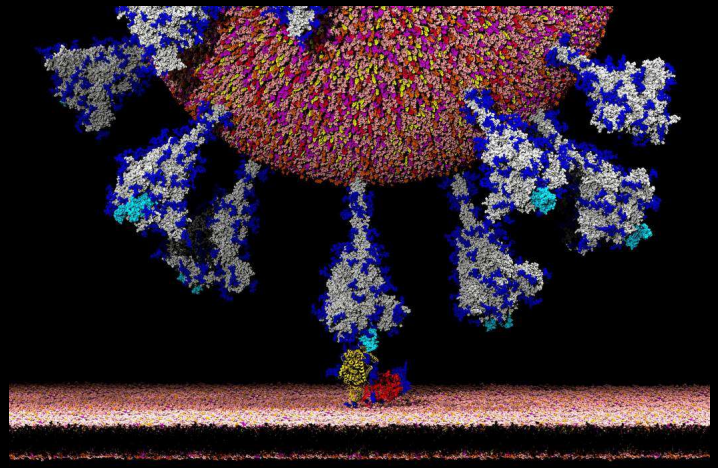
COVID-19 Treatment and Outcomes: Registries and Real-World Evidence



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Internal Medicine-Rheumatology, Environmental Health Sciences & OB/GYN

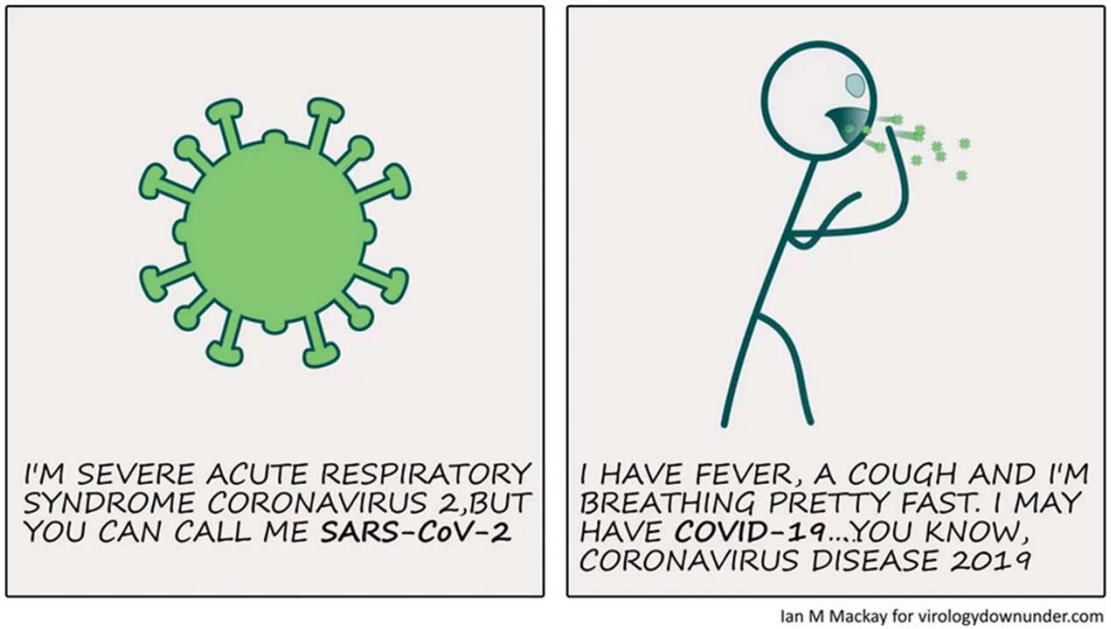
Interdisciplinary Research Initiatives Faculty Lead, MICHR

October 21, 2020

Photo: Lorenzo Casalino, Amaro Lab, U.C. San Diego

Outline

- Clinical research infrastructure – importance of harmonization and interdisciplinary collaboration
- Specific projects based on observational registry data



International Severe Acute Respiratory & Emerging Infection Consortium (ISARIC)

- Global federation of clinical research networks, providing a proficient, coordinated, and agile research response to outbreak-prone infectious diseases (inception 2011)
- Collaborative platform through which global, patient-oriented clinical studies can be developed, executed & shared
- Protocols & data tools developed in consultation with WHO colleagues
  - established in “peacetime” → maintained in a hibernating state and rapidly implemented when required
  - **“ISARIC/WHO Clinical Characterisation Protocol (CCP)”** – standardised generic research protocol created in 2012 for clinical characterisation of any emerging infection tools released under open-source license, ie, anyone can download, use, adapt, or distribute them

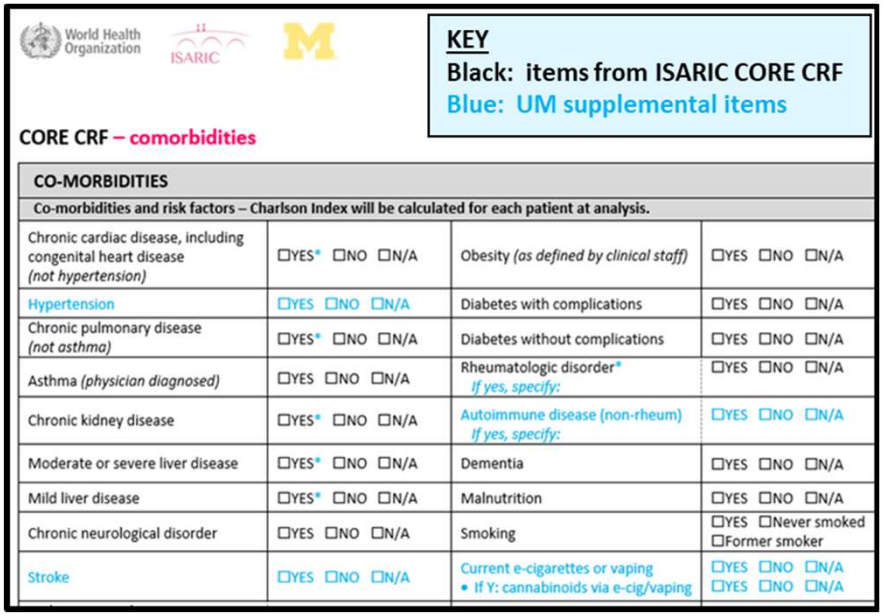
MICHR COVID-19
Rapid Response Registry (RRR)

MICHR COVID-19 RRR – harmonized with ISARIC

- UM one of 1st US sites to partner w/ISARIC for COVID-19
- Registry utilized ISARIC protocols/tools as starting point
- Supplemented data collection with additional details & modules; input from various investigators
- Through MICHR Research Development Core (RDC)/Interdisciplinary Research Initiatives, we developed a COVID-19 consultation process
- RRR intended as resource for UM scientific community to both access and contribute to
  - ➢ streamline/standardize data collection and identify synergies between groups

