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ORIGINAL ARTICLE

Effect of combination of molnupiravir with clarithromycin on blood biomarkers in patients with mild-to-moderate COVID-19

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ABSTRACT

Background: Molnupiravir is a type of medication used to treat coronavirus disease 2019 (COVID-19). However, no evidence regarding the therapeutic effect of molnupiravir combined with clarithromycin (CAM) on blood biomarkers is available.

Methods: Of the 156 rehabilitation patients, 124 patients with mild-to-moderate COVID-19 were treated with molnupiravir. Among these 124 patients, 54 were treated with CAM. The remaining 28 rehabilitation patients were negative for COVID-19. Blood biomarkers were assessed after administration of molnupiravir in patients receiving molnupiravir plus CAM or molnupiravir alone.

Results: Among the measured blood biomarkers, lactate dehydrogenase, potassium, white blood cells, C-reacted protein, neutron–lymphocyte ratio, fibrin degradation product, and prothrombin time–international normalized ratio values were significantly higher ($P < 0.05$) in the molnupiravir alone group than in the molnupiravir plus CAM group, and lymphocytes were significantly lower ($P < 0.05$) on day 5 after admission. In the molnupiravir plus CAM group, immunoglobulin (Ig) A levels increased and soluble interleukin 2-receptor levels (sIL2R) decreased ($P < 0.05$) on day 14 after admission. In addition, COVID-19-negative patients had higher IgA levels and lower sIL2R levels compared to infected patients ($P < 0.05$). The concomitant administration of molnupiravir plus CAM resulted in fewer sequelae after 12 months, and the incidence of venous thromboembolism was significantly reduced ($P < 0.05$).

Conclusion: In patients with mild-to-moderate COVID-19, concomitant administration of molnupiravir plus CAM showed several non-worsening blood biomarkers, elevated immune activity, and reduced post-infection sequelae.

Relevance for Patients: After administration of molnupiravir to patients with mild-to-moderate COVID-19, administration of CAM to patients suffering from secondary macrolide-sensitive bacterial infection was compared with administration of molnupiravir alone. D-dimer, IgA, and sIL2R are potential predictive factors of disease severity in critically ill patients with COVID-19.

1. Introduction

Sudden deterioration and death of patients suffering from mild-to-moderate coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is common on the clinical scene. In some cases, patients become severely ill without being aware of it and suffer from oxygen deficiency. It is necessary to prevent deterioration of COVID-19, tested positive by means of SARS-CoV-2 antigen test or

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SARS-CoV-2 PCR test, among patients with mild-to-moderate symptoms before respiration failure takes place. At the height of the COVID-19 pandemic, the hospitalization rates for patients with severe infections were high; naturally, the mild-to-moderate cases were asked to self-quarantine at home. Therefore, an approach to treating COVID-19 patients with mild-to-moderate symptoms is essential.

Molnupiravir has been proven to be a well-tolerated, direct-acting oral antiviral agent that prevents symptom progression in patients with mild-to-moderate COVID-19 [1,2]. Given the context of rapid spread of infection among hospitalized patients in isolation and closed wards, oral molnupiravir serves as an ideal medication due to the ease of administration [3,4]. However, even if molnupiravir is administered in mild-to-moderate cases, the possibility of deterioration cannot be avoided if a secondary infection occurs. In this study, we selected patients with macrolide-susceptible bacteria among the patients with secondary infections.

Macrolide (clarithromycin or azithromycin) antibiotics were incorporated in the treatment regimen in the early stages of the COVID-19 pandemic, especially considering that they may have anti-inflammatory effects. Macrolides have been extensively researched as broad adjunctive therapy for COVID-19 due to its immunostimulant abilities [5]. Adding clarithromycin (CAM) or azithromycin to the therapeutic protocols for COVID-19 could be beneficial for early control of fever and early PCR-negative conversion in mild COVID-19 cases [6]. It has been reported the first COVID-19-positive patient who recovered from the symptoms after the use of chloroquine and CAM was reported in Colombia [7]. CAM has immunomodulatory properties superior to those of azithromycin [8] and enhances antiviral secretory-IgA production and neutralizing activities through the induction of IgA class switching recombination [9]. Interleukin (IL)-6 and IL-2 trigger cytokine release syndrome observed in severe cases of COVID19. CAM significantly inhibited the production of IL-6 by dendritic cells and significantly decreased IL-2 productions [10]. The results of The ACHIEVE Open-Label Single-Arm Trial demonstrated that early CAM treatment leads to clinical improvement in patients with moderate COVID-19 [11].

At present, there is no evidence regarding therapeutic effect of molnupiravir combined with CAM on blood biomarkers in COVID-19 patients. Thus, the aim of this study is to investigate blood biomarkers in patients with mild-to-moderate COVID-19, compounded by secondary infection with macrolide-sensitive bacteria, who were treated with molnupiravir followed by administration of CAM. At the same time, blood biomarkers were also evaluated for COVID-19-negative patients, who were used as controls in this study despite being quarantined together with other COVID-19 patients. In addition, we compared the degree of sequelae 12 months after the COVID-19 treatment with molnupiravir plus CAM or molnupiravir alone.

2. Methods

2.1. Study design

A total of 156 patients who were hospitalized in a rehabilitation ward from May 2022 to July 2022 were recruited in this study. Of the 156 patients, 4 severe COVID-19 patients were transferred to other hospitals where endotracheal intubation and ventilator treatment were available. We administered molnupiravir (800 mg twice daily for 5 days) to 124 mild-to-moderate COVID-19 patients (Supplementary Data 1). Chest X-ray, computed tomography, and bacteriological examination were performed to detect the occurrence of secondary infection. A respiratory physician diagnosed 87 secondary infections and administered antibiotics based on the results of bacterial sensitivity test. Fifty four of the 124 patients had mycoplasma infection, Gram-positive coccal infection, pneumococcal infection, or Haemophilus influenza infection and received CAM (400 mg twice daily for 3 days). Of the 124 patients, 33 received antibiotics other than CAM. Twenty eight of the 156 patients were negative for COVID-19 despite being quarantined with other COVID-19-positive patients and were not treated with any drugs for COVID-19 (Figure 1).

2.2. Laboratory examinations

Nucleic acid detection tests and antigen tests were performed in accordance with the "Guidelines for Pathogen Testing of Novel Coronavirus Infectious Disease (COVID-19) March 17, 2022, Version 5.1" published by the Ministry of Health, Labor and Welfare of Japan [12]. Real-time RT-PCR was performed to detect SARS-CoV-2 nucleic acids using GeneFinder™ COVID-19 PLUS RealAmp Kit and ELITe InGenius® instrument. Antigen qualitative tests were conducted using the SARS CoV-2 Rapid Antigen Test Nasal kit (SD BIOSENSOR, Roche; REF: 9901-NCOV-03G; LOT: QCO 3811951). During hospitalization, blood samples were collected on the 5th day and 14th day from the start of oral molnupiravir administration at the time of infection according to the doctor's instruction. Blood biomarkers were assessed using an automated hematology analyzer. Uninfected patients were assumed to be infected when their roommates started taking molnupiravir, and their blood was collected for medical assessment, considering the possibility of infection from infected patients in the same room. To investigate predictive factors of molnupiravir plus CAM combination therapy in COVID-19 patients, the following biomarkers were measured: lactate dehydrogenase (LDH) [13], total cholesterol, triglyceride [14], uric acid [15], creatinine [16], potassium [17], white blood cells (WBC), hemoglobin (Hb) [18], platelet (PLT) [13], C-reactive protein (CRP) [19], neutrophils, lymphocytes [20], neutrophil–lymphocyte ratio (NLR) [21], fibrinogen [22], fibrin degradation product (FDP) [23], D-dimer [24], prothrombin time-international normalized ratio (PT-INR) [25], creatinine phosphokinase (CPK) [26], brain natriuretic peptide (BNP) [27], IgG [28], IgA [29], IgM [30], and soluble IL-2 receptor (sIL2R) [31]. Cutoff values are listed in Supplementary Data 2 and 3.

