Morning Brief : Scientific Review

10 June 2020

The purpose of the Morning Brief is to **summarize** and present key information, research articles and other relevant publications pertaining to critical care and COVID-19. We aim to prioritise information, articles and publications released in the preceding 24-48hours.

Stellenbosch University Research Response Team

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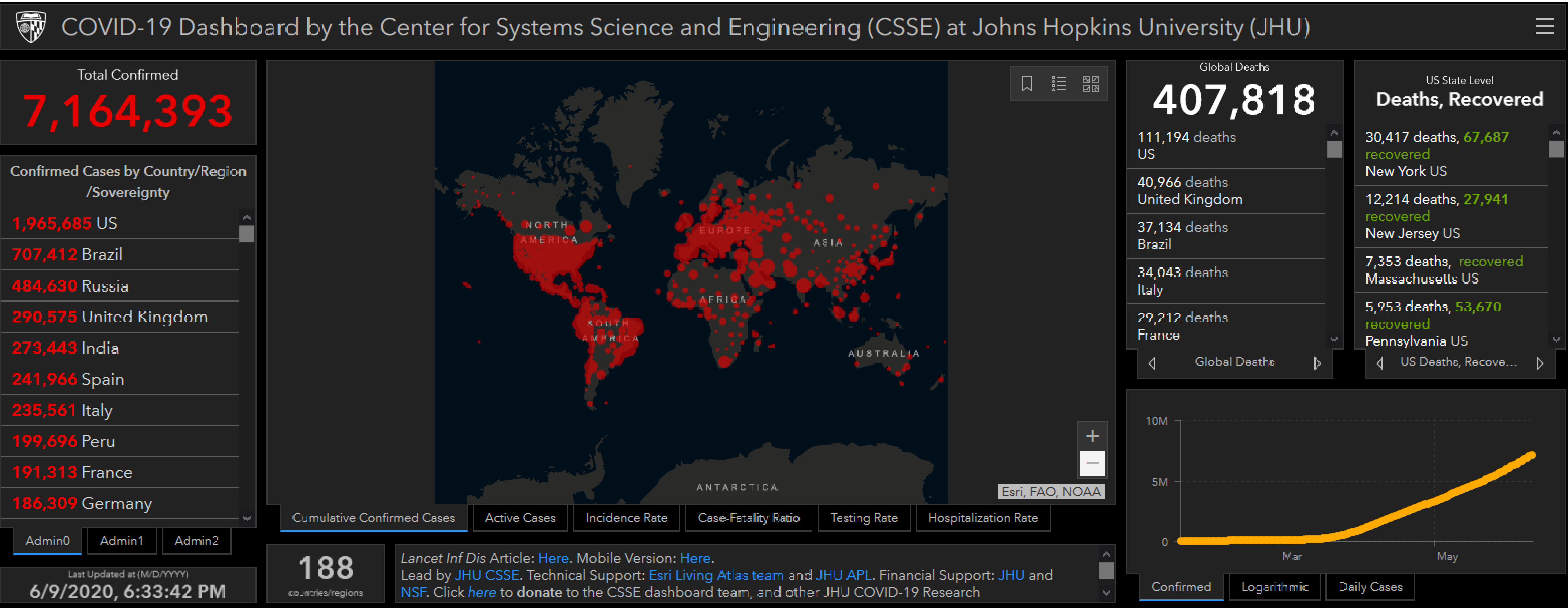
Content of the brief

- **Global Statistics**
- **South African Statistics**
- **Topic: Hydroxychloroquine and Convalescent Plasma**

