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### Article

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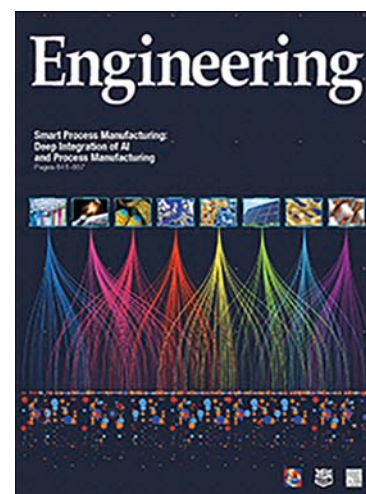
PII: S2095-8099(20)30063-1  
DOI: <https://doi.org/10.1016/j.eng.2020.03.007>  
Reference: ENG 392

To appear in: *Engineering*

Please cite this article as: Q. Cai, M. Yang, D. Liu, J. Chen, D. Shu, J. Xia, X. Liao, Y. Gu, Q. Cai, Y. Yang, C. Shen, X. Li, L. Peng, D. Huang, J. Zhang, S. Zhang, F. Wang, J. Liu, L. Chen, S. Chen, Z. Wang, Z. Zhang, R. Cao, W. Zhong, Y. Liu, L. Liu, Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study, *Engineering* (2020), doi: <https://doi.org/10.1016/j.eng.2020.03.007>

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# Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study

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## ARTICLE INFO

### Article history:

Received 7 March 2020

Revised 11 March 2020

Accepted 12 March 2020

Available online

### Keywords:

Favipiravir

COVID-19

SARS-CoV-2

Antiviral therapy

Open-label nonrandomized control study

## ABSTRACT

An outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and its caused coronavirus disease 2019 (COVID-19) has been reported in China since December 2019. More than 16% of patients developed acute respiratory distress syndrome, and the fatality ratio was about 1%–2%. No specific treatment has been reported. Herein, we examine the effects of Favipiravir (FPV) versus Lopinavir (LPV)/ritonavir (RTV) for the treatment of COVID-19. Patients with laboratory-confirmed COVID-19 who received oral FPV (Day 1: 1600 mg twice daily; Days 2–14: 600 mg twice daily) plus interferon (IFN)- $\alpha$  by aerosol inhalation (5 million U twice daily) were included in the FPV arm of this study, whereas patients who were treated with LPV/RTV (Days 1–14: 400 mg/100 mg twice daily) plus IFN- $\alpha$  by aerosol inhalation (5 million U twice daily) were included in the control arm. Changes in chest computed tomography (CT), viral clearance, and drug safety were compared between the two groups. For the 35 patients enrolled in the FPV arm and the 45 patients in the control arm, all baseline characteristics were comparable between the two arms. A shorter viral clearance time was found for the FPV arm versus the control arm (median (interquartile range, IQR), 4 (2.5–9) d versus 11 (8–13) d,  $P < 0.001$ ). The FPV arm also showed significant improvement in chest imaging compared with the control arm, with an improvement rate of 91.43% versus 62.22% ( $P = 0.004$ ). After adjustment for potential confounders, the FPV arm also showed a significantly higher improvement rate in chest imaging. Multivariable Cox regression showed that FPV was independently associated with faster viral clearance. In addition, fewer adverse reactions were found in the FPV arm than in the control arm. In this open-label nonrandomized control study, FPV showed significantly better treatment effects on COVID-19 in terms of disease progression and viral clearance; if causal, these results should be important information for establishing standard treatment guidelines to combat the SARS-CoV-2 infection.

## 1. Introduction

A recent outbreak of coronavirus disease 2019 (COVID-19) caused by the novel coronavirus designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) started in Wuhan, China, at the end of 2019. The clinical characteristics of COVID-19 include respiratory symptoms, fever, cough, dyspnea, and pneumonia [1–4]. As of 25 February 2020, at least 77 785 cases and 2666 deaths had been identified across China [5] and in other countries; in particular, 977 and 861 cases

were identified in South Korea and Japan, respectively. The outbreak has already caused global alarm. On 30 January 2020, the World Health Organization (WHO) declared that the outbreak of SARS-CoV-2 constituted a Public Health Emergency of International Concern (PHEIC), and issued advice in the form of temporary recommendations under the *International Health Regulations* (IHR).

It has been revealed that SARS-CoV-2 has a genome sequence that is 75%–80% identical to that of SARS-CoV, and has more similarities to several bat coronaviruses [6]. SARS-CoV-2 is the seventh reported human-infecting member of the family Coronaviridae, which also includes SARS-CoV and the Middle East respiratory syndrome (MERS)-CoV. It has been identified as the causative agent of COVID-19. Both the clinical and the epidemiological features of COVID-19 patients demonstrate that SARS-CoV-2 infection can lead to intensive care unit (ICU) admission and high mortality. About 16%–21% of people with the virus in China have become severely ill, with a 2%–3% mortality rate [1,4]. However, there is no specific treatment against the new virus. Therefore, it is urgently necessary to identify effective antiviral agents to combat the disease and explore the clinical effect of antiviral drugs.

One efficient approach to discover effective drugs is to test whether the existing antiviral drugs are effective in treating other related viral infections. Several drugs, such as ribavirin, interferon (IFN), Favipiravir (FPV), and Lopinavir (LPV)/ritonavir (RTV), have been used in patients with SARS or MERS, although the efficacy of some drugs remains controversial. It has recently been demonstrated that, as a prodrug, FPV (half maximal effective concentration ( $EC_{50}$ ) = 61.88  $\mu\text{mol}\cdot\text{L}^{-1}$ , half-maximal cytotoxic concentration ( $CC_{50}$ ) > 400  $\mu\text{mol}\cdot\text{L}^{-1}$ , selectivity index (SI) > 6.46) effectively inhibits the SARS-CoV-2 infection in Vero E6 cells (ATCC-1586) [7]. Furthermore, other reports show that FPV is effective in protecting mice against Ebola virus challenge, although its  $EC_{50}$  value in Vero E6 cells was as high as 67  $\mu\text{mol}\cdot\text{L}^{-1}$  [8]. Therefore, clinical studies are urgently needed to evaluate the efficacy and safety of this antiviral nucleoside for COVID-19 treatment.