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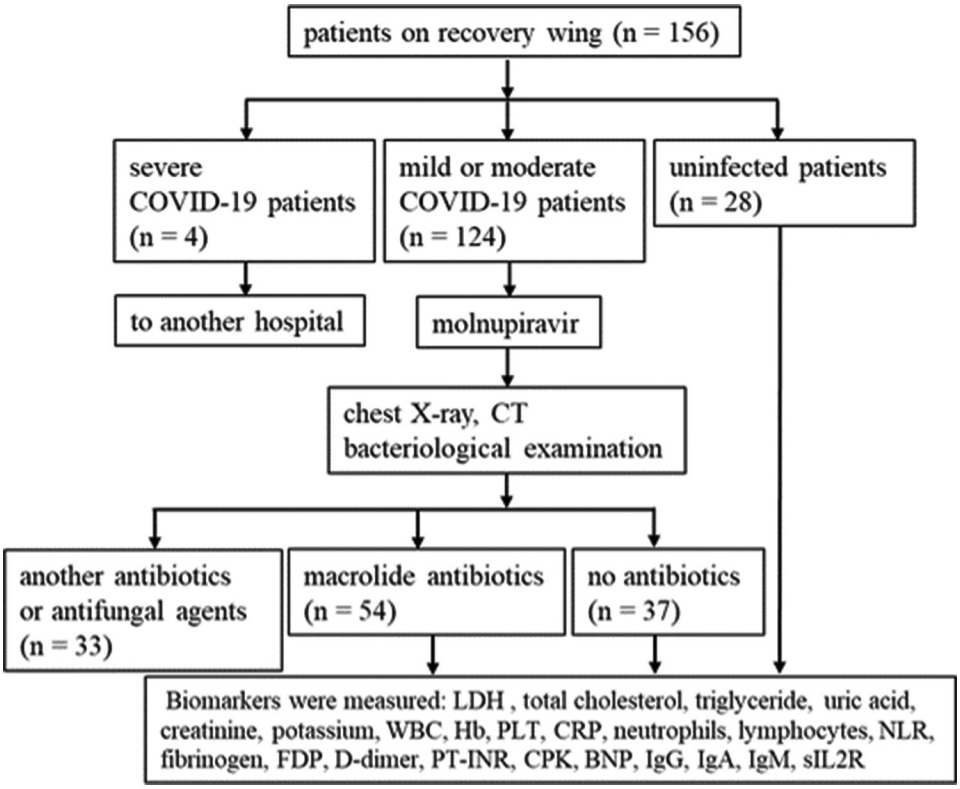

Figure 1. CONSORT flow chart detailing patient enrollment allocation, follow-up, and analysis. Out of the 156 rehabilitation patients, 124 patients with mild-to-moderate COVID-19 received molnupiravir (800 mg twice daily for 5 days), and 54 of this subset of patients received clarithromycin (400 mg twice daily for 3 days). The remaining 28 patients were negative for COVID-19 despite being isolated from other COVID-19-positive patients and were not administered drugs.
Abbreviations: CT: Computed tomography, LDH: Lactate dehydrogenase, WBC: White blood cells, Hb: Hemoglobin, PLT: Platelet, CRP: C-reacted protein, NLR: Neutron–lymphocyte ratio, FDP: Fibrin degradation product, PT-INR: Prothrombin time–International Normalized Ratio, CPK: Creatinine phosphor kinase, BNP: Brain natriuretic peptide, Ig; Immunoglobulin, sIL2R: Soluble interleukin 2 receptor.

2.3. Statistics analysis

Student's *t*-test was used for statistical data analysis. A $P < 0.05$ was considered significant. Data are presented as SD±. Cox proportional hazard models were utilized to assess the impact of risk factors. SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis.

3. Results

3.1. Baseline characteristics of COVID-19 patients treated with molnupiravir plus clarithromycin and molnupiravir alone and uninfected patients

Between the molnupiravir plus CAM group and molnupiravir alone group, significant differences were observed in baseline symptoms of fever, cough and sputa, shortness of breath, chest tightness, and dyspnea, and in baseline comorbidity of respiratory diseases ($P < 0.05$). Some baseline symptoms were significantly different between uninfected rehabilitation patients and those receiving molnupiravir plus CAM or molnupiravir alone. However, there was no significant difference in baseline comorbidity (Supplementary Data 4).

On Okinawa Island, the rollout of Pfizer-BioNTech COVID-19 mRNA vaccines began in December 2021. More than 90% of the patients had received at least one vaccine shot within 6 months before admission, and none of them received vaccine during hospitalization. However, only 89.3% of the uninfected rehabilitation patients had been vaccinated (Supplementary Data 4).

3.2. Dynamics of blood biomarkers during disease progression in molnupiravir alone group, molnupiravir plus clarithromycin group, and uninfected group

LDH, potassium, WBC, CRP, NLR, FDP, and PT-INR values were significantly higher ($P < 0.05$) in the molnupiravir alone group than in the molnupiravir plus CAM combination group on day 5, and lymphocyte count was significantly lower ($P < 0.05$). On the 14th day, WBC, CRP, neutrophils, and NLR were all significantly high ($P < 0.05$), and lymphocyte count was significantly low ($P < 0.05$).

In the molnupiravir alone group, LDH, potassium, WBC, CRP, neutrophils, NLR, fibrinogen, FDP, PT-INR, and CPK significantly increased on day 5 after admission ($P < 0.05$) and total cholesterol, triglyceride, uric acid, PLT, and lymphocytes

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significantly decreased ($P < 0.05$). D-dimer decreased significantly on day 14 after admission ($P < 0.05$), and CRP was significantly elevated ($P < 0.05$).

In the molnupiravir plus CAM group, there were no significant differences in any of the biomarkers between admission and day 5. In addition, the values of D-dimer decreased significantly on day 14 after admission ($P < 0.05$).

In the uninfected group, no significant differences in biomarkers were observed before infection, on day 5, and on day 14. The values of biomarkers, except for BNP, were within normal limits (Figure 2 and Supplementary Data 2).

3.3. Dynamics of IgG, IgA, IgM, and sIl2R in advanced stages of disease in molnupiravir alone group, molnupiravir plus clarithromycin group, and uninfected group

We measured baseline levels of immunological biomarkers on days 5 and 14 from the start of oral administration at the time of infection in the molnupiravir alone group and the molnupiravir plus CAM group and on the day of admission in the uninfected group (Figure 3 and Supplementary Data 3).

The IgA level at admission in the uninfected group was significantly higher than the IgA level on day 5 in both the molnupiravir alone group and the molnupiravir plus CAM group ($P < 0.05$).

The sIL2R level at admission in the uninfected group was significantly lower than the sIL2R level on day 5 in both the molnupiravir alone group and the molnupiravir plus CAM group ($P < 0.05$).

In the molnupiravir plus CAM group, the IgA level on day 14 was significantly higher than that on day 5, and the sIL2R level on day 14 was significantly lower than that on day 5 ($P < 0.05$).

In the molnupiravir plus CAM group, the IgA level on day 14 was significantly higher ($P < 0.05$) and the sIL2R level was significantly lower ($P < 0.05$) than in the molnupiravir alone group. The values of IgG and IgM were within the normal limit.

3.4. Predictive factors as blood biomarker in molnupiravir alone group and molnupiravir plus clarithromycin group

Multivariate logistic regression analysis based on the collection and analysis of clinical and laboratory data for the

