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Morning Brief : Scientific Review

15 May 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

STELLENBOSCH UNIVERSITY PULMONOLOGY

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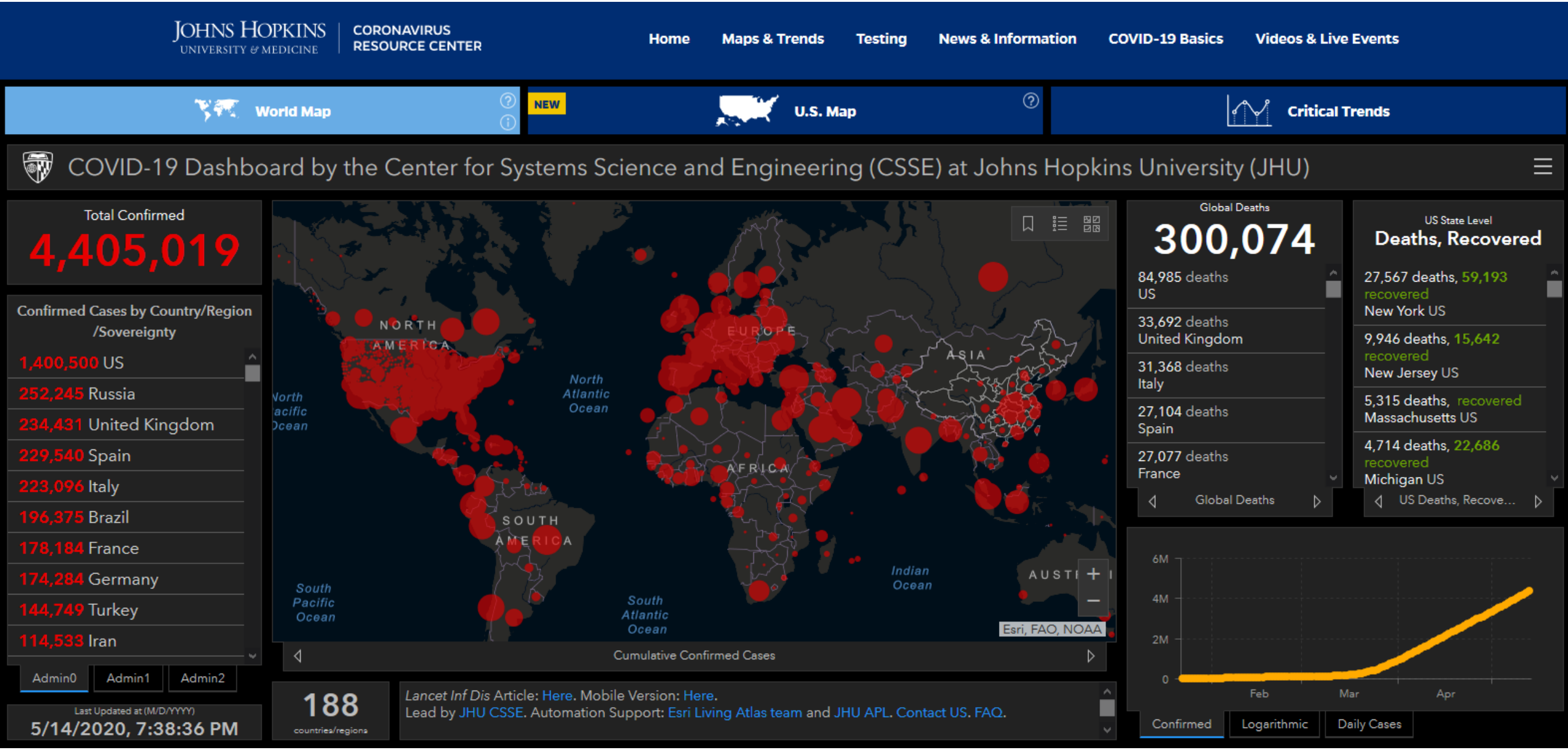
Content of the brief

