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Inequities in Antiviral Therapy for Diabetic Individuals Affected by COVID-19

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ABSTRACT

Diabetes patients are more vulnerable to COVID-19 infections, which can cause serious respiratory conditions. In this study, the effect of the antiviral medication with molnupiravir and favipiravir was compared in COVID-19 patients with underlying diabetes. The current investigation included a cohort of 100 people who had been diagnosed with diabetes, had a SARS-CoV-2 infection, and had been admitted sequentially. The antiviral drugs were administered to these patients according to regional recommendations: favipiravir was administered for 10 days for group F (51 instances), while molnupiravir was administered for 5 days to group M (49 cases). Compared to group M, group F showed a higher mean hospitalisation rate (11.29 ± 2.27 vs. 7.14 ± 3.16, $P < 0.001$). At the end of treatment, group M's risk score for severe evolution was less statistically significant (156.29 ± 61.32; 160.59 ± 59.41, $P < 0.001$). When molnupiravir was administered instead of favipiravir, the number of deaths among COVID-19 patients was reduced [2 (4.08%) vs. 9 (17.65%), $P = 0.034$]. Molnupiravir outperformed favipiravir when it came to treating SARS-CoV-2 infections in diabetic patients. Diagnosing or treating diabetes is essential to halting the critical course of COVID-19 in individuals. Its promise in the treatment of SARS-CoV-2-infected individuals requires more investigation.

Keywords: COVID-19 infections, Antiviral Treatment, Diabetic Patients, SARS-CoV-2 infection

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Introduction

High levels of pathogenicity and contagion are characteristics of the infectious disease coronavirus [1]. This illness is a result of the recent epidemic, which has resulted in thousands of deaths and many confirmed infections globally, and the numbers are still rising.

The term "coronavirus" refers to the microscopic look of the viral surface, which has spike glycoproteins and resembles a crown. The spike (S) protein, which is essential for virus infection because it makes it easier for the virus to adhere to the surface of host cells, has a significant impact on the coronavirus's tropism [2]. The viral genome encodes both structural and non-structural proteins [1]. Non-structural proteins are essential for the transcription and replication of the virus, whereas structural proteins guarantee infectivity, viral attachment, morphological structure creation, and exocytosis [1-3].

The first cases of severe pneumonia of unknown origin appeared in China in December 2019. The coronavirus known as severe acute respiratory syndrome 2 (SARS-CoV-2) was identified as the cause of these cases after further research [4]. Due to both immediate and delayed consequences, the symptoms of COVID-19 can range widely from the usual signs of an acute respiratory infection. The most commonly reported symptoms were fever (56.66%), cough (54.52%), dyspnoea (30.82%), asthenia (28.16%), dysphagia (14.41%), diarrhoea (9.59%), productive cough (25.33%), myalgia (16.9%), headache (12.17%), neurological manifestations (20.82%), and chest pain (11.49%), according to a study by Da Rosa Mesquita *et al.* [5] published in November 2020 that examined 152 publications and 41,409 COVID-19 patients.

For this infection, there are now non-specific antiviral treatments and vaccinations. To limit the spread of infection, a variety of vaccines have been developed and given. However, the global healthcare system's efforts are complicated by the introduction of several viral variations due to mutations in the viral sequence [5].

Combining antiviral therapy with other pharmaceuticals, such as anticoagulants, antibiotics, monoclonal antibodies, immunomodulatory agents, glucocorticoids, probiotics, nutrition therapy, and customised rehabilitation programs, is one way to treat SARS-CoV-2 infection [6, 7]. There is currently no approved antiviral medication designed especially for SARS-CoV-2 infection. Nonetheless, some antiviral medications, such as remdesivir, have been authorised and are being used to treat COVID-19 [8]. Clinical trials are also being conducted to evaluate additional antiviral medications, such as favipiravir, molnupiravir, and nirmatrelvir/ritonavir [9, 10]. However, as of yet, no antiviral drug has been proven to be both safe and effective for COVID-19.

Originally known as T-705, favipiravir was first used to combat SARS-CoV-2 in Wuhan, which was at the centre of the outbreak [11].

