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Efficacy and Safety of Andrographolide and Favipiravir Versus Favipiravir Monotherapy in Patients with Mild COVID-19 Infection: A Multicenter Randomized Controlled Trial

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Abstract

Reports indicate that Andrographolide inhibits viral replication and reduces COVID-19 symptoms. This study aimed to determine Andrographolide's additional effect and safety in mild COVID-19 patients treated with favipiravir. A multicenter, open-labeled, randomized controlled trial was conducted from October 2021 to February 2022. The patients were randomized to receive a combination of Andrographolide and favipiravir or favipiravir monotherapy. The primary outcome was the occurrence rate of severe pneumonia. The secondary outcomes were symptom improvement, inflammatory biomarkers, and adverse events on days 7 and 14. 82 mild COVID-19 patients were enrolled; 43 and 39 patients

received either combination therapy or favipiravir alone. Baseline characteristics were comparable. None developed severe pneumonia, requiring a mechanical ventilator. The Andrographolide group had a significant reduction of cough compared to the controlled group; 13 (30.2%) vs. 22 (56.4%), p = 0.017 on day 7 and 4 (9.3%) vs. 7 (17.9%), p = 0.025 on day 14. Moreover, the Andrographolide group had significantly lower levels of inflammatory markers on day 7, CRP (5.8 vs. 18.4 mg/L; p = 0.019) and IL-6 (2.0 vs. 21.8 pg/mL; p = 0.001) but not on day 14. Regarding safety outcomes, the Andrographolide group had significantly higher AST levels on day 7 (40.3 vs. 32.2 U/L; p = 0.030) and both AST and ALT levels on day 14 (55.3 vs. 32.0; p = 0.014 and 63.8 vs. 40.0; p = 0.022, respectively). In mild COVID-19 patients, the combination of Andrographolide and favipiravir did not demonstrate additional benefits over favipiravir alone in preventing severe pneumonia. However, Andrographolide significantly reduced cough symptoms, especially during the first week. Furthermore, despite mild transaminitis, patients treated with Andrographolide showed improvements in inflammatory markers.

Keywords
Andrographolide; favipiravir; coronavirus-2019; COVID-19; SARS-CoV-2

1. Introduction

One of the key strategies in managing COVID-19 is the prevention of pneumonia. A recent meta-analysis and a randomized controlled trial have underscored the significant improvement in clinical outcomes using favipiravir, especially in the early treatment of symptomatic SARS-CoV-2 or COVID-19 patients who have not yet developed pneumonia [1, 2]. Despite the positive impact on clinical outcomes, it is crucial to note that favipiravir does not exhibit efficacy in preventing pneumonia or reducing mortality [3]. At the same time, the COVID-19 virus from the delta variant and omicron variant has an incidence of severe pneumonia development that requires mechanical ventilator and ICU admission of up to 9-25%, respectively [4].

Andrographis paniculate extract or Andrographolide has been used in traditional Thai medicine to treat fever and sore throat, and the potential benefits may include a reduction in the severity and duration of symptoms [5, 6]. This herbal remedy demonstrates both direct and indirect mechanisms for treating COVID-19 infection. Firstly, it has anti-inflammatory and immunomodulatory properties, which help to mitigate the host inflammatory response phase associated with severe infection. The bioactive components of Andrographolide are enriched in processes associated with responses to chemical stress, cytokine-mediated signaling pathways, and inflammatory responses [7-9]. Secondly, Andrographolide has the potential to inhibit viruses from entering human cells by blocking the receptor-binding domain of the spike glycoprotein of SARS-CoV-2 and the angiotensin-converting enzyme-2 (ACE-2) receptor on host cells, which the virus binds to prior to entering human cells [10, 11]. Thirdly, Andrographolide can inhibit viral replication by blocking the RNA-dependent RNA polymerase and papain-like protease of SARS-CoV-2, which are essential enzymes for viral replication, transcription, and spread of infection [12, 13].

To date, limited data exists on the effectiveness of Andrographolide in treating COVID-19. A previous randomized controlled trial in China examined the efficacy of Xiyanping, an extract from *Andrographis paniculata*. It demonstrated a significant reduction in fever and cough among mild to moderate COVID-19 patients compared to the control group [14]. In contrast, a recent randomized controlled trial by Siripongboonsitti et al. revealed no additional clinical or virological benefits of Andrographolides in non-severe COVID-19 patients. However, an interesting observation indicated a significant early reduction in interleukin-1β (IL-1β), a proinflammatory cytokine, on day four in patients treated with a combination of Andrographolide and favipiravir. This reduction may hold potential implications for preventing the hyperinflammation phase and disease progression [15].

This study investigates the efficacy of combining Andrographolide with favipiravir compared to administering favipiravir alone in preventing pneumonia onset in mild COVID-19 infection. Additionally, we will compare the severity of COVID-19 symptoms and inflammatory markers, including CRP and IL-6, between the two groups.

2. Materials and Methods

2.1 Study Design and Participants

Two provincial hospitals in two regions of Thailand conducted a multicenter, open-labeled, randomized controlled trial from October 2021 to February 2022.

Patients older than 18 diagnosed with mild COVID-19 infection met the inclusion criteria. Confirmation of SARS-CoV-2 infection diagnosis was conducted using a real-time polymerase chain reaction (RT-PCR) from nasal and throat swabs collected within 72 hours. According to the COVID-19 Treatment Guidelines from the National Institutes of Health [16, 17], mild severity was defined as the presence of minimal symptoms, such as fever, cough, myalgia, headache, sore throat, rhinitis, anosmia, or diarrhea without clinical symptoms and signs of pneumonia. We also stratified the patients into low-risk and high-risk groups. Patients with risk factors for developing severe COVID-19, including age ≥50 years, obesity with a body mass index (BMI) ≥30 kg/m^2, type 2 diabetes, cardiovascular disease, chronic kidney disease, cancer, and immunocompromised state, are defined as high-risk patients [18].

The recording and grading of chest X-rays (CXR) were done as follows:

CXR grade 1: Normal.

CXR grade 2: Low probability of COVID-19 pneumonia; suboptimal inspiration, non-significant findings unrelated to COVID-19 pneumonia.