- Global Statistics
- South African Statistics
- Topic: 2 Treatment trials



Accessed at 19:50 on 14 May 2020
Source: https://coronavirus.jhu.edu/map.html

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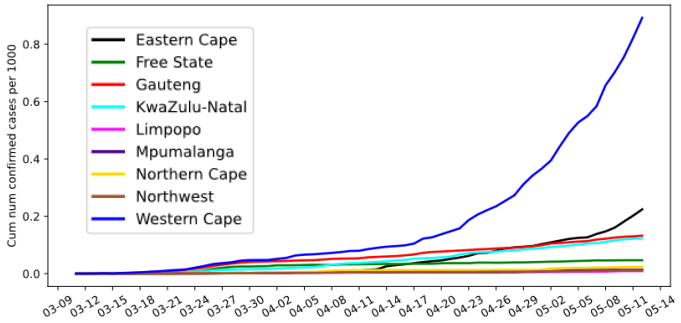
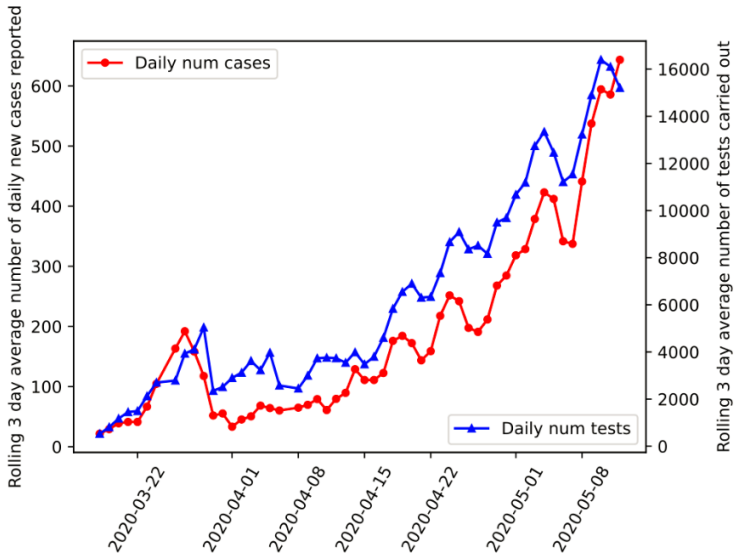
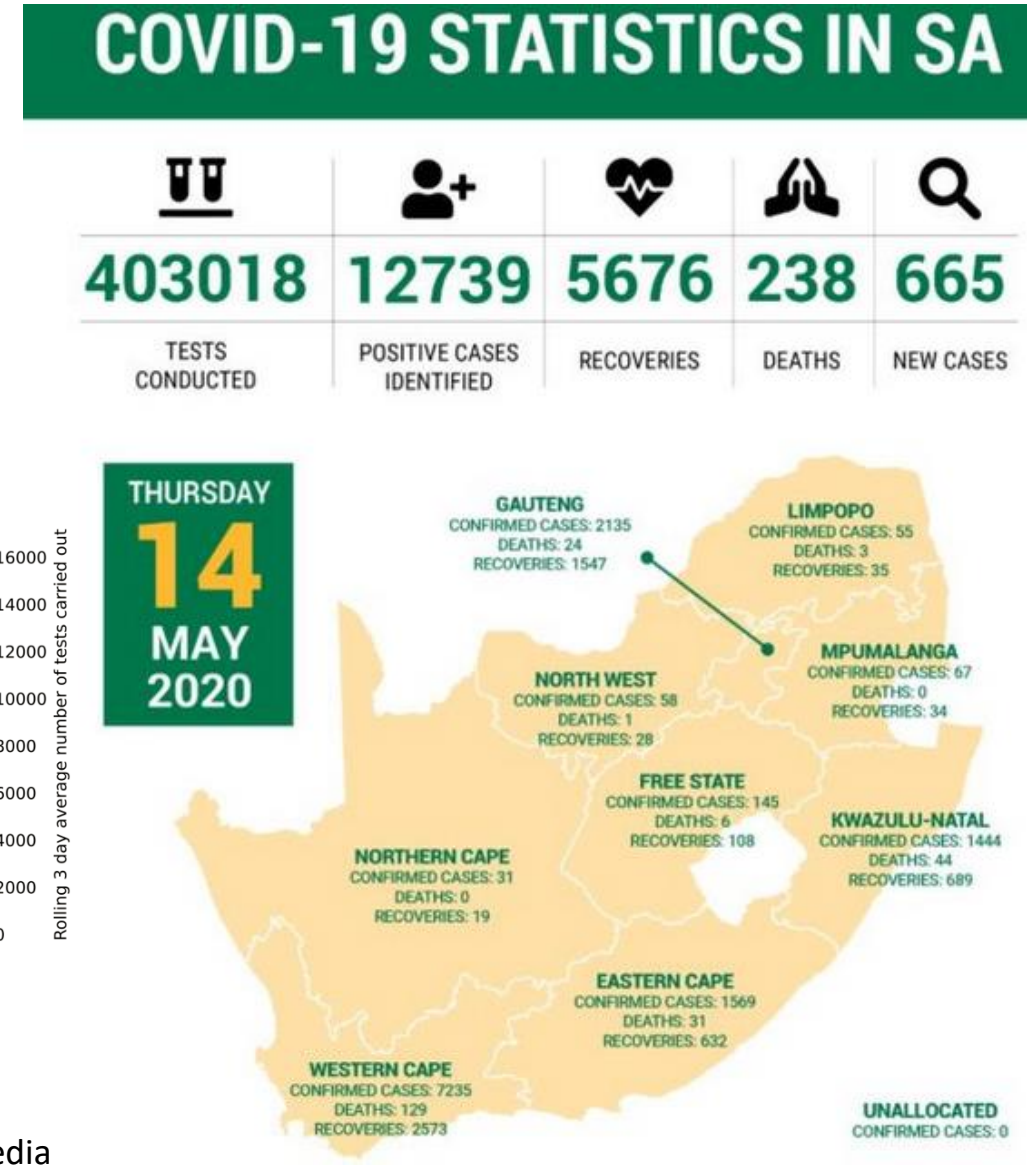
South African Statistics