Since then, it has proven to be effective against ribonucleic acid (RNA) viruses, including respiratory syncytial virus, rhinoviruses, and Ebola virus [12]. Favipiravir functions as an inhibitor of RNA-dependent RNA polymerase (RdRp). It is changed by host enzymes into T-705 ribofuranosyl 5'-triphosphate, which acts as a nucleotide analogue to selectively inhibit viral RdRp activity [13, 14]. Comparing favipiravir to standard supportive care, studies have demonstrated that individuals with mild and moderate COVID-19 showed good tolerance and a favourable clinical evolution [15, 16]. Hepatocytolysis syndrome, neutropenia, diarrhoea, and hyperuricemia are the most frequently reported side effects of favipiravir [16].

Molnupiravir, a prodrug that is the isopropyl ester of the ribonucleoside analogue β-D-N4-hydroxycytidine [17], has attracted a lot of attention in recent years because of its ability to prevent SARS-CoV-2 replication, remove the virus quickly, lower the viral load, and help COVID-19 patients recover quickly. In vitro, molnupiravir is a strong inhibitor of SARS-CoV-2 replication, with an effective half-maximum concentration in the submicromolar range [18, 19]. Fischer et al.'s study [20] of 202 patients treated with molnupiravir revealed that the period needed to eliminate viral RNA was much shorter in molnupiravir-treated patients (92.5%) than in placebo-treated patients (80.3%). In 50% of mild and moderate COVID-19 cases, molnupiravir is safe and beneficial in lowering the likelihood of hospitalisation and unfavourable outcomes. This is especially true for individuals who have underlying risk factors for negative outcomes, such as cardiovascular illnesses, age more than 60, or diabetes mellitus [21].

Both favipiravir and molnupiravir are antiviral drugs that have been incorporated into the treatment plan for COVID-19 patients, including those who are also dealing with diabetes mellitus. Significant medical evaluations have indicated the potential effectiveness of both antivirals, suggesting that they can shorten recovery periods and reduce the intensity of symptoms in COVID-19 patients. Surprisingly, new research has even indicated that favipiravir may improve survival rates for people who experience the disease's more severe symptoms [15]. It's also important to note that favipiravir has shown excellent tolerance in the diabetic patient population, indicating that it can be used without causing notable adverse effects or major changes in blood glucose levels. According to a systematic literature review by Singh *et al.* [22] completed in 2021, molnupiravir helps people with milder types of COVID-19, but further research is needed for severe and intermediate versions of the illness.

Unfavourable outcomes in SARS-CoV-2 infection cases are impacted by several important risk factors, including old age, especially over 60, obesity, cardiovascular disease, chronic obstructive pulmonary disease, diabetes mellitus, and chronic kidney disease, as well as an individual's history of cancer or organ transplantation, which are also identified as being particularly susceptible to severe consequences in the context of COVID-19 infection. These risk variables collectively highlight the intricate interaction of multiple health determinants in determining the progression and impact of SARS-CoV-2 infection [23].

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Both favipiravir and molnupiravir have shown promise as possible therapy options for people with COVID-19, according to the corpus of current research. It's crucial to remember that research offers varying opinions regarding these antivirals' efficacy [15, 20, 21]. To confirm these results and fully comprehend the complex safety and effectiveness profiles of favipiravir and molnupiravir in the treatment of COVID-19 patients with diabetes mellitus, more research is necessary. In light of the previously indicated background, this research aimed to assess the therapeutic efficacy of antiviral treatments that included both favipiravir and molnupiravir in the group of adult patients who were also coping with COVID-19 and diabetes mellitus.

Materials and Methods

Study Design

A retrospective analysis involving consecutively admitted diabetic patients with COVID-19 was conducted at the Emergency County Clinical Hospital in Oradea, Romania, between November 2021 and April 2022.

All patients were given informed consent both at the time of hospital admission and before starting antiviral therapy. The study complied with the World Medical Association's Code of Ethics (Declaration of Helsinki, 1967) and was authorised by the University of Oradea's Faculty of Pharmacy and Ethics Committee of Medicine (Approval No. 31466/05.11.2020).

The inclusion and exclusion criteria were used to choose the first cohort (**Figure 1**). The research's inclusion requirements included: Having a type II diabetes diagnosis before study enrolment; pregnancy and death before the end of the antiviral therapy period were the study's exclusion criteria; failure to attend the 10-day follow-up visit at the hospital outpatient clinic following hospitalisation; and the requirement to switch to an alternative antiviral medication.