CXR grade C: Low probability for COVID-19 pneumonia with other diseases: bacterial pneumonia, active tuberculosis, congestive heart failure.

CXR grade 3: Indeterminate for COVID-19 pneumonia; features subtle, poorly defined opacities indistinguishable between early/atypical COVID-19 pneumonia and requiring clinical correlation.

CXR grade 4: Highly suspicious for early COVID-19 pneumonia; single unilateral or small poorly defined ground-glass opacity.

CXR grade 5: Typical for COVID-19 pneumonia; multifocal, bilateral peripheral or opacities with rounded morphology.

The exclusion criteria were as follows: 1) Severe COVID-19 infection is defined as patients with pneumonia exhibiting signs of respiratory distress (respiration rate ≥30 breaths per minute, oxygen saturation ≤93%, or ≤PaO_2/FiO_2 300) or patients requiring high-flow nasal cannula (HFNC) or non-

invasive ventilation (NIV) [16]; 2) Andrographolide or favipiravir allergy; 3) aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels on admission greater than five times the upper limit of the normal range; 4) liver cirrhosis; 5) chronic lung disease or chronic obstructive pulmonary disease; 6) CXR on admission grade 3 or above; 7) pregnancy and breastfeeding patients; and 8) patients who declined to participate in the study.

All participants provided written informed consent, and thorough reviews of medical records were conducted.

The Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (IRB No.723/64) approved the study protocol and followed the Helsinki Declaration 1983. The study was registered in the Thai Clinical Trials Registry (TCTR20210906002) on September 6, 2021.

2.2 Interventions

We enrolled patients with mild COVID-19 infection who were allocated with computer randomization using a block of 4 to the intervention arm and control arm. Patients in the intervention group received a combination of Andrographolide (180 mg per day for 5 days) and favipiravir (3,600 mg per day on the first day followed by 1,600 mg per day for 4 days), while patients in the control group received only favipiravir (3,600 mg per day on the first day followed by 1,600 mg per day for 4 days). Clinical symptoms and laboratory data were collected and recorded at baseline and on days 7 and 14 of enrollment.

In our study, the preparation of Andrographolide was undertaken by the Abhaibhubejhr Hospital Foundation (Prachin Buri, Thailand), which possesses approval from the Thai Food and Drug Administration (FDA) (registration number G512/60) and the Government Pharmaceutical Organization (GPO). The Andrographolide was processed into capsules with the same lot number. Each capsule contained 60 mg of Andrographolide extract, adhering to recommended manufacturing guidelines during transportation and storage. The dose administered was 180 mg daily, divided into three doses daily. The medicine underwent thorough checks for potential drug-drug interactions with Andrographolide and favipiravir before prescribing them to the patients.

2.3 Outcomes

The primary outcome was the occurrence rate of severe pneumonia within the 14-day study period, measured from the enrollment date. The secondary outcomes were symptom improvement, inflammatory biomarkers (CRP and IL-6 levels on days 0, 7, and 14), laboratory differences, and adverse events on days 7 and 14.

2.4 Statistical Analysis

Due to the lack of clinical studies on Andrographolide, we referenced a previous study conducted in China, which estimates that patients in the intervention group exhibited a 64% improvement compared to the control group [14]. The sample size was calculated with 90% power and a two-sided type 1 error of 0.01. Each group required a minimum sample size of 32. With an anticipated dropout rate of 10%, the calculated sample size for each arm was 40. Continuous variables were reported as mean ± standard deviation (SD) and analyzed using unpaired t-tests when the data were normally distributed. Skewed variables were expressed as median (interquartile range; IQR) and

assessed using the Mann-Whitney U test. Categorical variables were compared using Fisher's exact test or the X2 test as appropriate. The statistical analyses were performed using the SPSS package version 22.0.0 (SPSS Inc., Chicago, Illinois, USA). A p-value of <0.05 was considered statistically significant.

3. Results

3.1 Baseline Patient Characteristics

Eighty-two patients with mild COVID-19 infection were eligible for the study enrollment. Of those, 44 (53.7%) patients were male, with an average age of 43.9 ± 15.2 years and a mean BMI of 25.6 ± 6.3 kg/m2. Of those, 12 (14.6%) patients had hypertension, 10 (12.2%) had type 2 diabetes, 6 (7.3%) had dyslipidemia, 3 (3.7%) had ischemic heart disease, and 2 (2.4%) had chronic kidney disease. The most common presenting symptoms were cough (59 patients, 72.0%), followed by sore throat (42, 51.2%), fever (40, 48.8%), rhinitis (31, 37.8%), headache (10, 12.2%), myalgia and anosmia (7, 8.5%), respectively.

Baseline characteristics, symptoms at presentation, and laboratory values were comparable between both groups, with two exceptions. Firstly, the age in the intervention group is significantly younger than that in the control group (39.7 ± 12.0 vs. 48.5 ± 17.1; p = 0.016). Secondly, the ALT level is higher in the intervention group compared to the control group (36.3 ± 24.6 vs. 25.2 ± 18.7 U/L; p = 0.040). Table 1 presents the baseline characteristics of the entire cohort.

Table 1 Baseline characteristics of COVID-19 infected patients in the study cohort (n = 82).

Variables	Total (n = 82)	Intervention arm (n = 43)	Control arm (n = 39)	p-valve
Age (year)	43.9 ± 15.2	39.7 ± 12.0	48.5 ± 17.1	0.016
Male, n (%)	44 (53.7%)	24 (55.8%)	20 (51.3%)	0.850
BMI (kg/m^2)	25.6 ± 6.3	26.8 ± 6.7	24.2 ± 5.6	0.065
Hypertension, n (%)	12 (14.6%)	3 (7.0%)	9 (23.1%)	0.081
Type 2 diabetes, n (%)	10 (12.2%)	5 (11.6%)	5 (12.8%)	0.869
Dyslipidemia, n (%)	6 (7.3%)	1 (2.3%)	5 (12.8%)	0.097
Ischemic heart disease, n (%)	3 (3.7%)	1 (2.3%)	2 (5.1%)	0.602
Chronic kidney disease, n (%)	2 (2.4%)	0 (0.0%)	2 (5.1%)	0.223
Symptoms at presentation, n (%)				
Fever	40 (48.8%)	20 (46.5%)	20 (51.3%)	0.666
Cough	59 (72.0%)	29 (67.4%)	30 (76.9%)	0.644
Myalgia	7 (8.5%)	4 (9.3%)	3 (7.7%)	0.794
Headache	10 (12.2%)	4 (9.3%)	6 (15.4%)	0.401
Sore throat	42 (51.2%)	22 (51.2%)	20 (51.3%)	0.991
Rhinitis	31 (37.8%)	15 (34.9%)	16 (41.0%)	0.567
Anosmia	7 (8.5%)	5 (11.6%)	2 (5.1%)	0.461
Diarrhea	4 (4.9%)	3 (7.0%)	1 (2.6%)	0.354
Previous Andrographolide used, n (%)	11 (13.4%)	7 (16.3%)	4 (10.3%)	0.424

Laboratories at baseline				
Hb (g/dL)	13.6 ± 1.6	13.8 ± 1.6	13.3 ± 1.5	0.733
WBC (/mm^3)	6,200 ± 1,988	6,230 ± 1,695	6,165 ± 2,290	0.886
Platelet (/mm^3)	224.3 ± 60.5	225.1 ± 61.2	223.3 ± 60.5	0.892
PT	11.6 ± 0.7	11.6 ± 0.7	11.7 ± 0.6	0.720
INR	1.05 ± 0.06	1.05 ± 0.07	1.05 ± 0.06	0.651
PTT	25.4 ± 2.6	25.0 ± 2.4	25.9 ± 2.7	0.903
BUN (mg/dL)	12.2 ± 4.1	11.8 ± 3.2	12.5 ± 4.9	0.466
Cr (mg/dL)	0.87 ± 0.27	0.83 ± 0.20	0.92 ± 0.32	0.120
Albumin (g/dL)	4.1 ± 0.3	4.2 ± 0.3	4.1 ± 0.3	0.238
Globulin (g/dL)	3.3 ± 0.4	3.3 ± 0.4	3.3 ± 0.4	0.635
TB (mg/dL)	0.5 ± 0.2	0.5 ± 0.2	0.6 ± 0.2	0.243
AST (U/L)	**37.4 ± 40.0**	**42.7 ± 52.6**	**31.5 ± 16.6**	**0.164**
ALT (U/L)	**31.1 ± 22.5**	**36.3 ± 24.6**	**25.2 ± 18.7**	**0.040**
ALP (U/L)	**73.7 ± 18.8**	**72.8 ± 18.4**	**74.7 ± 19.5**	**0.660**
CRP (mg/L)	**14.2 ± 15.7**	**14.7 ± 16.4**	**13.6 ± 15.0**	**0.763**
IL-6 (pg/mL)	**4.11 ± 6.25**	**3.2 ± 3.8**	**5.1 ± 8.1**	**0.169**
PCR-CT	**21.8 ± 5.0**	**21.8 ± 5.5**	**21.8 ± 4.6**	**0.995**
CXR grade				0.299
1	32 (39.0%)	16 (37.2%)	16 (41.0%)	
2	2 (2.4%)	0 (0.0%)	2 (5.1%)	
3	11 (13.4%)	5 (11.6%)	6 (15.4%)	
4	25 (30.5%)	15 (34.9%)	10 (25.6%)	
5	2 (2.4%)	2 (4.7%)	0 (0.0%)	
Treatment				
Dexamethasone	12 (14.6%)	5 (11.6%)	7 (17.9%)	0.419
Remdesivir	3 (3.7%)	0 (0.0%)	3 (7.7%)	0.103
Tocilizumab	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
Plasma exchange	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
LOS (day)	14.0 ± 2.2	14.2 ± 2.0	14.0 ± 2.5	0.670
Expired, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA

BMI: body mass index. Hb: hemoglobin. WBC: white blood cell count. PT: prothrombin time. INR: international normalized ratio. PTT: partial thromboplastin time. TB: total bilirubin. AST: aspartate aminotransferase. ALT: alanine aminotransferase. ALP: alkaline phosphatase. CRP: C-reactive protein. IL-6: interleukin-6. PCR-CT: polymerase chain reaction-cycle threshold. CXR: chest X-rays. LOS: length of stay. SD: standard deviation. IQR: interquartile range. kg/m^2: kilogram per square meter. g/dL: gram per deciliter. mg/dL: milligram per liter. U/L: international units per liter. pg/mL: picogram per milliliter.

Of those, 43 patients were enrolled in the combination therapy intervention group, and 39 patients were in the control group receiving favipiravir alone (Figure 1). None of the patients developed severe pneumonia, requiring a mechanical ventilator.

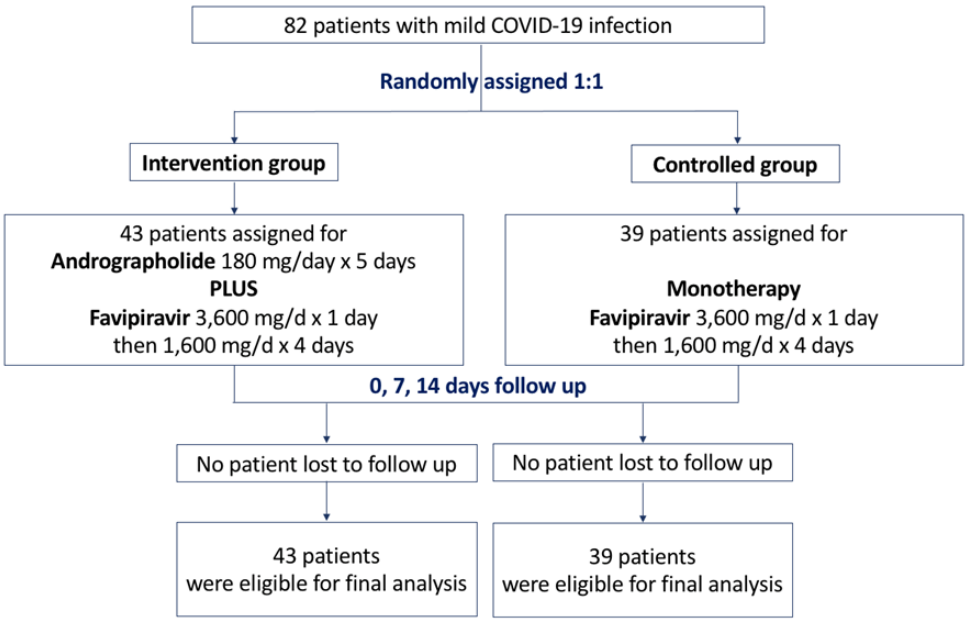

Figure 1 Study enrollment.

3.2 Clinical Symptom Outcomes

The intervention group had a significant reduction of cough compared to the control group: 13 (30.2%) vs. 22 (56.4%) patients; p = 0.017 and 4 (9.3%) vs. 7 (17.9%) patients; p = 0.025 on day 7, and 14, respectively (Figure 2A). However, the two groups had no significant difference in other symptom improvement, including fever, myalgia, headache, sore throat, or rhinitis (Table 2).

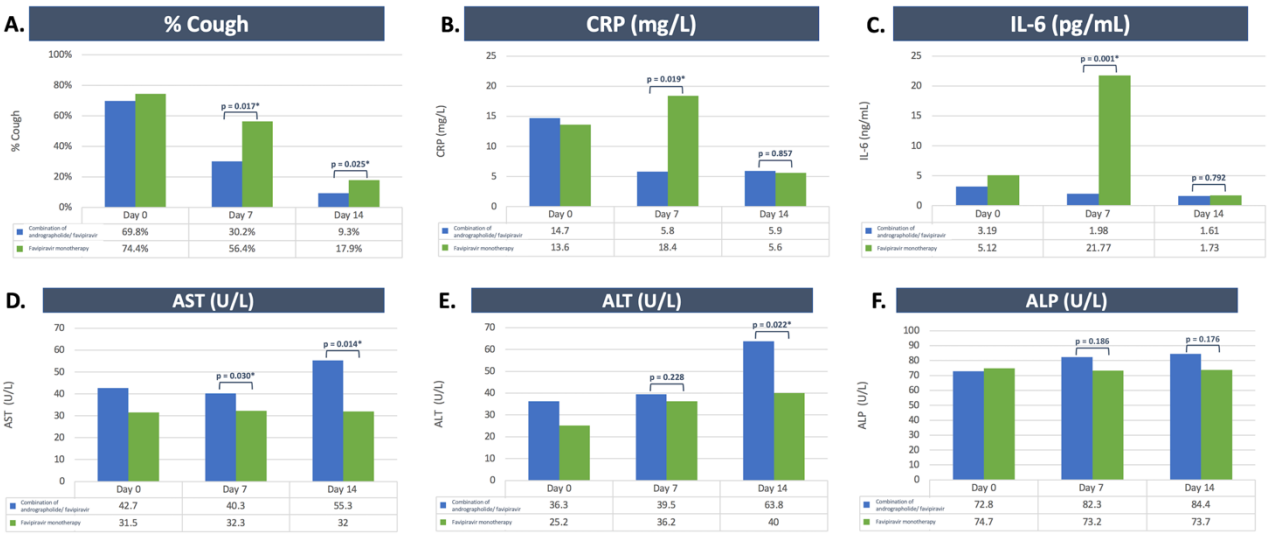

Figure 2 Comparison of symptom outcomes, inflammatory biomarkers, and liver enzymes on days 0, 7, and 14. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; IL-6, interleukin-6.

Table 2 Compare variables on days 7 and 14 after enrollment.

Variables	Intervention arm (n = 43)	Control arm (n = 39)	p-valve
Symptoms day 7, n (%)			
Fever 21 (25.6%)	10 (23.3%)	11 (28.2%)	0.608
Cough 35 (42.7%)	13 (30.2%)	22 (56.4%)	0.017
Myalgia 3 (3.7%)	1 (2.3%)	2 (5.1%)	0.602
Headache 5 (6.1%)	2 (4.7%)	3 (7.7%)	0.665
Sore throat 23 (28.0%)	10 (23.3%)	13 (33.3%)	0.310
Rhinitis 18 (22.0%)	7 (16.3%)	11 (28.2%)	0.193
Laboratories DAY 7			
Hb (g/dL)	14.0 ± 1.6	14.0 ± 3.2	0.969
WBC (/mm^3)	8,408 ± 8,310	6,976 ± 2,755	0.314
Platelet (/mm^3)	260.2 ± 78.5	327.3 ± 449.9	0.339
PT	11.7 ± 0.7	11.8 ± 0.7	0.883
INR	1.27 ± 1.38	1.07 ± 0.06	0.354
PTT	20.7 ± 8.4	21.2 ± 8.3	0.771
BUN (mg/dL)	11.8 ± 3.1	14.2 ± 5.7	0.025
Cr (mg/dL)	0.84 ± 0.18	0.89 ± 0.30	0.354
Albumin (g/dL)	4.1 ± 0.3	4.1 ± 0.3	0.332
Globulin (g/dL)	3.3 ± 0.4	3.4 ± 0.4	0.127
TB (mg/dL)	0.5 ± 0.2	0.7 ± 0.3	0.053
AST (U/L)	**40.3 ± 39.1**	**32.2 ± 10.9**	0.030
ALT (U/L)	**39.5 ± 26.8**	**36.2 ± 28.6**	0.228
ALP (U/L)	**82.3 ± 38.0**	**73.2 ± 16.7**	0.186
CRP (mg/L)	**5.8 ± 7.3**	**18.4 ± 31.4**	0.019
IL-6 (pg/mL)	**2.0 ± 2.4**	**21.8 ± 68.3**	0.001
PCR-CT	**26.6 ± 5.3**	**25.8 ± 5.8**	0.727
Laboratories DAY 14			
Symptoms day 14, n (%)			
Fever 3 (3.7%)	1 (2.3%)	2 (5.1%)	0.602
Cough 10 (12.2%)	4 (9.3%)	7 (17.9%)	0.025
Myalgia 0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
Headache 1 (1.2%)	0 (0.0%)	1 (2.6%)	NA
Sore throat 2 (2.4%)	1 (2.3%)	1 (2.6%)	1.000
Rhinitis 1 (2.4%)	1 (2.3%)	1 (2.6%)	1.000
Hb (g/dL)	13.9 ± 1.5	13.2 ± 1.6	0.059
WBC (/mm^3)	8,796 ± 3,252	8,361 ± 3,900	0.623
Platelet (/mm^3)	290.1 ± 86.7	325.4 ± 99.9	0.133
PT	11.4 ± 2.0	11.7 ± 0.7	0.537
INR	1.06 ± 0.10	1.06 ± 0.06	0.773
PTT	23.7 ± 2.7	24.2 ± 3.2	0.536
BUN (mg/dL)	12.6 ± 3.4	14.9 ± 9.1	0.162

Cr (mg/dL)	0.80 ± 0.18	0.86 ± 0.35	0.385
Albumin (g/dL)	4.1 ± 0.4	3.8 ± 0.5	0.022
Globulin (g/dL)	3.3 ± 0.4	3.2 ± 0.4	0.682
TB (mg/dL)	0.6 ± 0.2	0.6 ± 0.2	0.799
AST (U/L)	**55.3 ± 151.1**	**32.0 ± 17.1**	0.014
ALT (U/L)	**63.8 ± 115.2**	**40.0 ± 31.7**	0.022
ALP (U/L)	**84.4 ± 37.9**	**73.7 ± 16.3**	0.176
CRP (mg/L)	**5.9 ± 7.1**	**5.6 ± 5.9**	0.857
IL-6 (pg/mL)	**1.6 ± 2.0**	**1.7 ± 1.6**	0.792

3.3 Inflammatory Markers Outcome

We evaluated inflammatory markers, including C-reactive protein (CRP) and interleukin-6 (IL-6). Regardless of symptoms, the intervention group had significantly lower levels of both inflammatory markers on day 7 after enrollment compared to the control group; CRP (5.8 ± 7.3 vs. 18.4 ± 31.4 mg/L; p = 0.019) and IL-6 (2.0 ± 2.4 vs. 21.8 ± 68.3 pg/mL; p = 0.001) (Figure 2B-2C). Nevertheless, the difference between both markers did not reach statistical significance on day 14 after enrollment.

We further analyzed the median changes in CRP and IL-6 levels between specific timeframes, from days 0-7 and 7-14. The median changes in CRP between day 0-7 and IL-6 between day 0-7 in the intervention arm were significantly higher than in the control arm: 4.8 vs. 3.0 mg/L; p = 0.031 and 0.9 vs. 0.4 pg/mL; p = 0.038, respectively. However, the median changes in CRP between days 7-14 in the intervention arm were lower than in the control arm, 0.4 vs. 1.7 mg/L; p = 0.012, whereas there was no difference in IL-6 between days 7-14 in both arms.

3.4 Adverse Events

For safety outcomes, the intervention group had significantly slightly elevated AST levels compared to the control group on day 7 (40.3 ± 39.1 vs. 32.2 ± 10.9 U/L; p = 0.030), and both AST and ALT on day 14 (55.3 ± 151.1 vs. 32.0 ± 17.1 U/L; p = 0.014 and 63.8 ± 115.2 vs. 40.0 ± 31.7; p = 0.022 U/L, respectively). However, the two groups had no significant difference in alkaline phosphatase (ALP). All patients with elevated levels of AST or ALT levels showed no clinical symptoms of hepatitis, and none of them developed liver failure or required treatment (Figure 2D-2F).

3.5 Subgroup Analysis of High-Risk and Low-Risk Patients

The patients were stratified into high-risk and low-risk groups of 59 and 23, respectively. The baseline characteristics of patients in these groups were compared and presented in Table 3. High-risk patients have a statistically significant older age compared to low-risk patients (48.2 ± 15.1 vs. 32.9 ± 8.3 years; p < 0.001). Symptom presentation and laboratory values were similar between both groups, including CRP and IL-6 levels at enrollment.

Table 3 Baseline characteristics of COVID-19 infected patients in the study subgroup categorized by low-risk and high-risk groups.

Variables	High-risk (n = 59)	Low-risk (n = 23)	p-valve
Age (year)	48.2 ± 15.1	32.9 ± 8.3	<0.001
Male, n (%)	31 (52.5%)	13 (56.5%)	0.745
BMI (kg/m^2)	22.4 ± 3.9	26.8 ± 6.6	0.001
Laboratories at baseline			
Hb (g/dL)	13.6 ± 1.7	13.6 ± 1.3	0.943
WBC (/mm^3)	6,159 ± 1,856	6,302 ± 2,336	0.771
Platelet (/mm^3)	224.2 ± 61.9	224.5 ± 58.2	0.981
PT	11.6 ± 0.6	11.8 ± 0.7	0.298
INR	1.05 ± 0.06	1.07 ± 0.07	0.229
PTT	24.9 ± 2.4	26.8 ± 2.6	0.005
Albumin (g/dL)	4.1 ± 0.4	4.2 ± 0.2	0.125
Globulin (g/dL)	3.4 ± 0.4	3.2 ± 0.5	0.096
TB (mg/dL)	0.5 ± 0.2	0.6 ± 0.3	0.251
AST (U/L)	40.7 ± 46.2	29.0 ± 11.7	0.077
ALT (U/L)	32.7 ± 22.7	26.8 ± 21.9	0.291
ALP (U/L)	72.9 ± 17.1	75.7 ± 22.9	0.551
CRP (mg/L)	14.6 ± 16.7	13.2 ± 13.1	0.729
IL-6 (pg/mL)	3.31 ± 2.80	4.41 ± 7.13	0.326
PCR-CT	22.2 ± 4.7	21.9 ± 5.7	0.289
Laboratories DAY 7			
AST (U/L)	37.8 ± 31.3	31.2 ± 16.4	0.218
ALT (U/L)	40.3 ± 26.6	32.3 ± 29.4	0.242
ALP (U/L)	78.0 ± 31.7	75.8 ± 20.2	0.758
CRP (mg/L)	15.8 ± 27.0	3.3 ± 3.1	0.002
IL-6 (pg/mL)	15.1 ± 56.1	1.9 ± 1.8	0.042
PCR-CT	26.8 ± 5.9	24.4 ± 3.6	0.355
Laboratories DAY 14			
AST (U/L)	48.3 ± 126.6	32.1 ± 19.2	0.385
ALT (U/L)	57.8 ± 98.3	36.3 ± 28.0	0.171
ALP (U/L)	79.8 ± 31.0	77.4 ± 20.9	0.775
CRP (mg/L)	6.3 ± 6.0	4.3 ± 7.5	0.018
IL-6 (pg/mL)	1.6 ± 1.4	1.8 ± 2.6	0.651

Within the high-risk group, the combination of Andrographolide and favipiravir provided significantly lower levels of inflammatory markers on day 7 after enrolment when compared to favipiravir monotherapy; CRP 6.8 ± 8.1 vs. 27.2 ± 37.0 mg/L (p = 0.002) and IL-6 2.0 ± 2.7 vs. 32.5 ± 83.4 pg/mL (p = 0.007) (Figure 3A). However, the difference between both markers did not reach statistical significance on day 14 after enrollment, which is consistent with the results of the entire cohort. There were no differences in AST and ALT levels in the subgroup analysis (Table 4).