Province	Total cases for 14 May 2020	Percentage total
Eastern Cape	1569	12,3
Free State	145	1,1
Gauteng	2135	16,8
KwaZulu-Natal	1444	11,3
Limpopo	55	0,4
Mpumalanga	67	0,5
North West	58	0,5
Northern Cape	31	0,2
Western Cape	7235	56,8
Unknown	0	0,0
Total	12 739	100,0

Province	Deaths	Recoveries
Eastern Cape	31	643
Free State	6	108
Gauteng	24	1547
KwaZulu Natal	44	689
Limpopo	3	35
Mpumalanga	0	34
North West	1	28
Northern Cape	0	19
Western Cape	129	2573
Total	238	5676

Accessed at 19:33 on 14 May 2020
Source: https://sacoronavirus.co.za, wikipedia

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Articles of Interest

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ORIGINAL ARTICLE

Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19

Joshua Geleris, M.D., Yifei Sun, Ph.D., Jonathan Platt, Ph.D., Jason Zucker, M.D., Matthew Baldwin, M.D., George Hripcsak, M.D., Angelena Labella, M.D., Daniel Manson, M.D., Christine Kubin, Pharm.D., R. Graham Barr, M.D., Dr.P.H., Magdalena E. Sobieszczyk, M.D., M.P.H., and Neil W. Schluger, M.D.

Geleris, J et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19, NEJM, May 7, 2020 DOI: 10.1056/NEJMoa2012410

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Background

- Chloroquine and hydroxhloroquine are widely used in the treatment of rheumatological diseases
- They have been suggested as effective treatments for COVID-19 on the grounds of both antiinflammatory and antiviral effects
- to date, there have been no robust clinical trials that have shown efficacy of these agents for COVID-19
- And the data that are available come from small studies that have either been
  - uncontrolled or
  - Underpowered to detect meaningful clinical effects

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- Recent work suggests that hydroxychloroquine has more potent antiviral properties than chloroquine, as well as a better safety profile.
- Therefore its use in this study for hospitalized patients with Covid-19 and respiratory difficulty

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Aim

“the association between hydroxychloroquine use and respiratory failure at a large medical center in New York City”

Hypothesis

“hydroxychloroquine use would be associated with a lower risk of a composite end point of intubation or death”

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Methods

- Conducted this study at a quaternary, acute care hospital in northern Manhattan between 07 March and 08 April 2020
- Follow up continued through 25 April 2020
- Data were obtained regarding consecutive patients hospitalized with Covid-19,
- They excluded those who were intubated, died, or discharged within 24 hours after presentation to the emergency department (study baseline).
- The primary end point was a composite of intubation or death in a time-to-event analysis.
- They compared outcomes in patients who received HCQ with those in patients who did not

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- Patients with Covid-19 who presented with moderate-to-severe respiratory illness, which was defined as a resting oxygen saturation of less than 94% on RA
- The suggested hydroxychloroquine regimen was a loading dose of 600 mg twice on day 1, followed by 400 mg daily for 4 additional days.
- Azithromycin at a dose of 500 mg on day 1 and then 250 mg daily for 4 more days in combination with hydroxychloroquine was an additional suggested therapeutic option.
- The decision to prescribe either or both medications was left to the discretion of the treating team for each individual patient.

