Critical appraisal of multidrug therapy in the ambulatory management of patients with COVID-19 and hypoxemia

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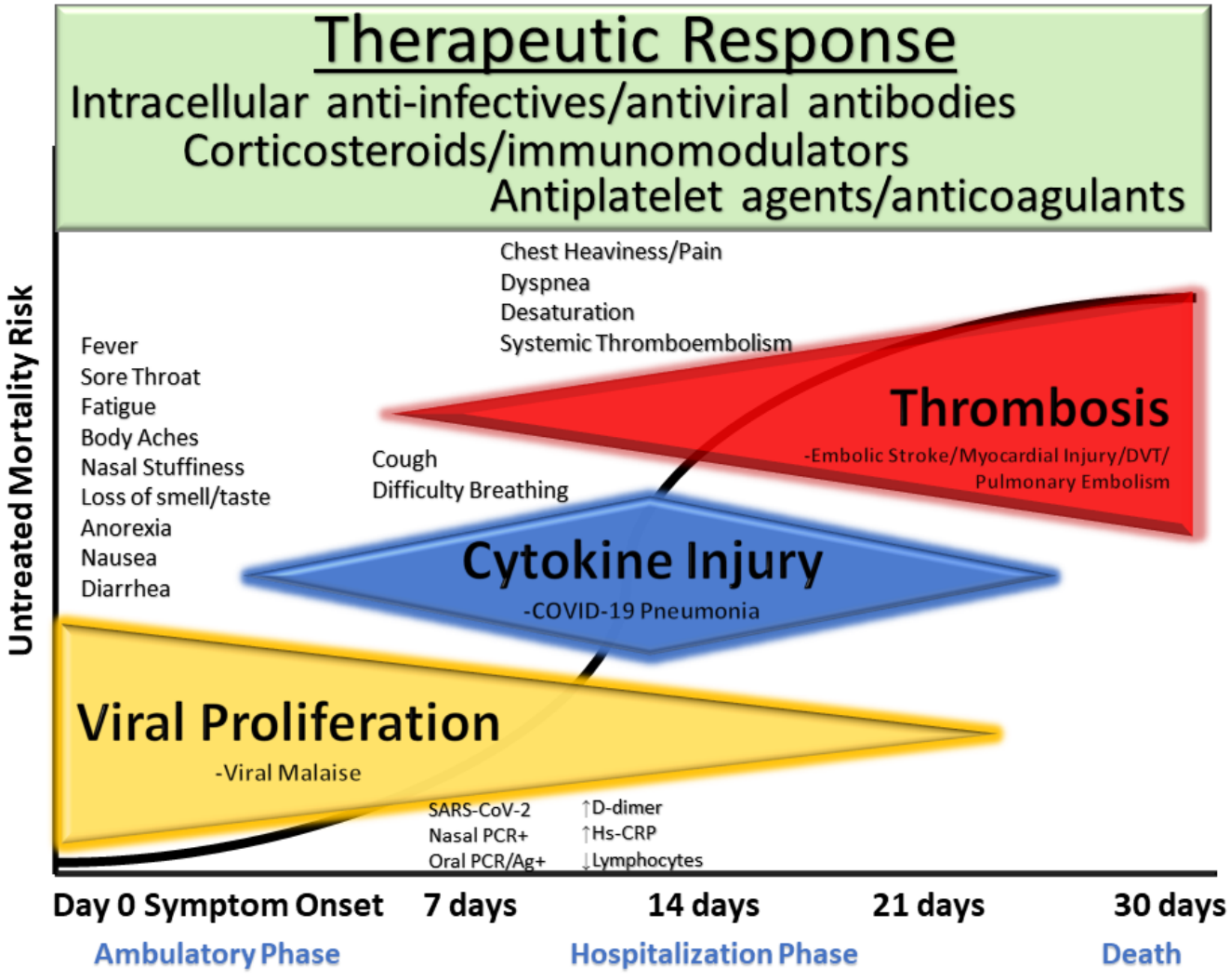
April, 2024

COVID-19 as a triphasic illness



McCullough protocol: Sequenced multidrug treatment

icine

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IMR Press

Review

Multifaceted highly targeted sequential multidrug treatment of early ambulatory high-risk SARS-CoV-2 infection (COVID-19)

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- **Treat early:** Within 3 days from onset of symptoms
- Nutraceutical bundle: zinc, Vitamin D, Vitamin C, Quercetin
- Combination antiviral therapy: (hydroxychloroquine or ivermectin) and (azithromycin or doxycycline)
- Corticosteroids/immunomodulators: to modulate cytokine storm and control cytokine injury
- Anticoagulants: to resolve/prevent blood clots
- **No single drug is necessary nor sufficient to achieve treatment efficacy towards reducing hospitalizations and deaths**