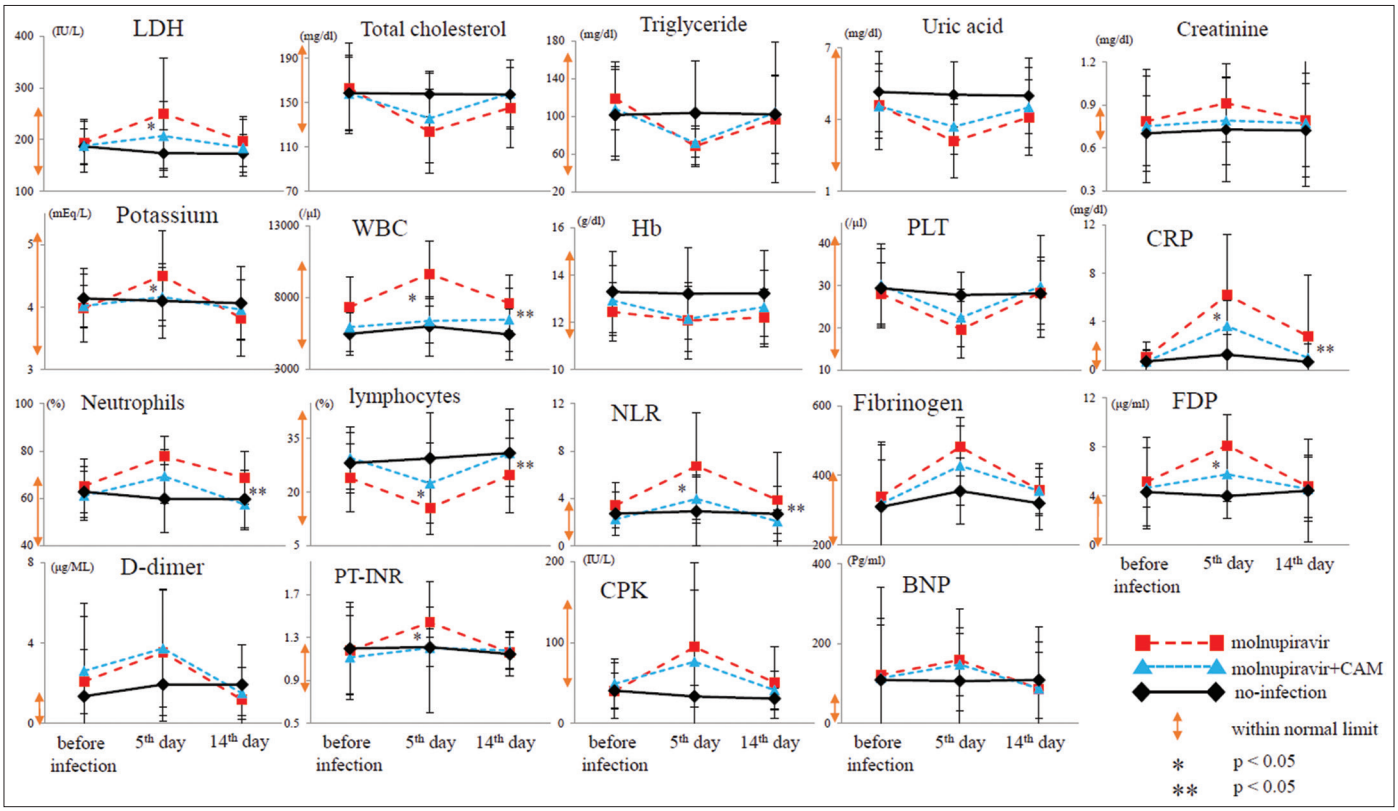

Figure 2. Time-series dynamics of blood biomarkers in the molnupiravir alone group, the molnupiravir plus clarithromycin (CAM) group, and the uninfected group. The molnupiravir plus CAM group had lower or higher values than the molnupiravir alone group and were close to the values of the uninfected group. The vertical axis indicates the value of each biomarker, while the horizontal axis indicates before infection, 5th days and 14th days after administration of molnupiravir. Red squares and dashed lines indicate molnupiravir; blue triangles and dotted lines indicate molnupiravir + CAM; black diamonds and bar-shaped line indicate no infection; double-headed arrow indicates within normal limits. *$P < 0.05$, **$P < 0.05$.
Abbreviations: LDH: Lactate dehydrogenase, WBC: White blood cells, Hb: Hemoglobin, PLT: Platelet, CRP: C-reacted protein, NLR: Neutron–lymphocyte ratio, FDP: Fibrin degradation product, PT-INR: Prothrombin time–International Normalized Ratio, CPK: Creatinine phosphor kinase, BNP: Brain natriuretic peptide.

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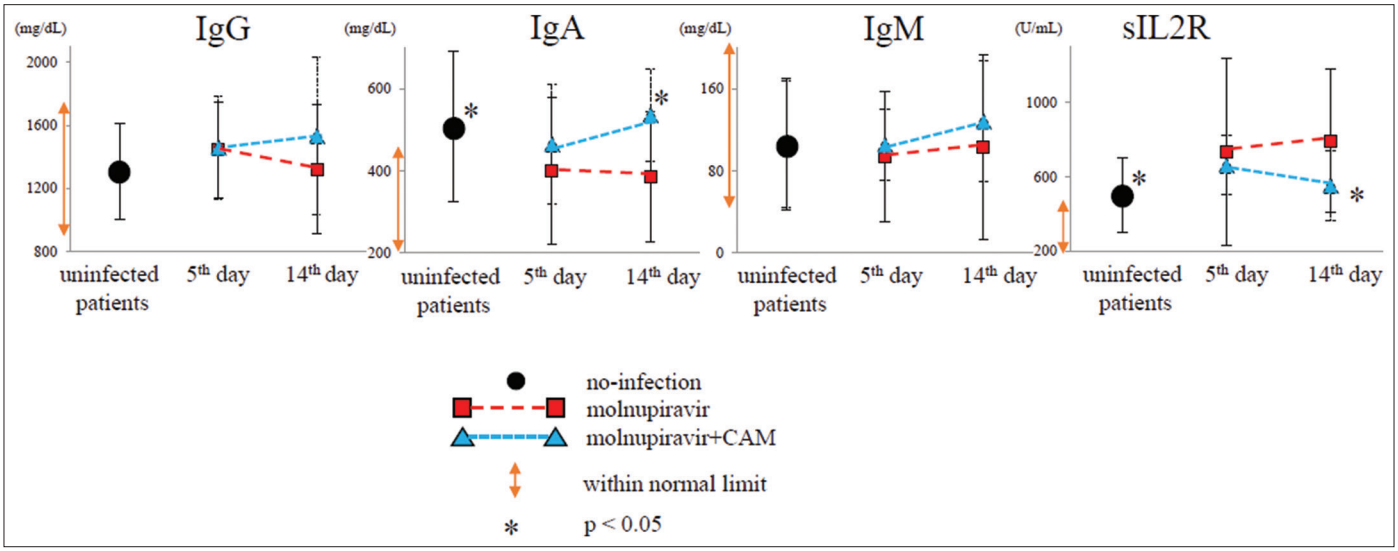

Figure 3. Time-series dynamics of immune biomarkers in the molnupiravir alone group, the molnupiravir plus clarithromycin (CAM) group, and the uninfected group. Uninfected individuals had higher IgA levels and lower sIL2R levels than infected individuals. IgA levels increased and sIL2R levels decreased in the molnupiravir plus CAM group. On day 14 after administration, IgA levels were higher and sIL2R levels were lower in the molnupiravir plus CAM group than in the molnupiravir alone group. The vertical axis indicates the value of each biomarker, while the horizontal axis indicates the duration of hospitalization for an uninfected patient during drug administration, and the 5th and 14th days for an infected patient after administration. Red squares and dashed lines indicate molnupiravir; blue triangles and dotted line indicate molnupiravir + CAM; double-headed arrow indicates within normal limit. *$P < 0.05$.

molnupiravir alone group and the molnupiravir plus CAM group showed that predictive factors were D-dimer (OR = 1.08, 95% CI = 1.05 – 1.11, $P < 0.05$), IgA (OR = 1.06, 95% CI = 1.02 – 1.10, $P < 0.05$), and sIL2R (OR = 1.13, 95% CI = 1.09 – 1.17, $P < 0.05$) (Supplementary Data 5).

3.5. Comparison of severity of sequelae 12 months after COVID-19 treatment with molnupiravir plus clarithromycin or molnupiravir alone

Administration of molnupiravir plus CAM significantly reduced the incidence of venous thromboembolism compared to administration of molnupiravir alone ($P < 0.05$). There were no significant differences in other sequelae, but the incidence of sequelae was generally lower in the administration of molnupiravir plus CAM (Supplementary Data 6).

4. Discussion

Okinawa consists of more than 160 archipelagos, situated between Taiwan and the main island of Japan in the East China Sea. Remote islanders do not always have adequate medical care if they contract COVID-19, even if they become severely ill. Many of the islanders are over 90 years old. However, elderly patients with pre-existing conditions are more likely to become seriously ill if infected. Therefore, it is imperative to prevent the deterioration from mild or moderate COVID-19 to severe form, necessitating ventilator management among elderly patients, and it is also our responsibility as medical professionals to engage in the treatment of COVID-19-infected patients [32]. Preventing mild or moderate COVID-19 from worsening in medical settings stands as a model treatment approach in the face of the rapid surge in COVID-19 infections.