Global Statistics



Source: https://coronavirus.jhu.edu/map.html

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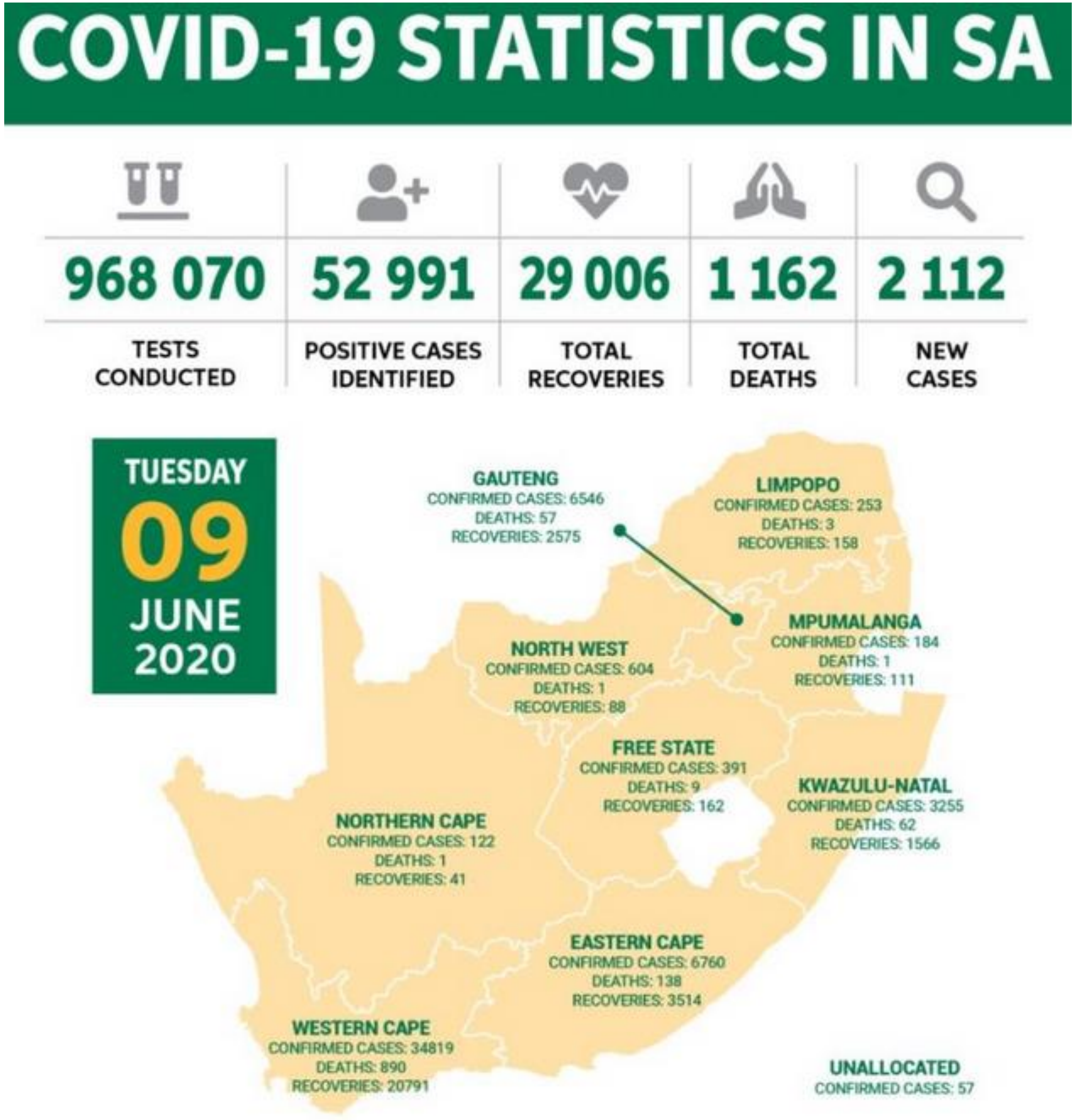
South African Statistics



Source: https://sacoronavirus.co.za

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Articles of Interest

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Surgisphere: governments and WHO changed Covid-19 policy based on suspect data from tiny US company

Surgisphere, whose employees appear to include a sci-fi writer and adult content model, provided database behind Lancet and New England Journal of Medicine hydroxychloroquine studies

Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Mandeep R Mehra, Sapan S Desai, Frank Ruschitzka, Amit N Patel

Summary

Background Hydroxychloroquine or chloroquine, often in combination with a second-generation macrolide, are being widely used for treatment of COVID-19, despite no conclusive evidence of their benefit. Although generally safe when used for approved indications such as autoimmune disease or malaria, the safety and benefit of these treatment regimens are poorly evaluated in COVID-19.

Methods We did a multinational registry analysis of the use of hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19. The registry comprised data from 671 hospitals in six continents. We included patients hospitalised between Dec 20, 2019, and April 14, 2020, with a positive laboratory finding for SARS-CoV-2. Patients who received one of the treatments of interest within 48 h of diagnosis were included in one of four treatment groups (chloroquine alone, chloroquine with a macrolide, hydroxychloroquine alone, or hydroxychloroquine with a macrolide), and patients who received none of these treatments formed the control group. Patients for whom one of the treatments of interest was initiated more than 48 h after diagnosis or while they were on mechanical ventilation,

Published Online
May 22, 2020
https://doi.org/10.1016/S0140-6736(20)31180-6
See Online/Comment
https://doi.org/10.1016/S0140-6736(20)31174-0

Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, Boston, MA, USA (Prof M R Mehra MD); Surgisphere Corporation, Chicago, IL, USA (S S Desai MD);

This article has been retracted.

