Traditional Vietnamese medicine Kovir capsule in patients with mild COVID-19: A double-blind randomized controlled trial

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Abstract
Kovir capsule, a polyherbal medicine developed from Ren Shen Bai Du San formulation, has been used in various diseases including respiratory infections. A randomized, placebo-controlled, double-blind study was conducted to evaluate the safety and efficacy of Kovir capsule (TD0069) in the treatment of mild COVID-19 patients. Patients aged from 18 to 65 years who were PCR-confirmed with SARS-CoV-2 and had the mild disease were recruited and randomized to either Kovir capsule (34 patients) or placebo (32 patients) for up to 14 days or until discharge. Efficacy outcomes were time to viral clearance, daily viral load, time to symptom resolution, daily symptom score based on 16 pre-defined symptoms, and progression to severe/critical COVID-19. Safety outcomes were adverse events. Viral load decreased over time similarly in the two groups. Viral clearance time was also similar in both groups (median: 8 days). Kovir group had a more rapid decrease of symptom score and significantly lower time to symptom resolution than placebo (median: 4 vs. 7 days). Two patients in the placebo group developed severe COVID-19. No patient experienced adverse events. Kovir capsule is safe and can improve symptom resolution in mild COVID-19 patients. A large-scale trial is required to confirm these findings.

Keywords
COVID-19, herbal, SARS-CoV-2, traditional medicine

1 | INTRODUCTION

Since first reported in December 2019 in Wuhan, China, coronavirus disease 2019 (COVID-19) has been spreading all over the world and causes the most serious pandemic ever. This is an acute respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of November 9, 2021, over 250 million people have been diagnosed with COVID-19 worldwide with more than 5 million deaths, according to the World Health Organization (WHO) (World Health Organization, 2021c). More than 7 billion vaccine doses have been administered and the vaccination is starting to have a substantial effect on the number of hospitalizations and severe cases in some countries (Ritchie et al., 2020; World Health Organization, 2021c). However, there is still inequity in vaccine access globally so many countries are still vulnerable, particularly low-to-middle income countries (LMICs). Even with full vaccination all the world, the duration of protection and efficacy against new SARS-CoV-2 variants of current vaccines are uncertain. Therefore, there remains an urgent need for effective treatments for COVID-19. Many drugs and treatments have been studied for COVID-19 during the last
2 years with more than 4,200 trials registered or ongoing, but very few treatments have been recommended by the WHO (Maguire & Guérin, 2020; World Health Organization, 2021b).

In some countries including Vietnam, traditional medicine plays an important role in the prevention and treatment of various diseases. In the theory of traditional medicine, COVID-19 is deemed as a category of “dampness–toxin pestilence” (Lyu et al., 2021; Zhao, Hou, Gao, & Wang, 2020). According to traditional medicine, COVID-19 can be divided into mild, moderate, severe, and critical. The main patterns in mild stage are cold–damp constraint and damp–heat accumulation in the lung, where dispersing lung, removing pathogenic factors, and resolving turbidity with aroma are needed. Ren Shen Bai Du San, a traditional herbal formulation, has been recommended by Vietnamese Ministry of Health to prevent and treat COVID-19 (Vietnam’s Ministry of Health, 2020). Recently, Kovir, a hard-capsule Vietnamese herbal medicine, has been developed based on the formula of Ren Shen Bai Du San remedy in order to support the treatment for patients with COVID-19 in Vietnam. This polyherbal medicine consists of 12 herbal ingredients which are grouped in four categories: Chief (Jun), Deputy (Chen), Assistant (Zuo), and Envoy (Shí). The “Chief” component is effective for fever, chills, headache, sore throat, and muscle pain. The “Deputy” component can enhance “Chief” component’s activities and increase the antipyretic and analgesic effects. The “Assistant” and “Envoy” components have a harmonization activity and can speed up the recovery of the body. Kovir has been used in various diseases such as respiratory infections, parotid gland infection, and hepatitis B with good results (Chen & Chen, 2009). With well-known components in treating acute respiratory infectious diseases, Kovir capsule is expected to be a good treatment of COVID-19.