Clinical characterization protocol (CCP)
COVID-19 hospitalizations

CRF excerpt



World Health Organization | ISARIC | M

KEY
Black: items from ISARIC CORE CRF
Blue: UM supplemental items

CORE CRF – comorbidities

CO-MORBIDITIES			
Co-morbidities and risk factors – Charlson Index will be calculated for each patient at analysis.			
Chronic cardiac disease, including congenital heart disease *(not hypertension)*	☐YES* ☐NO ☐N/A	Obesity *(as defined by clinical staff)*	☐YES ☐NO ☐N/A
Hypertension	☐YES ☐NO ☐N/A	Diabetes with complications	☐YES ☐NO ☐N/A
Chronic pulmonary disease *(not asthma)*	☐YES* ☐NO ☐N/A	Diabetes without complications	☐YES ☐NO ☐N/A
Asthma *(physician diagnosed)*	☐YES ☐NO ☐N/A	Rheumatologic disorder* *If yes, specify:*	☐YES ☐NO ☐N/A
Chronic kidney disease	☐YES* ☐NO ☐N/A	Autoimmune disease (non-rheum) *If yes, specify:*	☐YES ☐NO ☐N/A
Moderate or severe liver disease	☐YES* ☐NO ☐N/A	Dementia	☐YES ☐NO ☐N/A
Mild liver disease	☐YES* ☐NO ☐N/A	Malnutrition	☐YES ☐NO ☐N/A
Chronic neurological disorder	☐YES ☐NO ☐N/A	Smoking	☐YES ☐Never smoked ☐Former smoker
Stroke	☐YES ☐NO ☐N/A	Current e-cigarettes or vaping • If Y: cannabinoids via e-cig/vaping	☐YES ☐NO ☐N/A ☐YES ☐NO ☐N/A

manual abstraction of data

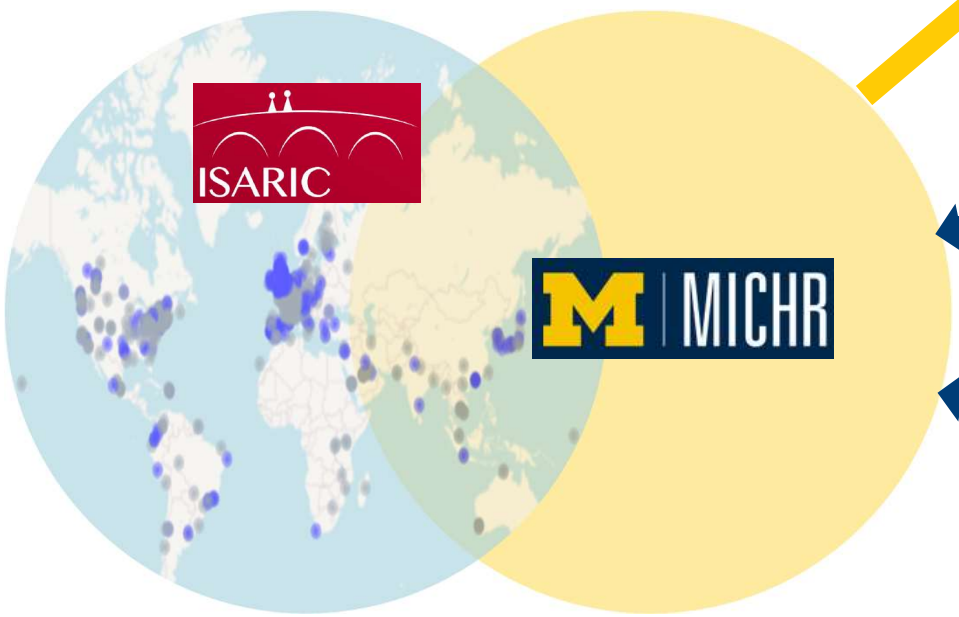
Major categories of data elements/CRFs

- Epidemiological factors
- Demographics
- Comorbidities
  - "Special populations" (eg, pregnancy, SOT, rheumatic disease, etc)
- Onset & admission (diagnosis, signs, symptoms, meds at onset)
- Pathogen testing
- DAILY assessment (during hospitalization)
  - Labs, imaging, medications/interventions, process of care, etc.
- Complications
- Outcomes (long-term outcomes also planned)

Registry structure overview

ISARIC Global Database

- 100,000+ patients
- 488 sites
- 37 countries



Core registry analyses

+ MODULES
eg, solid organ transplant

+ LINKAGES
EHR, specimens, assay results

Symptoms at hospital presentation

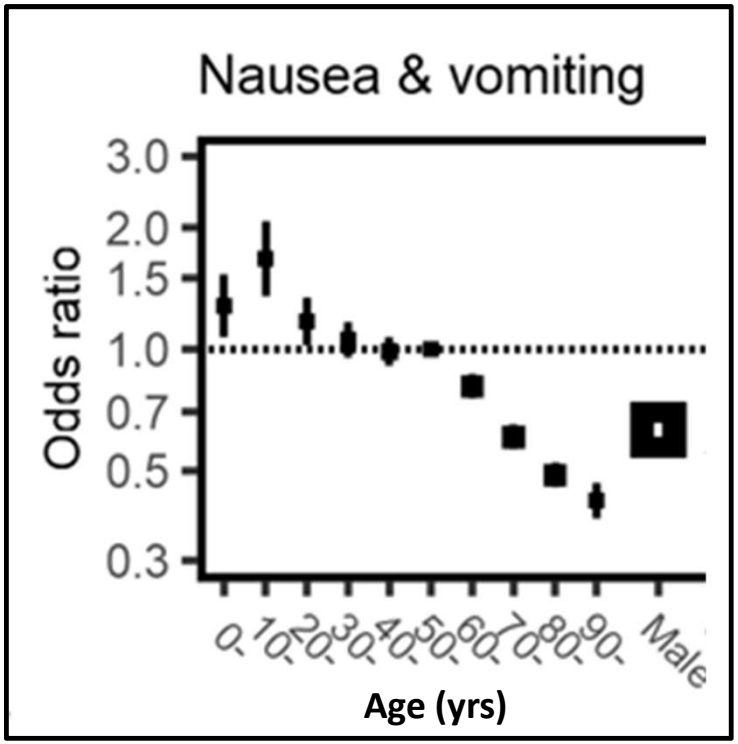
ISARIC Clinical Data Report – Oct 4, 2020

Sex differences

- Males: typical symptoms more prevalent
  - Cough, fever & shortness of breath
- Females: atypical symptoms more prevalent
  - confusion, nausea & vomiting, diarrhoea, chest pain, headache, abdominal pain

Age differences

- Children & older adults less likely to present with typical symptoms of cough, fever & shortness of breath
  - Nausea & vomiting, headache, abdominal pain, and sore throat each more frequent in younger age groups, decreasing with age
  - Confusion increased with age
  - Persist after adjustment for sex
- Commonly used clinical case definitions identified greater proportions of patients between the ages of 30 and 60 years



Risk stratification: 4C Mortality Score

- ISARIC 4C (Coronavirus Clinical Characterisation Consortium) Mortality Score
- easy-to-use prediction tool for in-hospital mortality
  - 8 variables readily available at hospital presentation
- outperformed 15 pre-existing risk stratification tools

Table 2 | Final 4C Mortality Score for in-hospital mortality in patients with covid-19. Prognostic index derived from penalised logistic regression (LASSO) model

Variable	4C Mortality Score
Age (years)	
<50	—
50-59	+2
60-69	+4
70-79	+6
≥80	+7
Sex at birth	
Female	—
Male	+1
No of comorbidities*	
0	—
1	+1
≥2	+2
Respiratory rate (breaths/min)	
<20	—
20-29	+1
≥30	+2
Peripheral oxygen saturation on room air (%)	
≥92	—
<92	+2
Glasgow coma scale score	
15	—
<15	+2
Urea (mmol/L)	
≤7	—
7-14	+1
>14	+3
C reactive protein (mg/dL)	
<50	—
50-99	+1
≥100	+2

Covid-19=coronavirus disease 2019.
*Comorbidities were defined by using Charlson comorbidity index, with the addition of clinician defined obesity.

thebmj | BMJ 2020;370:m3339 | doi: 10.1136/bmj.m3339
Sept 9, 2020

Corticosteroid Use

★June 16: RECOVERY RCT results★

Dexamethasone (6 mg/d x 10 d) reduced deaths by up to one third for patients receiving invasive mechanical ventilation & oxygen therapy, but not among patients who did not require respiratory support.

Corticosteroid Use – ISARIC Clinical Data Report, Oct 4, 2020

	Overall n=80,355	Admissions Since June 16 (n=4,711)
Invasive mechanical ventilation (IMV)	38.4%	72.8%
Oxygen therapy (not IMV)	18.2%	41.9%
No oxygen therapy	10.5%	15.1%

COVID-19 RRR

Re-purposing of RA drug for COVID-19

- Severe COVID-19 can manifest in rapid decompensation & respiratory failure with elevated inflammatory markers, including interleukin-6 (IL-6)
  - Resembles **cytokine release syndrome** for which IL-6 blockade is an approved treatment

- Tocilizumab: IL-6 receptor antagonist approved for rheumatoid arthritis & cytokine release syndrome

- Michigan Medicine early adopter of tocilizumab use for COVID-19 (standard dose 8 mg/kg × 1)
  - Antimicrobial Stewardship Program & Div of Infectious Diseases created usage criteria for when toci could be considered
    - Rapidly worsening respiratory status
    - Clinical suspicion cytokine release syndrome, supported by elevated inflammatory markers
    - Absence of systemic bacterial or fungal co-infection
  - Individualized decisions on tocilizumab usage made by attending physicians (differing views)
  - Concern for scare resource allocation, including access for RA patients

➢ **Evaluation of toci effectiveness using COVID-19 RRR identified as top priority**

IL-6 Inhibition in COVID-19

Respiratory failure in severe COVID-19 frequently characterized by high serum IL-6 concentrations

- Excessive IL-6 can induce **lung epithelial cells** to increase inflammatory responses, leading to increased macrophage response and ultimately pulmonary damage.
- IL-6 may also contribute to **thrombosis**
  - tissue and vascular endothelial cell injury, platelet aggregation and angiotensin II microvascular dysfunction
- Conversely, IL-6 is a critical cytokine in **organizing T-cell responses to infections** and may play a beneficial role in COVID-19
  - *eg*, suppression of viral reactivation, protection against superinfection, facilitation of lung repair and remodeling after viral injury

Michigan Medicine approach: administer tocilizumab in patients who were <u>rapidly desaturating or recently intubated</u> in an attempt to optimize the timing of administration for maximal benefit

- Dosing strategy (single, high dose of 8 mg/kg): attempt to saturate receptors to rapidly inhibit IL-6 signaling but also allow more rapid clearance in order to not interfere with tissue remodeling and limit immunosuppression

Clinical Infectious Diseases

MAJOR ARTICLE

Tocilizumab for Treatment of Mechanically Ventilated Patients With COVID-19

Emily C. Somers,[1,2,3,a] Gregory A. Eschenauer,[4,a] Jonathan P. Troost,[5] Jonathan L. Golob,[1] Tejal N. Gandhi,[1] Lu Wang,[6] Nina Zhou,[6] Lindsay A. Petty,[1] Ji Hoon Baang,[1] Nicholas O. Dillman,[7] David Frame,[4] Kevin S. Gregg,[1] Dan R. Kaul,[1] Jerod Nagel,[7] Twisha S. Patel,[7] Shiwei Zhou,[1] Adam S. Lauring,[1] David A. Hanauer,[8] Emily Martin,[9] Pratima Sharma,[1] Christopher M. Fung,[10] and Jason M. Pogue[4]

Comparative outcomes of mechanically ventilated patients who received tocilizumab and those who did not

- Patients admitted March 9–April 20, 2020
- Follow-up through May 19, 2020 (min 28 days f/up)

Primary outcome

- Survival after intubation

Secondary outcome

- Clinical progression at day 28: 6-level ordinal scale including superinfections (bloodstream infection and pneumonia)

Core Outcome Measures for COVID-19 Clinical Studies

❶ Viral Burden of SARS-CoV-2
- quantitative PCR or cycle threshold

❷ Survival (all-cause mortality)
- Hospital discharge
- 60 days

❸ Clinical Progression
- Ordinal scale
  (daily assessment during study)

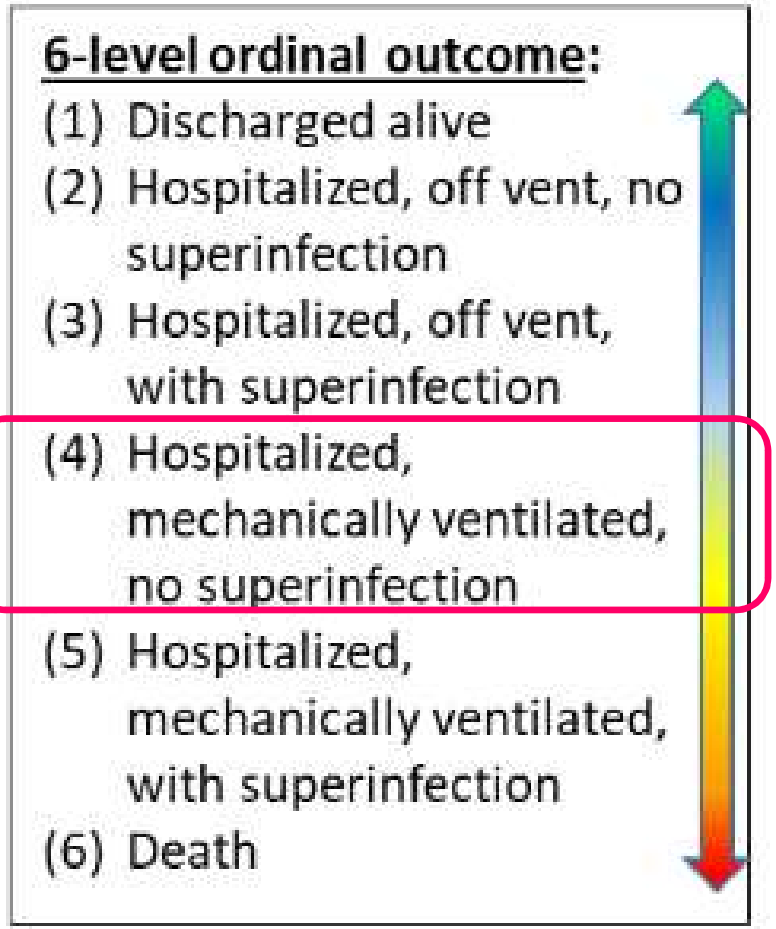
WHO Clinical Progression Scale

PATIENT STATE	DESCRIPTOR	Score
Uninfected	No evidence of infection (no viral RNA detected)	0
Ambulatory ***Mild disease***	Asymptomatic (viral RNA detected)	1
	Symptomatic – no limitation of activities	2
	Symptomatic – limitation of activities	3
Hospitalized ***Moderate disease***	No oxygen therapy	4
	Oxygen by mask or nasal prongs	5
Hospitalized ***Severe disease***	Oxygen by non-invasive ventilation or high-flow	6
	Intubation and mechanical ventilation	7
	Ventilation + additional organ support: pressors, renal replacement therapy, ECMO	8/9
Dead	Death	10

Lancet Infect Dis 2020;
20: e192–97
Published Online
June 12, 2020

*WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection**

Ordinal scale in tociluzimab study



Study Flow Chart

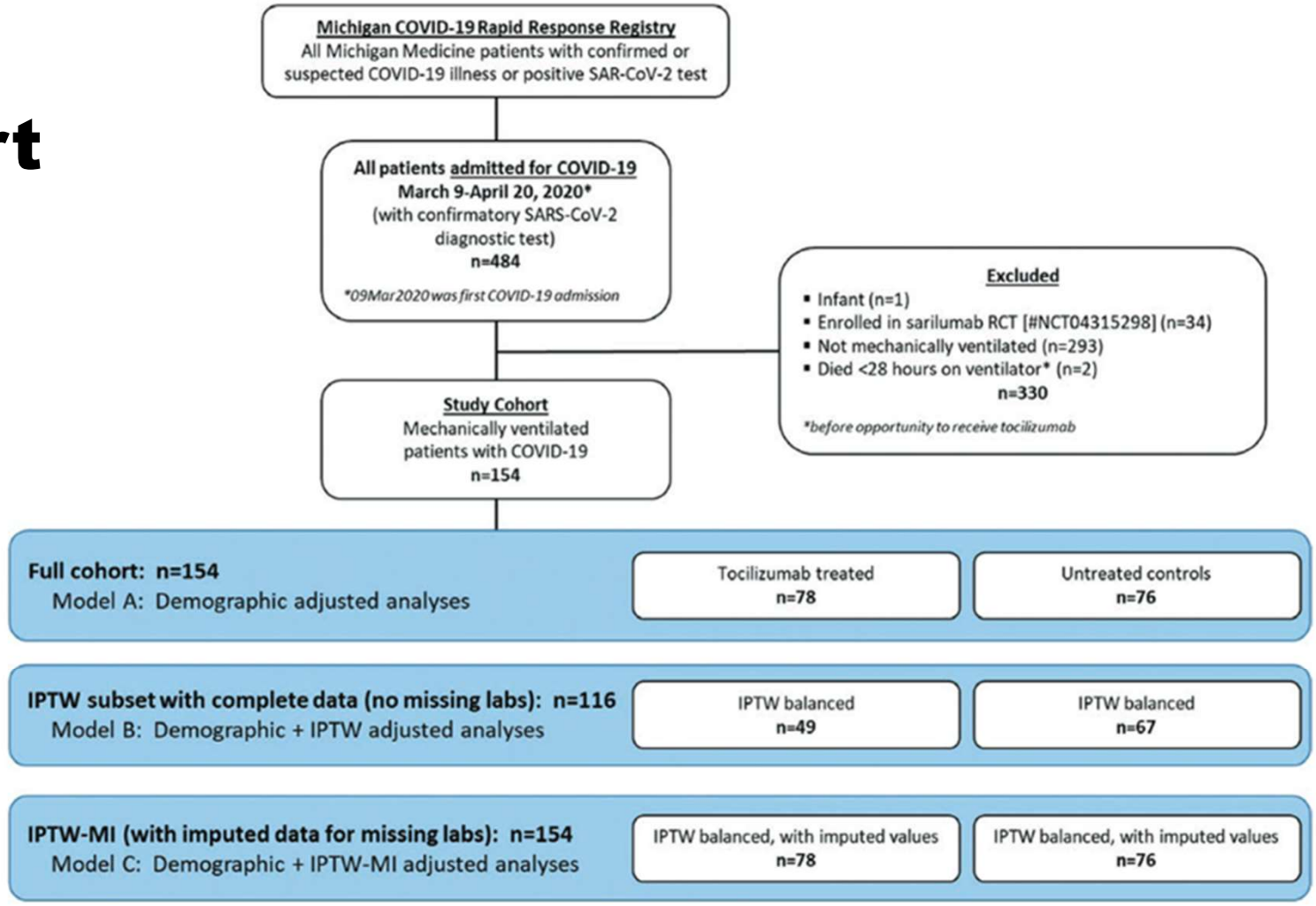


Figure 1. Study cohort flow chart. Abbreviations: COVID-19, coronavirus disease 2019; IPTW, inverse probability of treatment weighting; MI, multiple imputation; RCT, randomized controlled trial; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

IPTW

- *addresses non-randomized treatment allocation*

Inverse probability of treatment weighting (IPTW)

- Addresses non-randomized treatment allocation
- Calculated propensity scores by multivariable logistic regression with tocilizumab treatment as the binary outcome and potential confounding factors associated with both outcome and treatment assignment
- Using such propensity scores, we applied inverse probability of treatment weighting (IPTW) to create a pseudo-study cohort, where the weighted version can balance off the covariate bias and mimic a randomized treatment assignment situation:
  - IPT weights for tocilizumab-treated patients = 1/p (treated)
  - untreated patients = 1/(1 − p [treated])

Baseline Characteristics

abbreviated

Table 1. Characteristics of the Cohort

	Overall (n = 154)	Tocilizumab Treated (n = 78)	Untreated (n = 76)	*P*
Baseline characteristics				
Age,[a] years	58 ± 14.9	55 ± 14.9	60 ± 14.5	.05
Female, n (%)	52 (34)	25 (32)	27 (36)	.65
Race, n (%)				.48
Black	81 (53)	38 (49)	43 (57)	
White	41 (27)	24 (31)	17 (22)	
Other	32 (21)	16 (21)	16 (21)	
Weight,[a] kg	99 ± 28.5	101 ± 31.1	97 ± 26.2	.36
BMI,[a] kg/m^2	34.1 ± 9.5	34.7 ± 10.1	33.4 ± 8.8	.40
NEWS[b,c] (n = 61)	7 (4–8)	7 (5–8)	6 (4–8)	.31

National Early Warning Score

Survival
primary outcome

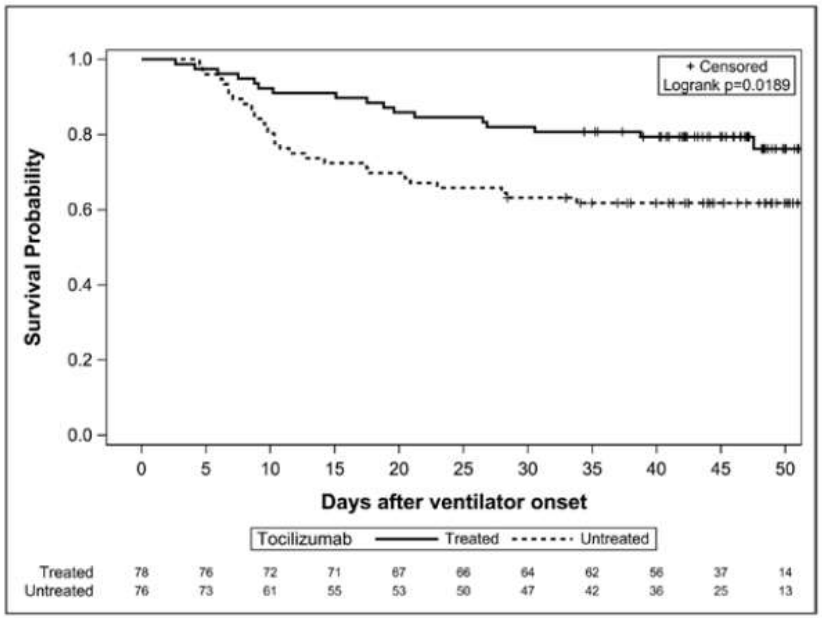


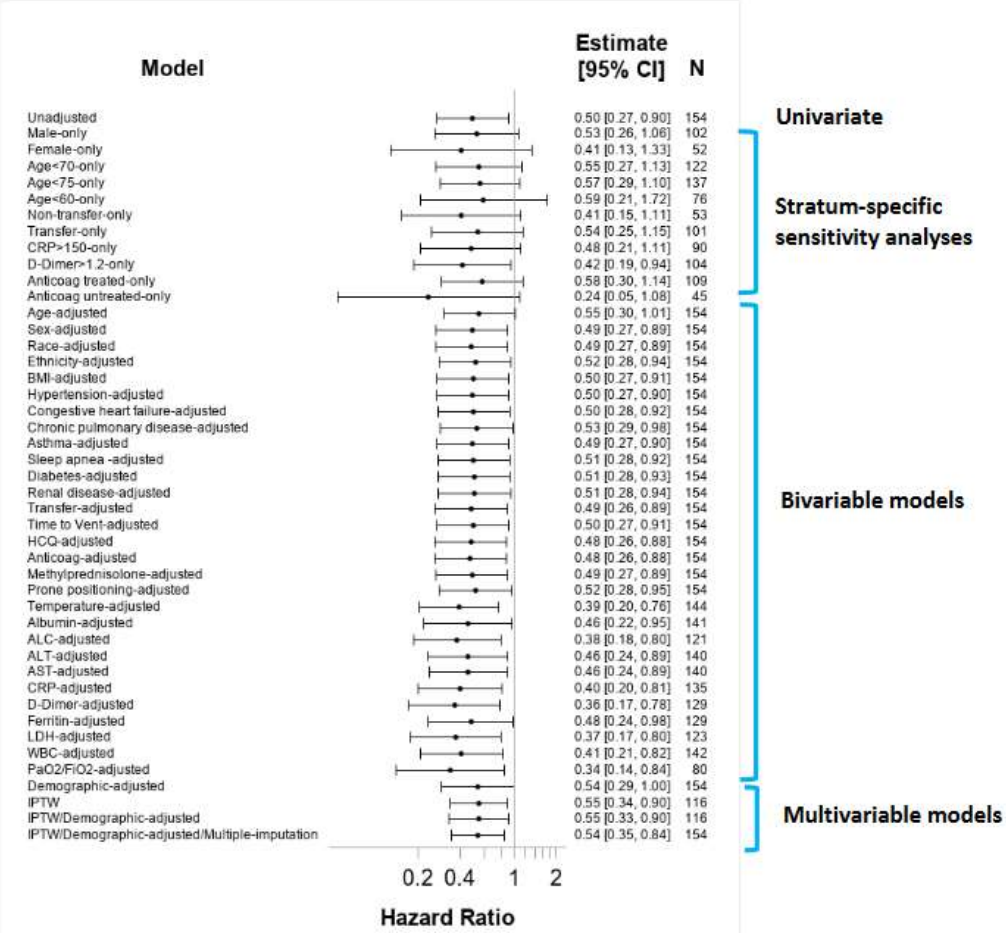
Figure 2. Kaplan-Meier estimates for probability of survival as a function of time since mechanical ventilation onset, stratified by tocilizumab treatment (n = 154; n = 46 deaths).

- Median follow-up time
  - 47 days (range, 28–67 days)
- Cox proportional hazards models
  - Tocilizumab associated with lower hazard of death after adjusting for covariates

Hazard ratios (95% CI) for tocilizumab vs control	
Model A: demographic adjusted	.54 (.29, 1.00)
Model B: demographic + IPTW adjusted (n = 116)	.55 (.33, .90)
Model C: demographic + IPTW-MI adjusted	.54 (.35, .84)

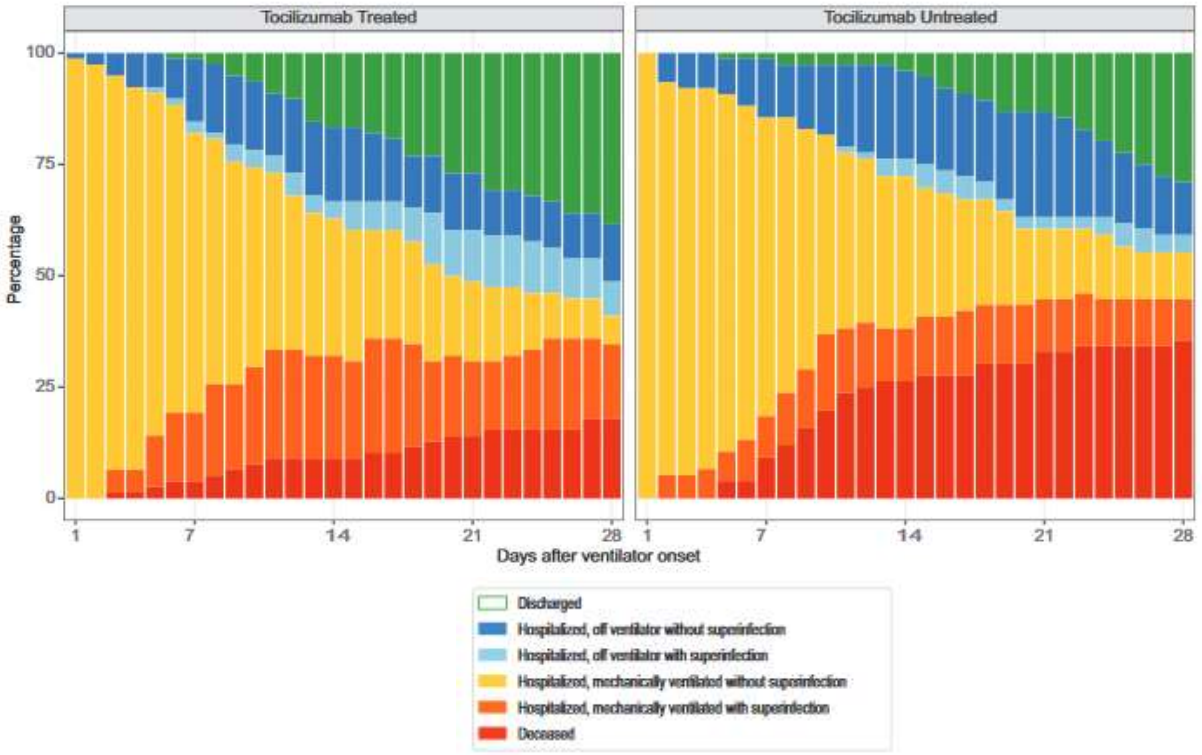
Sensitivity analyses

Figure S3. Hazard ratio estimates of the association between tocilizumab and survival.
Time from intubation to death or censoring. All hazard ratio estimates are for tocilizumab (treated vs. untreated) for the model specified. Full model results, including hazard ratios for other covariates in multivariable models, are shown in **Table S6**. Magnitude and direction of association between tocilizumab and outcome remained similar in each of the bivariable models, as well as the multivariable models.

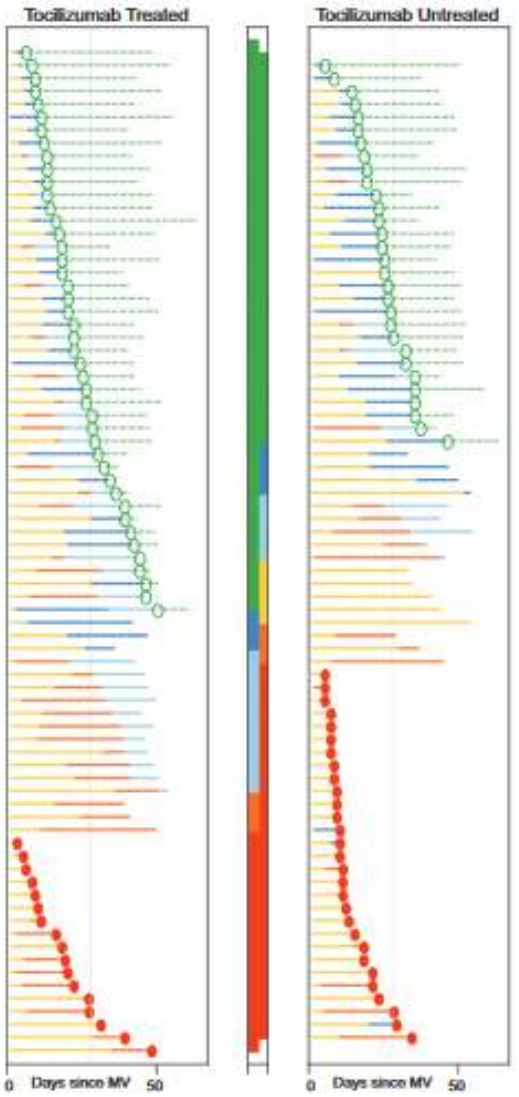


Clinical Progression
secondary outcome

Daily distribution of patient status after onset of mechanical ventilation (through Day 28), on a 6-level ordinal scale integrating superinfection occurrence.



Individual patient trajectories



Clinical progression & superinfection

	Tocilizumab Treated (n = 78)	Untreated (n = 76)	*P*
Odds ratios (95% CI) for proportional odds model for tocilizumab vs control (day 28)			
Model A: demographic adjusted	.60 (.34, 1.08)	Ref	.09
Model B: demographic + IPTW adjusted (n = 116)	.58 (.36, .94)	Ref	.03
Model C: demographic + IPTW-MI adjusted	.60 (.39, .91)	Ref	.02
Superinfection data			
Patients with a superinfection, n (%)	42 (54)	20 (26)	<.001
28-day case fatality rate[c]	8 (22)	5 (28)	.61

Case fatality rates at Day 28 similar among toci-treated pts with superinfection (22%) or without (15%); p=0.4

Superinfection

Novel finding: association between severe COVID-19 and staphylococcal pneumonia

- ~Half cases of superinfection in both toci & control groups due to *S. aureus*
- All infections reviewed by ID physician

Causative microbiology, n (%)		
Microbiology of pneumonia[d]	(n = 41)	(n = 22)
Staphylococcus aureus	21 (51)	11 (50)
Methicillin susceptible	15 (71)	5 (45)
Methicillin resistant	6 (29)	6 (55)

Conclusions: Tocilizumab Observational Study

- This was the first, well-controlled, comparative analysis assessing the safety and effectiveness of tocilizumab for severe COVID-19
  - Utilized Rapid Response Registry informed by an internationally designed clinical characterization protocol
- Tocilizumab associated with improved survival and clinical progression, despite higher occurrence of superinfections
- Heterogeneity in tocilizumab treatment decisions between providers at our institution provided opportunity to compare outcomes
  - Toci treated and untreated groups largely comparable
  - Slight imbalances in age, baseline D-dimer, CRP, comorbid chronic pulmonary disease, and transfer status
  - Utilized rigorous methods for observational data accounting for these factors and treatment propensity.
  - Tocilizumab remained associated with better outcomes across modeling strategies and various sensitivity analyses
    - Including when stratified by D-dimer and CRP thresholds previously associated with mortality
- Data reinforce concerns with superinfection risk due to IL-6 inhibition.
  - Limited data on superinfections in COVID-19

Observational studies vs RCTs

- Well-known limitations of observational studies
  - Confounding by indication
  - Residual confounding, unappreciated biases

- COVID-19
  - Many examples of early studies suggesting promising therapeutics later demonstrated as ineffective or even harmful
  - Hydroxychloroquine…

- What is role of real-world evidence?

ACCEPTED MANUSCRIPT

Decreased mortality in COVID-19 patients treated with Tocilizumab: a rapid systematic review and meta-analysis of observational studies

Jishnu Malgie ✉, Jan W Schoones, Bart G Pijls

Clinical Infectious Diseases, ciaa1445, https://doi.org/10.1093/cid/ciaa1445
Published: 23 September 2020 **Article history** ▾

- 10 studies (includes our Somers et al)
- 1358 patients
- Nine of ten studies considered high quality
- Tocilizumab lower mortality than control
  - Risk ratio (RR) = 0.27 (95% CI 0.12-0.59)
  - number needed to treat = 11 (for every 11 severe COVID-19 patients treated with tocilizumab, 1 death prevented).
- These results require confirmation by randomized controlled trials.

Oct 20, 2020

HEALTH

Rheumatoid arthritis drug tocilizumab advances as a COVID treatment, as other regimens fall back, studies show

Karen Weintraub USA TODAY

Published 2:23 p.m. ET Oct. 20, 2020

JAMA Network™

Oct 20, 2020 JAMA IntMed

- **3 toci studies (1 observational + RCTs)**

Details for consideration

- Timing of toci administration/clinical severity
- Dosing
- RCT designs and size

Longer-term outcomes need to be assessed to determine if blunting immune response with tocilizumab reduces morbidity and mortality over the long haul.

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Awaiting RECOVERY trial toci arm!

- >850 pts randomised to tocilizumab vs standard of care
- ~2x size of COVACTA trial

Table. Comparison of Major Tocilizumab COVID-19 Studies Reported to Date

Study characteristic	Gupta et al[3] (STOP-COVID)	Salvarani et al[1] (RCT-TCZ-COVID-19)	Hermine et al[2] (CORIMUNO-TOCI-1)	COVACTA[12]	EMPACTA[13]
Design					
Type	Observational retrospective	Randomized prospective	Randomized prospective	Randomized prospective	Randomized prospective
Blinded	NA	No	No	Yes (double)	Yes (double)
Placebo-controlled	NA	No	No	Yes	Yes
Enrollment					
No. of sites	68	24	9	67	69
Countries	US	Italy	France	Canada, Denmark, France, Germany, Italy, the Netherlands, Spain, United Kingdom, US	Brazil, Kenya, Mexico, Peru, South Africa, US
No. of participants	3924	126	131	450	389
No. tocilizumab treated	433	60[a]	63	225[b]	194[b]
Clinical severity[c]					
Moderate	No	No	No	No	No
Severe	Yes	Yes	Yes	Yes	Yes
Critical	Yes	No	No	Yes	No
Intervention					
Tocilizumab	Within 2 d of ICU admission	8 mg/kg ×2 Doses, 12 h apart	8 mg/kg ×1, Possible second dose on day 3	8 mg/kg ×1, Possible second dose	8 mg/kg ×1, Possible second dose
Comparator	Usual care	Usual care	Usual care	Usual care plus placebo	Usual care plus placebo
Outcomes[d]					
Primary, effect size	Time to death: Threshold for efficacy met; HR, 0.71 (95% CI, 0.56 to 0.92) 30-d mortality: Threshold for efficacy met; RD, 9.6% (95% CI, 3.1% to 16.0%)	Pao_2:Fio_2 <150 mm Hg, ICU admission, or death: Threshold for efficacy not met; RR, 1.05 (95% CI, 0.59 to 1.86)[e]	WHO-CPS score >5 on day 4: Threshold for efficacy not met; ARD, −9.0% (90% CrI, −21.0% to 3.1%); posterior probability of ARD <0 of 89.0% Survival without NIV or MV by day 14: Threshold for efficacy met; HR, 0.58 (90% CrI, 0.33 to 1.00), posterior probability of HR<1 of 95.0%	Difference in clinical status using a 7-category scale at day 28: Threshold for efficacy not met; OR, 1.19 (95% CI, 0.81 to 1.76)	Death or MV by day 28: Threshold for efficacy met; HR, 0.56 (95% CI, 0.32 to 0.97)
28- or 30-d mortality, tocilizumab vs comparator, effect size[f]	27.5% vs 37.1%; RD, 9.6% (95% CI, 3.1% to 16.0%)	3.3% vs 1.6%; RR, 2.10 (95% CI, 0.20 to 22.6)	11.1% vs 11.9%; aHR, 0.92 (95% CI, 0.33 to 2.53)	19.7% vs 19.4%; ARD, 0.3% (95% CI, −7.6% to 8.2%)	10.4% vs 8.6%; ARD, 2.0% (95% CI, −5.2% to 7.8%)
Trial registration	NCT04343898	NCT04346355	NCT04331808	NCT04320615	NCT04372186

RECOVERY
Randomised Evaluation of COVID-19 Therapy

No clinical benefit in hospitalised patients with COVID-19

- HCQ
- Lopinavir-ritonavir (antiviral used in HIV)

