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Efficacy and Safety of Atazanavir/Ritonavir Versus Lopinavir/Ritonavir in Hospitalized COVID-19 Patients: A Randomized Clinical Trial

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Abstract

Background: While several antivirals have been considered among the candidate repurposed drugs against SARS-CoV-2 infection, limited evidence exists on Atazanavir/Ritonavir.

Objectives: This trial was designed to assess the efficacy of Atazanavir/Ritonavir compared to Lopinavir/Ritonavir, another antiretroviral drug investigated in the previous studies.

Methods: This randomized, double-blind clinical trial was conducted on hospitalized patients with laboratory or confirmed SARS CoV-2 infection. Patients were randomly assigned (1:1) to receive either Lopinavir/Ritonavir (200mg Lopinavir+50mg Ritonavir, twice a day) or Atazanavir/Ritonavir (300mg Atazanavir+100 mg Ritonavir, once a day) for up to 14 days during their admission along with the standard care. The primary endpoint was total all-cause death in all patients during the hospitalization period. Secondary outcomes included length of hospitalization.

Results: Out of 103 adults included in the analysis 54 and 49 were assigned to Atazanavir/Ritonavir and Lopinavir/Ritonavir groups, respectively. The occurrence of adverse effects, defined as symptoms attributed to the drugs which no longer appear upon the cessation of the drug, was higher for cardiac side effects in Atazanavir/Ritonavir group. No statistically significant difference was observed between the two groups in terms of the length of hospitalization. After adjustment for other covariates in the study, treatment with Atazanavir/ritonavir did not result in a significant reduction in mortality compared to treatment with Lopinavir/Ritonavir.

Conclusion: The efficacy of Atazanavir/Ritonavir in this preliminary study was not superior to Lopinavir/Ritonavir in reducing mortality and length of hospitalization in COVID-19 patients. However, the limited efficacy of both compounds does not support their use in primary care for COVID-19 patients.

Keywords: Atazanavir, COVID-19, Lopinavir/Ritonavir, Randomized clinical trial, SARS-CoV-2

1. Background

The emergence of the novel member of coronaviruses, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in December 2019 led to the worldwide pandemic of Coronavirus disease 2019 (COVID-19). Infection with SARS-CoV-2 manifests itself in a wide spectrum of clinical presentations, ranging from asymptomatic infection and mild respiratory illness to severe pneumonia, multiorgan failure, and death (1). The symptomatic individuals demonstrate influenza-like symptoms, which may progress to hypoxemic failure requiring prolonged ventilatory support in some patients (2). Although many novel treatment modalities are currently being investigated, the efficacy of available therapeutic agents remains unsatisfactory. Therefore, the attempts to repurpose previously-approved medications to combat the disease might reduce the increasing mortality rates by rapidly formulating an effective treatment regimen.

The initial efforts towards the development of an effective treatment regimen against this viral infection focused on repurposing medications with previous *in vitro* activity against other coronaviruses (3,4). In this regard, targeting the Main protease (Mpro) enzyme of SARS-CoV-2 with repurposed antivirals, such as Lopinavir/ritonavir was the topic of several studies and comprised a large proportion of previous trials (1,5-7). The results of the trials conducted on this combined HIV protease inhibitor did not demonstrate a significant benefit over the standard of care for COVID-19; however, the evidence is limited regarding Atazanavir/Ritonavir which is another combined antiretroviral protease inhibitor.

In silico analyses in previous studies have demonstrated that the Mpro of SARS-CoV-2 is better targeted by Atazanavir, compared to Lopinavir which was later confirmed in *in vitro* studies (4). Furthermore, Atazanavir is reported to have fewer side effects and a safer profile, compared to Lopinavir in anti-HIV medications (4,8-10). Therefore, the existing evidence suggests that Atazanavir is a promising candidate for drug repurposing in COVID-19 and may outperform Lopinavir in combination with ritonavir, which increases the concentration of

its combined medication by acting as an inhibitor of cytochrome P450-mediated drug metabolism (4).

2. Objectives

This trial was conducted to evaluate the efficacy and safety of oral Atazanavir/ritonavir, compared to lopinavir/ritonavir for SARS-CoV-2 infection in hospitalized COVID-19 patients.