ORIGINAL ARTICLE

Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19

Mandeep R. Mehra, M.D., Sapan S. Desai, M.D., Ph.D., SreyRam Kuy, M.D., M.H.S., Timothy D. Henry, M.D., and Amit N. Patel, M.D.

Article Figures/Media Metrics

22 References 45 Citing Articles

May 1, 2020
DOI: 10.1056/NEJMoa2007621

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RECOVERY
Randomised Evaluation of COVID-19 Therapy

Statement from the Chief Investigators of the Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial on hydroxychloroquine, 5 June 2020

No clinical benefit from use of hydroxychloroquine in hospitalised patients with COVID-19

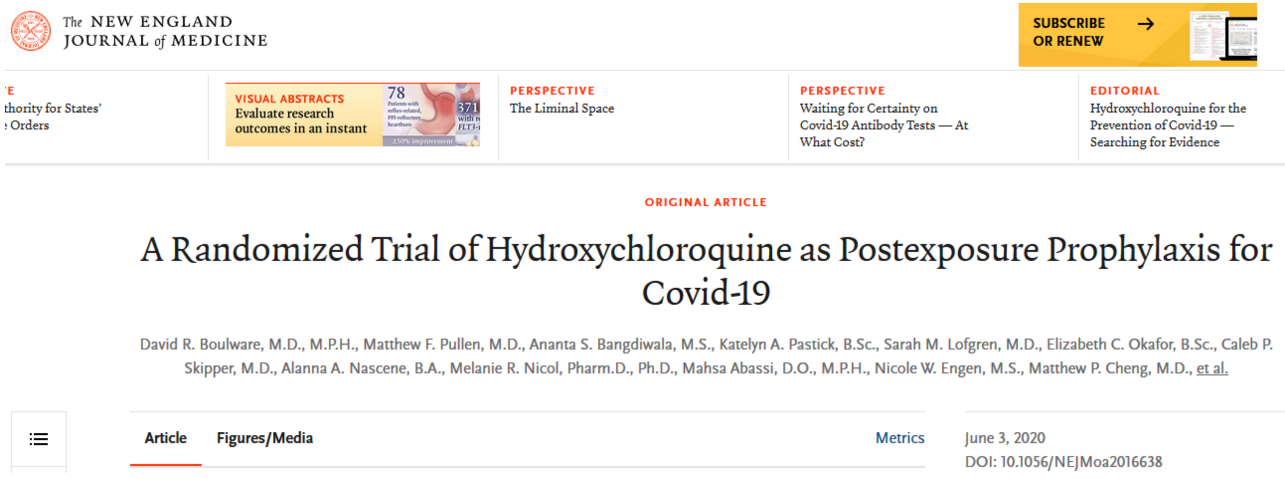
Professor Peter Horby and Professor Martin Landray, chief investigators of the RECOVERY Trial, said ‘In March this year, RECOVERY was established as a randomised clinical trial to test a range of potential drugs for COVID-19, including hydroxycholoroquine.

‘The trial has proceeded at unprecedented speed, enrolling over 11,000 patients from 175 NHS hospitals in the UK. Throughout this time, the independent Data Monitoring Committee has reviewed the emerging data about every two weeks to determine if there is evidence that would be strong enough to affect national and global treatment of COVID-19.

‘On Thursday 4 June, in response to a request from the UK Medicines and Healthcare Products Regulatory Agency (MHRA), the independent Data Monitoring Committee conducted a further review of the data. Last night, the Committee recommended the chief investigators review the unblinded data on the hydroxychloroquine arm of the trial.

‘We have concluded that there is no beneficial effect of hydroxychloroquine in patients hospitalised with COVID-19. We have therefore decided to stop enrolling participants to the hydroxychloroquine arm of the RECOVERY trial with immediate effect. We are now releasing the preliminary results as they have important implications for patient care and public health.

https://www.recoverytrial.net/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PERSPECTIVE The Liminal Space

PERSPECTIVE Waiting for Certainty on Covid-19 Antibody Tests — At What Cost?