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Results

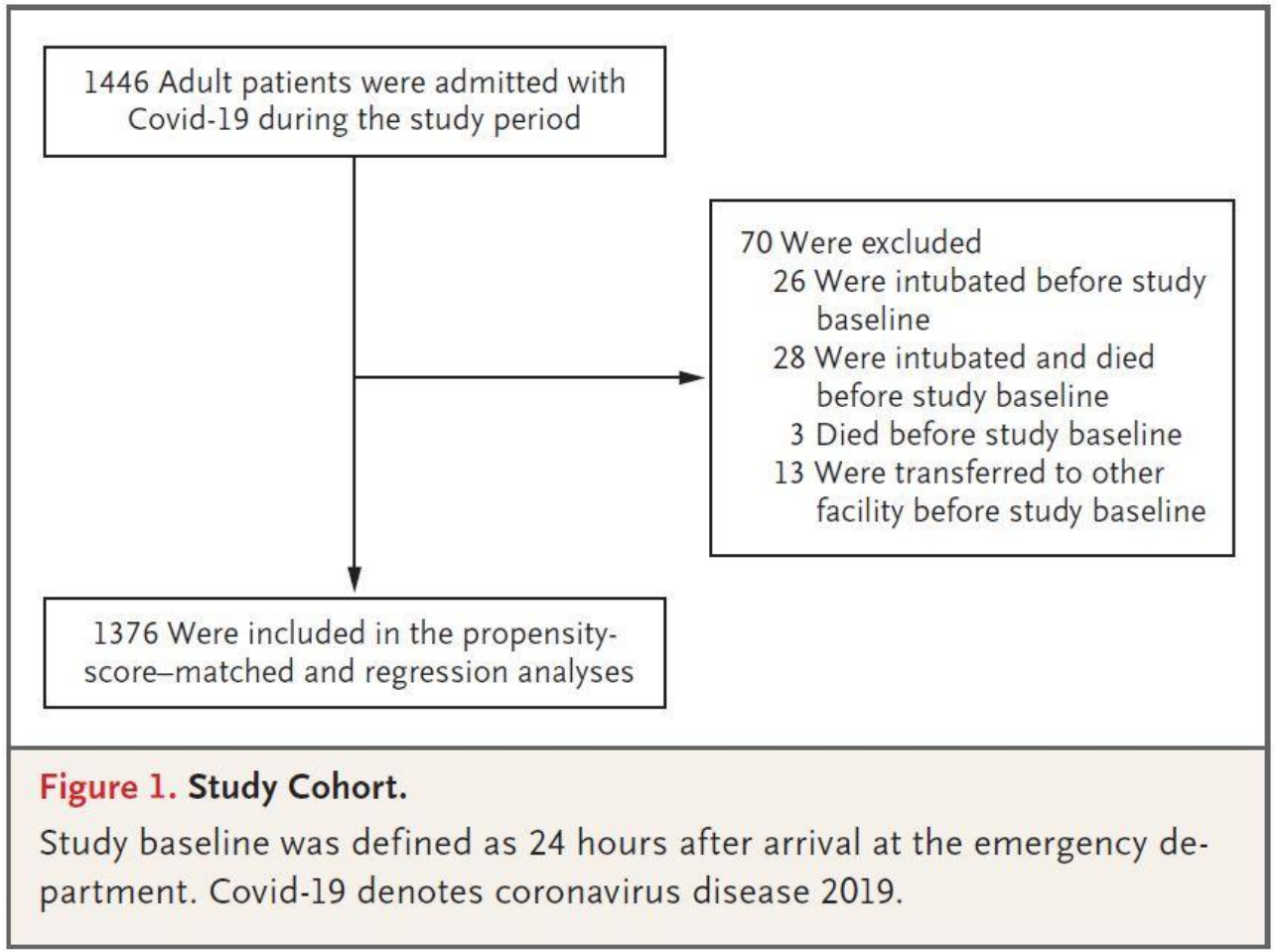

Figure 1. Study Cohort.

Study baseline was defined as 24 hours after arrival at the emergency department. Covid-19 denotes coronavirus disease 2019.

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Results

- 1446 consecutive patients with Covid-19 who were admitted to the hospital between March 7 and April 8, 2020,
- 70 patients were excluded because they had already
  - intubation or death,
  - were discharged after inpatient admission, or
  - were directly admitted to alternative facilities within 24 hours after presentation to the emergency department
- Therefore only 1376 patients were included in the analysis

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Study End Points

- the primary end point of respiratory failure developed in 346 patients (25.1%)
  - 180 patients were intubated, and 166 died without intubation
- In the primary multivariable analysis there was no significant association between hydroxychloroquine use and the composite primary end point.
- There was also no significant association between treatment with azithromycin and the composite end point

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Of note:

- Hydroxychloroquine-treated patients had a lower PF-ratio at baseline than did patients who did not receive hydroxychloroquine (median, 233 vs. 360 mm Hg).
- 27 patients received remdesivir according to compassionate use,
- 30 patients were enrolled in a randomized, blinded, placebo controlled trials of that investigational agent or of sarilumab.

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Shortcomings

- Not randomized
- The single-center design may limit the generalizability of these results.
- The authors adjusted for likely confounders such as age, race and ethnic group, body-mass index, diabetes, underlying kidney disease, chronic lung disease, hypertension, baseline vital signs, Pao2:Fio2, and inflammatory markers.
  - Despite this extensive adjustment, it is still possible that some amount of unmeasured confounding remains

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Conclusion

- Therefore the risk of intubation or death was not significantly higher or lower among patients who received hydroxychloroquine than among those who did not (hazard ratio, 1.04; 95% CI, 0.82 to 1.32).