Vietnam has witnessed a large outbreak of COVID-19 in the second half of 2021. The number of severe cases rapidly increased which promptly overwhelmed the healthcare system. There has been an urgent need for effective treatments that can prevent the progression to severe/critical illness. In this context, this trial was conducted to evaluate the safety and efficacy of Kovir capsule as a combination regimen with standard treatment in terms of reduction of viral load, clearance of signs and symptoms, and prevention of progression to severe/critical disease, in the comparison with placebo for patients with mild COVID-19.

2 | METHODS

2.1 | Study design

This was a double-blind randomized, placebo-controlled, single-centre study to assess the safety and efficacy of oral Kovir capsule (TD0069) in adults (aged ≥18 years) admitted to hospital with mild COVID-19. The trial was done at Temporary Hospital for COVID-19 No. 3 (Ho Chi Minh city, Vietnam) from July to September 2021. At the time of conducting this study, in Vietnam, all people with a positive reverse transcription-polymerase chain reaction (RT-PCR) test for SARS-CoV-2 had to be quarantined in a hospital. When the outbreak in Ho Chi Minh city was ongoing in July, there were four levels of the hospital for COVID-19 patients: level 1 was for positive cases without symptoms and comorbidities, level 2 was for positive cases with symptoms but without comorbidities, level 3 was for positive cases with comorbidities because they were considered as high-risk patients, and level 4 was for severe/critical COVID-19 patients. The hospital where this study was conducted was at level 2.

Ethical approval was obtained from the institutional review board of the Traditional Medicine Institute of Ho Chi Minh City. Written informed consent was obtained from all patients. The study was performed in accordance with the ethical principles of the Declaration of Helsinki (World Medical Association, 2013) and the International Conference on Harmonization-Good Clinical Practice guidelines. This study was registered with ClinicalTrials.gov, NCT05042141.

2.2 | Patients

Eligible patients were men and women who were aged from 18 to 65 years and were RT-PCR positive with SARS-CoV-2 with a cycle threshold (CT) value of <30, had mild disease with signs and symptoms of COVID-19, were able to be compliant with their treatment in the study, and agreed to participate by giving written informed consent. Exclusion criteria included any sign or symptom suggested severe or critical COVID-19 at enrolment according to the WHO severity definitions (World Health Organization, 2021a), known allergy or intolerance to any of the product ingredients, inability to administer the study drugs, and inability to comply with study procedures or inability to ensure compliance with study drug administration as assessed by investigators. Patients with known comorbidities such as hypertension, diabetes, cardiovascular diseases, malignancy and other chronic diseases were not included because they were considered as high-risk patients and were admitted to other hospitals.

2.3 | Investigational product

Kovir capsule (TD0069) was developed based on the Ren Shen Bai Du San formulation. Each 800 mg hard capsule contained 600 mg fine powder of mixed herbal medicines and 200 mg excipient (corn starch, calcium carbonate, aerosil, talc, magnesium stearate, and sodium benzoate). The powder of herbal mixture was extracted from 12 herbal ingredients (Table 1) with water as the extraction solvent. Placebo was with the same appearance (color, shape, size and smell) to Kovir capsule.

2.4 | Randomisation and masking

Eligible participants were randomly assigned in a 1:1 ratio to receive either Kovir capsule or placebo. Block randomisation with block size of four was prepared using SAS software version 9.4. Envelopes with ordered numbers were used to contain the randomisation codes. Only
one study member knew the true study drug of each randomisation code until the data were locked on September 1, 2021. Eligible patients were allocated to receive study drugs according to the sequential order of the recruitment.

2.5 Procedures

After randomisation, patients received either oral Kovir capsule (3 tablets 3 times a day [7,200 mg daily in total]) or the same amount of placebo for up to 14 days or until discharge. Patients were assessed once daily by study doctors and nurses to collect data on the severity of symptoms and safety. Study doctors evaluated 16 symptoms that were combined into four categories: respiratory group contained seven symptoms (nasal secretion, nasal congestion, sneeze, sore throat, hoarseness, cough, and chest pain); neurological group contained two symptoms (headache and loss of smell), skeletal-muscular group contained two symptoms (fatigue and muscle pain), general group contained four symptoms (fever, chill, sweating, and feeling sleepy), and other symptoms. Each symptom was assessed to four grades where 0 represented absence of the troublesome symptom, 1 represented mild, 2 represented moderate, and 3 represented severe symptom. The global symptom score was the total score of all 16 symptoms. Safety assessment included daily vital signs (body temperature, heart rate, blood pressure, and saturation of peripheral oxygen [\(\text{SpO}_2\]), monitoring for adverse events, and clinical laboratory testing (day 0 [randomisation] and another time-point on days 4–8).

Standard care was symptomatic treatment such as antipyretics, adequate nutrition and rehydration in accordance with the WHO guidelines (World Health Organization, 2021a). Patients were discharged when having no fever for at least 2 days and two negative RT-PCR results or RT-PCR results with a CT value of >30 on two consecutive specimens taken at least 24 hr apart.

Nasopharyngeal swabs were collected daily until discharge for viral RNA detection and quantification. Virological testing was done at the laboratory of the International Institute of Gene and Immunology (Ho Chi Minh City, Vietnam) using quantitative RT-PCR. RNA was extracted from samples using the QIAamp® Viral RNA mini kit (QIAGEN Group, Germantown, Maryland, US), detected and quantified by one-step RT-rPCR using specific primers and probe targeted the E gene of SARS-COV-2 followed strictly the protocol given by the WHO in 2020 (Corman et al., 2020). The limit of detection of this procedure was 5.2 copies/reaction. CD4 and CD8 T-cell counts were assessed by flow cytometry using BD FACSCanto II System (BD Biosciences, Erembodegem, Belgium). Among leukocyte population separated by anti-human CD45-APC, CD4 and CD8 T-cells were distinguished by monoclonal antibodies (anti-human CD3-PE, anti-human CD4-FITC and anti-human CD8-PerCP). All tests were done in accordance with the manufacturer’s specifications.

| Table 1 Composition of herbal mixture in one Kovir capsule |
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| No. | Latin name | Scientific name | Common name | Parts of plant used | Content (mg) |
| 1 | Radix Bupleuri chinensis | Bupleurum chinense DC. | Bupleurum Root/Chinese Thorowax Root/Chaihu | Root | 245 |
| 2 | Poria | Poria cocos (Schw.) Wolf. | Poria/Indian Bread/Fuling | Sclerotium without skin | 245 |
| 3 | Radix Codonopsis pilosulae | Codonopsis pilosula (Franch.) Nannf. | Codonopsis Root/Tangshen/Dangshen | Root | 245 |
| 4 | Radix Peucedani | Peucedanum decursivum Maxim (or) Peucedanum praeruptorum Dunn. | Hogfennel Root/Qianhu | Root | 245 |
| 5 | Radix et Rhizoma Glycyrrhizae | Glycyrrhiza uralensis Fisch. or Glycyrrhiza glabra L. | Liquorice Root and Rhizome/Gancao | Rhizome and root | 163 |
| 6 | Radix Platycodi grandiflori | Platycodon grandiflorus (Jacq.) A. DC. | Platycodon Root/Jiegeng | Root | 163 |
| 7 | Rhizoma Ligustici wallichii | Ligusticum wallichii Franch. | Sichuan Lovage Rhizome/Chuanxiong | Rhizome | 163 |
| 8 | Fructus Aurantii | Citrus aurantium L. | Immature Bitter Orange Fruit/Zhiqiao | Fruit | 163 |
| 9 | Rhizoma et Radix Notopterygii | Notopterygium incisum Ting ex H. T. Chang | Notopterygium Root and Rhizome/Qiang Huo | Rhizome and root | 163 |
| 10 | Radix Angelicae pubescents | Angelica pubescens Maxim. | Pubescent Angelica Root/Duhuo | Root | 163 |
| 11 | Rhizoma Zingiberis | Zingiber officinale Rose. | Fresh Ginger/Shengjiang | Rhizome | 82 |
| 12 | Herba Menthae | Mentha arvensis L. | Mint/Bohe | Whole plant | 82 |
The antiviral efficacy outcomes were time to viral RNA clearance, viral clearance after 7 days of the treatment, and daily viral load. Viral clearance time was defined as days since randomisation to the first timepoint where viral RNA was undetectable. The clinical efficacy outcomes were time to symptom resolution, daily severity of symptoms, and progression to severe/critical COVID-19. Time to symptom resolution was defined as days since randomisation to the first timepoint that all symptoms were resolved, that is, the global symptom score was 0. The daily severity of symptoms was assessed by daily global symptom score. Severe/critical COVID-19 was defined according to the WHO guidelines (World Health Organization, 2021a). Other efficacy outcomes were the changes of CD4 and CD8 T-cell counts, white blood cell count, neutrophil/lymphocyte ratio, and liver enzymes from baseline to 4–8 days after treatment. Safety outcomes included all adverse events, serious adverse events, and premature discontinuations of study drugs due to adverse events.