3. Methods

3.1. Trial Design and participants

This double-blind, single-center, randomized clinical trial was conducted in a university hospital. The trial was registered and approved by the Ethics Committee of Alborz University of Medical Sciences.

Eligible patients have hospitalized adults aged between 20 and 80 years who were diagnosed with COVID-19 with high-resolution computed tomography and suspected history and symptoms or positive SARS-CoV-2 RT-PCR test from nasal and pharyngeal swabs. Patients with elevated liver enzymes, persistent nausea and vomiting, and altered mental status were excluded. Consent was obtained upon admission from the patients or their legal representatives when applicable. The patients were free at any time to opt-out of the trial to continue receiving the standard of care. Data at baseline, patient demographics, concomitant diseases, symptoms upon admission, randomized group assignment, transfer to intensive care unit (ICU), and outcome data were acquired using patient medical records following their discharge or death. The flowchart of the study and the screening process of the study population is available in Figure 1.

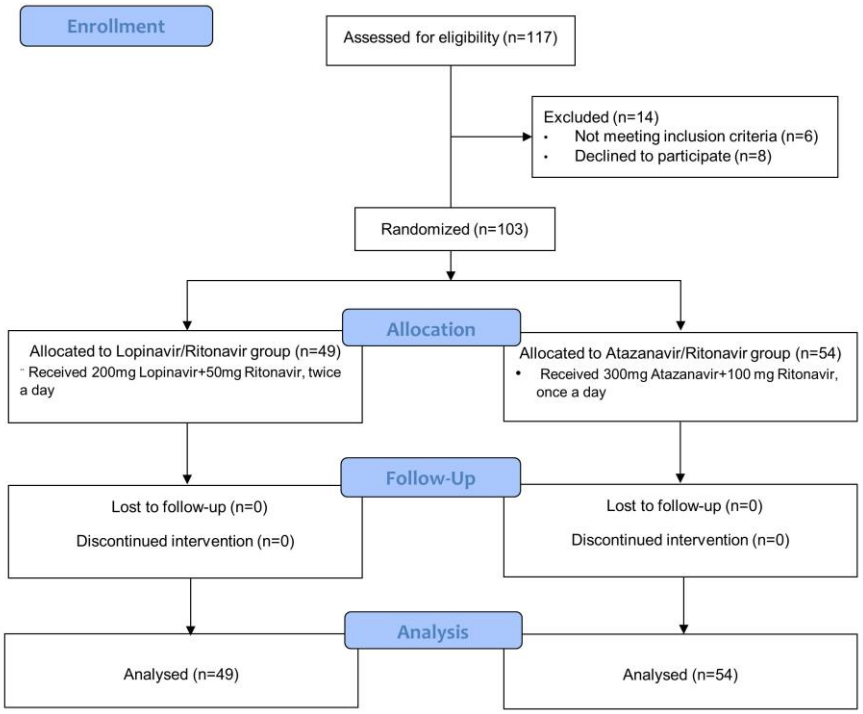

Figure 1. CONSORT Flowchart of the trial population

3.2. Randomization and Intervention

Participants were randomly assigned to Atazanavir/Ritonavir or Lopinavir/Ritonavir in a 1:1 ratio using a six-unit permuted block randomization with concealment of group assignment. The randomization was conducted in STATA software version 17 by generating random numbers for each included participant.

Pharmacological intervention for each group were administrated as tablets in medicine boxes labeled as A (Lopinavir/Ritonavir) and B (Atazanavir/ Ritonavir) by nurses uninvolved in the trial. The participants of each group were also assigned to different wards. Therefore, the trial investigators and patients were both blind to treatment assignment. Patients' compliance was confirmed with a timetable for the administration of the assigned drug. Patients were to receive IV glucocorticoids (methylprednisolone) based on worsening clinical status and the decision of the attending physician.

The treatment regimen for Atazanavir/Ritonavir (300mg Atazanavir+100 mg Ritonavir, once a day) and Lopinavir/Ritonavir (200mg Lopinavir+50mg Ritonavir, twice a day) groups continued for 14 days after randomization, patient discharge, or death. Cardiovascular (Tachycardia unrelated to sepsis, fever, or pneumonia and heart conduction problems)

and gastrointestinal (Hyperbilirubinemia, abnormal liver function test, abdominal pain, diarrhea, and constipation) adverse effects attributed to the drug use, not noted prior to admission, and unexplained by the ongoing disease which were observed until the cessation of the intervention were documented for each group by an expert clinician.

Patients were assessed upon admission and day 7 after randomization for serum levels of creatinine, blood urea nitrogen, C-reactive protein, and erythrocyte sedimentation rate. Measurements were done on blood samples that were collected in serum clot activator tubes. The samples were then assayed using standard commercial kits.

3.3. Outcomes and statistical analysis

As this study compared the effectiveness of Atazanavir/Ritonavir against Lopinavir/Ritonavir in a pilot randomized trial setting, a sample size of 103 participants was selected which was more than sufficient. The aim was to detect a clinically significant effect size of 20% between groups, using a two-sided Z-test of the difference between proportions with 90% power and a significance of 5% (11).

The primary outcome was designated as all-cause patient mortality during their hospitalization period in all patients who had undergone randomization and was analyzed using a logistic regression model and demonstrated using a Kaplan-Meier curve. The effectiveness of treatment assignment on outcome was derived from the odds ratio and 95% confidence interval (CI) adjusted for age and gender. The secondary analysis included the length of hospitalization in participants assessed by a linear regression model. The significance of a change in laboratory test results for each group was also analyzed using linear regression. All analyses were subsequently adjusted for age and gender as covariates. It should be mentioned that a *p*-value below 0.05 was considered to be significant. All statistical analysis models were performed in SPSS software (version 18).

4. Results

A total of 103 patients were included in the trial between 14 and 30 June 2020 with 54 patients receiving Atazanavir/Ritonavir and 49 patients receiving Lopinavir/Ritonavir. The mean age (±SD) of the included participants in this study was 58.88±15.45. A history of diabetes, hypertension, coexisting respiratory diseases (Asthma, Chronic obstructive pulmonary disease, and Interstitial lung diseases), hypercholesterolemia/hypertriglyceridemia, heart disease, and kidney disease were present in 20%, 39.8%, 10.7%, 3.9%, 12.6%, and 2.9% of the patients, respectively. It should be mentioned that laboratory results were not significantly different in the two groups. The ICU transfer throughout the study was significantly lower in Atazanavir/Ritonavir group, occurring in six patients in Atazanavir/Ritonavir group versus 16 patients in Lopinavir/Ritonavir (Table 1).

Table 1. Baseline characteristics, demographics, and comorbidities observed during the trial period in participants

Variables	Total (n=103)	Group Assignment		*P*-value
		Lopinavir/Ritonavir (n=49)	Atazanavir/Ritonavir (n=54)	
Age				
Mean±SD	58.88±15.45	62.29±15.36	55.80±15.00	0.033[a]
<59	49 (47.6 %)	21 (42.9 %)	28 (51.9 %)	0.361[b]
>=59	54 (52.4 %)	28 (57.1 %)	26 (48.1 %)	
Gender, N (%)				0.161[b]
Male	64 (62.1 %)	27 (55.1 %)	37 (68.5 %)	
Female	39 (37.9 %)	22 (44.9 %)	17 (31.5 %)	
Comorbidities, N (%)				
Any	63 (61.2 %)	32 (65.3 %)	31 (57.4 %)	0.416[b]
Hypertension	41 (39.8 %)	20 (40.8 %)	21 (38.9 %)	0.844[b]
Respiratory disease	11 (10.7 %)	8 (16.3 %)	3 (5.6 %)	0.086[b]
Diabetes mellitus	20 (19.4 %)	11 (22.4 %)	9 (16.7 %)	0.466[b]
Hypercholesterolemia/hypertriglyceridemia	4 (3.9 %)	2 (4.1 %)	2 (3.7 %)	0.922[b]
Heart disease	13 (12.6 %)	8 (16.3 %)	5 (9.3 %)	0.291[b]
Kidney disease	3 (2.9 %)	1 (2.0 %)	2 (3.7%)	0.616[b]
Signs and symptoms upon admission (%)				
Headache	18 (17.5 %)	6 (12.2 %)	12 (22.2 %)	0.205[b]
Myalgia	31 (30.1 %)	10 (20.4 %)	21 (38.9 %)	0.053[b]
Cough	81 (78.6 %)	39 (79.6 %)	42 (77.8 %)	0.756[b]
Dyspnea	96 (93.2 %)	47 (95.9 %)	49 (90.7 %)	0.441[b]
Diarrhea	8 (7.8 %)	1 (2.0 %)	7 (13.0 %)	0.062[b]
Nausea/Vomiting	17 (16.5 %)	7 (14.3 %)	10 (18.5 %)	0.605[b]
O2 Saturation assessed by pulse oximetry at baseline, N (%)				0.002[b]
Low<90%	48 (46.6 %)	16 (32.7 %)	32 (59.3 %)	
90%< Medium<93%	30 (29.1 %)	14 (28.6 %)	16 (29.6 %)	
High>93%	25 (24.3 %)	19 (38.8 %)	6 (11.1 %)	

Table 1. Continued					
Glucocorticoid use, N (%)					0.070[b]
Yes		68 (66.0 %)	28 (57.1 %)	40 (74.1 %)	
ICU transfer, N (%)					0.008[b]
Yes		22 (21.4 %)	16 (32.7 %)	6 (11.1 %)	
Biochemical profile and laboratory results	Evaluation time				
CR (mg/dl)	Upon admission	1.11±0.33	1.05±0.27	1.16±0.37	0.088[a]
BUN (mg/dl)	Upon admission	16.49±8.39	16.03±8.59	16.88±8.27	0.622[a]
CRP (mg/dl)	Upon admission	75.58±55.45	65.50±37.23	84.77±67.06	0.100[a]
ESR (ml/hr)	Upon admission	58.84±27.92	64.54±28.32	54.08±26.95	0.077[a]
CR (mg/dl)	After one week	1.13±0.46	1.05±0.43	1.22±0.49	0.281[a]
BUN (mg/dl)	After one week	25.53±18.62	23.51±17.05	28.08±20.75	0.486[a]
CRP (mg/dl)	After one week	42.29±45.55	51.68±38.83	27.26±55.92	0.370[a]
ESR (ml/hr)	After one week	55.90±39.69	55.00±32.23	56.80±50.03	0.948[a]

CR: Creatinine, BUN: Blood Urea Nitrogen, CRP: C-Reactive Protein, ESR: Erythrocyte Sedimentation Rate, PCT: Procalcitonin a: independent t-test, b: Pearson chi-square test

4.1. Outcomes and safety

The primary endpoint occurred in three (5.6%) patients in Atazanavir/Ritonavir group and 13 (26.5%) patients in Lopinavir/Ritonavir group (Figure 2), with a hazard ratio of 0.26 (95% CI: 0.05 - 1.20; *p*-value=0.101) adjusted for age and gender at baseline. Furthermore, regardless of group assignment, the primary outcome was also associated with other variables in this study including age (*p*-value=0.006), headache (*p*-value=0.038) and blood urea nitrogen (BUN, *p*-value=0.001) upon admission, creatinine (*p*-value=0.047) and BUN (*p*-value=0.022) one week after enrollment, and ICU transfer (*p*-value<0.001) assessed via two-sided independent t-test and Pearson chi-square test (Table 2).

Drug adverse effects were similarly observed in 20 participants, with 8 of them being in Lopinavir/Ritonavir group and 12 of them in Atazanavir/Ritonavir. Gastrointestinal and cardiac side effects were observed in seven and one patients in the Lopinavir/Ritonavir group and six and seven patients in the Atazanavir/Ritonavir group, respectively (Table 3; indicating a higher incidence of cardiac side effects in Atazanavir/Ritonavir group (Table 4). Hospitalization length (days) was numerically shorter for Atazanavir/Ritonavir vs. Lopinavir/Ritonavir (6.37±3.50 vs. 8.29±6.81, respectively); however, statistical analysis revealed no difference between groups (B: 1.89; 95% CI: -0.12, 4.07, *p*-value=0.195) (Table 3).

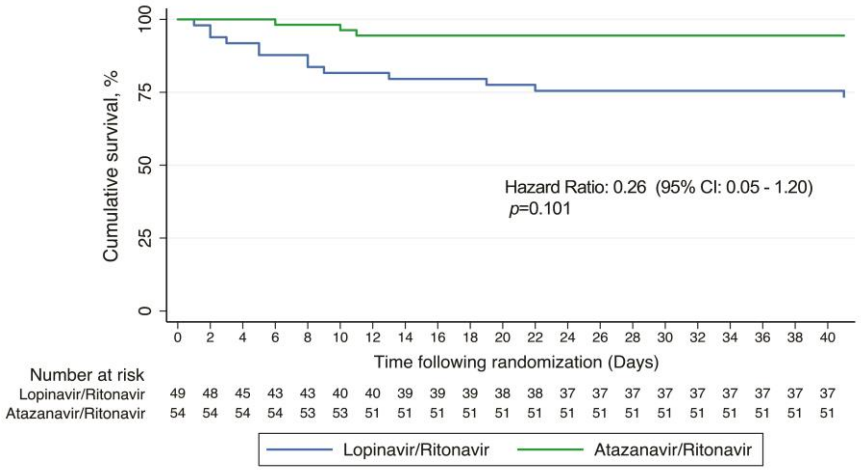

Figure 2. Cumulative survival in the study population. The reduction of mortality rate in the Atazanavir/Ritonavir group, compared to the Lopinavir/Ritonavir group did not reach statistical significance

Table 2. Association of baseline variables, demographics, comorbidities, and side effects of the interventions with the primary outcome

Variables	**Total (n=103)**	**Outcome measurement**		***P*-value**
		Survivor (n=86)	**Deceased (n=17)**	
Age				
Mean±SD	58.88±15.45	57.03±14.84	68.24±15.47	0.006[a]
<59	49 (47.6 %)	45 (52.3 %)	4 (23.5 %)	0.030
>=59	54 (52.4 %)	41 (47.7 %)	13 (76.5 %)	
Gender, N (%)				0.060[b]
Male	64 (62.1 %)	50 (58.1 %)	14 (82.4 %)	
Female	39 (37.9 %)	36 (41.9 %)	3 (17.6 %)	
Comorbidities, N (%)				

Table 2. Continued					
Any		63 (61.2 %)	53 (60.9%)	10 (62.5%)	0.905 [b]
Hypertension		41 (39.8 %)	37 (42.5%)	4 (25.0%)	0.188 [b]
Respiratory disease		11 (10.7 %)	8 (9.2%)	3 (18.8%)	0.255 [b]
Diabetes mellitus		20 (19.4 %)	16 (18.4%)	4 (25.0%)	0.539 [b]
Hypercholesterolemia/hypertriglyceridemia		4 (3.9 %)	3 (3.4%)	1 (6.3%)	0.594 [b]
Heart disease		13 (12.6 %)	11 (12.6%)	2 (12.5%)	0.987 [b]
Kidney disease		3 (2.9 %)	2 (2.3%)	1 (6.3%)	0.388 [b]
Signs and symptoms upon admission (%)					
Headache		18 (17.5 %)	18 (20.9 %)	0 (0 %)	0.038 [b]
Myalgia		31 (30.1 %)	57 (66.3 %)	15 (88.2 %)	0.071 [b]
Cough		81 (78.6 %)	29 (33.7 %)	2 (11.8 %)	0.756 [b]
Dyspnea		96 (93.2 %)	18 (20.9 %)	4 (23.5 %)	0.597 [b]
Diarrhea		8 (7.8 %)	68 (79.1 %)	13 (76.5 %)	0.347 [b]
Nausea/Vomiting		17 (16.5 %)	7 (8.1 %)	0 (0 %)	0.474 [b]
O2 Saturation assessed by pulse oximetry at baseline, N (%)					0.003 [b]
Low < 90%		48 (46.6 %)	46 (53.5 %)	2 (11.8 %)	
90%< Medium <93%		30 (29.1 %)	23 (26.7 %)	7 (41.2 %)	
High >93%		25 (24.3 %)	17 (19.8 %)	8 (47.1 %)	
Glucocorticoid use, N (%)					0.319 [b]
Yes		68 (66.0 %)	55 (64 %)	13 (76.5 %)	
ICU transfer, N (%)					<0.001 [b]
Yes		22 (21.4 %)	7 (8.1 %)	15 (88.2 %)	
Biochemical profile and laboratory results	Evaluation time				
CR (mg/dl)	Upon admission	1.11±0.33	1.10±0.32	1.17±0.38	0.496 [a]
BUN (mg/dl)	Upon admission	16.49±8.39	15.37±7.80	23.10±8.98	0.001 [a]
CRP (mg/dl)	Upon admission	75.58±55.45	74.97±58.09	78.47±42.24	0.826 [a]
ESR (ml/hr)	Upon admission	58.84±27.92	57.61±28.06	66.15±27.02	0.310 [a]
CR (mg/dl)	After one week	1.13±0.46	1.02±0.37	1.36±0.56	0.047 [a]
BUN (mg/dl)	After one week	25.53±18.62	19.48±12.55	40.04±23.17	0.022 [a]
CRP (mg/dl)	After one week	42.29±45.55	37.34±46.35	58.78±47.46	0.499 [a]
ESR (ml/hr)	After one week	55.90±39.69	56.14±42.88	55.33±39.63	0.978 [a]

CR: Creatinine, BUN: Blood Urea Nitrogen, CRP: C-Reactive Protein, ESR: Erythrocyte Sedimentation Rate, PCT: Procalcitonin a: independent t-test, b: Pearson chi-square test

Table 3. Side effects of the interventions and outcome measurements in the study participants.

Variables	Total (n=103)	Group Assignment		P-value
		Lopinavir/Ritonavir (n=49)	Atazanavir/Ritonavir (n=54)	
Drug side effects, N (%)				0.215 [a]
Any, Yes	20 (19.4 %)	7 (14.3 %)	13 (24 %)	
Gastrointestinal side effects, N (%)				0.628 [a]
Yes	13 (12.6 %)	7 (14.3 %)	6 (11.1 %)	
Cardiac side effects, N (%)				0.061 [a]
Yes	8 (7.8 %)	1 (2.0 %)	7 (13.2 %)	
Hospitalization length				
Mean ± SD	7.28±5.40	8.29±6.81	6.37±3.50	0.081 [b]
Median (Q1 - Q3)	6.00 (4.00–9.00)	6.00 (4.00–9.50)	6.00 (4.00–9.00)	
Death, N (%)				
Yes	16 (15.3 %)	13 (26.5 %)	3 (5.6 %)	0.008 [a]

a: Pearson chi-square test, b: independent t-test

5. Discussion

The findings of this double-blind, randomized comparative trial suggest that Atazanavir/Ritonavir is not superior to Lopinavir/Ritonavir in reducing mortality and hospitalization length in hospitalized COVID-19 patients. The results also demonstrated a higher incidence of cardiac side effects in the Atazanavir/Ritonavir group, but a similar total number of patients with observed drug adverse effects for Atazanavir/Ritonavir and Lopinavir/Ritonavir.

Evaluation of the outcomes of this study failed to demonstrate the higher efficacy of Atazanavir despite previous studies reporting the higher potency of Atazanavir in inhibiting viral Mpro (4,10,12). Nevertheless, the results of this study are in accordance with those of a research performed by Nekoukar et al., which revealed no difference in the mortality rate, the number of discharged patients within 10 days, and recovery within 14 days in those receiving hydroxychloroquine plus Atazanavir/Ritonavir, compared to those receiving hydroxychloroquine plus Lopinavir/Ritonavir (13). However, in contrast to the current study, Atazanavir/Ritonavir was better tolerated with lower rates of nausea and vomiting in the aforementioned study on moderately-ill COVID-19 patients.

Table 4. Statistical plan and analysis of the outcomes for the study groups. The use of Atazanavir/Ritonavir was accompanied by increased cardiac side effects

Statistical Model	Outcomes and Biochemical Profile	Unadjusted		Adjusted	
		OR (95% CI) / Beta (95% CI)	*P*-value	OR (95% CI) / Beta (95% CI)	*P*-value
Logistic regression (drug, Atazanavir/Ritonavir vs. Lopinavir/Ritonavir)	Drug Side Effect, yes vs. no	0.54 (0.19 - 1.43)	0.219	0.48 (0.16-1.34)	0.166[a]
	Gastrointestinal Side Effects, yes vs. no	0.75 (0.23 - 2.43)	0.629	0.75 (0.22-2.5)	0.647[a]
	Cardiac Side Effects, yes vs. no	7.3 (1.23 - 139.33)	0.068	12.18 (1.81-111.8)	0.029[a]
	Death, yes vs. no	0.16 (0.04 - 0.61)	0.01	0.26 (0.05–1.20)	0.101[b]
Linear regression (drug, Atazanavir/Ritonavir vs. Lopinavir/Ritonavir)	CR (in admission) ml/dl	0.12 (-0.02, 0.25)	0.088	0.11 (-0.02, 0.24)	0.102[a]
	BUN (in admission) ml/dl	0.85 (-2.56, 4.25)	0.622	1.79 (-1.28, 4.87)	0.250[a]
	CRP (in admission) ml/dl	19.27 (-4.31, 42.85)	0.108	13.74 (-10.71, 38.2)	0.267[a]
	ESR (in admission) ml/dl	-10.45 (-22.06, 1.15)	0.077	-7.14 (-19.19, 4.91)	0.242[a]
	CR (after one week) ml/dl	0.17 (-0.15, 0.5)	0.281	0.18 (-0.16, 0.52)	0.288[a]
	BUN (after one week) ml/dl	4.57 (-8.63, 17.77)	0.486	6.38 (-7.3, 20.05)	0.349[a]
	CRP (after one week) ml/dl	-24.42 (-81.87, 33.03)	0.370	-25.83 (-98.69, 47.04)	0.443[a]
	ESR (after one week) ml/dl	1.80 (-59.57, 63.17)	0.948	-18.67 (-109.78, 72.45)	0.634[a]
	Hospitalization length	1.92 (0.03, 4.13)	0.096	1.89 (-0.12, 4.07)	0.195[b]

a: adjusted for age and gender, b: adjusted for age, gender, and O2 saturation assessed by pulse oximetry

A prospective study comparing the effectiveness of Atazanavir/Ritonavir/Dolutegravir/Hydroxychloroquine and Lopinavir/Ritonavir/Hydroxychloroquine treatment regimens in moderate to severe cases of COVID-19 also failed to demonstrate differences between the participants of each group in terms of mortality rate, ICU admission rate, and hospitalization period (14).

Supportive care remains the mainstay approach to COVID-19 patients; however, preventive measures, such as social distancing and vaccine development have been far more successful in the reduction of mortality and morbidity rates in the ongoing COVID-19 pandemic (15,16). Nevertheless, efforts toward reducing the disease burden and decreasing the absolute number of infected individuals have been rendered futile by the limited effectiveness of the available therapeutic regimen in SARS-CoV-2 infections.

Given the increased incidence and mortality of COVID-19 around the globe and in estimated models (17), the search for efficient and cost-effective treatment approaches for the disease is of paramount importance. Drug repurposing, despite its challenges, would prove to be a superior strategy, compared to the development of novel interventions. Moreover, it would be more practical when faced with a global epidemic, considering the cost and time dedicated to de novo drug development (18) and the effectiveness of currently repurposed drugs, such as *Remdesivir* (19). The ever-growing burden of the COVID-19 pandemic on healthcare systems around the globe could lead to a reduction in the quality of the standard of care provided to individuals and increased mortality (16).

The rationale to use Atazanavir as a repurposed drug in COVID-19 must be backed by robust evidence regarding its efficacy to justify its use despite serious and life-threatening side effects, such as changes in heart rhythm and liver dysfunction (10). The cardiac side effects were observed in a number of patients in this study and the mortality rate was not significantly different between Atazanavir/Ritonavir and Lopinavir/Ritonavir groups. This may indicate that Atazanavir/Ritonavir does not provide further benefit, compared to Lopinavir/Ritonavir in the treatment regimen for COVID-19. However, this study was limited by numerous factors, including the limited incidence of outcomes, small sample size, concurrent drug use, and the inclusion of laboratory unconfirmed COVID-19 patients.

6. Conclusion

Overall, the results of this study did not demonstrate greater efficacy of Atazanavir/Ritonavir vs. Lopinavir/Ritovanir in the reduction of mortality rate and length of hospital stay of COVID-19 patients. Future studies would benefit from the incorporation of patient viral loads as an outcome, accessing a larger and therefore, more representative sample size, and the inclusion of a placebo group.

Acknowledgments

None.

Footnotes

Conflicts of Interest: None to declare.
Clinical Trial Registration number: IRCT20200504047298N1
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