Journal Club at the Laboratory of Clinical Psychopharmacology of Addictions (LCPA) is a monthly gathering to discuss research papers with a focus on addiction.

Mission: to promote a better understanding of the research process and an improve ability to critically appraise research in addiction and related diseases (e.g. infectious, mental health, etc.).

Discussion topics and learning objectives include (but not limited by) the concepts of addiction, terminology used in the field, socio-cultural and biological risk factors, contemporary public health issues and policies, prevention, treatment and treatment systems.

Values:

- Learning
- Respect
- Collaboration
- Multidisciplinary
- Excellence

Please be open, flexible, realistic, and understanding!

Housekeeping notes

Video-recording

The meeting will be entirely video-recording and published on the Pavlov University website and YouTube, so if you wish not be in the recorded video, please make sure that your webcam off during the meeting.

Q&A

The seminar is interactive and we strongly encourage you to actively ask questions during the presentation but keep in mind that we have dedicated time at the end of the webinar (10 minutes) to group discussion and Q&A. Please raise your hand if you have any questions or comment. You also may use chat option to post your questions or comments.

Mic and Video

Please keep your mic mute during entire meeting unless you want to make a question or comment. We recommend keeping your camera on during the meeting.

Post-meeting survey

After the meeting we would like to send you the survey. Please make sure that we have your email.

CONTACTS

- Presenter: Borovskaya Valentina
  valentine.borovskaya@gmail.com

- Mentor: Marina V. Vetrova
  mvetrova111@gmail.com

A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19

B. Cao, Y. Wang, D. Wen

Presenter: Borovskaya Valentina,
5-year medical student

1й Мед
ФГБОУ ВО ПСПбГМУ им. Павлова Минздрава России

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19

B. Cao, Y. Wang, D. Wen, W. Liu, Jingli Wang, G. Fan, L. Ruan, B. Song, Y. Cai, M. Wei, X. Li, J. Xia, N. Chen, J. Xiang, T. Yu, T. Bai, X. Xie, L. Zhang, C. Li, Y. Yuan, H. Chen, Huadong Li, H. Huang, S. Tu, F. Gong, Y. Liu, Y. Wei, C. Dong, F. Zhou, X. Gu, J. Xu, Z. Liu, Y. Zhang, Hui Li, L. Shang, K. Wang, K. Li, X. Zhou, X. Dong, Z. Qu, S. Lu, X. Hu, S. Ruan, S. Luo, J. Wu, L. Peng, F. Cheng, L. Pan, J. Zou, C. Jia, Juan Wang, X. Liu, S. Wang, X. Wu, Q. Ge, J. He, H. Zhan, F. Qiu, L. Guo, C. Huang, T. Jaki, F.G. Hayden, P.W. Horby, D. Zhang, and C. Wang

Supported by grants from Major Projects of National Science and Technology on New Drug Creation and Development (2020ZX09201001) and (2020ZX09201012);
the Chinese Academy of Medical Sciences (CAMS) Emergency Project of Covid-19 (2020HY320001);
and a National Science Grant for Distinguished Young Scholars (81425001/H0104).