Almost all biomarkers were reduced surprisingly by the combined administration of molnupiravir and CAM as compared to the molnupiravir alone administration (Figure 2). However, even in the molnupiravir plus CAM group, CRP, neutrophils, fibrinogen, and FDP exceeded the standard values. Thus, it is necessary to consider medications other than CAM considering drug–drug interactions (DDI), anti-inflammatory effect, and thrombosis prevention. In the molnupiravir plus CAM group, the values were almost equivalent to those of uninfected patients, and within at least 2 weeks, the biomarkers fell within the reference range, suggesting the abrogation of COVID-19 deterioration regardless of symptoms at the time of infection. The presence of cerebrovascular and cardiovascular disorders is the reason that D-dimer and BNP values exceeded the standard values regardless of the duration of drug administration in patients, whether uninfected or infected. Interestingly, the D-dimer and BNP levels on the 14th day after administration of molnupiravir were lower than those before infection and were also lower than those in uninfected subjects. Molnupiravir may be effective in preventing thrombosis and improving heart failure.

Furthermore, after 12 months, the incidence of venous thromboembolism was significantly reduced in the molnupiravir plus CAM group (Supplementary Data 6), suggesting that D-dimer is a potential predictive factor. On the same note, identifying D-dimer as a predictive factor for venous thromboembolism is tantamount to recognizing the thrombotic tendency among COVD-19 patients. Both the target patients and rehabilitation patients at our hospital suffered from cerebrovascular and cardiovascular disorders, and

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their D-dimer and BNP levels surpassed the standard values at the time of admission, requiring anticoagulants for thrombosis prevention. It has been reported that thrombosis can be induced in patients with COVD-19. However, the current findings show that fibrinogen and FDP levels remain high after infection, but they became lower than before infection, although not within the standard values, after 14 days of molnupiravir administration. Furthermore, concomitant administration of CAM improved coagulation factor elevation and intravascular coagulation, and venous thromboembolism and pulmonary thromboembolism were not observed in the target patients. This might be the reason why no patients from the current cohort died of COVID-19 and were successfully discharged from the hospital.

Based on our results, IgA and sIL2R are potential predictive factors. Uninfected individuals had significantly higher IgA levels and lower sIL2R levels than infected individuals. This can be one of the reasons why there were no new infection cases even after 14 days although the rehabilitation patients had had close contact with COVID-19-positive roommates in a closed ward (Figure 3). In addition, molnupiravir administration sustained the effect of IgM even on day 14, but molnupiravir plus CAM administration resulted in higher IgG levels on day 14. Although there was no significant difference, CAM might maintain humoral immunity even after 10 days of administration. SARS-CoV-2, the virus that causes COVID-19, infects cells on mucosal surfaces. Serum-neutralizing antibody responses are variable, and neutralizing antibodies appear to be generally low in patients with COVID-19. Potent IgG antibodies neutralize the virus, but secretory antibody responses such as IgA, which can affect initial viral spread and transmissibility across mucosa, may be of particular value for defense against SARS-CoV-2 [33]. This result is consistent with the effect of molnupiravir plus CAM administration, *i.e.*, increase in IgA and decrease in sIL2R (Figure 3).

Molnupiravir (MK-4482, EIDD-2801) is a promising broad-spectrum experimental antiviral agent developed by Merck & Co. It was originally developed to treat influenza infections because it exerts antiviral activity through RNA-dependent RNA polymerase to induce huge numbers of copy errors. Molnupiravir has demonstrated potent *in vitro* antiviral activity with low cytotoxicity and high resistance barrier against positive-sense RNA viruses, including SARS-CoV-2 [34]. When the pandemic began, molnupiravir was in pre-clinical development for the treatment of seasonal influenza but has evolved into a potential agent for the prevention and treatment of COVID-19 [35]. Influenza infections occur year-round on the main island, and we have reported that the non-infected individuals had higher IgA levels than the influenza-infected individuals [36]. IgA levels in nasal discharge and alveolar lavage fluid, which were markedly decreased when anti-influenza drugs were administered alone, significantly recovered to high levels when the drug was administered in combination with CAM, a macrolide with immuno-modulating effects. In addition, IgA production was significantly enhanced by nearly 10-fold in patients who were co-administered with CAM, although it was not observed after the administration of anti-influenza drugs alone [9]. CAM combined administration may increase IgA, which is low in the human body, by encouraging its production, as observed in this study.

Indeed, vaccines can induce secretory IgA antibodies and are effective. However, there is still an urgent need for antiviral drugs with potent activity to defend against the emerging SARS-CoV-2 variants for which existing vaccines may be less effective. Certainly, early treatment with molnupiravir reduced the risk of hospitalization or death in unvaccinated adults at risk for COVID-19 (Funded by Merck Sharp and Dohme; MOVe-OUT ClinicalTrials.gov number, NCT04575597) [37]. As an early treatment for patients with COVID-19, molnupiravir administration is therapeutically effective, but there is the potential for co-infection or potentially life-threatening recurrence in patients after treatment. The need for highly synergistic agent integrating molnupiravir is also becoming increasingly important. To control for confounding factors, we investigated the number of vaccinations in rehabilitation patients who were uninfected despite being quarantined with other COVID-19 patients. As a result, uninfected patients received fewer vaccinations than those with COVID-19. Therefore, in this study, vaccination was excluded as a confounding factor, and blood biomarkers were analyzed for their capacity, without the influence of vaccination, to prevent COVID-19 deterioration.

Our results show that IgA levels increased when molnupiravir was co-administered with CAM. CAM effects are not limited to only anti-inflammatory [38]. Molnupiravir plus CAM may alter and improve the clinical course of patients with COVID-19 infection, at least through an indirect mechanism that relies on several variable anti-inflammatory and/or immunomodulatory effects in addition to its well-known antibacterial activity. Compared to uninfected patients, IgA may be a predictive factor for the improvement of COVID-19 infection, and sIL2R may be a predictive factor for the prevention of secondary infection.

There are several limitations in this study. First, the present work is essentially an exploratory retrospective study. There is no previous clinical evidence evaluating the therapeutic efficacy of molnupiravir and CAM against COVID-19, and the sample size was based on the feasible number of consented patients who were hospitalized. Second, without knowing DDI, many antivirals and anti-inflammatory drugs have been approved to treat COVID-19 patients, but potential DDIs that can enhance the safety and efficacy of molnupiravir and CAM remain elusive [39]. Third, the target sample size of this study is small. Fourth, uninfected patients who could not be transferred were managed in a closed ward and inspection was performed on both the infected and uninfected individuals, but there might be a bias in terms of examination date. Furthermore, bias from patients and attending physicians cannot be completely avoided. Fifth, this study was conducted only at medical institutions on the main island of Okinawa and included only Japanese patients undergoing rehabilitation treatment. Sixth, macrolides increase the risk of some cardiac side effects, especially in the elderly. These constraints have limited generalization of the current set of findings.

5. Conclusion

D-dimer, IgA, and sIL2R are potential predictive factors of COVID-19 severity in patients with mild-to-moderate symptoms receiving molnupiravir plus CAM.

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Conflict of Interest

The authors declare no competing interest in this study or its publication.

Ethics Approval and Consent to Participate

The study was conducted according to the guidelines of the Declaration of Helsinki, and it was registered and approved by the Ethics Committee and Review Board of Daido Central Hospital (approval ID: daido0036) (May 2022). Written informed consent was obtained from all the subjects before their participation in the study.

Consent for Publication

Written informed consent for releasing their data and/or images in this paper was obtained from all the subjects in the study.

Availability of Data

Data are available from the corresponding author upon reasonable request.

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ORIGINAL ARTICLE

Effect of combination of molnupiravir with clarithromycin on blood biomarkers in patients with mild-to-moderate COVID-19

Supplementary File

Supplementary Data 1

Main inclusion/exclusion criteria for the global phase III study [MOVe-OUT (002) study]

1. SARS-CoV-2-positive patients (confirmed by PCR test, etc. using samples collected within 5 days before randomization).
2. SARS-CoV-2 infection symptom onset within 5 days and 1 or more symptoms associated with SARS-CoV-2 infection can be recognized (cough, sore throat, nasal congestion, runny nose, shortness of breath or difficulty breathing during exertion, muscle or body pain, fatigue, fever [above 38.0°C], chills, headache, nausea, vomiting, diarrhea, loss of sense of smell, and loss of taste).
3. Mild or moderate patient as defined below.

[Mild] Satisfy A and B

A. All of the following are recognized.
Breathing rate is <20 breaths/min, heart rate is less than 90 times/min, SpO_2 is more than 93% (value in indoor air or in a state where oxygen is administered for reasons other than infection with SARS-CoV-2 and the amount of oxygen has not been increased since the onset of symptoms of infection with SARS-CoV-2)

B. Neither of the following are recognized.
Shortness of breath at rest or during exertion or incomplete breathing (when one or more of the following (1) to (4) is required: (1) endotracheal intubation and ventilator, (2) high-flow oxygen therapy using nasal cannula [flow rate over 20 L/min, oxygen ratio of 0.5 or more], (3) non-invasive positive pressure ventilation, (4) ECMO, shock state, multi-organ dysfunction)

[Moderate disease] Satisfy all of A to B

A. One or more of the following is recognized
Shortness of breath during exertion, respiratory rate is more than 20 times/min but less than 30 times/min, heart rate of 90 beats/min or more and less than 125 beats/min

B. Any of the following is recognized
   a. SpO_2 is over 93% (value in indoor air or in a state where oxygen is administered for reasons other than infection with SARS-CoV-2, and the amount of oxygen has not been increased since the onset of symptoms of infection with SARS-CoV-2)
   b. Requiring oxygen administration of 4 L/min or less due to infection by SARS-CoV-2 regardless of SpO_2.

C. None of the following are recognized
Shortness of breath at rest or incomplete breathing (when one or more of the following (1) to (4) is required: (1) endotracheal intubation and ventilator, (2) high-flow oxygen therapy using nasal cannula [flow rate over 20 L/min, oxygen ratio of 0.5 or more], (3) non-invasive positive pressure ventilation, (4) ECMO, shock state, multi-organ dysfunction)

4. Have one or more of the following risk factors for severe SARS-CoV-2 infection:
   (1) 61 years old or older active cancers (excludes cancers that do not involve immunosuppression or high mortality)
   (2) Chronic kidney disease
   (3) Chronic obstructive pulmonary disease
   (4) Obesity (BMI 30 kg/m^2 more)
   (5) Serious heart disease (incomplete heart, coronary artery disease, or cardiomyopathy)
   (6) Diabetes

Molnupiravir has been evaluated in phase I, phase II, and phase III trials that have demonstrated favorable efficacy, dose-dependent pharmacokinetics, and a robust safety profile. In an interim analysis of a phase III trial, treatment with molnupiravir reduced the risk of hospitalization or death in COVID-19 patients by 50% [1]. On December 24, 2021, the Japanese Ministry of Health, Labor and Welfare granted special approval for domestic marketing of molnupiravir, an oral antiviral drug for COVID-19, based on the evaluation in the phase III trial. Molnupiravir can be administered to non-hospitalized patients aged 18 years and older with mild-to-moderate disease who have risk factors for severe disease [2]. For the use of molnupiravir, we referred to the guidelines from the World Health Organization (WHO) [3], Food and Drug Administration (FDA) [4], and National Institutes of Health (NIH) [5].

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Supplementary Data 2

Table 1. Baseline levels of blood biomarkers on admission, 5 days, and 14 days after starting treatment for infection in molnupiravir alone, molnupiravir plus clarithromycin (CAM), and unaffected groups

Blood biomarkers	Admission	Day 5	*P*-value[1]		Day 14	*P*-value[2]
Biochemistry biomarkers						
LDH (IU/L)						
Molnupiravir	193.1±41.2	250.2±107.3	<0.05		196.7±48.4	n.s.
Molnupiravir + CAM	187.7±50.7	206.7±67.3	n.s.		183.7±55.3	n.s.
Uninfected	186.5±33.5	173.1±45.2	n.s.		172.5±36.4	n.s.
P-value*	n.s.	<0.05		*P*-value**	n.s.	
Total cholesterol (mg/dl)						
Molnupiravir	163±41.1	123.7±37.9	<0.05		145.2±35.9	n.s.
Molnupiravir + CAM	158.0±32.5	135.7±40.4	n.s.		158.2±30.2	n.s.
Uninfected	158.6±34.0	157.7±20.0	n.s.		157.2±31.0	n.s.
P-value*	n.s.	n.s.		*P*-value**	n.s.	
Triglyceride (mg/dl)						
Molnupiravir	118.8±33.5	68.3±21.5	<0.05		96.1±46.2	n.s.
Molnupiravir + CAM	107.5±49.8	71.6±14.9	n.s.		103.9±74.4	n.s.
Uninfected	101.3±47.8	103.4±55.0	n.s.		101.8±41.5	n.s.
P-value*	n.s.	n.s.		*P*-value**	n.s.	
Uric acid (mg/dl)						
Molnupiravir	4.6±1.4	3.0±1.5	<0.05		4.0±1.5	n.s.
Molnupiravir + CAM	4.5±1.8	3.7±1.1	n.s.		4.5±1.6	n.s.
Uninfected	5.1±1.6	5.0±1.3	n.s.		5±1.5	n.s.
P-value*	n.s.	n.s.		*P*-value**	n.s.	
Creatinine (mg/dl)						
Molnupiravir	0.78±0.31	0.91±0.27	n.s.		0.79±0.32	n.s.
Molnupiravir + CAM	0.75±0.39	0.79±0.30	n.s.		0.77±0.44	n.s.
Uninfected	0.70±0.26	0.72±0.36	n.s.		0.72±0.32	n.s.
P-value*	n.s.	n.s.		*P*-value**	n.s.	
Potassium (mEq/l)						
Molnupiravir	3.9±0.5	4.5±0.7	<0.05		3.8±0.6	n.s.
Molnupiravir + CAM	4.0±0.3	4.1±0.4	n.s.		3.9±0.4	n.s.
Uninfected	4.1±0.4	4.1±0.6	n.s.		4.0±0.5	n.s.
P-value*	n.s.	<0.05		*P*-value**	n.s.	
Blood routine biomarkers						
WBC ($\times 10^2/\mu l$)						
Molnupiravir	73.2±20.7	96.4±22.5	<0.05		76.0±19.3	n.s.

(*Contd...*)

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Table 1. (*Continued*)

