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ORIGINAL ARTICLE

# Use of molnupiravir in patients who developed SARS-CoV2-Infection during hospitalization

Gülçin Telli Dizman[1]
ORCID: 0000-0001-8195-3345

Yahya Çakır[2]
ORCID: 0000-0003-0790-9519

Gamze Korubük[3]
ORCID: 0009-0009-2532-497X

Gökhan Metan[1]
ORCID: 0000-0002-2676-4557

Serhat Ünal[1]
ORCID: 0000-0003-1184-4711

[1]Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Hacettepe University, Ankara, Türkiye.

[2]Department of Internal Medicine, Faculty of Medicine, Hacettepe University, Ankara, Türkiye.

[3]Hacettepe University Hospitals, Hospital Pharmacy, Ankara, Turkiye.

Corresponding Author: Gülçin Telli Dizman
E-mail: gulcintelli@hotmail.com

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ABSTRACT

Background: Molnupiravir is an oral anti-viral that inhibits SARS-CoV-2 replication and reduces viral load. We aimed to investigate mortality rates and the factors affecting mortality in patients receiving molnupiravir who were hospitalized for reasons other than COVID-19 in a tertiary care university hospital.

Methods: Patients who received molnupiravir for COVID-19 according to Turkish Ministry of Health guidelines and were hospitalized for reasons other than COVID-19 were included in the study. Demographic and clinical characteristics of patients were compared according to survival status defined as 30-day mortality.

Results: The mortality rate of 101 patients with Covid-19 was found to be 6.93 %. The rates of corticosteroid use, oxygen support, and mechanical ventilation requirement were significantly higher in patients who died within 15 days of the PCR positivity. Although not statistically significant, the ratio of concomitant bacterial pneumonia was higher in patients who did not survive. Also, the mortality rate was lower in patients who were vaccinated three doses or more without statistical significance.

Conclusion: In patients who were hospitalized for other reasons and received molnupiravir treatment with a diagnosis of COVID-19, the development of respiratory failure was the only demographic factor that was statistically different in terms of mortality.

Keywords: Molnupiravir, COVID-19, SARS-CoV-2.

## INTRODUCTION

Early treatment with anti-virals is crucial for preventing severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) associated hospitalization and mortality [1]. Molnupiravir is an oral pro-drug of the ribonucleoside analogue N-hydroxycytidine (NHC). NHC spreads into cells, where it is metabolized to its triphosphate form, and inhibits SARS-CoV-2 replication and reduces viral load [2].

The effectivity of molnupiravir against SARS-CoV-2 was shown in preclinical trials. It was also evaluated in phase-1, 2, and 3 trials, and was reported as safe and well tolerated at a dose of 800 mg twice daily [3-8]. Placebo-controlled, industry-funded phase-3 trial (MOVe-OUT) was conducted in unvaccinated, non-hospitalized patients with at least one risk factor for severe Coronavirus disease 2019 (COVID-19). Treatment was initiated within the first five days of the symptoms and resulted with a 31% reduction in risk of hospitalization and death compared to placebo [8]. In another recent retrospective cohort study from Hong Kong involving 33,217 outpatients and 21,138 inpatients, 16.1% and 3.8% received molnupiravir, respectively. Molnupiravir treatment was found to be associated with reduced all-cause mortality and cost savings [9]. However, there was no reduction in the frequency of COVID-19-associated hospitalization or death for high-risk vaccinated adults in the largest randomized trial that compared molnupiravir plus usual care with usual care alone [1].

Molnupiravir started to be used in Turkey according to the COVID-19 treatment guideline of the Ministry of Health published on February 12th, 2022. Treatment was given to adult patients with mild to moderate COVID-19 at increased risk of adverse outcomes regardless of vaccination status [10].

In this study, we aimed to investigate mortality rates and the factors affecting mortality in patients receiving molnupiravir who were hospitalized for reasons other than COVID-19 and diagnosed with COVID-19 during their hospitalization in a tertiary care university hospital.

## MATERIAL AND METHODS

### Setting

This retrospective observational study was conducted in Hacettepe University Adult and Oncology Hospitals in Ankara, the capital city of Turkey. These tertiary care hospitals include 1040 and 119 beds, respectively.

Study Population

Patients who received molnupiravir for COVID-19 according to Turkish Ministry of Health guidelines and were hospitalized for reasons other than COVID-19 between 01.08.2022 and 01.12.2022 were extracted from the hospital pharmacy records. All patients were diagnosed with a positive SARS-CoV-2 reverse-transcriptase–polymerase-chain-reaction (RT-PCR) test from a nasopharyngeal sample. Adult patients (>18 years) with mild to moderate disease with at least one risk factor for severe COVID-19, regardless of vaccination status included in the study. Molnupiravir was initiated as soon as possible but not later than five days after the onset of signs or symptoms.

Advanced age, primary immunodeficiency, solid tumor or hematological malignancy (patients who have received chemotherapy in the last year and radiotherapy in the previous six months), solid organ or hematopoietic stem cell transplantations, Acquired Immune Deficiency Syndrome (AIDS), Down syndrome, liver cirrhosis, chronic renal failure with dialysis, sickle cell anemia, diabetes mellitus with end-organ damage, myocardial infarction, stroke, multiple sclerosis, motor neuron diseases, myasthenia gravis, Huntington's disease, Alzheimer, morbid obesity (Body mass index, (BMI) >40), stage 3 and stage 4 chronic obstructive pulmonary disease, emphysema and immunosuppressive therapies were defined as risk factors for severe COVID-19 according to the Turkish Ministry of Health Guideline. Molnupiravir, with a dose of 800 mg twice daily for five days, was provided by the Turkish Ministry of Health for these patients [10].

 

### Study Outcome

Demographic and clinical data such as; age, gender, PCR status, symptom day at onset of the therapy, comorbidities, Charlson Comorbidity Index (CCI), and vaccination status (vaccine types, date of last vaccine administration) were recorded.

Corticosteroid use, requirement of oxygen and mechanical ventilation support, and presence of concomitant bacterial pneumonia were also noted. Bacterial pneumonia was defined according to Centers for Disease Control and Prevention (CDC) definitions by evaluating clinical, radiological, microbiological features and laboratory results together. Follow-up SARS-CoV-2 PCR test after initial positive PCR was recorded for at least 28 days or until death, which came first.

### Statistical analysis

Demographic and clinical characteristics of patients were compared according to survival status defined as 30-day mortality. Categorical variables were presented as numbers and percentages. Means and standard deviations were calculated for continuous variables. Categorical variables were compared using the Pearson chi-square test/Fisher's exact test. Continuous variables were compared using the Student's t-test or Mann–Whitney U test according to the distribution of variables. For all statistical analyses, Statistical Packages for the Social Sciences (v17.0 SPSS 24 Inc. Chicago, IL) software was used.

The study was approved by the Institutional Non-Interventional Clinical Research Ethics Committee, Ankara, Turkey (2022/14-21).

## RESULTS

A total of 101 patients with COVID-19 were included in the study. All patients completed the 5-day treatment course. Discontinuation due to side effects was not observed. The mean age of the patients was 66 years (±17.46), and 59 (58.4 %) patients were female. Mortality rate was 6.93 % (Table 1). COVID-19 was diagnosed in mean 7.08 (±14.8) days of hospitalization. The most common reasons for hospitalization were malignancies and neurological disorders. The mean duration between symptom onset and molnupiravir treatment was 2.08 days (±1.026). All patients had a comorbid disease, and the most common comorbidities were malignancies and hypertension. Mean CCI was higher in patients who did not survive (6,71±1.11 vs 5,25±2.23), but this difference was not statistically significant (p=0.096).

Nineteen of the patients were unvaccinated, and no difference was detected in mortality rates between vaccinated patients and unvaccinated patients or those who were vaccinated at least one dose. The mortality rate was lower in patients who were vaccinated with three doses or more without statistical significance.

The rates of corticosteroid use, oxygen support, and mechanical ventilation requirement were found to be significantly higher in patients who died within 15 days of the PCR positivity.

Persistence SARS-CoV-2 PCR positivity one week after the first positive PCR test and positivity ten days after the first negativity were not different according to mortality status.

Secondary bacterial pneumonia was detected in 29 (29%) of all patients. Although not statistically significant presence of concomitant bacterial pneumonia ratio was higher in patients who did not survive (three of seven patients, 42.9 % vs. 26 of 93 patients, 28 %).

## DISCUSSION

Seven of the 101 patients at high risk for severe COVID-19 died (6.93%) who received molnupiravir regardless of the vaccine status in our study. The mortality rate was reported as 2.6% in a prospective observational multicenter study involving 856 patients who received a third dose of COVID-19 vaccination and were treated with molnupiravir [11]. In another retrospective cohort trial, molnupiravir was found associated lower risk of death, like nirmatrelvir-ritonavir, or sotrovimab, compared with no anti-viral treatment in high-risk patients [12]. Although there are many studies among outpatient or inpatient COVID-19 patients receiving molnupiravir, studies did not focus on patients with mild to moderate symptoms of COVID-19 who were hospitalized for other reasons. In a brief report including 44 hospitalized patients admitted for other diseases than COVID-19,

**Table 1.** Distribution of demographic and clinical characteristics between dead and survived patients

| Characteristic | | Survived N:94 | Dead N:7 | All Cases N: 101 | p |
|---|---|---|---|---|---|
| Gender n (%) | | | | | 0.131 |
| | Female | 53(52.5) | 6 (5.9) | 59 (58.4) | |
| | Male | 41(40.6) | 1 (1) | 42 (41.6) | |
| Age (Mean±SD ) Year | | 65,71±17.46 | 60,14±16.09 | 65,32 ±17.46 | 0,418 |
| Age Intervals n (%) | | | | | ,214 |
| The interval between symptom onset and initiation of molnupiravir (mean±SD) | | 2,06 ± 1.02 | 2,28±0.75 | 2,08 ±1.026 | 0,584 |
| CCI* (mean±SD) | | 5,25±2.23 | 6,71±1.11 | 5,35 ± 2.23 | 0,096 |
| Vaccination status | | | | | ,179 |
| (Mean±SD) | | 2,68 ±1.56 | 1,85± 1.46 | 2,62±1.561 | |
| n (%) | 0 | 17(16.8) | 2(2) | 19(18.8) | |
| | 1 | 2(2) | 0(0) | 2(2) | |
| | 2 | 15(14.9) | 3(3) | 18(17.8) | |
| | 3 | 30(29.7) | 1(1) | 31(30.7) | |
| | 4 | 20(19.8) | 1(1) | 21(20.8) | |
| | 5 | 10(9.9) | 0(0) | 10(9.9) | |
| | 4 | 8(7.9) | 0(0) | 8(7.9) | |
| | 5 | 2(2) | 0(0) | 2(2) | |
| Corticosteroid use** n (%) | | | | | <0.001 |
| | No | 76(75.2) | 1(1) | 77(76.2) | |
| | Yes | 18(17.8) | 6(5.9) | 24(23.8) | |
| Oxygen Support*** n (%) | | | | | ,006 |
| | No | 76(76) | 2(2) | 78(78) | |
| | Yes | 18(18) | 4(4) | 22(22) | |
| Mechanical ventilation support *** n (%) | | | | | <0.001 |
| | No | 91(90.1) | 2(2) | 93(92.1) | |
| | Yes | 3(3) | 5(5) | 8(7.9) | |
| PCR status one week after positivity n (%) | | | | | ,247 |
| | Negative | 61(60.4) | 3(3) | 64(63.4) | |
| | Positive | 33(32.7) | 4(4) | 37(36.6) | |
| PCR positivity ten days after first negativity n (%) | | | | | ,849 |
| | Negative | 82(82) | 6(6) | 88(88) | |
| | Positive | 11(11) | 1(1) | 12(12) | |
| Presence of Concomitant Bacterial Pneumonia n (%) | | | | | ,407 |
| | No | 67(67) | 4(4) | 71(71) | |
| | Yes | 26(26) | 3(3) | 29(29) | |

*Charlson comorbidity index

**Fifteen days within PCR positivity

molnupiravir was found safe and well tolerated. The mortality rate was reported as 11.4 %, and no patients' characteristics were found significantly associated with hospital mortality [13].

Advanced age and comorbidities were shown to be the most important risk factors for COVID-19 mortality [14]. In our study, the mean age of the patients who received molnupiravir was found to be similar between survivors and non-survivors. We investigated the impact of comorbidities with CCI. CCI is an easy-to-perform method that was also used for COVID-19 to estimate the risk of death related to comorbid diseases. A higher CCI score was reported as an independent risk factor for mortality in COVID-19 patients in two retrospective

 

studies from other centers in Turkiye [15, 16]. We also found a higher mean CCI score among non-survivors, which was not statistically significant. However, no mortality was detected in patients with a CCI score lower than six.

Early administration of anti-viral treatments was reported to be associated with lower hospitalization and mortality rates in several studies [8, 17, 18]. Most of these studies compared patients who were treated within 5–7 days of symptom onset with those treated in later periods. However, in a recent retrospective observational study that included 206 patients who received anti-viral agents, the interval between diagnosis and treatment as two days was found to be a significant independent predictor of moderate disease (OR = 2.27, 95% CI = 1.58–3.24, p <0.0001) [19]. We initiated anti-viral therapy within five days after symptom onset to all patients, with a mean of two days.

Early treatment with molnupiravir was found to be associated with a 30% reduced risk of hospitalization and mortality among high-risk unvaccinated adults with COVID-19 in an industry-conducted phase 3 trial [8]. However, in a recent pooled analysis of nine RCTs, any benefit of molnupiravir was not shown in hospitalized patients due to COVID-19 [20]. Our study included a different group of patients in whom hospitalization was not due to COVID-19. However, they had similar risk factors for developing severe COVID-19 like the patients in the community. The relatively low mortality rate in this study might encourage the use of molnupiravir in these patients despite the remaining controversy in the absence of a control group. In a study that analyzed 45 patients who were hospitalized for other reasons and used molnupiravir for COVID-19 that developed in the hospital, the use of molnupiravir was found to be safe[13], but further studies are required to understand the role of molnupiravir in this setting regarding respiratory insufficiency and mortality.

Our study has several limitations. First, it is a retrospective single-center trial, and the number of patients was limited because of the nature of the study. Second, there was no control group to compare patients who received molnupiravir or not due to ethical issues. Since all of the patients received molnupiravir, it was not possible to discuss the effects of treatment on mortality. Additionally, due to the low number of patients, factors influencing mortality could not be evaluated through multivariate analyses. Lastly, only pneumonia was recorded as a secondary bacterial infection that can affect mortality rates.

## CONCLUSION

In patients who were hospitalized for other reasons and received molnupiravir treatment with a diagnosis of COVID-19, the development of respiratory failure was the only demographic factor that was statistically different in terms of mortality. Multicenter case-control studies might be useful to understand the efficacy of molnupiravir in this setting.

### Competing interests

Gökhan Metan has received honoraria for speaking at symposia and lectures organized by Gilead; Merck, Sharp, and Dohme (MSD), and Pfizer. He received consultation fee from United Nations Turkiye Office. He has also received travel grants from MSD, Pfizer, and Gilead to participate in conferences. All other authors declare that they have no competing interests.

### Author contribution

Study conception and design: GTD, YÇ, GK, GM and SÜ; data collection: GTD, YÇ, and GK; analysis and interpretation of results: GTD ,YÇ, GM and SÜ; draft manuscript preparation: GTD, YÇ and GM. All authors reviewed the results and approved the final version of the manuscript.

### Ethical approval

The study was approved by the Institutional Non-Interventional Clinical Research Ethics Committee (Protocol no. 2022/14-21).

### Funding

The authors declare that the study received no funding.

### Conflict of interest

The authors declare that there is no conflict of interest.

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