World Health Organization

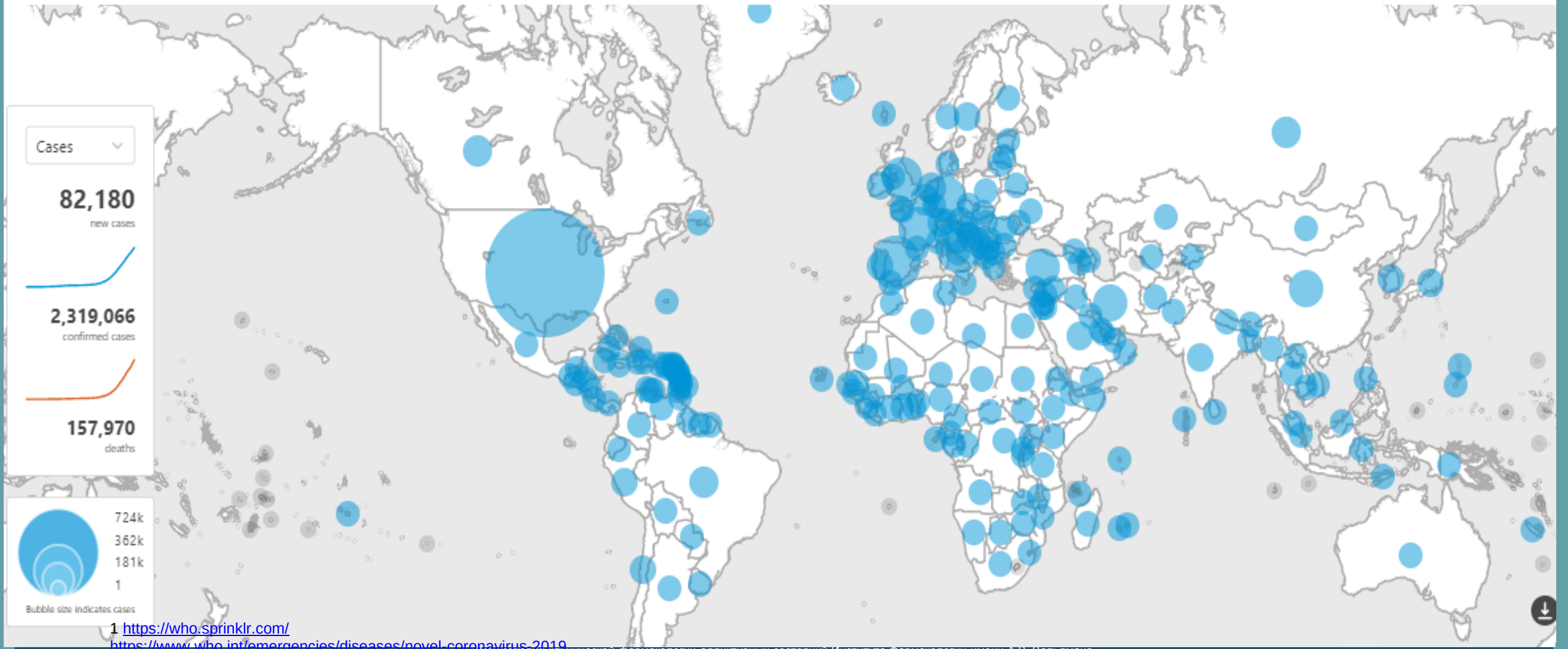
Search by Country, Territory, or Area

Over the world(21/04/2020)
Countries, areas or territories with cases - 213
Confirmed cases - 2 356 414
Deaths- 160 120
New cases– 82,180
New deaths -5,263

Coronavirus (COVID-19)

Last updated: 2020/4/21, 8:00am CEST

Overview



1 https://who.sprinklr.com/
https://www.who.int/emergencies/diseases/novel-coronavirus-2019

Covid-19 in Russia

21/04/2020
Confirmed cases - 52 763
Deaths- 456
New cases– 5 642
Death rate -0,7%

Москва	29433	2057	233
Московская область	5959	179	49
Санкт-Петербург	1973	280	11
Нижегородская область	860	28	5

https://news.mail.ru/story/incident/coronavirus/

PROBLEM

- SARS-CoV-2, has caused an international outbreak of respiratory illness,
- no therapeutics have been proven effective for the treatment of severe illness,
- we know less about this virus.

1 https://who.sprinklr.com/
https://www.who.int/emergencies/diseases/novel-coronavirus-2019

COVID-19 ClinicalTrials.gov Summary

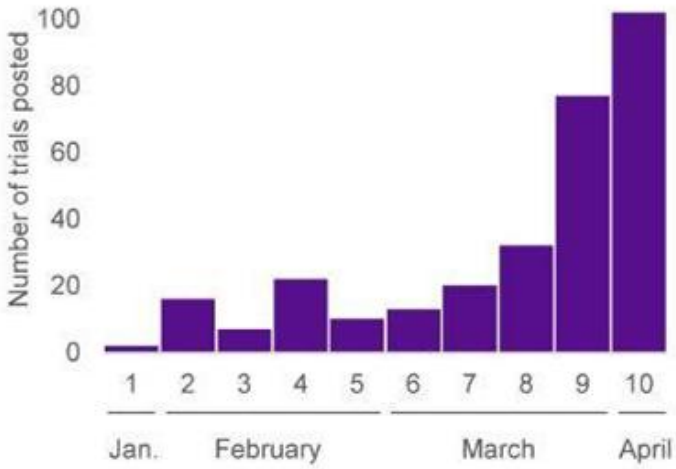
(as of 4/4/2020 by Jesse B. Rafel, MD)

301 trials

*Search terms: novel coronavirus, COVID, 2019-nCOV, SARS-CoV-2

New COVID-19 trials per week

ClinicalTrials.gov, Jan 28 to Feb 4 (n = 301)



Trial Locations (count)

China (89), USA (50), Italy (29), France (29), UK (14), Spain (13), Canada (12), Germany (7), Brazil (6), South Korea (6)

Countries with ≤5 trials

Australia, Belgium, Colombia, Denmark, Egypt, Greece, Hong Kong, Hungary, Iran, Ireland, Israel, Japan, Mexico, Netherlands, Norway, Pakistan, Poland, Romania, Saudi Arabia, Singapore, Sweden, Switzerland, Thailand, Turkey, Vietnam

Phase 1 n = 18 → Phase 2 n = 53 → Phase 3 n = 66 → Phase 4 n = 17

Interventional n = 197		Observational n = 101	Cohort	Case	Case-control
Randomized	124	Prospective	49	9	6
Non-randomized	18	Retrospective	7	2	5
No allocation	35	Cross-section.	4	3	0