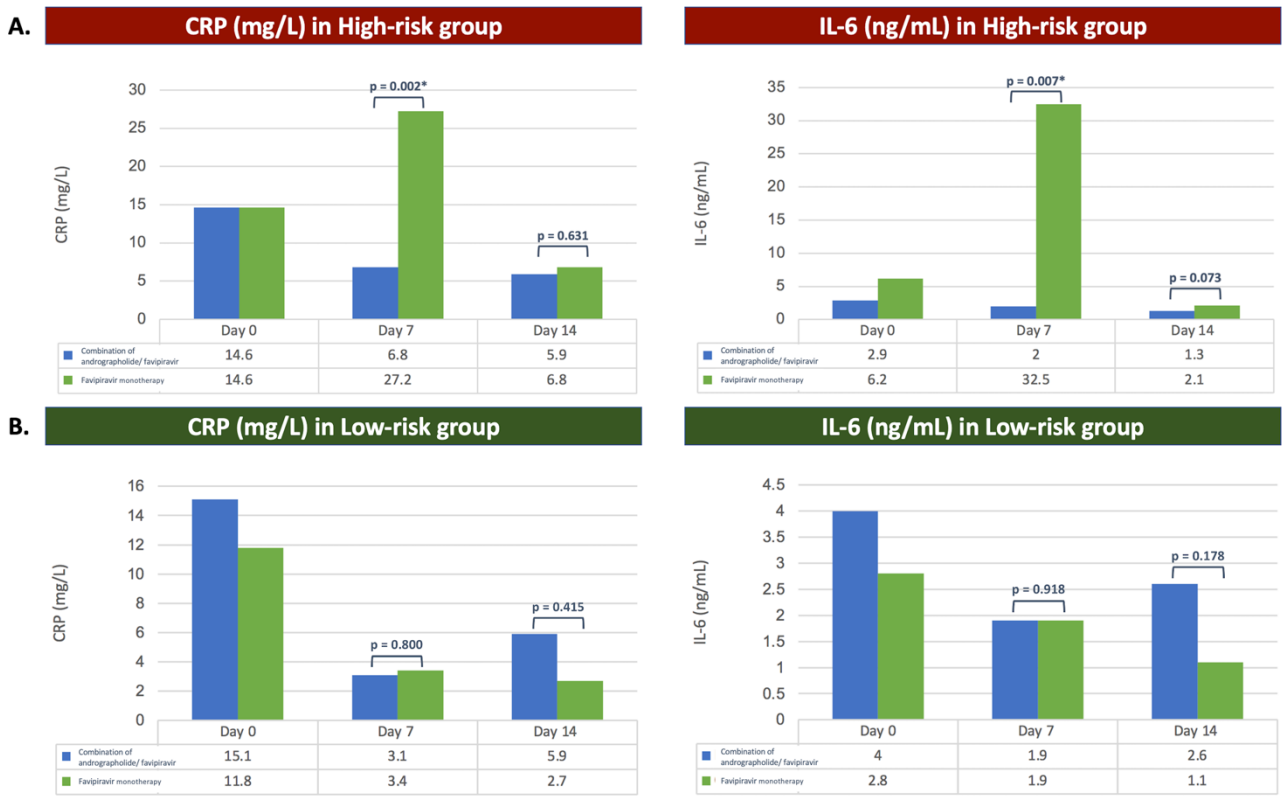

Figure 3 Comparison of inflammatory biomarkers on days 0, 7, and 14 in high-risk and low-risk patients.

Table 4 Subgroup analysis of inflammatory markers and liver enzymes among **high-risk patients** (n = 59).

Variables	Intervention arm (n = 33)	Control arm (n = 26)	p-valve
Laboratories at baseline			
Symptoms at presentation, n (%)			
Fever 26 (44.1%)	14 (42.4%)	12 (46.2%)	0.775
Cough 40 (67.8%)	22 (66.7%)	18 (69.2%)	0.834
Myalgia 5 (8.5%)	3 (9.1%)	2 (7.7%)	0.848
Headache 6 (10.2%)	2 (6.1%)	4 (15.4%)	0.239
Sore throat 24 (40.7%)	15 (45.5%)	0 (34.6%)	0.400
Rhinitis 23 (39.0%)	12 (36.4%)	11 (42.3%)	0.642
Anosmia 4 (6.8%)	3 (10.0%)	1 (5.9%)	0.627
Diarrhea 2 (3.4%)	2 (6.1%)	0 (0.0%)	0.202
AST (U/L)	45.9 ± 59.5	34.0 ± 18.8	0.282
ALT (U/L)	37.0 ± 23.6	27.3 ± 20.8	0.098
CRP (mg/L)	14.6 ± 16.7	14.6 ± 17.0	0.997
IL-6 (pg/mL)	2.9 ± 4.0	6.2 ± 9.5	0.082
PCR-CT	22.6 ± 5.4	21.7 ± 3.6	0.513
Laboratories DAY 7			
Symptoms day 7, n (%)			

Fever 14 (23.7%)	8 (24.2%)	6 (23.1%)	0.917
Cough 23 (39.0%)	10 (30.3%)	13 (50.0%)	0.124
Myalgia 2 (3.4%)	0 (0.0%)	2 (7.7%)	0.105
Headache 3 (5.1%)	1 (3.0%)	2 (7.7%)	0.418
Sore throat 12 (20.3%)	6 (18.2%)	6 (23.1%)	0.643
Rhinitis 15 (25.4%)	6 (18.2%)	9 (34.6%)	0.150
Anosmia 0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Diarrhea 0 (0.0%)	0 (0.0%)	0 (0.0%)	-
AST (U/L)	44.8 ± 46.7	32.8 ± 9.0	0.157
ALT (U/L)	42.0 ± 25.0	38.0 ± 29.1	0.580
CRP (mg/L)	6.8 ± 8.1	27.2 ± 37.0	0.002
IL-6 (pg/mL)	2.0 ± 2.7	32.5 ± 83.4	0.007
PCR-CT	26.6 ± 5.8	27.0 ± 6.3	0.872
Laboratories DAY 14			
Symptoms day 14, n (%)			
Fever 3 (5.1%)	1 (3.0%)	2 (7.7%)	0.418
Cough 8 (13.6%)	2 (6.1%)	6 (23.1%)	0.055
Myalgia 0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Headache 0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Sore throat 1 (1.7%)	0 (0.0%)	1 (3.8%)	0.256
Rhinitis 1 (1.7%)	0 (0.0%)	1 (3.8%)	0.256
Anosmia 0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Diarrhea 0 (0.0%)	0 (0.0%)	0 (0.0%)	-
AST (U/L)	64.2 ± 171.7	29.7 ± 13.1	0.308
ALT (U/L)	73.3 ± 129.6	39.7 ± 31.9	0.204
CRP (mg/L)	5.9 ± 5.8	6.8 ± 6.4	0.631
IL-6 (pg/mL)	1.3 ± 0.8	2.1 ± 1.9	0.073

Conversely, in the low-risk group, no significant differences in inflammatory biomarkers (Figure 3B) or AST and ALT levels were observed on days 0, 7, and 14 after enrollment (Table 5).

Table 5 Subgroup analysis of inflammatory markers and liver enzymes among **low-risk patients** (n = 23).

Variables	**Intervention arm (n = 10)**	**Control arm (n = 13)**	**p-valve**
Laboratories at baseline			
Symptoms at presentation, n (%)			
Fever 14 (60.9%)	6 (60.0%)	8 (61.5%)	0.940
Cough 19 (82.6%)	8 (42.1%)	11 (57.9%)	0.772
Myalgia 2 (8.7%)	1 (10.0%)	1 (7.7%)	0.846
Headache 4 (17.4%)	2 (20.0%)	2 (15.4%)	0.772
Sore throat 18 (78.3%)	7 (70.0%)	11 (84.6%)	0.400
Rhinitis 8 (34.8%)	3 (30.0%)	5 (38.5%)	0.673
Anosmia 3 (13.0%)	2 (20.0%)	1 (7.7%)	0.396

Diarrhea 2 (8.7%)	1 (10.0%)	1 (7.7%)	0.846
AST (U/L)	32.0 ± 13.5	26.7 ± 10.1	0.291
ALT (U/L)	34.0 ± 29.0	21.3 ± 13.3	0.175
CRP (mg/L)	15.1 ± 16.4	11.8 ± 10.4	0.560
IL-6 (pg/mL)	4.0 ± 3.0	2.8 ± 2.6	0.322
PCR-CT	19.4 ± 5.4	22.0 ± 6.0	0.298
Laboratories DAY 7			
Symptoms day 7, n (%)			
Fever 6 (26.1%)	1 (10.0%)	5 (38.5%)	0.108
Cough 12 (52.2%)	3 (30.0%)	9 (69.2%)	0.059
Myalgia 1 (4.3%)	1 (10.0%)	0 (0.0%)	0.244
Headache 2 (8.7%)	1 (10.0%)	1 (7.7%)	0.846
Sore throat 11 (47.8%)	4 (40.0%)	7 (53.8%)	0.510
Rhinitis 3 (13.0%)	1 (10.0%)	2 (15.4%)	0.704
Anosmia 0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Diarrhea 0 (0.0%)	0 (0.0%)	0 (0.0%)	-
AST (U/L)	32.1 ± 17.1	30.0 ± 16.3	0.771
ALT (U/L)	31.4 ± 32.2	33.0 ± 28.3	0.903
CRP (mg/L)	3.1 ± 3.0	3.4 ± 3.4	0.800
IL-6 (pg/mL)	1.9 ± 1.4	1.9 ± 2.1	0.918
PCR-CT	26.6 ± 0.6	23.3 ± 4.1	0.344
Laboratories DAY 14			
Symptoms day 14, n (%)			
Fever 0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Cough 2 (8.7%)	1 (10.0%)	1 (7.7%)	0.846
Myalgia 0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Headache 1 (4.3%)	0 (0.0%)	1 (7.7%)	0.370
Sore throat 1 (4.3%)	1 (10.0%)	0 (0.0%)	0.244
Rhinitis 1 (4.3%)	1 (10.0%)	0 (0.0%)	0.244
Anosmia 0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Diarrhea 0 (0.0%)	0 (0.0%)	0 (0.0%)	-
AST (U/L)	25.4 ± 7.0	38.8 ± 25.3	0.172
ALT (U/L)	31.8 ± 23.0	40.9 ± 33.2	0.533
CRP (mg/L)	5.9 ± 10.1	2.7 ± 3.4	0.415
IL-6 (pg/mL)	2.6 ± 3.7	1.1 ± 0.6	0.178

4. Discussion

Our study aimed to investigate the therapeutic potential of combining Andrographolide and favipiravir compared with favipiravir monotherapy in preventing severe pneumonia. We focused on patients with mild COVID-19, encompassing low-risk and high-risk individuals with factors predisposing them to severe COVID-19 infection. High-risk patients exhibited signs of respiratory distress, such as a respiration rate ≥30 breaths per minute, oxygen saturation ≤93%, or ≤PaO_2/FiO_2 300. Additionally, high-risk patients included those requiring high-flow nasal cannula (HFNC) or non-

invasive ventilation (NIV) [16]. Despite these criteria, none of the participants in our study developed pneumonia requiring the use of HFNC or NIV. Consequently, we could not observe any differences in treatment outcomes between the two groups regarding this aspect.

The secondary treatment outcome showed that Andrographolide combined with favipiravir reduced cough on day 7 more effectively than favipiravir monotherapy. This finding is consistent with previous studies on *Andrographis paniculata*, a component of Xiyanping that demonstrated significant effectiveness in ameliorating cough and fever [14].

Regarding the inflammatory biomarkers issue, COVID-19 infection can be categorized into three stages based on its natural course: 1) the early infection or viral response phase, 2) the pulmonary phase, and 3) the hyperinflammation phase or host inflammatory response phase [19-21]. According to the mechanism of favipiravir, it plays a crucial role in reducing viral shedding in the viral response phase. In contrast, Andrographolide inhibits the viral replication pathway and exerts anti-inflammatory effects. Therefore, Andrographolide is potentially beneficial for reducing disease severity in all stages.

Our study confirmed that the critical inflammatory biomarkers, including CRP and IL-6, exhibited a significant reduction in patients who received early treatment with a combination of Andrographolide and favipiravir compared with those treated with favipiravir monotherapy on day 7. Since day 7 is the transition period from the viral phase to the inflammatory response phases, during which severe infection or pneumonia typically manifest, the advantage of combination therapy by reducing viral replication and inflammatory response may be the critical effect for this observation. Moreover, the inflammatory biomarkers comprising CRP and IL-6 returned to nearly normal levels sooner on day 7, with no significant difference observed between the two groups on day 14 of treatment, following the natural course of mild infection. This result highlights that the early administration of combined Andrographolide with favipiravir may help reduce the occurrence of the inflammatory process and decrease the incidence of severe disease during the hyperinflammation phase.

For the issue of patient age, most studies predominantly report on elderly patients over 65 years, highlighting their impact on the severity of COVID-19 [22]. However, only a few studies focus on inflammatory markers in subgroup analysis and found that the 45-65 age group had baseline inflammatory markers, including CRP, higher than the 18-45 age group [23]. It is noteworthy that in our study, even though the baseline characteristics of the intervention group indicate a significantly younger age compared to the control group, there were no differences in baseline inflammatory markers, including CRP and IL-6.

Our study further demonstrated that the combination of Andrographolide and favipiravir reduced both CRP and IL-6 inflammatory biomarkers on day 7 of treatment in the high-risk patients, in contrast to those treated with favipiravir alone. On the contrary, there was no difference in inflammatory markers after treatment in low-risk patients. These findings support the key findings that Andrographolide can reduce inflammation, particularly in the high-risk group at risk of progressing to severe disease. Our findings are consistent with those of a previous randomized control trial that demonstrated a reduction in IL-1β among patients treated with combination therapy [15], affirming the anti-inflammatory effect of Andrographolide in COVID-19.

Notably, three patients in the control group received remdesivir, potentially introducing confounding factors in assessing changes in inflammatory markers after treatment. However, due

to the small number of patients treated with remdesivir, it was observed that the inflammatory markers, including CRP and IL-6, did not significantly decrease compared to the entire group.

Both Andrographolide and favipiravir have been reported to cause mild hepatitis during treatment [24], concerning adverse events. In our study, baseline AST was comparable. We found that patients receiving a combination of Andrographolide with favipiravir experienced a statistically significant increase in AST levels on days 7 and 14 of treatment compared to those receiving favipiravir monotherapy. Although ALT baseline levels in the intervention group were higher than in the control group, no significant differences were observed on day 7. However, on day 14, similar to AST, the group receiving the combination of Andrographolide with favipiravir exhibited a statistically significant increase in ALT levels compared to favipiravir monotherapy. However, the severity of AST and ALT elevation was mild, and no patients experienced clinical symptoms of liver dysfunction. Additionally, this finding could be attributed to the higher pretreatment levels of AST and ALT in the Andrographolide group compared to the control group.

Our study has several strengths. We enrolled a specific group of mild COVID-19 patients, including high-risk and low-risk. We initiated treatment within 72 hours of symptom onset to ensure the effectiveness of both treatment regimens based on the natural course of COVID-19 progression. Additionally, we closely monitored clinical symptoms and biochemical data on days 7 and 14, which enabled us to evaluate each stage of infection progression comprehensively.

Nonetheless, this study has some limitations. Firstly, we did not recruit patients with severe COVID-19, so we could not evaluate the effectiveness of Andrographolide in improving severe COVID-19 infections. This limits the generalizability of these treatments in severe COVID-19 cases. Secondly, during our study, Molnupiravir and the combination of Nirmatrelvir-ritonavir (Paxlovid®) were not available in Thailand; therefore, we were unable to demonstrate the additional benefits of Andrographolide compared to the current standard treatment with these more efficacious regimens. Thirdly, the timing and types of vaccinations varied among participants due to the ongoing trial period during enrollment. As a result, it was challenging to detail the COVID-19 immunization status of each participant comprehensively. Finally, this study did not analyze the different strains of COVID-19. Though the study was conducted during the Delta and Omicron variants, it is essential to note that the severity of infection from these two variants differs significantly. Thus, future studies focusing on applying Andrographolide in combination with current standard treatment for COVID-19 patients, especially in severe cases and different variants, are interesting and worthwhile topics to pursue.

5. Conclusion

In mild COVID-19 patients, a combination of Andrographolide and favipiravir could not demonstrate additional benefits beyond favipiravir alone to prevent severe pneumonia. However, Andrographolide significantly reduced cough symptoms, especially during the first week, compared to favipiravir monotherapy. Furthermore, inflammatory markers showed improvement despite mild transaminitis in the patients treated with Andrographolide.

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Author Contributions

Thaninee Prasoppokakorn, Supachaya Sriphoosanaphan, Rungsun Rerknimitr - Conceptual design of the work; Nutbordee Nalinthassanai, Thitaporn Roongrawee, Pongtorn Hanboonkunupakarn, Pisit Tangkijvanich - Data collection and data acquisition; Thaninee Prasoppokakorn, Supachaya Sriphoosanaphan, Rungsun Rerknimitr - Data analysis and interpretation; Thaninee Prasoppokakorn - Drafting the manuscript; Supachaya Sriphoosanaphan, Rungsun Rerknimitr - Critical revision of the manuscript; All authors - Final approval of the version to be published.

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Competing Interests

The authors declare no conflicts of interests.

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