In this study, we performed a comprehensive evaluation of the clinical efficacy of treatment for COVID-19 patients at The Third People's Hospital of Shenzhen. We aimed to compare the clinical effect of FPV and LPV/RTV on COVID-19 patients. These findings will help provide guidance for the clinical treatment of the SARS-CoV-2 infection.

## 2. Methods

### 2.1. Study design

For the specific epidemic situation of COVID-19, we chose to conduct an open-label nonrandomized control study in the isolation ward of the national clinical research center for infectious diseases (The Third People's Hospital of Shenzhen), Shenzhen, China. From 30 January to 14 February 2020, laboratory-confirmed patients with COVID-19 were consecutively screened, and eligible patients were included in the FPV arm of the study. Patients who had initially been treated with antiviral therapy with LPV/RTV from 24 January to 30 January 2020 were screened, and eligible patients were included in the control arm of the study. The study was conducted according to the guidelines of the *Declaration of Helsinki* and the principles of good clinical practice, and was approved by the ethics committee of The Third People's Hospital of Shenzhen (No.:2020-002-02). Written informed consent was obtained from all patients. The study was reported according to the *Consolidated Standards of Reporting Trials* guidelines and was registered on the Chinese Clinical Trial Registry (ID: ChiCTR2000029600)

### 2.2. Eligibility criteria

All patients admitted to both the FPV and the control arms of the study were assessed for eligibility criteria. The inclusion criteria included: aged 16–75 years old; respiratory or blood samples tested positive for the novel coronavirus; duration from disease onset to enrolment was less than 7 d; willing to take contraception during the study and within 7 d after treatment; and no difficulty in swallowing the pills. The exclusion criteria included the following: severe clinical condition (meeting one of the following criteria: a resting respiratory rate greater than 30 per minute, oxygen saturation below 93%, oxygenation index (OI) < 300 mmHg (1 mmHg = 133.3 Pa), respiratory failure, shock, and/or combined failure of other organs that required ICU monitoring and treatment); chronic liver and kidney disease and reaching end stage; previous history of allergic reactions to FPV or LPV/RTV; pregnant or lactating women; women of a childbearing age with a positive pregnancy test, breastfeeding, miscarriage, or within 2 weeks after delivery; and participated in another clinical trial against SARS-CoV-2 treatment currently or in the past 28 d.

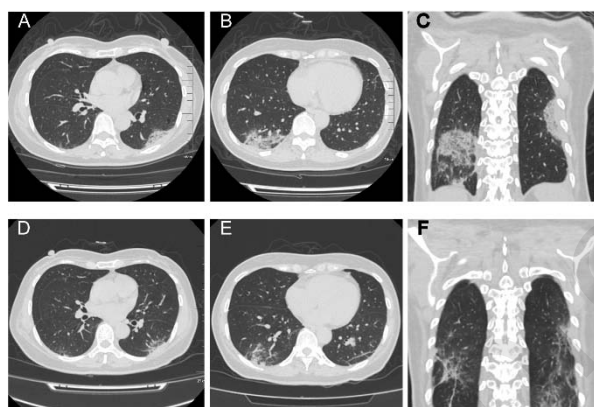
### 2.3. Trial treatment

FPV (Haizheng Pharmaceutical Co., 200 mg per tablet) was given orally. The dose was 1600 mg twice daily on Day 1 and 600 mg twice daily on Days 2–14. LPV/RTV (AbbVie Inc., 200 mg/50 mg per tablet) were given orally. The dose was LPV 400 mg/RTV 100 mg twice daily. Both FPV and LPV/RTV were continued until the viral clearance was confirmed or until 14 d had passed. In addition, all participants received IFN- $\alpha$ 1b 60  $\mu\text{g}$  (Beijing Tri-Prime Gene Pharmaceutical Co., 30  $\mu\text{g}$  per ampule) twice daily by aerosol inhalation. Standard care included oxygen inhalation, oral or intravenous rehydration, electrolyte correction, antipyretics, analgesics, and antiemetic drugs.

### 2.4. Efficacy measures

The efficacy of the treatment was assessed by the time of viral clearance and the improvement rate of chest computed tomography (CT) scans on Day 14 after treatment. Chest CT scans were conducted on Days 4, 9, and 14 after treatment, with a fluctuate of 2 d. The CT findings were graded and scored using the method described previously [9,10] by two medical

diagnostic radiographers who were blind to grouping. The CT findings were graded on a three-point scale: 1 as normal attenuation, 2 as ground-glass attenuation, and 3 as consolidation. Each lung zone—with a total of six lung zones in each patient—was assigned a score on the following scale, according to the distribution of the affected lung parenchyma, using a method modified from a previously described protocol [10]: 0 as normal, 1 as 25% abnormality, 2 as 25%–50% abnormality, 3 as 50%–75% abnormality, and 4 as 75% abnormality. The four-point scale of the lung parenchyma distribution was then multiplied by the radiologic scale described above. Points from all zones were added for a final total cumulative score, with a value ranging from 0 to 72 (Fig. 1). A change of “Improve” in the chest CT was defined as the total cumulative score being lower than before medication; a change of “Worse” was defined as the total cumulative score being higher than before medication; and a change of “Constant” was defined as the total cumulative score being the same as before treatment (Fig. 1).