Drug or Biologic (trial count)	Mechanism
Hydroxychloroquine / chloroquine (45) ↑	Quinoline TLR inhibitor
Lopinavir / ritonavir / darunavir (20) ↑	HIV protease inhibitor
Tocilizumab / sarilumab / siltuximab (19) ↑	IL-6 antagonist
Azithromycin / carrimycin (11)	Macrolide, anti-inflammatory effects
Convalescent plasma (10) ↑	Passive immunity
Mesenchymal stem cells (10)	Immune modulation, regeneration
Remdesivir (9)	Nucleotide analog
Traditional Chinese medicine (9)	Various reported
ACEi / ARB (8) ↑	RAAS inhibitor
Systemic glucocorticoids (7)	Myriad anti-inflammatory effects
Vaccines (7)	Active immunity
IFNα inhalation (5)	Cytokine with antimicrobial effects
Umifenovir (5)	Influenza antiviral
Baricitinib / ruoxlitinib / tofacitinb (4) ↑	JAK inhibitor
Inhaled nitric oxide / sildenafil (4)	Pulmonary smooth muscle vasodilation
Favipiravir (4)	Viral RNA-polymerase inhibitor
Colchicine (3)	Microtubule polymerization inhibitor
Eculizumab / IFX-1 (3) ↑	Complement inhibitor
Inhaled corticosteroids / ciclesonide (3) ✹	Anti-inflammatory
Oseltamivir (3)	Influenza neuraminidase inhibitor
Anakinra (2)	IL-1 receptor antagonist
Bevacizumab (2)	VEGF-A inhibitor
NK cells (2)	Innate immunity
PD-1 inhibitor (2)	Immune checkpoint blockade
Thalidomide (2)	TNFα inhibitor
Thymosin (2)	Polypeptide hormone immune modulator
Acellular amniotic fluid	Anti-inflammatory
Angiotensin (1-7) ✹	Opposite effects of Ang II
Aviptadil	Synthetic VIP with vasodilatory effects
Bromhexine	Mucolytic
Camostat mesylate	Inhibits TMPRSS2 serine protease
CD24Fc	Inflammatory cytokine inhibitor
Danoprevir	HCV protease inhibitor
DAS181	Blocks viral entry on resp epithelial cells
Deferoxamine ✹	Binds free iron
Emapalumab	INFγ inhibitor
Escin	Induces endothelial NO synthesis
Fingolimod	Sphingosine-1-phosphate receptor mod.
Hyperbaric oxygen ✹	Improve oxygenation
IVIG	Multifactorial anti-inflammatory
Levamisole ✹	Anti-parasitic with lymphocyte stimulation
Meplazumab	Anti-CD147 antibody
NSAID therapy	COX inhibitor
Pegylated IFNλ-1a ✹	Stimulate cell-mediated immunity
Piclidenoson ✹	Inhibits inflammatory cytokines
Pirfenidone	Lung growth factor inhibitor in IPF
PUL-042 Inhalation Solution	Lung epithelial TLR agonist
Ribavirin	Nucleoside analog
Sargamostim ✹	Recombinant GM-CSF
Tetrandrine	Ebola viral entry inhibitor
Tradipitant ✹	Neurokinin 1 antag. (inhib substance P)

↑: Increasing

✹: New

Valdman Institute of Pharmacology, First Pavlov State Medical University of St. Petersburg, Saint-Petersburg, Russia

CURRENT TREATMENT OPTIONS

I. Antimalarial Treatments

- Hydroxychloroquine
- Chloroquine
- Mefloquin

II. Antiviral Treatments

- **Lopinavir/Ritonavir**
- Remdesivir
- Favipiravir
- Umifenovir
- Triazavirin
- Baloxavir marboxil
- Danoprevir/ritonavir,
- Azvudine,
- Sofosbuvir/ledipasvir,
- Sofosbuvir/daclatasvir,
- Darunavir/cobicistat
- Emtricitabine/Tenofovir

III. Immunosuppressants/ immunomodulators

- Tocilizumab
- Adalimumab
- Eculizumab
- Sarilumab
- Ixekizumab
- Fingolimod
- Meplazumab

LOPINAVIR–RITONAVIR

- known as a treatment of human immunodeficiency virus (HIV) type 1
- **Lopinavir** - aspartate protease inhibitor,
- **Ritonavir-** is combined with lopinavir to increase its plasma halflife through the inhibition of cytochrome P450.

Lopinavir/Ritonavir was investigated for efficacy against SARS-CoV in 2004[1] and found to be effective when compared to historical control

- [1] 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.
- 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.
- 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.

OBJECTIVE

To examine the efficacy and safety of oral lopinavir–ritonavir in the treatment of hospitalized adult patients with severe respiratory illness COVID-19.

STUDY DESIGN

Randomized, controlled, open-label, parallel group clinical trial

Because of the emergency nature of the trial, placebos of lopinavir–ritonavir were not prepared.

Where: Jin Yin-Tan Hospital, Wuhan, Hubei Province, China

When: January 18, 2020 - February 3, 2020
(the date of enrollment of the last patient)

PARTICIPANTS, N =199

Inclusion criteria:

- age >=18
- positive for SARS-CoV-2[1] on RT-PCR[2] (respiratory tract sample),
- In the state of no oxygen at rest, the patient's oxygen saturation (SpO2)<=94%
- the oxygenation index (Pao2:Fio2[3]) is less than 300mmHg.

[1]Severe acute respiratory syndrome coronavirus 2
[2]reverse-transcriptase–polymerasechain-reaction
[3]partial pressure of oxygen to the fraction of inspired oxygen

Exclusion criteria:

1. Any situation that makes the programme cannot proceed safely;

2. allergy or hypersensitivity reaction to lopinavir / ritonavir;

3. ↑alanine aminotransferase (ALT) / aspartate aminotransferase (AST) >5 times the upper limit of normal;

4. Use of medications that are contraindicated with lopinavir / ritonavir and that cannot be replaced or stopped during the study period, such as CYP3A inhibitors;

5. Pregnancy: positive pregnancy test;

6. Known HIV infection, to prevent resistance development to lopinavir/ritonavir if used without combination with other anti-HIV drugs;

7. Patient likely to be transferred to a non-participating hospital within 72 hours;

8. Researchers consider unsuitable.

STUDY MEDICATIONS

- For 14 days:

Lopinavir–ritonavir

Orally 400 mg and 100 mg,
twice a day
+
standard care

Glucocorticoid therapy:
32 patients

Standard care

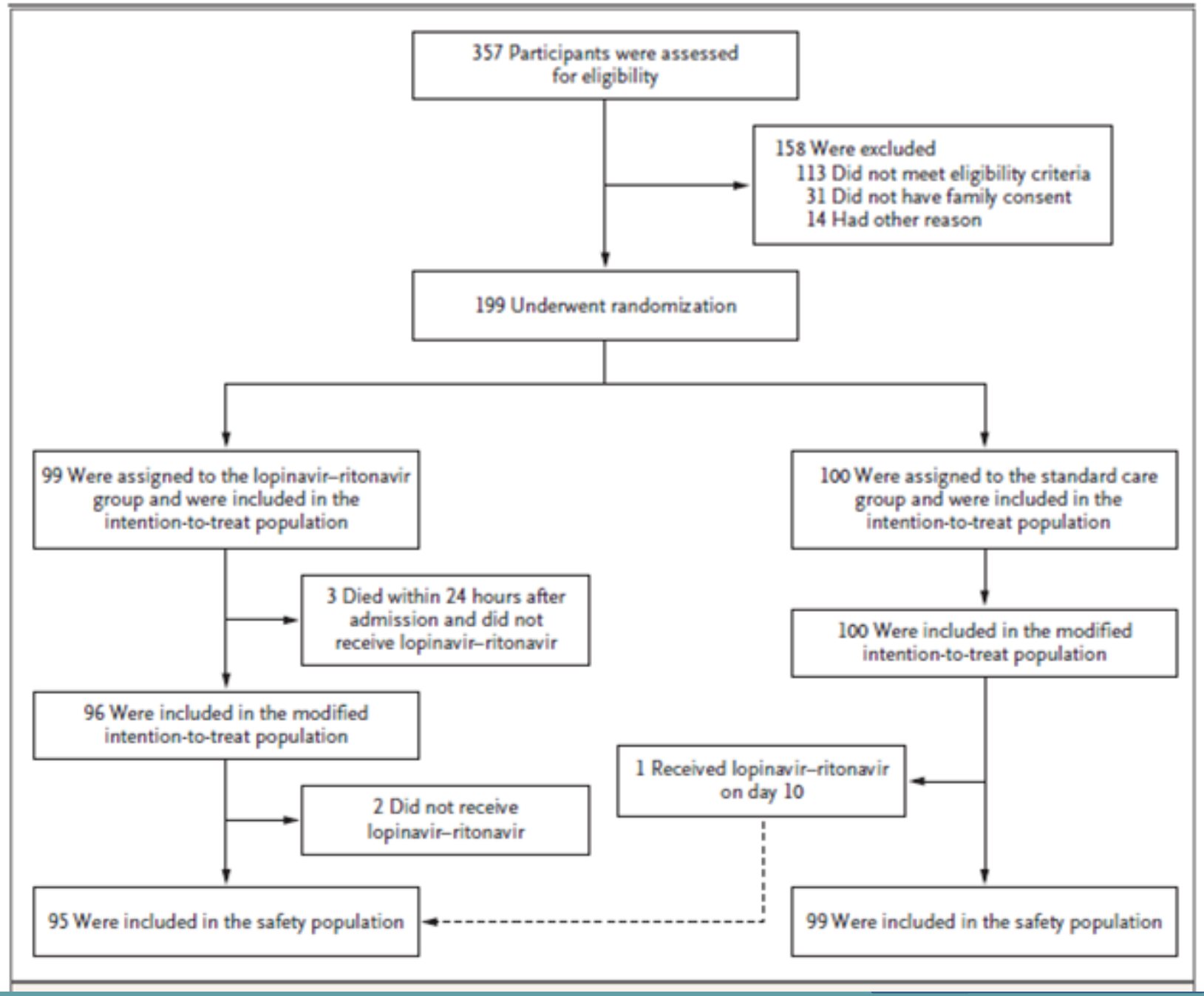
- supplemental oxygen,
- noninvasive and invasive ventilation
- antibiotics
- vasopressor support
- renal-replacement therapy
- extracorporeal membrane oxygenation (ECMO).

Glucocorticoid therapy:
35 patients

Study flow

The median age: 58 years (49 to 68 years),

Male sex: 60.3%



The seven- category scale

1 - discharged to normal function;

2 - discharged,but unable to resume normal function;

3 - hospitalized, not requiring supplemental oxygen;

4 - hospitalized, requiring supplemental oxygen;

5 - hospitalized, requiring nasal high-flow oxygen therapy and/or noninvasive mechanical ventilation;

6 - admission to ECMO and/or invasive mechanical ventilation;

7- death

Day: once daily

Measurement: time to clinical improvement
(primary outcome)

Method: The 7- category scale

Time to clinical improvement - time from randomization to an improvement of **2** points on a seven-category scale from the status at randomization

Time to clinical deterioration - a one-category increase on the seven-category scale