Antivirals were administered to patients in compliance with the regional treatment guidelines that were in effect during the study period and the hospital's supply of molecules at the time of observation. Participants in the study were divided into two groups: group F received favipiravir treatment, whereas group M received molnupiravir treatment. Favipiravir was given to group F for 10 days at a loading dose of 1600 mg twice daily (TID) and then 600 mg TID in succession. Molnupiravir was given to group M at a dose of 800 mg TID for five days.

All patients were given the COVID-GRAM risk score (**Figure 2**), a clinical risk assessment instrument, both at the time of admission and after antiviral treatment. The score method was created to evaluate the prognostic outlook and clinical risk of hospitalised COVID-19 patients. A wide range of evaluation parameters was included in the grading criteria. Direct bilirubin level, unconsciousness, neutrophil-lymphocyte ratio, age, pulmonary imaging changes, dyspnoea, number of comorbidities (0–5), haemoptysis, lactate dehydrogenase (LDH) level, and history of cancer are some of these factors. An online calculator was used to assess the score, incorporating multiple comorbidities such as hepatitis B, diabetes mellitus, cancer, chronic kidney disease, hypertension, coronary heart disease, cerebrovascular disease, chronic obstructive pulmonary disease, and chronic heart disease [27, 28].

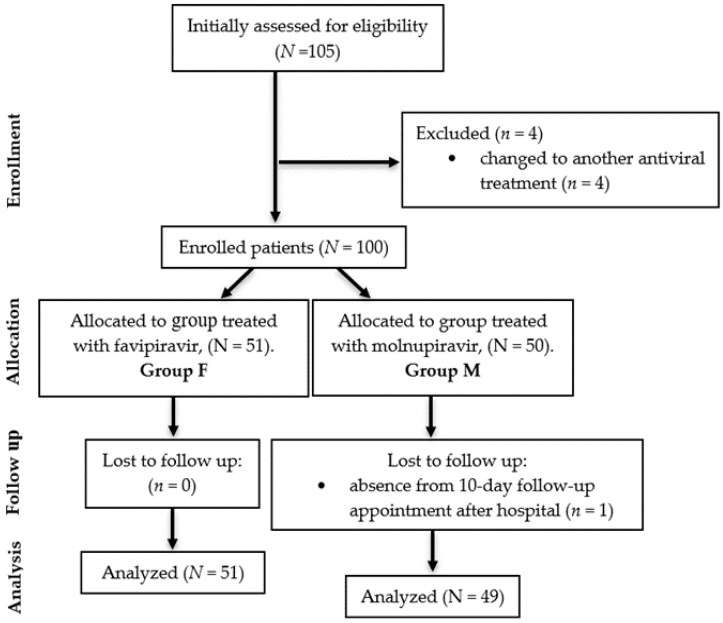


Figure 1. CONSORT flowchart depicting the study; n: number, M: molnupiravir, and F: favipiravir.

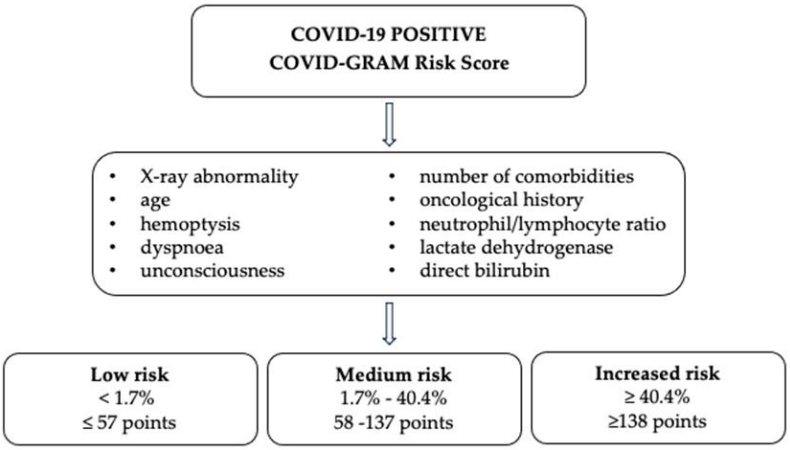


Figure 2. COVID-GRAM risk score flowchart

Data Collection

The patient's medical records were used to collect demographic details, including age, sex, and place of origin, along with their medical history and any COVID-19 vaccinations received in the past 12 months (VHC). Clinical data were also recorded, covering symptoms such as stomatitis, diarrhea, abdominal pain, nausea, vomiting, dizziness, oxygen saturation (SpO2), BMI, and the time from symptom onset to hospitalization (POH). Additionally, information on the length of hospital stay and paraclinical assessments, including complete blood count (CBC), ferritin, D-dimers, CRP, HbA1c, LDH, direct bilirubin, and chest computed tomography (CCT), was gathered. The COVID-GRAM risk score and certain paraclinical tests (ALAT, D-dimers) were evaluated in two phases:

t_0 = before starting the treatment with molnupiravir and favipiravir;

t_1 = at the end of the antiviral treatment.