**Fig. 1.** Score of chest CT scan for a 56-year-old female patient with COVID-19 from the FPV arm. (a–c) show parts of the CT images obtained prior to the FPV treatment, which were scored as 15 according to the scoring method. (d–f) show parts of the CT images obtained on Day 12 after the FPV treatment, which were scored as 6.

The presence of SARS-CoV-2 was detected by the real-time quantitative polymerase chain reaction (qPCR) method, as previously reported [5]. Viral ribonucleic acids (RNAs) were extracted from the samples using the QIAamp RNA Viral Kit (Qiagen, Heiden, Germany), and quantitative reverse transcription polymerase chain reaction (qRT-PCR) was performed using a commercial kit specific for SARS-CoV-2 detection (GeneDX Co., Ltd., Shanghai, China), which was approved by the China Food and Drug Administration (CFDA) (rebranded and restructured as the National Medical Products Administration of the State Administration for Market Regulation of PRC since 2018). “Viral clearance” was defined as the presence of two consecutive negative results with qPCR detection over an interval of 24 h.

### 2.5. Safety analysis

Safety was assessed by a standardized questionnaire for adverse events and by laboratory tests.

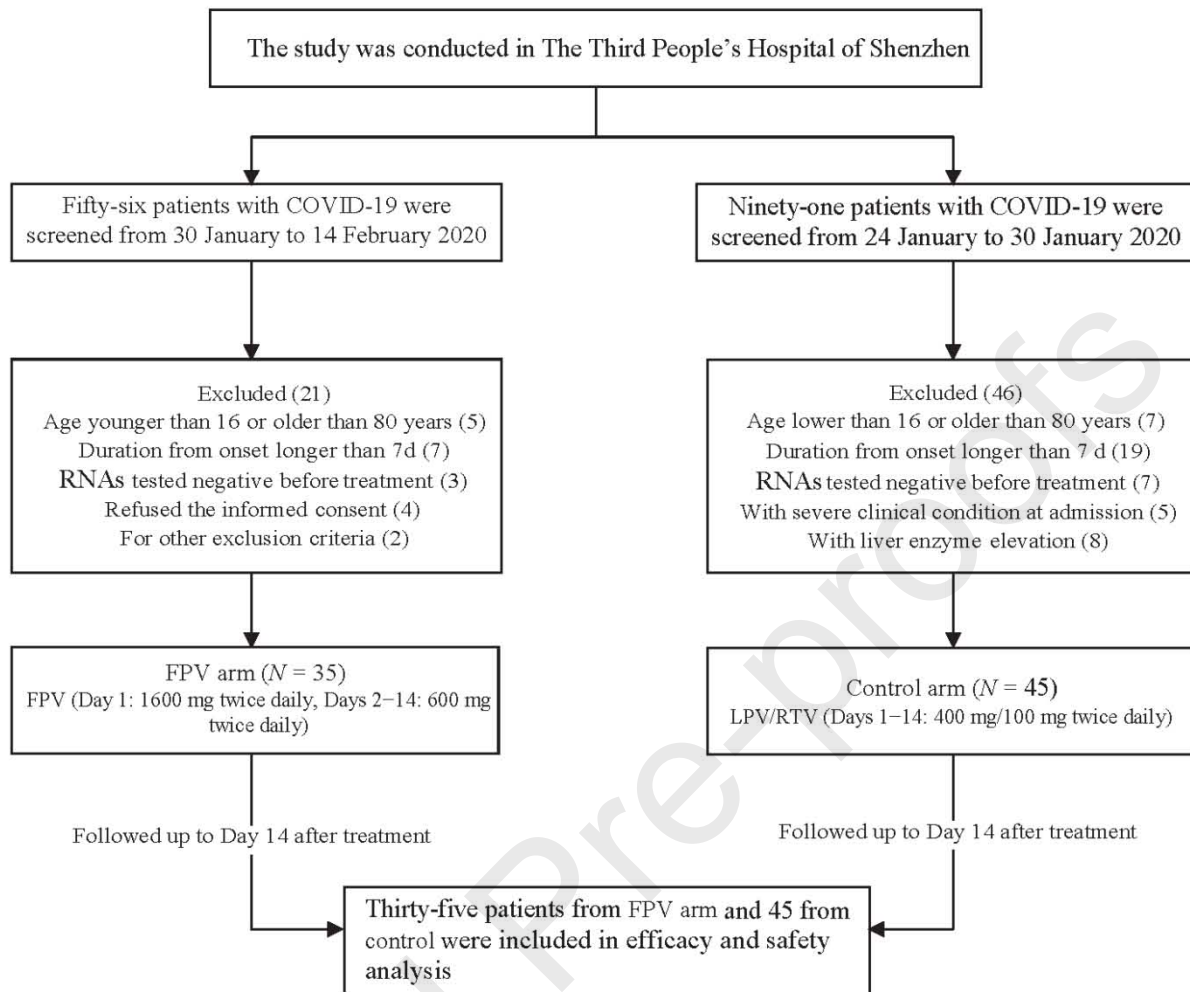
### 2.6. Statistics analysis

The quantitative data were described as the mean  $\pm$  standard deviation, or as the median (min–max). The qualitative data were described by number of cases (proportion, %). Patient characteristics were compared using the  $\chi^2$  test or Fisher’s exact test for categorical data, and the Wilcoxon rank-sum test or Student’s *t* test for continuous data. The factors affecting the changes in chest CT were analyzed using binary logistic regression. The analysis of viral clearance time was calculated using the Kaplan-Meier method and the difference analysis of the viral clearance time under different treatments was calculated using the log-rank test. Potential influencing factors of viral clearance were analyzed by univariate and multivariate Cox regression models. A *P* value lower than 0.05 was required for statistical significance. All of the analysis was performed using SPSS Version 22.0 and GraphPad Prism 7.0.

## 3. Results

### 3.1. Patients and baseline analysis

From 30 January, 56 patients with laboratory-confirmed COVID-19 were screened, of which 35 were eligible for the FPV arm of the study. A total of 91 laboratory-confirmed COVID-19 patients who had started treatment with LPV/RTV between 24 January and 30 January 2020 were screened, of which 45 were eligible for the control arm of this study. All enrolled patients finished the therapy and were followed up for 14 d after the treatment began (Fig. 2). All the baseline characteristics were compared between the FPV arm and the control. As shown in Table 1, there were no significant differences between the baseline characteristics of the two arms.



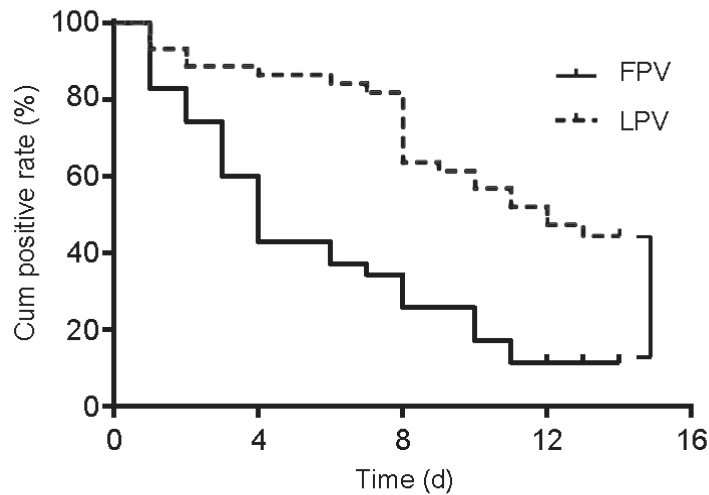
**Table 1**  
Baseline characteristics of patients with SARS-COV-2 infection.

| Characteristic                 | COVID-19 patients    |                       |                      | P value |
|--------------------------------|----------------------|-----------------------|----------------------|---------|
|                                | Total (N = 80)       | FPV (N = 35)          | LPV/RTV (N = 45)     |         |
| Age, median (IQR)              | 47 (35.75–61)        | 43 (35.5–59)          | 49 (36–61)           | 0.61    |
| Age subgroup (year)            |                      |                       |                      |         |
| 15–44                          | 36 (45.0%)           | 18 (51.4%)            | 18 (40.0%)           |         |
| 45–64                          | 33 (41.3%)           | 13 (37.1%)            | 20 (44.4%)           |         |
| ≥ 65                           | 11 (13.7%)           | 4 (11.4%)             | 7 (15.6%)            | 0.47    |
| Male                           | 35 (43.8%)           | 14 (40.0%)            | 21 (46.7%)           | 0.55    |
| BMI, median (IQR)              | 22.9 (16.2–31.6)     | 22.7 (16.2–31.6)      | 23.1 (16.4–28.4)     | 0.51    |
| Epidemiology                   |                      |                       |                      |         |
| History of visiting Wuhan City | 46 (57.5%)           | 20(57.1%)             | 26 (57.8%)           |         |
| Not been to Wuhan City         | 34 (42.5%)           | 15(20.0%)             | 19 (17.8%)           | 0.95    |
| Onset symptoms                 |                      |                       |                      |         |
| Fever                          | 59 (73.8%)           | 22 (62.9%)            | 37 (82.2%)           | 0.11    |
| Cough                          | 22 (27.5%)           | 12 (34.3%)            | 10 (22.2%)           | 0.23    |
| Headache/myalgia               | 8 (10.0%)            | 3 (8.6%)              | 5 (11.1%)            | 1.00    |
| Chill                          | 1 (1.3%)             | 0 (0%)                | 1 (2.2%)             | 1.00    |
| Diarrhea                       | 1 (1.3%)             | 1 (2.9%)              | 0 (0%)               | 0.44    |
| Stuffy nose/sore throat        | 8 (10.0%)            | 6 (17.1%)             | 2 (4.4%)             | 0.13    |
| Laboratory test, median (IQR)  |                      |                       |                      |         |
| WBC ( $10^9 L^{-1}$ )          | 6.0 (3.5–5.2)        | 8.1 (3.8–6.6)         | 4.3 (3.4–4.9)        | 0.21    |
| Neutrophils ( $10^9 L^{-1}$ )  | 2.8 (2.1–3.4)        | 3.0 (2.1–3.7)         | 2.6 (2.1–3.1)        | 0.43    |
| Lymphocyte ( $10^9 L^{-1}$ )   | 1.3 (0.9–1.6)        | 1.5 (1.0–1.8)         | 1.2 (0.9–1.4)        | 0.06    |
| ALT (U·L <sup>-1</sup> )       | 22.2 (15.0–26.3)     | 21.6 (15.0–24.0)      | 22.6 (15.5–27.0)     | 0.54    |
| AST (U·L <sup>-1</sup> )       | 25.1 (18.0–28.0)     | 24.1 (18.0–26.0)      | 25.8 (19.0–31.0)     | 0.47    |
| GGT (U·L <sup>-1</sup> )       | 25.5 (14–31.1)       | 26.9 (14.0–33.0)      | 24.4 (14.4–31.1)     | 0.48    |
| CRP (mg·dL <sup>-1</sup> )     | 18.6 (5.0–20.0)      | 15.0 (3.0–19.2)       | 21.4 (5.0–23.2)      | 0.33    |
| IL-6 (ng·L <sup>-1</sup> )     | 13.4 (4.4–16.2)      | 14.0 (3.5–11.0)       | 12.9 (5.3–16.8)      | 0.77    |
| T lymphocyte count             | 973.8 (594.3–1227.0) | 1046.7 (600.8–1314.8) | 925.2 (572.8–1211.5) | 0.40    |
| CD4+ T lymphocyte count        | 562.3 (382.5–733)    | 593.3 (369.0–802.75)  | 542.3 (388.0–689.0)  | 0.54    |
| CD8+ T lymphocyte count        | 354.4 (206.5–496.5)  | 397.8 (212.3–528.5)   | 326.4 (207.5–423)    | 0.76    |
| Ct values, median (range)      | 29.8 (18.8–37.9)     | 30.7 (21.2–37.0)      | 29 (18.8–38.0)       | 0.38    |
| Chest CT score, median (range) | 9.5(4.0–14.0)        | 12(4.0–14.0)          | 10(4.5–13.5)         | 0.78    |

