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Morning Brief:
Scientific Review

20 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.

Stellenbosch University Research Response Team

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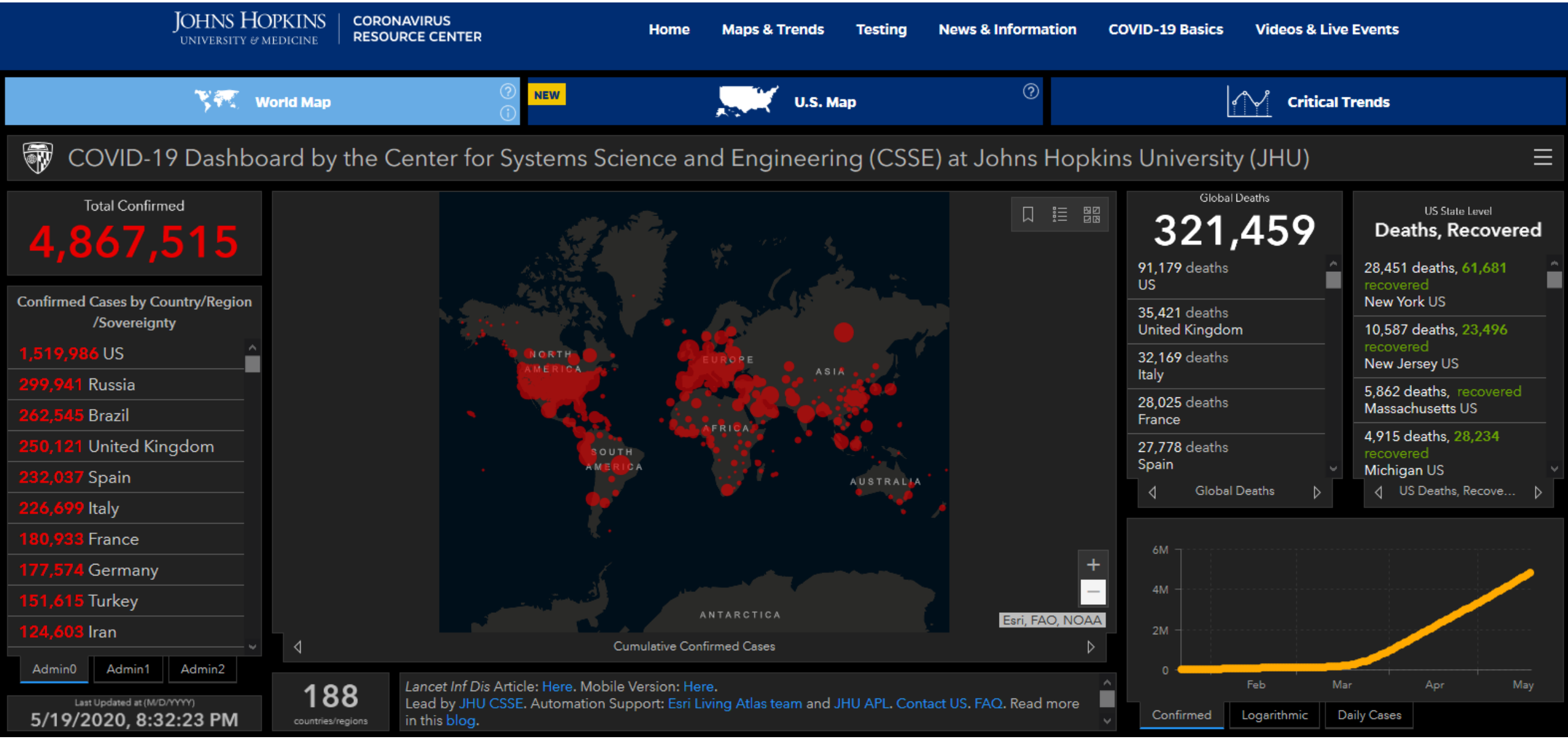
Content of the brief

- Global Statistics
- South African Statistics
- Topics:
  - 2 hydroxychloroquine papers