CRP values were taken at the time of admission (t0), after antiviral therapy (t1: 5 days for the M group, 10 days for the F group), and on day 10 after hospitalisation, if M group patients were released before 10 days. On day 10, patients who were released earlier than ten days were scheduled for a follow-up appointment at the hospital's outpatient clinic.

To guarantee anonymity, the gathered data was encoded. The severity of COVID-19 in the enrolled individuals was compared using ferritin, LDH, and SpO2 levels, clinical data, demographic information, and prior medical history. Every patient had a CCT scan at the time of hospitalisation.

According to the World Health Organization's (WHO) guidelines, the diagnosis of COVID-19 was confirmed by either a single positive real-time polymerase chain reaction test or the identification of SARS-CoV-2 antigens (i.e., a fast test). Specimens from the pharynx and oropharynx were gathered and transported following the WHO's recommendations [29].

A human pulse oximeter (Human Accurate Bio-Medical Technology Co., Ltd., China) was used to measure the patients' SpO2.

Using particular vacutainer tubes for each test, laboratory analyses such as CBC, direct bilirubin, HbA1c, D-dimers, ferritin, and LDH were obtained from venous blood samples. As an anticoagulant, ethylenediaminetetraacetic acid (EDTA) was used to collect venous blood samples using tubes for the CBC. All samples were collected and sent right away to the hospital's lab for examination. The Beckman Coulter 628134 UniCel DxH Haematology Analyser 800, manufactured by Beckman Coulter International S.A., USA, was used to perform the CBC examination. The patient's age and gender were taken into consideration when interpreting the reference values. Venous blood samples were drawn using vacutainer tubes containing EDTA as an anticoagulant to measure the HbA1c levels. The samples were then examined using the ALINITY AC analyser (Indonesia). The reference values were calculated based on the age and gender of the patient.

Venous blood samples were drawn in vacutainer tubes containing 0.105 M sodium citrate to measure the levels of D-dimer. The ALINITY AC analyser (Indonesia) was used for analysis. Venous blood samples were obtained using vacutainer tubes without the use of any anticoagulant agents to measure the ferritin levels, and the Alinity Abbott analyser (Indonesia) was used for analysis. Venous blood samples were put in anticoagulant-free tubes to measure the blood transaminase level. The Beckman Coulter AU5811 Chemistry analyser, a product of Beckman Coulter International S.A., was used to make the measurement. Blood samples were drawn in vacutainer tubes devoid of anticoagulant to determine the CRP values. The Beckman Coulter AU5811 was then used for analysis. To ensure appropriate interpretation of the data, reference values for the transaminase level were established based on variables like age, sex, and the particular assay used. Every sample was taken while fasting and sent right away to the hospital's lab for examination.

Statistical Analysis

The total number of adult patients hospitalised throughout the observed period was taken into account when calculating the sample size of patients included in the study. We took into account the following factors when determining the sample size:

• P: the phenomenon's probability, where $0 \leq P < 1$.

• Q: $q = 1-p$, the complementary probability

N is the population size; t is the probability factor; and Δx is the allowable margin of error.

• We applied the following formula to get the sample size of cases: $(\Delta x2 + t2pq /N) = n = t2pq$. The formula applies to research where the observed feature is binary (in this example, comparing favipiravir with molnupiravir treatment). When both "p" and "q" equal 0.5, the product "pq" is at its maximum, and the value of "n" is at its maximum as well. A "t" value of 1.96 implies a 95% likelihood. It has been determined that 0.1 is an acceptable margin of error. It is possible to overlook the ratio "t2pq/N" if "N" is huge (more than 10,000). The minimum sample size for an adult population of 1031 people hospitalised over the observed time is 96. Statistical analysis was performed utilizing the Statistical Package for Social Sciences (SPSS), version 26 (IBM Corp., Armonk, New York, United States) [30]. Numerical values (N), proportions (%), means (M), and standard deviations (SD) were used to display the data. The log-rank test for the Kaplan-Meier technique, the Student's t-test, and the chi-squared test were used to calculate the statistical significance (P-value).

Results and Discussion

105 participants with both coronavirus and blood sugar disease met the inclusion requirements for the trial during its course. Five participants in all were removed from the research after switching antiviral medications before finishing the term. The study involved 100 participants, 51 of whom were patients in group F and 49 of whom were patients in group M. The demographic features of the two groups did not differ statistically significantly

[COVID-GRAM risk score (group F, P = 0.057); (group M, P = 0.064); (Shapiro-Wilk test)] (**Table 1**). The samples were distributed normally.

Table 1. COVID-19 group characteristics.

Parameter	Group F (n = 51)	Group M (n = 49)	P-value
DD			
Age (years, mean ± SD)	71.16 ± 12.50	65.84 ± 16.66	0.075[a]
Male gender (n (%))	17 (33.33)	22 (44.90)	0.643[b]
Urban residence (n (%))	16 (31.37)	21 (42.86)	0.411[b]
VHC (n (%))	2 (3.92)	1 (2.04)	0.563[b]
Clinical data			
Stomatitis (n (%))	0 (0)	1 (2)	0.317[b]
Diarrhea (n (%))	3 (5.88)	4 (8.16)	0.705[b]
Abdominal pain (n (%))	4 (7.84)	3 (6.12)	0.705[b]
Nausea (n (%))	6 (11.76)	3(6.12)	0.317[b]
Vomiting (n (%))	3 (5.88)	0 (0)	0.083[b]
Dizziness (n (%))	2 (3.92)	1 (2)	0.563[b]
SpO_2 (M ± SD)	92.29 ± 6.59	92.67 ± 7.14	0.783[a]
POH (M ± SD)	4.31 ± 1.35	4.55 ± 1.57	0.420[a]
BMI (M ± SD)	28.91 ± 3.98	28.26 ± 3.52	0.390[a]
PMH			
CVC (n (%))	40 (78.43)	33 (67.35)	0.412[b]
CKD (n (%))	11 (21.57)	12 (24.49)	0.834[b]
N (n (%))	2 (3.92)	1 (2.04)	0.563[b]
CPD (n (%))	1 (1.96)	2 (4.08)	0.563[b]
CVD (n (%))	8 (15.69)	5 (10.20)	0.692[b]
Hep B (n (%))	1 (1.96)	0 (0.00)	0.317[b]
ID (n (%))	1 (1.96)	2 (4.08)	0.563[b]
Paraclinical investigations (mean ± SD)			
Ferritin (ng/mL)	1314.06 ± 1266.20	843.53 ± 1160.23	0.061[a]
HbA1c (mg%)	7.24 ± 0.57	7.25 ± 0.65	0.924[a]
D-dimer (ng/mL)	1039.18 ± 801.80	1106.02 ±1439.30	0.776[a]
ALAT (mg%)	33.78 ± 15.24	32.91±15.99	0.781[a]
CRP (mg/L)	92.02 ± 90.96	60.92 ± 73.41	0.062[a]
COVID-GRAM risk score	178.14 ± 43.78	160.59 ± 59.41	0.129[a]

Demographic information (DD); medical history (PMH); body mass index (BMI); and history of COVID-19 vaccinations within the last 12 months (VHC); levels of oxygen saturation (SpO2); comorbidities of cardiovascular disease (CVC); chronic kidney disease (CKD); N stands for neoplasm; POH for period from onset to hospitalisation; CPD for chronic pulmonary disease; CVD for cerebral vascular disease; hepatitis B and Hep B immunodeficiency, or ID; alanine aminotransferase, or ALAT; glycated haemoglobin, or HbA1c; C-reactive protein, or CRP; n, or number; SD stands for standard deviation; M for mean; P, value as established by a Chi-squared test or a t-test.

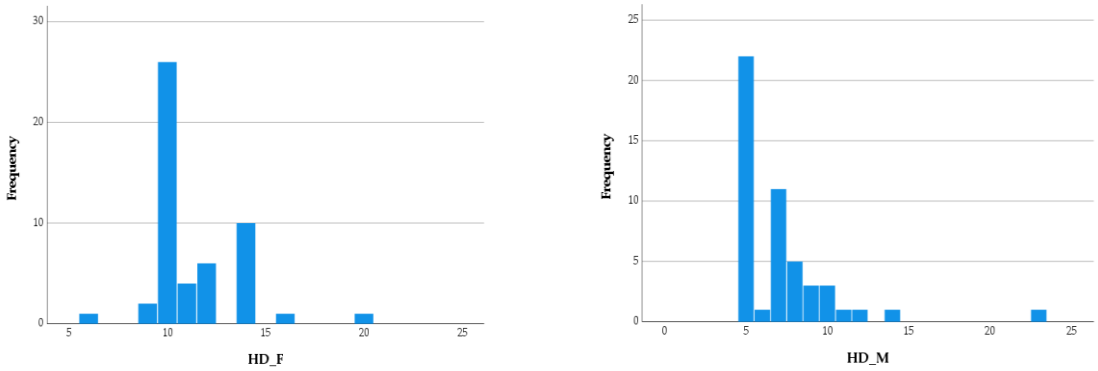
Only in the M group did the COVID-GRAM risk score show a statistically significant decline from baseline after the therapy period (156.29 ± 61.32; 160.59 ± 59.41, P < 0.001).
Although both groups showed a little drop in the number of high-risk patients for severe disease, this decline was not statistically significant (**Table 2**).

Table 2. Progression of subjects based on their COVID-GRAM risk score

Risk of critical illness	t_0	t_1	P-value
Group F			
Low (n (%))	0 (0%)	0 (0%)	-
Medium (n (%))	9 (17.65%)	10 (19.61%)	0.818[a]
High (n (%))	42 (82.35%)	41 (80.39%)	0.912[a]
Group M			
Low (n (%))	1 (2.04%)	1 (2.04%)	1.000[a]
Medium (n (%))	19 (38.78%)	22 (44.90%)	0.639[a]
High (n (%))	29 (59.18%)	26 (53.06%)	0.685[a]

t_0: starting time of the antiviral; t_1: end time of the antiviral; F: favipiravir group; M: molnupiravir group; n: number; P: value as determined by [a] chi-square test.

Compared to group F, group M had a significantly lower number of patients who died after taking antiviral medication but during the present hospital stay [2 (4.08%) vs. 9 (17.65%), P = 0.034]. Compared to patients treated with favipiravir (7.14 ± 3.16; 11.29 ± 2.27; P < 0.001), those treated with molnupiravir spent 4.15 fewer days in the hospital (**Figure 3**).



a) b)

Figure 3. Histogram depicting the number of hospitalization days; HD: hospitalization days, F: favipiravir, and M: molnupiravir

Only the group receiving molnupiravir had lower statistically significant D-dimer values on admission to the hospital (t0) compared to the end of antiviral treatment (t1) [group F (t0:1039.18 ± 801.80 ng/mL, t1: 987.31 ± 695.82 ng/mL, P = 0.311); group M (t0:1106.02 ± 1439.30 ng/mL, t1: 754.69 ± 783.01 ng/mL, P = 0.016)].
At the end of the molnupiravir therapy, the CRP values were statistically significantly lower than those of the group that received favipiravir treatment [group F (t0: 93.02 ± 90.96 mg/L, t1: 87.47 ± 91.38 mg/L, P = 0.088); group M (t0: 60.92 ± 73.41 mg/L, t1: 52.75 ± 65.40 mg/L, P < 0.001)]. There was a substantial difference between the two groups in the number of patients who had CRP normalisation 10 days following hospital admission [33 (67.35%) in the M group vs. 16 (31.37%) in the F group, P < 0.001] (**Figure 4**).