IQR: interquartile range; BMI: body mass index; WBC: white blood cell; ALT: alanine aminotransferase; AST: aspartate aminotransferases; GGT:  $\gamma$ -glutamyl transpeptidase; CRP: c-reactive protein; IL: interleukin; Ct: cycle threshold.

### 3.2. Viral response to the antiviral therapy

The Kaplan-Meier survival curves for the length of time until viral clearance for both kinds of antiviral therapy were presented in Fig. 3. The median time of viral clearance for the patients treated with FPV, designated as Group A, was estimated to be 4 d (IQR: 2.5–9), which was significantly shorter than the time for patients in the control group, designated as Group B, which was 11 d (IQR: 8–13) ( $P < 0.001$ ).



**Fig 3.** Kaplan-Meier survival curves for the length of time until viral clearance for both kinds of antiviral therapy ( $P < 0.001$ ).

### 3.3. Chest CT changes in COVID-19 patients' response to treatment

The non-parametric Mann-Whitney U test was used to determine the significance of the difference between the chest CT changes in response to the two different treatments (Table 2). Meanwhile, the improvement rates of the chest CT changes for the two arms of the study were compared on Days 4, 9, and 14 after treatment. No significant difference in the improvement rates was found between the two arms on Days 4 and 8 ( $P > 0.05$ ). However, on Day 14 after treatment, the improvement rates of the chest CT changes in the FPV arm were significantly higher than those in the control arm (91.4% versus 62.2%, 32/35 versus 28/45,  $P = 0.004$ ).

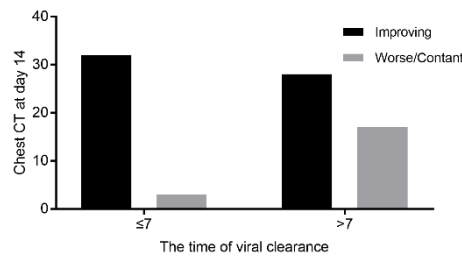
**Table 2**

Chest CT changes in patients with COVID-19 after treatment.

| Chest CT changes                   | COVID-19 patients (N = 80) |                  | P value |
|------------------------------------|----------------------------|------------------|---------|
|                                    | FPV (N = 35)               | LPV/RTV (N = 45) |         |
| Day 4 after treatment              |                            |                  |         |
| Improve                            | 8 (22.86%)                 | 8 (17.78%)       | 0.42    |
| Worse                              | 9 (25.71%)                 | 15 (33.33%)      |         |
| Constant                           | 18 (51.43%)                | 22 (48.89%)      |         |
| Day 9 after treatment <sup>a</sup> |                            |                  |         |
| Improve                            | 18 (56.25%)                | 16 (35.55%)      | 0.11    |
| Worse                              | 8 (25.00%)                 | 16 (35.55%)      |         |
| Constant                           | 6 (18.75%)                 | 13 (28.90%)      |         |
| Day 14 after treatment             |                            |                  |         |
| Improve                            | 32 (91.43%)                | 28 (62.22%)      | 0.004   |
| Worse                              | 1 (3.23%)                  | 9 (20.00%)       |         |
| Constant                           | 2 (6.45%)                  | 8 (17.78%)       |         |

<sup>a</sup> For three patients in the FPV arm, the lung CT scan on Days 6–9 after medication was not carried out.

Furthermore, the patients were divided into two groups based on the time of viral shedding. On Day 14 after treatment, the improvement rates of the chest CT changes in the group with viral clearance within 7 d of treatment were significantly higher than those of the patients with viral clearance after 7 d of treatment (Fig. 4).



**Fig 4.** Time of viral shedding and improving chest CT scan on Day 14 after treatment.

### 3.4. Multivariate analysis of the changes in chest CT

Univariate analysis using  $\chi^2$  test,  $t$  test, or Wilcoxon rank-sum test was conducted before multivariate analysis; the significant variables ( $P < 0.10$ ) in the univariate analysis were as follows: antiviral therapy and whether or not fever was present. A multivariate logistic regression analysis was conducted to identify the independent factors affecting the changes in chest CT. We chose the change in chest CT (0 = no change or worse, 1 = improved) as the dependent variable, and the variables that were significant in the univariate analysis or were professionally significant (including age, underlying disease, and severity of disease in baseline) as the independent variables. The result showed that there were two statistically significant factors in the model: antiviral therapy (odds ratio (OR) = 3.190, 95% confidence interval (CI) = 1.041–9.78) and fever (OR = 3.622, 95%CI = 1.054–12.442). This means that antiviral therapy and fever were independent factors that affected the chest CT after we had controlled the confounding factors. The patients who were treated with FPV had greater improvement in chest CT (Table 3).