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

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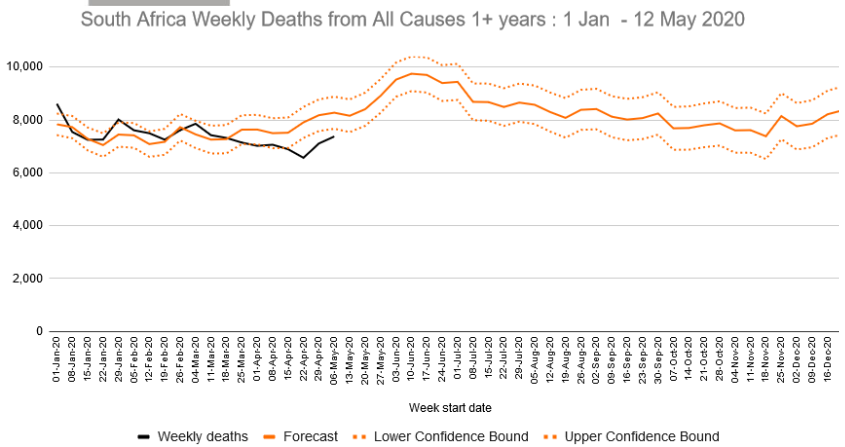
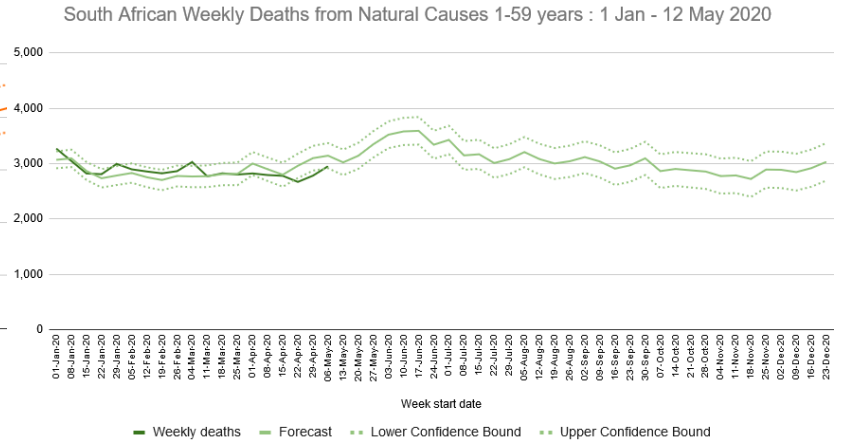
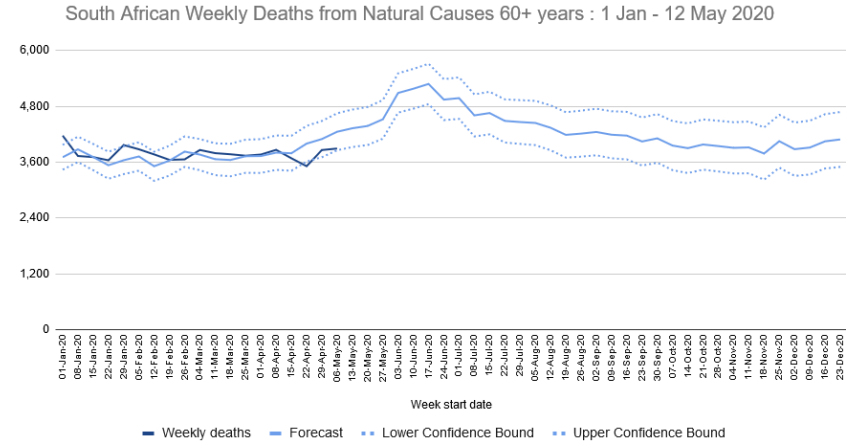
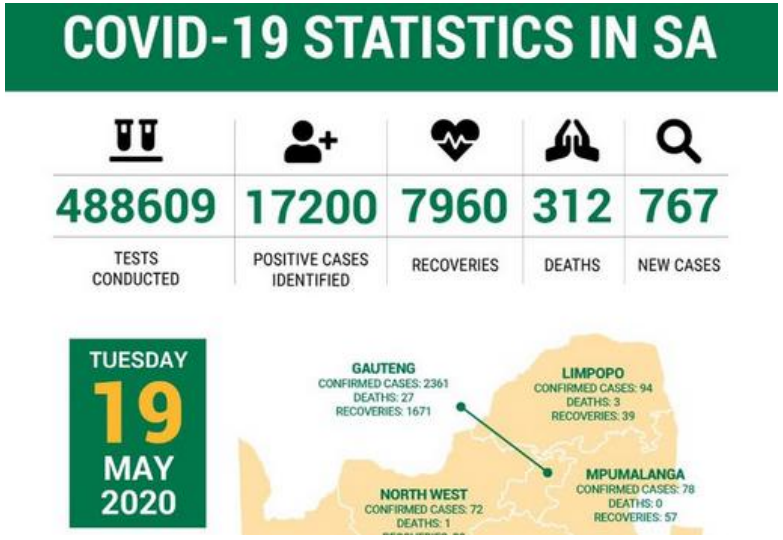
South African Statistics