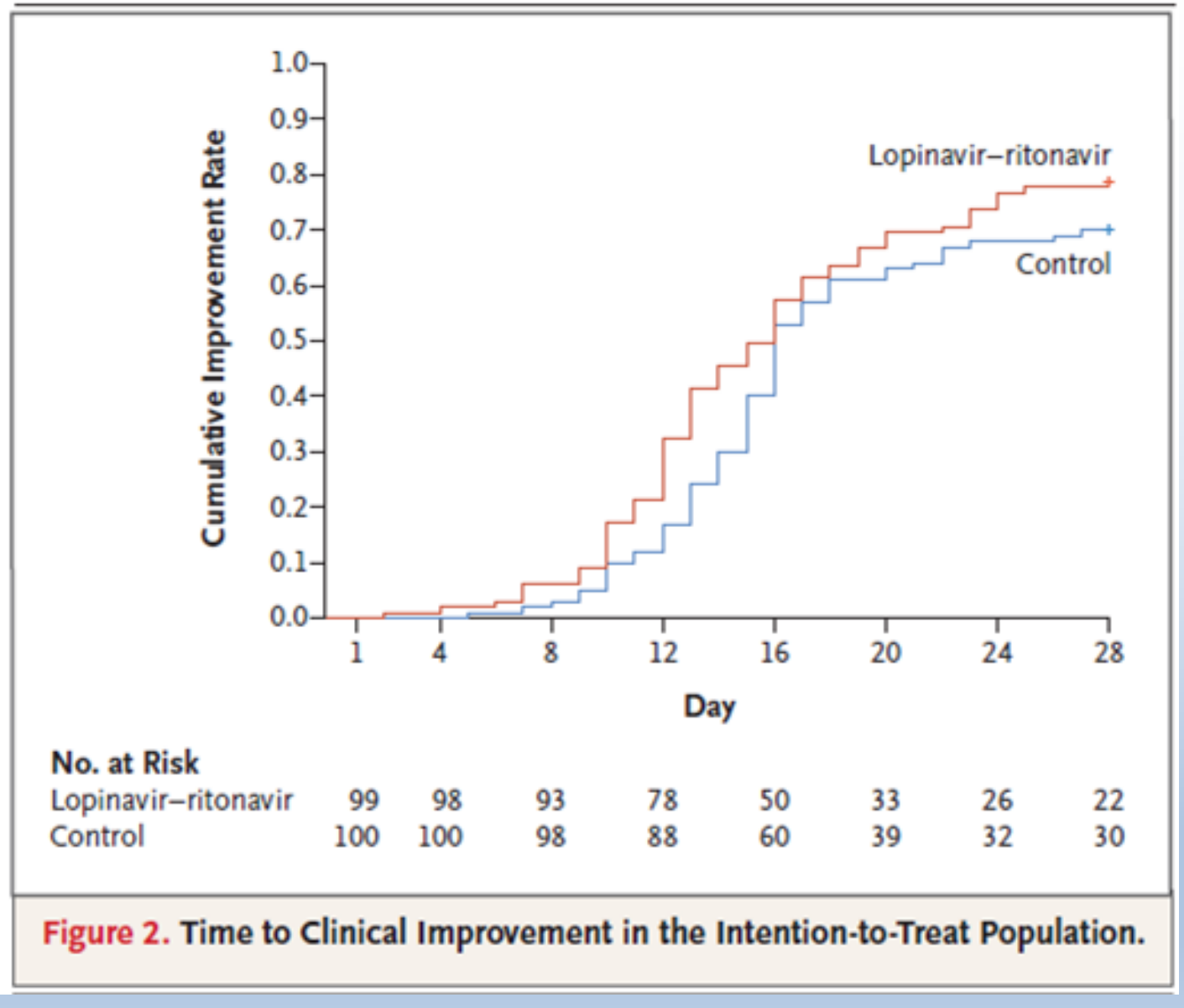


Figure 2. Time to Clinical Improvement in the Intention-to-Treat Population.

Cox proportional risk model

hazard ratio =1.31; 95% CI, 0.95 -1.85;

Table 2. Patients' Status and Treatments Received at or after Enrollment.*

Characteristic	Total (N=199)	Lopinavir–Ritonavir (N=99)	Standard Care (N=100)
NEWS2 score at day 1 — median (IQR)	5.0 (4.0–6.0)	5.0 (4.0–6.0)	5.0 (4.0–7.0)
Seven-category scale at day 1			
3: Hospitalization, not requiring supplemental oxygen — no. (%)	28 (14.1)	11 (11.1)	17 (17.0)
4: Hospitalization, requiring supplemental oxygen — no. (%)	139 (69.8)	72 (72.7)	67 (67.0)
5: Hospitalization, requiring HFNC or noninvasive mechanical ventilation — no. (%)	31 (15.6)	15 (15.2)	16 (16.0)
6: Hospitalization, requiring ECMO, invasive mechanical ventilation, or both — no. (%)	1 (0.5)	1 (1.0)	0
Score on seven-category scale at day 7 — no. of patients (%)			
2: Not hospitalized, but unable to resume normal activities	4 (2.0)	4 (4.0)	0
3: Hospitalization, not requiring supplemental oxygen	29 (14.6)	12 (12.1)	17 (17.0)
4: Hospitalization, requiring supplemental oxygen	109 (54.8)	58 (58.6)	51 (51.0)
5: Hospitalization, requiring HFNC or noninvasive mechanical ventilation	35 (17.6)	14 (14.1)	21 (21.0)
6: Hospitalization, requiring ECMO, invasive mechanical ventilation, or both	10 (5.0)	6 (6.1)	4 (4.0)
7: Death	12 (6.0)	5 (5.1)	7 (7.0)
Seven-category scale at day 14 — no. of patients (%)			
2: Not hospitalized, but unable to resume normal activities	71 (35.7)	43 (43.4)	28 (28.0)
3: Hospitalization, not requiring supplemental oxygen	32 (16.1)	8 (8.1)	24 (24.0)
4: Hospitalization, requiring supplemental oxygen	45 (22.6)	25 (25.3)	20 (20.0)
5: Hospitalization, requiring HFNC or noninvasive mechanical ventilation	11 (5.5)	5 (5.1)	6 (6.0)
6: Hospitalization, requiring ECMO, invasive mechanical ventilation, or both	8 (4.0)	3 (3.0)	5 (5.0)
7: Death	32 (16.1)	15 (15.2)	17 (17.0)

Day: №1, 7, 14

Measurement: Clinical status

Method: The 7- category scale

National Early Warning Score 2

Physiological Parameters	3	2	1	0	1	2	3
Respiration Rate (BPM)	≤8		9-11	12-20		21-24	≥25
Oxygen Saturations (%)	≤91	92-93	94-95	≥96			
Any Supplemental Oxygen		Yes		No			
Temperature (°C)	≤35		35.1-36.0	36.1-38.0	38.1-39.0	≥39.1	
Systolic Blood Pressure (mmHg)	≤90	19-100	101-110	111-219			≥220
Heart Rate (BPM)	≤40		41-50	51-90	91-110	111-130	≥131
Level of Consciousness				A			V, P or U

The NEWS trigger system aligned to the scale of clinical risk.