Goal of our study: Ivermectin-based treatment of hypoxemic patients

Critical appraisal of multidrug therapy in the ambulatory management of patients with COVID-19 and hypoxemia

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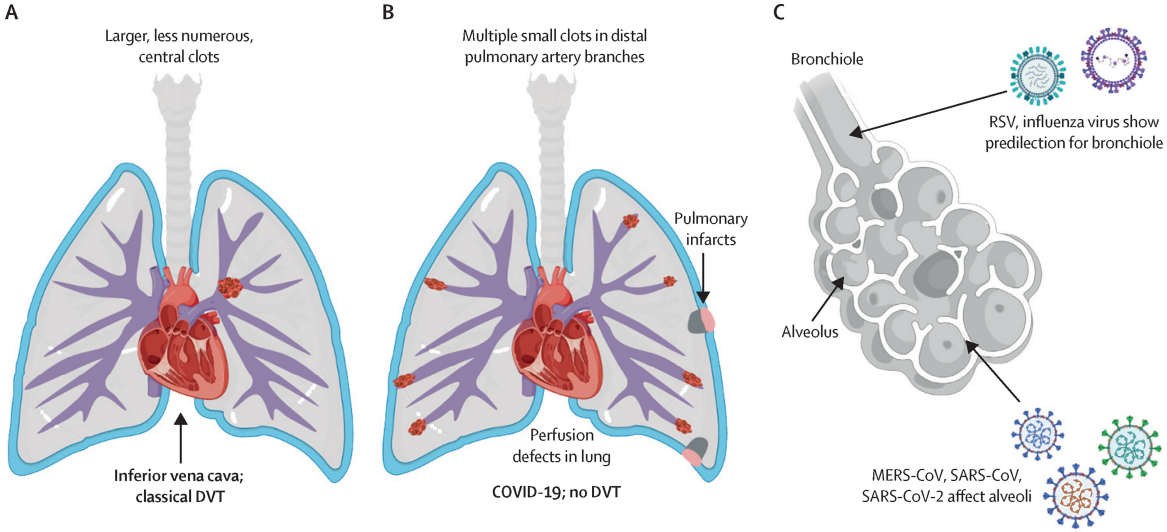
- Focus of study: hypothesis that an ivermectin-based multidrug treatment protocol can rescue patients with hypoxemia and result in the rapid recovery of peripheral oxygen saturation (SpO2) levels, upon initiation of treatment, by reversing the formation of microscopic red blood cell clumping in the lungs, responsible for the sudden decline in oxygen saturation in some patients with severe COVID-19
- The focus is on COVID-19 patients whose condition has deteriorated, either due to lack of early treatment or due to insufficient response to some initial attempt at early treatment.
- **Goal of study:** quantify the strength of the evidence in favor of the hypothesis that these multidrug protocols are ultimately efficacious in reducing hospitalizations and deaths.

McGonagle's tricompartmental model

COVID-19: Pathophysiology of Acute Disease 4

A tricompartmental model of lung oxygenation disruption to explain pulmonary and systemic pathology in severe COVID-19

Dennis McGonagle, Charlie Bridgewood, James F M Meaney



- Classic pulmonary venous thromboembolism presents with a preponderance of a smaller number of proximal large emboli. McGonagle *et al.*argues that the tendency of the SARS-CoV-2 virus to preferentially attack the alveoli, contrary to RSV and influenza viruses, triggers immunothrombosis, resulting in a larger number of microemboli in the pulmonary and bronchial distal arteries and in the alveoli, which in turn trigger pulmonary infarcts and cause oxygen desaturation.

Glycan bindings between red blood cells and viral particles

International Journal of
Molecular Sciences

MDPI

Review

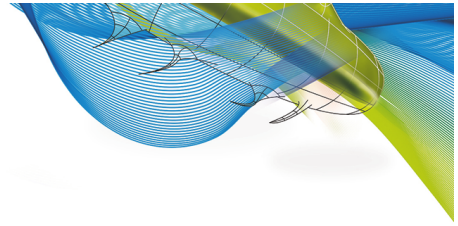
Sialylated Glycan Bindings from SARS-CoV-2 Spike Protein to Blood and Endothelial Cells Govern the Severe Morbidities of COVID-19

David E. Scheim [1,*], Paola Vottero [2], Alessandro D. Santin [3] and Allen G. Hirsh [4]