Case Data

Province	Total cases for 19 May 2020	Percentage total
Eastern Cape	2135	12,4
Free State	168	1,0
Gauteng	2361	13,7
KwaZulu-Natal	1616	9,4
Limpopo	94	0,5
Mpumalanga	78	0,5
North West	72	0,4
Northern Cape	37	0,2
Western Cape	10639	61,9
Unknown	0	0,0
Total	**17200**	**100,0**

Province	Deaths	Recoveries
Eastern Cape	41	839
Free State	6	118
Gauteng	27	1671
KwaZulu Natal	46	818
Limpopo	3	39
Mpumalanga	0	57
North West	1	28
Northern Cape	1	27
Western Cape	187	4363
Total	**312**	**7960**

Accessed at 21:00 on 19 May 2020

Sources: https://www.samrc.ac.za/reports/report-weekly-deaths-south-Africa, https://sacoronavirus.co.za

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Articles of Interest

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JAMA | Original Investigation

Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State

Eli S. Rosenberg, PhD; Elizabeth M. Dufort, MD; Tomoko Udo, PhD; Larissa A. Wilberschied, MS; Jessica Kumar, DO; James Tesoriero, PhD; Patti Weinberg, PA; James Kirkwood, MPH; Alison Muse, MPH; Jack DeHovitz, MD; Debra S. Blog, MD; Brad Hutton, MPH; David R. Holtgrave, PhD; Howard A. Zucker, MD

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Overview summary

What is known

- Robust evidence of efficacy of hydroxychloroquine (HCQ) with or without azithromycin (AZM) is pending
- There are concerns of safety in COVID-19 patients receiving potentially synergistic QTc-prolonging drugs (HCQ and AZM), especially with advancing age (risk factor for severe COVID-19 disease) and other risk factors for QT prolongation

What this study adds

- Among patients hospitalized with COVID-19 treatment with HCQ, AZM, or both was not associated with significantly lower in-hospital mortality
- Compared to patients receiving none of the interventional treatments, patients receiving HCQ + AZM were significantly more likely to have cardiac arrest, but not HCQ or AZM alone
- Abnormal ECGs more common in patients receiving HCQ + AZM or HCQ alone

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Methodology

Design:

- Secondary analysis of routinely collected data
- Observational study of COVID-19 confirmed patients admitted to 25 New York Metropolitan hospitals
- Hospital-stratified random sampling between 15 – 28 March 2020

Exposures:

- HCQ + AZM
- HCQ alone
- AZM alone
- Neither drug

Chloroquine initially planned, but low numbers led to exclusion

Outcomes:

- Primary
  - In-hospital mortality
- Secondary
  - Abnormal ECG (arrhythmia or prolonged QT interval)
  - Cardiac arrest