Blood biomarkers	Admission	Day 5	*P*-value[1]		Day 14	*P*-value[2]
Molnupiravir + CAM	59.2±16.8	63.5±15.3	n.s.		64.4±22.0	n.s.
Uninfected	54.5±14.6	59.8±20.7	n.s.		54.1±17.9	n.s.
P-value*	n.s.	<0.05		*P*-value**	<0.05	
Hb (g/dl)						
Molnupiravir	12.4±1.2	12.0±1.6	n.s.		12.2±1.2	n.s.
Molnupiravir + CAM	12.9±1.4	12.1±1.3	n.s.		12.6±1.5	n.s.
Uninfected	13.2±1.7	13.2±1.9	n.s.		13.2±1.8	n.s.
P-value*	n.s.	n.s.		*P*-value**	n.s.	
PLT (/µl)						
Molnupiravir	28.1±7.2	19.6±6.7	<0.05		28.4±7.5	n.s.
Molnupiravir + CAM	30.1±9.6	22.4±6.8	n.s.		29.8±12.0	n.s.
Uninfected	29.4±9.4	27.8±5.4	n.s.		28.1±8.6	n.s.
P-value*	n.s.	n.s.		*P*-value**	n.s.	
Inflammatory biomarkers						
CRP (mg/dl)						
Molnupiravir	1.0±1.2	6.1±4.9	<0.05		2.7±5.0	<0.05
Molnupiravir + CAM	0.6±0.8	3.6±2.1	n.s.		0.9±1.4	n.s.
Uninfected	0.6±0.9	1.2±1.6	n.s.		0.6±1.4	n.s.
P-value*	n.s.	<0.05		*P*-value**	<0.05	
Neutrophils (%)						
Molnupiravir	65.2±11.3	77.5±8.5	<0.05		68.5±11.2	n.s.
Molnupiravir + CAM	61.0±10.1	69.2±11.4	n.s.		57.2±10.4	n.s.
Uninfected	62.7±10.6	59.7±14.4	n.s.		59.5±12.0	n.s.
P-value*	n.s.	n.s.		*P*-value**	<0.05	
Lymphocytes (%)						
Molnupiravir	23.8±9.5	15.5±7.4	<0.05		24.6±10.3	n.s.
Molnupiravir + CAM	29.5±8.6	22.3±11.2	n.s.		30.9±9.3	n.s.
Uninfected	28.1±8.4	29.4±12.8	n.s.		30.9±12.2	n.s.
P-value*	n.s.	<0.05		*P*-value**	<0.05	
NLR						
Molnupiravir	3.4±1.9	6.7±4.5	<0.05		3.8±4.0	n.s.
Molnupiravir + CAM	2.2±1.4	3.9±2.0	n.s.		2.0±0.9	n.s.
Uninfected	2.7±1.8	2.9±2.9	n.s.		2.6±2.3	n.s.
P-value*	n.s.	<0.05		*P*-value**	<0.05	
Coagulation biomarkers						
Fibrinogen (mg/dl)						
Molnupiravir	340±156.9	482±83.8	<0.05		358.4±74.8	n.s.
Molnupiravir + CAM	319.8±169.1	428.8±113.1	n.s.		356.7±65.3	n.s.
Uninfected	310.3±134.0	355.0±94.4	n.s.		320.4±76.0	n.s.
P-value*	n.s.	n.s.		*P*-value**	n.s.	
FDP (µg/ml)						
Molnupiravir	5.1±3.6	8.1±2.5	<0.05		4.7±2.5	n.s.
Molnupiravir + CAM	4.6±3.3	5.7±2.2	n.s.		4.5±2.6	n.s.
Uninfected	4.3±1.2	4±1.7	n.s.		4.4±4.1	n.s.
P-value*	n.s.	<0.05		*P*-value**	n.s.	
D-dimer (µg/ML)						
Molnupiravir	2.0±1.5	3.5±3.1	n.s.		1.1±0.7	<0.05
Molnupiravir + CAM	2.6±3.3	3.7±2.9	n.s.		1.4±1.2	<0.05
Uninfected	1.3±3.9	1.9±1.7	n.s.		1.9±1.9	n.s.
P-value*	n.s.	n.s.		*P*-value**	n.s.	

(*Contd...*)

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Table 1. (*Continued*)

Blood biomarkers	Admission	Day 5	*P*-value[1]		Day 14	*P*-value[2]
PT-INR						
Molnupiravir	1.1±0.4	1.4±0.1	<0.05		1.1±0.1	n.s.
Molnupiravir + CAM	1.1±0.3	1.2±0.1	n.s.		1.1±0.1	n.s.
Uninfected	1.1±0.4	1.2±0.6	n.s.		1.1±0.2	n.s.
P-value*	n.s.	<0.05		*P*-value**	n.s.	
Cardiac biomarkers						
CPK (IU/L)						
Molnupiravir	40±22.2	94.3±103.5	<0.05		50.6±44.4	n.s.
Molnupiravir + CAM	49.0±30.5	76.25±88.2	n.s.		41.1±22.7	n.s.
Uninfected	40.3±34.0	33.3±13.2	n.s.		30.5±13.5	n.s.
P-value*	n.s.	n.s.		*P*-value**	n.s.	
BNP (pg/ml)						
Molnupiravir	121.3±142.3	158.4±128.2	n.s.		86.3±92.6	n.s.
Molnupiravir + CAM	113.4±228.6	147.0±78.3	n.s.		86.8±153.9	n.s.
Uninfected	108.3±139.6	105.7±132.8	n.s.		108.4±96.1	n.s.
P-value*	n.s.	n.s.		*P*-value**	n.s.	

Abbreviations: CAM: Clarithromycin, n.s.: No significant difference, LDH: Lactate dehydrogenase, WBC: White blood cells, Hb: Hemoglobin, PLT: Platelet, CRP: C-reacted protein, NLR: Neutron–lymphocyte ratio, FDP: Fibrin degradation product, PT-INR: Prothrombin time-International Normalized Ratio, CPK: Creatinine phosphor kinase, BNP: Brain natriuretic peptide.
P-value*: Molnupiravir alone group and molnupiravir + CAM group on the 5th day.
P-value**: Molnupiravir alone group and molnupiravir + CAM group on the 14th day.
P-value^{1}: The time of admission and on the 5th day from the start of admission.
P-value^{2}: The time of admission and on the 14th day from the start of admission.
Notes: The cutoff values were as follows: LDH (115 – 245 IU/L), total cholesterol (130 – 219 mg/dl), triglyceride (30 – 149 mg/dl), uric acid (2.5 – 7.0 mg/dl), creatinine (0.47 – 0.79 mg/dl), potassium (3.4 – 5.0 mEq/L), WBC (35 – 90×10^{2}/μl), Hb (11.5 – 15.2 g/dl), PLT (12 – 40×10^{4}/μl), CRP (<0.3 mg/dl), neutrophils (28 – 68%), lymphocytes (18 – 51%), NLR (0.55 – 3.78), fibrinogen (150 – 400 mg/dl), FDP (<4 μg/ml), D-dimer (<1.0 μg/ML), PT-INR (0.8 – 1.2), CPK (45 – 163 IU/L), BNP (<18.4 pg/ml)

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Supplementary Data 3

Table 2. Baseline levels of immunological biomarkers at admission, 5 days, and 14 days after infection in the molnupiravir alone, molnupiravir plus clarithromycin (CAM), and unaffected groups

Immunological biomarkers	Admission	Day 5	*p*-value[1]	Day 14	*p*-value[2]
IgG (mg/dl)					
Uninfected	1310.1±304.7	-		-	
Molnupiravir + CAM	-	1460±326.3	n.s.	1532.75±500.3	n.s.
Molnupiravir	-	1445.5±303.1	n.s.	1321.3±409.8	n.s.
P-value*		n.s.		n.s.	
IgA (mg/dl)					
Uninfected	509.7±183.6	-		-	
Molnupiravir + CAM	-	465.3±146.6	<0.05	536±112.7	<0.05
Molnupiravir	-	400.2±178.4	<0.05	385.2±159.7	n.s.
P-value*		n.s.		<0.05	
IgM (mg/dl)					
Uninfected	106.0±63.8	-		-	
Molnupiravir + CAM	-	105.4±34.7	n.s.	128.4±58.6	<0.05
Molnupiravir	-	94.2±63.7	n.s.	103.4±90.4	n.s.
P-value*		n.s.		n.s.	
sIL2R (U/dl)					
Uninfected	502.3±199.9	-		-	
Molnupiravir + CAM	-	661.2±158.6	<0.05	552.5±188.0	<0.05
Molnupiravir	-	732.3±500.3	<0.05	792.8±383.3	n.s.
P-value*		n.s.		<0.05	

Abbreviations: CAM: Clarithromycin, n.s.: No significant difference, Ig: Immunoglobulin, sIL2R: Soluble interleukin 2-receptor.

P-value[1]: Admission in unaffected patients and on the 5th day from the start of admission; administration at the time of infection (molnupiravir [5 days] + CAM [3 days], molnupiravir [5 days]).

P-value[2]: 5th day and 14th day from the start of admission; administration after infection (molnupiravir [5 days] + CAM [3 days], molnupiravir [5 days]).

P-value*: Molnupiravir + CAM group and molnupiravir alone group.

Notes: IgA, IgG, and IgM levels were measured using the immunoturbidimetric method, in which the antibody reacts with an antigen to form an immune complex precipitate; the aggregate is irradiated with light, and the attenuation (absorbance) of the irradiated light due to scattering is automatically detected (SRL Inc., Tokyo, Japan). The serum concentrations of sIL2R were determined using a chemiluminescent enzyme immunoassay (SRL Inc.). The cutoff values were as follows: IgG (870 – 1700 mg/dl), IgA (110 – 410 mg/dl), IgM (46 – 260 mg/dl), and sIL2R (157 – 474 U/ml). Data are presented as means±SD. The *P*-values were determined using Student's t-test. A *p*-value <0.05 was considered significant. SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis.

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Supplementary Data 4

Table 3a. Baseline characteristics of COVID-19 patients receiving molnupiravir plus clarithromycin or molnupiravir alone

Characteristics	Molnupiravir+ CAM (*n*=54)	Molnupiravir (*n*=37)	*P*-value
Female gender	26 (48.1%)	23 (62.2%)	n.s.
Age (years)	78 (49 – 96)	76 (67 – 100)	n.s.
Male gender	28 (51.9%)	14 (37.8%)	n.s.
Age (years)	74 (49 – 91)	73 (64 – 96)	n.s.
Baseline symptoms			
Fever	54 (100%)	0 (0%)	<0.05
Cough and sputa	53 (98.1%)	0 (0%)	<0.05
Fatigue	42 (77.8%)	21 (56.7%)	n.s.
Shortness of breath	36 (66.7%)	0 (0%)	<0.05
Chest tightness	32 (59.2%)	0 (0%)	<0.05
Dyspnea (93% < SpO_2< 96%)	30 (55.6%)	0 (0%)	<0.05
Nausea	21 (38.9%)	19 (51.3%)	n.s.
Vomit	17 (31.5%)	11 (29.7%)	n.s.
Headache	6 (11.1%)	4 (10.8%)	n.s.
Chills	5 (9.2%)	0 (0%)	n.s.
Diarrhea	3 (5.5%)	2 (5.4%)	n.s.
Hair removal	3 (5.5%)	1 (2.7%)	n.s.
Cingulum	2 (3.7%)	1 (2.7%)	n.s.
Skin rash	2 (3.7%)	2 (5.4%)	n.s.
Conjunctiva inflammation	1 (1.8%)	1 (2.7%)	n.s.
Myalgia	1 (1.8%)	0 (0%)	n.s.
Abdominal pain	1 (1.8%)	0 (0%)	n.s.
Blood cough	1 (1.8%)	0 (0%)	n.s.
Charlson index	25 (46.2%)	16 (43.2%)	n.s.
Baseline comorbidity			
Cardiovascular disease[1]	51 (94.4%)	34 (91.9%)	n.s.
Cerebrovascular disease[2]	42 (77.8%)	32 (86.5%)	n.s.
Respiratory diseases[3]	38 (70.3%)	0 (0%)	<0.05
Orthopedic disease[4]	36 (66.7%)	28 (75.7%)	n.s.
Hypertension	32 (59.2%)	26 (70.3%)	n.s.
Diabetes mellitus	28 (51.8%)	15 (40.5%)	n.s.
Cancer[5]	17 (31.5%)	13 (35.1%)	n.s.
Chronic renal failure	9 (16.6%)	8 (21.6%)	n.s.
Vaccination	51/54 (94.4%)	35/37 (94.6%)	n.s.
Within 6 months before admission	49/51 (96.1%)	33/35 (94.2%)	n.s.
1 vaccination	47/49 (95.9%)	31/33 (93.9%)	n.s.
2 vaccinations	2/49 (4.0%)	2/33 (6.1%)	n.s.
Within 3 months before admission	2/51 (3.9%)	2/35 (5.7%)	n.s.
1 vaccination	1/2 (50%)	1/2 (50%)	n.s.
2 vaccinations	1/2 (50%)	1/2 (50%)	n.s.

Abbreviations: CAM: Clarithromycin, n.s.: No significant difference.

[1]Heart failure, myocardial infarction, angina pectoris, arrhythmia, dilatation of the myocarditis, dissecting aneurysm of aorta

[2]Cerebral infarction, brain hemorrhage, subarachnoid hemorrhage, cerebral aneurysm

[3]Chronic obstructive pulmonary disease, chronic bronchitis, chronic interstitial pneumonia, bronchial asthma

[4]Fracture, prosthesis replacement

[5]Esophageal cancer, gastric cancer, pancreatic cancer, liver cancer, cholangiocarcinoma, colorectal cancer, lung cancer, breast cancer, ovarian cancer, laryngeal cancer, tongue cancer, meningioma

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Table 3b. Baseline characteristics of COVID-19 patients receiving molnupiravir plus clarithromycin (CAM) or uninfected patients

Characteristics	Molnupiravir + CAM (n=54)	Uninfected (n=28)	*P*-value
Female gender	26 (48.1%)	12 (42.8%)	n.s.
Age (years)	78 (49 – 96)	76 (69 – 100)	n.s.
Male gender	28 (51.9%)	16 (57.1%)	n.s.
Age (years)	74 (49 – 91)	73 (74 – 100)	n.s.
Baseline symptoms			
Fever	54 (100%)	0 (0%)	<0.05
Cough and sputa	53 (98.1%)	0 (0%)	<0.05
Fatigue	42 (77.8%)	0 (0%)	<0.05
Shortness of breath	36 (66.7%)	0 (0%)	<0.05
Chest tightness	32 (59.2%)	0 (0%)	<0.05
Dyspnea (93% < SpO_2< 96%)	30 (55.6%)	0 (0%)	<0.05
Nausea	21 (38.9%)	0 (0%)	<0.05
Vomit	17 (31.5%)	0 (0%)	<0.05
Headache	6 (11.1%)	0 (0%)	<0.05
Chills	5 (9.2%)	0 (0%)	<0.05
Diarrhea	3 (5.5%)	0 (0%)	<0.05
Hair removal	3 (5.5%)	0 (0%)	<0.05
Cingulum	2 (3.7%)	0 (0%)	<0.05
Skin rash	2 (3.7%)	0 (0%)	<0.05
Conjunctiva inflammation	1 (1.8%)	0 (0%)	<0.05
Myalgia	1 (1.8%)	0 (0%)	<0.05
Abdominal pain	1 (1.8%)	0 (0%)	<0.05
Blood cough	1 (1.8%)	0 (0%)	<0.05
Charlson index	25 (46.2%)	0 (0%)	<0.05
Baseline comorbidity			
Cardiovascular disease[1]	51 (94.4%)	24 (85.7%)	n.s.
Cerebrovascular disease[2]	42 (77.8%)	23 (82.1%)	n.s.
Respiratory diseases[3]	38 (70.3%)	19 (67.9%)	n.s.
Orthopedic disease[4]	36 (66.7%)	22 (78.6%)	n.s.
Hypertension	32 (59.2%)	21 (65.6%)	n.s.
Diabetes mellitus	28 (51.8%)	18 (64.3%)	n.s.
Cancer[5]	17 (31.5%)	15 (53.6%)	n.s.
Chronic renal failure	9 (16.6%)	11 (39.3%)	<0.05
Vaccination	51/54 (94.4%)	25/28 (89.3%)	n.s.
Within 6 months before admission	49/51 (96.1%)	21/25 (84%)	n.s.
1 vaccination	47/49 (95.9%)	19/21 (90.4%)	n.s.
2 vaccinations	2/49 (4.0%)	1/21 (4.7%)	n.s.
Within 3 months before admission	2/51 (3.9%)	1/25 (4.0%)	n.s.
1 vaccination	1/2 (50%)	0/1 (0%)	<0.05
2 vaccinations	1/2 (50%)	0/1 (0%)	<0.05

Abbreviations: CAM: Clarithromycin, n.s.: No significant difference.

[1]Heart failure, myocardial infarction, angina pectoris, arrhythmia, dilatation of the myocarditis, dissecting aneurysm of aorta

[2]Cerebral infarction, brain hemorrhage, subarachnoid hemorrhage, cerebral aneurysm

[3]Chronic obstructive pulmonary disease, chronic bronchitis, chronic interstitial pneumonia, bronchial asthma

[4]Fracture, prosthesis replacement

[5]Esophageal cancer, gastric cancer, pancreatic cancer, liver cancer, cholangiocarcinoma, colorectal cancer, lung cancer, breast cancer, ovarian cancer, laryngeal cancer, tongue cancer, meningioma.

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Table 3c. Baseline characteristics of COVID-19 patients receiving molnupiravir alone or uninfected patients

Characteristics	Molnupiravir (*n*=37)	Uninfected (*n*=28)	*P*-value
Female gender	23 (62.2%)	12 (42.8%)	n.s.
Age (years)	76 (67 – 100)	76 (69 – 100)	n.s.
Male gender	14 (37.8%)	16 (57.1%)	n.s.
Age (years)	73 (64 – 96)	73 (74 – 100)	n.s.
Baseline symptoms			
Fever	0 (0%)	0 (0%)	n.s.
Cough and sputa	0 (0%)	0 (0%)	n.s.
Fatigue	21 (56.7%)	0 (0%)	<0.05
Shortness of breath	0 (0%)	0 (0%)	n.s.
Chest tightness	0 (0%)	0 (0%)	n.s.
Dyspnea (93% < SpO_2 < 96%)	0 (0%)	0 (0%)	n.s.
Nausea	19 (51.3%)	0 (0%)	<0.05
Vomit	11 (29.7%)	0 (0%)	<0.05
Headache	4 (10.8%)	0 (0%)	<0.05
Chills	0 (0%)	0 (0%)	n.s.
Diarrhea	2 (5.4%)	0 (0%)	<0.05
Hair removal	1 (2.7%)	0 (0%)	<0.05
Cingulum	1 (2.7%)	0 (0%)	<0.05
Skin rash	2 (5.4%)	0 (0%)	<0.05
Conjunctiva inflammation	1 (2.7%)	0 (0%)	<0.05
Myalgia	0 (0%)	0 (0%)	n.s.
Abdominal pain	0 (0%)	0 (0%)	n.s.
Blood cough	0 (0%)	0 (0%)	n.s.
Charlson index	16 (43.2%)	0 (0%)	<0.05
Baseline comorbidity			
Cardiovascular disease[1]	34 (91.9%)	24 (85.7%)	n.s.
Cerebrovascular disease[2]	32 (86.5%)	23 (82.1%)	n.s.
Respiratory diseases[3]	0 (0%)	19 (67.9%)	n.s.
Orthopedic disease[4]	28 (75.7%)	22 (78.6%)	n.s.
Hypertension	26 (70.3%)	21 (65.6%)	n.s.
Diabetes mellitus	15 (40.5%)	18 (64.3%)	n.s.
Cancer[5]	13 (35.1%)	15 (53.6%)	n.s.
Chronic renal failure	8 (21.6%)	11 (39.3%)	n.s.
Vaccination	35/37 (94.6%)	25/28 (89.3%)	n.s.
Within 6 months before admission	33/35 (94.2%)	21/25 (84%)	n.s.
1 vaccination	31/33 (93.9%)	19/21 (90.4%)	n.s.
2 vaccinations	2/33 (6.1%)	1/21 (4.7%)	n.s.
Within 3 months before admission	2/35 (5.7%)	1/25 (4.0%)	n.s.
1 vaccination	1/2 (50%)	0/1 (0%)	<0.05
2 vaccinations	1/2 (50%)	0/1 (0%)	<0.05

Abbreviation: n.s.: No significant difference

[1]Heart failure, myocardial infarction, angina pectoris, arrhythmia, dilatation of the myocarditis, dissecting aneurysm of aorta

[2]Cerebral infarction, brain hemorrhage, subarachnoid hemorrhage, cerebral aneurysm

[3]Chronic obstructive pulmonary disease, chronic bronchitis, chronic interstitial pneumonia, bronchial asthma

[4]Fracture, prosthesis replacement

[5]Esophageal cancer, gastric cancer, pancreatic cancer, liver cancer, cholangiocarcinoma, colorectal cancer, lung cancer, breast cancer, ovarian cancer, laryngeal cancer, tongue cancer, meningioma

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Supplementary Data 5

Table 4. Risk predictive factors associated with clinical outcome in COVID-19 patients treated with molnupiravir alone and molnupiravir plus clarithromycin analyzed using a Cox proportional hazards model

Risk predictive factors	Univariate analysis*		Multivariate analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Biochemistry biomarkers				
Total cholesterol	0.46 (0.31 – 0.61)	<0.05		
Triglyceride	0.51 (0.46 – 0.56)	<0.05		
Uric acid	0.56 (0.45 – 0.67)	<0.05		
Blood routine biomarkers				
Hemoglobin	0.37 (0.25 – 0.49)	<0.01		
Platelet	0.41 (0.38 – 0.44)	<0.05		
Inflammatory biomarkers				
C-reactive protein	1.37 (1.29 – 1.45)	<0.01		
Neutrophils	1.25 (1.16 – 1.34)	<0.05		
Lymphocytes	0.33 (0.28 – 0.38)	<0.05		
Coagulation biomarkers				
Fibrinogen	1.37 (1.23 – 0.51)	<0.05		
FDP	1.14 (1.02 – 1.26)	<0.05		
D-dimer	1.32 (1.24 – 1.40)	<0.05	1.08 (1.05 – 1.11)	<0.05
Cardiac biomarkers				
CPK	1.36 (1.23 – 1.49)	<0.05		
BNP	1.03 (1.01 – 1.05)	<0.05		
Immunological markers				
IgA	1.32 (1.25 – 1.39)	<0.05	1.06 (1.02 – 1.10)	<0.05
sIL2R	0.46 (0.37 – 0.55)	<0.05	1.13 (1.09 – 1.17)	<0.05

Abbreviations: FDP: Fibrin degradation product; CPK: Creatinine phosphor kinase; BNP: Brain natriuretic peptide; Ig: Immunoglobulin; sIL2R: Soluble interleukin 2-receptor. *A total of 23 biomarkers were tested in the survival analysis and only variables with a significant hazard ratio (HR) at the significance level of $P<0.05$ are listed in table.

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Supplementary Data 6

Table 5. Comparison of severity of sequelae 12 months after COVID-19 treatment with molnupiravir+clarithromycin (CAM) or molnupiravir alone

Sequelae	Molnupiravir + CAM (*n*=54)	Molnupiravir (*n*=37)	*P*-value
Baseline symptoms			
Fever	0 (0%)	0 (0%)	n.s.
Fatigue	17 (31.5%)	13 (35.1%)	n.s.
Chest pain	6 (11.1%)	5 (13.5%)	n.s.
Dyspnea (93% < SpO_2 < 96%)	10 (18.5%)	8 (21.6%)	n.s.
Nausea	2 (3.7%)	2 (5.4%)	n.s.
Headache	8 (14.8%)	6 (16.2%)	n.s.
Sleep disorder	15 (27.8%)	11 (29.7%)	n.s.
Depression	12 (22.2%)	9 (24.3%)	n.s.
Anxiety	14 (25.9%)	10 (27.0%)	n.s.
Palpitations	4 (7.4%)	4 (10.8%)	n.s.
Effort intolerance	23 (42.6%)	16 (43.2%)	n.s.
Diarrhea	2 (3.7%)	2 (5.4%)	n.s.
Hair loss	4 (7.4%)	3 (8.1%)	n.s.
Loss of smell	9 (16.7%)	7 (18.9%)	n.s.
Loss of taste	6 (11.1%)	5 (13.5%)	n.s.
Cingulum	1 (1.9%)	2 (5.4%)	n.s.
Skin rash	0 (0%)	0 (0%)	n.s.
Conjunctiva inflammation	0 (0%)	0 (0%)	n.s.
Myalgia	10 (18.5%)	8 (21.6%)	n.s.
Joint pain	12 (22.2%)	9 (24.3%)	n.s.
Baseline comorbidity			
Cardiovascular disease[1]	53 (98.1%)	35 (94.6%)	n.s.
Cerebrovascular disease[2]	43 (80.0%)	33 (89.2%)	n.s.
Respiratory diseases[3]	39 (72.2%)	2 (5.4%)	n.s.
Orthopedic disease[4]	37 (68.5%)	29 (78.4%)	n.s.
Hypertension	34 (62.9.2%)	28 (75.7%)	n.s.
Diabetes mellitus	29 (53.7%)	18 (48.6%)	n.s.
Renal failure	10 (18.5%)	9 (24.3%)	n.s.
Skeletal muscle damages[5]	27 (50.0%)	19 (51.4%)	n.s.
Venous thromboembolism	13 (24.1%)	21 (56.8%)	<0.05
Lower urinary tract symptoms[6]	29 (53.7%)	20 (54.1%)	n.s.

Abbreviations: CAM: Clarithromycin; n.s.: No significant difference.
[1]Heart failure, myocardial infarction, angina pectoris, arrhythmia, dilatation of the myocarditis, dissecting aneurysm of aorta.
[2]Cerebral infarction, brain hemorrhage, subarachnoid hemorrhage, cerebral aneurysm.
[3]Chronic obstructive pulmonary disease, chronic bronchitis, chronic interstitial pneumonia, bronchial asthma.
[4]Fracture, prosthesis replacement.
[5]Reduction in the maximal voluntary contraction for quadriceps and biceps in recovering patients (54% and 69% of the predicted normal value, respectively).
[6]Postvoiding residual urine and voiding volume

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