### 2.7 Statistical analysis

As this is the first study to explore the efficacy and safety of Kovir capsule on mild COVID-19 patients, we decided to recruit a convenient sample of 30 participants in each treatment group. Considering a dropout rate of 10%, we recruited 66 patients for the study.

The efficacy analyses were done with an intention-to-treat (ITT) dataset. In the ITT dataset, all patients who were randomized to study drugs were included irrespective of their protocol adherence and continued participation in the study. Patients were analyzed according to their randomized study drugs. The safety analysis was done with the dataset of actual treatments (as-treated dataset). All patients who received at least one dose of the study drugs were included in this dataset. Patients were analyzed according to their actual treatment group.

Time to viral clearance and symptom resolution were illustrated using Kaplan–Meier plot and compared between groups by log-rank test. Daily viral load (in log-transformation), daily symptoms severity score and other continuous outcomes were compared by Wilcoxon Mann–Whitney-U test. Dichotomous outcomes (viral clearance after 7 days, progression to severe/critical COVID-19, and safety outcome) were compared by Fisher's exact test. Analyses were done using statistical software R version 4.1.0. All tests were two-sided and the statistical significance level was set at 0.05. We did not perform multiple testing adjustments as this study was exploratory.

### 3 RESULTS

Between July 28, 2021 and August 2, 2021, 68 patients were screened, of whom 66 were eligible for randomisation: 34 patients were assigned to receive Kovir capsule and 32 were assigned to receive placebo. All patients in the Kovir group completed their
treatment until discharge, whereas one patient in the placebo group stopped the treatment after 4 days because of the progression to severe disease and was transferred to another hospital. Finally, all 66 patients were included in the ITT and as-treated populations (Figure 1).

The median (25th; 75th percentiles) age of included patients was 34 (25; 44) years. Sex distribution was 18 men (52.9%) in the Kovir group versus 14 men (43.8%) in the placebo group. There were three patients (8.8%) with overweight/obesity and one (2.9%) with newly diagnosed diabetes in the Kovir group versus four patients (12.5%)
with overweight/obesity and one (3.1%) with newly diagnosed diabetes in the placebo group. None of the patients had received any dose of COVID-19 vaccine. Global symptom score and clinical laboratory results at enrolment were balanced between the groups. The Kovir group had a fairly higher viral load, CD4 and CD8 counts at baseline compared to the placebo group. Most patients were randomized at the day 2 after the first symptom onset (Table 3). The duration and amount of study drug used were balanced between groups. Some imbalances existed regarding other treatments, including more patients receiving antipyretic drugs in the Kovir group and more patients receiving antibiotic, antitussive, and antihistamine drugs, and oxygen supports in the placebo group. The median hospital length of stay was 9 days in both groups. No patient experienced any clinical or laboratory adverse event (Table 2).

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Viral RNA load decreased over time similarly in the two groups without a significant difference at any day since randomisation (Figure 2a). Viral clearance time was similar in both groups with a median of 8 days (Figure 2b). On day 7 after randomisation, 13 patients (38.2%) in the Kovir group and 10 (31.2%) in the placebo group had viral clearance (Table 4). Viral clearance time was unknown in 14 patients, including one patient with the progression to severe disease at day 3 who was then transferred to another hospital for intensive care, and 13 patients with full recovery whom the viral load was still detectable at discharge. All other patients had viral clearance before day 12.

Symptom severity score however differed between groups. The median global symptom score was similar between groups at days 0 and 1 (3 points) but the score decreased more rapidly in the Kovir group than in the placebo group thereafter (Figure 3a). Significant difference was found at day 2 (median score of 2 vs. 4), day 3 (1 vs. 2), day 4 (0 vs. 2), day 5 (0 vs. 2), and day 6 (0 vs. 1) when comparing Kovir and placebo groups, respectively. Time to symptom resolution was also significantly lower in the Kovir group than in the placebo group (median of 4 vs. 7 days) (Figure 3b). Two patients (6.3%) in the placebo group developed the severe disease; one was transferred to another hospital for intensive care (Table 4).

