European Review for Medical and Pharmacological Sciences 2024; 28: 433-443

# A study survey on molnupiravir treatment in COVID-19 patients at home in Ninh Thuan province, Vietnam

T. LE-HUY[1], M.G. BALZANELLI[2], P. THAI-PHUONG[1], T. TRAN THAI[1], H. NGUYEN VU NGOC[1], L. TRAN PHUC[1], T. LE QUOC[1], T. NGUYEN THANH[1], T. NAI THANH[1], T. LE VAN[1], L.P. THI BICH[3], R. LAZZARO[2], P. DISTRATIS[2], G. DIPALMA[4], R. MOROLLA[4], A.M. INCHINGOLO[4], L. DONGIOVANNI[4], F. TRIGGIANO[4], L. SANTACROCE[4], R. DEL PRETE[4], M. SERAFINI[4], A. PALERMO[5], K. CAO DIEM NGUYEN[4], F. INCHINGOLO[4], C. GARGIULO ISACCO[4]

[1]Ninh Thuan General Hospital, Ninh Thuan City, Ninh Thuan Province, Vietnam
[2]Department of Pre-hospital and Emergency, 118 SET, SG Giuseppe Moscati Hospital, Taranto, Italy
[3]Department of Health Ninh Thuan City, Ninh Thuan Province, Le Pham Thi Bich, Vietnam
[4]Department of Interdisciplinary Medicine, Section of Microbiology and Virology, School of Medicine, University of Bari "Aldo Moro", Bari, Italy
[5]College of Medicine and Dentistry Birmingham, University of Birmingham, Birmingham, UK

*T. Le-Huy and M. G. Balzanelli contributed equally as first authors*

*C. Gargiulo Isacco, K. Cao Diem Nguyen, and F. Inchingolo contributed equally to this work as last authors*

**Abstract. – OBJECTIVE: Molnupiravir (MOV) is an oral antiviral drug that received use authorization in Vietnam for the treatment of mild COVID-19 (F0). There was a need to develop alternative approaches that allowed patients to access medication, decongest hospitals, clinics, and facilities, and protect people from infection. During the COVID-19 crisis, the Ninh Thuan Health Authorities implemented the home delivery of medication by community health workers. This study conducted in collaboration with two important Italian entities [the Aldo Moro University of Bari City and the 118 Department of Territorial Emergency System (118 SET) of Taranto City] aimed to evaluate the implementation of home delivery F0 treatment package assessing the rate of infection recovering during the coronavirus pandemic in Ninh Thuan province, Vietnam.**

**PATIENTS AND METHODS: A convergent mixed methods research, based on a longitudinal study with quantitative research and qualitative assessments, evaluated four implementation outcomes: the feasibility, fidelity, coverage, sustainability, and effectiveness of the initiative. Data sources included routinely collected data, a telephonic survey of patients, an analysis of set-up and recurrent costs, as well as descriptive exploratory qualitative and quantitative analysis.**

**RESULTS: After taking the MOV for 5 days, only 35 out of the initial 400 F0 patients remained positive, while 365 patients (91.2%) were negative (CT≥30). Whilst, the successful rate after using the drug during the course accounted for 99.85% and 100% after the entire treatment course, without any death. After 5 days of taking the drug, a positive test result (CT<30) was associated with age group ≥60 (OR=2.7) and comorbidities (OR=3.0) ($p$<0.05) compared to negative and positive results (CT≥30). Negative factors impacting F0 at home include a shortage of healthcare workers, inadequate supply of thermometers and $SpO_2$ meters, and insufficient financial support for healthcare workers.**

**CONCLUSIONS: MOV caused a reduction in the risk of hospitalization or death in mild COVID-19 patients, and molnupiravir was also found to be well tolerated and safe without any major adverse events during the administration period.**

*Key Words:*
COVID-19, Molnupiravir (MOV), Mild COVID-19 patients/F0, General Hospital Ninh Thuan province-Vietnam.

*Corresponding Authors:* Francesco Inchingolo, MD; e-mail: francesco.inchingolo@uniba.it;
Gianna Dipalma, MD; e-mail: giannadipalma@tiscali.it;
Kieu CD Nguyen, MD, MD; e-mail: drkieukaren@gmail.com

## Introduction

The global pandemic of COVID-19 showed the world a crash course in modern medicine, both infectious and epidemiology[1], enhancing countries to launch health recovery programs to mitigate and solve the disease[2]. Coupled with the current treatment strategies, COVID-19 antivirals were also needed to limit virus spread and the course of the pandemic. Molnupiravir is a small-molecule antiviral prodrug against SARS-CoV-2 virus[3].

COVID-19 has not stopped spreading around the world and causing extremely serious consequences. More than 600 million confirmed COVID-19 (F0) cases, including 6,564,556 deaths, were reported to WHO. In Southeast Asia, more than 60 million infected patients, with nearly 800,000 deaths, were counted. In Vietnam alone, there have been more than 11 million cases with 43,000 deaths. In trying to alleviate the widespread epidemic that led to heavy pressure on the health system, scientists and policymakers around the world proposed different solutions to manage and treat COVID-19 patients. In particular, home treatment was one of the opted solutions with many advantages, able to either relieve pressure on the local medical facilities such as hospitals and hospices or perform direct treatment, reaching psychological comfort for patients as well[1].

Although models of COVID-19 transmission have been useful in understanding and controlling the spread of the virus, clarifying the etiopathogenesis dynamics of SARS-CoV-2 posed some essential problems. As we know, it is difficult to study the viral dynamics inside an infected cell. Therefore, it was hard to highlight the effects of antiviral drugs in these cells[4]. One of the major problems is that coronaviruses possess one of the largest genomes known and the most unique life cycles among the totality known single-stranded RNA viruses, features that somehow limited the use of current intracellular infection models[5]. Several key epidemiological metrics (e.g., virus infection rate, virus replication rate, virus clearance rate, and cell death rate) are needed to characterize within the host the pleiotropism of the SARS-CoV-2 virus, together with the antiviral efficacy[5].

MOV belongs to the class of ribonucleoside analog, which shows a similar structure to one of the building blocks of RNA, important for the replication of different viruses such as SARS-CoV-2 and SARS-CoV (SARS-CoV-2 99.4% sequence similarity and SARS-CoV 96.4% sequence identity)[5-7]. The N4-hydroxycytidine (NHC, EIDD 1921) was recently presented as a new isobutyryl ester prodrug tested in phase II and III trials[4] to treat SARS-CoV-2 infection and received the emergency use authorization by USA FDA for the treatment of mild-moderate to severe COVID-19[4,5]. Molnupiravir was seen to target RNA-dependent RNA polymerase (RdRp) and hinders the RNA-dependent translation and transcription of viral RNA by introducing copying errors during the replication process. These inhibitory effects were confirmed in animal models[5-7], showing a higher ability to neutralize the SARS-CoV-2 virus than other antiviral prodrugs.

Notably, the outcomes showed a significant impact on viral titer in the lungs at 48 h after administration of 500 mg/kg NHC[8]. Scientists assumed that the NHC not only affects the thermodynamics of the secondary structure of RdRp in SARS-CoV, blocking viral replication, but the results illustrated that MOV is a strong enhancer of viral RNA mutagenesis, reducing and arresting replication capacity of both SARS-CoV and SARS-CoV-2 (*in vitro* experiment conducted using Vero 76 cells)[5-10].

In our facility, it was conducted a modeling study of the SARS-CoV-2 virus impact on cells to assess the antiviral efficacy of MOV and the inhibition grade of infected cell replication. Thus, based on scientific evidence and anti-epidemic experience from our partners (Aldo Moro University of Medicine of Bari, Italy and 118 territorial Emergency System SET of Taranto, Italy), Vietnam has also issued specific guidelines (Accordingly, the People's Committee of Ninh Thuan province issued Plan No. 6022 on November 4, 2021, Law N 18/2011/TT-BYT and Law 4109/QD-BYT, official press release 8728/SYT-NVY dated 11/23/2021, by Ministry of Health of Vietnam) to manage F0 at home also by proposing a list of the drug included in ready-to-use packages.

General Hospital Ninh Thuan Province provided medicine packages according to the instructions to the qualified F0 in isolation at home. The implementation in Ninh Thuan province needed to be evaluated in terms of medical expertise to highlight the effectiveness and the reached objectives when using the F0 treatment package, considering some factors and variants that may influence the treatment outcomes. So, we decided to create this study with the following two objectives: to determine the rate of patients recovering and to reduce symptoms after using the F0 treatment package at home. Determine some factors related to the effectiveness of using the drug package.

## Patients and Methods

### Subjects of Study

#### Quantitative research

400 patients over 18 years old were diagnosed with COVID-19 *via* ora-nasal swab (Suzhou Jintai Antistatic Product Co. Ltd, Guoliang Qiing, China) analyzed by real-time polymerase chain reaction (RT-PCR) (Thermo ABI QuantStudio 7 Pro Real-Time PCR, 2023 Bio-Rad Laboratories, Inc., Hercules, CA, USA) and treated at home with a drug package issued by General hospital Ninh Thuan province from June to October 2022.

#### Qualitative research's members and staff

The qualitative research guidelines were implemented and executed at different levels by the Managers (Local Governement Health bodies management team in charge of the home treatment program F0); Staff directly treating F0 at home (Doctors and Nursing). Convenient sample size. In-depth interview (IDI): 10 managers, 5 doctors, and 5 nurses, 20 patients had negative test results, and 20 patients had positive results after 5 days of taking the drug to analyze the factors affecting the effectiveness of treatment through qualitative research.

### Selection Criteria

The patients were confirmed to have COVID-19 by oral-naso pharyngeal swabs analyzed by real-time polymerase chain reaction (RT-PCR).

### Exclusion Criteria

Patient with oncological existing conditions, liver cirrhosis, and kidney failure under dialysis treatment.

### Methods

Study Design: Longitudinal study, a combination of quantitative research and qualitative.

Sample size: Quantitative research.

Where n is the sample size, $Z^2_{(1-\alpha/2)}$ is the level of confidence (for this study, we select a confidence level of 95%, p is the percentage of COVID-19 patients who receive the drug package (here we choose $p$=80%, that is, 80% of F0 patients are expected to receive the package), an estimated error is d=0.05 (5%). So, the sample size n=368 was calculated (400 patients were included).

#### The CT threshold calculation

To validate the accuracy of the home treatment, we calculated the thermal cycle (CT) of the RT-PCR performed on each patient's sample. The CT, used as a quantitative technique, allowed us to measure the genetic material (the number of viral copies per cell) in each given sample. The lower the CT value, the higher the quantity of viral genetic material in the sample. The final, efficiency is calculated using the equation: $E = -1+10^{(-1/slope)}$.

### Research Rationale and Implementation

#### At-home treatment

Patients included in the study were infected by COVID-19 with only mild illness, which could receive home treatment. The main purpose was to relieve symptoms and included rest, fluids, anti-inflammatory drugs, and pain relievers. Adults over age 65 and people of any age with existing long-lasting pathologies such as heart or lung disease or diabetes were advised to maintain contact with Ninh Thuan Hospital's healthcare providers as soon as symptoms commenced. People with these conditions who get COVID-19 may also be eligible for certain treatments that had to be commenced within a few hours after symptoms started.

#### Emergency warning signs

When signs and symptoms got worse, Ninh Thuan Hospital's healthcare providers delivered a home pulse oximeter oxygen tank. Patients were given instructions on how to read test results and how to use the $O_2$ mask. For instance, if the oxygen saturation level is less than 92%, the hospital emergency unit should be called. If the level is between 93-95%, oxygen support is needed. Emergency signs include trouble breathing, persistent chest pain or pressure, confusion or somnolence, trouble staying awake, and pale, gray, or blue-colored skin, lips, or nail beds.

If F0 satisfied the conditions for home treatment, they received drug packages A, B, and C as follows[2].