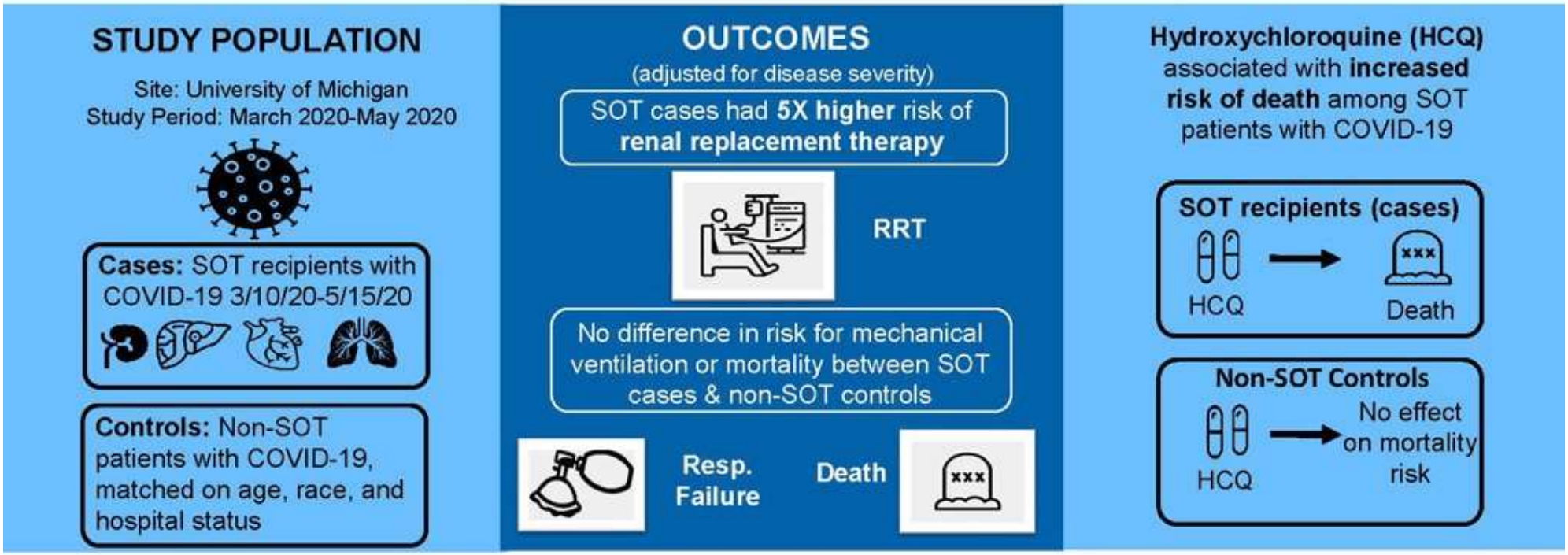
Benefit

- Dexamethasone - reduction of death by ~1/3 in those requiring respiratory support
  - timing of anti-inflammatory treatments in relation to the stage of disease is important
  - benefit of anti-inflammatory treatments likely observed only in patients who progress to an inflammatory state, which usually happens ~1 week into illness

Ongoing treatments being evaluated

- Low-dose Dexamethasone (now only recruiting children)
- Azithromycin (commonly used antibiotic)
- Tocilizumab (anti-inflammatory treatment given by injection)
- Convalescent plasma
- REGN-COV2 (combination of monoclonal antibodies directed against coronavirus)

COVID-19 outcomes among Solid Organ Transplant (SOT) Recipients: A Case Control Study



Sharma et al. *Transplantation*. Oct 2020

Transplantation

@TransplantJrnl

SOT Case Control Study

- Despite high renal replacement therapy (RRT) use in SOT recipients, the severe COVID-19 illness and short-term death were similar in SOT recipients and non-SOT controls

- Among SOT recipients, HCQ for the treatment of COVID-19 was associated with 10-fold higher risk of death

MICHR COVID-19 RRR: Data access

- Schedule Research Development Core/COVID consult to review options:

  michr-covid@umich.edu

  or

- Complete online request (MICHR website)

- ISARIC/pooled data – separate application process
  - Data Access Committee based @WHO reviews applications

MICHR COVID-19 RRR:
Principles for Evaluation & Prioritization of Requests

- Project aligned with Registry mission to advance understanding and management of COVID & consistent with IRB-approved uses
- Conducted in partnership with COVID-19 RRR team
- Planned project not duplicative
- Availability of resources and staffing needed to fulfill project goals
- Collaborative model: Registry end users also participate as contributors
  - New/supplemental data being generated as part of the project to be integrated with registry to the extent possible
  - Projects that involve data contributions that expand the Registry will receive prioritization
- We are committed to providing opportunities for trainees, early career faculty and those of diverse backgrounds to gain experience in interdisciplinary team science.
  - We will review team compositions and may recommend expansion to promote the broad goals of training/career development opportunities and diversity

Teamwork & Collaboration

> Catastrophes, such as pandemics, drive innovation and lead to marked social change. Within the scientific research community, we believe that perceptions of academic excellence have long undervalued teamwork and collegiality. We hope our colleagues across the world will make use of these tools, either in collaboration or independently, to harmonise clinical research efforts and fulfil the duties of medical science to humanity in the shortest time possible.

Thank you!

NIH
Oct 9, 2020

Figure 1. Recommendations for Pharmacologic Management of Patients with COVID-19 Based on Disease Severity

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS *(Recommendations are listed in order of preference in each category below; however, all options are considered acceptable.)*
Not Hospitalized ***or*** **Hospitalized but Does Not Require Supplemental Oxygen**	No specific antiviral or immunomodulatory therapy recommended The Panel **recommends against** the use of **dexamethasone (AI)** See the Remdesivir section for a discussion of the data on using this drug in hospitalized patients with moderate COVID-19.[a]
Hospitalized and Requires Supplemental Oxygen **(but Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)**	**Remdesivir** 200 mg IV for one day, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge, whichever comes first **(AI)**[b,c,d] ***or*** **Remdesivir** (dose and duration as above) plus **dexamethasone**[e] 6 mg IV or PO for up to 10 days or until hospital discharge, whichever comes first **(BIII)**[f] If **remdesivir** cannot be used, **dexamethasone**[e] may be used instead **(BIII)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	**Dexamethasone**[d] plus **remdesivir** at the doses and durations discussed above **(AIII)**[f] ***or*** **Dexamethasone**[d,e] at the dose and duration discussed above **(AI)**
Hospitalized and Requires Invasive Mechanical Ventilation or ECMO	**Dexamethasone**[d,e] at the dose and duration discussed above **(AI)** ***or*** **Dexamethasone**[e] plus **remdesivir** for patients who have recently been intubated at the doses and durations discussed above **(CIII)**[f]

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion