COVID-19
ONLINE EDUCATIONAL PROGRAM

Clinical Outcomes and Therapeutics of COVID-19

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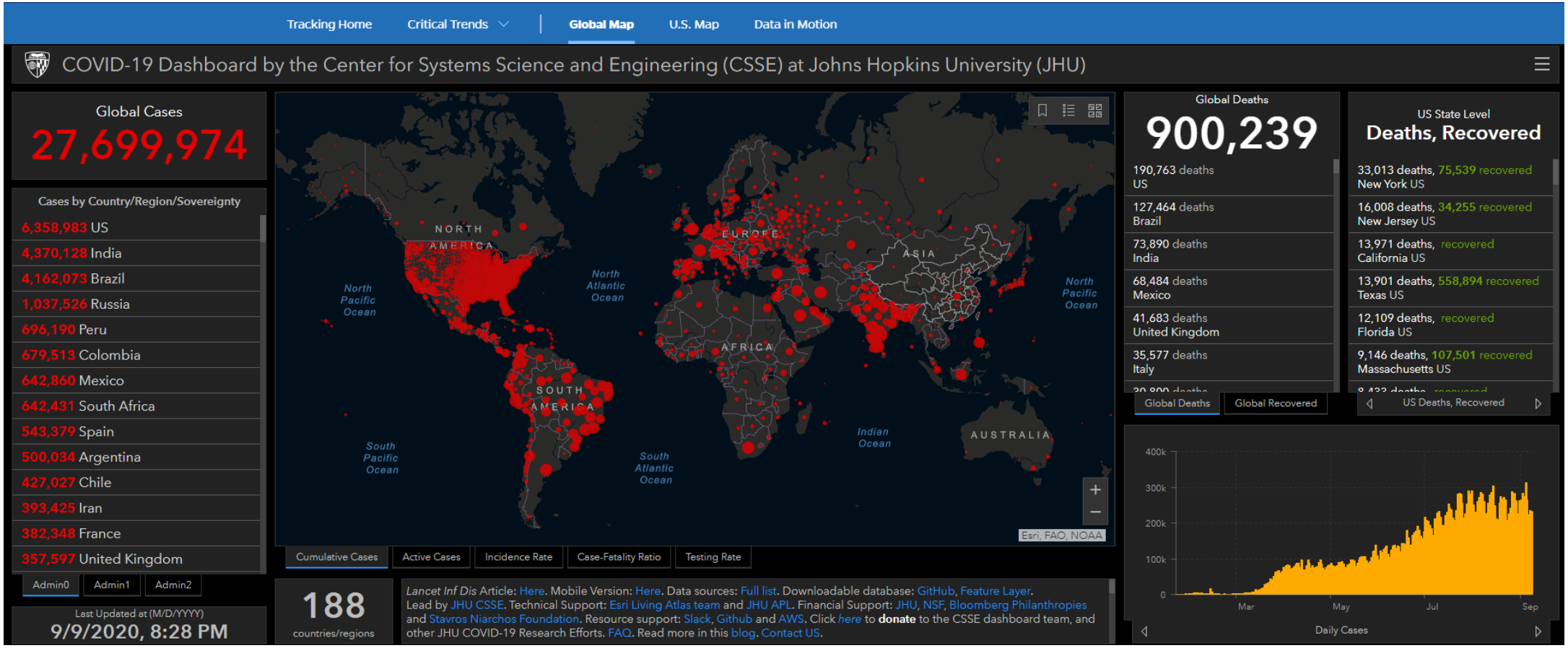
academic medical education

Disclosures

- **The speaker is a consultant to and has received honoraria and/or research support from the following companies:**
  - Atea
  - Gilead
  - GlaxoSmithKline
  - Merck
  - Novartis
  - ViiV

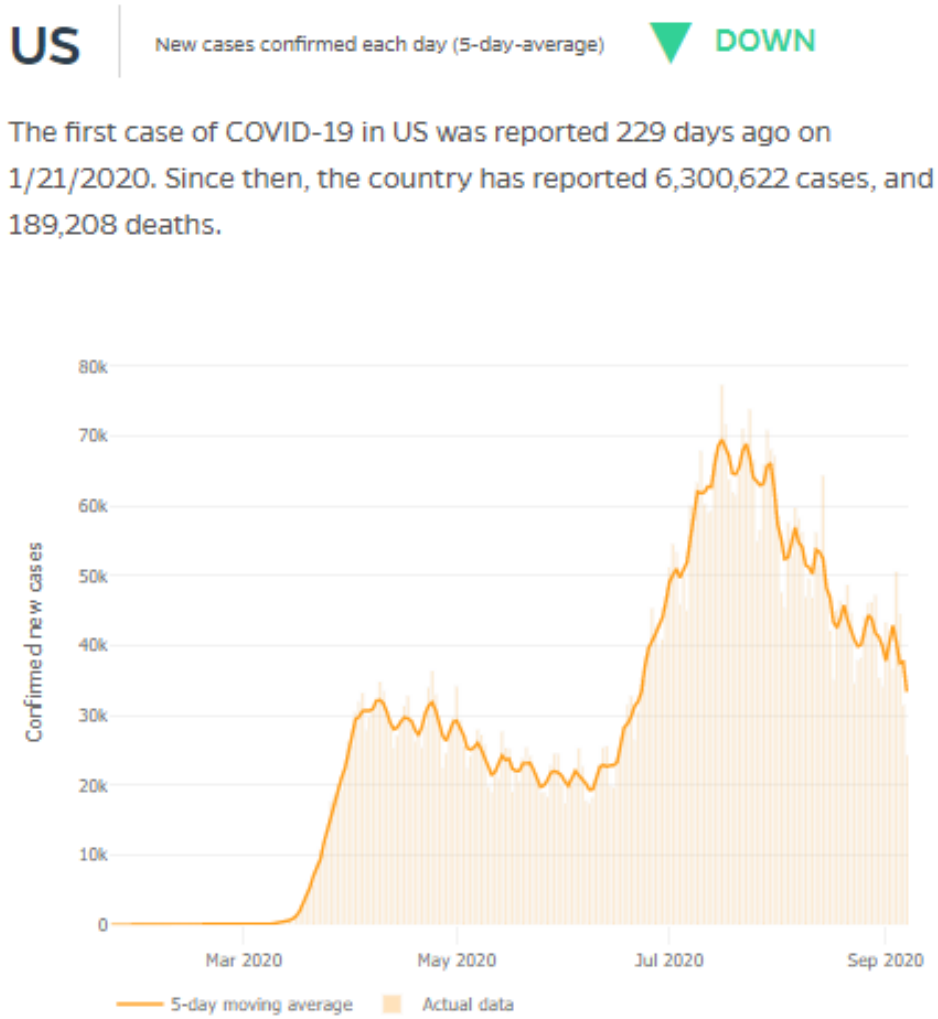
COVID-19: Clinical Update

Global incidence and mortality of COVID-19



Source: https://coronavirus.jhu.edu/map.html (accessed 9 Sept 2020)

US incidence of COVID-19 (5-day average)

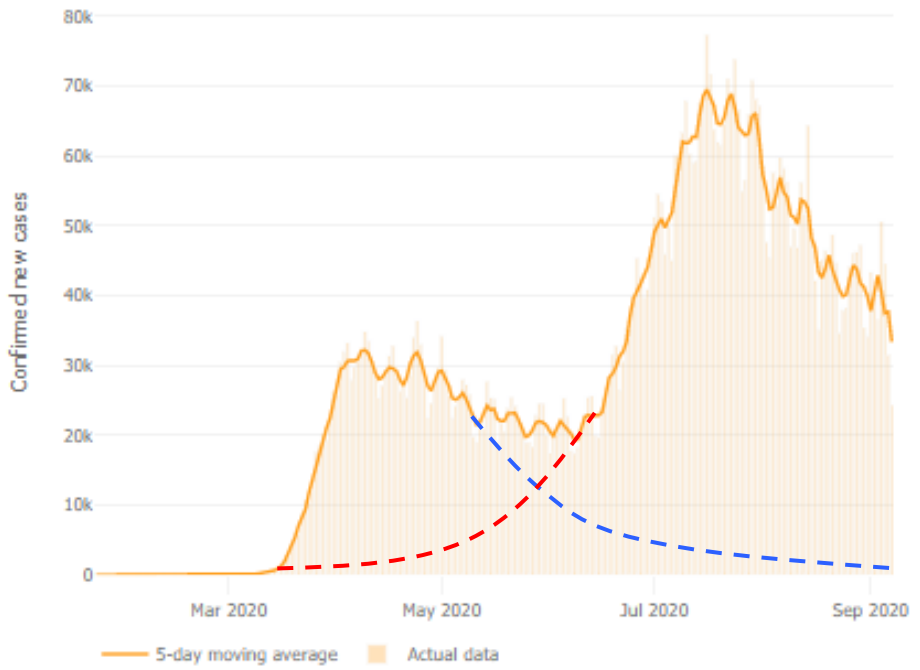


Source: https://coronavirus.jhu.edu/map.html (accessed 8 Sept 2020)

US incidence of COVID-19 (5-day average)

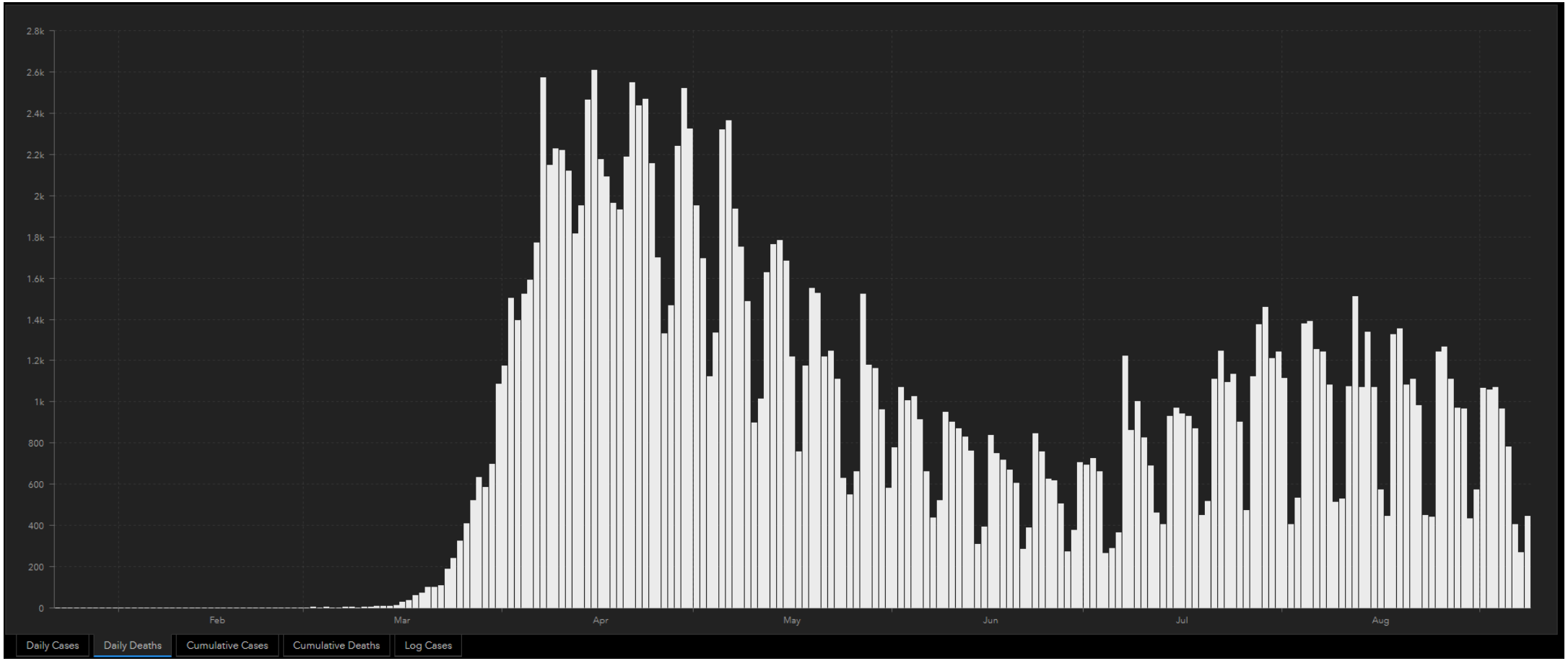
US | New cases confirmed each day (5-day-average) ▼ DOWN

The first case of COVID-19 in US was reported 229 days ago on 1/21/2020. Since then, the country has reported 6,300,622 cases, and 189,208 deaths.



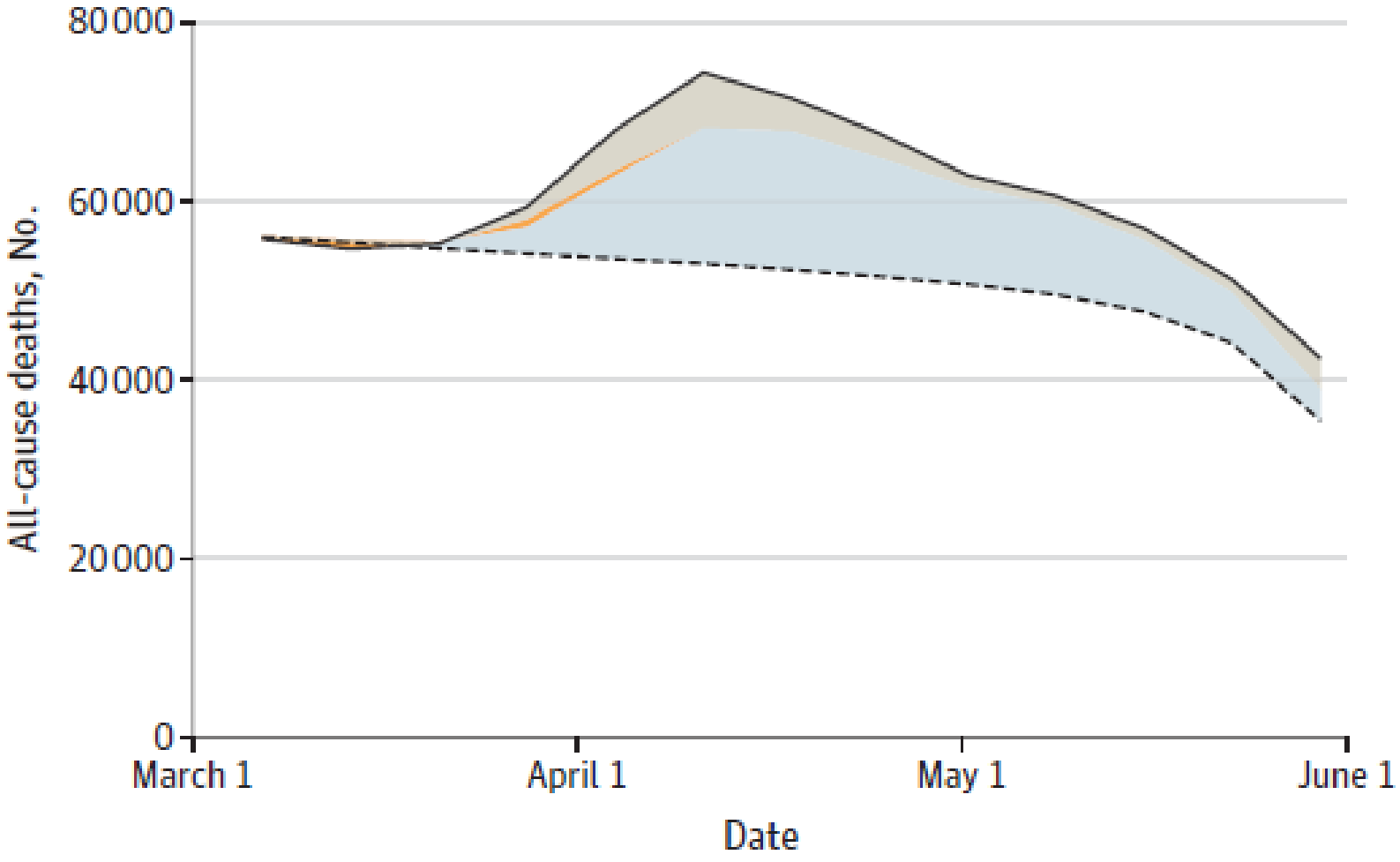
Source: https://coronavirus.jhu.edu/map.html (accessed 8 Sept 2020)

Daily deaths in US from COVID-19



Source: https://coronavirus.jhu.edu/map.html (accessed 9 Sept 2020)

Excess US mortality during initial COVID-19 era



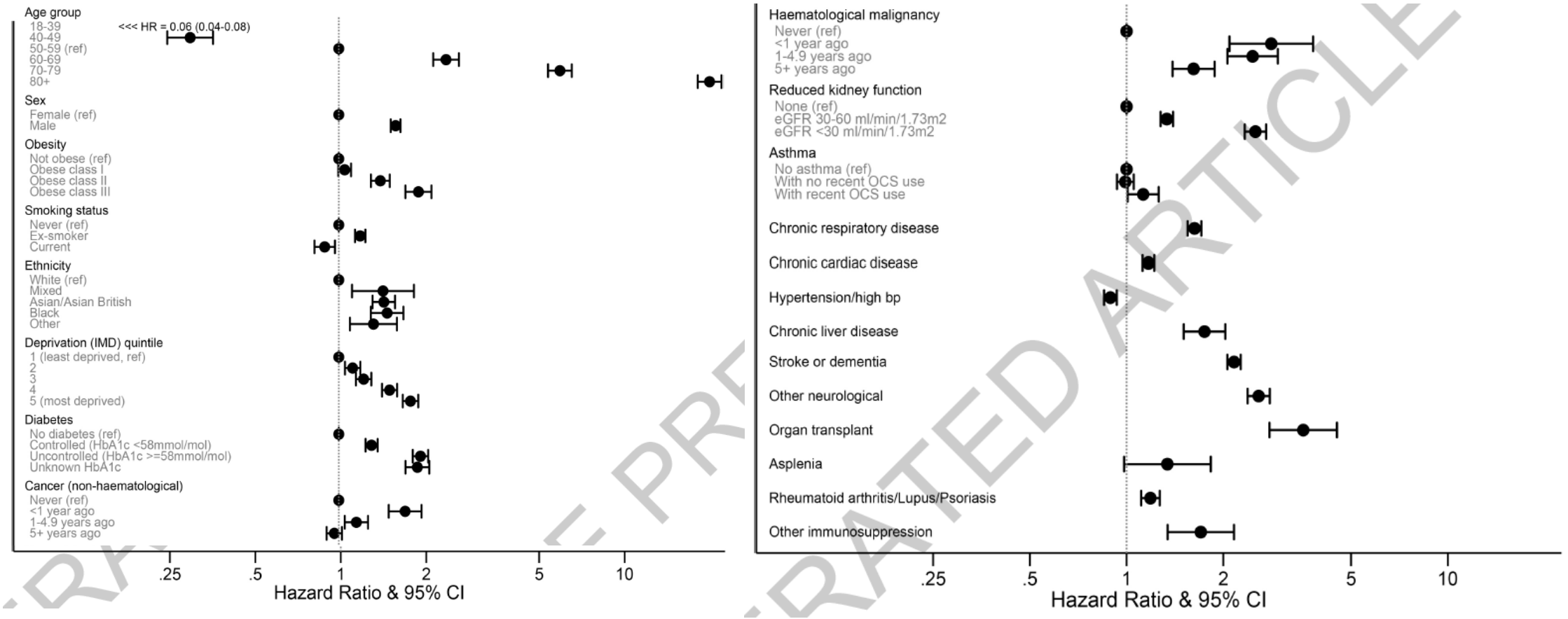
Weinberger DM et al JAMA Intern Med 2020

Excess US deaths March 1-April 25, 2020 due to COVID-19 or other causes

Jurisdiction	Expected deaths, No. (95% CI)[b]	Observed deaths, No.	Excess deaths, No. (95% CI)	COVID-19 deaths[c]		Deaths not attributed to COVID-19[c]	
				Reported deaths, No.	Excess deaths, %	Excess deaths, No. (95% CI)	Excess deaths, %
United States[d]	419 058 (418 636 to 419 481)	505 059	87 001 (86 578 to 87 423)	56 246	65	30 755 (30 332 to 31 177)	35
Jurisdictions with highest COVID-19 death counts[c]							
New York City	8369 (8310 to 8427)	29 703	21 334 (21 276 to 21 393)	14 952	70	6382 (6324 to 6441)	30
New Jersey	11 458 (11 388 to 11 528)	23 174	11 716 (11 646 to 11 786)	8037	69	3679 (3609 to 3749)	31
New York (excluding New York City)	15 603 (15 519 to 15 686)	24 611	9008 (8925 to 9092)	6569	73	2439 (2356 to 2523)	27
Michigan	15 217 (15 134 to 15 300)	20 232	5015 (4932 to 5098)	3372	67	1643 (1560 to 1726)	33
Massachusetts	9316 (9253 to 9378)	13 412	4096 (4034 to 4159)	3122	76	974 (912 to 1037)	24
Pennsylvania	17 178 (17 089 to 17 268)	22 304	5126 (5036 to 5215)	2752	54	2374 (2284 to 2463)	46

Woolf SH et al JAMA 2020

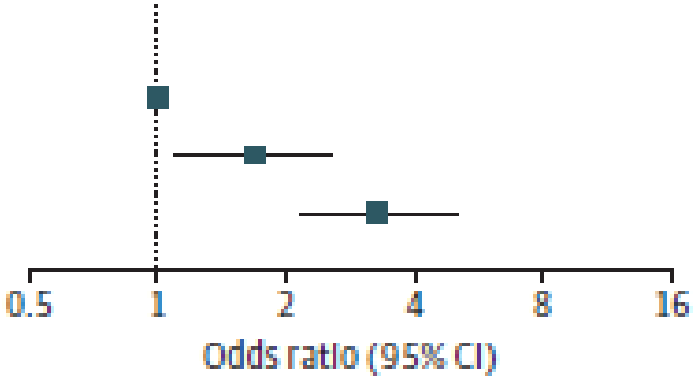
Predictors of COVID-19 mortality in England



Williamson EJ et al Nature 2020

Effect of hospital ICU beds on COVID-19 mortality

No. of ICU beds	
High (≥100)	1 [Reference]
Medium (50-99)	1.67 (1.10-2.53)
Low (<50)	3.28 (2.16-4.99)



Gupta S et al JAMA Intern Med 2020

COVID-19 Therapeutics

Treatment options for COVID-19

- Remdesivir
- Corticosteroids
- Convalescent plasma

Remdesivir

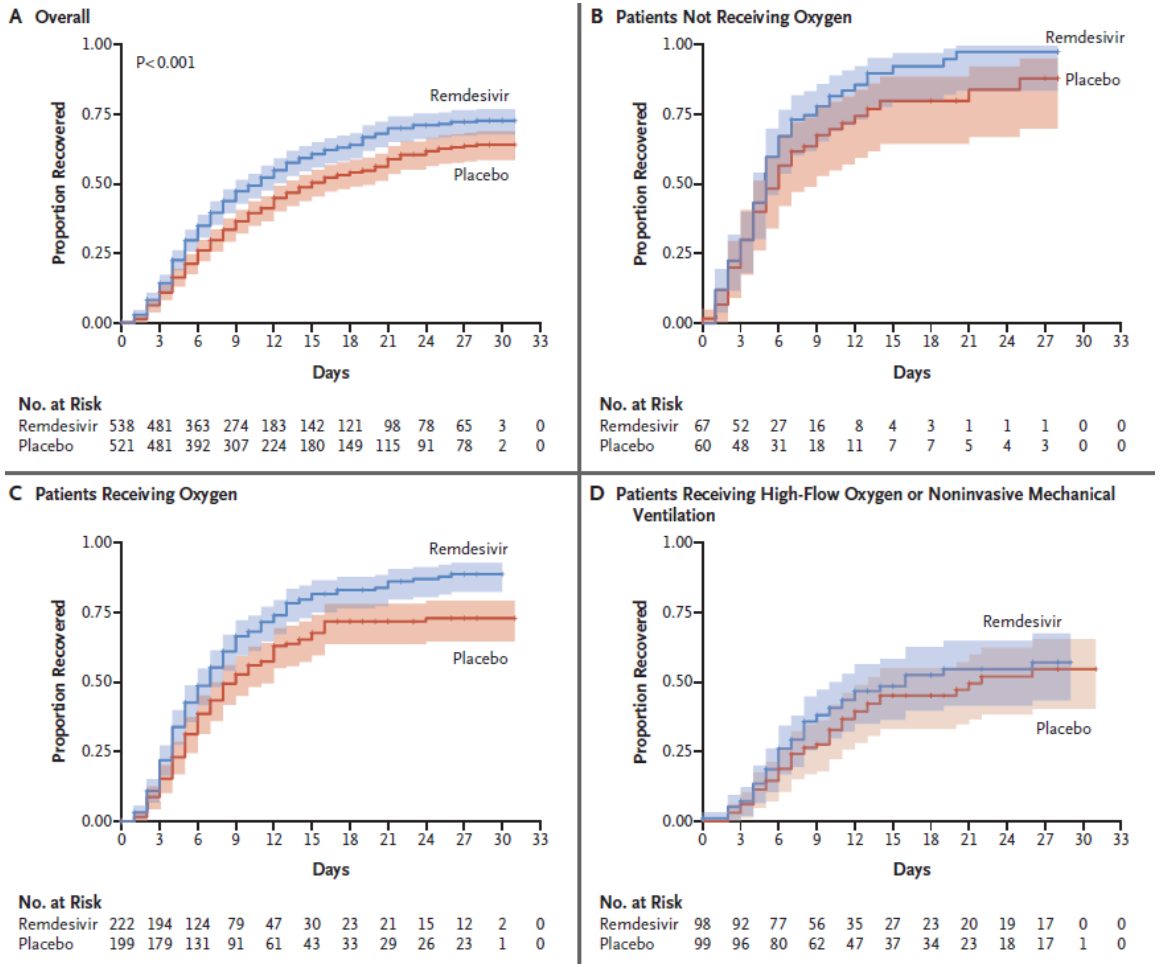
Remdesivir

- **RNA-dependent RNA polymerase inhibitor with in vitro activity against Ebola, SARS, MERS and SARS-CoV-2[1]**
- **Sub-micromolar EC50 against SARS-CoV-2 in vitro[2]**
- **Effective against SARS-CoV-2 in NHP[3]**

1. Sheahan TP et al Nat Commun 2020
2. Wang M et al Cell Res 2020
3. Williamson BN et al Nature 2020

ACTT-1 Study

- **Placebo-controlled, double-blind RCT in hospitalized adults with COVID-19 pneumonia**
- **Participants randomized 1:1 to RDV or placebo**
- **Primary endpoint: time to recovery within 28 days**
  - Preliminary analysis conducted after 606 recoveries were attained



Beigel JH et al N Engl J Med 2020

Most common Grade 3 or worse AEs in ACTT-1

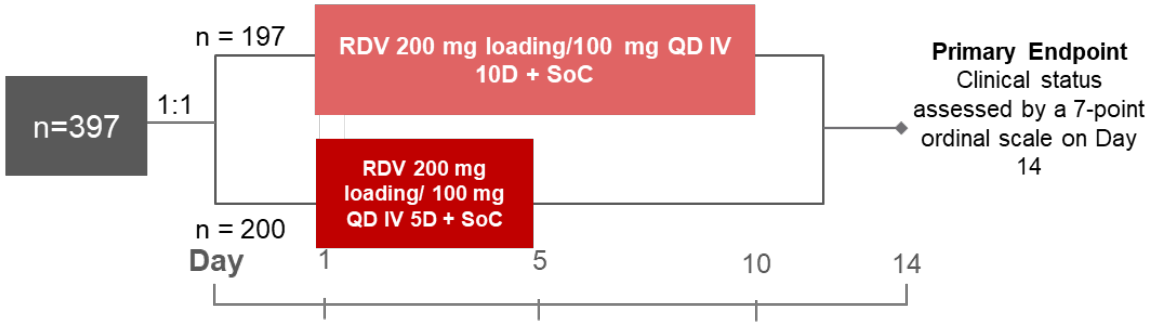
n (%)	Remdesivir N=538	Placebo N=521
Anemia or decreased hemoglobin	43 (8%)	47 (9%)
Acute kidney injury, decreased eGFR or creatinine renal clearance, or increased blood creatinine	40 (7%)	38 (7%)
Pyrexia	27 (5%)	17 (3%)
Hyperglycemia or increased blood glucose	22 (4%)	17 (3%)
Increased transaminases, including ALT and/or AST	22 (4%)	31 (6%)

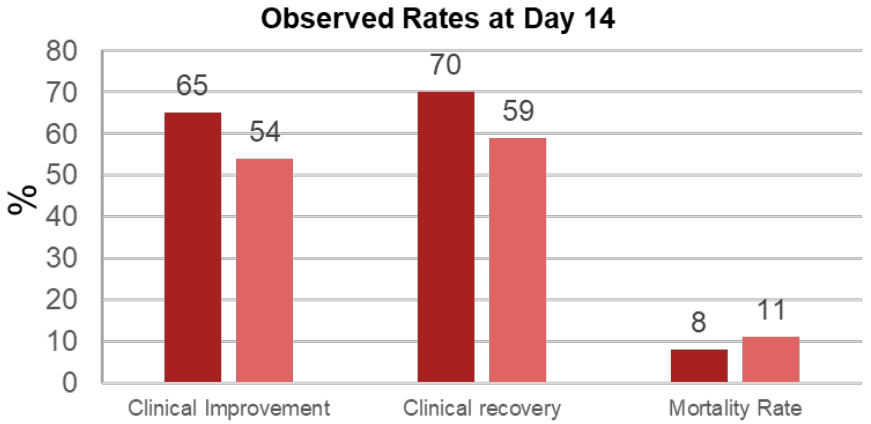
Source: Remdesivir EUA fact sheet; Goldman JD et al N Engl J Med 2020

Remdesevir SIMPLE trial: severe disease

Study GS- US 540-5774

Randomized, open-label, multicenter trial

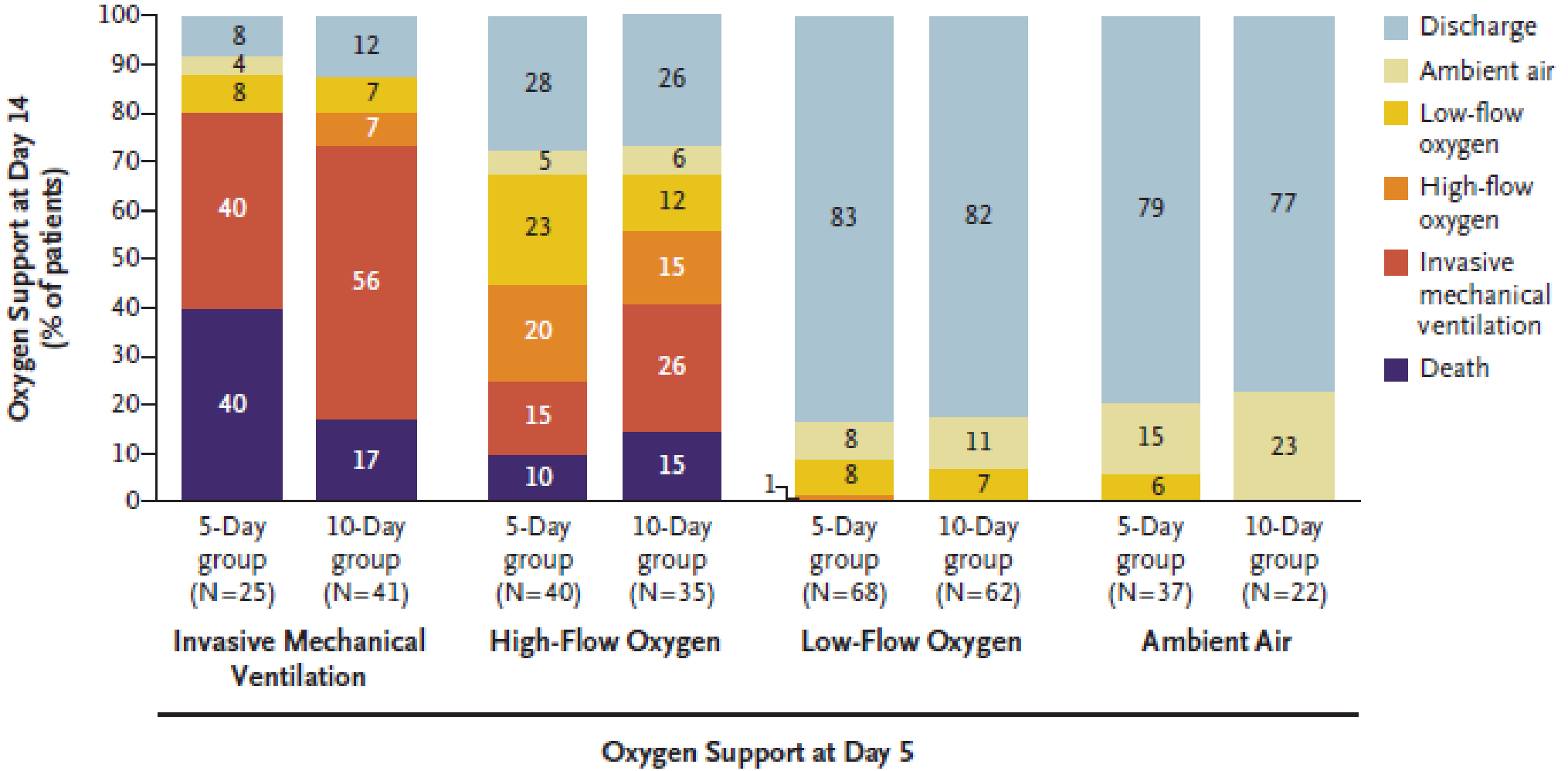




Clinical improvement was defined as an improvement of two or more points from baseline on a predefined 7-point scale, ranging from hospital discharge to increasing levels of oxygen support to death. Patients achieved clinical recovery if they no longer required oxygen support or were discharged from the hospital.

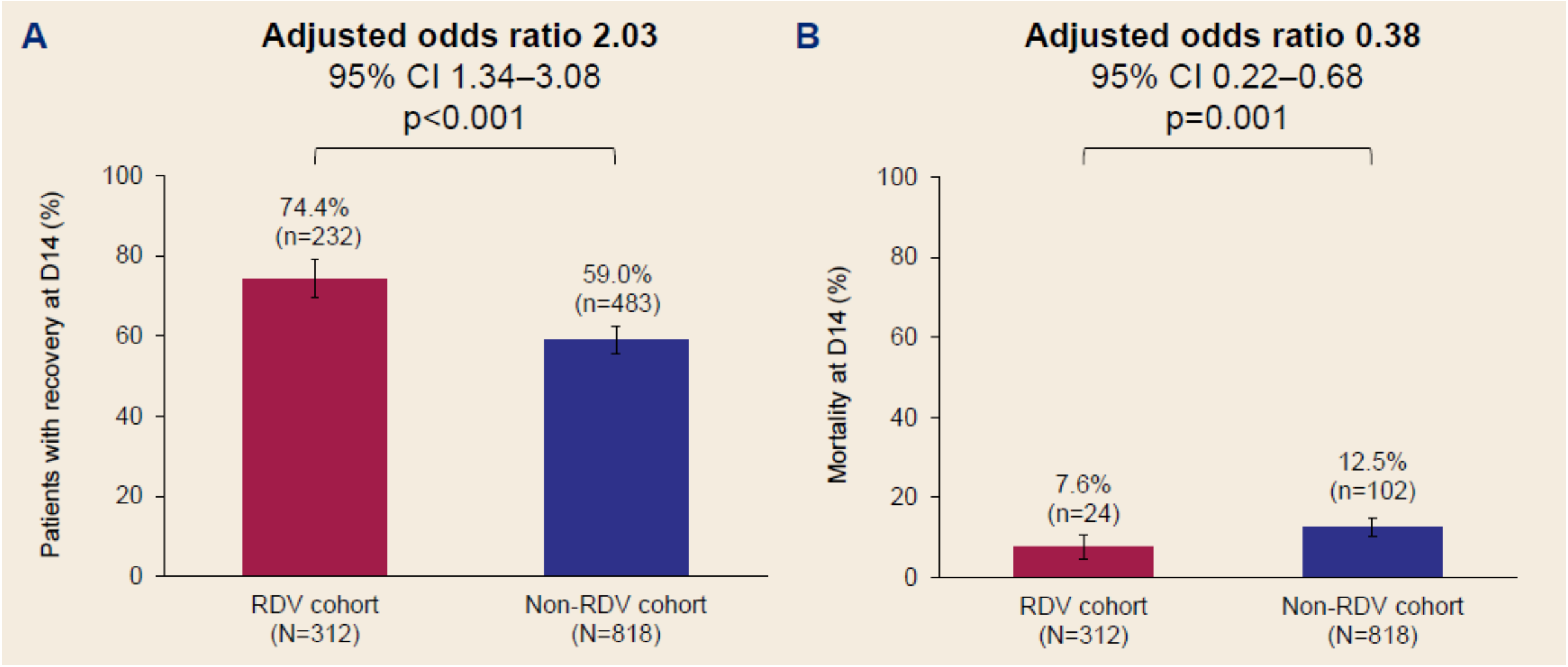
Source: Gilead Sciences; Goldman JD et al N Engl J Med 2020.

Remdesevir SIMPLE severe trial: change in required O_2 support



Goldman JD et al N Engl J Med 2020

Remdesivir for Severe COVID-19 Versus a Standard of Care Cohort: 14-day Outcomes

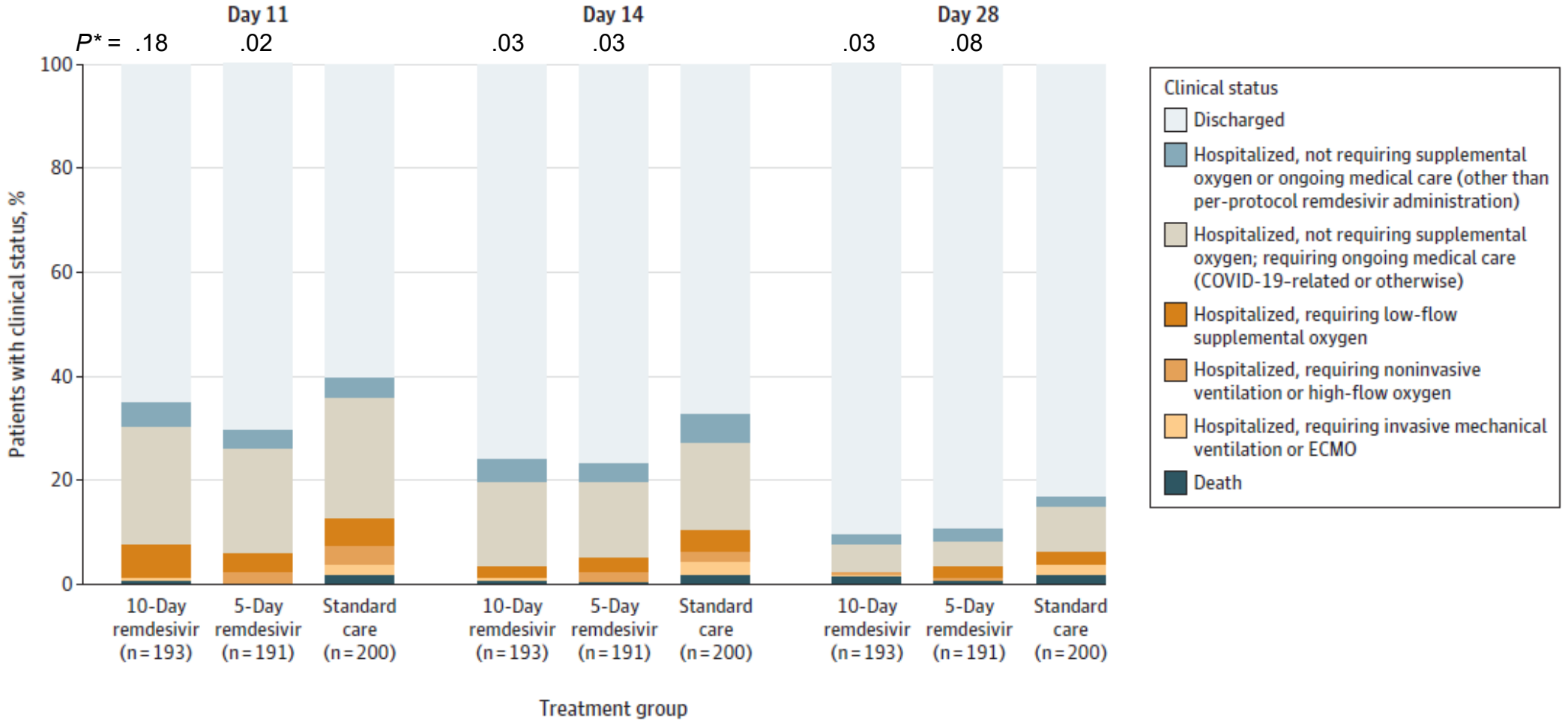


Remdesivir SIMPLE trial: moderate disease

- **3-arm, double-blind, placebo-controlled RCT**
  - 5 d vs 10 d vs SOC
- **Entry criteria:**
  - SARS-CoV-2+ PCR
  - SpO2 >94%
- **N=600**
- **Primary endpoint: clinical status at day 11**
- **5-day arm showed greater clinical improvement vs SOC**
  - OR 1.65 [95% CI 1.09-2.48]; p=0.017

Source: Gilead Sciences

Remdesivir SIMPLE trial: moderate disease results

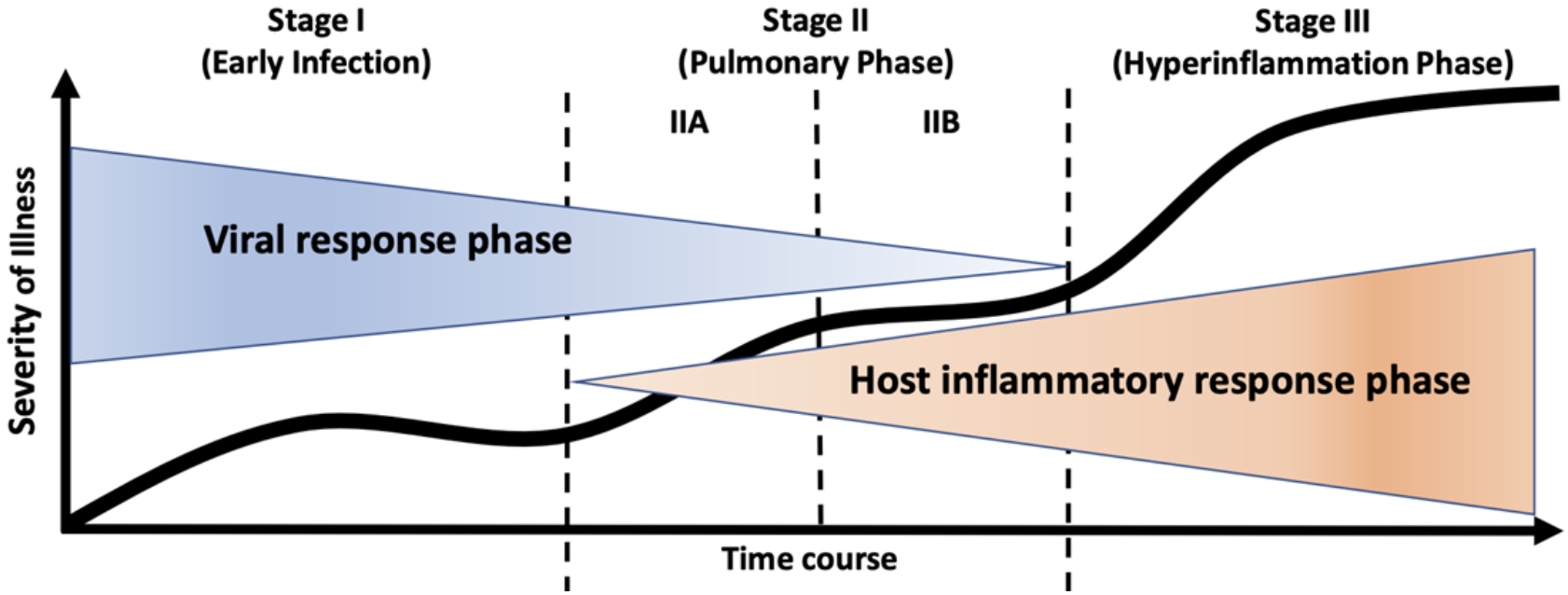


**P values for comparison of 10- and 5-day remdesivir arms, respectively, vs standard of care*

Spinner CD et al JAMA 2020

Corticosteroids

Immune response modifiers



- Second phase of COVID-19 characterized by immune activation, “cytokine storm” and high levels of IL-6
- mAbs that block inflammation generally or the IL-6/IL-6R axis specifically may be effective in preventing/moderating immune-mediated lung injury
- Pilot studies of immunomodulatory agents have shown promising results

Siddiqi HK J Heart Lung Transplant 2020
Xu 2020 chinaXiv:202003.00026v1

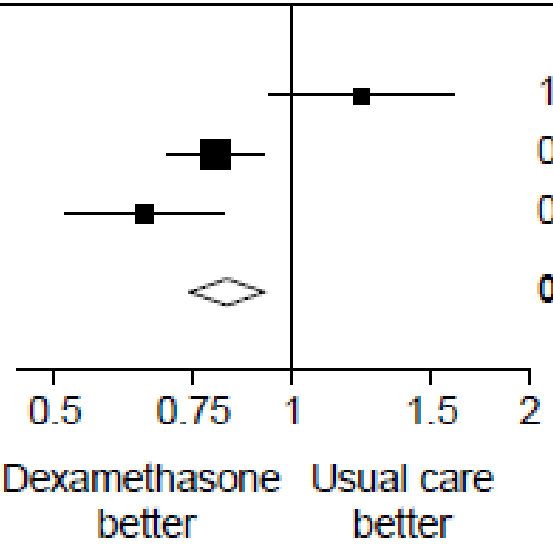
RECOVERY Trial

- **Large, randomized, placebo-controlled trial of possible treatments for patients admitted to hospital with COVID-19.**
- **More than 11,500 participants have been randomized to the following arms:**
  - Standard of care
  - Hydroxychloroquine
  - Low-dose dexamethasone (6 mg)
  - Lopinavir/ritonavir
  - Azithromycin
  - Tocilizumab
  - Convalescent plasma

Effect of dexamethasone on 28-day mortality by level of respiratory support at randomization

Respiratory support at randomization	Dexamethasone	Usual care	RR (95% CI)
No oxygen received	85/501 (17.0%)	137/1034 (13.2%)	1.22 (0.93–1.61)
Oxygen only	275/1279 (21.5%)	650/2604 (25.0%)	0.80 (0.70–0.92)
Invasive mechanical ventilation	94/324 (29.0%)	278/683 (40.7%)	0.65 (0.51–0.82)
All participants	**454/2104 (21.6%)**	**1065/4321 (24.6%)**	**0.83 (0.74–0.92) p<0.001**

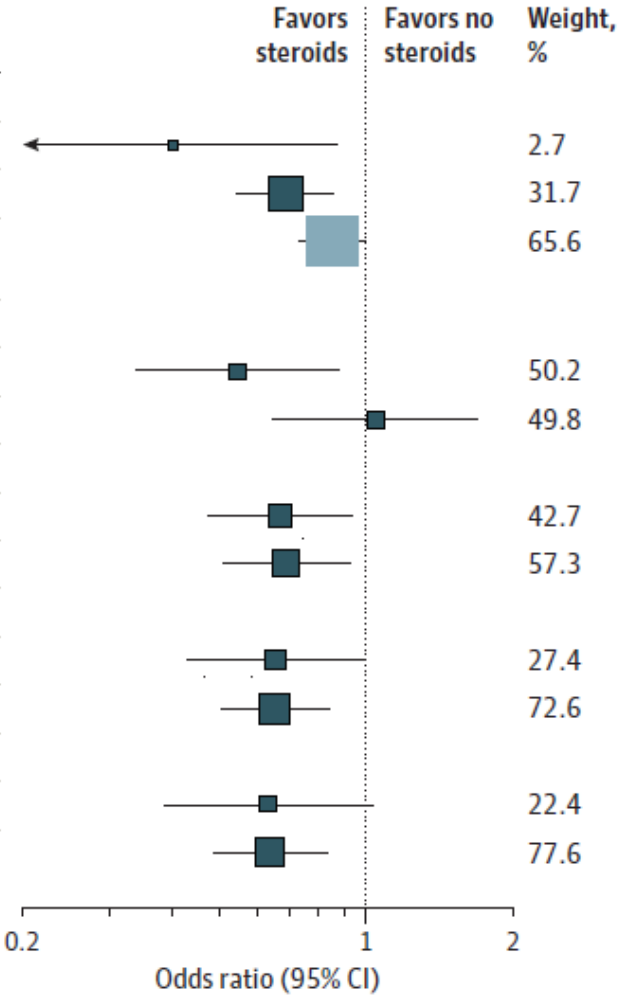
Trend across three categories: χ^2_1=11.49; p<0.001



Horby PW et al N Engl J Med 2020

Meta-analysis of steroid trials for COVID-19

Subgroup	No. of deaths/total No. of patients: Steroids	No. of deaths/total No. of patients: No steroids	Odds ratio (95% CI)	Weight, %
Invasive mechanical ventilation (IMV)				
No (I^2 = 0%)	14/70	28/74	0.41 (0.19-0.88)	2.7
Yes (I^2 = 44.1%)	208/608	397/951	0.69 (0.55-0.86)	31.7
Oxygen treatment without IMV (RECOVERY)	298/1279	682/2604	0.86 (0.73-1.00)	65.6
Taking vasoactive medication				
No (I^2 = 0%)	51/184	68/184	0.55 (0.34-0.88)	50.2
Yes (I^2 = 0%)	76/169	74/158	1.05 (0.65-1.69)	49.8
Age, y				
≤60 (I^2 = 0%)	72/338	141/483	0.67 (0.48-0.94)	42.7
>60 (I^2 = 49.7%)	150/339	284/541	0.69 (0.51-0.93)	57.3
Sex				
Female (I^2 = 0%)	60/202	106/286	0.66 (0.43-0.99)	27.4
Male (I^2 = 14.7%)	162/476	319/739	0.66 (0.51-0.84)	72.6
Symptomatic, d				
≤7 (I^2 = 69.1%)	51/130	99/211	0.63 (0.39-1.04)	22.4
>7 (I^2 = 0%)	139/418	293/693	0.64 (0.49-0.83)	77.6



Sterne C et al JAMA 2020

WHO Guidance on Corticosteroids for COVID-19

- **Recommendation 1**
  - *We recommend systemic corticosteroids rather than no corticosteroids for the treatment of patients with severe and critical COVID-19 (strong recommendation).*
- **Recommendation 2**
  - *We suggest not to use systemic corticosteroids in the treatment of patients with non-severe COVID-19 (conditional recommendation).*
- **The evidence**
  - *The panel made its recommendation on the basis of the moderate certainty evidence of a mortality reduction of 8.7% and 6.7% in patients with COVID-19 who are critically or severely ill.*
- **Key practical issues for the use of systemic corticosteroids**
  - 6 mg daily of oral dexamethasone or 50 mg iv every 8 hours of hydroxycortisone for 7-10 days

WHO/2019-nCoV/Corticosteroids/2020.1

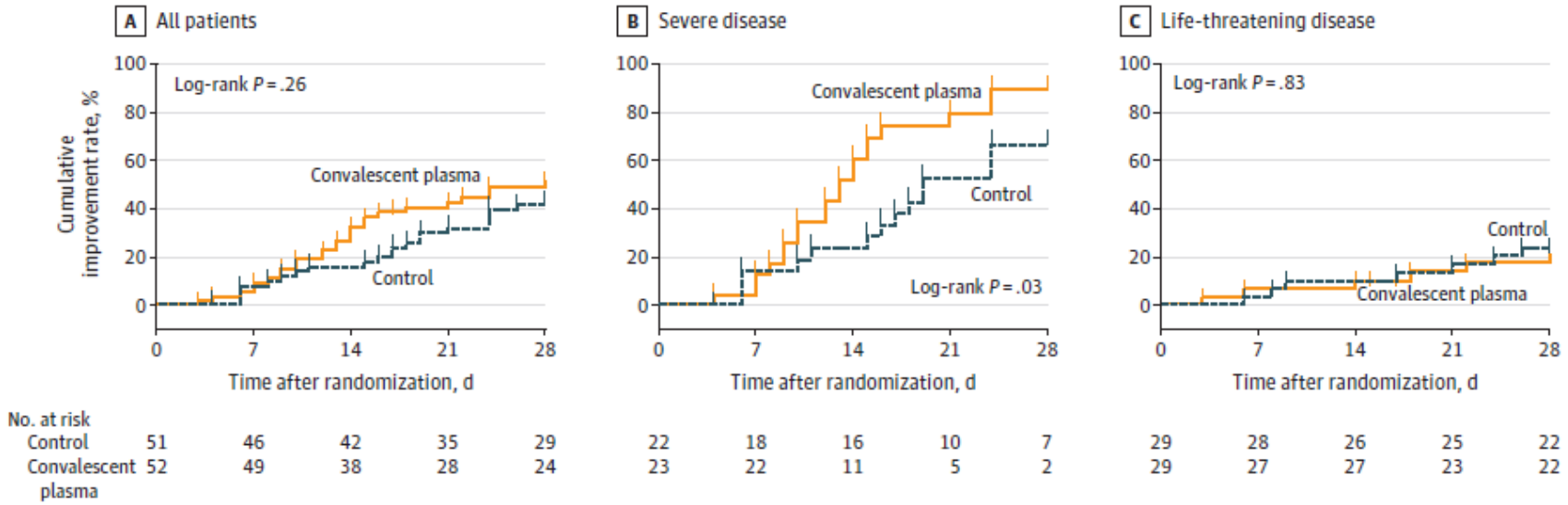
Convalescent plasma

Convalescent plasma

- Convalescent plasma from survivors of COVID-19 infection may contain high titers of neutralizing Ab
- Convalescent serum has shown some benefit in treatment of avian (H1N5) and H1N1 influenza and MERS
- Pilot studies and uncontrolled trials suggest possible benefit

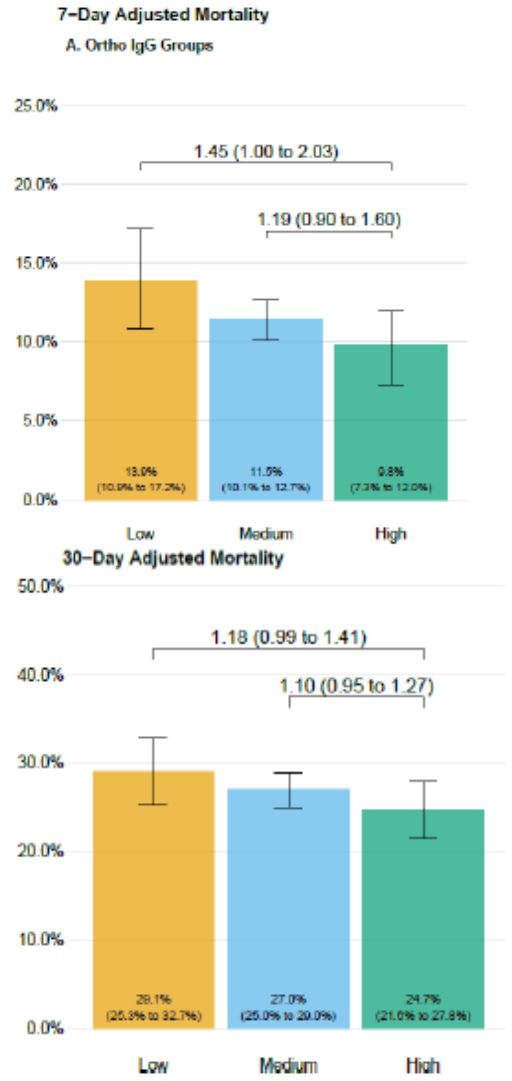
Phase 2 open-label RCT of convalescent plasma

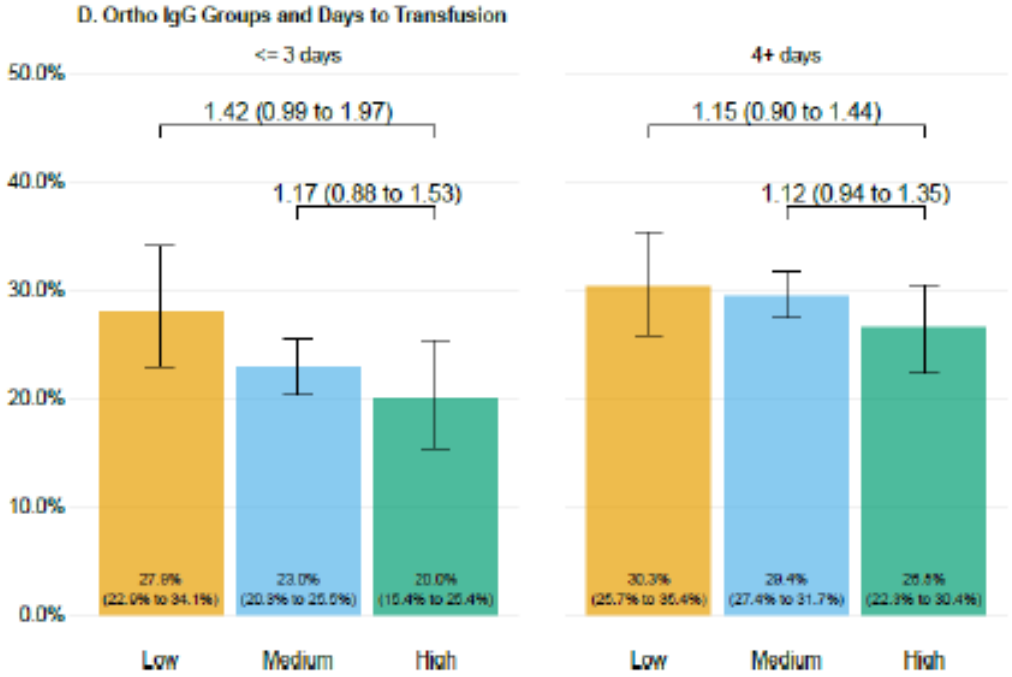
- 7 medical centers in Wuhan
- 103 participants randomized 1:1 to CP vs SOC
- Plasma units screened for S-RBD-specific IgG titer ≥1:640
- Primary endpoint: time to clinical improvement within 28 days



Li L et al JAMA 2020

COVID-19 Convalescent Plasma: EAP Results





Joyner MJ et al medRxiv accessed 9 Sept 2020

Summary

- **The COVID-19 pandemic has resulted in substantial excess deaths**
- **Remdesivir reduces time to recovery in patients with moderate and severe disease**
- **Corticosteroids improve survival in patients with COVID-19 who require supplemental oxygen or mechanical ventilation**
- **Convalescent plasma may provide benefit in patients with severe COVID-19, but still awaiting data from controlled trials**
  - Studies of SARS-CoV-2 mAbs underway