Supplemental Online Content

Diaz R, Orlandini A, Castellana N, et al; the ECLA PHRI COLCOVID Trial Investigators. Effect of colchicine vs usual care alone on intubation and 28-day mortality in patients hospitalized with COVID-19: a randomized clinical trial. *JAMA Netw Open*. 2021;4(12):e2141328. doi:10.1001/jamanetworkopen.2021.41328

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods.

Study organization

The trial was conducted at 42 Argentinian hospitals. The trial was coordinated by ECLA (Estudios Clinicos Latino America), the trial sponsor and with the collaboration of PHRI (Population Health Research Institute).
Treatment supply to local sites was supported by Spedrong Caillion Pharma and registry data was supported by Red Cap.

Protocol changes

COLCOVID is a randomized trial among patients hospitalized for COVID-19. All eligible patients receive usual standard of care in the participating hospital and are randomly allocated between no additional treatment and one active treatment arm.
The original and final protocols are included in the supplementary material to this publication, together with summaries of the changes made.
The following modifications were made to the protocol during the trial:

Version	**Date of release**	**Major modifications from previous version**
1.2	19-Mar-20	Initial version (protocol V1.2)
1.2	25-Apr-20	Title – Brief Summary
2.0	30-Nov-21	Eligibility criteria Co-primary outcomes Secondary outcomes Sample size recalculation ASS - Rivaroxaban arm allowed
2.1	5-Feb-21	Secondary Outcomes specification

Patients informed consents

Three methods of obtaining informed consent were accepted by our local health authorities (ANMAT):
a) Written consent
b) Oral consent in the presence of two witnesses belonging to the health team, who formally documented this act
c) If the patient could not give consent due to cognitive disfunction, and a legal representative was not available, the patient could be included based on the decision of at least two members of the health team, one of whom must be a doctor.

Confirmed positive PCR

Confirmed positive PCR is defined as Laboratory-confirmed SARS-CoV-2throug PCR at randomization or pending result at randomization and positive result confirmed later

Per protocol population

All randomized patients who have received study treatments (active or control) are included in this population. Patients are analyzed within the intervention group to which they were randomized after exclusion of non-compliant patients. Non-compliant patients for colchicine group were defined as patients who did not received colchicine or patients who received colchicine but discontinued. Non-compliant patients for standard care group were defined as patients who received colchicine.

Colchicine administration

The colchicine dosage schedule will vary according to the following scenarios:

1. In patients not receiving Lopinavir/Ritonavir
    - Loading dose of 1.5 mg followed by 0.5 mg after two hours (day 1)
    - The next day 0.5 mg bid for 14 days or until discharge.
2. In patients receiving Lopinavir/Ritonavir
    - Loading dose of 0.5 mg (day 1)
    - After 72 hours from the loading dose, 0.5 mg every 72 hours for 14 days or until discharge.
3. Patients under treatment with Colchicine that are starting with Lopinavir/Ritonavir
    - Dose of 0.5 mg 72 hours after starting Lopinavir/Ritonavir.
    - Continue with 0.5 mg every 72 hours for 14 days or until discharge.

Only the oral route will be used except in the case of patients associated with mechanical ventilation or with contraindications to the oral route, in whom it will be administered by nasogastric tube.

Colchicine drug interactions

Strong P-gp inhibitor	Loading dose 0.5 mg (day 1) then 0.5 mg after 72
Ciclosporine	Hs. and then 0.5 mg every 72 hs for 14 days or
Ranalozine	Until discharge
Strong/moderate CYP3A4 inhibitor	Loading dose 0.5 mg (day 1) then 0.5 mg after 72
Lopinavir/ritonavir	Hs. and then 0.5 mg every 72 hs for 14 days or
Lopinavir	Until discharge
Ritonavir	
Daranuvir/Ritonavir	
Claritromicine	
Telitromicine	
Nelfinavir	
Indinavir	
Saquinavir	
Tripanavir/Ritonavir	
Ataznavir	
Voxilaprevir	
Itroconazol	
Ketoconazol	
Voriconazol	
Atorvastatin	
Simvastatin	
Lovastatin	
Cloranfenicol	
Quinidine	
Amiodarone	
Verapamil	
Diltiazem	
Eritromicine	
Fluconazol	
Posaconazol	
Amprenavir	
Aprepitant	
Fosamprenavir	
Ciprofloxacine	
Fenofibrate	
Gemfibrozil	
Grapefruit Juice	
Pitavastatin	
Rosuvastatin	
Ceritinib	
Cobicistat	
Conivaptan	
Dronaderone	
Glecaprevir	
Indinavir	

Nefazonona	
Weak CYP3A4 inhibitor	Loading dose 1.5 mg (day 1) then 0.5 mg BID for
Azitromicine	14 days or until discharge
Amlodipine	
Carvedilol	
Cilostazol	
Naproxeno	
Nifedipine	
Paroxetine	
Propafenone	
Ticagrelor	

Renal failure dose adjustment

Creatinine clearance > 50 ml/min:

- Loading dose 1.5 mg follow by 0.5 mg 2 hours after the loading dose. (day 1)
- Day 2, 0.5 mg bid for 14 days or until discharge.

Creatinine clearance < 50ml/min:

- Loading dose 0.5 mg (day 1)
- New dose at 72 hours from the loading dose and then 0.5 mg every 72 hours until day 14 or until discharge.

Dosage in hepatic failure

Child-pugh A:

- Loading dose 1.5 mg follow by 0.5 mg 2 hours after the loading dose. (day 1)
- Day 2, 0.5 mg bid for 14 days or until discharge.

Child-pugh B:

- Loading dose 0.5 mg (day 1)
- New dose at 72 hours from the loading dose and then 0.5 mg every 72 hours until day 14 or until discharge.

Child-pugh C:

- Contraindicated

eTable 1. Summary Metrics of Hospital Stage and Colchicine Use Time

	Median	P25%	P75%
Hospital stage time (days)	7	4	13
Colchicine use time (days)	6	3	10

eTable 2. Causes of Death by Group

Death cause	Randomization Group	
	Usual Care N = 639	Colchicine N = 640
Respiratory failure, n (%)	125 (19.6)	108 (16.9)
Cardiovascular, n (%)	7 (1.1)	6 (1.2)
Major bleeding, n (%)	0 (0.0)	2 (0.3)
Septic shock, n (%)	8 (1.3)	10 (1.6)
Trauma, n (%)	0 (0.0)	4 (0.6)
Unknown origin, n (%)	2 (0.3)	1 (0.2)

eTable 3. Post Hoc Analysis of 28-Day Composite Outcome Hazard Risk Estimation Considering Different Time Periods

Time period	HR	95% CI	p-value
0 to 14 days	0.77	[0.61–0.96]	0.023
15 to 28 days	1.46	[0.76–2.78]	0.250

eTable 4. Summary of Adverse Events in the Safety Population

Adverse Event	Usual care N = 665	Colchicine N = 612
At least one adverse event, n /N (%)	229 /665 (34.5)	245 /612 (40.0)
Severe lymphopenia, n /N (%)	98 /661 (14.8)	92 /610 (15.1)
Severe anemia, n /N (%)	31 /661 (4.7)	25 /610 (4.1)
Severe thrombocytopenia, n /N (%)	16 /660 (2.4)	21 /610 (3.4)
Major bleeding, n /N (%)	6 /661 (0.9)	6 /610 (1.0)
Disseminated intravascular coagulation, n /N (%)	3 /661 (0.5)	3 /610 (0.5)
Cardiac arrest, n /N (%)	43 /661 (6.5)	41 /610 (6.7)
Heart failure, n /N (%)	32 /661 (4.8)	20 /610 (3.3)
Myocarditis, n /N (%)	4 /661 (0.6)	4 /610 (0.7)
Myocardial infarction, n /N (%)	5 /661 (0.8)	1 /610 (0.2)
ECMO, n /N (%)	4 /661 (0.6)	0 /610 (0.0)
Sepsis, bacterial suspected, n /N (%)	104 /661 (15.7)	102 /610 (16.7)
Septic shock, n /N (%)	74 /661 (11.2)	67 /610 (11.0)
Acute kidney injury, n /N (%)	53 /661 (8.0)	51 /610 (8.4)
Renal replacement therapy, n /N (%)	11 /661 (1.7)	13 /610 (2.1)

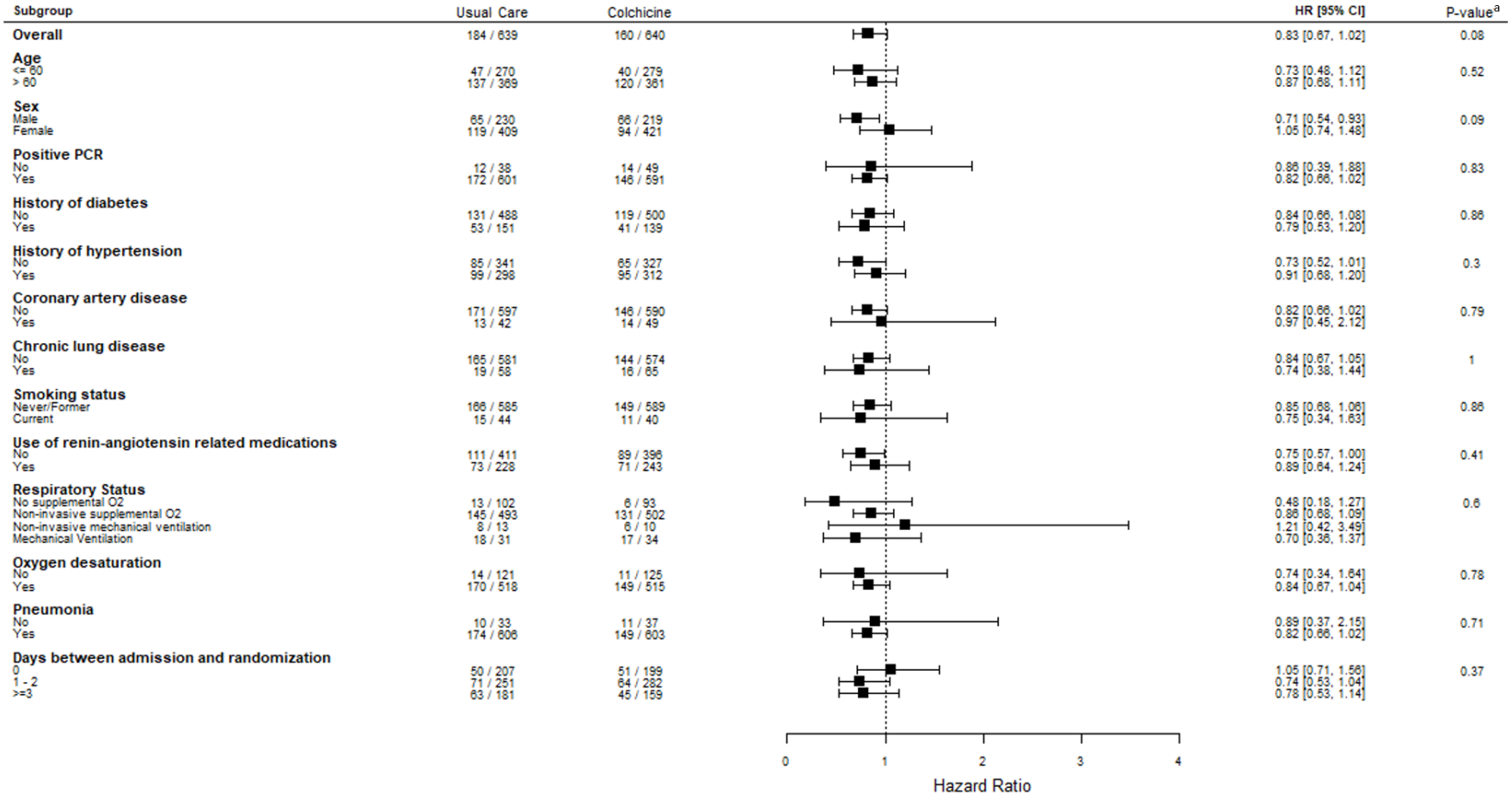
Adverse Event	Usual care N = 665	Colchicine N = 612
Severe diarrhea, n /N (%)[a]	13 /288 (4.5)	69 /608 (11.3)
GI bleeding, n /N (%)	0 /665 (0.0)	2 /612 (0.3)
Laboratory abnormality, n /N (%)	0 /665 (0.0)	4 /612 (0.7)
Pulmonary embolism, n /N (%)	5 /661 (0.8)	6 /610 (1.0)
Stroke, n /N (%)[a]	2 /324 (0.6)	1 /303 (0.3)
Deep venous thrombosis, n /N (%)[a]	1 /323 (0.3)	1 /302 (0.3)
Acute limb ischemia, n /N (%)[a]	0 /324 (0.0)	1 /304 (0.3)

Adverse events that occurred in more than 1 patient after randomization through day 28 are shown.
Percentages are based on the safety population, which comprised all the patients who underwent randomization and who received study treatments. Patients are analyzed according to the treatment they actually received
[a] Stroke, Deep venous thrombosis and acute limb ischemia questions were incorporated in eCRF on January 01 2021. Severe diarrhea for Usual Caregroup question was also incorporated at the same time

eTable 5. Adverse Events of Special Interest Listed by System Organ Class in the Safety Population

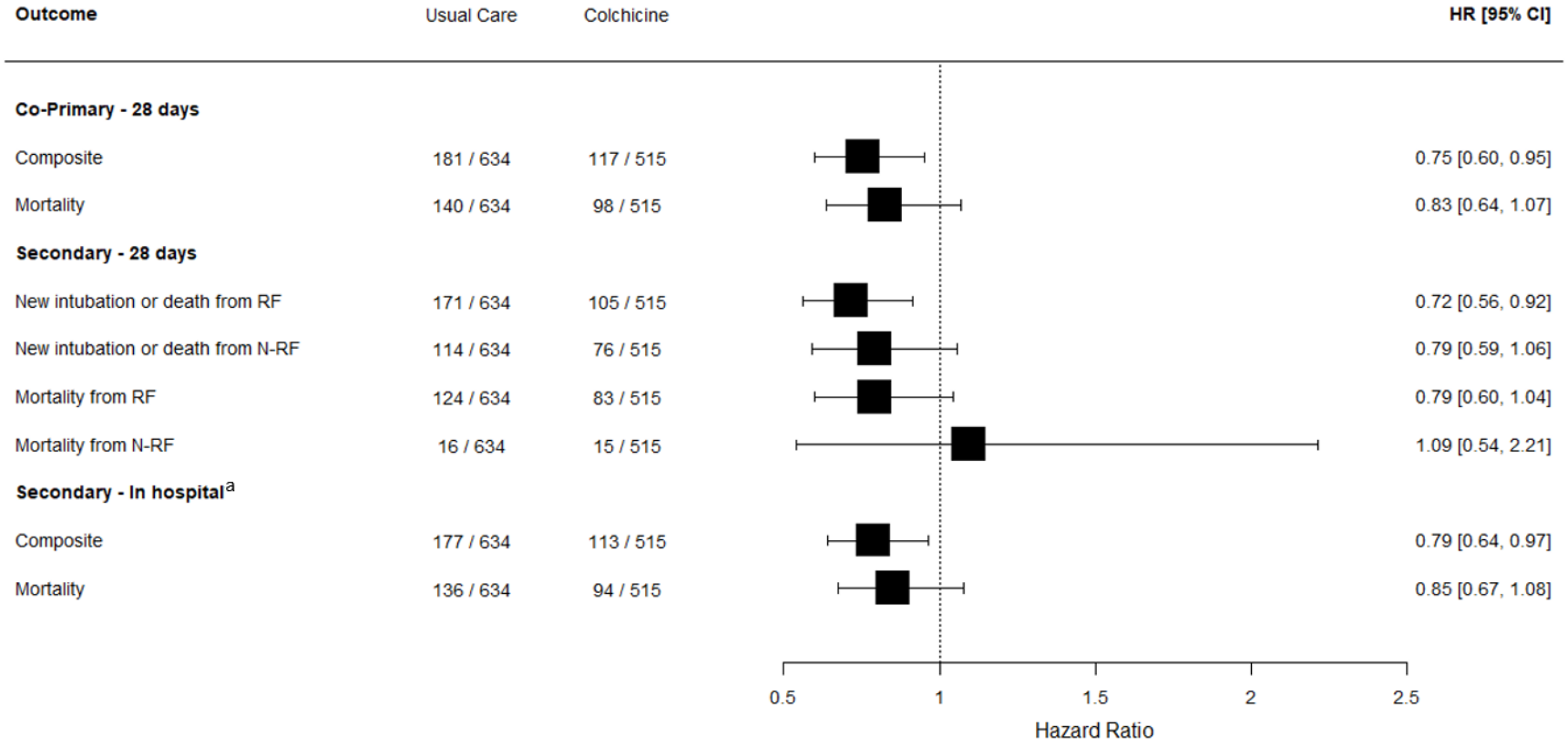
System Organ Class	Usual care N = 665	Colchicine N = 612
At least one adverse event, n (%)	229 (34.4)	245 (40.0)
Blood and lymphatic system disorders, n (%)	114 (17.1)	112 (18.3)
Infections and infestations, n (%)	116 (17.5)	110 (18.0)
Cardiac disorders, n (%)	74 (11.2)	54 (8.8)
Renal and urinary disorders, n (%)	56 (8.4)	51 (8.3)
Gastrointestinal disorders, n (%)	13 (1.9)	70 (11.4)
Vascular disorders, n (%)	8 (1.2)	9 (1.5)
Investigations, n (%)	0 (0.0)	4 (0.7)

eFigure 1. Forest Plot for 28-Day Composite Outcome by Prespecified Subgroups



[a] p-value for interaction

eFigure 2. Forest Plot for Primary and Secondary Outcomes Considering the Per Protocol Population



Patients are analyzed within the intervention group to which they were randomized after exclusion of patients who were non-compliant.
Patients defined as non-compliant for the colchicine group did not receive colchicine or received colchicine but discontinued (N=125).
Patients defined as non-compliant for the usual care group received colchicine (N=5).
Abbreviations: RF, respiratory failure; N-RF, Non respiratory failure
[a] Relative Risk and 95% CI for in-hospital outcomes