- Scheim *et al.*recently explained that this immunothrombotic process is mediated by glycan bindings between red blood cells and the SARS-CoV-2 viral spike protein, and noted that the reason why common cold strains do not cause a similar formation of microemboli is because common cold viruses, unlike SARS, SARS-CoV-2, and MERS, express hemagglutinin esterase, which releases these glycan bindings.
- Thus, a multidrug treatment regimen with both immunomodulating and anticoagulant mechanisms of actions, that can also release the glycan bindings between the viral spike protein and red blood cells, could rapidly restore the ability of the lungs to oxygenate, by addressing the pulmonary microemboli and restoring the oxygenation supply from both the distal bronchial and pulmonary arteries and from the alveoli/
- Agents that may reduce RBC clumping include: hydroxychloroquine, ivermectin, and fluvoxamine.

Prehospital hypoxemic patient treatment: Hazan case series

Effectiveness of ivermectin-based multidrug therapy in severely hypoxic, ambulatory COVID-19 patients



Sabine Hazan*,[1], Sonya Dave[2], Anoja W Gunaratne[3], Sibasish Dolai[3], Robert L Clancy[3], Peter A McCullough[4] & Thomas J Borody[3]

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- 24 patient case series: 23 patients with baseline room air SpO2 $\leq$ 90%
- Between August 2020 and February 2021
- Patients were excluded from clinical trial, declined hospitalization, were treated off-label.
- 10 day treatment with ivermectin (variable dose), doxycycline, zinc, Vitamin D, Vitamin C
- Rapid recover of SpO2 levels within 24-48 hours
- 0 deaths and 0 hospitalizations; no supplemental oxygen

Prehospital hypoxemic patient treatment: Stone case series

biologics

MDPI

Article

Changes in SpO2 on Room Air for 34 Severe COVID-19 Patients after Ivermectin-Based Combination Treatment: 62% Normalization within 24 Hours

Jaqueline C. Stone [1], Pisirai Ndarukwa [2,3], David E. Scheim [4,*], Barry M. Dancis [5], Jerome Dancis [6], Martin G. Gill [7] and Colleen Aldous [8]

- 34 patient case series: 28 patients with baseline room air SpO2 $\leq$ 90%. All patients with baseline room air SpO2 $\leq$ 93%
- between August 2020 and May 2021
- 10 day treatment with nebulized nanosilver, ivermectin (variable dose), doxycycline, zinc, Vitamin D, Vitamin C; adjunct use of corticosteroids and anticoagulants.
- Rapid recover of SpO2 levels within 24-48 hours
- Availability of supplemental oxygen very limited
- 0 deaths and 0 hospitalizations; no supplemental oxygen.

Prehospital hypoxemic patient treatment: Babalola case series

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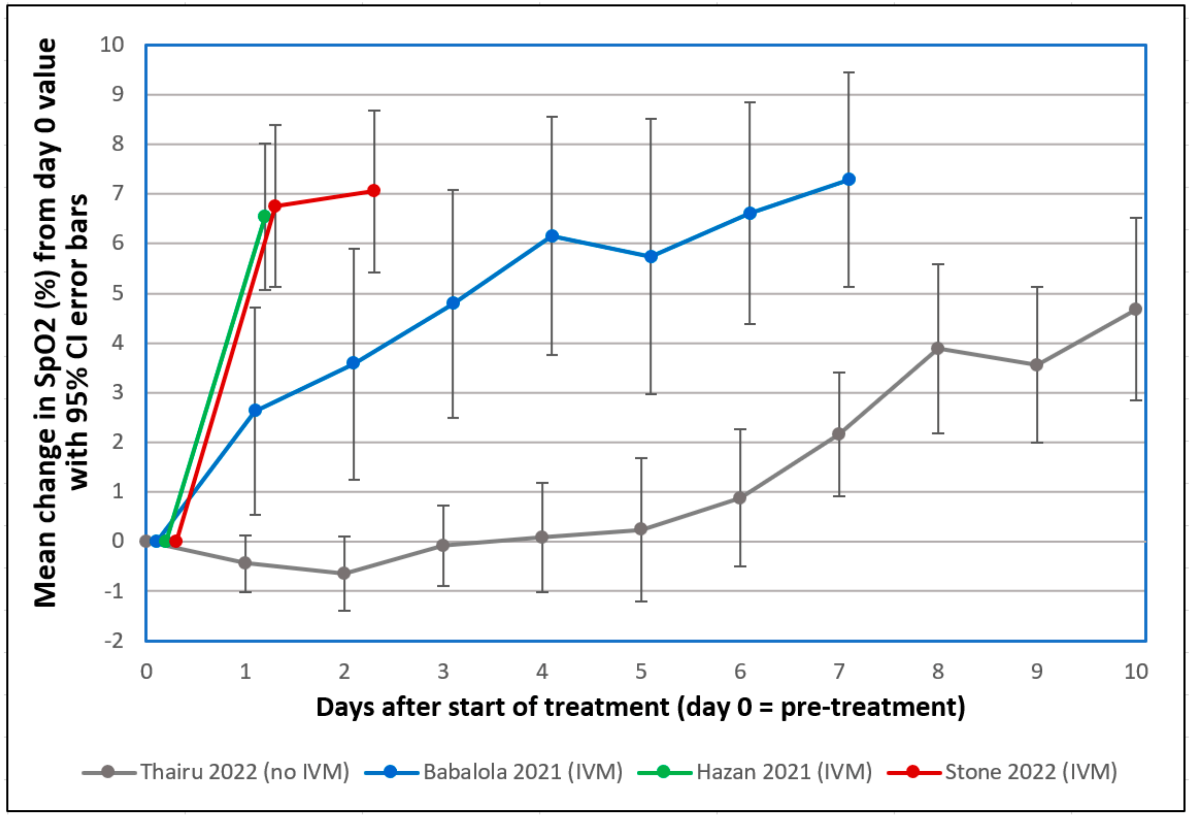
RANDOMISED DRUG TRIAL

