Darunavir-cobicistat versus lopinavir-ritonavir in the treatment of COVID-19 infection (DOLCI): A multicenter observational study

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Abstract

Background

Coronavirus Disease 2019 (COVID-19) is an evolving pandemic that urged the need to investigate various antiviral therapies. This study was conducted to compare efficacy and safety outcomes of darunavir-cobicistat versus lopinavir-ritonavir in treating patients with COVID-19 pneumonia.

Methods and findings

This retrospective, multicenter, observational study was conducted on adult patients hospitalized in one of the COVID-19 facilities in Qatar. Patients were included if they received darunavir-cobicistat or lopinavir-ritonavir for at least three days as part of their COVID-19 treatments. Data were collected from patients’ electronic medical records. The primary outcome was a composite endpoint of time to clinical improvement and/or virological clearance. Descriptive and inferential statistics were used at alpha level of 0.05. A total of 400 patients was analyzed, of whom 100 received darunavir-cobicistat and 300 received lopinavir-ritonavir. Majority of patients were male (92.5%), with a mean (SD) time from symptoms onset to start of therapy of 7.57 days (4.89). Patients received lopinavir-ritonavir had significantly faster time to clinical improvement and/or virological clearance than patients received darunavir-cobicistat (4 days [IQR 3–7] vs. 6.5 days [IQR 4–12]; HR 1.345 [95%CI: 1.070–1.691], P = 0.011). Patients received lopinavir-ritonavir had significantly faster time to clinical improvement (5 days [IQR 3–8] vs. 8 days [IQR 4–13]; HR 1.520 [95%CI: 1.2–1.925], P = 0.000), and slower time to virological clearance than patients received darunavir-cobicistat (25 days [IQR 15–33] vs. 21 days [IQR 12.8–30]; HR 0.772 [95%CI: 0.607–0.982], P = 0.035). No significant difference in the incidence or severity of adverse events between groups. The study was limited to its retrospective nature and the possibility of covariates, which was accounted for by multivariate analyses.
Conclusion

In patients with COVID-19 pneumonia, early treatment with lopinavir-ritonavir was associated with faster time to clinical improvement and/or virological clearance than darunavir-cobicistat. Future trials are warranted to confirm these findings.

Trial registration

ClinicalTrials.gov number, NCT04425382.

Introduction

Novel Coronavirus Disease 2019 (COVID-19) was first emerged in Wuhan, China, at the end of 2019, resulting in a pandemic crisis [1, 2]. It is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus, that spread rapidly to other countries resulting in more than 150 million confirmed cases and over three million deaths worldwide [3]. The estimated global mortality rate is more than 5.7% posing a significant threat to global health [4]. As of May 01, 2021, there were 206,302 positive cases, 14,766 active cases under treatment and 465 deaths in the country [3].

The spectrum of the infection ranges from mild, self-limiting respiratory symptoms to severe progressive pneumonia, acute respiratory distress syndrome (ARDS) requiring Intensive Care Unit (ICU) admission, and eventually death [5–7]. Numerous candidate agents have been investigated for the treatment of COVID-19 in previous studies at different parts of the world with inconclusive outcomes [8]. Protease inhibitors, developed to treat HIV infections, were studied as potential agents due to their in vitro inhibitory activity against SARS-CoV, Middle East Respiratory Syndrome coronavirus, and SARS-CoV-2 [9–12].

Many studies were conducted to evaluate the safety and efficacy of various protease inhibitors in COVID-19 patients, with lopinavir-ritonavir being the most commonly investigated agent followed by darunavir-cobicistat [13]. However, their use was limited because of side effects and significant drug interactions, mainly due to the inhibition of hepatic cytochrome P450 3A4 and p-glycoprotein [14, 15]. In a report from South Korea, lopinavir-ritonavir showed some efficacy in a patient with COVID-19 [16]. In contrast, in another trial of patients with severe COVID-19, no statistically significant difference was observed in the time to clinical improvement compared to the standard of care group [17].

Darunavir-cobicistat, at high concentration, was also associated with in vitro inhibition of SARS-CoV-2 [12]. It has better safety and tolerability profile than lopinavir-ritonavir [18]. Compared to ritonavir, cobicistat had a lower potential for undesirable drug-drug interactions and a better safety profile [19]. Thus, its efficacy and safety were evaluated in a small pilot study of patients with COVID-19 pneumonia with no significant outcomes [20].

Since the start of the pandemic, multiple organizations and healthcare institutions developed guidelines for the management of patients with COVID-19 infection. These guidelines were continuously updated as new scientific knowledge and research findings emerge [21–24]. In Qatar, we have fifteen versions of treatment guidelines for COVID-19 infection and these guidelines had dramatic changes based on the latest local data and evidence-based recommendations.

Up to our knowledge, no head-to-head study compared darunavir-cobicistat versus lopinavir-ritonavir for treatment of COVID-19 infection. Therefore, this study was conducted to
compare darunavir-cobicistat versus lopinavir-ritonavir’s efficacy and safety outcomes in the treatment of patients with COVID-19 pneumonia.

Materials and methods

Study design

This was a retrospective, multicenter, observational study design, comparing the outcomes of patients who received either darunavir-cobicistat (Rezolsta® [800mg Darunavir/150mg Cobicistat] 1 tablet orally once daily) or lopinavir-ritonavir (Kaletra® [200mg Lopinavir/50mg Ritonavir] 2 tablets orally twice daily) as part of their COVID-19 management according to the national treatment guideline in Qatar.

Ethical consideration

The study was approved by the Institutional Review Board at Hamad Medical Corporation (HMC) Medical Research Center (MRC# 05–069) and registered at ClinicalTrials.gov (NCT04425382). The study was granted a waiver of documentation of consent, in which research information sheets were provided to patients/family members for data collection. No additional administrative permissions were required to access the raw data. All data used in this study were fully anonymized before their use.

Study location and timeline

The study was conducted at HMC, the principal public healthcare organization that provides care to all COVID-19 patients in the State of Qatar. It provides secondary and tertiary care for hospitalized patients in thirteen hospitals across the country. The study was carried out between 1st March 2020 and 29th April 2020.

Study population and sampling method

The study population include hospitalized patients who were 18 years of age or older, with laboratory-confirmed COVID-19 infection, with radiological evidence of pneumonia, and received at least three days of either darunavir-cobicistat or lopinavir-ritonavir as part of the treatment regimen for COVID-19 pneumonia. The use of darunavir-cobicistat and lopinavir-ritonavir was implemented as a standard-of-care in the country and the selection of a particular regimen was made at the discretion of the treating physician.

Diagnosis of COVID-19 infection done by positive RT-PCR assays from nasopharyngeal/oropharyngeal respiratory samples using TaqPath COVID-19 Combo Kit (Thermo Fisher Scientific, Waltham, Massachusetts) or Cobas SARS-CoV-2 Test (Roche Diagnostics, Rotkreuz, Switzerland). Pneumonia was defined as the presence of infiltrate, ground-glass or patchy opacities, or consolidation on the chest x-ray or CT scan imaging.

At the time of the study, treatment regimen for COVID-19 pneumonia in the national guideline included supportive care, chloroquine/hydroxychloroquine, azithromycin, oseltamivir, protease inhibitors, antibiotics, and/or ribavirin. Steroids, pegylated-interferon a2a, or tocilizumab can be added for those with severe disease not responding to other treatment modalities, has evidence of significant systemic inflammation, ARDS, and/or septic shock with evidence of cytokine release syndrome. Regimens were individualized based on the severity of the disease. The intended duration of protease inhibitors as per the treatment protocol was 14 days. No exclusion criteria were applied in this study. All patients admitted in one of the COVID-19 facilities and fulfilled the inclusion criteria were included.
**Outcome measures**

The study’s primary outcome was a composite endpoint of time to clinical improvement and/or virological clearance up to 90 days. Clinical Improvement was defined as the time to normalization of fever (defined as temperature <37.8°C for 72 hours) and/or the resolution of baseline sign and symptoms without the need for symptomatic treatment. Virological clearance was defined as the time to two consecutive negative and/or inconclusive COVID-19 PCR results. These endpoints of clinical improvement and virological clearance were used in previous COVID-19 studies, and the definitions were previously recommended in the World Health Organization (WHO) guideline [25–29]. This study was conducted before the release of the recommended outcome measures for COVID-19 clinical research by the WHO COVID-19 management working group [30].

Secondary outcomes included virological clearance at day 14, day 21, and day 28, clinical deterioration (defined as the need for respiratory support, vasopressor use, corticosteroid/immunomodulation therapy use, or prone positioning), the incidence of adverse events as assessed by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [31], development of ARDS as per Berlin Definition [32], length of hospital-stay, all-cause mortality at 30-days, and the rate of premature discontinuation of study treatment.

**Data collection procedure**

Data were collected from patient’s electronic medical records (Cerner Millennium® Software) by the research investigators and independently validated by different investigators to ensure the accuracy and consistency of the collected data. Variables collected including patients’ demographics, clinical, radiological, and laboratory data.

For baseline signs and symptoms, the onset of symptom date was defined as the day when the first symptom was noticed. The date of resolution of symptoms was defined as the first date without symptoms or the need for symptomatic treatment. The patients’ full medical history, comorbidities, medications details were collected. Electrocardiograms were reviewed to assess QTc intervals at baseline and after starting therapy. Safety data pertaining to the treatment adverse drug reactions (ADRs) and the reasons for premature discontinuation of therapy were also collected. Premature therapy discontinuation was defined as receiving <75% of the planned treatment duration (<11 days). Clinical deterioration was considered an outcome of the study therapy if it occurred ≥ two days from starting protease inhibitors.

**Statistical analysis**

Data were gathered in Excel program. All statistical analyses were done using the statistical package, SPSS version 26 (Armonk, NY: IBM Corp.). Descriptive statistics have been used to summarize patient’s characteristics. Categorical data were expressed by frequency (percentage), while continuous values were expressed as mean ± SD or median and interquartile range (IQR). Data normality was tested using Kolmogorov-Smirnov test. The means of two groups were examined with the Mann–Whitney U or independent t-test (depends on normal distribution of data) and categorical data was analyzed with the chi-square or Fisher’s exact tests (as appropriate). The clinical progresses, i.e. the time to clinical improvement and virological clearance were presented by Kaplan–Meier plot and the difference was compared using a log-rank test. The hazard ratios with 95% confidence intervals were calculated using the Cox proportional-hazards model, which allows other explanatory variables (covariates) to be consideration. A two-sided p-value of <0.05 was considered statistically significant.
Results

Patients’ characteristics

A total of 517 patients were screened, and 400 patients met the eligibility criteria and included in the analysis 100 (25%) patients in the darunavir-cobicistat group and 300 (75%) patients in the lopinavir-ritonavir group. The majority of the patients were male (n = 370, 92.5%), with a mean age of 45.80 years (SD ±12.26). Half of the study population (n = 215, 53.8%) were previously healthy and had no comorbidities, with 85.8% (n = 343) of the patients has normal oxygen saturation at baseline. Study therapy was started within seven days of symptoms onset in 56.6% of the patients.

Table 1 summarized baseline demographic and clinical characteristics of the two groups. Patients in the lopinavir-ritonavir group had younger age (p = 0.006) and fewer comorbidities (p = 0.010) compared with patients in the darunavir-cobicistat group. Around half of the patients who received darunavir-cobicistat received ribavirin therapy (48% vs 7.3%, p = 0.001). Fever, cough, shortness of breath were the most common presenting symptoms in both treatment arms.

Primary outcome

Patients in the lopinavir-ritonavir group had a significantly faster median time to clinical improvement and/or virological clearance than darunavir-cobicistat group (4 days [IQR 3–7] vs. 6.5 days [IQR 4–12]; HR 1.345 [95%CI: 1.070–1.691], p = 0.011). Patients in the lopinavir-ritonavir group had a significantly faster median time to clinical improvement than the darunavir-cobicistat group (5 days [IQR 3–8] vs. 8 days [IQR 4–13]; HR 1.520 [95%CI: 1.2–1.925], p = 0.000), while they have significantly slower time to virological clearance when compared with patients who received darunavir-cobicistat (25 days [IQR 15–33] vs. 21 days [IQR 12.8–30.0]; HR 0.772 [95%CI: 0.607–0.982], p = 0.035). Results of primary outcomes are presented in Fig 1 and Table 2.

Adjustment for covariates

Due to the retrospective nature of the study, multiple confounders might contribute to the observed outcomes. Therefore, the Cox proportional-hazards model was used and adjusted for the statistically significant and clinically relevant baseline variables. Variables were limited to 10 factors to avoid over fitting the model. These factors include the region of origin, age, bilateral radiological abnormalities, infiltration, shortness of breath, time to start of therapy (early vs delayed), CCI of <1, hypertension, oxygen saturation >94% at baseline, and receiving ribavirin therapy.

The results of the primary outcomes after adjustments for covariates were summarized in the supporting information section S1 Table. The Cox’s proportional hazards models for the three outcome measures were significant (p < 0.01). The Kaplan-Meier analysis on the time to primary outcomes was used to compare survival curves using log rank test. The findings indicated that there were significant differences in the survival curves for different covariates.

Secondary outcomes

Table 3 illustrates the results of the secondary outcomes. For the percentage of virological clearance, more patients in the darunavir-cobicistat group had significantly achieved virological clearance at day 21 and day 28 when compared to patients in the lopinavir-ritonavir group. However, the difference in virological clearance was not significant on day 14. Furthermore, third of the patients who received darunavir-cobicistat clinically deteriorated after two days of
Table 1. Baseline characteristics of the study population.

| Characteristic                  | Total       | Lopinavir-Ritonavir (n = 300) | Darunavir-Cobicistat (n = 100) | p-value |
|--------------------------------|-------------|-------------------------------|-------------------------------|---------|
| Demographic Data               |             |                               |                               |         |
| Gender                         |             |                               |                               | 0.273   |
| Male                           | 370 (92.5)  | 280 (93.3)                    | 90 (90)                       |         |
| Age (years)                    | 45.8 ± 12.3 | 44.7 ± 11.4                   | 49.1 ± 14.2                   | 0.006   |
| Age group                      |             |                               |                               | 0.111   |
| < 60 Years                      | 333 (83.3)  | 258 (86)                      | 75 (75)                       |         |
| ≥ 60 Years                     | 67 (16.8)   | 42 (14)                       | 25 (25)                       |         |
| Region of origin               |             |                               |                               | 0.000   |
| South Asia                      | 296 (74)    | 236 (78.7)                    | 60 (60)                       |         |
| Middle East                     | 77 (19.3)   | 44 (14.7)                     | 33 (33)                       |         |
| East Africa                     | 14 (3.5)    | 12 (4)                        | 2 (2)                         |         |
| Europe                          | 8 (2)       | 7 (2.3)                       | 1 (1)                         |         |
| America                         | 5 (1.3)     | 1 (0.3)                       | 4 (4)                         |         |
| Smoking status                  |             |                               |                               | 0.613   |
| Smoker                          | 258 (64.5)  | 192 (64.0)                    | 66 (66)                       |         |
| Ex-smoker                       | 20 (5.0)    | 13 (4.3)                      | 7 (7)                         |         |
| Never smoked                    | 28 (7.0)    | 21 (7)                        | 7 (7)                         |         |
| Unknown                         | 94 (23.5)   | 74 (24.7)                     | 20 (20)                       |         |
| Clinical Data                   |             |                               |                               |         |
| Documented fever                | 308 (77.0)  | 235 (78.3)                    | 73 (73)                       | 0.272   |
| Symptomatic at baseline         | 368 (92.0)  | 275 (91.7)                    | 93 (93.0)                     | 0.670   |
| Fever                           | 366 (91.5)  | 276 (92.0)                    | 90 (90.0)                     | 0.535   |
| Cough                           | 350 (87.5)  | 264 (88.0)                    | 86 (86.0)                     | 0.600   |
| Sore throat                     | 132 (33.0)  | 100 (33.3)                    | 32 (32.0)                     | 0.806   |
| Runny nose                      | 34 (8.5)    | 25 (8.3)                      | 9 (9.0)                       | 0.836   |
| Chest pain                      | 31 (7.8)    | 23 (7.7)                      | 8 (8.0)                       | 0.914   |
| Shortness of breath             | 164 (41)    | 114 (38.0)                    | 50 (50.0)                     | 0.035   |
| Nausea/Vomiting                 | 53 (13.3)   | 34 (11.3)                     | 19 (19.0)                     | 0.050   |
| Diarrhea                        | 32 (8.0)    | 26 (8.7)                      | 6 (6.0)                       | 0.395   |
| On respiratory support at baseline | 57 (14.2) | 31 (10.3)                     | 26 (26)                       | 0.000   |
| Time from onset of symptoms to hospital admission | 5.75 ± 4.65 | 5.55 ± 4.27 | 6.36 ± 5.61 | 0.188 |
| Time from onset of symptoms to start of therapy | 7.57 ± 4.89 | 7.25 ± 4.45 | 8.53 ± 5.93 | 0.052 |
| Early ≤ 7 days                  | 226 (56.6)  | 180 (60)                      | 46 (46.5)                     | 0.018   |
| Delayed >7 days                 | 173 (43.4)  | 120 (40)                      | 53 (53.5)                     |         |
| Duration of therapy (days)      | 13.03 (3.01) | 13.01 (2.82) | 13.08 (3.55) | 0.848 |
| Vital signs                     |             |                               |                               |         |
| Systolic BP                     | 146.5 [26]  | 144 [24]                      | 155 [34]                      | 0.000   |
| Diastolic BP                    | 92 [13]     | 91.0 [12]                     | 94.5 [16]                     | 0.192   |
| Pulse Rate                      | 100 [23]    | 102.0 [23]                    | 101.0 [30]                    | 0.758   |
| Respiratory Rate                | 18 [2]      | 18.0 [2]                      | 19.0 [4]                      | 0.685   |
| Temperature                     | 37.6 [1.4]  | 37.7 [1.3]                    | 37.6 [1.4]                    | 0.823   |
| Oxygen Saturation               | 97.0 [4]    | 97.0 [3]                      | 97.0 [5]                      | 0.036   |
| Laboratory findings            |             |                               |                               |         |
| WBC (x10^9/L)                   | 6.5 [2.9]   | 6.0 [3.1]                     | 6.2 [3.3]                     | 0.804   |
| Lymphocytes (x10^9/L)           | 1.4 [0.7]   | 1.2 [0.6]                     | 1.1 [0.8]                     | 0.115   |
| Neutrophils (x10^9/L)           | 4.2 [2.5]   | 4.2 [2.8]                     | 4.4 [2.6]                     | 0.889   |
| CRP (mg/dL)                     | 51.1 [52.2] | 57.3 [88.4]                   | 63.9 [93.0]                   | 0.573   |