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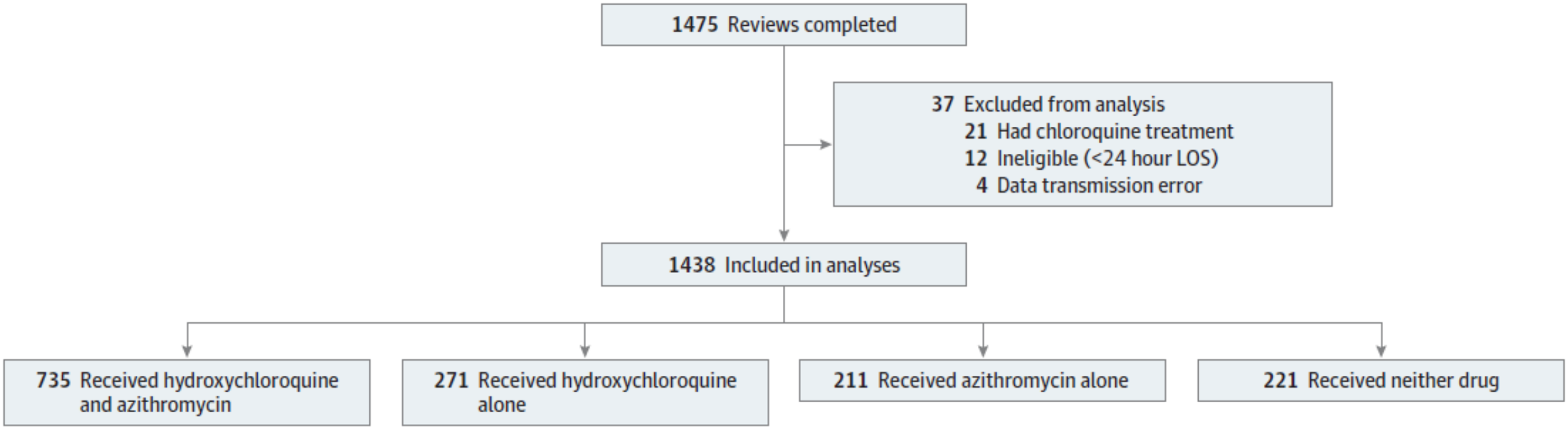
Methodology

Sample size:

- Calculated as 1500, assuming a 3:2 ratio of HCQ use vs non-use
- Sample size was estimated to have 90% power to detect a significant HCQ use vs non-use mortality hazard ratio (HR) of 0.65, assuming 19% mortality among those not receiving HCQ, and 95% power for HR of 0.50 when mortality was 10%



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Results: Primary outcome

- Overall in-hospital mortality was 20.3% (95% CI 18.2% - 22.4%)

Table 3. Model-Adjusted Risk of In-Hospital Death, Cardiac Arrest, Arrhythmia

Outcome	Model type[a]	Estimate (95% CI)			
		Hydroxychloroquine + azithromycin vs neither drug	Hydroxychloroquine alone vs neither drug	Azithromycin alone vs neither drug	Hydroxychloroquine alone vs azithromycin alone
In-hospital death (hazard ratio)	Cox proportional hazards	1.35 (0.76-2.40)	1.08 (0.63-1.85)	0.56 (0.26-1.21)	1.92 (0.99-3.74)
Cardiac arrest (odds ratio)	GEE logistic regression	2.13 (1.12-4.05)	1.91 (0.96-3.81)	0.64 (0.27-1.56)	2.97 (1.56-5.64)
Abnormal ECG findings (odds ratio)[b]	GEE logistic regression	1.55 (0.89-2.67)	1.50 (0.88-2.58)	0.95 (0.47-1.94)	1.58 (0.77-3.24)

Abbreviations: ECG, electrocardiogram; GEE, generalized estimating equation.

[a] Models adjusted for sex, age category (<65 vs ≥65 years), diabetes, any chronic lung disease, cardiovascular disease, abnormal chest imaging, respiration rate >22/min, O_2 saturation <90%, elevated creatinine, and AST >40 U/L as fixed effects and repeated measures for hospital.

[b] Abnormal ECG included prolonged QT and arrhythmia.

After adjusting for demographics, specific hospital, preexisting conditions, and illness severity, no significant differences in mortality were found.