Package A drug (used for 7 days) included antipyretics and supplements as follow:

1. Paracetamol 500 mg (UPSA-ASA Lille-France) 1 tablet every 6 hours can be repeated every 4-6 hours if fever persists (20 tablets to be taken when fever reaches 38.5°C).
2. Vitamin C1 (UPSA-ASA Lille-France), 7 tablets, 7 days.

Package B (used for 3 days):

1. Methylprednisolone 16 mg (Menison Pymepharco, HCM City, Vietnam), 6 tablets, 3 days (when there are signs of shortness of

breath, or shortness of breath that increases with movements). To be taken after meals: 1 tablet in the morning, 1 tablet in the afternoon.

2. Rivaroxaban 10 mg (Xarelto, Bayer, Germany), anticoagulant and anti-inflammatory, 3 tablets, 3 days (when there are signs of shortness of breath, or shortness of breath that increases with movements). To be taken after meals, 1 tablet in the morning.

Package C (5-day use):

Molnupiravir Capsules 200 mg (Merck-NYSE, Miami, FL, USA), 40 capsules, 5 days to be taken 4 tablets/time, 2 times a day, 12 hours apart (morning and evening).

Patients participating in the program were given 01 medical drug pack for 5 days, including 40 molnupiravir 200 mg capsules, taken 4 tablets/time, twice a day, or 20 tablets of molnupiravir 400 mg, 2 tablets/time, twice a day.

Total follow-up time is about 14 days, including:

- Screening time: within 1 day (24 hours) before dispensing drugs.
- Duration of drug use: 5 days.
- Follow-up time of drug use up to day 14.
- Assess viral testing after day 5 (RT-PCR).

### Statistical Analysis

SPSS 22.0 Statistical Software (IBM Corp., Armonk, NY, USA) was used for all calculations. Qualitative variables are expressed as percentages (%). Use medians and percentile ranges (25 and 75) to describe quantitative variables that are not normally distributed. Chi-square test or Fischer's exact test for categorical variables and student's *t*-test, McNemar's test or Mann-Whitney U test for continuous variables as appropriate. The $p<0.05$ was considered as statistically significant.

## Results

### The Rate of Recover, Symptom Relief After Using the Drug Pack

The results on COVID-19-related hospitalization and mortality upon admission reached a borderline significance. Our study contains data that are completely in line with worldwide data that show MOV's effectiveness in treating mild COVID-19-related infections (Tables I and II). Overall, the study showed the safety of the drug; specifically, only 2 patients using packages A and C experienced side effects (headache, low blood pressure) accounting for 0.5% (Table III). After 5 days of using the drug, 168 patients had negative test results (42.0%), and 197 patients had positive results at CT value ≥30. Thus, the percentage of patients after using the package had negative test results after 5 days, positive or negative (CT≥30), accounting for 91.2% (Table IV).

Females accounted for 54.2%, mostly in the age groups of 30-39 (32.5%) and 40-49 (23.0%), the median age of the study group being 40.

The proportion of patients with fever (>37.5°C) accounted for 34.0%, low $SpO_2$ (≤93%) was 1.8%, and hypertension was 10.8%. The majority of patients who were tired accounted for 74.0%, followed by a dry cough (66.0%), chills (26.8%), and loss of taste 79.0%; there was 1 case of hemoptysis (0.3%).

77.3% of patients used drug packages A and C, 5.3% used packages B and C, and 100% used drug package C. 2 patients using packages A and C experienced side effects (headache, low blood pressure), accounting for 0.5%.

The number of patients after 5 days of home treatment was 365 or 91.2%, composed of two sub-groups: (i), absolute negative of 168 patients (Blue color or 42%); (ii), relative negative 197 (CT values ≥30) (Green color or 49.3%).

Before taking the drug, 400 patients had positive test results. After 5 days of taking the drug, the number of positive patients decreased to 35 patients, and the number of patients with negative or positive test results (CT≥30) increased to 365; the difference was statistically significant ($p<0.05$). Recover accounted for 99.8%; there was 1 patient moved to the intensive care unit (ICU), and no patient died (0.0%).

100% had negative test results (total recovery) after finishing the treatment period.

A notable correlation was observed between the age group of 60 and older (OR=2.7) and the presence of comorbidities (OR=3.0) with a positive test result (CT<30) as opposed to both negative and positive results (CT≥30) after a 5-day period of drug administration ($p<0.05$).

## Discussion

The home-based medication use and MOV showed the ability to prevent COVID-19-related respiratory and general worsening with statistical significance. Furthermore, MOV was shown to prevent COVID-19-related severe respiratory failure and mortality upon hospitalization for the infection[11-23].

**Table I.** General characteristics of the study sample (N=400).

| General characteristics of the study sample (N=400) | | | |
|---|---|---|---|
| **Characteristics** | | **Frequency** | **(%)** |
| Gender | Male | 183 | 45.8 |
| | Female | 217 | 54.2 |
| Age group | ≥18 | 3 | 0.8 |
| | 20-29 | 67 | 16.8 |
| | 30-39 | 130 | 32.5 |
| | 40-49 | 92 | 23.0 |
| | 50-59 | 58 | 14.5 |
| | 60-69 | 32 | 8.0 |
| | 70-79 | 16 | 4.0 |
| | ≥80 | 2 | 0.5 |
| Median age ($25^{th}$- $75^{th}$): 40 (32-51) | | | |

Data obtained from a study[24] conducted in Italy also suggested the effectiveness of both MOV and Remdesivir; while patients treated with MOV showed a lower risk of hospitalizations and earlier recovery, the age, body mass index, and underlying co-morbidities showed to play a certain impact in the final outcomes. As also reported in our study, in the final evaluation, we should consider fragile individuals such as the elderly, hematology and oncologic patients, solid organ transplant recipients, and patients with chronic respiratory diseases a category on its own[24-29].

**Table III.** Percentage of patients using drug package and side effects (N=400).

| Drug package | Frequency | (%) |
|---|---|---|
| Drug package A and C | 309 | 77.3 |
| Drug package B and C | 21 | 5.3 |
| Drug package C | 400 | 100 |
| Side effects | 02 | 0.5 |

**Table II.** Clinical symptoms (N=400).

| | Clinical symptoms | Frequency | (%) |
|---|---|---|---|
| Comorbidities | | | |
| | Yes | 59 | 14.8 |
| | No | 341 | 85.2 |
| Fever | | | |
| | Yes | 136 | 34.0 |
| | No | 264 | 66.0 |
| $SpO_2$ | | | |
| | Normal (≥94%) | 393 | 98.3 |
| | Low (≤93%) | 7 | 1.8 |
| Blood Pressure | | | |
| | Optimal | 198 | 49.5 |
| | Normal | 159 | 39.8 |
| | Hypertension | 43 | 10.8 |
| Tired | | | |
| | Yes | 296 | 74.0% |
| | No | 104 | 26.0 |
| A dry cough | | | |
| | Yes | 264 | 66.0 |
| | No | 136 | 34.0 |
| Chills | | | |
| | Yes | 107 | 26.8 |
| | No | 293 | 73.3 |
| A loss of taste | | | |
| | Yes | 84 | 21.0 |
| | No | 316 | 79.0 |
| Conjunctivitis | | | |
| | Yes | 19 | 4.8 |
| | No | 381 | 95.3 |
| Diarrhea | | | |
| | Yes | 14 | 3.5 |
| | No | 386 | 96.5 |
| Hemoptysis | | | |
| | Yes | 1 | 0.3 |
| | No | 399 | 99.8 |

**Table IV.** Test results after 5 days of using the drug package by using RT-PCR calculating the CT- Cycle threshold.

| Result | Frequency | (%) | |
|---|---|---|---|
| Negative absolute<br>Negative with CT≥30 | 168<br>197 | 42.0<br>49.3 | 91.2* |
| Positive (CT<30) | 35 | 8.8* | |
| **Total** | **400** | **100** | |

*$p$-value<0.001

A phase 3 clinical study[21] of 1,408 unvaccinated participants demonstrated that MOV treatment for 5 days reduced the risk of hospitalization and death by 30%. The authors confirmed the ability of MOV to meet the prespecified superiority criterion at the time of the analysis. At day 29, the percentage of hospitalized patients or deceased was significantly lower in the group that received MOV [7.3% (28 of 385 participants)] than in the placebo group [14.1% (53 of 377 participants)], a treatment difference of -6.8 points [95% confidence interval (CI), -11.3 to -2.4; $p$=0.001][30].

Another aspect to be mentioned was the effectiveness of MOV on vaccinated patients. A phase 2 experimental study[29] called AGILE CST-2 included 180 participants, an average of 43 years old, both vaccinated patients and unvaccinated for COVID-19. The majority received the first dose of the COVID-19 vaccine against different variants, alpha (37 of 180), delta (72 of 180), omicron (38 of 180), and EU1 (28 of 180)[29]. In general the overall results regarding the use of MOV tended showed that patients who received MOV negativized earlier (confirmed by RT-PCR) 8 days earlier compared to the placebo group (11 days)[29].

Given the grade of effectiveness and safety of the obtained results at the time of the analysis, the Ninh Thuan People's Health Committee data monitoring authority recommended an early stop for the recruitment of new patients in the trial. The majority of the affected patients recovered from the acute infection with irrelevant consequences[31-36]. One advantage of MOV over other treatments for SARS-CoV-2 spike protein is its effectiveness against variants. The mechanism of action of MOV works regardless of the mutations of the spike protein, which can affect the effectiveness of either monoclonal antibody treatments or vaccines[37-44].

**Table V.** Percentage of patients recovered after using the drug package.

| Test results | Frequency | (%) |
|---|---|---|
| Complete Recovery | 399 | 99.8 |
| Move to ICU | 01 | 0.2 |
| Death | 00 | 0.0 |
| **Total** | **400** | **100** |

### *The Recovery Rate and Symptom Relief After Using the Drug Pack*

The proportion of males and females with COVID-19 in our study was slightly different from that of China, where 51.4% of males had COVID-19[3]. More similar to Malaysia, 54.5% are females with COVID-19[45]. The median age of patients with COVID-19 is similar to the study of Jayk Bernal et al[46] (43 years old).

The proportion of patients with underlying diseases (blood pressure, diabetes, etc.) and fever, respectively 14.8% and 34.0%. This is a low rate because these subjects have mild infections and are being treated at home. The study results also showed that the majority of patients who were tired accounted for 74.0%, followed by a dry cough (66.0%), chills (26.8%), loss of taste 79.0%; there was 1 case of hemoptysis (0.3%). Wang et al[15] (2020), tired 69.6% and dry cough 59.4%, and diarrhea has a low rate of 10.1%.

Overall, the study showed the safety of the drug. Specifically, only 2 patients using packages A and C experienced side effects (headache, low blood pressure) accounting for 0.5% (Table III). After 5 days of using the drug, 168 patients had negative test results (42.0%), and 197 patients had positive results at CT value ≥30. Thus, the percentage of patients who used the package had negative test results after 5 days. Positive or negative (CT≥30) accounted for 91.2% (Table IV). Fischer et al[20] demonstrated that after 3 days of using molnupiravir, only 1.9% of patients had positive results for SARS-CoV-2, and on day 5 virus was not detected from any of the patients who received 400 or 800 mg of MOV[20].

**Table VI.** Percentage of negative test after end of treatment.

| Test results | Frequency | (%) |
|---|---|---|
| Negative | 400 | 100 |
| Positive | 0 | 0.0 |
| **Total** | **400** | **100** |



438

**Table VII.** Some associated factors of the effectiveness.

| Characteristics | Test results after 5 days of taking the drug | | | |
|---|---|---|---|---|
| | Positive incl. Pax CT<30 | Negative incl. Pax | OR (95% CI) CT≥30 | *p*-value |
| ≥60 years old | 9 | 41 | 2.7 (1.2-6.2) | 0.01 |
| Comorbidities | 11 | 48 | 3.0 (1.4-6.6) | 0.01 |
| Fever | 16 | 120 | 1.7 (0.8-3.5) | 0.1 |
| Tired | 28 | 268 | 1.4 (0.6-3.4) | 0.4 |
| A dry cough | 25 | 239 | 1.3 (0.6-2.8) | 0.5 |
| Chills | 10 | 97 | 1.1 (0.5-2.4) | 0.8 |
| Conjunctivitis | 2 | 17 | 1.2 (0.3-5.6) | 0.8 |
| A loss of taste | 7 | 77 | 0.9 (0.4-2.2) | 0.9 |
| Diarrhea | 1 | 13 | 0.8 (0.1-6.3) | 0.8 |

In addition, to evaluate the effectiveness of the drug package, we analyzed the positive rate for SARS-CoV-2 before and after 5 days of treatment. The results showed that before taking the drug, there were 400 patients with positive test results; while, after 5 days of taking the drug, the number of positive patients decreased to 35 patients and the number of patients who had negative or positive test results (CT≥30) increased to 365 ($p$<0.05). This shows that the effectiveness of the treatment is very high. Recover accounted for 99.8%; there was 1 patient moved upstairs, and no patient died (0.0%). 100% have negative test results (complete recovery) after finishing the treatment period.

### Some Associated Demographic Factors Regarding the Effectiveness of Home Treatment

Therefore, in order to have a basis for predicting the effectiveness of drug use, we analyzed some factors related to demographic patterns and clinical manifestations of patients to test results after 5 days of using the drug package. There are interesting but underestimated side observations to be declared. As shown in Tables IV and V, the isolation of the SARS-CoV-2 virus from a clinical sample with a low concentration of viral RNA, reflecting the PCR CT value ≥30, is of foremost importance, due to the current hygiene concepts that rely on the statistical assumption that infection rate decreases concomitantly to the increase of the CT-value[27,29]. While this could be correct under certain circumstances, the conclusion that patients with high CT values are not infectious anymore was recently considered a matter of debate[47].

Nevertheless, we should consider in this regard the grade of influence of demographic factors such as the young age of Vietnamese people[48]. The increased capacity of the young immune system is clinically evident, as aging is associated with morbidity and mortality at higher rates due to various causes and infections[49]. As of today, worldwide data show that age has to be considered the primary risk factor associated with COVID-19 progression to acute respiratory distress syndrome (ARDS), pulmonary embolism, and end-organ failure. The overall pictures often revealed these patterns as common features in patients with new or ongoing dyspnea after COVID-19 infection, which requires day-per-day treatment strategies[30,31]. There are significant and graded associations between the average population age and the incidence of that mentioned condition, which may guide the health authorities during the clinical responding phase[50-54]. For this reason, the Ninh Thuan Health authorities decided to adopt the home treatment policy either to limit person-to-person transmission or control hospital overloading.

Our results showed a statistically significant association between the group ≥60 years old with positive test results (RT-PCR) (CT<30) and negative and positive (CT≥30) after 5 days of taking the drug (OR=2.7, $p$<0.05). Tables VI and VII show that there is a statistically significant relationship between comorbidities and positive test results (CT<30) with negative and positive (CT≥30) after 5 days of taking the drug (OR=3.0, $p$<0.05).

### Some Aspects that May Have Negatively Impacted Our Qualitative Research

Just like any other health care program or service, the program using F0 treatment packages at home had to rely on manpower. One of the limitations of this study concerns the lack of professionals in the area, considered key players, necessary to maintain the standard of this type of community service during the pandemic emergency. Due


439

to low income and inadequate financial support for medical staff to fight the epidemic, the number of medical staff who left their jobs was very high. In addition, some patients needed to purchase themselves with basic medical tools such as blood pressure and oximeter devices.

## Conclusions

Reducing COVID-19-related critical hospitalizations and controlling community transmission rate by intervening earlier to clear infection were the main priorities of the study. Evidence from research shows that MOV caused a reduction in the risk of hospitalization or death in mild COVID-19-affected patients; MOV was also found to be well tolerated and safe without any major adverse events on use. In conclusion, this trial of mildly affected individuals with confirmed SARS-CoV-2 infection showed that early home treatment with MOV did reduce hospital admissions and deaths. Our findings suggest that the avoidance of hospitalization and death would primarily be achieved *via* understanding the various severity grades of the COVID-19 infection, focusing on population age. The benefits of MOV are faster time to recovery, reduced person-to-person contact or contact with general medical practitioners and reduced viral load. Further studies and health economic analysis are underway; international standard procedures are still being followed up to establish the effect of acute COVID-19 treatment with home treatment and MOV on longer-term symptoms. The lack of healthcare workers to examine and advise F0 at home was one of the limitations of this study, which would eventually support the patient's adherence to treatment. Financial support was the main issue in recruiting home healthcare staff.

### Conflict of Interest
The authors declare that they have no conflict of interests.

### Data Availability
The original contribution presented in this study is included in the article. Further inquiries can be directed to the corresponding author.

### Authors' Contribution
Conceptualization, T.L.H., P.T.P., T.T.T., H.N.V.N., and L.T.P.; methodology, T.L.Q., T.N.T. (Tin Nguyen Thanh), T.N.T. (Thuc Nai-Thanh) and T.L.V.; software, L.P.T.B., M.G.B., P.D., and R.L.; validation, L.S., R.D.P., and F.T.; formal analysis, C.G.I., A.P., L.D., F.I., G.D., M.S., and N.C.D.K.; resources, A.M.I., R.M., T.L.H., P.T.P., and H.N.V.N.; data curation, T.T.T., L.T.P., T.L.Q., and T.L.V.; writing-original draft preparation, T.L.H., T.N.T.(Tin Nguyen Thanh), T.N.T.(Thuc Nai-Thanh), L.P.T.B., L.D., P.D., and M.G.B.; writing-review and editing, R.L., A.P., L.D., L.S., R.D.P., N.C.D.K. and A.M.I.; visualization, F.T., C.G.I., F.I., G.D. and R.M.; supervision, P.T.P., F.I. and G.D.; project administration, T.L.H., K.C.D.N. and C.G.I. All authors have read and agreed to the published version of the manuscript.

### Informed Consent
Informed consent was obtained from all subjects involved in the study.

### Ethics Approval
This study was conducted according to the People's Committee of Ninh Thuan Province issued Plan No. 6022 on November 4, 2021, Law N 18/2011/TT-BYT and Law 4109/QD-BYT, official press release 8728/SYT-NVY dated 11/23/2021, by Ministry of Health of Vietnam.

### Funding
This review article and work received no specific grant, financial aid, or funding from any funding agency in the public, university, or commercial sectors.

### Availability of Data and Materials
Data and materials are available upon request.

## References

1) World Health Organization. WHO Coronavirus (COVID-19) Dashboard 2022. Available at: https://covid19.who.int/.
2) The Ministry of Health MoH - Vietnamese (2021), Temporary guidance on outpatient drugs for COVID-19 patients at home (Issued together with Decision No. 4109 dated August 26, 2021).
3) Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. Zhonghua Liu Xing Bing Xue Za Zhi 2020; 41: 145-151.
4) Teli D, Balar P, Patel K, Sharma A, Chavda V, Vora L. Molnupiravir: A Versatile Prodrug against SARS-CoV-2 Variants. Metabolites 2023; 13: 309.
5) Yip AJW, Low ZY, Chow VTK, Lal SK. Repurposing Molnupiravir for COVID-19: The Mechanisms of Antiviral Activity. Viruses 2022; 14: 1345.
6) Ghazali SM, Singh S, Zulkifli AA, Cheong YL, Md Iderus NH, Md Zamri ASS, Ahmad Jaafar N, Lai

CH, Wan Mohamed Noor WN, Rusli N, Chong CK, Aris T, Mohd Ibrahim H, Dass SC, Gill BS. COVID-19 in Malaysia: Descriptive Epidemiologic Characteristics of the First Wave. Int J Environ Res Public Health 2022; 19: 3828.

7) Chen G, Wu MZ, Qin CJ, Wu BB, Luo WR, Liu L, Liu JY. Epidemiological analysis of 18 patients with COVID-19. Eur Rev Med Pharmacol Sci 2020; 24: 12522-12526.
8) Chen J, Zhu YF, Du ZQ, Li WF, Zhang MJ, Zhao SD, Ying JW, Li Z, Miao HJ. Predictors of mechanical ventilation for COVID-19: combined data from three designated hospitals. Eur Rev Med Pharmacol Sci 2020; 24: 3065-13071.
9) Yoshimoto FK. The Proteins of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2 or n-COV19), the Cause of COVID-19. Protein J 2020; 39: 198-216.
10) Pashaki PA, Roudkenar MH, Rahim F, Ebrahimi A. From SARS-CoV to SARS-CoV2: a potential guide to better understanding of pathophysiology of the disease and potential therapeutic modality. Eur Rev Med Pharmacol Sci 2020; 24: 7816-7825.
11) Inchingolo AD, Inchingolo AM, Bordea IR, Malcangi G, Xhajanka E, Scarano A, Lorusso F, Farronato M, Tartaglia GM, Isacco CG, Marinelli G, D'Oria MT, Hazballa D, Santacroce L, Ballini A, Contaldo M, Inchingolo F, Dipalma G. SARS-CoV-2 Disease Adjuvant Therapies and Supplements Breakthrough for the Infection Prevention. Microorganisms 2021; 9: 525.
12) Pruijssers AJ, Denison MR. Nucleoside Analogues for the Treatment of Coronavirus Infections. Curr Opin Virol 2019; 35: 57-62.
13) Barnard DL, Hubbard VD, Burton J, Smee DF, Morrey JD, Otto MJ, Sidwell RW. Inhibition of Severe Acute Respiratory Syndrome-Associated Coronavirus (SARSCoV) by Calpain Inhibitors and β-D-N4-Hydroxycytidine. Antivir Chem Chemother 2004; 15: 15-22.
14) Malcangi G, Inchingolo AD, Inchingolo AM, Piras F, Settanni V, Garofoli G, Palmieri G, Ceci S, Patano A, Mancini A, Vimercati L, Nemore D, Scardapane A, Rapone B, Semjonova A, D'Oria MT, Macchia L, Bordea IR, Migliore G, Scarano A, Lorusso F, Tartaglia GM, Giovanniello D, Nucci L, Maggialetti N, Parisi A, Domenico MD, Brienza N, Tafuri S, Stefanizzi P, Curatoli L, Corriero A, Contaldo M, Inchingolo F, Dipalma G. COVID-19 Infection in Children and Infants: Current Status on Therapies and Vaccines. Children 2022; 9: 249.
15) Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; 323: 1061-1069.
16) Madelain V, Nguyen THT, Olivo A, De Lamballerie X, Guedj J, Taburet AM, Mentré F. Ebola virus infection: review of the pharmacokinetic and pharmacodynamic properties of drugs considered for testing in human efficacy trials. Clin Pharmacokinet 2016; 55: 907-923.
17) Singh AK, Singh A, Singh R, Misra A. Molnupiravir in COVID-19: A systematic review of literature. Diabetes Metab. Syndr. Clin Res Rev 2021; 15: 02329.
18) CCIDER. Interim Recommendation on Clinical Management of Adult Cases with Coronavirus Disease 2019 (COVID-19); HA Central Committee on Infectious Diseases: Hong Kong, China, 2022; p. 34.
19) Pham VH, Isacco CG, Nguyen KC, Le SH, Tran DK, Nguyen QV, Pham HT, Aityan S, Pham ST, Cantore S, Inchingolo AM. Rapid and sensitive diagnostic procedure for multiple detection of pandemic Coronaviridae family members SARS-CoV-2, SARS-CoV, MERS-CoV and HCoV: a translational research and cooperation between the Phan Chau Trinh University in Vietnam and University of Bari "Aldo Moro" in Italy. Eur Rev Med Pharmacol Sci 2020; 24: 7173-7191.
20) Fischer WA 2nd, Eron JJ Jr, Holman W, Cohen MS, Fang L, Szewczyk LJ, Sheahan TP, Baric R, Mollan KR, Wolfe CR, Duke ER, Azizad MM, Borroto-Esoda K, Wohl DA, Coombs RW, James Loftis A, Alabanza P, Lipansky F, Painter WP. A phase 2a clinical trial of molnupiravir in patients with COVID-19 shows accelerated SARS-CoV-2 RNA clearance and elimination of infectious virus. Sci Transl Med 2022; 14: eabl7430.
21) Balzanelli MG, Distratis P, Dipalma G, Vimercati L, Inchingolo AD, Lazzaro R, Aityan SK, Maggiore ME, Mancini A, Laforgia R, Pezzolla A, Tomassone D, Pham VH, Iacobone D, Castrignano A, Scarano A, Lorusso F, Tafuri S, Migliore G, Inchingolo AM, Nguyen KCD, Toai TC, Inchingolo F, Isacco CG. Sars-CoV-2 Virus Infection May Interfere CD34+ Hematopoietic Stem Cells and Megakaryocyte-Erythroid Progenitors Differentiation Contributing to Platelet Defection towards Insurgence of Thrombocytopenia and Thrombophilia. Microorganisms 2021; 9: 1632.
22) Lai CC, Wang YH, Chen KH, Chen CH, Wang CY. The clinical efficacy and safety of anti-viral agents for non-hospitalized patients with COVID-19: A systematic review and network meta-analysis of randomized controlled trials. Viruses 2022; 14: 1706.
23) Inchingolo AD, Dipalma G, Inchingolo AM, Malcangi G, Santacroce L, D'Oria MT, Isacco CG, Bordea IR, Candrea S, Scarano A, Morandi B, Del Fabbro M, Farronato M, Tartaglia GM, Balzanelli MG, Ballini A, Nucci L, Lorusso F, Taschieri S, Inchingolo F. The 15-Months Clinical Experience of SARS-CoV-2: A Literature Review of Therapies and Adjuvants. Antioxidants 2021; 10: 881.
24) Del Borgo C, Garattini S, Bortignon C, Carraro A et al., Di Trento D, Gasperin A, Grimaldi A, De Maria SG, Corazza S, Tieghi T, Belvisi V, Kertusha B, De Masi M, D'Onofrio O , Bagaglini G, Bonanni G, Zuccalà P, Fabietti P, Tortellini E, Guardiani M, Spagnoli A, Marocco R, Alunni Fegatelli D, Lichtner M, Latina Covid-Group. Effectiveness, Tolerability and Prescribing Choice of Antiviral Molecu-

les Molnupiravir, Remdesivir and Nirmatrelvir/r: A Real-World Comparison in the First Ten Months of Use. Viruses 2023; 15: 1025.

25) Wan EYF, Wang B, Mathur S, Chan CIY, Yan VKC, Lai FTT, Chui CSL, Li X, Wong CKH, Li PH, Lau CS, Wong ICK, Chan EWY. Molnupiravir and nirmatrelvir-ritonavir reduce mortality risk during post-acute COVID-19 phase. J Infect 2023; 86: 622-625.

26) Bellocchio L, Bordea IR, Ballini A, Lorusso F, Hazballa D, Isacco CG, Malcangi G, Inchingolo AD, Dipalma G, Inchingolo F, Piscitelli P, Logroscino G, Miani A. Environmental Issues and Neurological Manifestations Associated with COVID-19 Pandemic: New Aspects of the Disease? Int J Environ Res Public Health 2020; 17: 8049.

27) Kwok WC, Tsoi MF, Leung SH, Tsui CK, Tam TC, Ho JC, Lam DC, Ip MS, Ho PL. Real-World Study on Effectiveness of Molnupiravir and Nirmatrelvir-Ritonavir in Unvaccinated Patients with Chronic Respiratory Diseases with Confirmed SARS-CoV-2 Infection Managed in Out-Patient Setting. Viruses 2023; 15: 610.

28) Pitre T, Van Alstine R, Chick G, Leung G, Mikhail D, Cusano E, Khalid F, Zeraatkar D. Antiviral drug treatment for severe COVID-19: a systematic review and network meta-analysis. CMAJ 2022; 194: E969-E980.

29) Khoo SH, FitzGerald R, Saunders G, Middleton C, Ahmad S, Edwards CJ, Hadjiyiannakis D, Walker L, Lyon R, Shaw V, Mozgunov P, Periselneris J, Woods C, Bullock K, Hale C, Reynolds H, Downs N , Ewings S, Buadi A, Cameron D, Edwards T, Knox E, Donovan-Banfield I, Greenhalf W, Chiong J, Lavelle-Langham L, Jacobs M, Northey J, Painter W, Holman W, Lalloo DG, Tetlow M, Hiscox JA, Jaki T, Fletcher T, Griffiths G; AGILE CST-2 Study Group. Molnupiravir versus placebo in unvaccinated and vaccinated patients with early SARS-CoV-2 infection in the UK (AGILE CST-2): a randomized, placebo-controlled, double-blind, phase 2 trial. Lancet Infect Dis 2023; 23: 183-195.

30) Meo SA, Meo AS, Al-Jassir FF, Klonoff DC. Omicron SARS-CoV-2 new variant: global prevalence and biological and clinical characteristics. Eur Rev Med Pharmacol Sci 2021; 25: 8012-8018.

31) Kucukdemirci Kaya P, Kucukdemirci O, Caliskan G, Kelebek Girgin N. Effects of COVID-19 variation on the treatment response and disease severity in critical illness: a retrospective observational cohort study. Eur Rev Med Pharmacol Sci 2022; 26: 2602-2609.

32) De Vito A, Geremia N, Princic E, Fanelli C, Napodano P, Muredda AA, Fiore V, Maida I, Fois AG, Babudieri S, Madeddu G. Does angiotensin II receptor blockers increase the risk of SARS-CoV-2 infection? A real-life experience. Eur Rev Med Pharmacol Sci 2021; 25: 523-526.

33) Wong CKH, Au ICH, Lau KTK, Lau EHY, Cowling BJ, Leung GM. Real-world effectiveness of molnupiravir and nirmatrelvir plus ritonavir against mortality, hospitalization, and in-hospital outcomes among community-dwelling, ambulatory patients with confirmed SARS-CoV-2 infection during the omicron wave in Hong Kong: an observational study. Lancet 2022; 400: 1213-1222.

34) Caraco Y, Crofoot G, Moncada PA, Galustyan AN, Musungaue DB, Payne B, Kovalchuk E, Gonzalez A, Brown ML, Williams-Diaz A, Gao W, Strinzki JM, Grobler J, Du J, Assais CA, Paschke A, Butterton JR, Johanson MG, De Anda C. Phase 2/3 trial of molnupiravir for treatment of Covid-19 in nonhospitalized adults. NEJM Evid 2022; 1.

35) Stokes EK, Zambrano LD, Anderson KN, Marder EP, Raz KM, EL Burai Felix S, Tie Y, Fullerton KE. Coronavirus disease 2019 case surveillance-United States, January 22-May 30, 2020. MMWR Morb Mortal Wkly Rep 2020; 69: 759-765.

36) Tenforde MW, Kim SS, Lindsell CJ, Billig Rose E, Shapiro NI, Files DC, Gibbs KW, Erickson HL, Steingrub JS, Smithline HA, Gong MN, Aboodi MS, Exline MC, Henning DJ, Wilson JG, Khan A, Qadir N, Brown SM, Peltan ID, Rice TW, Hager DN, Ginde AA, Stubblefield WB, Patel MM, Self WH, Feldstein LR; IVY Network Investigators; CDC COVID-19 Response Team; IVY Network Investigators. Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network - United States, March-June 2020. MMWR Morb Mortal Wkly Rep 2020; 69: 993-998.

37) Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, Martín-Quirós A, Caraco Y, Williams-Diaz A, Brown ML, Du J, Pedley A, Assaid C, Strizki J, Grobler JA, Shamsuddin HH, Tipping R, Wan H, Paschke A, Butterton JR, Johnson MG, De Anda C; MOVe-OUT Study Group. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. N Engl J Med 2022; 386 : 509-520.

38) Tian L, Pang Z, Li M, Lou F, An X, Zhu S, Song L, Tong Y, Fan H, Fan J. Molnupiravir and Its Antiviral Activity Against COVID-19. Front Immunol 2022; 13: 855496.

39) Ekici A, Ekici M, Baççıoğlu A, Akyüz İnanç F, Aslan H. Pulmonary embolism in patients with dyspnea after COVID-19 infection. Eur Rev Med Pharmacol Sci 2022; 26: 3751-3759.

40) Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, Akdis CA, Gao YD. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020; 75: 1730-1741.

41) La Scola B, Le Bideau M, Andreani J, Hoang VT, Grimaldier C, Colson P, Gautret P, Raoult D. Viral RNA load as determined by cell culture as a management tool for discharge of ARS-CoV -2 patients from infectious disease wards. Official publication of the European ociety of Clinical Microbiology. Eur J Clin Microbiol Infected Dis 2020; 39: 1059-1061.

42) Platten M, Hoffmann D, Grosser R, Wisplinghoff F, Wisplinghoff H, Wiesmüller G, Schildgen O, Schildgen V. SARS-CoV-2, CT-Values, and Infectivity-Conclusions to Be Drawn from Side Observations. Viruses 2021; 13: 1459.

43) Bartleson JM, Radenkovic D, Covarrubias AJ, Furman D, Winer DA, Verdin E. SARS-CoV-2, COVID-19 and the Ageing Immune System. Nat Aging 2021; 1: 769-782.

44) Rossi AP, Gottin L, Donadello K, Schweiger V, Nocini R, Taiana M, Zamboni M, Polati E. Obesity as a risk factor for unfavorable outcomes in critically ill patients affected by Covid 19. NMCD 2021; 31: 762-768.

45) Dallocchio RN, Dessì A, De Vito A, Delogu G, Serra PA, Madeddu G. Early combination treatment with existing HIV antivirals: an effective treatment for COVID-19? Eur Rev Med Pharmacol Sci 2021; 25: 2435-2448.

46) Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, Martín-Quirós A, Caraco Y, Williams-Diaz A, Brown ML, Du J, Pedley A, Assaid C, Strizki J, Grobler JA, Shamsuddin HH, Tipping R, Wan H, Paschke A, Butterton JR, Johnson MG, De Anda C; MOVe-OUT Study Group. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. N Engl J Med 2022; 386: 509-520.

47) Ballini A, Cantore S, Serretiello E, Troiano G, Smimmo A, Dioguardi M, Spirito F, Sasso FC, De Vito D, Lo Muzio L, Di Domenico M. Multiparametric correlation of laboratory biomarkers to multiorgan failure outcome in hospitalized COVID-19 patients: a retrospective observational study. Eur Rev Med Pharmacol Sci 2023; 27: 8962-8974.

48) Karabulut A, Şahin M. Inflammatory markers and neopterin levels in relation to mild COVID-19. Eur Rev Med Pharmacol Sci 2023; 27: 8943-8951.

49) Yang H, Kim MS, Rhee SY, Lee J, Cho W, Min C, Lee SW, Shin JI, Oh J, Choi Y, Lee JH, Kim H, Rahmati M, Yeo SG, Yon DK. National prevalence and socioeconomic factors associated with the acceptance of COVID-19 vaccines in South Korea: a large-scale representative study in 2021. Eur Rev Med Pharmacol Sci 2023; 27: 8943-8951.

50) Macías-Gómez N, Montañez-Valdez O, Leal-Ugarte E, Vázquez-Zaragoza D, Sigala-Arellano R. Clinical and thyroid profile in patients with COVID-19 hospitalized in an intensive care unit. Eur Rev Med Pharmacol Sci 2023; 27: 8301-8313.

51) Ilginel MT, Yesilyurt AO, Ozyilmaz E, Ilginel OO, Sener M, Tunay DL, Karacaer F, Biricik E, Ucar MA. Evaluation of factors affecting treatment and mortality in patients over 65 years of age and without chronic disease, followed in the Intensive Care Unit due to COVID-19. Eur Rev Med Pharmacol Sci 2023; 27: 8301-8313.