A Randomized Controlled Trial of Ivermectin Monotherapy versus Hydroxychloroquine, Ivermectin, and Azithromycin Combination Therapy in COVID- 19 Patients in Nigeria

Babalola OE[1], Ndanusa YA[2], Ajayi AA[3], Ogedengbe JO[4], Thairu Y[4] and Omede O[5]*

- 61 patients in clinical trial, 23 patients with baseline room air SpO2 $\leq$ 93% and 10 patients with baseline room air SpO2 $\leq$ 90%
- 5 day treatment with ivermectin, zinc, Vitamin C; for 31 patients 3-day adjunct treatment with hydroxychloroquine (low dose) and azithromycin
- 0 deaths, 2 ventilated, 3 used supplemental oxygen

Bradford Hill criteria: Biological gradient



- Mean change to room air SpO2 levels from initial value at Day 0 for the patients in the Hazan, Stone, and Babalola case series with baseline room air SpO2 $\leq$ 93%, with error bars showing 95% confidence intervals
- The slowest increase is observed under a conventional standard of care (lopinavir/ritonavir, remdesivir, azithromycin, enoxaparin, zinc sulfate, and vitamin C) by 26 patients with median age 45 by Thairu *et al.*

Case series threshold analysis method. I. Visualization

COVID

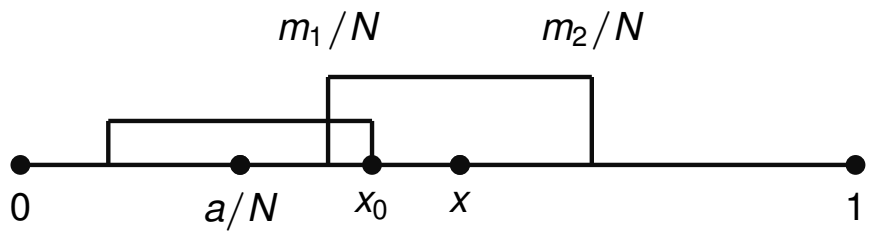
MDPI

Article

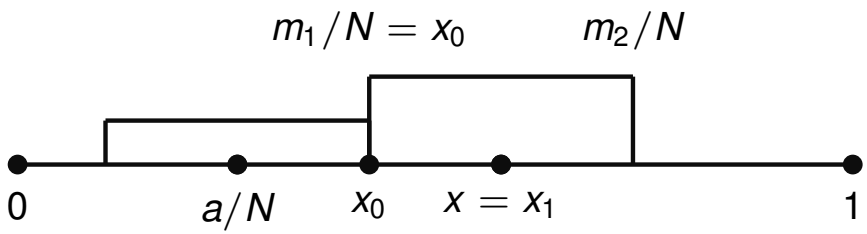
Statistical Analysis Methods Applied to Early Outpatient COVID-19 Treatment Case Series Data

Eleftherios Gkioulekas [1,*], Peter A. McCullough [2] and Vladimir Zelenko [3,†]

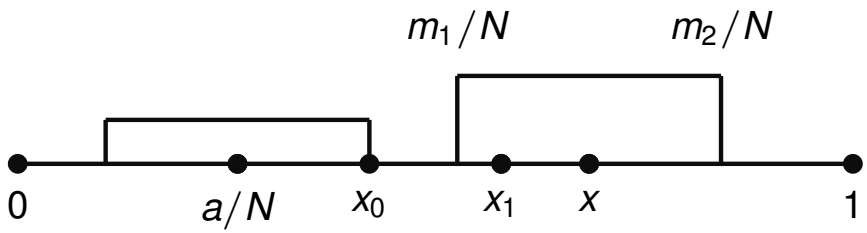
- **Preponderance of the evidence**



- **Crossover to clear and convincing**



- **Clear and convincing**



Case series threshold analysis method. II. Adjusted efficacy threshold

- To compare a case series of (N, a) of N treated patients with a adverse events against population level probability $x \in [p_1, p_2]$ of adverse event without treatment:
- Let $p(N, a, x)$ be the p-value for observing the case series (N, a) if treatment has no effect.

$$p(N, a, x) = \sum_{n=0}^{N} \mathrm{pr}(N, n|x)\ H(\mathrm{pr}(N, a|x) - \mathrm{pr}(N, n|x)),$$

$$\mathrm{pr}(N, a|x) = \binom{N}{a} x^a (1-x)^{N-a}.$$

- Calculate an efficacy threshold $x_0(N, a, p_0)$ to control p-value

$$x > x_0(N, a, p_0) \Longrightarrow p(N, a, x) < p_0$$

- Use Bayesian technique to obtain adjusted efficacy threshold $y_0(N, a, p_0)$ to control both p value and Bayesian factor:

$$x > y_0(N, a, p_0) \Longrightarrow p(N, a, x) < p_0 \wedge B(N, a, x, p_2) > 5(1-p_0)/p_0$$

with $B(N, a, x, p_2)$ given by

$$B(N, a, x, p_2) = \max_{t \in (0, x]} \frac{\mathrm{pr}(N, a|H_1(x, t))}{\mathrm{pr}(N, a|H_0(x, p_2))}, \tag{1}$$

$$\mathrm{pr}(N, a|H_0(x, p_2)) = \frac{1}{p_2 - x} \binom{N}{a} \int_x^{p_2} q^a (1-q)^{N-a}\, \mathrm{d}q, \tag{2}$$

$$\mathrm{pr}(N, a|H_1(x, t)) = \frac{1}{t} \binom{N}{a} \int_0^{t} q^a (1-q)^{N-a}\, \mathrm{d}q. \tag{3}$$

Case series threshold analysis method. III. Random selection bias threshold

- Calculate random selection bias threshold $x_1(N, y_0, p_0) > y_0$ such that

$$x > x_1(N, y_0, p_0) \Longrightarrow p(N, \lceil y_0 N \rceil, p_0) < p_0$$

- Systemic selection bias: it is more likely to select healthy patients rather than unhealthy patients by a factor of f
- The corresponding systemic selection bias threshold, as a function of f, is given by

$$x_1(f|N, y_0, p_0) = \frac{f x_1(N, y_0, p_0)}{1 + (f-1)x_1(N, y_0, p_0)}.$$

- Suppose that we are able to bound the probability x of an adverse outcome without treatment in the interval $p_1 < x < p_2$, by use of the historical control.
- The corresponding selection bias tolerance F is obtained by solving the equation

$$x_1(f|N, y_0, p_0) = p_1$$

- The solution $f = F$ is given by

$$F = \frac{p_1[1 - x_1(N, y_0, p_0)]}{x_1(N, y_0, p_0)(1 - p_1)}.$$

Method: Hospitalization rate reduction

- To investigate the existence of some ***hospitalization rate reduction***:
  - Assume that at least all patients with SpO2 $\leq$ 90% would have been hospitalized if one followed standard guidelines
  - Simplified self-control method: the same case series is used both as a treatment and control group
  - As treatment group: use of supplemental oxygen or ventilation are counted as hospitalization events
  - As self-control: all patients with SpO2 $\leq$ 90% are counted as counterfactual hospitalization events
  - Comparison with: exact Fisher test and case series threshold analysis

	Patients with baseline SpO2					
Case series	$\leq$ 100%	$\leq$ 93%	$\leq$ 90% (p_1)	**Deaths**	**Deterioration**	**Time Period**
Hazan	24	23	23 (95.8%)	0	0	2020-08 to 2021-02
Stone	34	34	28 (82.3%)	0	0	2020-08 to 2021-05
Babalola	61	21	10 (16.4%)	0	5	2021-04 to 2021-06
Hazan + Stone	58	57	51 (87.9%)	0	0	2020-08 to 2021-05
Hazan + Stone + Babalola	119	78	61 (51.3%)	0	5	2020-08 to 2021-06