NEWS Scores	Clinical Risk
0 Aggregate 1 - 4	Low
RED Score* (Individual parameter scoring 3) Aggregate 5 - 6	Medium
Aggregate 7 or more	High

Day №1

Measurement: Clinical risk

Method: National Early Warning Score 2 (NEWS2)

Virus testing in oropharyngeal swab samples:

Day: №1 (before lopinavir–ritonavir was administered) , 5, 10, 14, 21, 28 until discharge or death

Measurement: RT-PCR proportions with viral RNA detection over time

Method: RT-PCR

RESULTS: PRIMARY OUTCOMES

	Intention-to-treat population		modified intention-to-treat population*	
	lopinavir–ritonavir group	standard care group	lopinavir–ritonavir group	standard care group
clinical improvement	16 days	16 days	15 days	16 days
	hazard ratio =1.31; 95% CI, 0.95 -1.85;		hazard ratio = 1.39, 95% CI 1.00-1.91	

*excludes 3 patients who died within 24 hours of randomization before receiving lopinavir/ritonavir

RESULTS: SECONDARY OUTCOMES

Table 3. Outcomes in the Intention-to-Treat Population.*

Characteristic	Total (N=199)	Lopinavir–Ritonavir (N=99)	Standard Care (N=100)	Difference†
Time to clinical improvement — median no. of days (IQR)	16.0 (15.0 to 17.0)	16.0 (13.0 to 17.0)	16.0 (15.0 to 18.0)	1.31 (0.95 to 1.80)‡
Day 28 mortality — no. (%)	44 (22.1)	19 (19.2)§	25 (25.0)	−5.8 (−17.3 to 5.7)
Earlier (≤12 days after onset of symptoms)	21 (23.3)	8 (19.0)	13 (27.1)	−8.0 (−25.3 to 9.3)
Later (>12 days after onset of symptoms)	23 (21.1)	11 (19.3)	12 (23.1)	−3.8 (−19.1 to 11.6)
Clinical improvement — no. (%)				
Day 7	8 (4.0)	6 (6.1)	2 (2.0)	4.1 (−1.4 to 9.5)
Day 14	75 (37.7)	45 (45.5)	30 (30.0)	15.5 (2.2 to 28.8)
Day 28	148 (74.4)	78 (78.8)	70 (70.0)	8.8 (−3.3 to 20.9)
ICU length of stay — median no. of days (IQR)	10 (5 to 14)	6 (2 to 11)	11 (7 to 17)	−5 (−9 to 0)
Of survivors	10 (8 to 17)	9 (5 to 44)	11 (9 to 14)	−1 (−16 to 38)
Of nonsurvivors	10 (4 to 14)	6 (2 to 11)	12 (7 to 17)	−6 (−11 to 0)
Duration of invasive mechanical ventilation — median no. of days (IQR)	5 (3 to 9)	4 (3 to 7)	5 (3 to 9)	−1 (−4 to 2)
Oxygen support — days (IQR)	13 (8 to 16)	12 (9 to 16)	13 (6 to 16)	0 (−2 to 2)
Hospital stay — median no. of days (IQR)	15 (12 to 17)	14 (12 to 17)	16 (13 to 18)	1 (0 to 2)
Time from randomization to discharge — median no. of days (IQR)	13 (10 to 16)	12 (10 to 16)	14 (11 to 16)	1 (0 to 3)
Time from randomization to death — median no. of days (IQR)	10 (6 to 15)	9 (6 to 13)	12 (6 to 15)	−3 (−6 to 2)

Characteristic	Total (N=199)	Lopinavir–Ritonavir (N=99)	Standard Care (N=100)	Difference†
Score on seven-category scale at day 7 — no. of patients (%)				
2: Not hospitalized, but unable to resume normal activities	4 (2.0)	4 (4.0)	0	
3: Hospitalization, not requiring supplemental oxygen	29 (14.6)	12 (12.1)	17 (17.0)	
4: Hospitalization, requiring supplemental oxygen	109 (54.8)	58 (58.6)	51 (51.0)	
5: Hospitalization, requiring HFNC or noninvasive mechanical ventilation	35 (17.6)	14 (14.1)	21 (21.0)	
6: Hospitalization, requiring ECMO, invasive mechanical ventilation, or both	10 (5.0)	6 (6.1)	4 (4.0)	
7: Death	12 (6.0)	5 (5.1)	7 (7.0)	
Seven-category scale at day 14 — no. of patients (%)				
2: Not hospitalized, but unable to resume normal activities	71 (35.7)	43 (43.4)	28 (28.0)	
3: Hospitalization, not requiring supplemental oxygen	32 (16.1)	8 (8.1)	24 (24.0)	
4: Hospitalization, requiring supplemental oxygen	45 (22.6)	25 (25.3)	20 (20.0)	
5: Hospitalization, requiring HFNC or noninvasive mechanical ventilation	11 (5.5)	5 (5.1)	6 (6.0)	
6: Hospitalization, requiring ECMO, invasive mechanical ventilation, or both	8 (4.0)	3 (3.0)	5 (5.0)	
7: Death	32 (16.1)	15 (15.2)	17 (17.0)	

VIROLOGY

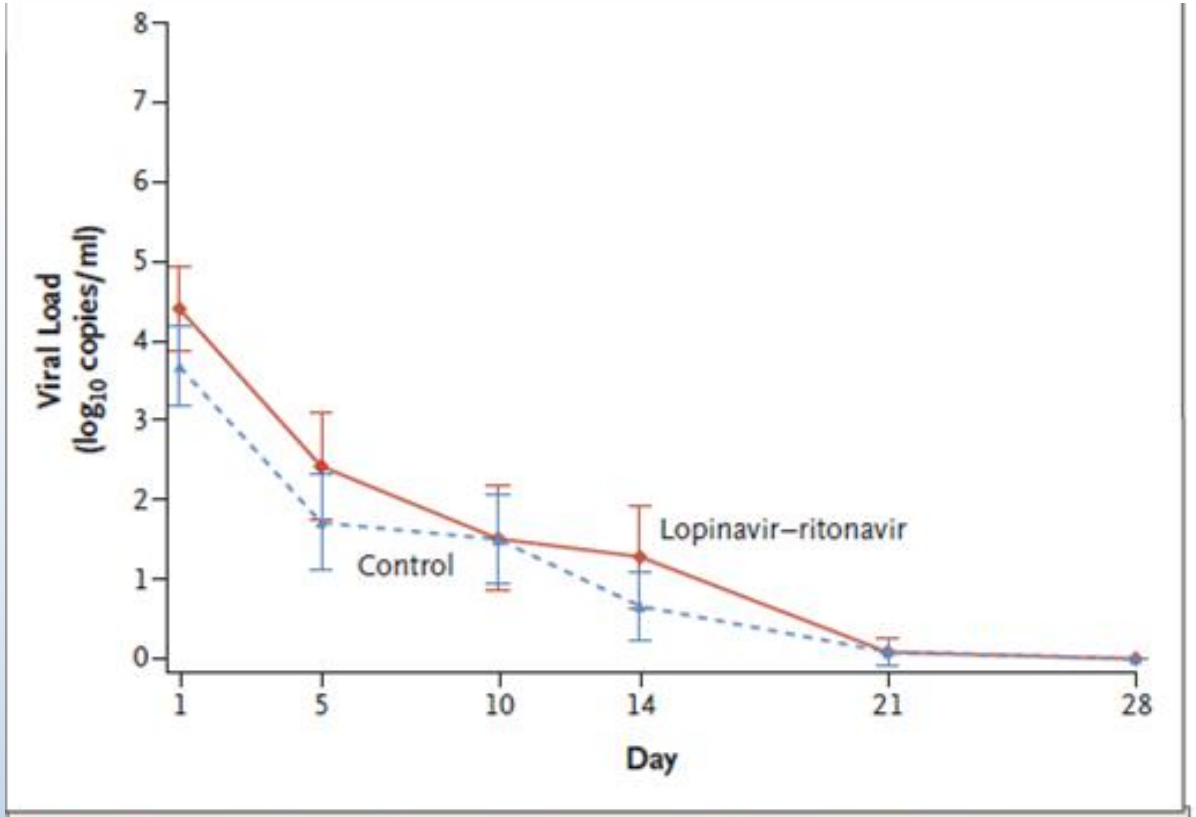


Figure 3. Mean Change from Baseline in SARS-CoV-2 Viral RNA Load by qPCR on Throat Swabs.

I bars indicate 95% confidence intervals. Results less than the lower limit of quantification of polymerase-chain-reaction (PCR) assay and greater than the limit of qualitative detection are imputed with 1 $\log_{10}$ copies per milliliter; results for patients with viral-negative RNA are imputed with 0 $\log_{10}$ copies per milliliter. Among the 199 patients, 130 (59 patients in the lopinavir–ritonavir group and 71 in the standard-care group) had virologic data that were used for viral load calculation, whereas the rest of the patients had undetectable viral RNA on throat swabs over the time.

SAFETY

Event	Lopinavir/Ritonavir group	Standard care group
Adverse events	46 patients (48.4%)	49 (49.5%)
Gastrointestinal adverse events (nausea, vomiting, and diarrhea)	more common	
Percentages of patients with **laboratory abnormalities**	Similar	
Serious adverse events	19 patients	32 patients
Serious gastrointestinal adverse events	4 patients	none
Respiratory failure, acute kidney injury, and secondary infection		more common
Deaths	unrelated to the intervention	

Table 4. Summary of Adverse Events in the Safety Population.*

Event	Lopinavir–Ritonavir (N=95)		Standard Care (N=99)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number (percent)			
Any adverse event	46 (48.4)	20 (21.1)	49 (49.5)	11 (11.1)
Lymphopenia	16 (16.8)	12 (12.6)	12 (12.1)	5 (5.1)
Nausea	9 (9.5)	1 (1.1)	0	0
Thrombocytopenia	6 (6.3)	1 (1.1)	10 (10.1)	2 (2.0)
Leukopenia	7 (7.4)	1 (1.1)	13 (13.1)	0
Vomiting	6 (6.3)	0	0	0
Increased aspartate aminotransferase	2 (2.1)	2 (2.1)	5 (5.1)	4 (4.0)
Abdominal discomfort	4 (4.2)	0	2 (2.1)	0
Diarrhea	4 (4.2)	0	0	0
Stomach ache	4 (4.2)	1 (1.1)	1 (1.0)	0
Neutropenia	4 (4.2)	1 (1.1)	8 (7.6)	0
Increased total bilirubin	3 (3.2)	3 (3.2)	3 (3.0)	2 (2.0)
Increased creatinine	2 (2.1)	2 (2.1)	7 (7.1)	6 (6.1)
Anemia	2 (2.1)	2 (2.1)	5 (5.0)	4 (4.0)
Rash	2 (2.1)	0	0	0
Hypoalbuminemia	1 (1.1)	1 (1.1)	4 (4.0)	1 (1.0)
Increased alanine aminotransferase	1 (1.1)	1 (1.1)	4 (4.0)	1 (1.0)
Increased creatine kinase	0	0	1 (1.0)	0

National Cancer Institute Common Terminology
Criteria for Adverse Events, version 4.0.