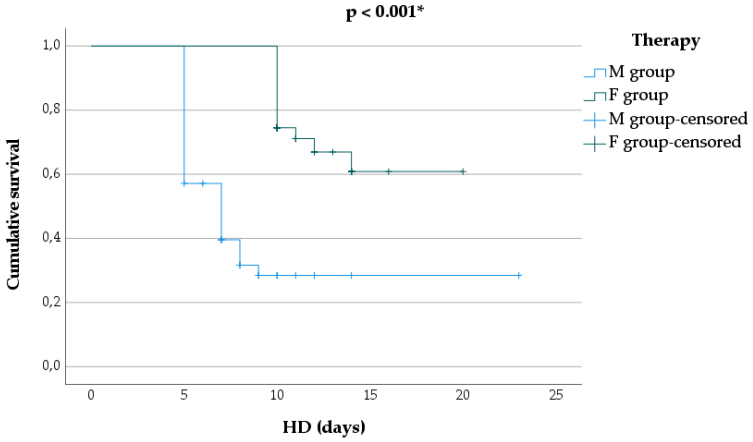


Figure 4. Kaplan-Meier curves showing the time to normalization of CRP levels; HD: hospitalization days, F: favipiravir, M: molnupiravir; *P = 0.001, statistical significance according to log-rank test

The group of individuals receiving favipiravir experienced adverse effects statistically considerably more frequently (**Table 3**). Diarrhoea was more frequently seen in the group that received the favipiravir protocol among the clinical symptoms that participants reported as having a negative influence during antiviral treatment.

Table 3. Adverse reactions in patients receiving antiviral therapy

Adverse effects (n (%))	M Group	F group	P-value[a]
Stomatitis	8 (15.69)	7 (14.29)	0.796
Diarrhea	1 (1.96)	9 (18.37)	**0.011**
Abdominal pain	2 (3.92)	3 (6.12)	0.654
Nausea	8 (15.69)	14 (28.57)	0.2
Vomiting	1 (1.96)	4 (8.16)	0.179
Dizziness	5 (9.80)	9 (18.37)	0.285
ALAT elevated	1 (1.96)	3 (4.08)	0.317
Total	26 (50.98)	48 (97.96)	**0.010**

N: number; ALAT: alanine aminotransferase; P: value determined by [a] chi-square test; significant p-values are noted in bold print.

At the end of the antiviral treatment, there was no statistically significant difference in the ALAT values in the two groups [group M (38.17 ± 7.26) vs. group F (39.87 ± 8.45), P = 0.282, t-test].

Since 2019, COVID-19 has grown to be a significant worldwide concern. Millions of people have been impacted by the SARS-CoV-2 illness, which has increased the number of deaths in all communities, caused misery, and placed a strain on healthcare systems. In the battle against the pandemic, antiviral medication has been essential. Introduced in 2020, the COVID-GRAM risk score was used to determine hospitalised COVID-19 patients' mortality, need for mechanical ventilation, and admission to the ICU [28]. The soundtrack tracks ten distinct factors that are commonly used to track a hospitalised COVID-19 patient's progress. Following therapy (t1), the M group's COVID-GRAM risk score decreased statistically significantly from its initial value (t0) (156.29 ± 61.32; 160.59 ± 59.41, P < 0.001). Both groups saw a slight decline in the number of high-risk individuals for severe illness, although this decline was not statistically significant. The number of patients who passed away during the current hospital stay after finishing antiviral medication was substantially lower in the M group than in the F group [M group: 2 (4.08%) vs. F group: 9 (17.65%), P = 0.034].

According to a 2023 retrospective study by Prajapati *et al.* [31], which included a cohort of 26,554 corona virus patients in the US with at least one predictor of severe progression, patients treated with molnupiravir required invasive mechanical ventilation in 0.1% of cases, oxygen therapy in 0.1% of cases, and an admission to intensive care in a low percentage of 0.3% of cases. Several studies have examined the use of molnupiravir since the Omicron versions were discovered in November 2021 [32, 33], utilising data from the US, Israel, and Hong Kong, which include people with risk factors for severe coronavirus. The majority of patients in the U.S. and Israeli studies had only had one COVID-19 vaccination. Within a month of beginning molnupiravir medication, 4.5% of older patients (ages 68 to 75 years) died or were admitted to the hospital, per a study conducted by the U.S. Veterans Health Administration [34-37]. In the MOVe-OUT study, the one-month hospitalization/death rate for molnupiravir was 6.8% [34]. Monopiravir had a 1% 28-day hospitalization/mortality rate in the PANORAMA research, which was also the case with standard treatment. However, patients in the highest risk groups who are clinically highly vulnerable were not included in the population of this study. The study by Al-Muhsen *et al.* [37] found that favipiravir was linked to longer hospital stays and a higher mortality rate compared to no favipiravir regimen in 598 hospitalised patients with moderate/severe COVID-19, while the PIONEER study, which looked at 499 hospitalised COVID-19 patients, found no significant difference in the 28-day mortality rate (10% in the favipiravir group vs. 14% in the standard care group) [36, 37]. According to Özlüşen and colleagues' meta-analysis of 2702 trials, patients with severe/moderate forms of COVID-19 treated with favipiravir did not differ statistically significantly from those getting standard care in terms of death rates or the need for mechanical ventilation [38]. Our findings are consistent with medical research on moderate-to-severe COVID-19 in people over 65 who have risk factors for severe progression (in this case, diabetes) and who are primarily unvaccinated.