(Continued)
Table 1. (Continued)

| Characteristic                        | Total | Lopinavir-Ritonavir (n = 300) | Darunavir-Cobicistat (n = 100) | p-value |
|---------------------------------------|-------|-------------------------------|-------------------------------|---------|
| Procalcitonin (ng/ml)                 | 0.2 [0.3] | 0.3 [0.9] | 0.4 [0.7] | 0.005 |
| D-Dimer (mg/L)                        | 1.3 [3.3] | 1.1 [1.0] | 0.9 [1.2] | 0.305 |
| Ferritin (ug/L)                       | 704.4 [720.7] | 658.5 [777.3] | 1011.0 [770.0] | 0.006 |
| Serum Creatinine (umol/L)             | 79.1 [20.0] | 86.0 [22.0] | 86.5 [29.0] | 0.055 |
| ALT (U/L)                             | 49.5 [53.7] | 35.0 [27.0] | 30.0 [19.7] | 0.147 |
| AST (U/L)                             | 36.0 [26] | 38.0 [27] | 38.5 [28] | 0.933 |

Radiological finding

|                   | Total | Lopinavir-Ritonavir (n = 300) | Darunavir-Cobicistat (n = 100) | p-value |
|-------------------|-------|-------------------------------|-------------------------------|---------|
| Bilateral Abnormalities | 261 (65.3) | 190 (63.3) | 71 (71) | 0.163 |
| Infiltration       | 142 (35.5) | 118 (39.3) | 24 (24) | 0.006 |
| Ground glass Opacity | 62 (15.5) | 54 (18) | 8 (8) | 0.017 |
| Patchy Opacity    | 226 (56.5) | 162 (54) | 64 (64) | 0.081 |
| Consolidation      | 89 (22.3) | 61 (20.3) | 28 (28) | 0.110 |

Location of Abnormality

|       | Total | Lopinavir-Ritonavir (n = 300) | Darunavir-Cobicistat (n = 100) | p-value |
|-------|-------|-------------------------------|-------------------------------|---------|
| Upper | 15 (3.8) | 14 (4.7) | 1 (1) | 0.043 |
| Middle| 43 (10.8) | 35 (11.7) | 8 (8) | 0.110 |
| Lower | 114 (36) | 110 (36.7) | 34 (34) | 0.081 |
| Upper-Middle | 4 (1) | 4 (1.3) | 0 (0) | 0.017 |
| Lower-Middle | 112 (28) | 78 (26) | 34 (34) | 0.092 |
| All Over | 21 (5.3) | 11 (3.7) | 10 (10) | 0.022 |

Had HRCT scan

|       | Total | Lopinavir-Ritonavir (n = 300) | Darunavir-Cobicistat (n = 100) | p-value |
|-------|-------|-------------------------------|-------------------------------|---------|
| Had baseline ECG | 382 (95.5) | 291 (97.0) | 91 (91.0) | 0.012 |
| QTc Interval (ms) | 425.8 ± 31.2 | 425.7 ± 30.5 | 426.3 ± 33.6 | 0.870 |

Comorbidities

|               | Total | Lopinavir-Ritonavir (n = 300) | Darunavir-Cobicistat (n = 100) | p-value |
|---------------|-------|-------------------------------|-------------------------------|---------|
| No comorbidities | 215 (53.8) | 170 (56.7) | 45 (45) | 0.043 |
| DM            | 115 (28.7) | 79 (26.3) | 36 (36) | 0.064 |
| HTN           | 106 (26.5) | 69 (23) | 37 (37) | 0.006 |
| Dyslipidemia  | 43 (10.8) | 24 (8.0) | 19 (19) | 0.002 |
| CKD (moderate to severe) | 16 (4) | 6 (2.0) | 10 (10.0) | 0.000 |
| MI            | 15 (3.8) | 10 (3.3) | 5 (5.0) | 0.447 |
| COPD/Asthma   | 20 (5.0) | 16 (5.3) | 4 (4.0) | 0.596 |
| Chronic liver disease (moderate to severe) | 2 (0.5) | 0 (0) | 2 (2.0) | 0.062 |
| Solid tumor   | 4 (1) | 1 (0.3) | 3 (3.0) | 0.050 |
| CCI           | 0.59 ± 1.07 | 0.49 ± 0.85 | 0.91 ± 1.53 | 0.010 |

Co-Medications

|               | Total | Lopinavir-Ritonavir (n = 300) | Darunavir-Cobicistat (n = 100) | p-value |
|---------------|-------|-------------------------------|-------------------------------|---------|
| Oseltamivir   | 400 (100) | 300 (100) | 100 (100) | NA |
| Chloroquine/hydroxychloroquine | 399 (99.8) | 299 (99.7) | 100 (100) | 0.563 |
| Azithromycin  | 391 (97.8) | 299 (99.7) | 92 (92) | 0.000 |
| B-lactam antibiotics | 395 (98.8) | 298 (99.3) | 97 (97) | 0.069 |
| Ribavirin     | 70 (17.5) | 22 (7.3) | 48 (48) | 0.000 |
| Anticoagulants | 359 (89.8) | 266 (88.7) | 93 (93) | 0.216 |

Data presented as number (percentage), mean ± standard deviation, or median [interquartile range]
Abbreviations: WBC: White blood cells, CRP: C-Reactive Protein, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, HRCT: High-Resolution Computed Tomography, ECG: Electrocardiogram, DM: Diabetes mellitus, HTN: Hypertension, CKD: Chronic kidney disease, MI: Myocardial infarction, COPD: Chronic obstructive pulmonary disease, CCI: Charlson Comorbidity Index
Note: The total percentage is based on valid percent after considering for missing data; Independent t-test and Chi-square test were used at alpha level = 0.05

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Fig 1. Kaplan-Meier curve for the time to primary outcomes. (A) Time to clinical improvement. (B) Time to viral clearance. (C) Time to first composite of primary outcome.

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therapy, mainly due to the need for corticosteroids/immunomodulation therapy and the need for respiratory support.

Fewer patients in the lopinavir-ritonavir group developed ARDS when compared to patients who received darunavir-cobicistat (p = 0.001). Furthermore, the length of hospital stay was significantly shorter for patients in lopinavir-ritonavir treatment (p = 0.015). All-cause mortality at day 30 was significantly lower in the lopinavir-ritonavir group when compared to the darunavir-cobicistat group (p = 0.001).

**Safety outcomes**

The difference between the two treatment arms in term of incidence of adverse events were not significant except for QTc interval prolongation Table 4. More patients in the darunavir-cobicistat group had prolonged QTc interval > 500 ms (13% vs 2.7%, p = 0.000). Twenty-four ADRs occurred in the lopinavir-ritonavir group, which were mainly due to elevated liver transaminase levels. The majority of reported ADRs were of grade 1 and grade 3 (11 (2.8%) and 10 (2.5%), respectively). The rate of premature therapy discontinuation was not different among both groups.

**Discussion**

This multicenter observational study was the first study to compare the efficacy and safety outcomes of two protease inhibitors used to treat COVID-19 infection. In this study, we found that in hospitalized patients with COVID-19 pneumonia, early treatment with lopinavir-

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**Table 2. Results of the primary study outcomes.**

| Outcome                              | Total    | Lopinavir-Ritonavir | Darunavir-Cobicistat | p-value | Log rank | p-value | HR        | 95% CI     | P-value |
|--------------------------------------|----------|---------------------|----------------------|---------|----------|---------|-----------|-----------|---------|
| Time to clinical improvement (days)  | 5 [3–9]  | 5 [3–8]             | 8 [4–13]             | 0.000   | 14.215   | 0.000   | 1.520     | 1.200–1.925| 0.000   |
| Time to virological clearance (days) | 24 [14–33]| 25 [15.0–33.0]    | 21.0 [12.8–30.0]    | 0.009   | 4.688    | 0.030   | 0.772     | 0.607–0.982| 0.035   |
| Time to composite primary outcome (days) | 5 [3–9] | 4 [3–7]             | 6.5 [4–12]           | 0.000   | 7.547    | 0.006   | 1.345     | 1.070–1.691| 0.011   |

Data presented as median [Interquartile range]

Note: HR = Hazard ratio

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**Table 3. Results of the secondary outcomes.**

| Outcome                              | Total    | Lopinavir-Ritonavir | Darunavir-Cobicistat | p-value |
|--------------------------------------|----------|---------------------|----------------------|---------|
| Virological clearance at day 14      | 113 (28.2)| 79 (26.3)           | 34 (34)              | 0.140   |
| Virological clearance at day 21      | 176 (44) | 123 (41)            | 53 (53)              | 0.036   |
| Virological clearance at day 28      | 256 (64) | 183 (61)            | 73 (73)              | 0.030   |
| Clinical deterioration (composite)   | 100 (25) | 66 (22)             | 34 (34)              | 0.016   |
| Need for respiratory support         | 53 (13.3)| 39 (13)             | 14 (14)              | 0.798   |
| Vasopressor use                      | 17 (4.3) | 10 (3.3)            | 7 (7)                | 0.102   |
| Corticosteroids/ immunomodulation use| 62 (15.5)| 39 (13)             | 23 (23)              | 0.017   |
| Prone positioning                    | 29 (7.2) | 19 (6.3)            | 10 (10)              | 0.221   |
| Development of acute respiratory distress syndrome | 76 (19.0) | 46 (15.3) | 30 (30.0) | 0.001 |
| Length of hospital stay              | 13.71 (17.8)| 12.04 (19.8) | 15.26 (11.5) | 0.001 |
| All-cause mortality at 30-days       | 5 (1.3)  | 0 (0)               | 5 (5.0)              | 0.001   |

Data presented as number (percentage)

Note: The total percentage is based on valid percent after considering for missing data; Mann-Whitney test and Chi-square/Fisher’s Exact test were used at alpha level = 0.05

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ritonavir (within seven days of symptoms onset) in addition to standard of care is associated with a significantly shorter time to clinical improvement and/or virological clearance when compared to treatment with darunavir-cobicistat therapy. The observed effect was mainly attributed to significantly shorter time to clinical improvement (P = 0.000). On the other hand, treatment with lopinavir-ritonavir was associated with a significantly longer time to virological clearance. These results were consistent after adjusting for possible covariates. Our patient population was heterogenous at baseline in terms of severity of the disease and duration of antiviral therapy compared to previously published studies that evaluated the effect of protease inhibitors in COVID-19 separately [16, 17, 20, 33]. After the positive effect of lopinavir-ritonavir use in a COVID-19 patient with mild symptoms in Korea [16], authors recommended its use from the early stage of infection. However, subsequent controlled studies used lopinavir-ritonavir in patients with more severe disease and after seven days of symptoms onset [17, 33]. B.Cao et al. studied the effect of lopinavir-ritonavir is severe COVID-19 infection in which all study population were in respiratory distress at baseline with a median time from symptoms onset to start of therapy of 13 days [17]. Additionally, 74% of patients in the RECOVERY trial required respiratory support at baseline and treatment was started within eight days of symptoms onset, which could have contributed to the negative effect of the treatment in both studies [33]. It is important to note the importance of early initiation of antiviral therapy during the viral replication phase of COVID-19 pathogenesis over the host inflammatory response phase, which can be translated into the lack of clinically significant anti-SARS-CoV-2 activity if used in late or severe stages of the disease [34]. This hypothesis was also emphasized in the National Institutes of Health COVID-19 Treatment Guideline where the role of antiviral medications in treating mild, moderate, severe, and critical illness was stressed in order to optimize the treatment for people with COVID-19 [A]. In our study, only 14.2% of the population had the severe disease at baseline and the median time from symptoms onset to start therapy was approximately 7 days, which could contribute to the significant effect observed.

Table 4. Safety outcomes of the study population.

| Outcome | Total | Lopinavir-Ritonavir | Darunavir-Cobicistat | P value |
|---------|-------|---------------------|---------------------|--------|
| Incidence of adverse events | 28 (7.2) | 23 (8.0) | 5 (5.0) | 0.316 |
| Type of ADR: | | | | 0.219 |
| Elevated liver transaminase levels | 21 (5.3) | 19 (6.3) | 2 (2.0) | |
| PR prolongation | 1 (0.3) | 1 (0.3) | 0 (0) | |
| Renal impairment | 5 (1.3) | 2 (0.7) | 3 (3.0) | |
| Neutropenia | 1 (0.3) | 1 (0.3) | 0 (0) | |
| QTc interval prolongation | | | | |
| QTc prolongation > 500 | 21 (5.3) | 8 (2.7) | 13 (13.0) | 0.000 |
| QTc prolongation > 550 | 7 (1.8) | 3 (1.0) | 4 (4.0) | 0.048 |
| Grade of ADR: | | | | 0.749 |
| Grade 1 | 11 (2.8) | 9 (3.0) | 2 (2.0) | |
| Grade 2 | 7 (1.8) | 5 (1.7) | 2 (2.0) | |
| Grade 3 | 10 (2.5) | 9 (3.0) | 1 (1.0) | |
| Grade 4 | 1 (0.3) | 1 (0.3) | 0 (0) | |
| Time to ADRs development | 9.0 [3.5] | 9.0 [3] | 10.0 [3.0] | 0.114 |
| Rate of premature discontinuation of study treatment | 70 (17.5) | 51 (17.0) | 19 (19.0) | 0.649 |
| Reason for premature discontinuation | | | | 0.658 |
| ADR | 29 (7.2) | 24 (8.0) | 5 (5.0) | |
| Drug interaction | 3 (0.8) | 2 (0.7) | 1 (1.0) | |
| Others | 73 (18.3) | 52 (17.3) | 21 (21.0) | |
Treatment with darunavir-cobicistat was associated with faster virological clearance and higher rate of negative conversion of SARS CoV-2 at day 21 and day 28 compared to lopinavir-ritonavir. These findings are in line with previous evidence showing that the median duration of COVID-19 viral shedding in patients with mild-moderate disease is 20 days [35].

Protease inhibitors are mainly used for the treatment of HIV infection by binding to the HIV-1 protease activity site. This led to the inhibition of the viral Gag-Pol precursors cleavage into individual functional proteins, resulting in a noninfectious, immature viral particles [36]. In fact, the target protease enzymes involved by HIV and SARS-CoV-2 are different, as the HIV protease is an aspartic protease, whereas SARS-CoV-2 is a cysteine protease [37]. Both darunavir/cobicistat and lopinavir/ritonavir were proposed as a candidate therapies for COVID-19 as they inhibit the enzymes that activate envelope glycoproteins as part of the viral entry process. Furthermore, Both drugs have been shown to bind well to the SARS-CoV 3C-like protease (3CLpro), which is involved in the viral replication process [38]. Nevertheless, they are likely to behave differently in the treatment of COVID-19 patients and also to display different side effects. In some articles lopinavir was found to have a higher theoretical affinity for SARS-CoV-2 3CLpro than that of darunavir [39, 40], while others showed that darunavir has larger binding free energies to SARS-CoV-2 3CLpro [41–43]. Therefore, the exact mechanism by which these drugs may contribute to virological clearance of SARS-CoV-2 remains to be elucidated.

Additionally, our study showed that patients in the darunavir-cobicistat group had more clinical deteriorations, more incidence of ARDS, and all-cause mortality at day 30. However, it is unclear whether the observed difference is due to the antiviral therapy or the concomitant medications (ex. ribavirin) or the baseline clinical status of the patients. In a recent retrospective report conducted in Qatar, the use of darunavir-cobicistat plus ribavirin was associated with a more complicated course in term of the need for ICU admission, intubation, and progression to ARDS [44]. Furthermore, it is important to note that patients who received darunavir-cobicistat had older age, more comorbidities, and more severe disease at baseline. Therefore, these findings are mainly hypothesis-generating and need to be confirmed in well-conducted randomized trials.

The overall mortality rate in our study was very low (1.3%), which is substantially lower than the mortality reported in previous studies (20–23%) [17, 33]. This indicates the milder disease the patients had and reflects the relatively low mortality rate in the country.

The safety profile in this study was somewhat consistent with the previous studies. Our study is the first one that assessed the effect of protease inhibitors on QTc interval prolongation [17, 33].

Both drugs were well-tolerated, and the majority of the ADRs that led to premature treatment discontinuation were of grade 1 and were due to the elevation of liver transaminases.

Our study, which is the first to compare the clinical, laboratory, virological, and radiological outcomes of two protease inhibitors in COVID-19, has several limitations. First, the retrospective observational nature of the study. Multivariate analyses were used to evaluate the association of possible covariates on study outcomes. Additionally, only adverse events that led to treatment discontinuation were reported, and details about side effects (ex. gastrointestinal side effects) occurring during the treatment course were not collected. These side effects are well-known and have been studied and reported in previous studies [17].

Conclusion
In hospitalized patients with COVID-19 pneumonia, early treatment with lopinavir-ritonavir was associated with significantly faster time to clinical improvement and/or virological
clearance than darunavir-cobicistat. Treating patients with lopinavir-ritonavir resulted in a faster time to clinical improvement, while treating patients with darunavir-cobicistat resulted in a faster clearance of the virus. The safety profile of both protease inhibitors was comparable, with more incidence of QTc interval prolongation, ARDS development, clinical deterioration, and mortality in darunavir-cobicistat group. Future prospective trials are warranted to confirm these findings.

Supporting information
S1 Table. Results of primary outcome after adjustments for covariates.
(DOCX)
S1 Dataset. Minimal data set.
(XLSX)

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References
1. Yang Y, Lu Q, Liu M, et al. Epidemiological and clinical features of the 2019 novel coronavirus outbreak in China. https://doi.org/10.1101/2020.02.10.20021675
2. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents. 2020 Feb 17;105924. https://doi.org/10.1016/j.ijantimicag.2020.105924 PMID: 32081636
3. WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data [Internet]. [cited 2021 May 01]. Available from: https://covid19.who.int/
4. Baud D, Qi X, Nielsen-Saines K, Musso D, Pomar L, Favre G. Real estimates of mortality following COVID-19 infection. Lancet Infect Dis 2020, https://doi.org/10.1016/S1473-3099(20)30195-X PMID: 32171390
5. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395: 507–13. https://doi.org/10.1016/S0140-6736(20)30211-7 PMID: 32007143
6. Liu K, Fang YY, Deng Y, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin Med J (Engl) 2020 February 7. https://doi.org/10.1097/CM9.000000000000744 PMID: 32044814

7. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7042881/?report=reader https://doi.org/10.1001/jama.2020.1585 PMID: 32031570

8. WHO. Landscape Analysis of COVID Therapeutics as 21 March 2020.; 2020. Available from: https://www.who.int/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf?ua=1.

9. Chu CM, Cheng VC, Hung IF, et al. Role of Lopinavir-Ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax 2004; 59: 252–6. https://doi.org/10.1136/thorax.2003.012658 PMID: 14985565

10. Chen F, Chan KH, Jiang Y, et al. In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J Clin Virol 2004; 31: 69–75. https://doi.org/10.1016/j.jcv.2004.03.003 PMID: 15288617

11. Wu C-Y, Jan J-T, Ma S-H, et al. Small molecules targeting severe acute respiratory syndrome human coronavirus. Proc Natl Acad Sci U S A 2004; 101: 10012–7. https://doi.org/10.1073/pnas.0403596101 PMID: 15226499

12. Yamamoto N, Matsuyama S, Hoshino T, et al. Nelfinavir inhibits replication of severe acute respiratory syndrome coronavirus 2 in vitro. bioRxiv. Posted Apr 8, 2020. Preprint (not peer re-viewed). https://doi.org/10.1101/2020.04.06.026476

13. Review R. Should protease inhibitors be used for COVID-19? 2021; 14(March 2020): 1–7.

14. Zeldin RK, Petruschke RA. Pharmacological and therapeutic properties of ritonavir-boosted protease inhibitor therapy in HIV-infected patients. J Antimicrob Chemother. 2004; 53:4–9. Epub 2003/12/06. https://doi.org/10.1093/jac/dkh029 PMID: 14657084

15. Renjifo B, van Wyk J, Salem AH, Bow D, Ng J, Norton M. Pharmacokinetic enhancement in HIV antiretroviral therapy: a comparison of ritonavir and cobicistat. AIDS reviews. 2015; 17:37–46. Epub 2015/01/15. PMID: 25586481

16. Lim J, Jeon S, Shin HY, et al. Case of the Index Patient Who Caused Tertiary Transmission of COVID-19 Infection in Korea: the Application of Lopinavir-Ritonavir for the Treatment of COVID-19 Infected Pneumonia Monitored by Quantitative RT-PCR. J Korean Med Sci. 2020; 35(6):e79. https://doi.org/10.3346/jkms.2020.35.e79 PMID: 32056407

17. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020:1–13. https://doi.org/10.1056/NEJMoa2001282 PMID: 32187464

18. Orkin C, DeJesus E, Khanlou H, et al. Final 192-week efficacy and safety of once daily darunavir/ritonavir compared with Lopinavir-Ritonavir in HIV-1-infected treatment-naive patients in the ARTEMIS trial. HIV Med 2013; 14:49–59. https://doi.org/10.1111/j.1468-1293.2012.01060.x PMID: 23088336

19. Deeks ED. Cobicistat: a review of its use as a pharmacokinetic enhancer of atazanavir and darunavir in patients with HIV-1 infection. Drugs. 2014; 74 (2):195–206. https://doi.org/10.1007/s40265-013-0160-x PMID: 24343782

20. Chen J, Xia L, Liu L, et al. Antiviral Activity and Safety of Darunavir / Cobicistat for the Treatment of COVID-19. 2020:1–5. https://doi.org/10.1093/ofid/ofaa24

21. COVID-19 Treatment Guidelines 2. [cited 2022 Jan 10]; Available from: https://www.covid19treatmentguidelines.nih.gov/

22. IDSA Guidelines on the Treatment and Management of Patients with COVID-19 [Internet]. [cited 2022 Jan 10]. Available from: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

23. Therapeutics and COVID-19: living guideline [Internet]. [cited 2022 Jan 10]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.1

24. D. Management of Patients with Confirmed 2019-nCoV | CDC [Internet]. [cited 2022 Jan 10]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html

25. Walsh KA, Jordan K, Clyne B, et al. SARS-CoV-2 detection, viral load and infectivity over the course of an infection. Vol. 81, Journal of Infection. W.B. Saunders Ltd; 2020. Available from: /pmc/articles/PMC7323671/https://doi.org/10.1016/j.jinf.2020.06.067 PMID: 32815199

26. Xu W, Piper-Vallillo AJ, Bindal P, et al. Time to SARS-CoV-2 clearance among patients with cancer and COVID-19. Cancer Med. 2021 Feb 9. https://doi.org/10.1002/cam4.3708 PMID: 33560590

27. WHO | Laboratory testing for Middle East Respiratory Syndrome Coronavirus. WHO 2018; Available from: http://www.who.int/csr/disease/coronavirus_infections/mers-laboratory-testing/en/
28. Almazeedi S, Al-Youha S, Jamal MH, et al. Characteristics, risk factors and outcomes among the first consecutive 1096 patients diagnosed with COVID-19 in Kuwait. EClinicalMedicine. 2020 Jul 1; 24. Available from: https://doi.org/10.1016/j.eclinm.2020.100448

29. Gottlieb RL, Nirula A, Chen P, et al. Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19. JAMA. 2021 Feb 16; 325(7):632. Available from: https://jamanetwork.com/journals/jama/fullarticle/2775647 https://doi.org/10.1001/jama.2021.0202 PMID: 33475701

30. Marshall JC, Murthy S, Diaz J, et al. Personal View A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis. 2020; Available from: www.thelancet.com/infectionPublishedonline

31. Cancer Therapy Evaluation Program (CTEP). Common Terminology Criteria for Adverse Events (CTCAE). v.5.0 [5x7]. Cancer Ther Eval Prgr. 2017:155. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50.

32. The ARDS Definition Task Force. Acute Respiratory Distress Syndrome: The Berlin Definition. JAMA 2012; May 21, 2012. https://doi.org/10.1001/jama.2012.14126 PMID: 23168824

33. Horby PW, Maham M, Bell JL, et al. Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2020; 396(10259):1345–52. https://doi.org/10.1016/S0140-6736(20)32013-4 PMID: 33031764

34. Cevik M, Kuppalii K, Kindrachuk J, et al. Virology, transmission, and pathogenesis of SARS-CoV-2. BMJ. 2020; 371:1–6.

35. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet [Internet]. 2020; 395(10229):1054–62. Available from: https://doi.org/10.1016/S0140-6736(20)30566-3 PMID: 32171076

36. Destache CJ. Brain as an HIV sequestered site: Use of nanoparticles as a therapeutic option. Prog Brain Res. 2009; 180(C):225–33. https://doi.org/10.1016/S0079-6123(08)80012-X PMID: 20302837

37. Magro P, Zanello I, Pescarolo M, Castelli F, Quiros-Roldan E. Lopinavir/ritonavir: Repurposing an old drug for HIV infection in COVID-19 treatment. Biomed J. 2021 Feb 1; 44(1):43–53. https://doi.org/10.1016/j.bi.2020.11.005 PMID: 33608241

38. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet [Internet]. 2020; 395(10229):1054–62. Available from: https://doi.org/10.1016/S0140-6736(20)30566-3 PMID: 32171076

39. Lin S, Shen R, He J, Li X, Guo X. Molecular Modeling Evaluation of the Binding Effect of Ritonavir, Lopinavir and Darunavir to Severe Acute Respiratory Syndrome Coronavirus 2 Proteases. bioRxiv [Internet]. 2020 Feb 18 [cited 2022 Jan 10];2020.01.31.929695. Available from: https://www.biorxiv.org/content/10.1101/2020.01.31.929695v2

40. Beck BR, Shin B, Choi Y, Park S, Kang K. Predicting commercially available antiviral drugs that may act on the novel coronavirus (SARS-CoV-2) through a drug-target interaction deep learning model. Comput Struct Biotechnol J [Internet]. 2020 Jan 1 [cited 2022 Jan 14]; 18:784–90. Available from: https://pubmed.ncbi.nlm.nih.gov/32280433/ https://doi.org/10.1016/j.csbj.2020.03.025 PMID: 32280433

41. Sang P, Tian S-H, Meng Z-H, Yang L-Q. Anti-HIV drug repurposing against SARS-CoV-2 †. 2020 [cited 2022 Jan 10]; Available from: http://www.pdb.org

42. Khan SA, Zia K, Ashraf S, Uddin R, Ul-Haq Z. Identification of chymotrypsin-like protease inhibitors of SARS-CoV-2 via integrated computational approach. J Biomol Struct Dyn [Internet]. 2021 [cited 2022 Jan 17]; 39(7):2607–16. Available from: https://pubmed.ncbi.nlm.nih.gov/32238094/ https://doi.org/10.1080/07391102.2020.1751298 PMID: 32238094

43. Ngo ST, Quynh Anh Pham N, Thi Le L, Pham DH, Vu V. Computational Determination of Potential Inhibitors of SARS-CoV-2 Main Protease. J Chem Inf Model [Internet]. 2020 Dec 28 [cited 2022 Jan 17]; 60(12):5771–80. Available from: https://pubmed.ncbi.nlm.nih.gov/32530282/ https://doi.org/10.1021/acs.jcim.0c00491 PMID: 32530282

44. Elajez R, Abdullah O, Alnaimi S, et al. Exploring Potential Synergism Between Darunavir/Cobicistat and Ribavirin for the Treatment of Covid-19 Patients: A Retrospective Comparison Study. Open Access J Biomed Sci. 2021; 3(5):880–6.