**Table 3**

Logistic regression of changes in lung CT.

| Factors              | B      | S.E.      | Wald  | Sig   | OR         | OR 95% CI    |
|----------------------|--------|-----------|-------|-------|------------|--------------|
| Age                  | -0.019 | 0.018     | 1.167 | 0.280 | 0.981      | 0.947–1.016  |
| Antiviral therapy    | 1.160  | 0.572     | 4.121 | 0.042 | 3.190      | 1.041–9.78   |
| Fever                | 1.287  | 0.630     | 4.177 | 0.041 | 3.622      | 1.054–12.442 |
| Underlying diseases  | 0.279  | 0.961     | 0.084 | 0.771 | 1.322      | 0.201–8.693  |
| Severity in baseline | 21.080 | 40192.970 | 0.000 | 1.000 | 1.43E + 09 | 0–∞          |
| Constant             | 0.036  | 1.040     | 0.001 | 0.973 | 1.036      |              |

### 3.5. Multivariate analysis of viral clearance

Univariate analysis using the log-rank test and univariate Cox regression was conducted before the multivariate analysis; the significant variables ( $P < 0.10$ ) in the univariate analysis were as follows: antiviral therapy, white blood cell (WBC), hemoglobin (Hb), platelet (PLT), Neutrophils, T lymphocyte count, and illness to treatment time. A multivariate Cox regression model was used to explore the independent factors affecting viral clearance. The time of viral clearance was set as the TIME variable, viral clearance (0 = no, 1 = yes) was set as the status, and the variables that were significant ( $P < 0.10$ ) in the univariate Cox analysis or were professionally significant (including age, and whether underlying diseases were present or not) were set as independent variables. The result showed that the model was significant ( $P = 0.003$ ). The significant factors were as follows: T lymphocyte count ((hazard ratio (HR) = 1.002, 95%CI = 1.000–1.005) and antiviral therapy (HR = 3.434, 95%CI = 1.162–10.148). This means that the treatment and T lymphocyte count were independent factors that affected the viral clearance after we controlled the other confounding factors. As the result shows, compared with LPV/RTV, FPV has a greater effect on viral clearance (Table 4).

**Table 4**

Cox regression of viral clearance.

| Factors            | B      | S.E.  | Wald  | Sig   | HR    | HR 95% CI   |
|--------------------|--------|-------|-------|-------|-------|-------------|
| WBC                | -0.866 | 0.602 | 2.072 | 0.150 | 0.421 | 0.129–1.368 |
| Hb                 | 0.002  | 0.017 | 0.011 | 0.917 | 1.002 | 0.969–1.036 |
| PLT                | 0.011  | 0.006 | 2.818 | 0.093 | 1.011 | 0.998–1.024 |
| Neutrophils        | 0.805  | 0.657 | 1.500 | 0.221 | 2.236 | 0.617–8.105 |
| T lymphocyte count | 0.002  | 0.001 | 5.165 | 0.023 | 1.002 | 1.000–1.005 |



|                              |        |       |       |       |       |              |
|------------------------------|--------|-------|-------|-------|-------|--------------|
| CD8+ T lymphocyte            | -0.005 | 0.002 | 1.557 | 0.212 | 0.997 | 0.993–1.002  |
| Time from onset to treatment | 0.196  | 0.102 | 3.675 | 0.055 | 1.217 | 0.996–1.486  |
| FPV versus LPV/RTV           | 1.234  | 0.553 | 4.980 | 0.026 | 3.434 | 1.162–10.148 |
| Age                          | 0.000  | 0.015 | 0.000 | 0.988 | 1.000 | 0.971–1.029  |
| Underlying diseases          | -0.785 | 1.006 | 0.609 | 0.435 | 0.456 | 0.064–3.275  |

### 3.6. Adverse reactions after medication

The total number of adverse reactions in the FPV arm of the study was four (11.43%), which was significantly fewer than the 25 adverse reactions (55.56%) in the control arm ( $P < 0.001$ ). Two patients had diarrhea, one had a liver injury, and one had a poor diet in the FPV arm. Meanwhile, there were five patients with diarrhea, five with vomiting, six with nausea, four with rash, three with liver injury, and two with chest tightness and palpitations in the control arm (Table 5).

**Table 5**  
Statistics of adverse reactions after medication.

| Characteristic                    | Treatment    |                  | P value |
|-----------------------------------|--------------|------------------|---------|
|                                   | FPV (N = 35) | LPV/RTV (N = 45) |         |
| Total number of adverse reactions | 4 (11.43%)   | 25 (55.56%)      | < 0.001 |
| Diarrhea                          | 2 (5.71%)    | 5 (11.11%)       | 0.46    |
| Vomiting                          | 0 (0%)       | 5 (11.11%)       | 0.06    |
| Nausea                            | 0 (0%)       | 6 (13.33%)       | 0.03    |
| Rash                              | 0 (0%)       | 4 (8.89%)        | 0.13    |
| Liver and kidney injury           | 1 (2.86%)    | 3 (6.67%)        | 0.63    |
| Others                            | 1 (2.86%)    | 2 (4.44%)        | 1.00    |

## 4. Discussion

This study investigated the effect of FPV versus LPV/RTV on the treatment of COVID-19. It was found that FPV was independently associated with faster viral clearance and a higher improvement rate in chest imaging. These findings suggest that FPV has significantly better treatment effects on COVID-19 in terms of disease progression and viral clearance, as compared with LPV/RTV. FPV, which is known as a prodrug, is a novel RNA-dependent RNA polymerase (RdRp) inhibitor, which has been shown to be effective in the treatment of influenza and Ebola virus [8,11–15]. Recently, a report from Wang et al. [7] showed that both FPV and remdesivir are effective in reducing the SARS-CoV-2 infection *in vitro* ( $EC_{50} = 61.88 \mu\text{mol}\cdot\text{L}^{-1}$ ,  $CC_{50} > 400 \mu\text{mol}\cdot\text{L}^{-1}$ ,  $SI > 6.46$ ). The finding of the preset study confirms the hypotheses conceived from the laboratory finding: that FPV is effective treatment for COVID-19.

The limitation of the present study is that it was not a randomized double-blinded placebo-controlled clinical trial, which led to inevitable selection bias in patient recruitment. However, given the high number of patients presenting simultaneously and the very high infectivity of the disease, it was ethically unacceptable to allocate patients to receive a different experimental drug using a randomization process impossible for most of the patients to understand. Furthermore, in the context of rumors and distrust of hospital isolation, using a randomized design at the outset might have led even more patients to refuse being isolated. Therefore, we chose to conduct a nonrandomized trial, in which patients consecutively admitted to the hospital during two separate periods were included in two groups, respectively. Importantly, all baseline characteristics of the two groups were comparable and the effectiveness of FPV remained significant after adjustment for potential confounders.

The current study also found that early viral clearance contributed to the improvement of chest imaging on Day 14. This finding suggests that improvement of the disease may depend on inhibition of the SARS-CoV-2, and that FPV controls the disease progression of COVID-19 by inhibiting the SARS-CoV-2. Until recently, the pathogenesis of COVID-19 had not been well clarified. Since the infection of SARS-CoV-2 was thought to be self-limited and characterized by systemic inflammation reaction, symptomatic and supportive treatment was mainly recommended by the WHO and the National Health Commission of the PRC. This description is similar to MERS-CoV, for which nonspecific therapeutic interventions are often introduced to prevent severe morbidity and mortality [16]. How antivirals would contribute to control of the disease is controversial. Although there have been many registered clinical trials focusing on antiviral drugs for COVID-19, the timing, duration of treatment, and study endpoints have not been unified. In the current study, the time of viral clearance was introduced as a primary endpoint to evaluate the antiviral effect of FPV on the SARS-CoV-2 and successfully identify the priority of FPV. The relationship between the time of viral clearance and the improvement in CT image indicates that viral clearance is an ideal surrogate for the clinical endpoint. A limitation of the present study was that the relationship between the viral titer and the clinical prognosis was not well clarified. Future research could pay more attention to this point.

More adverse events were observed in the control arm than in the experimental arm, and were similar to the adverse events observed in studies of AIDS treated by LPV/RTV. It is worth mentioning that the treatment duration of FPV in the present study was twice as long as that used for the treatment of influenza. However, the adverse events in the experimental arm were rare and tolerable, and none of the patients needed to discontinue FPV treatment. These results seem to suggest that the treatment duration of FPV can be prolonged if necessary.

SARS-CoV-2 infection has now spread quickly all over the world. At present, no effective treatment has been demonstrated. The task at hand was to run a well-designed trial to identify effective treatments based on a high level of evidence. However, at the beginning of this study, certain conditions did not allow the randomization of patients to receive either standard care or an experimental drug. In this pilot study of a non-randomized control trial, we found that FPV showed significantly better treatment effects on COVID-19 in terms of disease progression and viral clearance; if causal, these results should be important information for establishing standard treatment guidelines to combat the SARS-CoV-2 infection. Furthermore, we introduced the time of viral clearance as a primary endpoint for experimental antiviral treatment and demonstrated it to be a surrogate of clinical endpoint; this will be helpful for designing COVID-19 research.

### Contributions

LL, YL, QC, MY, and JC contributed to the study design. QC, MY, DS, JX, XL, DL, YG, QC, XL, LP, DH, and JZ contributed to the collection of clinical data. QC, MY, SZ, FW, LC, SC, ZW, and ZZ contributed to the data analysis. QC, MY, JC, YY, CS, and WZ contributed to the manuscript preparation. All the authors have read and approved the manuscript.

### Acknowledgements

The authors are very grateful to Professor Li Song for his guidance in the study design and clinical research. This work was supported by the National Science and Technology Major Project (2017ZX10204401, 2018ZX10711001, 2017ZX10103011, 2018ZX09711003, 2020YFC0841700), Sanming Project of Medicine in Shenzhen (SZSM201412003, SZSM201512005), Shenzhen Science and Technology Research and Development Project (202002073000001), China Postdoctoral Science Foundation (2019M660836), Guangdong Special Fund for Science and Technology Innovation Strategy in 2020, and the Science and Technology Emergency Project for the prevention and control of the novel coronavirus by the Department of Science and Technology of Guangdong Province (2020B111105001)

### Compliance with ethics guidelines

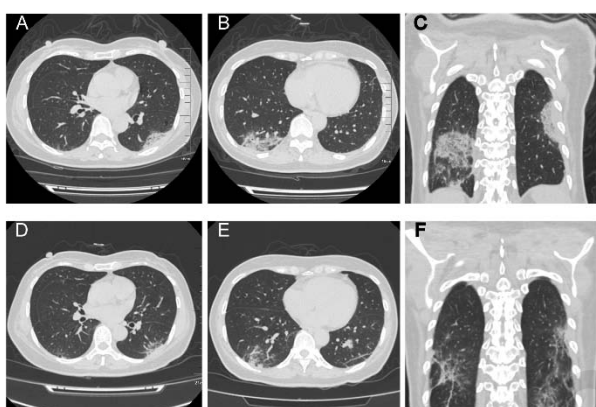
Qingxian Cai, Minghui Yang, Dongjing Liu, Jun Chen, Dan Shu, Junxia Xia, Xuejiao Liao, Yuanbo Gu, Qiue Cai, Yang Yang, Chenguang Shen, Xiaohu Li, Ling Peng, Deliang Huang, Jing Zhang, Shurong Zhang, Fuxiang Wang, Jiaye Liu, Li Chen, Shuyan Chen, Zhaoqin Wang, Zheng Zhang, Ruiyuan Cao, Wu Zhong, Yingxia Liu, and Lei Liu declare no competing interests.

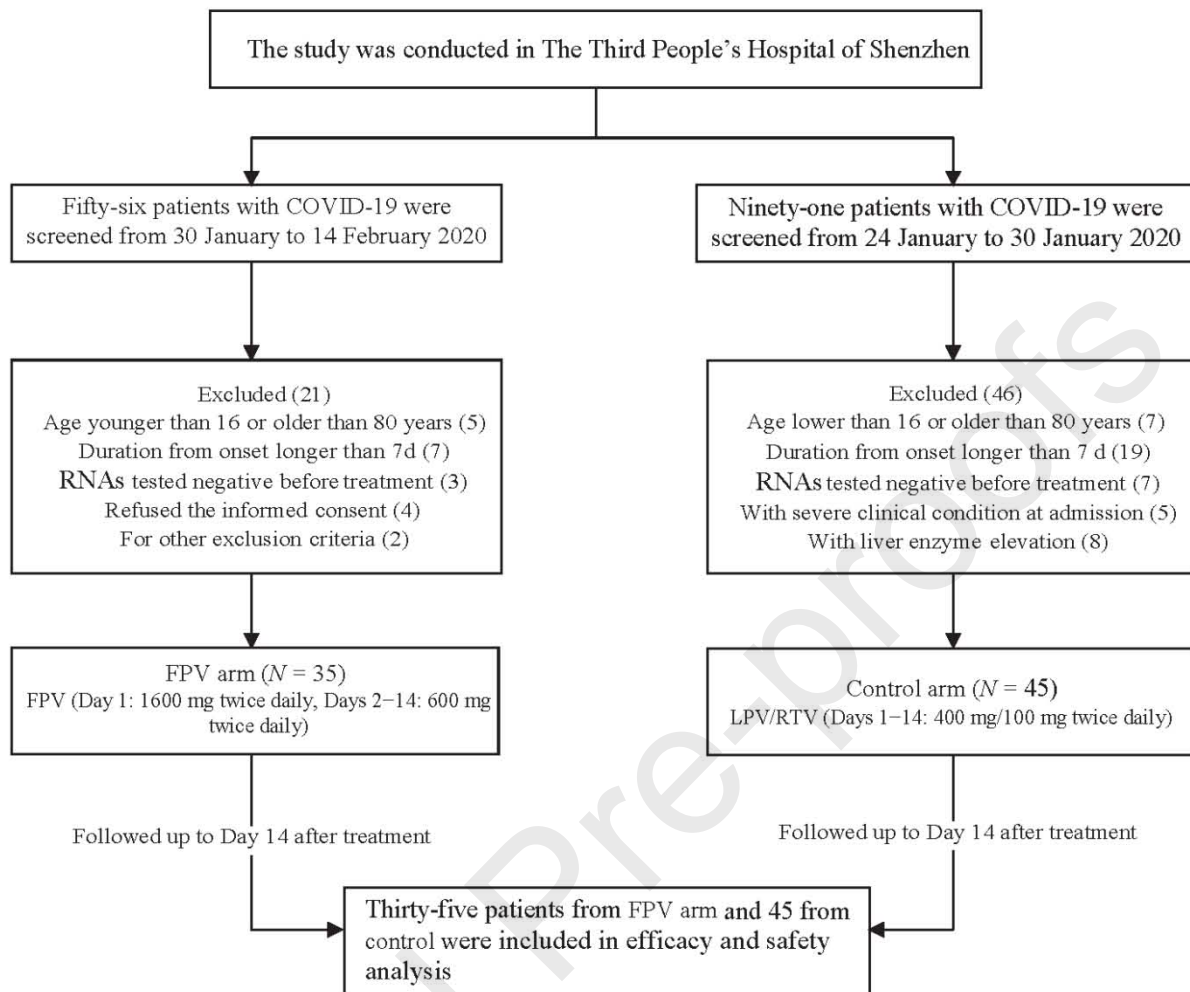
### References

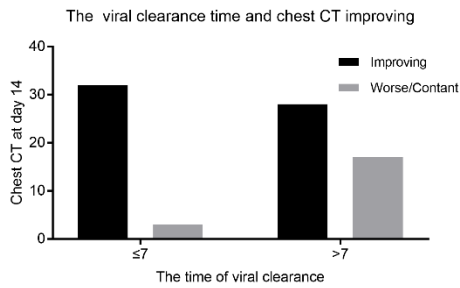
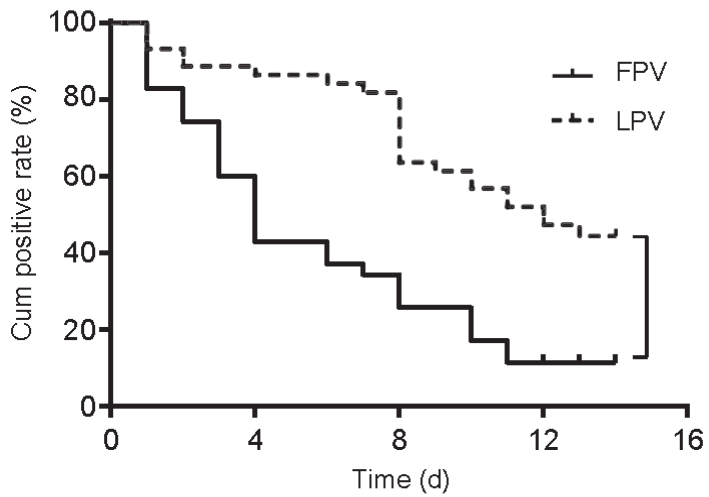
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#### Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: