reactants and some other blood tests were measured in the consecutive participants followed at Istanbul Medical School and Cerrahpaşa Medical School, agreed or did not agree to use molnupiravir. Nasopharyngeal swab samples on day 1, 3, 5, 10 and 14 were taken to analyze the presence and quantity of SARS-CoV-2 RNA by using SARS-CoV-2 Omicron™ RT-qPCR kit

(GenMark) and BioRAD CFX96™ Touch (Bio-Rad Laboratories Inc., ABD) platform. Blood samples on day 1 and day 10 of the study were taken to define the kinetics of serum glucose, BUN, creatinine, AST, ALT, CRP, LDH, procalcitonin, D-Dimer levels, blood leukocyte, neutrophil and lymphocyte, erythrocyte and platelet counts during follow-up. Blood samples on day 1 and 28 were taken to measure the serum SARS-CoV-2 spike IgG level by using, Abbott SARS-CoV-2 Spike Antibody test and Abbott Architect i2000 SR device. Finally presence of any adverse effects of the molnupiravir was questioned during and after treatment until 6th months of therapy.

Statistical Methods

Descriptive statistics were reported as frequencies and percentages for categorical variables and as mean $\pm$ standard deviation (SD) for continuous variables. Associations between categorical variables were assessed using the Chi-square test when expected cell counts were ≥ 5 and Fisher's exact test when expected counts were < 5 . Effect sizes for categorical comparisons were reported using Cramer's V for tables larger than 2×2 and Phi (ϕ) for 2×2 tables, interpreted according to conventional thresholds (0.1 small, 0.3 medium, 0.5 large). For dichotomous outcomes in univariable analyses, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using the Wald method.

Continuous variables were compared using the Student's *t*-test for independent samples when normally distributed and the Mann–Whitney *U* test for non-normal distributions. Normality was assessed visually and analytically prior to group comparisons. Homogeneity of variances was evaluated using Levene's test. When variances were equal, effect sizes were expressed as Cohen's *d* using pooled standard deviations; when variance heterogeneity was present, Glass's Δ was reported based on the standard deviation of the reference group. Effect size estimates were interpreted using standard thresholds (0.2 small, 0.5 medium, 0.8 large). The primary outcome was analyzed as a time-to-event variable. In the unmatched cohort, independent risk factors for

the primary outcome were evaluated using multivariable Cox proportional hazards regression analysis, and effect sizes were reported as hazard ratios (HRs) with 95% confidence intervals. Those statistical analyses were performed using SPSS software (version 20.0; IBM Corp).

Propensity score matching (PSM) was performed to reduce baseline imbalances between molnupiravir-treated and untreated patients. A 1:1 nearest-neighbor matching without replacement was conducted using the MatchIt package (version 4.5.5) in R, based on age, Charlson Comorbidity Index (CCI), World Health Organization (WHO) ordinal clinical severity scale on day 1, and SARS-CoV-2 vaccination status. After matching, the primary outcome in the PSM cohort was evaluated using Kaplan–Meier survival curves and compared between groups using the log-rank test. Cox regression analysis was not performed in the matched cohort due to the limited number of outcome events.

Repeated-measures analysis of variance (ANOVA) was used to evaluate longitudinal changes in nasopharyngeal viral load, WHO clinical severity scores, and selected laboratory parameters measured at multiple time points using SPSS software (version 20.0; IBM Corp). When necessary, $\log_{10}$ or $\log_2$ transformations were applied to approximate normality. For statistically significant main or interaction effects, post-hoc pairwise comparisons and graphical visualizations were generated using jamovi (version 2.5) with the ClinicoPath module.

Baseline nasopharyngeal viral loads and anti-spike antibody concentrations, as well as anti-spike antibody concentrations measured on day 28, were compared in relation to multiple clinical parameters using *Clinicopath* module in *jamovi* (v.2.3.28) software and graphically and/or numerically presented using *StatsDirect* statistical software (<http://www.statsdirect.com>).

Missing data were minimal and were handled by complete-case analysis. Participants with missing data for a given variable were excluded from analyses involving that variable.

Participants were contacted by telephone to obtain follow-up information and minimize loss to follow-up.

A total of 2600 participants (1300 molnupiravir and 1300 no drug group) was planned to include in to the study and with these numbers the power of the study would have been 84% with an 5% type 1 error rate and 0.11 effect size. Calculations were made assuming that COVID-19 would lead to hospitalization/death/oxygen need in 10% of the patients during Omicron period and molnupiravir would reduce those outcomes by 30% which was the rate reported in the Phase 3 trial of the drug. With the achieved sample size of 844 participants (402 molnupiravir, 442 no-drug), and the same baseline assumption of 10% events in the control group, the study would be able to detect a $\geq 50\%$ relative reduction in events (corresponding to an approximate 4.8% risk in the molnupiravir group) with 80% statistical power.

To minimize potential sources of bias, consecutive eligible patients presenting within the first five days of symptom onset were enrolled according to predefined inclusion and exclusion criteria. Data were collected using standardized case report forms to reduce information bias. Clinical outcomes and follow-up data were obtained through medical records and telephone follow-up using the same procedures for both groups. In addition, baseline characteristics were compared and adjusted for in the statistical analyses to reduce potential confounding.

This study was registered to the Clinical Trials with the number of NCT06223932.

All participants gave an informed consent and signed the consent form before included in the study.

Results

A total of 852 patients were included in the study from 29.03.2022 to 29.09.2023. Due to sharp decrease of the cases and SARS-CoV-2 testing after the first peak of Omicron in Türkiye, planned number of the participants could not be recruited despite the 6 months extension of the

study period and sponsor decided to complete the study. 844 patients (402 molnupiravir group, 442 no molnupiravir group) who completed the study with enough data were included in to the final primary out-come analysis (Supplementary Documents Figure S1).

458 (54.3%) of the patients were female and mean age of the cohort was 66.34 ± 13.50 . Seventy five percent of the cases were vaccinated against COVID-19 and 24% of them had another COVID-19 episode previously. Comparison of patients who used and did not use the molnupiravir were given in Table 1. Patients who received molnupiravir differed significantly from those who did not, being older, having a higher burden of comorbidities, and more frequently being immunosuppressed. In addition, these patients more often acquired the infection nosocomially, had lower SpO₂ levels at the time of initial diagnosis, and had received a lower number of COVID-19 vaccine doses ($p < 0.005$ for all) (Table 1).

Table 1. Comparison of demographic, clinical and laboratory features of patients treated* or not treated with molnupiravir.**

Feature	Did not used molnupiravir (n=442)	Used molnupiravir (n=402)	SMD ³ or OR ⁴ (95% Confidence Interval), Effect size ⁵	P
Gender, female, n (%)	257 (56.1)	201 (43.9)	1.389 (1.058-1.823)	0.018
Age, mean $\pm$ SD	64.5 $\pm$ 13.2	68.4 $\pm$ 13.6	0.291 (0.155-0.427)	<0.001
BMI, mean $\pm$ SD	28.2 $\pm$ 12.6	27.7 $\pm$ 15.5	-0.036 (-2.36-1.36)	0.158
COVID-19 Vaccination, n(%)				
Vaccinated	328 (74.2)	297 (73.9)	0.983 (0.722-1.338)	0.914
mRNA vaccine, only	86 (19.5)	45 (11.2)	0.552 (0.354-0.770)	<0.001
Inactivated virus, only	30 (6.8)	38 (9.5)	1.434 (0.870-2.361)	0.155
mRNA+ inactivated virus vaccines	212 (53.4)	216 (53.9)	1.267 (0.966-1.661)	0.087
Previous COVID-19, n (%)	116 (26.2)	88 (21.9)	0.788 (0.573-1.082)	0.140
Number of received COVID-19 vaccines, n (%)	3.46 $\pm$ 1.23	3.01 $\pm$ 1.20	-0.038 (-0.51- -0.24)	<0.001
Symptoms				
Sore throat, n (%)	209 (47.5)	191 (47.5)	1.007 (0.768-1.322)	0.957
Sneezing, n (%)	191 (43.2)	180 (44.8)	1.063 (0.809-1.398)	0.659

Fever, n (%)	177 (40)	177 (44)	1.176 (0.894-1.549)	0.246
Headache, n (%)	134 (30.3)	94 (23.4)	0.699 (0.514-0.951)	0.022
Myalgia or arthralgia, n (%)	205 (46.4)	164 (40.8)	0.793 (0.603-1.043)	0.097
Malaise, n (%)	240 (54.3)	214 (53.2)	0.955 (0.727-1.254)	0.739
Cough, n (%)	287 (64.9)	271 (67.4)	1.115 (0.835-1.489)	0.459
Dyspnea, n (%)	38 (8.6)	37 (9.2)	1.076 (0.670-1.730)	0.762
Sputum production, n (%)	82 (18.1)	90 (22.4)	1.265 (0.904-1.770)	0.170
Anosmia, n (%)	39 (8.8)	24 (5.97)	0.655 (0.386-1.110)	0.114
Loss of taste, n (%)	37(8.8)	24 (5.97)	0.694 (0.407-1.182)	0.177
CCI (age included)), mean±SD	2.87±1.73	3.59±1.86	0.40 (0.26-0.54)	<0.001
Hypertension, n (%)	235 (53.2)	227 (56.5)	1.077 (0.816-1.423)	0.600
Diabetes mellitus, n (%)	118 (26.7)	127(31.6)	1.222 (0.906-1.650)	0.189
COPD, n (%)	23 (5.2)	24 (5.97)	1.123 (0.623-2.024)	0.700
Coronary artery disease, n (%)	68 (15.4)	68 (16.9)	1.083 (0.749-1.566)	0.670
Congestive heart failure, n (%)	13 (2.9)	12 (3)	0.986 (0.444-2.188)	0.973
Chronic renal failure, n (%)	13 (3)	16 (4)	1.329 (0.631-2.800)	0.453
Hemodialysis, n (%)	2 (0.5)	4 (1)	2.149 (0.391-11.802)	0.367
Connective tissue disorder, n (%)	20 (4.5)	23 (5.7)	1.243 (0.672-2.302)	0.487
Neurodegenerative diseases, n (%)	20 (4.5)	17 (4.2)	1.310 (0.676-2.535)	0.454
Active solid cancer receiving chemotherapy and/or radiotherapy, n (%)	9 (2)	8 (2)	0.949 (0.362-2.485)	0.915
Hematologic malignancy, n (%)	4 (0.9)	17 (4.2)	4.703 (1.569-14.103)	0.002
Solid organ transplantation, n (%)	4 (0.9)	7 (1.7)	1.886 (0.548-6.494)	0.307
Immunosuppression, any, n (%)	27 (6.1)	49 (12.2)	2.083 (1.274-3.407)	0.003
Current smoker, n (%)	59 (13.3)	69 (17.2)	1.345 (0.922-1.962)	0.123
Current alcohol drinking, n (%)	57 (13)	66 (16.4)	1.327 (0.904-1.947)	0.148
Pulmonary involvement on chest CT , n (%) (available only for 290)	7/191(2.1)	4/99 (4)	1.107 (0.316-3.875)	0.874
Nosocomial COVID-19, n	22 (5)	56 (13.9)	3.090 (1.849-5.162)	<0.001

(%), n (%)				
Temperature , °C, mean±SD	36.4±0.5	36.5±0.5	0.20 (0.13-0.27)	0.005
Pulse rate/minute, mean±SD	81.3±12.6	80.9±11.4	-0.033 (-0.168- 0.102)	0.868
TA systolic, mmHg, mean±SD	126.6±16.8	124.1±16.99	-0.148 (-0.283- - 0.013)	0.057
TA diastolic, mmHg, mean±SD	74.8±11.98	72.9±12.4	-0.16 (-0.22- -0.10)	0.054
Respiratory rate, mean±SD	18.96±2.3	18.91±2.8	-0.02 (-0.08-0.04)	0.458
Finger tip O2 saturation <95, n (%)	22(5)	56 (13.9)	3.09 (1.85-5.14), 0.154	<0.001
Hospital admission/death/new O2 need on Day 3, n (%)	1 (0.2)	2 (0.50)	2.205 (0.199- 24.410)	0.608
Hospital admission/death/new O2 need on Day 5, n (%)	1 (0.2)	3 (0.7)	3.316 (0.344- 32.006)	0.352
Hospital admission/death/new O2 need on Day 7, n (%)	1 (0.2)	5 (1.2)	5.554 (0.646- 47.704)	0.108
Hospital admission/death/new O2 need on Day 10, n (%)	1 (0.2)	6 (1.5)	6.682 (0.801- 55.742)	0.058
Hospital admission/death/new O2 need on Day 14, n (%)	1 (0.2)	7 (1.7)	7.815 (0.957- 63.800)	0.031
Hospital admission/death/new O2 need on Day 28, n (%)	1 (0.2)	7 (1.7)	7.815 (0.954- 63.800)	0.031
Hospital admission/death/new O2 need on 3 rd month, n (%)	2 (0.5)	7 (1.7)	3.955 (0.817- 19.150)	0.093
Hospital admission/death/new O2 need on 6 th month, n (%)	3 (0.7) (2 dead)	9 (2.3) (2 dead)	3.399 (0.914- 12.648)	0.079
Total number of households, mean±SD	1.17±1.04	0.98±0.96	0.190 (0.052-0.328)	0.005
Total number of COVID- 19 transmission to households on Day 14/total number of patients with data (%)	160/390 (41)	131/372 (35)	0.78 (0.58-1.05), 0.06	0.099

Nasopharyngeal SARS-CoV-2 viral clearance, n(%)

Day 3 (28 versus 79 patients)	5 (18)	26 (33)	2.26 (0.77-6.61), 0.15	0.131
Day 5 (28 versus 79 patients)	13/28 (46)	39/79 (49)	1.13 (0.47-2.67), 0.026	0.630
Day 10 (27 versus 73 patients)	21 (78)	46 (63)	0.49 (0.17-1.36), 0.14	0.163
Day 14 (27 versus 65 patients)	23(85)	55 (84.6)	0.96 (0.27-3.36), 0.01	0.940

*** Patients treated with molnupiravir: Molnupiravir 2X800mg/day, 5 days plus symptomatic and supportive care**

**** Patients not treated with molnupiravir: Symptomatic and supportive care alone.**

³ SMD: Standardized Mean Difference (Cohen's d / Hedges' g)

⁴ OR: Odds Ratio (for categorical variables)

⁵ Effect size: and ϕ , (for categorical variables)

The primary outcome (hospitalization or new oxygen need or death due to COVID-19 at 28th day of the study) occurred in a total of eight patients and was more frequent in the molnupiravir treated group (7/402, 1.7%) compared to the untreated group (1/442, 0.2%) (p=0.031).

To define the risk factors for primary outcomes we compared the groups with and without primary outcome first in univariate analysis (Table S1), than in Cox regression multivariate analysis. In univariate analysis, it was found that patients with primary outcome were older, had higher CCI, had productive cough complaints more frequently, more frequently treated with molnupiravir and acquired COVID-19 more frequently from the hospital. In multivariate analysis by Cox regression, only risk factor for primary outcome was found to be nosocomial acquisition of COVID-19 (OR 14.98, %95 CI 3.527-63.618), and molnupiravir usage was not found to be a risk factor (Table 2).

Table 2. Results of Multivariate Cox regression Analysis of Risk Factors for Primary Outcome (hospitalization or new oxygen need or death due to COVID-19 at 28th day of the study) among patients with COVID-19.

Variate	P	Hazard Ratio	95% CI
Age	0.095	1.055	0.991-1.124
Nosocomial COVID-19	<0.001	14.98	3.527-63.618

Additionally, in the propensity score–matched (PSM) cohort of 408 patients, in which patients who received molnupiravir and those who did not were matched according to age, Charlson Comorbidity Index (CCI), WHO clinical severity score, and COVID-19 vaccination status, nosocomial acquisition of COVID-19 was identified as the only risk factor associated with the primary outcome ($p=0.005$, OR 25.86, 95%CI 2.63-254.22), while molnupiravir use itself was not found to be associated with the primary outcome ($p=0.318$) (Figure 1A).

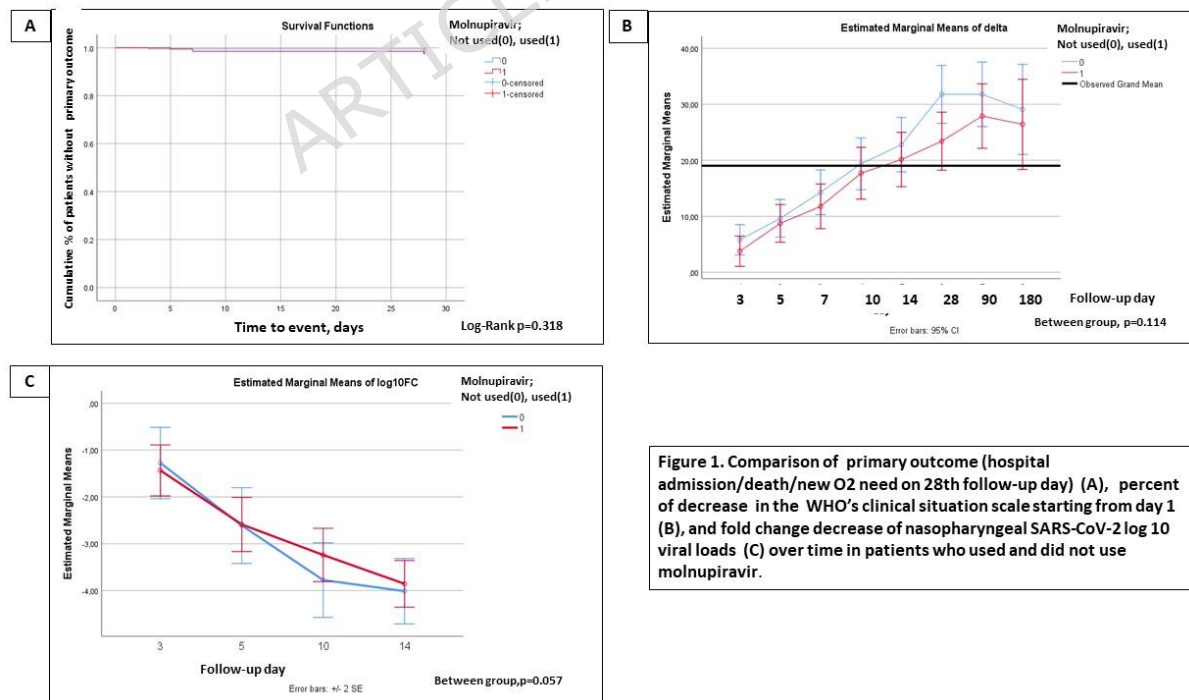


Figure 1. Comparison of primary outcome (hospital admission/death/new O2 need on 28th follow-up day) (A), percent of decrease in the WHO's clinical situation scale starting from day 1 (B), and fold change decrease of nasopharyngeal SARS-CoV-2 log 10 viral loads (C) over time in patients who used and did not use molnupiravir.

Figure 1. Comparison of primary outcomes (hospital admission/death/new O2 need on Day 28) (A), changes in the WHO's clinical situation scale (B), and nasopharyngeal SARS-CoV-2 log 10 viral loads (C) over time in patients who used and did not use molnupiravir over time in patients who used and did not use molnupiravir.

Hospitalization/new oxygen need/death rate of whole cohort at 3rd and 6th month of follow-up were not different between the molnupiravir treated and untreated groups ($P=0.105$ and $p=0.409$, respectively).

WHO clinical severity scores were significantly higher among molnupiravir treated groups than the no antiviral group, at the beginning and all the time points (3., 5., 7., 10., 14., 28. Days and 3. and 6. th months). Although the score decreased in both groups at every time point, there was not any statistically different decrease between the groups ($p=0.114$) (Figure 1B).

Dead/hospitalization/oxygen need composite outcome was observed in 12 patients at 6th month of follow-up (4 death, 8 hospital admission/new oxygen demand) .

There were a total of 260 individuals living in the households of patients who received molnupiravir and 307 individuals living in the households of patients who did not receive molnupiravir. Within 14 days after the index patient was diagnosed with COVID-19, COVID-19 was diagnosed in 106 of the 260 household members in the molnupiravir group (40.8%) and in 127 of the 307 household members in the non-molnupiravir group (41.4%) ($p=0.885$).

Nasopharyngeal SARS-CoV-2 viral load, serum SARS-CoV-2 spike antibody and other blood tests levels were measured in the specimens obtained from 109 consecutive patients (30 no antiviral, 79 molnupiravir). All five-time point nasopharyngeal SARS-CoV-2 viral load test

results were available for 72 of them (24 no antiviral, 48 molnupiravir). While viral clearance rate on the 3rd day of treatment was higher in the molnupiravir treated group (32.9% vs 17.9%) with a +15% absolute difference ($p=0.131$), viral clearance rate on the 10th day was higher in the control group with a +14.8% absolute difference ($p=0.163$) (Table S2-S4). Although nasopharyngeal viral loads decreased significantly within days in both of the groups ($p<0.001$), decrease rate did not differ between those who took or did not take the medication ($p=0.057$) (Figure 1C, Table S2-S4)

Serum Log10 SARS-CoV-2 antibody level was found to be lower in the molnupiravir treated group, both at the beginning and at the end of therapy, but only at the end of therapy level were significantly lower ($p=0.040$) (Figure 2). Additionally Log-10 fold changes of serum SARS-CoV-2 spike IgG antibody level from baseline to the follow up day of 28 were found to be lower among patients treated with molnupiravir (0.41 (95% CI 0.06-0.84)) than in those not treated (0.60 (95%CI 0.37-0.77), but the difference was not statistically significant ($p=0.228$).

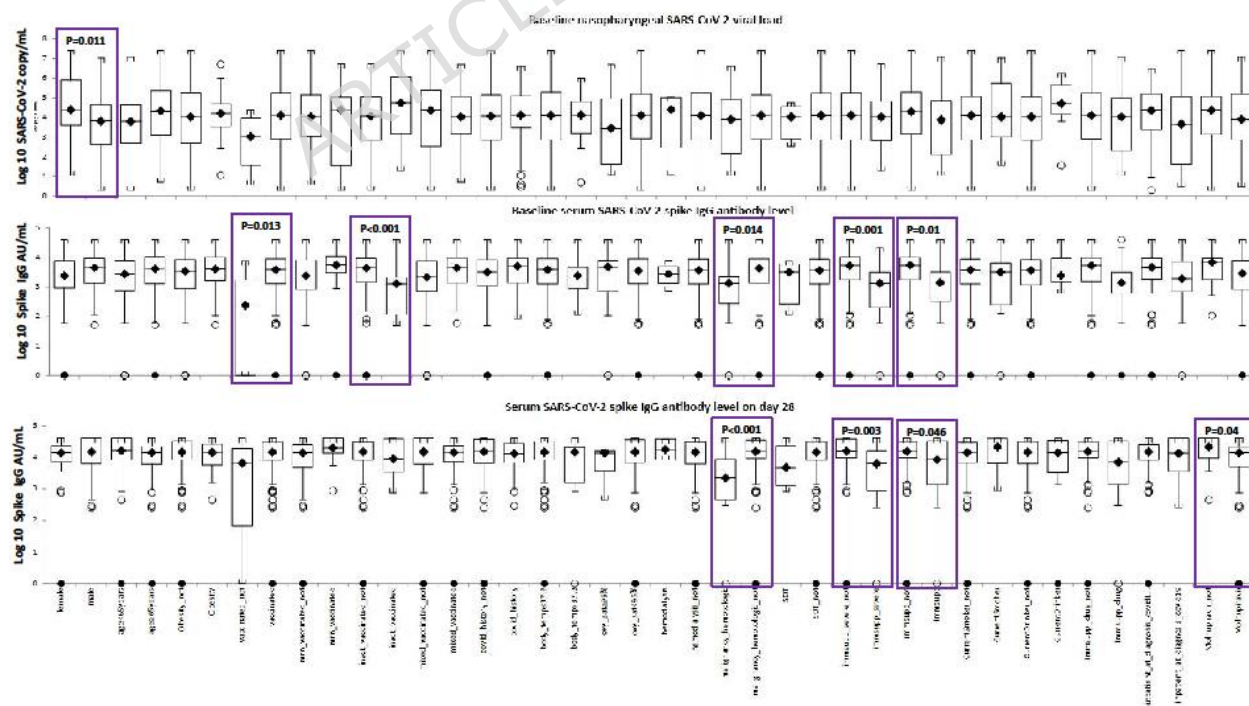


Figure 2. Comparison of baseline nasopharyngeal SARS-CoV-2 viral load (A) and serum SARS CoV-2 spike antibody levels on the first (B) and 28th (C) day of follow-up among COVID-19 patients with different characteristics.

Serum glucose, BUN, creatinine, AST, ALT, CRP, LDH, procalcitonin and D-Dimer levels and blood WBC, PNL, lymphocyte, erythrocyte and platelet counts on the first and 10th day of follow up were compared between the molnupiravir treated (70) and not treated (28) patients. At the first day, molnupiravir group had significantly lower lymphocyte count ($p=0.025$) and higher serum ferritin ($p=0.023$) and D-Dimer ($p=0.010$) levels than non-molnupiravir group. There was not any difference in the kinetics of serum inflammatory and other tests from the beginning to the 28th day of follow-up between the groups ($p > 0.05$ for all) (Table 3).

Table 3. Comparison of Log 2 fold changes (Log 2 FC) of serum and blood test results of patients who received and did not receive molnupiravir, from Day 1 (baseline) to Day 10.

Log2 fold changes of blood /serum test results from Day 1 to Day 10	Patients received molnupiravir				Patients did not receive molnupiravir				p
	n	Media n	IQR		n	Med ian	IQR		
Blood leucocyte count, log2-FC	28	0,21	- 0,13	0,42	76	0,20	- 0,25	0,50	0,780
Blood hemoglobin level, Log2-FC	28	-0,02	- 0,07	0,05	76	0,01	- 0,05	0,09	0,087
Blood platelet count, Log2-FC	28	0,39	0,17	0,65	76	0,32	- 0,17	0,66	0,265
Blood PNL count, Log2-FC	28	0,12	- 0,18	0,44	76	0,20	- 0,39	0,56	0,841
Blood lymphocyte count, Log2-FC	28	0,51	0,00	1,00	76	0,48	0,07	0,94	0,980
Serum CRP level, Log2-FC	28	-2,40	- 3,45	- 1,16	76	-2,59	- 3,39	- 0,20	0,777

Serum procalcitonin level, Log2-FC	2 8	-1,00 2,32	- 0,00	0,00 7	-0,58 6	- 1,81	0,2 6	0,1 83
Serum ferritin level, Log2-FC	2 8	-0,35 0,46	- 0,04	- 7	-0,11 6	- 0,50	0,1 8	0,2 37
Serum D-dimer level, Log2-FC	2 8	0,04 0,53	- 0,51	7 6	-0,03 6	- 0,37	0,3 2	0,9 18
Serum LDH level, Log2-FC	2 8	0,02 0,07	- 0,20	7 6	0,06 6	- 0,15	0,2 1	0,8 56
Serum AST level, Log2-FC	2 8	-0,14 0,33	- 0,07	7 6	-0,12 6	- 0,40	0,2 5	0,9 32
Serum ALT level, Log2-FC	2 8	-0,11 0,50	- 0,26	7 6	-0,08 6	- 0,51	0,5 1	0,6 70
Serum creatinine level, Log2-FC	2 8	-0,06 0,23	- 0,07	7 6	-0,02 6	- 0,20	0,0 9	0,5 85
Serum level glucose level, Log2-FC	2 8	-0,10 0,26	- 0,17	7 6	-0,02 6	- 0,38	0,2 4	0,6 85

Adverse events were described in 12 of 404 (2.97%) molnupiravir users, including 5 diarrhea, 4 nausea, 2 dizziness, 2 rash, and 1 serum AST/ALT increase. Molnupiravir has to be stopped because of those side-effects in 4 patients. While 6 of them female, The mean age of 12 patients with adverse event was 65 (ranges 34-88), and 7 of them older than 65.

While 78 (9.2%) of the cases acquired COVID-19 during hospitalization (nosocomial COVID-19), 766 (90.8%) acquired COVID-19 from the community. Compared to community-acquired COVID-19 cases, nosocomial COVID-19 cases had lower frequency of some symptoms including headache, sore throat, runny nose, muscle/joint pain, malaise, loss of taste and smell, but higher frequency of shortness of breath symptom (all $p < 0.05$). In nosocomial COVID-19 cases, the number of comorbidities, CHF, CRF, hemodialysis, neurovascular disease, moderate/advanced

liver disease, hematological malignancy, severe immunosuppression or immunosuppression, and molnupiravir use were also significantly higher than in patients who acquired COVID-19 from the community (all $p<0.05$). In patients with nosocomial COVID-19, the duration of symptoms was shorter (2.93 days vs. 3.25 days, $p=0.081$), the mean fingertip saturation value at diagnosis was lower (96.2% vs. 95.1%, $p<0.001$), and intra-familial transmission was also lower ($p<0.005$) than the patients with community acquired COVID-19. Oxygen requirement or death occurred more frequently in nosocomial COVID-19 cases on the 5th, 10th, 14th, 28th days and at the 3rd and 6th months of follow-up (Table 3).

Table 3. Comparison of nosocomial and community acquired COVID-19 cases.

Feature	Community acquired COVID-19 (n=766)	Nosocomial COVID-19 (n=78)	p
Gender, female, n (%)	423	35	0.080
Age, $\text{ort}\pm\text{SD}$	66.26 $\pm$ 13.11	66.67 $\pm$ 16.56	0.802
Weight, kg, $\text{mean}\pm\text{SD}$	75.914 $\pm$ 14.72	71.76 $\pm$ 13.47	0.019
Height, cm, $\text{mean}\pm\text{SD}$	165 $\pm$ 9.50	166 $\pm$ 9.7	0.515
BMI, $\text{mean}\pm\text{SD}$	27.84 $\pm$ 11.7	25.69 $\pm$ 3.93	0.004
COVID-19 vaccination, n			
Vaccinated	556	69	0.002
mRNA vaccine	122	9	0.308
Inactivated virus	50	18	<0.001
mRNA+ inactivated virus vaccines	18	42	0.487
Number of received COVID-19 vaccines,	3.00 $\pm$ 1.03	3.32 $\pm$ 1.64	0.181
Previous COVID-19, n	175	19	0.540
Duration of symptoms	3.27 $\pm$ 1.22	3.00 $\pm$ 1.29	0.081
Sore throat, n	378	24	0.002
Sneezing, n	352	19	<0.001
Fever, n	324	30	0.589
Headache, n	218	10	0.004
Myalgia or arthralgia, n	345	24	0.021
Malaise, n	418	36	0.199
Cough, n	503	55	0.282
Dyspnea, n	62	13	0.009

Sputum production, n	157	15	0.845
Anosmia, n	62	1	0.023
Loss of taste, n	60	1	0.035
CCI, mean±SD	3.08±1.69	4.55±2.41	<0.001
Immunosuppression, any, n	46	30	<0.001
Temperature ≥37.3 °C, n	36.45±0.49	36.54±0.54	0.153
Pulse rate/minute, mean±SD	81.16±12.18	80.86±10.95	0.833
TA systolic, mmHg, mean±SD	126±16	118±15	<0.001
TA diastolic, mmHg, mean±SD	74±12	71±10	0.081
Respiratory rate, mean±SD	18.99±2.48	18.44±1.65	0.034
Finger tip O2 saturation, mean±SD	96±2.5	95±2.45	0.002
Hospital admission/death/new O2 need on Day 3, n (%)	2	1	0.253
Hospital admission/death/new O2 need on Day 5, n (%)	2	2	0.045
Hospital admission/death/new O2 need on Day 7, n (%)	2	4	0.001
Hospital admission/death/new O2 need on Day 10, n (%)	3	4	0.002
Hospital admission/death/new O2 need on Day 14, n (%)	3	5	<0.001
Hospital admission/death/new O2 need on Day 28, n (%)	3	5	<0.001
Hospital admission/death/new O2 need on 3rd month, n (%)	3	6	<0.001
Hospital admission/death/new O2 need on 6th month, n (%)	5	7	<0.001
Total number of households, mean±SD	1.17±1.04	0.98±0.96	
Household COVID-19 transmission by symptoms or confirmed, n	289	17	<0.001

Discussion

Molnupiravir was recommended to all COVID-19 patients included in this study, but those who accepted to use the drug were more likely to be older with more comorbidities and immunocompromised. In the 6th year of the COVID-19 Pandemic, the groups in which the outcomes of the disease may be poor are reported to be the same groups; for example, in a study conducted in the USA, COVID-19-related deaths in the late omicron period were seen mainly in

those aged >65 and with >3 comorbidities [7]. This data actually shows that people who need medication are aware of this need, and indications for antiviral treatment should be revised according to the current risk groups for the severe COVID-19.

In our study which include mainly the older COVID-19 patients with multi-comorbidity, we found that molnupiravir started in the first 5 days of the disease had no effect on the rates of hospitalization, oxygen requirement, mortality or clinical recovery. These results may be due to the fact that the majority of our patients (93%) were vaccinated against COVID-19 with at least three vaccines. Additionally our study was conducted during a period when the Omicron variant was in circulation, a variant characterized by reduced mortality relative to earlier SARS-CoV-2 strains [8]. Due to all of those factors, the rate of death/ hospitalization/ oxygen need in the cohort was as low as 0.95%, therefore the total number of patients needed to demonstrate the effectiveness of molnupiravir for COVID-19 may not have been reached. In a recent meta-analysis of randomized controlled trials involving 34,570 patients, molnupiravir was shown to reduce the rate of hospitalization (relative risk [RR] = 0.63, 95% CI: 0.47–0.85), mechanical ventilation (RR = 0.37, 95% CI: 0.19–0.72) and shorten the time to recovery (mean difference [MD] = -2.91 days, 95% CI: -3.66 - -2.16), it was shown to had no significant effect on all-cause mortality, viral clearance time and hospital stay [9]. In an other meta-analysis of 30 cohort studies including 48,808 patients, it was shown that molnupiravir slightly reduced the rate of death and hospitalization in the first 35 days (RR 0.75, 95%CI 0.67–0.85; I² = 32%; low evidence), but the evidence on the effect of vaccination status was found to be inconsistent and authors concluded that additional studies should be conducted on the use of molnupiravir in vaccinated patients [10]. Finally, another meta-analysis study including 8 RCTs and 5 observational studies reported that molnupiravir reduced all-cause mortality in the general population (RR 0.28; 95% CI: 0.20-0.79, I² Z 0%), but did not reduce hospitalization (RR 0.67;

95% CI: 0.45-1.00), and no benefit was observed in the vaccinated group [11]. Results of those meta-analysis and our study suggest that effect of molnupiravir among vaccinated COVID-19 patients may be nonsignificant and along with the molnupiravir's proven less effectiveness in reducing death/hospitalization due to COVID-19 even in unvaccinated groups than other agents (nirmatrevir or remdesivir) with which it was compared, molnupiravir should not be the first-line treatment for COVID-19. Indeed, in all current COVID-19 treatment guidelines, it is recommended to use it in cases where first-line drugs such as nirmatrelvir and remdesivir cannot be used [12]. But, because of drug-drug interactions of nirmatrelvir/r and IV route of administration of remdesivir, there is still a need for an orally administered COVID-19 drug, such as molnupiravir, as a result additional studies including a sufficient numbers of patients to demonstrate even small amount of effectiveness of molnupiravir in vaccinated groups are needed.

In our study, it was observed that viral clearance on the 3rd day of follow-up was higher in those using molnupiravir, but after stopping the drug, on the 10th day of follow-up, viral clearance were higher in those not using the drug. Another meta-analysis study including 8 RCTs and 5 observational studies showed that molnupiravir increased viral clearance on the 5th day (RR 2.68; 95% CI: 1.94-4.22) [11]. In the Phase 3 study of molnupiravir, which included much younger patients with fewer comorbidities than in our study, the decrease in mean viral load in the molnupiravir treatment group was greater on days 3 and 5 compared to placebo, but this was not observed to continue on the following days, and the decrease in the first 5 days was less than 1 log₁₀ copies/ml, as in our study [1]. Similar to our data, in a study recently published as a sub-analysis of the PANORAMIC study, a significant decrease in viral load was initially seen after 5 days of molnupiravir administration, but it was observed that the treatment was independently associated with greater viral persistence on the 14th day, suggesting that the 5-day treatment

period was insufficient. Authors suggested that treatment discontinuation without pathogen clearance is rare in the treatment of infectious diseases, and therefore 5 days of treatment could be insufficient for viral clearance, which may be the reason why molnupiravir was not effective in the main studies [13]. Considering that 50% of the patients in our study were still positive on the stopping day of treatment and that viral clearance slowed down after the discontinuation of treatment, it was thought that a molnupiravir treatment period of 5 days might not be sufficient and additional studies are also needed on this topic.

We found that serum SARS-CoV-2 antibody levels of the patients also increased less in the molnupiravir group, and while the antibody results were not different at the beginning, it was noted that antibody levels in those who received the drug were significantly lower than those who did not on the 28th day of follow-up. In the secondary analysis of the PANAROMIC study mentioned above, it was observed that spike antibody level on the 14th day were lower in those treated with molnupiravir, and it was suggested that this decrease may be due to the initial viral suppression achieved with molnupiravir and/or viral genetic changes [13]. It is reasonable that antiviral treatments applied at an early stage in viral infections affect the antibody response by reducing antigen, but it is also clear that additional studies are required on the incidence, causes and consequences of this phenomenon.

We did not define any effect of molnupiravir on blood cell counts, serum CRP, procalcitonin, ferritin, D-dimer, LDH, AST, ALT, creatinine, and glucose levels of the COVID-19 patients. A secondary analysis of the MoveOut study found that compared to placebo serum CRP level and SpO₂ normalization were faster in molnupiravir starting from the 3rd day of treatment [14]. In our study, although molnupiravir treated patients had higher baseline level of serum inflammatory markers probably resulting from not COVID-19 itself, but accompanying comorbidities; fold changes of those tests under treatment were not different between the groups

used or not used the molnupiravir.

The frequency of adverse drug reactions associated with molnupiravir including diarrhea, nausea/vomiting, dizziness, and rash was determined as 2.97%, and only 1% of patients had to discontinue the drug due to these effects; six of the 12 patients who developed adverse drug reactions were female and seven patients were ≥ 65 years of age. Additionally we did not see any side effect of molnupiravir on the liver and kidney function tests including AST, ALT, BUN, creatinine. In the examination of 2.285 adverse events reports that may be related to molnupiravir and 114.291 reports related to other COVID-19 drugs in the US FDA drug adverse event reporting system, it was determined that the frequency of adverse effects with molnupiravir was lower than other drugs, and the most common adverse effects were seen in patients aged >65 (70%) and in women (54%), and the most frequently identified adverse effects were diarrhea, rash, nausea, and dizziness, as in our study [15].

The fact that nosocomial COVID-19 was detected in 10% of the cases in our study emphasizes the importance of COVID-19 transmission in hospitals. Consistent with the literature, we found that patients with nosocomial COVID-19 had more comorbidities and severe diseases and that oxygen requirement/death outcome developed more frequently [16-18], those findings also show the vital importance of preventing COVID-19 for hospitalized patients. Although we found a significant differences between the symptoms of nosocomial and community-acquired COVID-19 cases in our study these findings should be interpreted with caution, as baseline characteristics differ between the two groups, limiting the validity of direct comparisons [18].

Within 14 days after the index patient was diagnosed with COVID-19, COVID-19 was diagnosed in 106 of the 260 household members in the molnupiravir group and in 127 of the 307 household members in the non-molnupiravir group ($p=0.885$). Although there was 4.5% lower secondary

COVID-19 household transmission among patients received or not received molnupiravir, but the number of people living in the house at the beginning was also significantly lower in the group receiving the drug, as a result lower rate of secondary transmission was not attributed to the molnupiravir treatment in our study.

In a randomized controlled trial investigating the efficacy of molnupiravir to prevent COVID-19 in household contacts of people with COVID-19, it was observed that 6.5% of 763 contacts who received molnupiravir and 8.5% of 764 contacts who received placebo developed COVID-19 within 14 days (one-way $p=0.085$), and superiority over placebo could not be demonstrated in this regard [19].

Our study have some strengths, we prospectively followed the patients, included both nosocomial and community acquired patients and were able to check the kinetics of so many test including SARS-CoV-2 antibody and acute phase reactants which enabled us to define the side effects of the molnupiravir on organ functions more precisely. Also by measuring the antibody response at the beginning and 28th day of the follow up, we were able to define the effect of molnupiravir on antibody response.

Our study have also some limitations; for reasons beyond our control we were unable to reach our targeted total patient number which would have been enabled us to define the effect of molnupiravir more precisely. While the achieved sample size was smaller than initially targeted, the cohort remains suitable for evaluating clinically meaningful larger effect magnitudes and contributes reliable real-world evidence toward understanding treatment impact.

Additionally due to non-interventional method of the study, molnupiravir was used mainly in more vulnerable groups with comorbidities. To avoid this biases we used multivariate Cox regression analysis and propensity score matching of the cohort.

Conclusions

In COVID-19 cases who have developed a certain level of immunity against the disease by vaccination or exposure previously, molnupiravir may not have sufficient effect on reducing hospitalization/death and accelerating clinical recovery, therefore it should not be considered as the first-line treatment for COVID-19 in risk groups. Although molnupiravir leads to higher viral clearance in nasopharyngeal samples of COVID-19 patients in the first days, studies are needed on the necessity of longer-term administration since positivity can be detected in a significant proportion of patients on the 5th day of treatment and it may lead to an increase in viral load after treatment is discontinued. SARS-CoV-2 spike antibody levels may be lower in patients using molnupiravir, and additional studies are needed on the clinical significance of this situation. In cases developing nosocomial COVID-19, the risk of poor outcome is high, especially due to the patients' severe underlying comorbidities, therefore it is vital to take precautions to prevent COVID-19 transmission in the hospital.

Conflict of interest: None

The study was approved by the Ethical Board of Istanbul University Istanbul Medical School on 26.04.2022 with the registration number of 011-KAEK-57 – 751.

The work described has been carried out in accordance with The Code of Ethics of the World Medical Association

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Data availability statements: All data generated or analyzed during this study are included in the supplementary files. Additionally, all data from all patients used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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