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

ADL - Activities of Daily Living
AE- adverse event

Event	Lopinavir–Ritonavir (N=95)		Standard Care (N=99)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Increased alanine aminotransferase	1 (1.1)	1 (1.1)	4 (4.0)	1 (1.0)
Increased creatine kinase	0	0	1 (1.0)	0
Decreased appetite	2 (2.1)	0	0	0
Prolonged QT interval	1 (1.1)	0	0	0
Sleep disorders and disturbances	1 (1.1)	0	0	0
Facial flushing	1 (1.1)	0	0	0
Serious adverse event	19 (20.0)	17 (17.9)	32 (32.3)	31 (31.3)
Respiratory failure or ARDS	12 (12.6)	12 (12.6)	27 (27.3)	27 (27.3)
Acute kidney injury	3 (3.2)	2 (2.1)	6 (6.1)	5 (5.1)
Secondary infection	1 (1.1)	1 (1.1)	6 (6.1)	6 (6.1)
Shock	2 (2.1)	2 (2.1)	2 (2.0)	2 (2.0)
Severe anemia	3 (3.2)	3 (3.2)	0	0
Acute gastritis	2 (2.1)	0	0	0
Hemorrhage of lower digestive tract	2 (2.1)	1 (1.1)	0	0
Pneumothorax	0	0	2 (2.0)	2 (2.0)
Unconsciousness	1 (1.1)	0	0	0
Disseminated intravascular coagulation	1 (1.1)	0	1 (1.0)	1 (1.0)
Sepsis	0	0	1 (1.0)	1 (1.0)
Acute heart failure	0	0	1 (1.0)	1 (1.0)

CONCLUSION

- Were patients randomized?

  ✔Yes

- Was randomization concealed?

  ✔No

- Were patients analyzed in the groups to which they were randomized?

  ✔Yes

- Were methods (oropharyngeal swab samples) optimal?

  ✓ They were taken intermittently (on days 1, 5, 10, 14, 21, 28)

  ✓ Previous studies have shown that throat-swab specimens have lower viral loads than nasopharyngeal samples

  ✓ The researchers were unable to do sampling of lower respiratory tract secretions

- Can we use higher or more prolonged lopinavir–ritonavir dose regimens in efforts to improve outcomes?

  ✓ 14% lopinavir–ritonavir recipients were unable to complete the full 14-day course of administration due to adverse events

- What are the differences between groups in the frequency of use of concurrent pharmacologic interventions (Ex.glucocorticoids, antibiotics, vasopressors)?

  ✓ This might have been another confounder.

CONCLUSION

Lopinavir–ritonavir treatment

- no efficacy in a randomised open-label study (lopinavir/ritonavir vs standard care)
- no significant benefit in overall mortality or reduction in viral load.
- reduced serious complications or requiring non- or invasive mechanical ventilation for respiratory failure

Limitations:

- lack of treatment blinding- reducing study objectivity.
- lack of information about used medications

WILL THE RESULTS HELP ME IN CARING FOR MY PATIENTS?

-Yes, lopinavir-ritonavir treatment is used for seriously ill patients with Covid-19 in Russia

Discussion notes

1)Why only 130 patients (total amount=199) viral load was detectable and analyzed?

- The swab samples were taken only from the throat, and the localization of the virus can depend on the duration of the disease each patient individually

(e.g. if the disease started long ago it will localize more often in the lower part of respiratory tract, and when we take only throat swabs - the results might be incorrect)

2) Is it enough to use subjective clinical scale as a primary outcome measure and only one objective laboratory method (which shown limitation) to analyze the results of the clinical trial?

- Usually subjective method is not superior to objective, however given the uncertainty in the mechanism of disease the clinical scale might be good source for assessing treatment effect. However only RT-PCR testing is not enough. Its necessary to use a combination of methods: inflammation markers (Ex.C-reactive protein), which can correlate with the severity of disease, CT scan in addition to the clinical picture based on 7-category scale. However, we still do not know which inflammatory markers would be sensitive to assess the effect of therapy and we do not know how long it might take to see CT scan changes (probably too much time)

Discussion notes (continue)

3) The usage of the glucocorticoids could influence greatly on the results of both groups. Today is known, that this medicine is not recommended to use for patients with Covid19, as it can intensify the cytokine storm and increase the viral loads.

4) The increasing of dose regimes can lead only to the rising of adverse events. Less benefits than risk.

5) To examine possible impact of aggressive course of the disease on the clinical improvement was chosen the <=/>12th day after onset of symptoms as it is the median time from symptom onset to laboratory confirmation. The suggestion was to use 5-7 days as a cutoff.

More information about the trial you can find on website:
http://www.chictr.org.cn/showprojen.aspx?proj=48684

Presenter: valentine.borovskaya@gmail.com

Mentor: mvetrova111@gmail.com