COVID-19 Update October 21,2020

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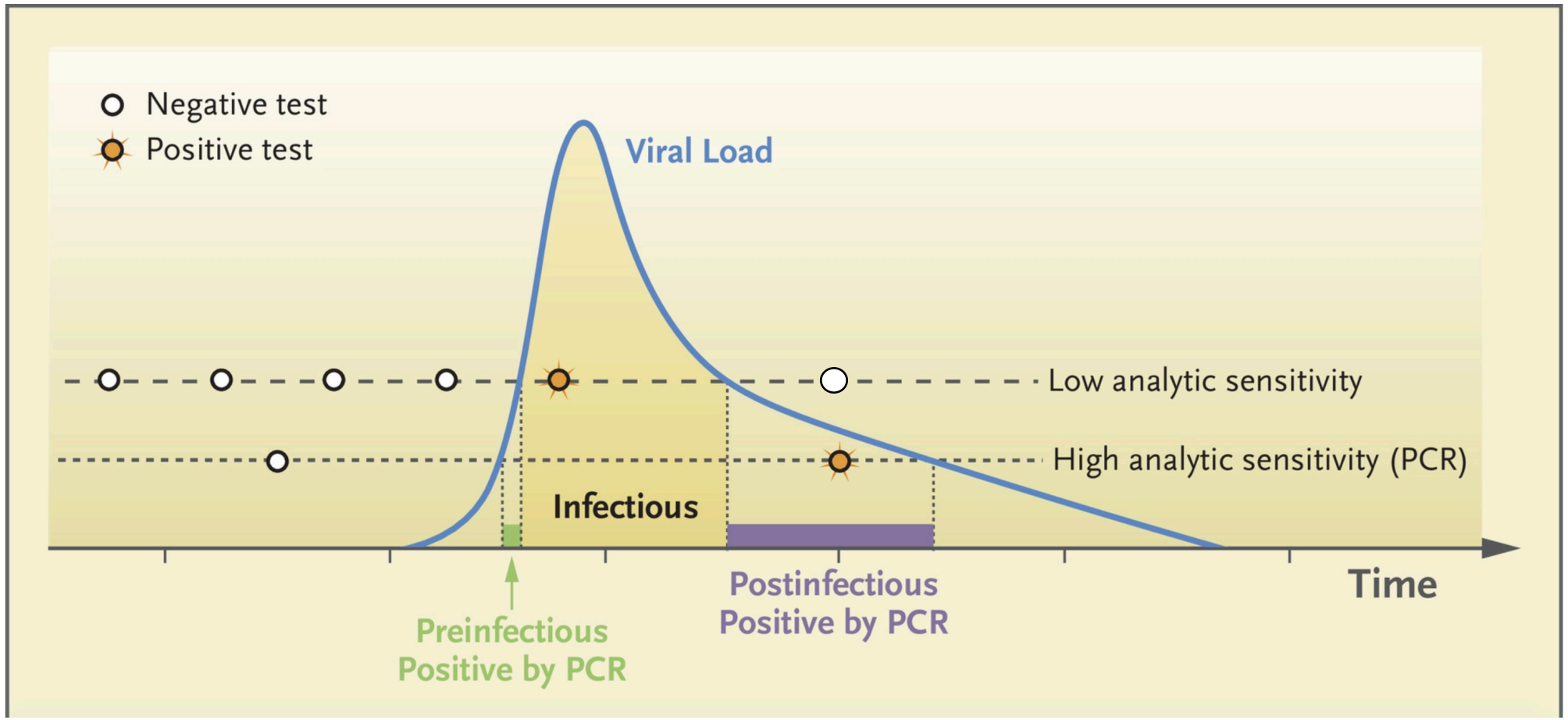
Rethinking Covid-19 Test Sensitivity A Strategy for Containment

NEJM. September 30, 2020.

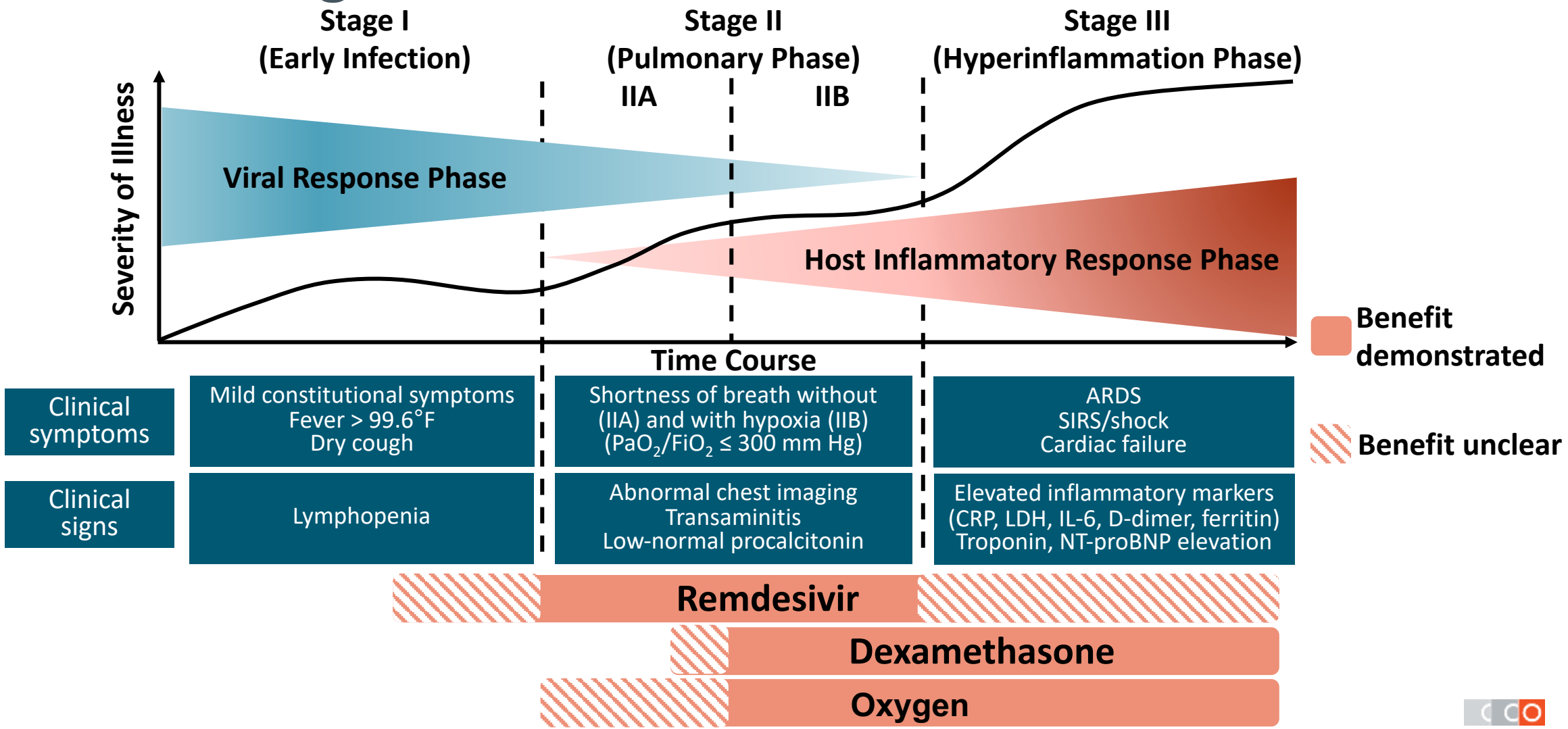
- An effective Covid filter for surveillance will need tests that:
  - Capture most infections while they are still infectious
  - Are cheap (<$5)
  - Can be produced in the tens of millions or more per week
  - Could even be performed at home

Rethinking Covid-19 Test Sensitivity
A Strategy for Containment



NEJM. September 30, 2020. DOI: 10.1056/NEJMp2025631

COVID-19 Therapies Predicted to Provide Benefit at Different Stages



Siddiqi. J Heart Lung Transplant. 2020;39:405.

Slide credit: clinicaloptions.com

IDSA Recommendations on Treatment and Management of Patients With COVID-19

- Overarching goal: recruit patients into ongoing trials to provide needed evidence regarding efficacy and safety of potential therapies

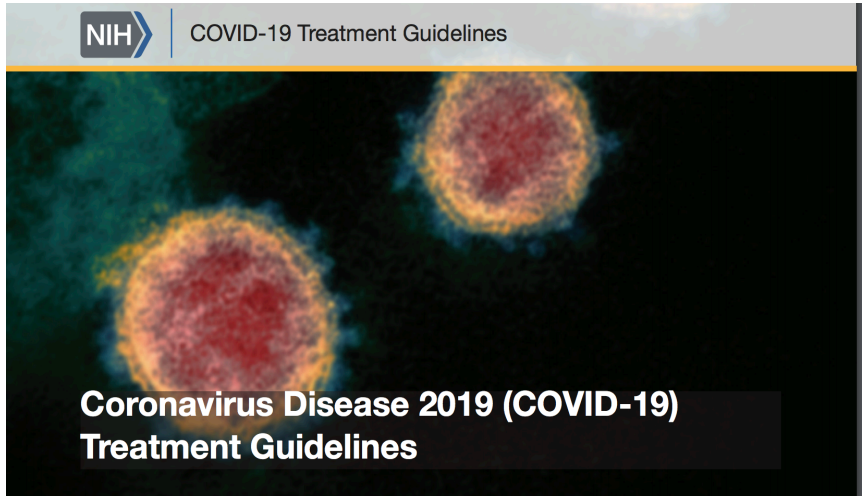
IDSA Guidance	Patient Population	Treatment
Recommends	▪ Hospitalized with critical* COVID-19	▪ Dexamethasone†
Suggests	▪ Hospitalized with severe‡ COVID-19 ▪ Hospitalized with severe*‡ COVID-19	▪ Dexamethasone† ▪ Remdesivir‖
Recommends only in clinical trial	▪ Hospitalized with COVID-19 ▪ Hospitalized with COVID-19	▪ Lopinavir/ritonavir ▪ Convalescent plasma
Recommends against	▪ COVID-19 ▪ Hospitalized with COVID-19	▪ (Hydroxy)chloroquine ▪ (Hydroxy)chloroquine + azithromycin
Suggests against	▪ Hospitalized with nonsevere§ COVID-19 ▪ Hospitalized with COVID-19	▪ Glucocorticoids ▪ Tocilizumab
Suggests against outside clinical trial	▪ Hospitalized with severe COVID-19	▪ Famotidine

*Mechanical ventilation or ECMO. †If unavailable, methylprednisolone and prednisone acceptable at equivalent total daily doses. ‡SpO_2 ≤ 94% on room air, including those on supplemental oxygen. § SpO_2 > 94%, no supplemental oxygen. ‖For patients on supplemental oxygen, 5 days suggested; for patients on mechanical ventilation or ECMO, 10 days.

IDSA. COVID-19 Guideline, Part 1: Treatment and Management. Version 3.3.0.

Slide credit: clinicaloptions.com

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



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

[a] The Panel recognizes that there may be situations in which a clinician judges that remdesivir is an appropriate treatment for a hospitalized patient with moderate COVID-19 (e.g., a patient who is at a particularly high risk for clinical deterioration). However, the Panel finds the data insufficient to recommend either for or against using remdesivir as routine treatment for all hospitalized patients with moderate COVID-19.
[b] Treatment duration may be extended to up to 10 days if there is no substantial clinical improvement by Day 5.
[c] The Panel recognizes there is a theoretical rationale for initiating remdesivir plus dexamethasone in patients with rapidly progressing COVID-19.
[d] For patients who are receiving remdesivir but progress to requiring oxygen through a high-flow device, noninvasive ventilation, invasive mechanical

Does Remdesivir Work for COVID-19?

Remdesivir for the Treatment of Covid-19 — Final Report NEJM October 2020

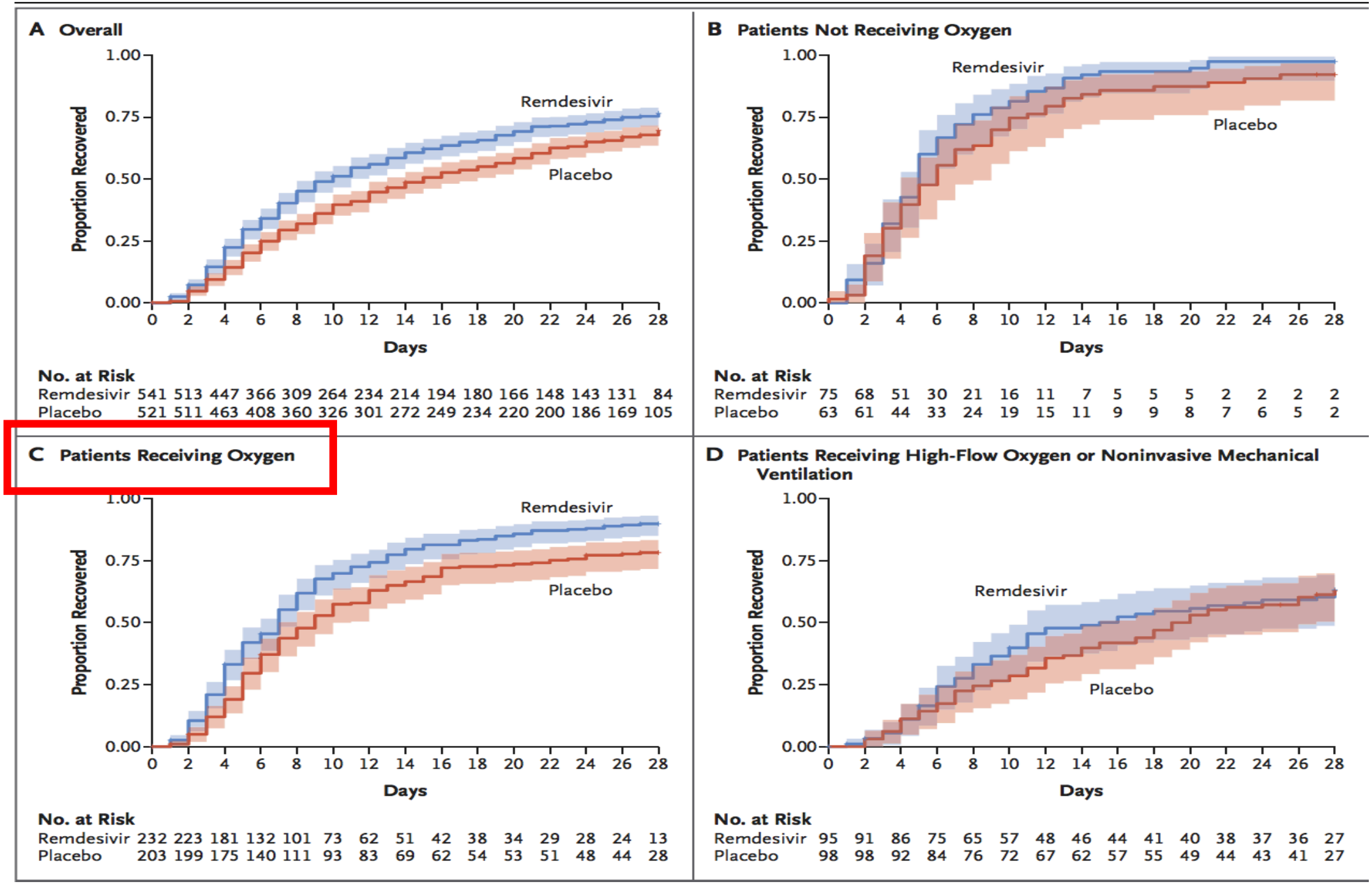
- **BACKGROUND**
  - No COVID-19 antiviral agents have yet been shown to be efficacious.
- **METHODS**
  - Double-blind, randomized, placebo-controlled trial of up to 10 days intravenous remdesivir (RDS) in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection.
  - The primary outcome was the time to recovery
- **RESULTS**
  - A total of 1062 patients underwent randomization (with 541 assigned to remdesivir and 521 to placebo).
  - The RDS arm had a median recovery time of 10 days (95% CI, 9 to 11), as compared with 15 days (95% CI, 13 to 18) in the placebo group
- **CONCLUSIONS**
  - Remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection.

Remdesivir for the Treatment of Covid-19 — Final Report NEJM October 2020

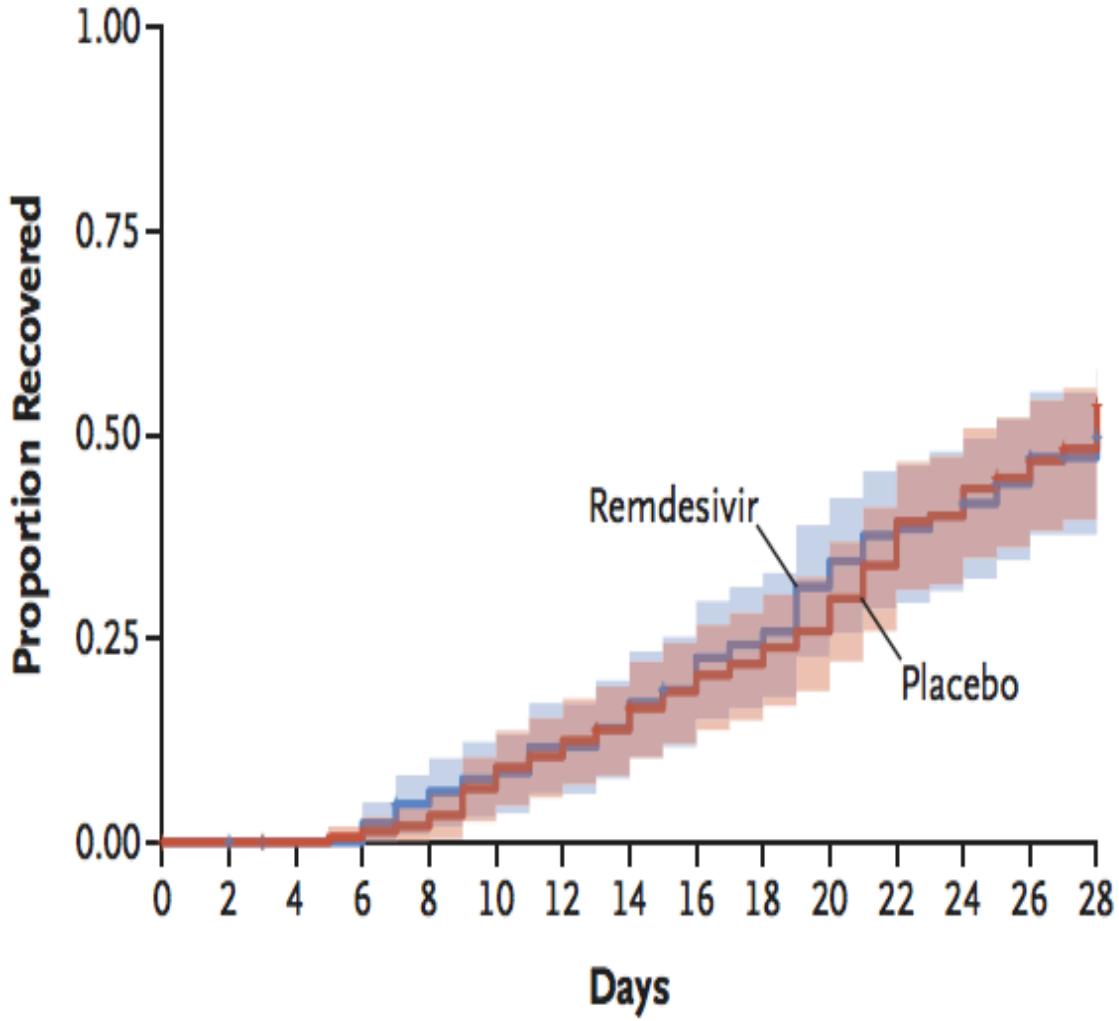
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	All (N=1062)	Remdesivir (N=541)	Placebo (N=521)
Age — yr	58.9±15.0	58.6±14.6	59.2±15.4
Male sex — no. (%)	684 (64.4)	352 (65.1)	332 (63.7)
Race or ethnic group — no. (%)†			
American Indian or Alaska Native	7 (0.7)	4 (0.7)	3 (0.6)
Asian	135 (12.7)	79 (14.6)	56 (10.7)
Black or African American	226 (21.3)	109 (20.1)	117 (22.5)
White	566 (53.3)	279 (51.6)	287 (55.1)
Hispanic or Latino — no. (%)	250 (23.5)	134 (24.8)	116 (22.3)
Median time (IQR) from symptom onset to randomization — days‡	9 (6–12)	9 (6–12)	9 (7–13
No. of coexisting conditions — no. /total no. (%)‡			
None	194/1048 (18.5)	97/531 (18.3)	97/517 (18.8)
One	275/1048 (26.2)	138/531 (26.0)	137/517 (26.5)
Two or more	579/1048 (55.2)	296/531 (55.7)	283/517 (54.7)
Coexisting conditions — no./total no. (%)			
Type 2 diabetes	322/1051 (30.6)	164/532 (30.8)	158/519 (30.4)
Hypertension	533/1051 (50.7)	269/532 (50.6)	264/519 (50.9)
Obesity	476/1049 (45.4)	242/531 (45.6)	234/518 (45.2)
Score on ordinal scale — no. (%)			
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (Covid-19–related or otherwise)	138 (13.0)	75 (13.9)	63 (12.1)
5. Hospitalized, requiring supplemental oxygen	435 (41.0)	232 (42.9)	203 (39.0)
6. Hospitalized, receiving noninvasive ventilation or high-flow oxygen devices	193 (18.2)	95 (17.6)	98 (18.8)
7. Hospitalized, receiving invasive mechanical ventilation or ECMO	285 (26.8)	131 (24.2)	154 (29.6)
Baseline score missing	11 (1.0)	8 (1.5)	3 (0.6)

- * Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. IQR denotes interquartile range, and ECMO extracorporeal membrane oxygenation. The full table of baseline characteristics is available in the Supplementary Appendix.
- † Race and ethnic group were reported by the patients. The number of patients in other races and ethnic groups are listed in Table S1 in the Supplementary Appendix.
- ‡ Data on symptom onset were missing for 3 patients; data on coexisting conditions were missing for 11 patients and were incomplete for 3 patients.


A Overall
Proportion Recovered
1.00
0.75
0.50
0.25
0.00
Remdesivir
Placebo
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
Days
No. at Risk
Remdesivir 541 513 447 366 309 264 234 214 194 180 166 148 143 131 84
Placebo 521 511 463 408 360 326 301 272 249 234 220 200 186 169 105
B Patients Not Receiving Oxygen
Proportion Recovered
1.00
0.75
0.50
0.25
0.00
Remdesivir
Placebo
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
Days
No. at Risk
Remdesivir 75 68 51 30 21 16 11 7 5 5 5 2 2 2 2
Placebo 63 61 44 33 24 19 15 11 9 9 8 7 6 5 2
C Patients Receiving Oxygen
Proportion Recovered
1.00
0.75
0.50
0.25
0.00
Remdesivir
Placebo
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
Days
No. at Risk
Remdesivir 232 223 181 132 101 73 62 51 42 38 34 29 28 24 13
Placebo 203 199 175 140 111 93 83 69 62 54 53 51 48 44 28
D Patients Receiving High-Flow Oxygen or Noninvasive Mechanical Ventilation
Proportion Recovered
1.00
0.75
0.50
0.25
0.00
Remdesivir
Placebo
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
Days
No. at Risk
Remdesivir 95 91 86 75 65 57 48 46 44 41 40 38 37 36 27
Placebo 98 98 92 84 76 72 67 62 57 55 49 44 43 41 27

E **Patients Receiving Mechanical Ventilation or ECMO**



No. at Risk

Remdesivir	131	131	129	129	122	118	113	110	103	96	87	79	76	69	42
Placebo	154	153	152	151	149	142	136	130	121	116	110	98	89	79	48

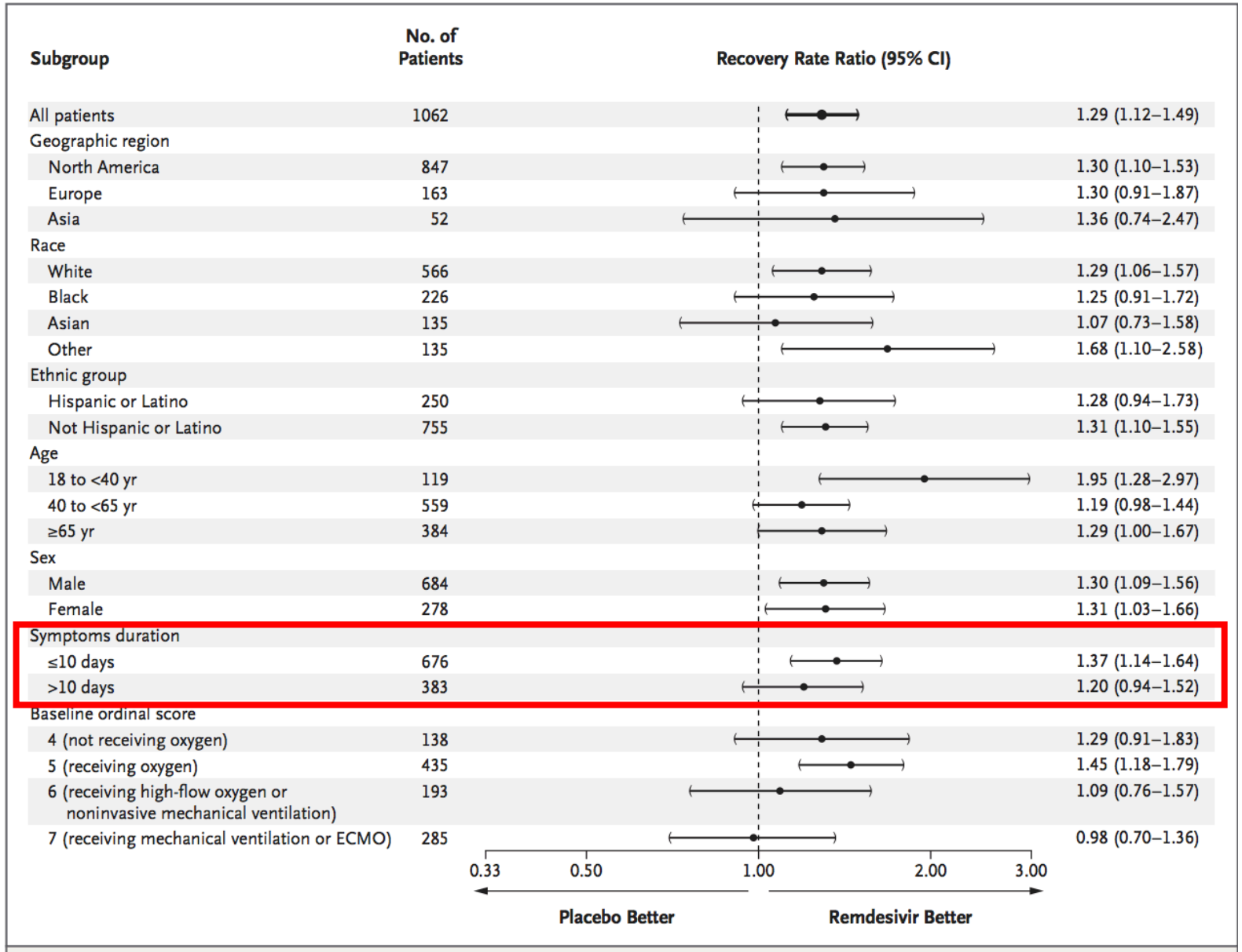


Figure 3. Time to Recovery According to Subgroup.

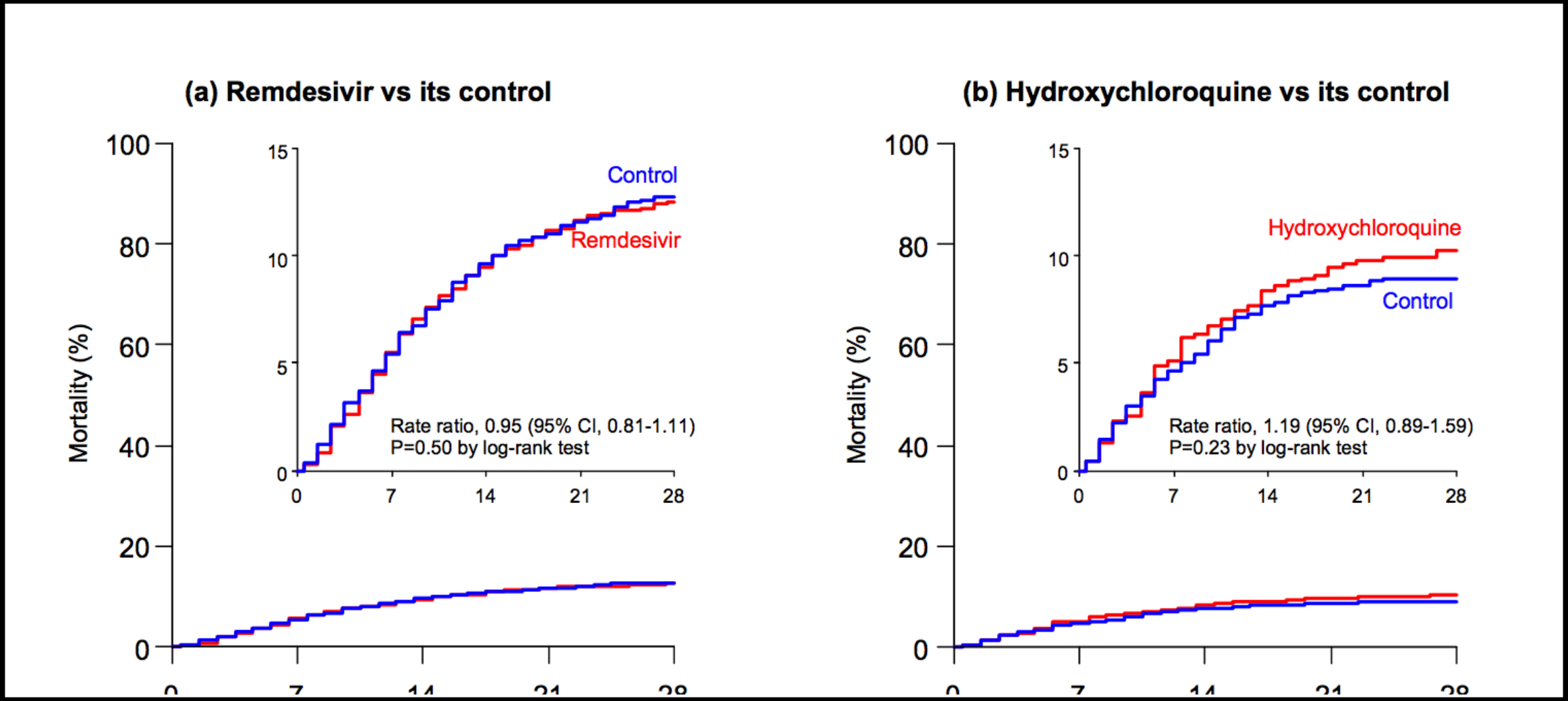
The widths of the confidence intervals have not been adjusted for multiplicity and therefore cannot be used to infer treatment effects. Race and ethnic group were reported by the patients.

Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results WHO Solidarity trial consortium

- **METHODS**
  - Study drugs were Remdesivir, Hydroxychloroquine, Lopinavir/ritonavir and Interferon-β1a
  - COVID-19 inpatients were randomized equally between whichever study drugs were locally available and open control

- **RESULTS**
  - In 405 hospitals in 30 countries 11,266 adults were randomized, with the following allocation:
    - 2750 Remdesivir
    - 954 Hydroxychloroquine
    - 1411 Lopinavir
    - 651 Interferon plus Lopinavir
    - 1412 only Interferon
    - 4088 no study drug.
  - No study drug reduced mortality (in unventilated patients or any other subgroup of entry characteristics), initiation of ventilation or hospitalization duration.

- **CONCLUSIONS**
  - Remdesivir, Hydroxychloroquine, Lopinavir and Interferon regimens appeared to have little or no effect on hospitalized COVID-19, as indicated by overall mortality, initiation of ventilation and duration of hospital stay.



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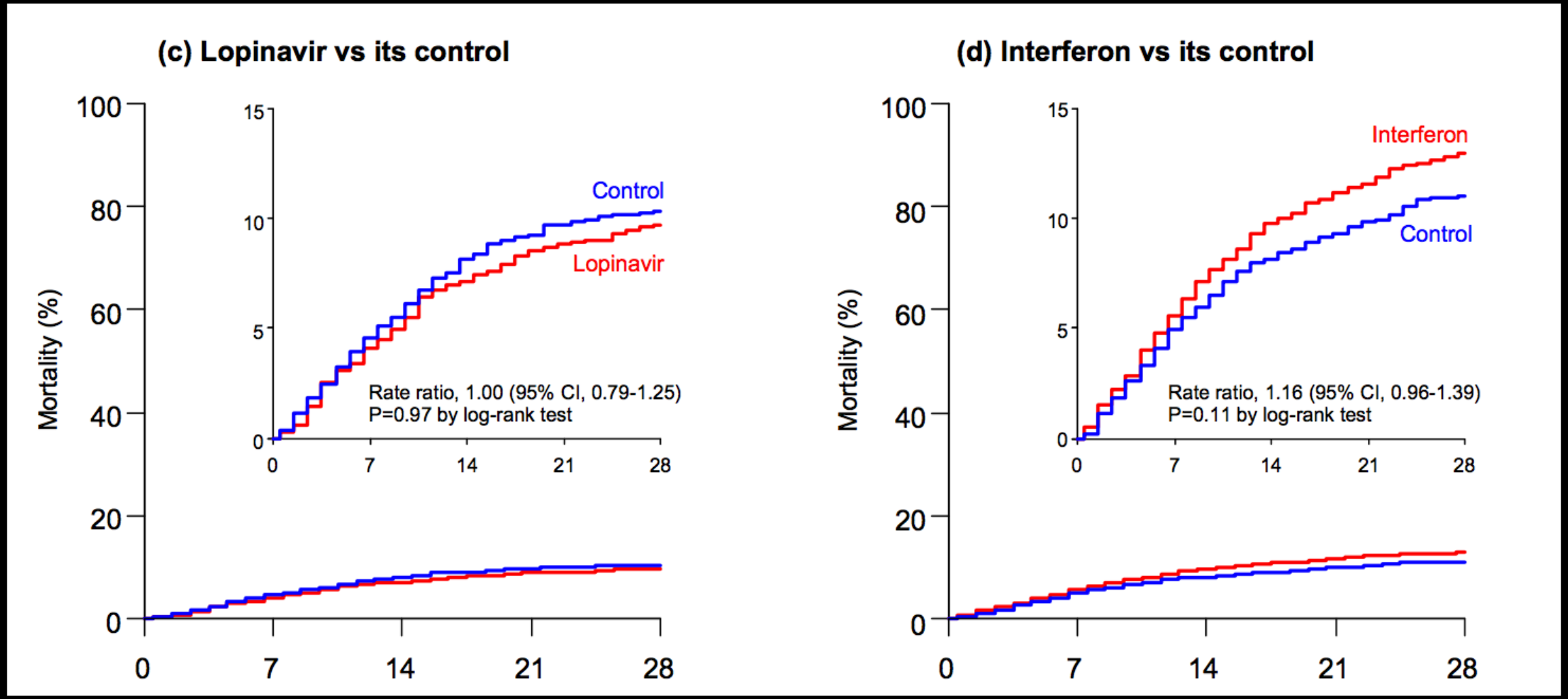


Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results WHO Solidarity trial consortium

Does Remdesivir Work or NOT?

- **Solidarity:** Very large sample size but not all critical data
  - **Duration of symptoms before treatment not reported**
- **ACCT-1:** Smaller sample but had most critical data
  - **Remdesivir may work if patients < 10 days of symptoms onset**
  - **Requiring oxygen but not too much oxygen**

- Antivirals for acute infectious diseases usually work when given early
  - Oseltamivir/baloxavir for influenza
  - Valacyclovir/acyclovir for Herpes simplex and Herpes zoster
  - **Why would we expect something different for COVID-19?**

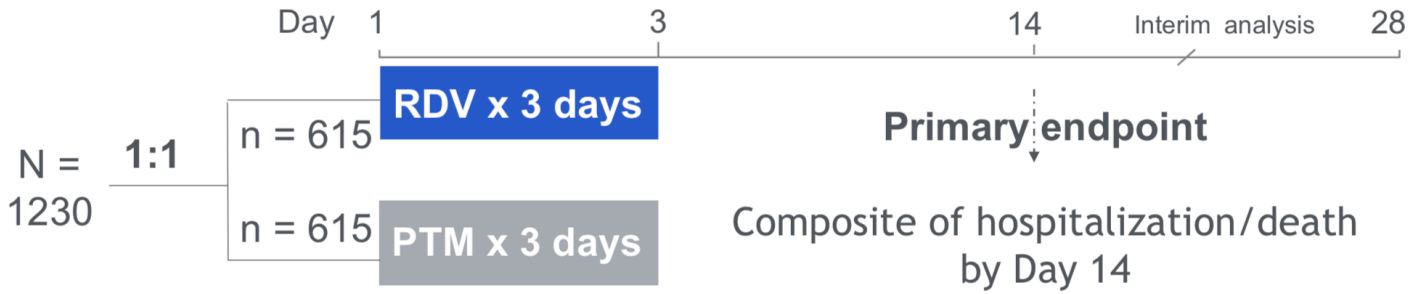
Paul E. Sax, MD
Infectious Disease Observations
October 18th, 2020

So for now, the answer to the question, “Does remdesivir actually work?” is a cautious *maybe*. Sometimes. For some people.”

“Which, given the absence of anything else right now and its low toxicity, means I’d still recommend it for most hospitalized people with COVID-19 — with the hope of giving it sooner rather than later, especially for those on oxygen at high risk for disease progression”.

How will we find the answer?

Study Design



- Design
  - Randomized, double-blind, placebo controlled study
  - Sites in Spain, Denmark, Germany United Kingdom, and the United States
- Non-hospitalized participants with early stage COVID-19 and at least one risk factor for disease progression

- **PROTOCOL GS-US-540-9012:** A Phase 3 Randomized, Double-Blind Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Remdesivir (GS-5734™) Treatment of COVID-19 in an Outpatient Setting

Dying in a Leadership Vacuum

The Editors
NEJM October 8,2020

“Anyone else who recklessly squandered lives and money in this way would be suffering legal consequences. Our leaders have largely claimed immunity for their actions. But this election gives us the power to render judgment. Reasonable people will certainly disagree about the many political positions taken by candidates. But truth is neither liberal nor conservative. When it comes to the response to the largest public health crisis of our time, our current political leaders have demonstrated that they are dangerously incompetent. We should not abet them and enable the deaths of thousands more Americans by allowing them to keep their jobs.”