Both CD4 and CD8 counts increased from baseline to day 4–8 in the two groups but the change was lower in the Kovir group than in the placebo group (median CD4 and CD8 count changes were 124 and 86 versus 180 and 166 cells/μL, respectively). Regarding other laboratory parameters (white cell count, neutrophil/lymphocyte ratio, and liver enzymes), the changes were not marked and similar between the two groups (Table 4).

### DISCUSSION

Our trial found that Kovir capsule, a Vietnamese polyherbal medicine, significantly improved daily symptom severity and the time to symptom resolution for patients with mild COVID-19 compared with placebo. However, viral load and viral clearance time were similar between the treatments. Only two patients in the placebo group developed severe disease so we could not draw any conclusion in preventing disease progression to severe/critical COVID-19. Without adverse events, this study showed a good safety profile of Kovir capsule in patients with mild COVID-19.

Several herbal/traditional medicines have been investigated for the treatment of mild and severe/critical COVID-19. They come from countries with well-known traditional medicine such as China (Xia et al., 2021; Xiao et al., 2020; Xu et al., 2021; Zhang et al., 2021; Zhou et al., 2021), India (Devpura et al., 2021; Natarajan et al., 2021; Srivastava et al., 2021), and Iran (Karimi et al., 2021; Valizadeh et al., 2020). These studies showed that herbal medicines could reduce SARS-CoV-2 viral load, hospital length of stay, time to symptom resolution in mild COVID-19 patients, and mortality rate in patients with severe/critical COVID-19, when compared with placebo. These herbal medicines share a remarkable feature which is symptom relief. Only some of them showed evidence of reducing viral load. Nevertheless, it is not necessary to reduce SARS-CoV-2 viral load in order to improve the clinical outcomes of COVID-19 patients. Until now, there is no evidence that the viral load is associated with disease severity (Abdulrahman, Mallah, & Alqahtani, 2021;
The underlying pathological mechanism of severe COVID-19 remains largely unexplored. The pathogenesis of the disease involves a complex interplay between the virus and the host immune response (Zhang et al., 2021). Currently, recommended drugs by the WHO for COVID-19 patients are mostly those that affect the host immune system which might be the crucial part of severe disease, particularly at later phases.

Our study showed similar effects of Kovir capsule on COVID-19 to other herbal medicines. We could not find an antiviral effect of Kovir capsule, but it had a marked improvement of clinical symptoms. Similar to traditional Chinese medicine, the principles of traditional Vietnamese medicine are for diagnosing and describing the location and nature of the body’s imbalance. Treatments are then catered toward each individual patient mainly based on the symptoms, among other factors.
TABLE 4 Efficacy outcomes

|                      | Kovir (n = 34) | Placebo (n = 32) | p value |
|----------------------|---------------|-----------------|---------|
| Viral clearance at day 7 | 13 (38.2)     | 10 (31.2)       | .612    |
| Progression to severe/critical COVID-19 | 0 (0.0)       | 2 (6.3)         | .231    |
| CD4 count at day 4–8, cells/μL | 1,001 (855; 1,162) | 895 (762; 1,154) | .229    |
| CD4 count change, cells/μL | 124 (38; 306)  | 180 (104; 386)  | .078    |
| CD8 count at day 4–8, cells/μL | 702 (586; 794) | 692 (620; 810)  | .859    |
| CD8 count change, cells/μL | 86 (–27; 145)  | 166 (122; 257)  | .002    |
| CD4/CD8 ratio at day 4–8 | 1.44 (1.19; 1.75) | 1.35 (1.08; 1.71) | .407    |
| CD4/CD8 ratio change | 0.06 (–0.04; 0.13) | –0.12 (–0.20; 0.11) | .049    |
| White blood cell count at day 4–8, ×10⁹/L | 7.69 (6.50; 8.65) | 7.32 (6.04; 7.83) | .482    |
| White blood cell count change, ×10⁹/L | 1.03 (0.45; 1.83) | 1.63 (0.56; 2.30) | .205    |
| Neutrophil/lymphocyte ratio at day 4–8 | 1.68 (1.40; 2.11) | 1.74 (1.55; 2.22) | .461    |
| Neutrophil/lymphocyte ratio change | 0.03 (–0.29; 0.40) | –0.02 (–0.33; 0.40) | .518    |
| Aspartate aminotransferase at day 4–8, U/L | 26 (21; 42)    | 27 (20; 32)     | .839    |
| Aspartate aminotransferase change, U/L | –4 (–9; 2)     | –6 (–18; –2)    | .165    |
| Alanine aminotransferase at day 4–8, U/L | 32 (24; 62)    | 36 (26; 51)     | .845    |
| Alanine aminotransferase change, U/L | 1 (–7; –6)     | 2 (–6; 13)      | .888    |

Note: Summary statistics are median (25th; 75th percentiles) or n (%).

those, herbal medicines with their healing properties are used to restore balance in the body. The mechanism of action in COVID-19 patients is similar: Kovir capsule resolves the symptoms more rapidly than placebo. This is important in preventing severe/critical disease since an outbreak can easily overwhelm fragile health systems in LMICs. As of November 9, 2021, only human antibody drugs are recommended by the WHO for patients with non-severe COVID-19 (World Health Organization, 2021b), but they have limited applicability given the cost and availability of the drugs and the requirement for intravenous administration. However, the effects of Kovir capsule in severe/critical COVID-19 patients need to be investigated in future studies.

The role of T-cell immune responses in COVID-19 pathogenesis and long-term protective immunity is still questionable. For many viral infections, it usually takes 7–10 days to develop adaptive T-cell immune responses to control the virus. CD4 and CD8 T-cell counts were found to decrease in the early phase of COVID-19 (Jiang et al., 2020) and most recovered patients established CD4 and CD8 responses to SARS-CoV-2 (Grifoni et al., 2020). A meta-analysis showed that oral Chinese herbal medicine improved CD4, CD4/CD8 ratio, CD3, and reduced TNF-alpha (Shi et al., 2021). However, the level of evidence is low-to-moderate. Whether herbal medicines improve clinical parameters of COVID-19 patients through the immunity profile requires more studies. In our study, we observed both CD4 and CD8 T-cell counts increased from baseline to days 4–8, but Kovir group had lower changes than placebo. Since the sample size was relatively small and we measured only CD4 and CD8 T-cell counts at only two time-points, the effects of Kovir capsule on modulating immune effectors during COVID-19 are unclear and require further investigations. Other inflammatory responses are also unclear because we did not aim to investigate the effects of Kovir capsule on some laboratory parameters such as C-reactive protein, ferritin, D-dimer, and lactate dehydrogenase. However, the changes in total leukocyte count and neutrophil/lymphocyte ratio were not marked and similar between the two groups. Another issue of herbal medicines in COVID-19 patients is the effect on the digestive system and liver functions, which should not be neglected (Shi et al., 2021). In our study, we did not focus on digestive signs and symptoms but we did not observe any noticeable side effects of Kovir capsule in the digestive system. With respect to liver enzymes, no remarkable change was found in both Kovir and placebo groups.

This study has several limitations. First, this trial is exploratory and the sample size is small, thus, the study does not have enough power to prove the efficacy of Kovir capsule in preventing the progression to severe/critical COVID-19. Second, most included patients are young and without comorbidities. This limits the generalizability of the results to the general population of mild COVID-19 patients. A large-scale trial is required to solve these two limitations and better demonstrate the efficacy of the drug. Third, we did not test some inflammatory markers so we could not investigate the effect of Kovir capsule on the inflammatory response of the patients. Also, the follow-up period might be inadequate to determine the effect of Kovir capsule on liver functions.

In conclusion, Kovir capsule, a Vietnamese polyherbal medicine, is safe and potentially effective in the treatment of mild COVID-19 patients. It significantly improves symptoms of the patients and reduces the time to symptom resolution when compared to placebo. The effects on the reduction of SARS-CoV-2 viral load and immune responses are unclear. This study’s results encourage the integration of traditional Vietnamese medicine with standard treatment for...
COVID-19 patients. A large-scale trial is required to strengthen the findings of this study.

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CONFLICT OF INTEREST
All authors confirm that they have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author, [Nguyen Lam Vuong], upon reasonable request.
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