Existence of hospitalization rate reduction

- **Self-controlled Exact Fisher test comparisons**

Case series	(N, a)	(N, b)	**OR (95% CI)**	***p*-value**
Hazan	(24, 0)	(24, 23)	0 (0 – 0.02)	10^{-12}
Stone	(34, 0)	(34, 28)	0 (0 – 0.04)	10^{-13}
Babalola	(61, 5)	(61, 10)	0.46 (0.11 – 1.59)	0.27
Hazan + Stone	(58, 0)	(58, 51)	0 (0 – 0.01)	10^{-25}
Hazan + Stone + Babalola	(119, 5)	(119, 61)	0.04 (0.01 – 0.11)	10^{-17}

- **Hospitalization rate reduction thresholds using 95% confidence intervals**

Case series (SpO2 $\leq$ 100%)	(N, a)	x_0	$\log_{10} B$	p_2	y_0	x_1
Hazan	(24, 0)	14.0%	2.94	95.8%	14.0%	37.3%
Stone	(34, 0)	9.9%	2.98	82.3%	9.9%	27.7%
Babalola	(61, 5)	17.9%	1.64	34.4%	20.0%	33.6%
Hazan + Stone	(58, 0)	6.5%	3.39	87.9%	6.5%	17.0%
Hazan + Stone + Babalola	(119, 5)	9.6%	2.36	51.3%	9.6%	17.2%

- p_2 is chosen equal to the percentage of patients with room air baseline SpO2 $\leq$ 90%, except for the Babalola case series, where p_2 is chosen equal to the percentage of patients with room air baseline SpO2 $\leq$ 93%
- Compare x_1 with p_2: **clear and convincing** hospitalization rate reduction for Stone, Hazan, Stone+Hazan, Stone+Hazan+Babalola case series.
- Systemic selection bias tolerence: Hazan ($F = 38.3$); Stone ($F = 12.1$); Hazan+Stone ($F = 35.5$); Hazan+Stone+Babalola ($F = 5.1$). All very resilient.

Method: Mortality rate reduction

- To investigate ***mortality rate reduction***:
  - Use the risk-stratified subseries of all patients with SpO2 $\leq$ 90% (counterfactual hospitalizations under standard guidelines)
  - Compare against the Case Fatality Rate (CFR) of hospitalized patients
  - Comparison using: exact Fisher test and case series threshold analysis
- Summary of case series thresholds for risk-stratified subseries with SpO2 $\leq$ 90%

Mortality rate reduction thresholds using 95% confidence intervals						
Case series (SpO2 $\leq$ 90%)	(N, a)	x_0	$\log_{10} B$	p_2	y_0	x_1
Hazan	(23, 0)	14.6%	1.99	23.48%	14.7%	38.9%
Stone	(28, 0)	12.0%	2.13	23.3%	12.0%	32.0%
Hazan + Stone	(51, 0)	7.4%	1.97	10%	7.6%	18.5%
Hazan + Stone + Babalola	(61, 0)	6.2%	2.12	10%	6.2%	16.2%

- Thresholds are then compared with hospitalized CFR from the following external control groups:
  1. CDC COVID-19 case surveillance public use data with geography
  2. Zimbabwe: Parirenyatwa hospitals; Masholand West Province
  3. South Africa hospitalized CFR (larger sample sizes)
  4. World Heart Federation Study: Global hospitalized CFR and hospitalized CFR for LMIC nations

External control for hospitalized CFR: World Heart Federation

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ON BEHALF OF THE WHF COVID-19 STUDY COLLABORATORS

*Author affiliations can be found in the back matter of this article

- World Heart Federation: 5313 consecutive patients prospectively recruited between June 2020 and September 2021 from 40 hospitals across 23 different countries.
- 15.08% Global hospitalized CFR
- 19.48% LMIC hospitalized CFR

External control for hospitalized CFR: United States

- **CDC "COVID-19 case surveillance public use data with geography" database**

Timing	Cases	Died	Lived	CFR
CFR for confirmed hospitalizations over all age groups				
Hazan (treatment interval): 2020-08 to 2021-02	491152	45868	204620	9.34% to 18.31%
Hazan (cumulative): 2020-01 to 2021-02	775369	82427	337539	10.63% to 19.63%
CFR for confirmed hospitalizations for age $\geq$ 50				
Hazan (treatment interval): 2020-08 to 2021-02	372828	45214	147387	12.13% to 23.48%
Hazan (cumulative): 2020-01 to 2021-02	568399	80586	227912	14.18% to 26.12%

- CDC database lower bound: assume all patients with unknown outcome have survived
- CDC database upper bound: assume all patients with unknown outcome have same likelihood of survival as patients with known outcome.

Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score

Stephen R Knight,[1] Antonia Ho,[2,3] Riinu Pius,[1] Iain Buchan,[4] Gail Carson,[5] Thomas M Drake,[1] Jake Dunning,[6,7] Cameron J Fairfield,[1] Carrol Gamble,[8] Christopher A Green,[9] Rishi Gupta,[10] Sophie Halpin,[8] Hayley E Hardwick,[11] Karl A Holden,[11] Peter W Horby,[5] Clare Jackson,[8] Kenneth A Mclean,[1] Laura Merson,[5] Jonathan S Nguyen-Van-Tam,[12] Lisa Norman,[1] Mahdad Noursadeghi,[13] Piero L Olliaro,[14] Mark G Pritchard,[14] Clark D Russell,[15] Catherine A Shaw,[1] Aziz Sheikh,[1] Tom Solomon,[11,16] Cathie Sudlow,[17] Olivia V Swann,[18] Lance CW Turtle,[11,19] Peter JM Openshaw,[7] J Kenneth Baillie,[20,21] Malcolm G Semple,[11,22] Annemarie B Docherty,[1,21] Ewen M Harrison,[1,23] on behalf of the ISARIC4C investigators

BMJ: first published as 10.1136/bmj.m333

- 4C model: Hypoxemia as a risk factor is equivalent to age $\geq$ 50 years
- For Hazan case series, lower bound for mortality rate of external control is 12%

External controls for hospitalized CFR: Zimbabwe

- **External control: Masholand Province, Zimbabwe**

  Factors associated with COVID-19 fatality among patients admitted in Mashonaland West Province, Zimbabwe 2020-2022: a secondary data analysis

  Kudzai Madamombe, Gerald Shambira, Gift Masoja, Tapiwa Dhliwayo, Tsitsi Patience Juru, Notion Tafara Gombe, Addmore Chadambuka, Mujinga Karakadzai, Mufuta Tshimanga

- **External control: South Africa**

  Difference in mortality among individuals admitted to hospital with COVID-19 during the first and second waves in South Africa: a cohort study

  Waasila Jassat, Caroline Mudara, Lovelyn Ozougwu, Stefano Tempia, Lucille Blumberg, Mary-Ann Davies, Yogan Pillay, Terence Carter, Ramphelane Morewane, Milani Wolmarans, Anne von Gottberg, Jinal N Bhiman, Sibongile Walaza, Cheryl Cohen, DATCOV author group

Location	Timing	Cases	Died	CFR
CFR for confirmed hospitalizations over all age groups				
South Africa (first wave)	2020-03 to 2020-08	83742	17042	20.35%
South Africa (beta)	2020-09 to 2021-03	135472	33999	25.1%
South Africa (combined)	2020-03 to 2021-03	219214	51041	23.28%
Zimbabwe (Parirenyatwa hospitals)	2020-06 to 2020-12	336	119	35.42%
Zimbabwe (Masholand West Province)	2020-04 to 2022-04	673	157	23.33%
World Heart Federation study (all patients)	2020-06 to 2021-09	5313	801	15.08%
World Heart Federation study (LMIC)	2020-06 to 2021-09	2526	492	19.48%

Mortality rate reduction: Hazan case series

- **Exact Fisher test comparisons with external controls**

External control	(N, a)	(M, b)	OR (95% CI)	p-value
Hazan case series compared with				
CDC (treatment interval, any age)	(23, 0)	(491152, 45868)	0 (0 – 1.69)	0.267
CDC (treatment interval, age $\geq$ 50)	(23, 0)	(372828, 45214)	0 (0 – 1.26)	0.103
CDC (cumulative, any age)	(23, 0)	(775369, 82427)	0 (0 – 1.46)	0.165
CDC (cumulative, age $\geq$ 50)	(23, 0)	(568399, 80586)	0 (0 – 1.05)	0.065
World Heart Federation (global)	(23, 0)	(5313, 801)	0 (0 – 0.98)	0.039

- **Case series threshold analysis**

Mortality rate reduction thresholds using 95% confidence intervals						
Case series (SpO2 $\leq$ 90%)	(N, a)	x_0	$\log_{10} B$	p_2	y_0	x_1
Hazan	(23, 0)	14.6%	1.99	23.48%	14.7%	38.9%

- Choice of p_2: the smallest number between (a) peak month by month hospitalized CFR without age restriction and (b) upper endpoint of estimated hospitalized CFR interval with age $\geq$ 50 years averaged over treatment period
- **Failure to show** existence of mortality rate reduction efficacy, because:
  1. External control CFR $\geq$ 12%
  2. Adjusted efficacy threshold $y_0 = 14.7\%$

Mortality rate reduction: Stone case series

- **Exact Fisher test comparisons with external controls**

External control	(N, a)	(M, b)	OR (95% CI)	p-value
Stone case series compared with				
Zimbabwe (Parirenyatwa hospitals)	(28, 0)	(336, 119)	0 (0 – 0.26)	10^{-5}
Zimbabwe (Masholand West Province)	(28, 0)	(673, 157)	0 (0 – 0.47)	10^{-4}
South Africa (beta)	(28, 0)	(135472, 33999)	0 (0 – 0.42)	10^{-4}
South Africa (combined)	(28, 0)	(219214, 51041)	0 (0 – 0.46)	0.001
World Heart Federation study (LMIC)	(28, 0)	(2526, 492)	0 (0 – 0.58)	0.003

- **Case series threshold analysis**

Mortality rate reduction thresholds using 95% confidence intervals						
Case series (SpO2 $\leq$ 90%)	(N, a)	x_0	$\log_{10} B$	p_2	y_0	x_1
Stone	(28, 0)	12.0%	2.13	23.3%	12.0%	32.0%

- Choice of p_2: smallest number between (a) hospitalized CFR reported in Harare, Zimbabwe and (b) hospitalized CFR reported in Masholand West Province
- Mortality rate reduction established by the **preponderance of evidence** because:
  1. External control hospitalized CFR $\geq$ 20%
  2. Adjusted efficacy threshold $y_0 = 12.0\%$
  3. Random selection bias threshold $x_1 = 32.0\%$

Mortality rate reduction: combined case series

- **Exact Fisher test comparisons with external controls**

External control	(N, a)	(M, b)	OR (95% CI)	p-value
Hazan + Stone case series compared with				
CDC (treatment interval, any age)	(51, 0)	(491152, 45868)	0 (0 – 0.73)	0.013
CDC (treatment interval, age $\geq$ 50)	(51, 0)	(372828, 45214)	0 (0 – 0.54)	0.002
World Heart Federation (global)	(51, 0)	(5313, 801)	0 (0 – 0.42)	10^{-4}
Hazan + Stone + Babalola case series compared with				
CDC (treatment interval, any age)	(61, 0)	(491152, 45868)	0 (0 – 0.61)	0.006
CDC (treatment interval, age $\geq$ 50)	(61, 0)	(372828, 45214)	0 (0 – 0.45)	10^{-4}
World Heart Federation (global)	(61, 0)	(5313, 801)	0 (0 – 0.35)	10^{-5}

- **Case series threshold analysis**

Mortality rate reduction thresholds using 95% confidence intervals						
Case series (SpO2 $\leq$ 90%)	(N, a)	x_0	$\log_{10} B$	p_2	y_0	x_1
Hazan + Stone	(51, 0)	7.4%	1.97	10%	7.6%	18.5%
Hazan + Stone + Babalola	(61, 0)	6.2%	2.12	10%	6.2%	16.2%

- **Hazan + Stone case series:** Mortality rate reduction is decisively established by the **preponderance of evidence** in comparison with hospitalized CFR $\geq$ 12%
- **Hazan + Stone + Babalola case series:** Crossover to **clear and convincing** when compared against hospitalized average CFR $\geq$ 16.7% (using CFR $\geq$ 12% for Hazan patients and CFR $\geq$ 19.5% (WHF/LMIC) for Stone+Babalola)

Conclusion – Bradford Hill criteria

- Sir Bradford Hill proposed several criteria that can be used together to establish causality: i.e. that treatment caused the reduction in mortality and hospitalization rates.
- **Strength of association:**
  1. Clear and convincing hospitalization rate reduction
  2. Preponderance of evidence in support of mortality rate reduction
- **Biological plausibility**
  1. The process causing oxygen desaturation is understood.
  2. Our paper reviews the biological mechanisms of action for the medications used in the treatment of the Hazan and Stone case series.
- **Consistency:** Positive results have been obtained in three different countries (United States, Zimbabwe, and Nigeria)
- **Temporality:** Recovery of oxygen levels occurs rapidly at the onset of treatment within 24-48 hours
- **Biological gradient:** Recovery of SpO2 levels is more rapid with more aggressive protocols (Stone and Hazan; IVM+DOXY+ZINC), less rapid with less aggressive protocols (Babalola IVM+ZINC), and slowest with standard of care (no IVM, no DOXY, no zinc)
- **More data is available but doctors using these treatments are being persecuted by authorities (licensing or certification boards), sometimes at the instigation of academic scientists.**

Thank you!