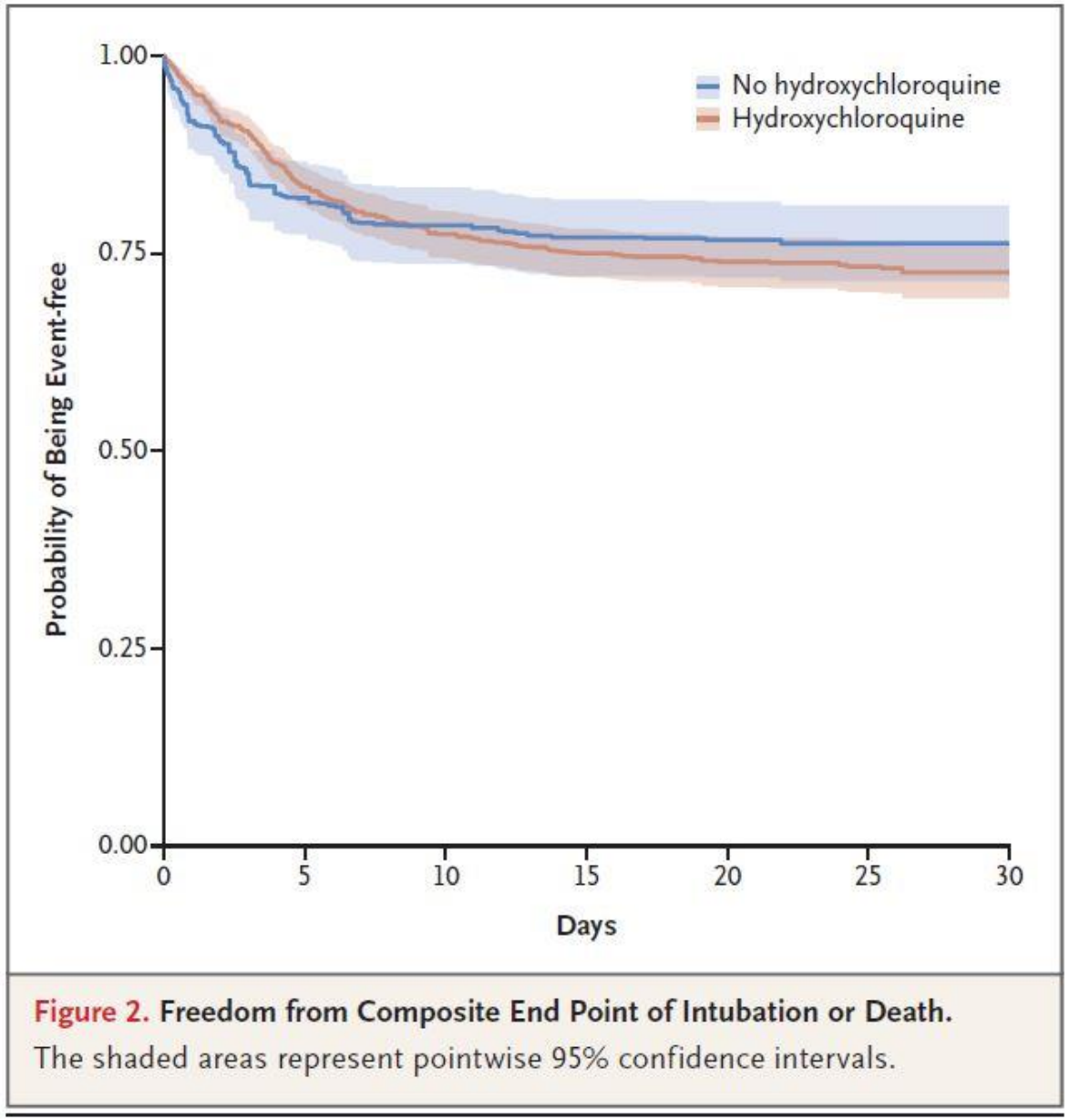

Figure 2. Freedom from Composite End Point of Intubation or Death.
The shaded areas represent pointwise 95% confidence intervals.

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Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial

Ivan Fan-Ngai Hung, Kwok-Cheung Lung, Eugene Yuk-Keung Tso, Raymond Liu, Tom Wai-Hin Chung, Man-Yee Chu, Yuk-Yung Ng, Jenny Lo, Jacky Chan, Anthony Raymond Tam, Hoi-Ping Shum, Veronica Chan, Alan Ka-Lun Wu, Kit-Man Sin, Wai-Shing Leung, Wai-Lam Law, David Christopher Lung, Simon Sin, Pauline Yeung, Cyril Chik-Yan Yip, Ricky Ruiqi Zhang, Agnes Yim-Fong Fung, Erica Yuen-Wing Yan, Kit-Hang Leung, Jonathan Daniel Ip, Allen Wing-Ho Chu, Wan-Mui Chan, Anthony Chin-Ki Ng, Rodney Lee, Kitty Fung, Alwin Yeung, Tak-Chiu Wu, Johnny Wai-Man Chan, Wing-Wah Yan, Wai-Ming Chan, Jasper Fuk-Woo Chan, Albert Kwok-Wai Lie, Owen Tak-Yin Tsang, Vincent Chi-Chung Cheng, Tak-Lun Que, Chak-Sing Lau , Kwok-Hung Chan, Kelvin Kai-Wang To, Kwok-Yung Yuen

Hung, IFN et al. Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial, May 8, 2020 https://doi.org/10.1016/S0140-6736(20)31042-4.

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Background

- Many repurposed drugs have been shown to have in-vitro activity against the close relatives of SARS-CoV-2
- Lopinavir and many interferons, particularly interferon beta, have been shown to have modest activity in vitro against SARS-CoV and Middle East respiratory syndrome (MERS)-CoV, and can be used synergistically with ribavirin.

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Historically 2003

- An open-label trial using historical controls, and showed that a combination of lopinavir–ritonavir with ribavirin reduced the mortality and need for intensive respiratory support of patients with SARS who had been admitted to hospital.

RESPIRATORY INFECTION

Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings

C M Chu, V C C Cheng, I F N Hung, M M L Wong, K H Chan, K S Chan, R Y T Kao, L L M Poon, C L P Wong, Y Guan, J S M Peiris, K Y Yuen, on behalf of the HKU/UCH SARS Study Group*

Thorax 2004;**59**:252–256. doi: 10.1136/thorax.2003.012658

See end of article for authors' affiliations

Correspondence to: Professor K Y Yuen, Department of Microbiology, The University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Hong Kong Special Administrative Region, China; kyyuen@hkucc.hku.hk

Received 8 July 2003
Accepted 8 October 2003

Background: The clinical response of patients with severe acute respiratory syndrome (SARS) to a combination of lopinavir/ritonavir and ribavirin was examined after establishing the in vitro antiviral susceptibility of the SARS associated coronavirus to a panel of antiviral agents.

Methods: The in vitro susceptibility of the prototype of SARS associated coronavirus to a panel of nucleoside analogues and protease inhibitors currently licensed for clinical use was studied. Forty one patients with SARS followed for 3 weeks were treated with a combination of lopinavir/ritonavir and ribavirin. The clinical progress and virological outcomes were monitored and compared with 111 patients treated with ribavirin only who served as historical controls.

Results: In vitro antiviral activity against SARS associated coronavirus was demonstrated for lopinavir and ribavirin at concentrations of 4 μg/ml and 50 μg/ml, respectively, only at 48 hours. The adverse clinical outcome (ARDS or death) was significantly lower in the treatment group than in the historical controls (2.4% v 28.8%, $p<0.001$) at day 21 after the onset of symptoms. The adverse outcome remained significantly lower in the treatment group than in the controls—both those diagnosed early ($p<0.001$) and those diagnosed later in the course of the epidemic ($p=0.002$)—but there was no significant difference in adverse outcome rates between the two time periods ($p=0.548$). No time related difference in outcome was observed in the control groups. A reduction in steroid usage and nosocomial infections was seen in patients initially treated with lopinavir/ritonavir, and these patients had a decreasing viral load and rising peripheral lymphocyte count. Multivariate analysis showed that age, hepatitis B carrier status, and lack of treatment with this antiviral combination were independent predictors of an adverse outcome. Lopinavir/ritonavir treatment was associated with a better outcome even when adjusted for baseline lactate dehydrogenase level.

Conclusions: The apparent favourable clinical response with lopinavir/ritonavir and ribavirin supports further randomised placebo controlled trials in patients with SARS.

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J Infect Dis. 2015 Dec 15

- lopinavir–ritonavir or interferon beta-1b has been shown to reduce viral load and improve lung pathology in a common marmoset model

Treatment With Lopinavir/Ritonavir or Interferon-β1b Improves Outcome of MERS-CoV Infection in a Nonhuman Primate Model of Common Marmoset

Jasper Fuk-Woo Chan,[1,2,3,4,a] Yanfeng Yao,[5,a] Man-Lung Yeung,[2] Wei Deng,[5] Linlin Bao,[5] Lilong Jia,[2] Fengdi Li,[5] Chong Xiao,[5] Hong Gao,[5] Pin Yu,[5] Jian-Piao Cai,[2] Hin Chu,[2] Jie Zhou,[2] Honglin Chen,[1,2,3,4] Chuan Qin,[5,b] and Kwok-Yung Yuen[1,2,3,4,b]

[1]State Key Laboratory of Emerging Infectious Diseases, [2]Department of Microbiology, [3]Research Centre of Infection and Immunology, [4]Carol Yu Centre for Infection, The University of Hong Kong, Hong Kong Special Administrative Region, and [5]Institute of Laboratory Animal Sciences, Chinese Academy of Medical Sciences, Beijing, China

Middle East respiratory syndrome coronavirus (MERS-CoV) causes severe disease in human with an overall case-fatality rate of >35%. Effective antivirals are crucial for improving the clinical outcome of MERS. Although a number of repurposed drugs, convalescent-phase plasma, antiviral peptides, and neutralizing antibodies exhibit anti-MERS-CoV activity in vitro, most are not readily available or have not been evaluated in nonhuman primates. We assessed 3 repurposed drugs with potent in vitro anti-MERS-CoV activity (mycophenolate mofetil [MMF], lopinavir/ritonavir, and interferon-β1b) in common marmosets with severe disease resembling MERS in humans. The lopinavir/ritonavir-treated and interferon-β1b-treated animals had better outcome than the untreated animals, with improved clinical (mean clinical scores ↓50.9%–95.0% and ↓weight loss than the untreated animals), radiological (minimal pulmonary infiltrates), and pathological (mild bronchointerstitial pneumonia) findings, and lower mean viral loads in necropsied lung (↓0.59–1.06 $\log_{10}$ copies/glyceraldehyde 3-phosphate dehydrogenase [GAPDH]; $P < .050$) and extrapulmonary (↓0.11–1.29 $\log_{10}$ copies/GAPDH; $P < .050$ in kidney) tissues. In contrast, all MMF-treated animals developed severe and/or fatal disease with higher mean viral loads (↑0.15–0.54 $\log_{10}$ copies/GAPDH) than the untreated animals. The mortality rate at 36 hours postinoculation was 67% (untreated and MMF-treated) versus 0–33% (lopinavir/ritonavir-treated and interferon-β1b-treated). Lopinavir/ritonavir and interferon-β1b alone or in combination should be evaluated in clinical trials. MMF alone may worsen MERS and should not be used.

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2020

- This phase 2 randomised trial to establish whether a combination of three modestly active drugs against SARS-CoV-2 can improve the viral load profile and clinical parameters in adults with COVID-19 requiring hospital admission.

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Methods

- This was a multicentre, prospective, open-label, randomised, phase 2 trial in adults with COVID-19 who were admitted to six hospitals in Hong Kong
- Patients were randomly assigned (2:1) to a 14-day combination of lopinavir 400 mg and ritonavir 100 mg every 12 h, ribavirin 400 mg every 12 h, and three doses of 8 million international units of interferon beta-1b on alternate days (combination group) or
- to 14 days of lopinavir 400 mg and ritonavir 100 mg every 12 h (control group).

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- The primary endpoint was the time to achieve a negative nasopharyngeal swab for SARS-CoV-2,

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- Secondary clinical endpoints were
  - time to resolution of symptoms defined as a NEWS2 of 0 maintained for 24 h;
  - daily NEWS2 and sequential organ failure assessment (SOFA) score;
  - length of hospital stay; and
  - 30-day mortality.

- Safety endpoints were the frequencies and duration of adverse events.

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Results

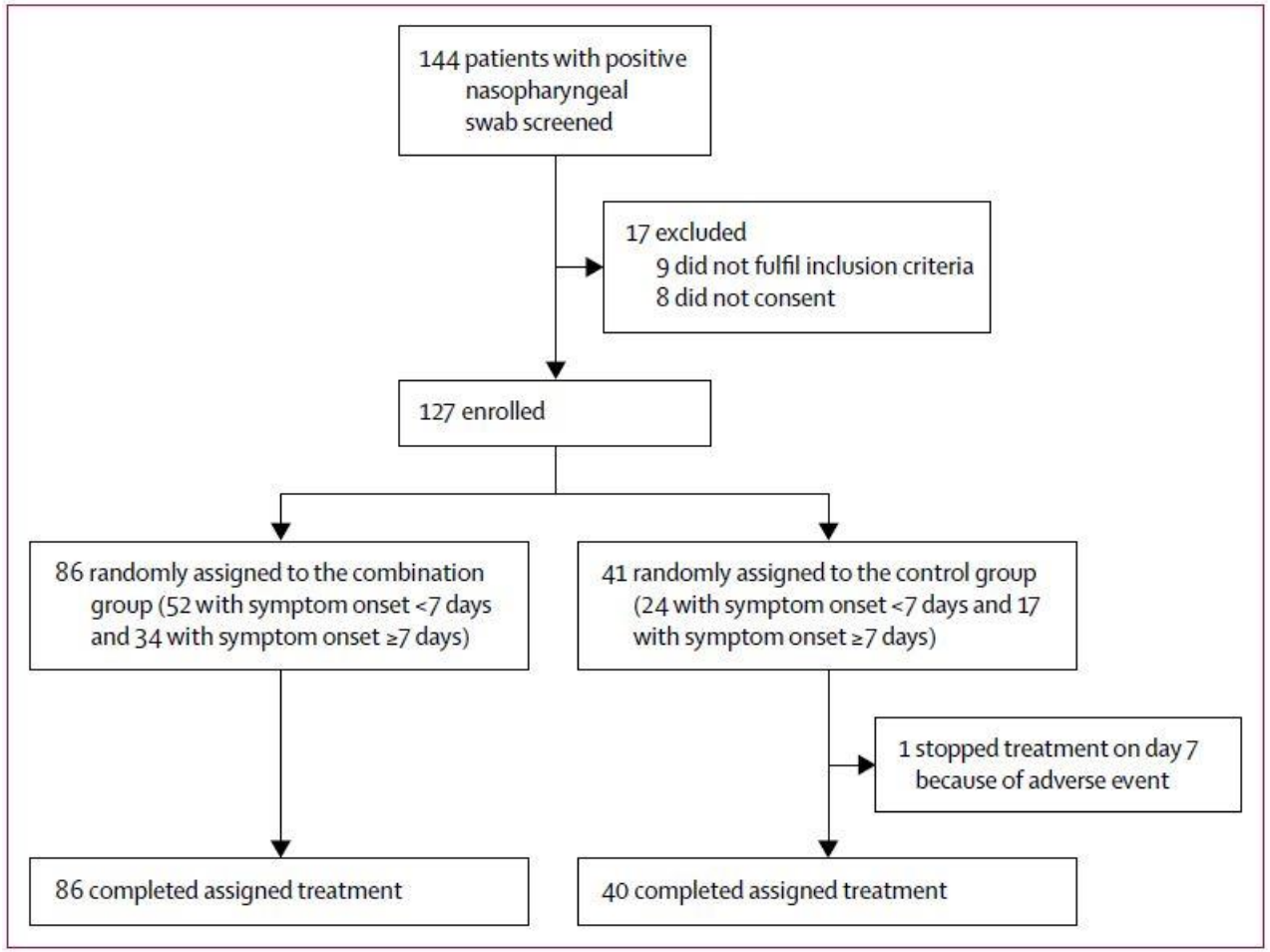

Figure 1: Trial profile

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Results

- Between Feb 10 and March 20, 2020,
- 144 patients were screened, and
- 127 patients were recruited
- All patients had a SARS-CoV-2 positive baseline nasopharyngeal swab.
- median age was 52 years (IQR 32–62);
- 68 (54%) patients were men versus 59 (46%) women
- 51 (40%) patients had underlying diseases
- The age, sex, and baseline demographics in each group were similar

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- Among the 127 patients, 86 were randomly assigned to the combination group and 41 patients were assigned to the control group.
- Disease severity upon presentation was mild based on NEWS2 and SOFA scores
- The baseline viral loads for all specimens were similar between the combination group and control group

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- For the primary endpoint of time from start of study treatment to negative nasopharyngeal swab, the combination group had a significantly shorter median time (7 days [IQR 5–11]) than the control group (12 days [8–15]; HR 4・37 [95% CI 1・86–10・24], p=0・0010)
- **Clinical improvement was significantly better in the combination group, with a significantly shorter time to complete alleviation of symptoms**, defined as a NEWS2 of 0 (4 days [IQR 3–8] in the combination group *vs* 8 days [7–9] in the control group, HR 3,92 and SOFA score of 0 (3・0 days [1・0–8・0] *vs* 8・0 days [6・5–9・0]; HR 1・89

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- The significantly better clinical and virological response is also reflected in the shorter median hospital stay in the combination group than in the control group (9・0 days [7・0–13・0] *vs* 14・5 days [9・3–16・0]; HR 2・72 [1・2–6・13], p=0・016).

- All urine samples tested negative for viral load.

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- Post-hoc subgroup comparison of the 76 patients who started treatment less than 7 days after onset of symptoms showed better clinical and virological outcomes in the combination group than the control group

- However, no significant differences between the treatment groups were measured in these outcomes in the 51 patients who were treated 7 days or more after symptom onset

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- Adverse events were reported by 41 (48%) of 86 patients in the combination group and 20 (49%) of 41 patients in the control group.
- There were no differences between incidence of any of the adverse events
- No serious adverse events were reported in the combination group
- One patient in the control group had a serious adverse event of impaired hepatic enzymes requiring discontinuation of treatment
- No patients died during the study.

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	Combination group (n=86)	Control group (n=41)	p value
Adverse events			
Nausea	30 (35%)	13 (32%)	0·87
Diarrhoea	34 (40%)	18 (44%)	0·54
Increased alanine aminotransferase	11 (13%)	7 (17%)	0·32
Hyperbilirubinaemia	4 (5%)	3 (7%)	0·54
Sinus bradycardia	3 (4%)	1 (2%)	0·77
Fever	32 (37%)	16 (39%)	0·73
Serious adverse events	0	1 (2%)	0·15
Duration of nausea, days	2 (1–2)	2 (1–2)	0·80
Duration of diarrhoea, days	3 (3–3)	3 (3–3)	0·88

Table 4: **Adverse events in the study population**

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- Triple antiviral therapy with interferon beta-1b, lopinavir–ritonavir, and ribavirin were safe and superior to lopinavir–ritonavir alone in
  - shortening virus shedding,
  - alleviating symptoms, and
  - facilitating discharge of patients with mild to moderate COVID-19.

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Shortcomings

- Open-label, without a placebo group
- No critically ill patients – therefore these finding be generalized to severe cases

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