D-dimer levels are doubled in SARS-CoV-2 infection compared to infection with community-acquired pneumonia [30]. Numerous studies have established D-dimer as a prognostic factor in COVID-19 patients by implying an indirect association between elevated D-dimer levels and an increased risk of thrombosis [30, 39–41]. According to this study, D-dimer readings were lower in the group receiving molnupiravir medication than in the group receiving favipiravir treatment. The results of a study by Pontolillo *et al.* [42] that included 100 people with mild to moderate COVID-19 showed that D-dimer levels did not change at 7 or 10 days after starting molnupiravir medication. According to the findings of a study conducted by Mutair *et al.* [43] with 538 COVID-19 patients,

50% of whom were treated with favipiravir and the other 50% receiving other antiviral therapies, patients treated with favipiravir had lower D-dimer levels than those treated with other antiviral drugs.

Interleukin-6, a pro-inflammatory cytokine, stimulates the hepatic synthesis of CRP in the context of tissue damage caused by trauma or a particular pathological disease; in practice, this is connected with the severity of the inflammatory process. Wang *et al.* [44] contend that a one-unit rise in CRP corresponds to a 5% increase in the likelihood of developing severe disease in a research involving 209 adult patients with non-severe COVID-19. Our results show that the group treated with molnupiravir had significantly lower CRP readings after antiviral therapy. Additionally, given that the distinction was made after the antiviral treatment period (5 days for molnupiravir and ten days for favipiravir) and the fact that group M had a significantly higher number of patients with normal CRP values on day 10 of hospitalisation, it is noteworthy that this reduction is faster. Our findings are consistent with those of Johnson *et al.* [45], who claim that during the third day of antiviral treatment, CRP readings in adult COVID-19 patients receiving molnupiravir showed a statistically significant improvement in the MOVe-OUT trial. In a research including 100 COVID-19 participants, Pontolillo *et al.* [42] report a statistically significant improvement in CRP readings 7–10 days after starting molnupiravir medication. However, medical research on the impact of favipiravir on CRP shows contradictory findings [46, 47].

Because of their high severity, the need to stop treatment, patients' difficulty adhering to the treatment, or potential drug combinations, adverse drug responses might result in treatment inefficiency. Adverse responses occurred in both groups of patients under observation in this trial, however, they were statistically considerably more common in the group treated with favipiravir. Additionally, this group reported diarrhoea at a statistically significantly higher rate. As of right now, the US Food and Drug Administration (FDA) has approved molnupiravir (as of October 3, 2023) for the treatment of individuals with mild to moderate forms of COVID-19 and risk factors. Adverse responses are being monitored [48]. The most often reported complaints were gastrointestinal (diarrhoea, nausea) and cutaneous, according to research by Santi Laurini *et al.* [49] based on adverse effects documented in the FDA Adverse Event Reporting System relating to molnupiravir medication. In the study by Ergür *et al.* [50] on a sample of 357 patients, hepatic impairment and gastrointestinal complaints (diarrhoea, nausea, and abdominal discomfort) were most commonly linked to adverse events after the administration of favipiravir. Our findings are consistent with recent medical research, however, it appears that molnupiravir is more tolerable than favipiravir. However, research over a longer period is required to support this observation.

Conclusion

Molnupiravir may be a promising therapeutic choice for hospitalised adult COVID-19 patients with diabetes, according to the current study. It has shown promise in lowering the risk of serious consequences, managing inflammation, and improving tolerability. Spending less time in the hospital results in lower related expenses, particularly for those over 65. Because COVID-19 can cause a wide range of problems in the short and long term, stopping viral replication early in the illness is essential to re-establishing homeostasis. Further long-term research is necessary to validate these results and evaluate the safety and effectiveness of molnupiravir in the treatment of COVID-19.

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