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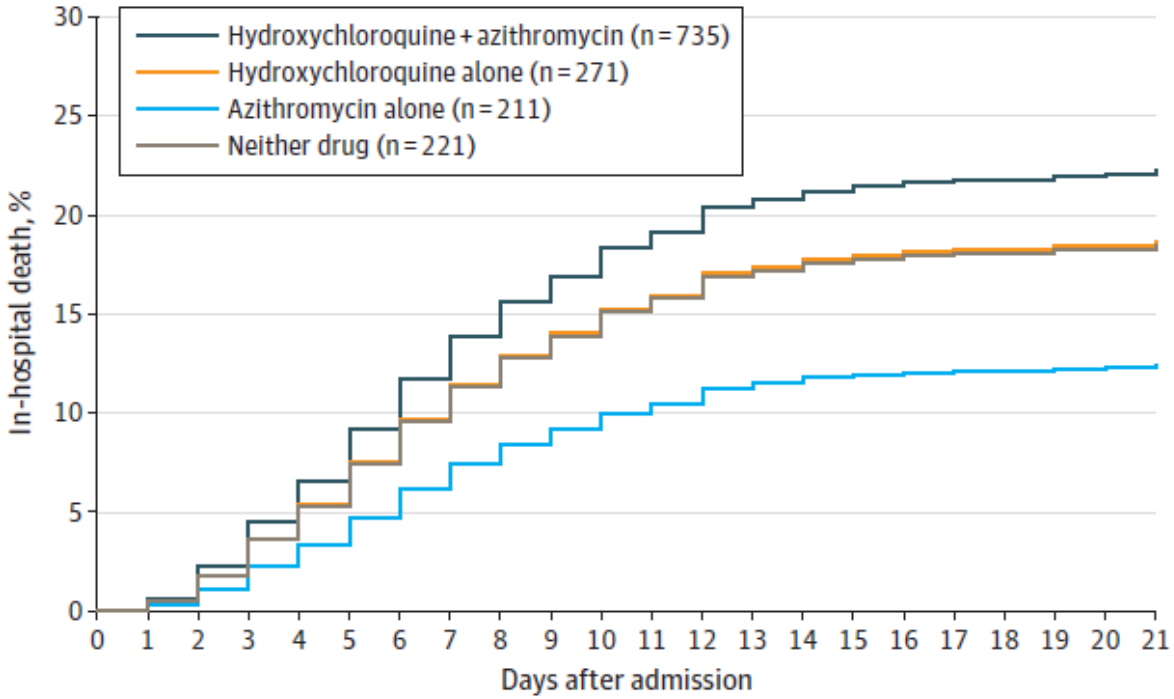
Results: Primary outcome

Figure 2. Model-Adjusted Estimated In-Hospital Mortality, by Treatment Group



No. at risk (in hospital)

	Admission	Day 7	Day 14	Day 21
Hydroxychloroquine + azithromycin	735	653 (384)	568 (106)	557 (47)
Hydroxychloroquine alone	271	245 (136)	226 (59)	220 (28)
Azithromycin alone	211	191 (33)	190 (4)	190 (2)
Neither drug	221	206 (63)	197 (19)	195 (13)

Graph is based on a Cox proportional hazards model. Sample sizes provided reflect the source data observed, which informed the creation of the model. Compared with the neither-drug group, none of the 3 treatment groups had statistically different rates of death, at α = .05: hydroxychloroquine + azithromycin, *P* = .31; hydroxychloroquine alone, *P* = .79; and azithromycin alone, *P* = .14.

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Results: Primary outcome

- Model-based, estimated direct-adjusted mortality at 21 days was:
  - 22.5% (95% CI 19.7% - 25.1%) with HCQ + AZM
  - 18.9% (95% CI 14.3% - 23.2%) with HCQ alone
  - 10.9% (95% CI 5.8% - 15.6%) with AZM alone
  - 17.8% (95% CI 11.1% - 23.9%) with neither drug

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Results: Secondary outcomes

Table 4. Adverse Events Reported During Hospitalization

	No./total No. (%)				
	Hydroxychloroquine + azithromycin (n = 735)	Hydroxychloroquine alone (n = 271)	Azithromycin alone (n = 211)	Neither drug (n = 221)	*P* value
Diarrhea	85 (11.6)	22 (17.0)	16 (8.5)	16 (7.2)	.003
Hypoglycemia	25 (3.4)	9 (3.3)	1 (0.5)	6 (2.7)	.15
Cardiac arrest	114 (15.5)	37 (13.7)	13 (6.2)	15 (6.8)	<.001
Abnormal ECG[a]					
Total sample	199 (27.1)	74 (27.3)	34 (16.1)	31 (14.0)	<.001
Among ECG screened	192/634 (30.3)	73/233 (31.3)	34/180 (18.9)	31/155 (20.2)	.002
Arrhythmia					
Overall	150 (20.4)	44 (16.2)	23 (10.9)	23 (10.4)	<.001
Among ECG screened	144/634 (22.7)	43/233 (18.5)	23/180 (12.8)	23/155 (14.8)	<.001
QT prolongation					
Overall	81 (11.0)	39 (14.4)	15 (7.1)	13 (5.9)	.006
Among ECG screened	80/634 (12.6)	39/233 (16.7)	15/180 (8.3)	3/155 (8.4)	.03

Abbreviation: ECG, electrocardiogram.

[a] Abnormal ECG combined arrhythmia and QT prolongation. Screening of adverse ECG at any point during hospitalization was reported in 634 (86.3%) of the hydroxychloroquine + azithromycin group, 233 (86.0%) of the hydroxychloroquine alone group, 180 (85.3%) of the azithromycin alone group, and 155 (70.1%) of the neither-drug group (χ^2 group differences, $P < .001$).

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Results: Secondary outcomes

Table 3. Model-Adjusted Risk of In-Hospital Death, Cardiac Arrest, Arrhythmia

Outcome	Model type[a]	Estimate (95% CI)			
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[b] Abnormal ECG included prolonged QT and arrhythmia.

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Results: Secondary outcomes

Abnormal ECG

- Abnormal ECG more common in patients receiving HCQ + AZM (27.1%), or HCQ alone (27.3%)
- In logistic regression models of abnormal ECGs, no significant difference between HCQ + AZM and HCQ alone vs neither

		Estimate (95% CI)			
Outcome	Model type[a]	Hydroxychloroquine + azithromycin vs neither drug	Hydroxychloroquine alone vs neither drug	Azithromycin alone vs neither drug	Hydroxychloroquine alone vs azithromycin alone
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Cardiac arrest

- Cardiac arrest more common in patients receiving HCQ + AZM (15.5%), or HCQ alone (13.7%)
- In adjusted models, cardiac arrest more common in HCQ + AZM than HCQ alone or AZM alone (compared to neither)

		Estimate (95% CI)			
Outcome	Model type[a]	Hydroxychloroquine + azithromycin vs neither drug	Hydroxychloroquine alone vs neither drug	Azithromycin alone vs neither drug	Hydroxychloroquine alone vs azithromycin alone
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Results: Supplementary material

eTable 1. Medication Prescription Patterns

	No./total No. (%)		
	Initial prescription [a]	Second prescription	Third prescription
Hydroxychloroquine[b]			
Dose			
200mg	46/1,006 (4.6)	483/679 (71.1)	20/36 (55.6)
400mg	908/1,006 (90.3)	191/679 (28.1)	15/36 (41.7)
600mg	28/1,006 (2.8)	1/679 (0.2)	1/36 (2.8)
Other	15/1,006 (1.5)	3/679 (0.4)	0/36 (0.0)
Unknown	9/1,006 (0.9)	1/679 (0.2)	0/36 (0.0)
Frequency			
Once a day	247/1,006 (24.6)	167/680 (24.6)	9/36 (25.0)
Twice a day	708/1,006 (70.4)	497/680 (73.1)	26/36 (72.2)
Other	22/1,006 (2.2)	7/680 (1.0)	1/36 (2.8)
Unknown	29/1,006 (2.9)	9/680 (1.3)	0/36 (0.0)
Azithromycin			
Dose			
200mg	5/946 (0.5)	1/385 (0.3)	0/51 (0.0)
250mg	53/946 (5.6)	135/385 (35.1)	23/51 (45.1)
400mg	4/946 (0.4)	0/385 (0.0)	0/51 (0.0)
500mg	870/946 (92.0)	248/385 (64.4)	28/51 (54.9)
Other	2/946 (0.2)	1/385 (0.3)	0/51 (0.0)
Unknown	12/946 (1.3)	0/385 (0.0)	0/51 (0.0)

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Supplementary material

- Interesting to note that 2 common factors associated with severe COVID-19, obesity & chronic lung conditions, were not associated with more in-hospital death in this cohort:
  - Obesity: RR 0.96 (95% CI 0.75 - 1.22) P=0.74
  - Chronic lung disease: RR 1.15 (95% CI 0.90 - 1.48) P=0.27

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Limitations

- Secondary analysis of routinely collected data
- Cannot contribute causality to in-hospital death

- Patients receiving HCQ + AZM or HCQ alone had higher levels of ICU admission and mechanical ventilation than those receiving AZM alone or neither drug. However, patients receiving HCQ also had the highest levels of chronic lung disease and cardiovascular conditions
- Patients in the treatment groups, particularly HCQ + AZM, presented as having more clinically severe disease than the neither drug group. It was adjusted for in analysis, but then had small samples in non-HCQ groups
- Association of absolute increased abnormal ECGs in patients receiving HCQ may have been detection bias (= more frequent ECGs due to known risk)
- Unmeasured confounders may render significant cardiac arrest association non-significant

RESEARCH

Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial

Wei Tang,[1,2] Zhujun Cao,[3] Mingfeng Han,[4] Zhengyan Wang,[5] Junwen Chen,[6] Wenjin Sun,[7] Yaojie Wu,[8] Wei Xiao,[9] Shengyong Liu,[10] Erzhen Chen,[11] Wei Chen,[1,2] Xiongbiao Wang,[12] Jiuyong Yang,[13] Jun Lin,[14] Qingxia Zhao,[15] Youqin Yan,[16] Zhibin Xie,[17] Dan Li,[18] Yaofeng Yang,[19] Leshan Liu,[20] Jieming Qu,[1,2] Guang Ning,[21] Guochao Shi,[1,2] Qing Xie[3]

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Methodology

OBJECTIVE

To assess the efficacy and safety of hydroxychloroquine plus standard of care compared with standard of care alone in adults with coronavirus disease 2019 (covid-19).

DESIGN

Multicentre, open label, randomised controlled trial.

SETTING

16 government designated covid-19 treatment centres in China, 11 to 29 February 2020.

PARTICIPANTS

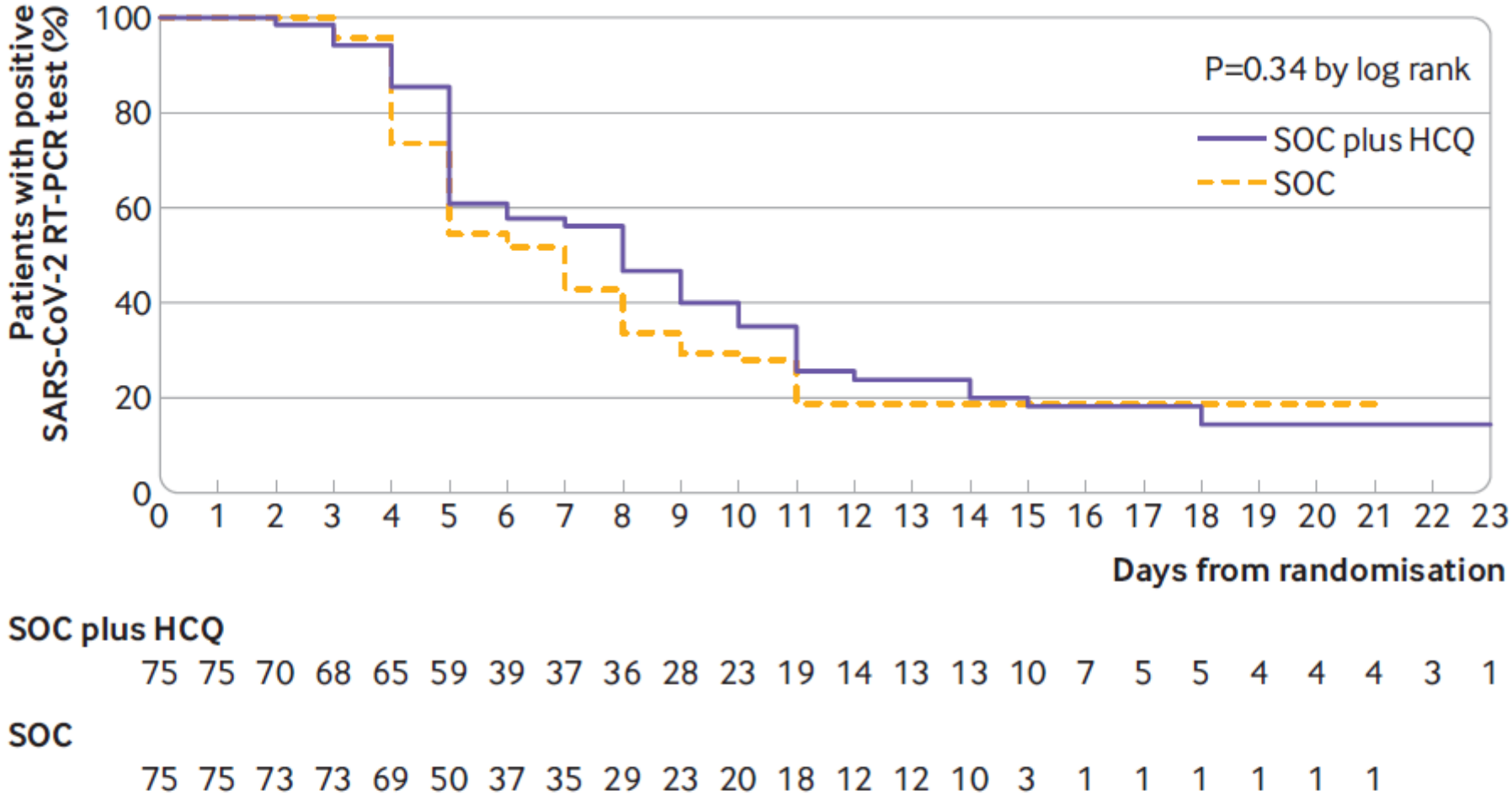
150 patients admitted to hospital with laboratory confirmed covid-19 were included in the intention to treat analysis (75 patients assigned to hydroxychloroquine plus standard of care, 75 to standard of care alone).

INTERVENTIONS

Hydroxychloroquine administrated at a loading dose of 1200 mg daily for three days followed by a maintenance dose of 800 mg daily (total treatment duration: two or three weeks for patients with mild to moderate or severe disease, respectively).

MAIN OUTCOME MEASURE

Negative conversion of severe acute respiratory syndrome coronavirus 2 by 28 days, analysed according to the intention to treat principle. Adverse events were analysed in the safety population in which hydroxychloroquine recipients were participants who received at least one dose of hydroxychloroquine and hydroxychloroquine non-recipients were those managed with standard of care alone.



SOC plus HCQ	75	75	70	68	65	59	39	37	36	28	23	19	14	13	13	10	7	5	5	4	4	4	3	1
SOC	75	75	73	73	69	50	37	35	29	23	20	18	12	12	10	3	1	1	1	1	1	1		

Fig 2 | Kaplan-Meier curves of time to negative conversion of SARS-CoV-2 on real time reverse transcription polymerase chain reaction (RT-PCR) test in standard of care (SOC) plus hydroxychloroquine (HCQ) versus SOC in intention to treat population. Data are shown for 75 patients assigned to SOC plus HCQ and 75 assigned to SOC. Overall probability of negative conversion by 28 days was 85.4% (95% CI 73.8% to 93.8%) in SOC plus HCQ group and 81.3% (71.2% to 89.6%) in SOC group (P=0.34). Difference between groups was 4.1% (95% CI −10.3% to 18.5%). Median time to negative conversion was 8 (95% CI 5 to 10) days in SOC plus HCQ group and 7 (5 to 8) days SOC group (hazard ratio 0.85, 95% CI 0.58 to 1.23; P=0.34 by log rank test). Data from patients who did not have negative conversion were censored (tick marks) at last visit date

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Results

Table 3 | Summary of adverse events in safety population. Values are numbers (percentages)

Adverse events*	SOC plus HCQ (n=70)	SOC (n=80)
Any adverse event	21 (30)	7 (9)
Serious adverse event	2 (3)	0
Disease progression	1 (1)	0
Upper respiratory tract infection	1 (1)	0
Non-serious adverse event	19 (27)	7 (9)
Diarrhoea	7 (10)	0
Vomiting	2 (3)	0
Nausea	1 (1)	0

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Considerations for interpretation

- Emerging data indicate treatments for COVID-19 (incl. HCQ) mostly only effective if given early
  - Esp. for mild to moderate disease
  - Extrapolating data from influenza[1] & prev. coronavirus outbreaks[2]

- Mean (SD) days from disease onset to randomization:
  - 16.0 (9.9) (n=73) for SOC + HCQ
  - 17.1 (11.1) (n=74) for SOC

- Very high HCQ doses may have accounted for increased AEs

- This study highlights the need for trials with early initiation of treatments against SARS-Cov-2 in patients with mild to moderate COVID-19

1. Aoki FY, Macleod MD, Paggiaro P, et al. Early administration of oral oseltamivir increases the benefits of influenza treatment. J Antimicrob Chemother 2003;51(1):123- 129. https://doi.org/10.1093/jac/dkg007
2. Tai DYH. Pharmacologic Treatment of SARS: Current Knowledge and Recommendations. Ann Acad Med Singapore 2007;36:438 – 443.

This summary was prepared by Dr Roland van Rensburg as part of the daily brief to the TBH ICU team.

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References

1. Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero J, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. JAMA. 2020 May 11.

2. Tang Wei, Cao Zhujun, Han Mingfeng, Wang Zhengyan, Chen Junwen, Sun Wenjin et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ 2020; 369:m1849