EDITORIAL Hydroxychloroquine for the Prevention of Covid-19 — Searching for Evidence

ORIGINAL ARTICLE

A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19

David R. Boulware, M.D., M.P.H., Matthew F. Pullen, M.D., Ananta S. Bangdiwala, M.S., Katelyn A. Pastick, B.Sc., Sarah M. Lofgren, M.D., Elizabeth C. Okafor, B.Sc., Caleb P. Skipper, M.D., Alanna A. Nascene, B.A., Melanie R. Nicol, Pharm.D., Ph.D., Mahsa Abassi, D.O., M.P.H., Nicole W. Engen, M.S., Matthew P. Cheng, M.D., et al.

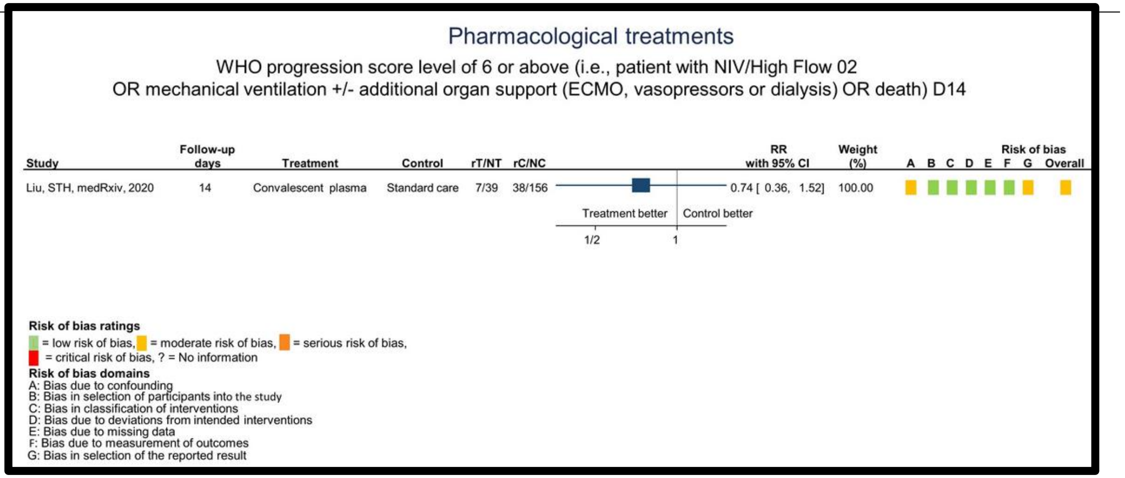
Article Figures/Media Metrics

June 3, 2020
DOI: 10.1056/NEJMoa2016638

Boulware, D R et al, NEJM, June 3, 2020 DOI: 10.1056/NEJMoa2016638

Trial *
Publication Liu, STH, medRxiv, 2020
Dates: 3/24/2020 to 4/8/2020

Methods	Quasi-Experimental Study Location : Single center / USA Follow-up duration (days): 14
Inclusion criteria	Adult patients were identified as eligible for COVID-19 convalescent plasma transfusion under the criteria established for the FDA single patient emergency investigational new drug (eIND) process.
Exclusion criteria	Missing Data
Interventions	**Treatment** Convalescent plasma (2 units (approx 250ml X2)) Co-Intervention: Standard care Duration : Over 2-3 hours **Control** Standard care **Definition of Standard care:** In addition to receiving convalescent plasma transfusion, many recipients received a variety of inpatient pharmacotherapies throughout their hospitalizations (Table 2). There were no significant differences between plasma recipients and control patients in exposures to measured pharmacotherapies, except for therapeutic anticoagulation.



Participants	**Randomized** 195 participants (n_1=156 / n_2= 39) **Characteristics of participants** N=195 Mean age : 54,3 131 males Severity : Mild: n=0 / Moderate: n=32/ Severe: n=143
Primary outcome	**In the register** NR **In the report** Supplemental O2 requirements and Survival
Documents avalaible	**Protocol** No **Statistical plan** No **Data-sharing stated** Yes
Risk of bias Overall The overall risk of bias reported in the table corresponds to the highest risk of bias for the outcomes assessed for the systematic review	Moderate

Quasi-experimental study

https://covid-nma.com/emulated/ Accessed 9 June 2020, 16:00

Trial ChiCTR2000029757
Publication Li L, Jama, 2020
Dates: 2/14/2020 to 4/1/2020
Funding: Public

https://covid-nma.com/living_data/index.php/ Accessed 9 June 2020, 16:00

Randomised controlled trial

Methods	RCT Location : Multicenter / china Follow-up duration (days): 28
Inclusion criteria	(1) signed informed consent; (2) aged at least 18 years; (3) COVID-19 diagnosis based on polymerase chain reaction (PCR) testing; (4) positive PCR resultwithin 72 hours prior to randomization; (5) pneumonia confirmed by chest imaging; (6) clinical symptomsmeeting the definitions of severe or life-threatening COVID-19; (7) acceptance of random group assignment; (8) hospital admission; (9)willingness to participate in all necessary research studies and be able to complete the study follow-up; and (10) no participation in other clinical trials, such as antiviral trials, during the study period.
Exclusion criteria	(1) pregnancy or lactation; (2) immunoglobulin allergy; (3) IgA deficiency; (4) preexisting comorbidity that could increase the risk of thrombosis; (5) life expectancy less than 24 hours; (6) disseminated intravascular coagulation; (7) severe septic shock; (8) PaO2/ FIO2 of less than 100; (9) severe congestive heart failure; (10) detection of high titer of S proteinRBD-specific (receptor binding domain) IgG antibody (?1:640); (11) other contraindications as determined by the patients physicians; and (12) participation in any antiviral clinical trials for COVID-19 within 30 days prior to enrollment.
Interventions	**Treatment** Convalescent plasma (4 to 13 mL/kg) Co-Intervention: Standard care Duration : Over 2-3 hours **Control** Standard care **Definition of Standard care:** Standard treatment consisted of symptomatic control and supportive care for COVID-19, mostly based on the evolving Chinese national COVID-19 treatment guidelines and hospital practice.12 Possible treatments included antiviral medications, antibacterial medications, steroids, human immunoglobulin, Chinese herbal medicines, and other medications.
Participants	**Randomized** 103 participants (n_1=51 / n_2= 52) **Characteristics of participants** N=103 Mean age : NR 60 males Severity : Mild: n=0 / Moderate: n=0/ Severe: n=45
Primary outcome	**In the register** the number of days between randomised grouping and clinical improvement **In the report** time to clinical improvement within 28 days
Documents avalaible	**Protocol** Yes. In English **Statistical plan** Yes **Data-sharing stated** yes
Risk of bias Overall The overall risk of bias reported in the table corresponds to the highest risk of bias for the outcomes assessed for the systematic review	High

In addition to all available versions of the published/pre-print article, the study registry, protocol, and statistical analysis plan were used in data extraction and risk of bias assessment. There is no change from the trial registration in the intervention and control treatments. The primary outcome in the report reflects the primary outcome indicated in the registry. The containment of the pandemic in Wuhan led to a decrease in new Covid-19 cases. This did not permit the study to reach its recruitment target. After discussion with the expert committee of the Institute of Blood Transfusion, the study was terminated on 1/4/20 by the sponsor (Chinese Academy ofMedical Sciences) and the leading primary investigator on April 1, 2020. Some analyses (e.g., clinical improvement rates) were not pre-specified. Some pre-specified secondary outcomes are not reported in the paper (e.g., duration of ECMO). The authors report only adverse events related to plasma convalescent therapy.

Trial ChiCTR2000029757
Publication Li L, Jama, 2020

Pharmacological treatments

Incidence of viral negative conversion D3

Study	Follow up days	Intervention1	Intervention2	r1/N1	r2/N2	RR with 95% CI	Weights(%)	Risk of Bias
Moderate/severe								
Li L, Jama, 2020	28	Convalescent plasma	Standard Care	41/52	16/51	2.51 [1.64,3.86]	100%	A B C D E Overall
						2.51 [1.64,3.86]		

Intervention2 better | Intervention1 better

0.2 1 5

Risk Ratio

Risk of bias ratings:
Low Risk of Bias · Some Concerns · High Risk of Bias

Risk of Bias Domains:
A: Bias due to randomization
B: Bias due to deviation from intended intervention
C: Bias due to missing data
D: Bias due to outcome measurement
E: Bias due to selection of reported result

Deviations from intervention

High

Comment: Unblinded study. One participant in the control group received the treatment group intervention. Information on co-interventions is presented in Table 2. A greater proportion of participants in the treatment group received interferon, human immunoglobulin, antifungal and steroid co-interventions, compared to the control group. This could have been affected by knowledge of participants' allocation and it could, in turn, have affected the outcomes. Efficacy outcome data were analyzed by using intention-to-treat analysis. Safety outcomes were analyzed as-treated.

https://covid-nma.com/living_data/index.php/ Accessed 9 June 2020, 16:00

This summary was prepared by Dr E Maasdorp as part of the daily brief to the TBH ICU team.