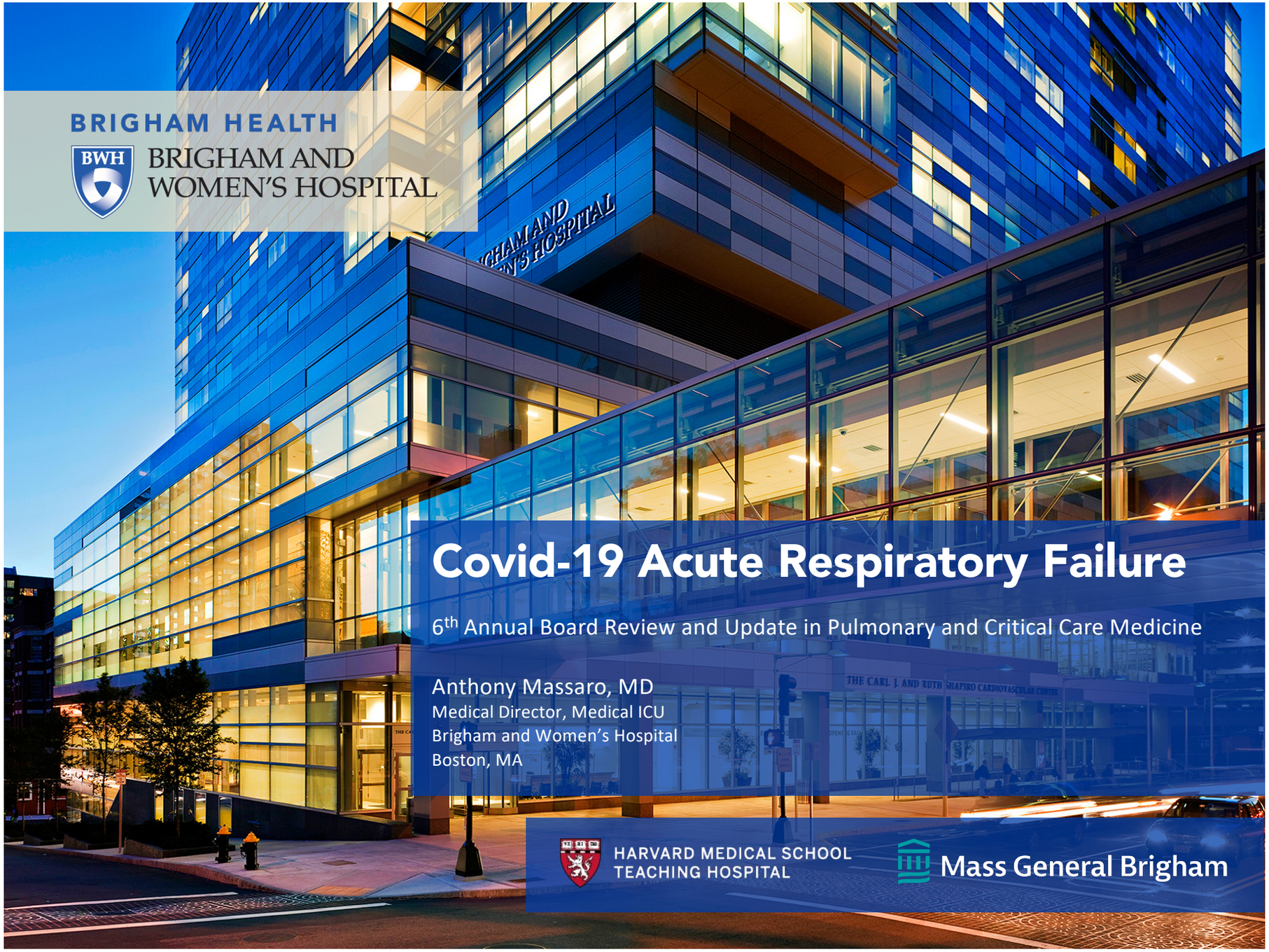

BRIGHAM HEALTH
BWH
BRIGHAM AND
WOMEN'S HOSPITAL
Covid-19 Acute Respiratory Failure
6th Annual Board Review and Update in Pulmonary and Critical Care Medicine
Anthony Massaro, MD
Medical Director, Medical ICU
Brigham and Women's Hospital
Boston, MA
HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL
Mass General Brigham

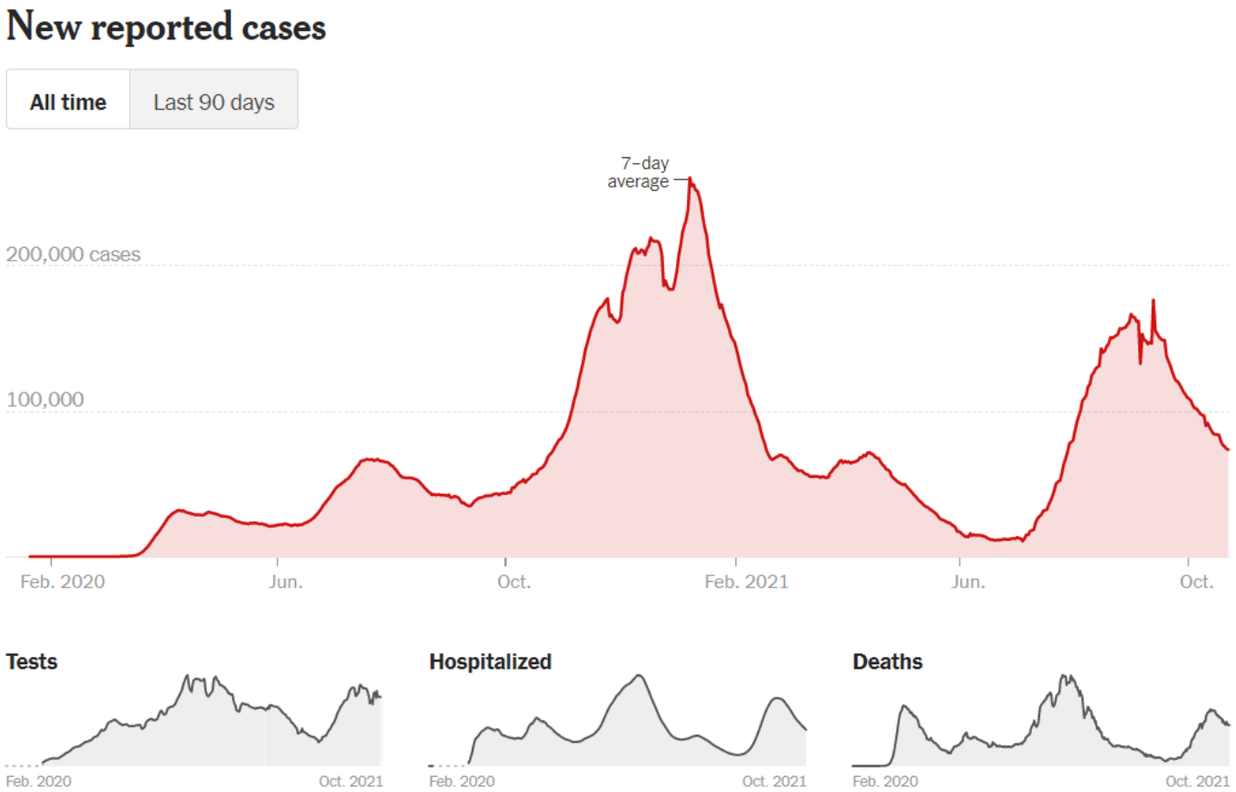
Disclosures

- No disclosures

Objectives

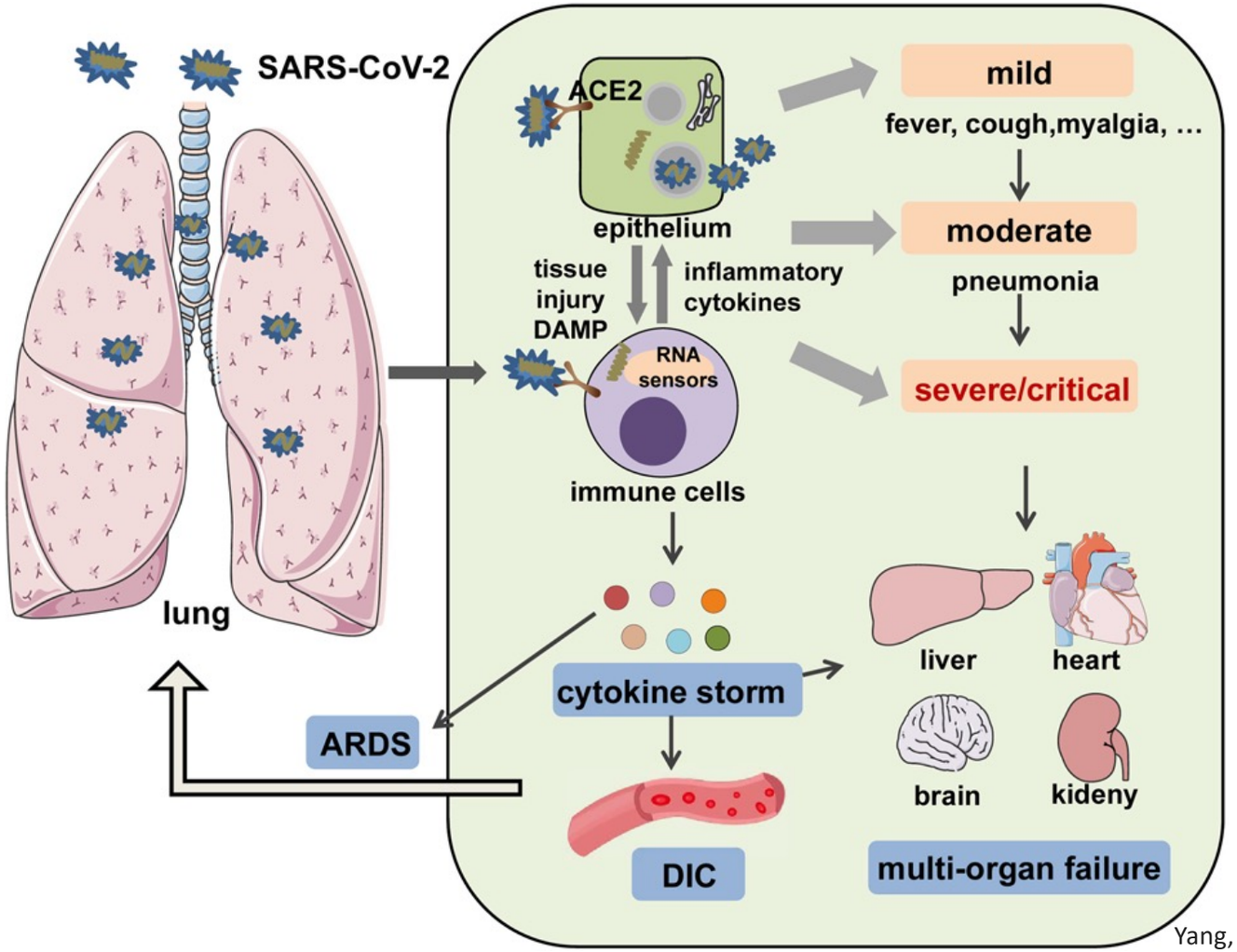
- Management of Acute Respiratory Failure
  - Therapies Prior to Intubation
    - High Flow Nasal Cannula
    - Non-Invasive Ventilation
  - Intubation / Invasive ventilatory support
    - Mechanical Ventilation Settings
      - Is Covid-19 ARDS different from ARDS?
- Role of Immunomodulation

Covid-19 United States



Cases: >45 million
Deaths:> 735,000

New York Times



Yang, L., Xie, *et al.* The signal pathways and treatment of cytokine storm in COVID-19. *Sig Transduct Target Ther* **6,** 255 (2021).

Hospitalized Covid-19 Patients Require ICU care

- NY Langone
  - 2729 Admissions
    - 36.1% Critical Illness
      - (Mechanical Ventilation, ICU admission or died)

- Henry Ford Health System
  - 355 Admissions
    - 39.7 % Critical Illness
      - (ICU admission)

Acute Respiratory Failure with Hypoxemia is the Predominant Problem

- 990 Patients with Critical Illness
  - 65.4% Mechanical Ventilation (MV)
  - 10.3% ICU Admission but no MV
  - 24.3% Died or Hospice without ICU or MV

Petrilli et al. BMJ 2020;369:m1966 http://dx.doi.org/10.1136/bmj.m1966

- 141 Patients with Critical Illness
  - 80.8% Mechanical Ventilation (MV)
  - 73.8% ARDS
  - 39.0 % In hospital Mortality

Suleyman G etal.. *JAMA Netw Open.* 2020;3(6):e2012270. doi:10.1001/jamanetworkopen.2020.12270

Covid-19 Critical Illness Clinical Characteristics

		Wuhan	Wuhan	Lombardy	Seattle	New York
		n=52	N=36	n=1591	n=24	N=257
Mechanical Ventilation (invasive and non-invasive)		71%	89%	99%	75%	80%
Vasopressors		35%	36%		71%	66%
Renal Replacement Therapy		17%	6%			31%
Antibiotics		94%	>64%			89%
Mortality		61.5%	17%	26%	50%	39%

Yang et al. Lancet 2020; 8(5): 475-481
Wang et al. JAMA 2020; 323(11):1061-1069
Graselli et al. JAMA 2020: 323(16):1754-1581
Bhatraju PK et al. N Engl J Med 2020;382:2012-2022
Cummings et al. Lancet. https://doi.org/10.1016/ S0140-6736(20)31189-2

Management of Covid-19
Acute Respiratory Failure with Hypoxemia

- Goals:
  - Maintain target SpO2 92-96%
  - Maintain stable work of breathing
    - Goal respiratory rate < 24
    - Target normal respiratory effort (no signs of accessory muscle use or obvious increased respiratory work)
      - Avoid excessive intrathoracic pressure
        - Patient Self Induced Lung Injury (P-SILI)

ICU Acute Respiratory Failure Therapies

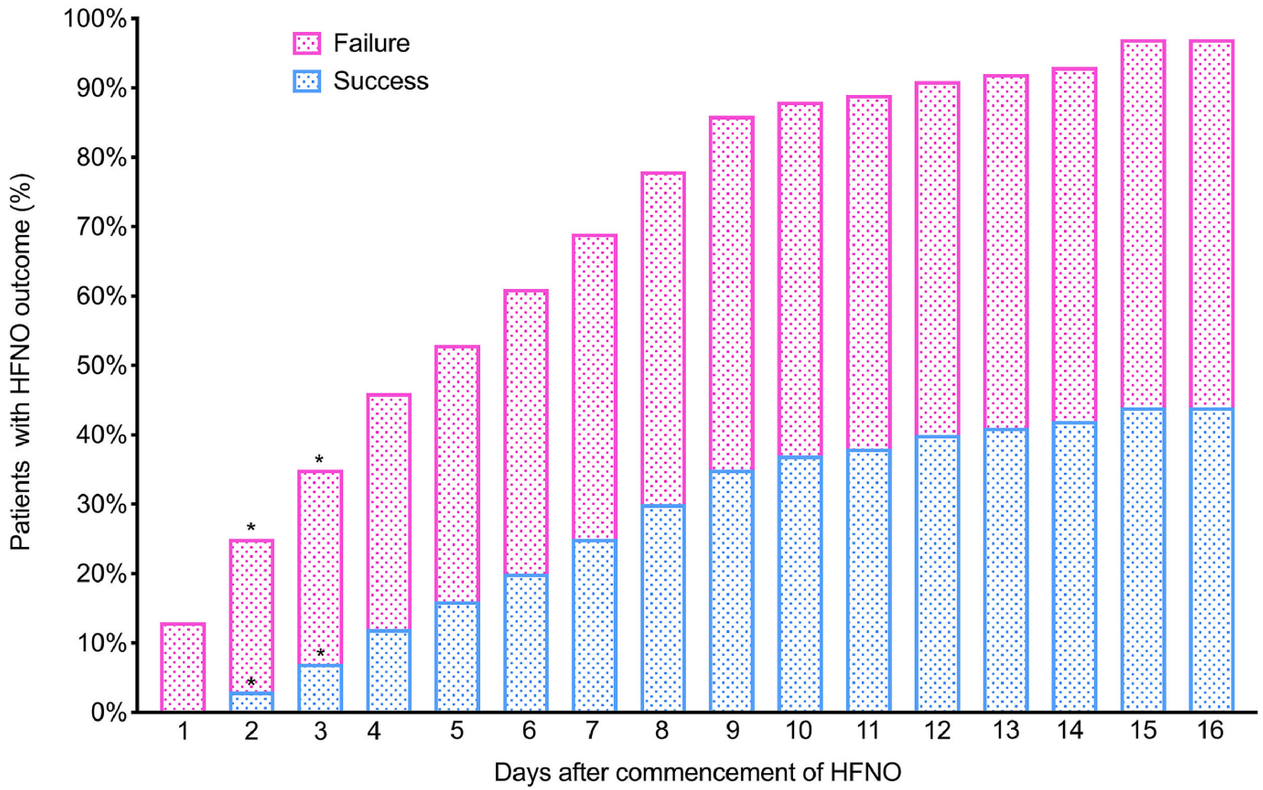
		Wuhan	Wuhan	Lombardy	Seattle	New York
		n=52	N=36	n=1591	n=24	N=257
High Flow Nasal Cannula (HFNC)		63.5%	11.1%		42%	5%
CPAP or Non-Invasive Ventilation		56.0%	41.7%	11%	0%	1%
Invasive Mechanical Ventilation		42.0%	47.2%	88%	75%	79%
	Prone Ventilation	11.5%		27%	28%	17%
	Neuromuscular blockade				39%	25%
	Inhaled Pulmonary Vasodilator				28%	11%
	Extracorporeal Membrane Oxygenation	11.5%	11.1%	1%	0%	3%

Yang et al. Lancet 2020; 8(5): 475-481
Wang et al. JAMA 2020; 323(11):1061-1069
Graselli et al. JAMA 2020: 323(16):1754-1581
Bhatraju PK et al. N Engl J Med 2020;382:2012-2022
Cummings et al. Lancet. https://doi.org/10.1016/ S0140-6736(20)31189-2

High Flow Nasal Cannula (HFNC)

- Con
  - Particle dispersion and risk to healthcare workers
    - Conflicting, confusing data
    - Concern for rapid deterioration and need for urgent intubation.
  - Patient Self Induced Lung Injury (P-SILI)
  - Utilization of potentially limited supplemental oxygen supplies
- Pro
  - Proven Efficacy in Acute Respiratory Failure with Hypoxia
  - Potentially administer outside the ICU
  - Conserve ventilators

The utility of high-flow nasal oxygen for severe COVID-19 pneumonia in a resource-constrained setting: A multi-centre prospective observational study



Two Tertiary Care Hospitals
Cape Town , South Africa

Prospective

293 Patients
105 ICU
188 Covid ward

Primary Endpoint - Proportion of patients weaned off HFNC

47% of patients successfully weaned off HFNC

Calligaro et al. The utility of high-flow nasal oxygen for severe COVID-19 pneumonia in a resource-constrained setting: Amulti-centre prospective observational study EClinicalMedicine 2020 28DOI: (10.1016/j.eclinm.2020.100570)

Impact of HFNC on Mechanical Ventilation and Mortality

	HFNC	No HFNC	
# Patients	146 (34%)	233 (66%)	
PaO2/FiO2	126	138	p=0.43
SOFA Day 1	4	6	p=0.001
Results			
Mech Vent Day 28	56% (95% CI 47-64)	75% (95% CI 70-81)	p<0.001
Mortality	21%	30%	HR=0.69 CI 0.45-1.07
Results Propensity Match			
# Patients	137	137	
Mech Vent Day 28	55% (95% CI 46-63)	72% (95% CI 64-79)	P<0.0001
Mortality	21%	22%	HR=1.35 CI 0.56-3.26

Retrospective Study
4 ICUs France
2/2020-4/2020
379 patients

Demoule et al. Am J Respir Crit Care Med 2020:202:1039

Noninvasive Positive Pressure Ventilation

- Con
  - Particle dispersion / Safety
  - Not proven for ARDS pre-Covid
  - Requires increased resources outside ICU
- Pro
  - Proven Efficacy in Select Populations
    - COPD Acute Exacerbations
    - Pulmonary Edema
  - Conserve ventilators

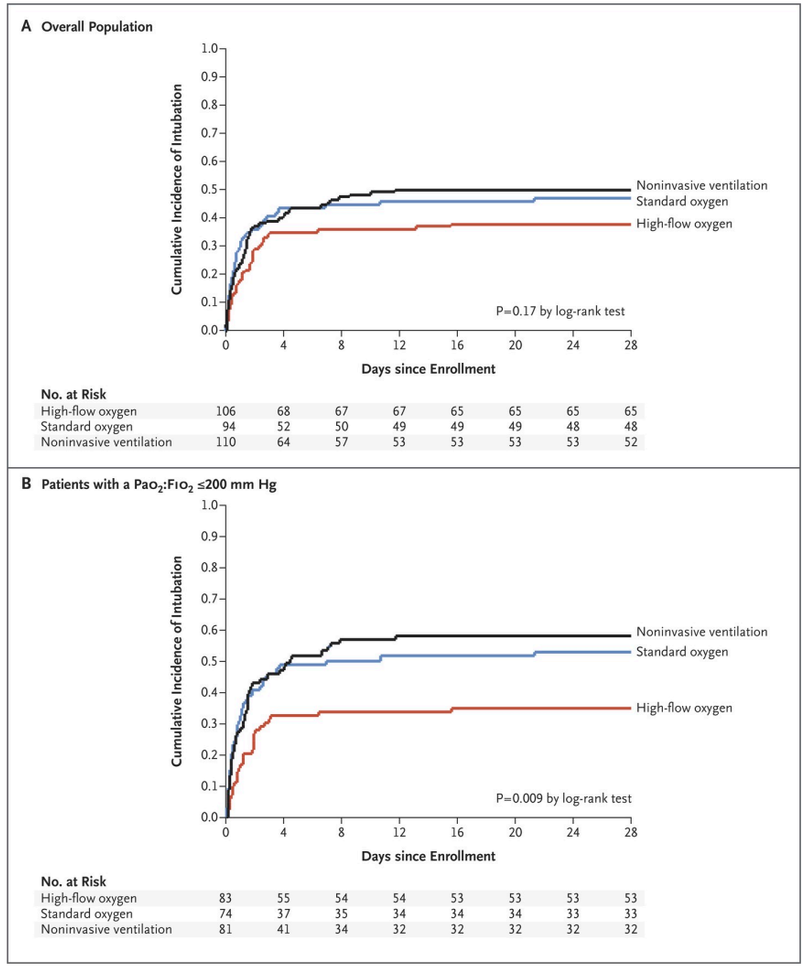
HFNC vs NIV vs CPAP

	Total	HFNC			CPAP			NIV		
	Total	HFNC	OR	P	N=	OR	P-	N=	OR	p-value
# Patients	670 (100)	163 (24.3)			330 (49.3)			177 (26.4)		
Intubation										
Crude	178 (26.6)	47 (28.8)	1.1 (0.8-1.7)	0.45	82 (24.8)	0.8 (0.6-1.2)	0.32	49 (27.7)	1.1 (0.7-1.6)	0.80
Adjusted			1.5 (0.6-4.1)	0.39		0.9 (0.5-1.7)	0.76		1.2 (0.5-3.3)	0.65
30 Day Mortality										
Crude	180 (26.9)	26 (15.9)	0.43 (0.3-0.7)	<0.01	100 (30.3)	1.4 (0.9-2)	0.05	54 (30.5)	3.4 (0.5-1.9)	0.20
Adjusted			0.52 (0.1-1.2)	0.10		1. (0.8-4.3)	0.11		1.1 (0.3-3.7)	0.88

Observational Study
Italy
March – May 2020
9 Hospitals
Non-ICU
670 consecutive pts

Franco C et al. Feasibility and clinical impact of out-of-ICU noninvasive respiratory support in patients with COVID-19-related pneumonia. Eur Respir J 2020; 56

High Flow Nasal Cannula in Acute Respiratory Failure

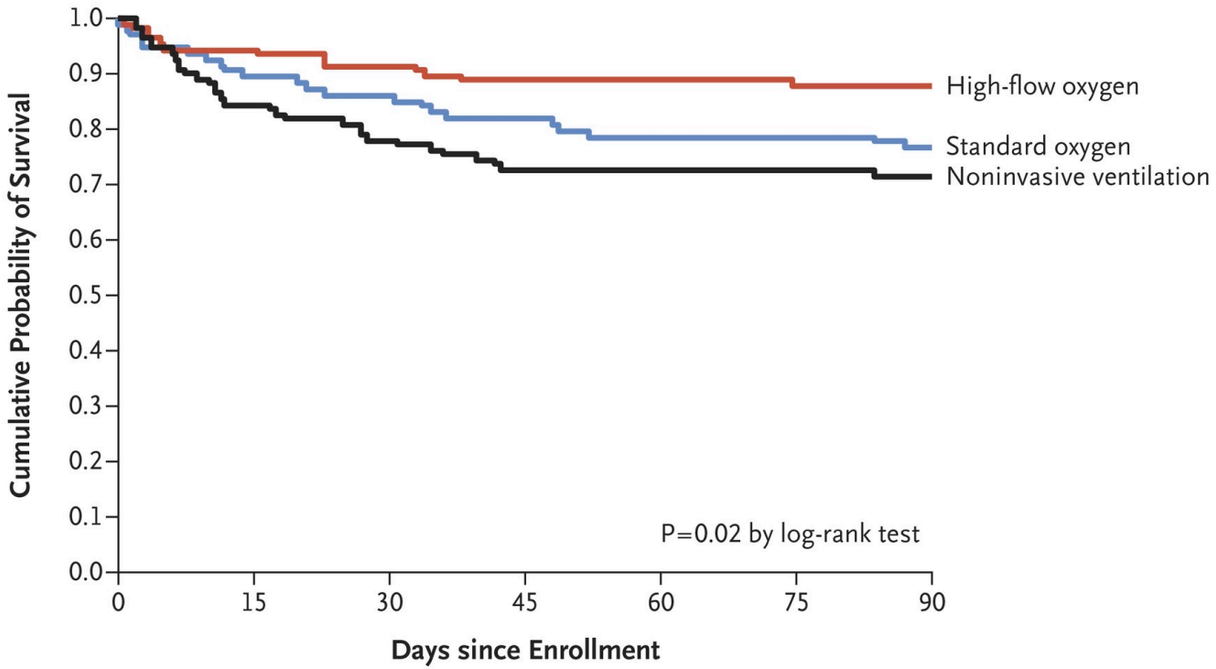


Kaplan–Meier Plots of the Cumulative Incidence of Intubation from Randomization to Day 28

FLORALI Study Group

Frat J-P et al. N Engl J Med 2015;372:2185-2196

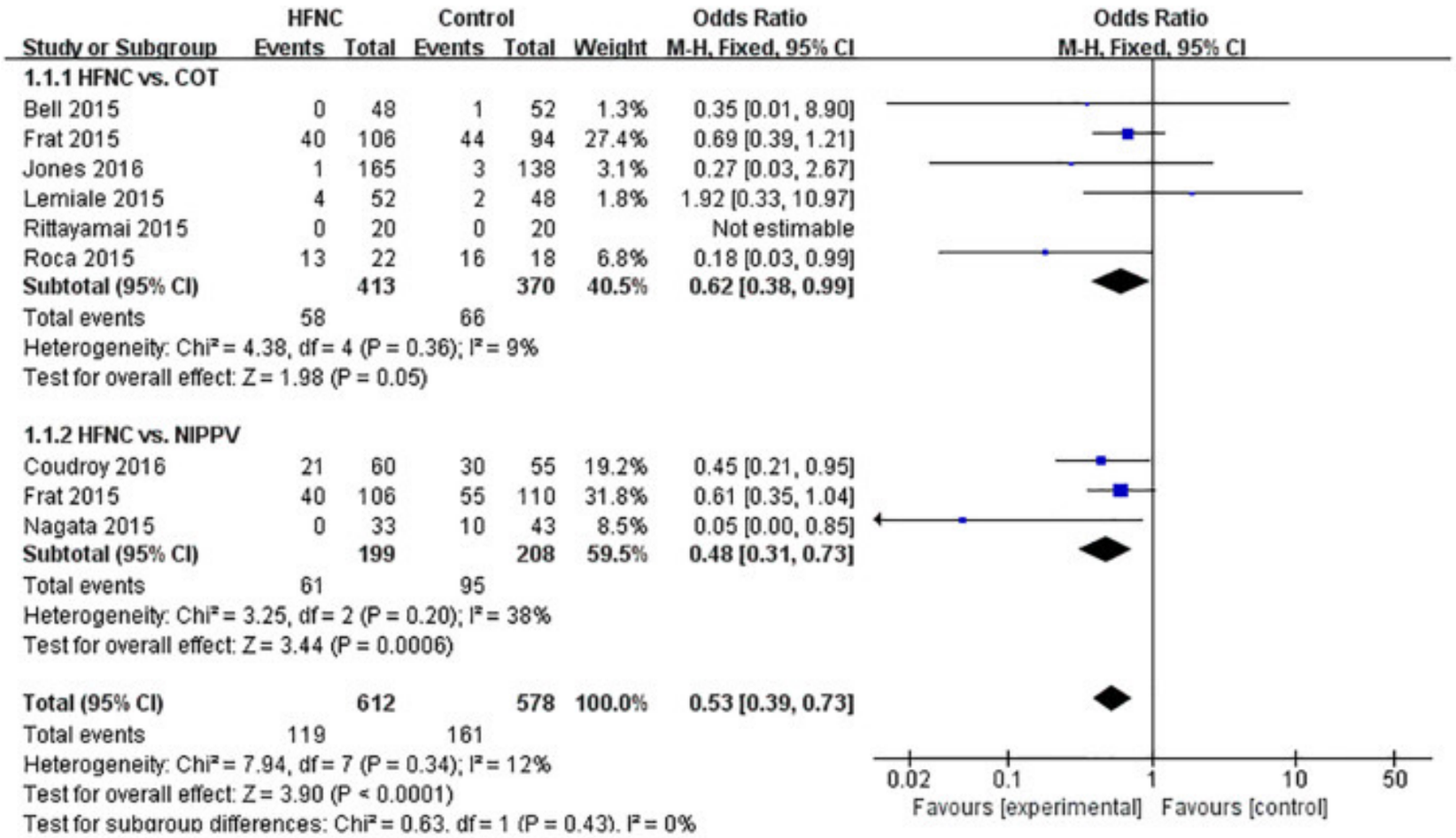
Kaplan–Meier Plot of the Probability of Survival from Randomization to Day 90.



No. at Risk							
High-flow oxygen	106	100	97	94	94	93	93
Standard oxygen	94	84	81	77	74	73	72
Noninvasive ventilation	110	93	86	80	79	78	77

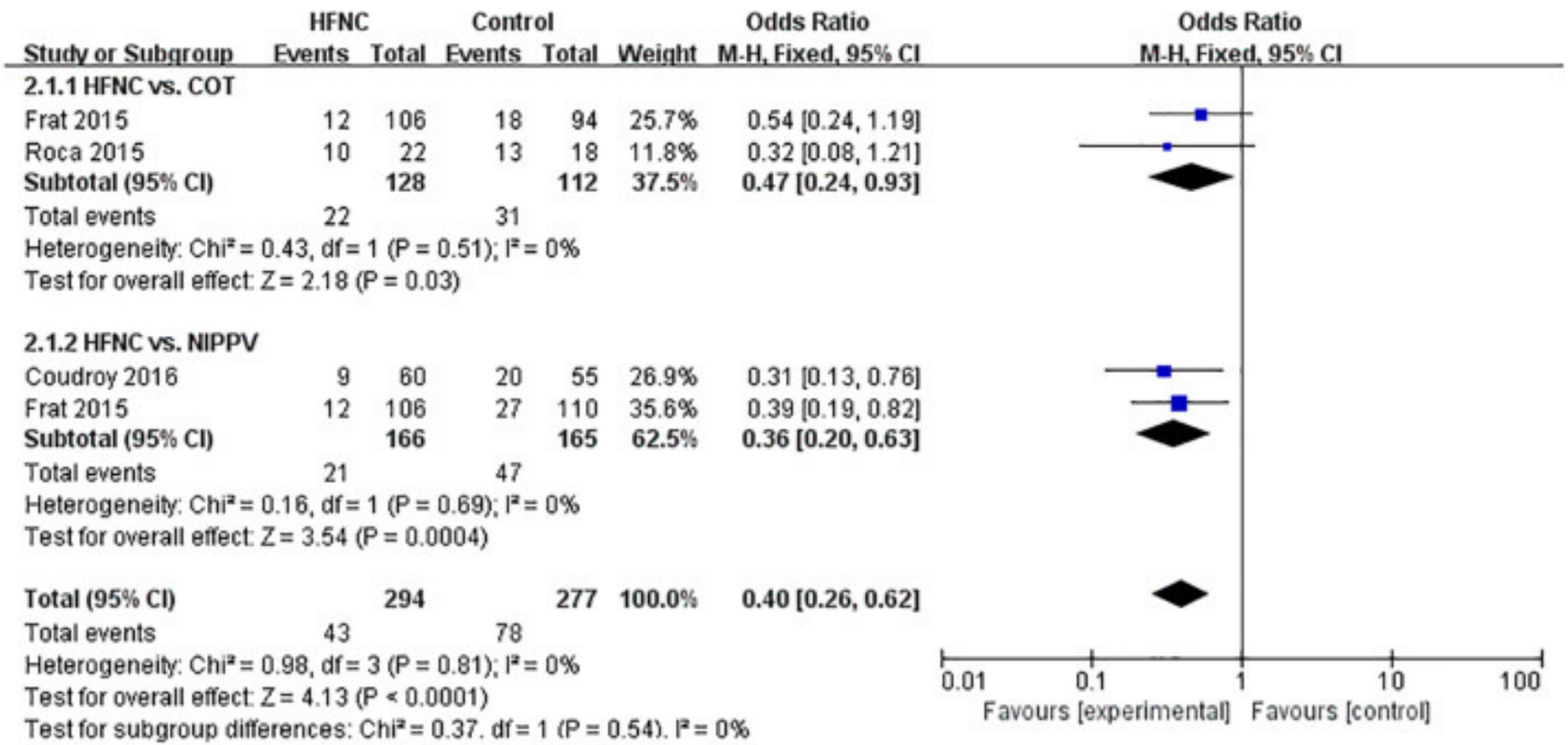
Frat J-P et al. N Engl J Med 2015;372:2185-2196

Effect of HFNC on Intubation – Meta-Analysis



Ni, Y. N., et al. (2018) Am J Emerg Med **36**(2): 226-233.

Effect of HFNC on ICU Mortality – Meta-Analysis



Ni, Y. N., et al. (2018) Am J Emerg Med **36**(2): 226-233.

2021: Role of High Flow Nasal Cannula in Covid-19

- May help avoid intubation.
- 30-60 % of patients proceed to invasive mechanical ventilation
- True impact on MV rates and Mortality unclear.
- Initiate after multidisciplinary discussion
- Requires full Enhanced Respiratory Precautions PPE
- Use mitigation interventions if possible
  - Mask on patient
  - Start low flow

2021: Role of Noninvasive Positive Pressure Ventilation in Covid-19

- May have role in select populations
  - Patients on nocturnal CPAP or BiPAP
  - Chronic respiratory failure
  - DNI or DNI / DNR patients
- Initiate after multidisciplinary discussion
- Requires full Enhanced Respiratory Precautions PPE
- Dual limb circuit
  - No anti-asphyxiation port
  - Filter expiratory limb
- Optimize fit of mask

Timing of Intubation

- Important to have goals of care discussion
- Close observation
- Early discussion with anesthesia to make aware
- “Earlier rather than later”
  - Trajectory
  - High flow > 60-70%
  - Excessive work of breathing
  - Evidence of hemodynamic compromise

Is Covid-19 ARDS Unique?

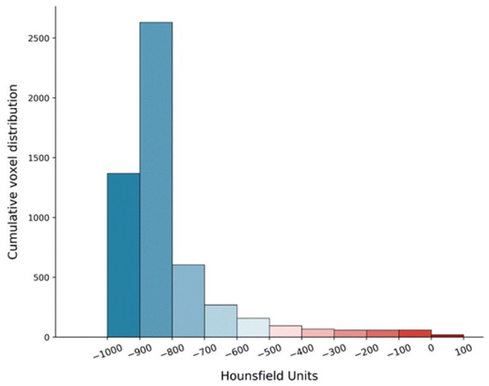
Severe Hypoxemia with preserved Respiratory System Compliance ?

Difference between early and late in disease?

	Type L	Type H
Elastance	Low	High
	Low V/Q	High Shunt
Lung weight	Low	High
Lung Recruitability	Low	High

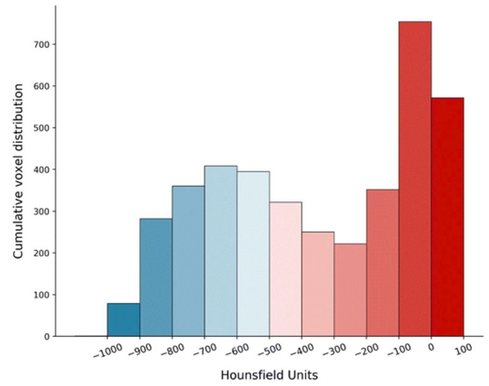
A

PaO_2/FiO_2
95 mmHg



B

PaO_2/FiO_2
84 mmHg

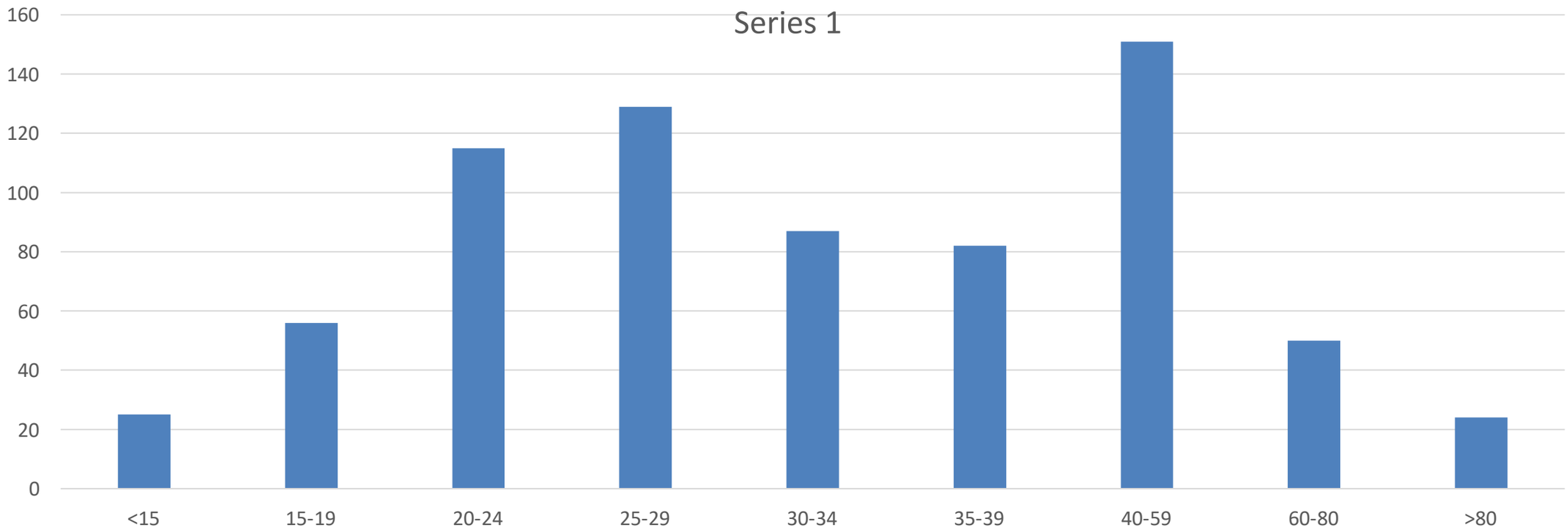


Gattinoni, L. *et al.* COVID-19 pneumonia: different respiratory treatments for different phenotypes?. *Intensive Care Med* (2020). https://doi.org/10.1007/s00134-020-06033-2

	# Patients	PaO2 / FiO2 ratio	Compliance	
Creteil, France	30	119 (97-163)	44 (35-51)	Haudebourg et al.
New York	222	129 (80-203)	27 (22-36)	Cummings et al.
Seattle	18		29 (25-36)	Bhatraju et al.
Boston	66	182 (135-245)	35 (30-43)	Ziehr et al.
Philadelphia	75	162	37.8	Pandya et al

Haudebourg et al. *Am J Respir Crit Care Med, 202*(2), 287-290. doi:10.1164/rccm.202004-1226LE
Cummings, M..J. et al. *The Lancet, 395*(10239), 1763-1770. doi:10.1016/S0140-6736(20)31189-2
Bhatraju, P. K. Et al. *New England Journal of Medicine, 382*(21), 2012-2022. doi:10.1056/NEJMoa2004500
Ziehr, D. R. et al. *Am J Respir Crit Care Med, 0*(ja), null. doi:10.1164/rccm.202004-1163LE
Pandya, A. et al. *Chest*. doi:10.1016/j.chest.2020.08.2084

LUNG SAFE Compliance



Bellani, G. etal.(2016). *JAMA, 315*(8), 788-800. doi:10.1001/jama.2016.0291 Supplemental Material

- At current time
  - No convincing data the Covid ARDS physiology is unique or separates into unique phenotypes
    - Non Covid ARDS is heterogeneous
    - Covid ARDS is heterogeneous
- Additional studies needed
  - Prospective, large cohort assessment
  - Well documented timepoints of symptom onset

Ventilator Management in Covid-19 ARDS (CARDS)

- Low Tidal Volume Protective Ventilation
- Setting PEEP
- Prone Ventilation
- Neuromuscular Blockade
- Inhaled Pulmonary vasodilators
- ECMO

Immunomodulatory therapy

- Corticosteroids
- IL-6 Receptor Antibodies
- Janus Kinase Inhibitors

Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury

THE LANCET

- Feb 7, 2020 Commentary

- Prior experience in
  - Influenza
  - SARS-CoV
  - MERS-CoV
  - RSV

- No improvement in mortality
- Reduced viral clearance
- Psychosis
- Hyperglycemia
- Avascular necrosis

Russell, Clark D et al. The Lancet, Volume 395, Issue 10223, 473 – 475. https://doi.org/10.1016/S0140-6736(20)30317-2

RESEARCH Open Access

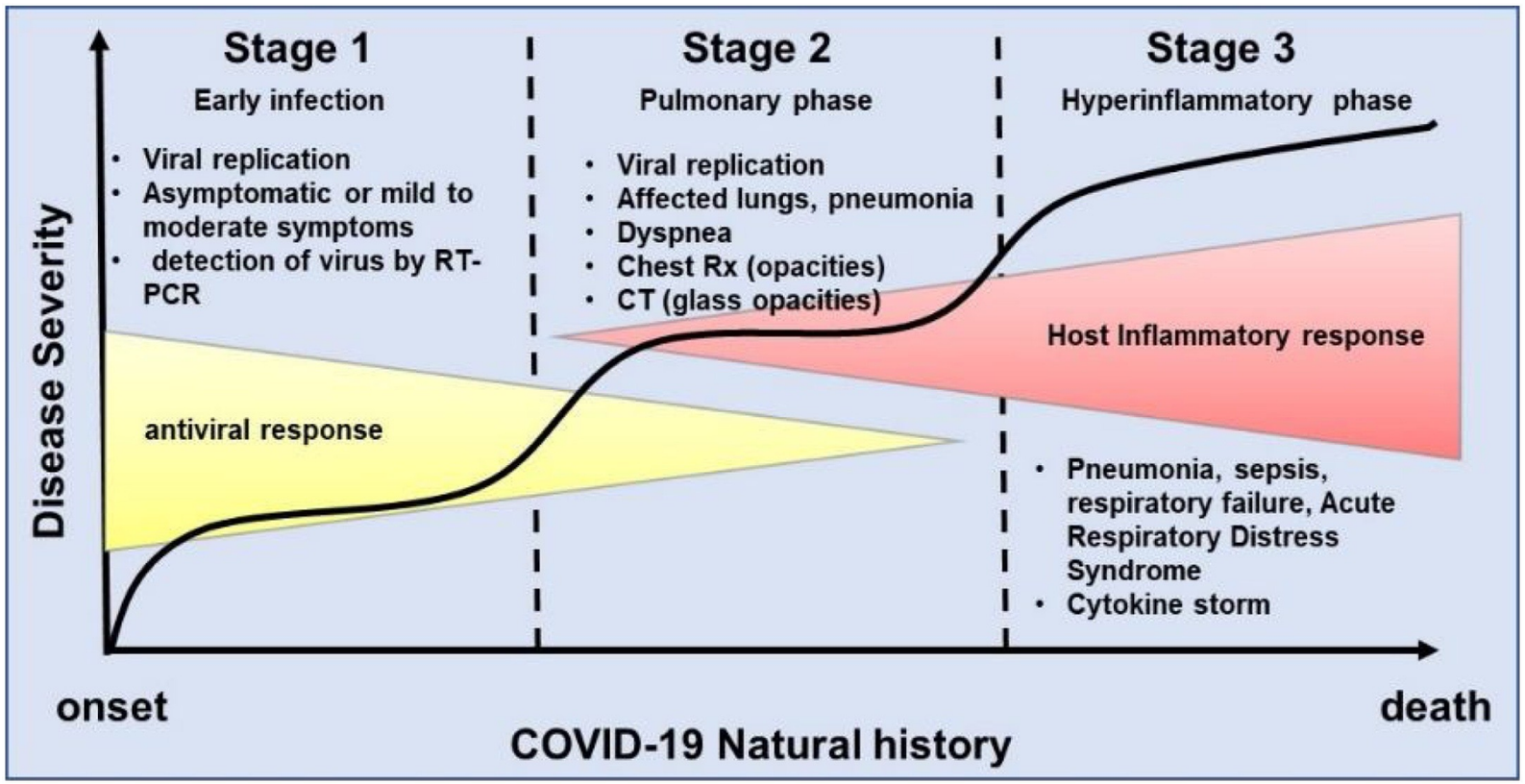
The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis

	RR	MD	95% CI	P value
Mortality	1.75		1.30 - 2.46	P= 0.0002
	Mortality higher with corticosteroids			
MV Days		0.8	-1.22 - 2.84	P= 0.44
	No significant effect on mechanical ventilation days			
ICU LOS		2.14	1.17 – 3.10	P< 0.0001
	ICU LOS longer with corticosteroids			
Secondary Infection	1.98		1.04 - 3.78	P=0.04
	Secondary infection rate higher with corticosteroids			

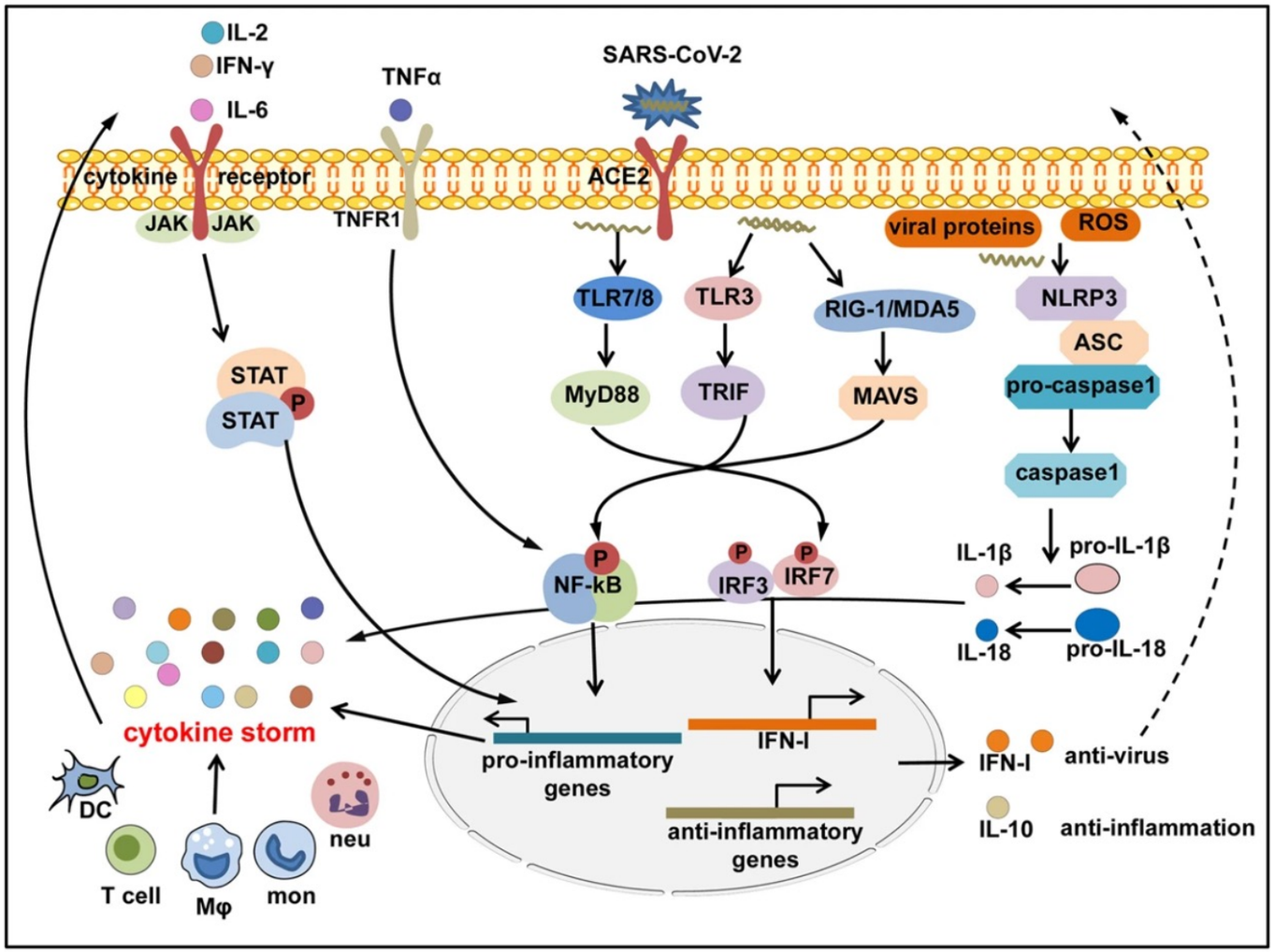
10 Trials
6548 Patients
MD=Mean Difference

Ni, Y., Chen, G., Sun, J. *et al. Crit Care* **23,** 99 (2019). https://doi.org/10.1186/s13054-019-2395-8

Covid – 19 Clinical Patterns and Treatment Targets



Dos Santos WG. Natural history of COVID-19 and current knowledge on treatment therapeutic options. Biomed Pharmacother. 2020 Sep;129:110493.



Yang, L., Xie, *et al.* The signal pathways and treatment of cytokine storm in COVID-19. *Sig Transduct Target Ther* **6,** 255 (2021).

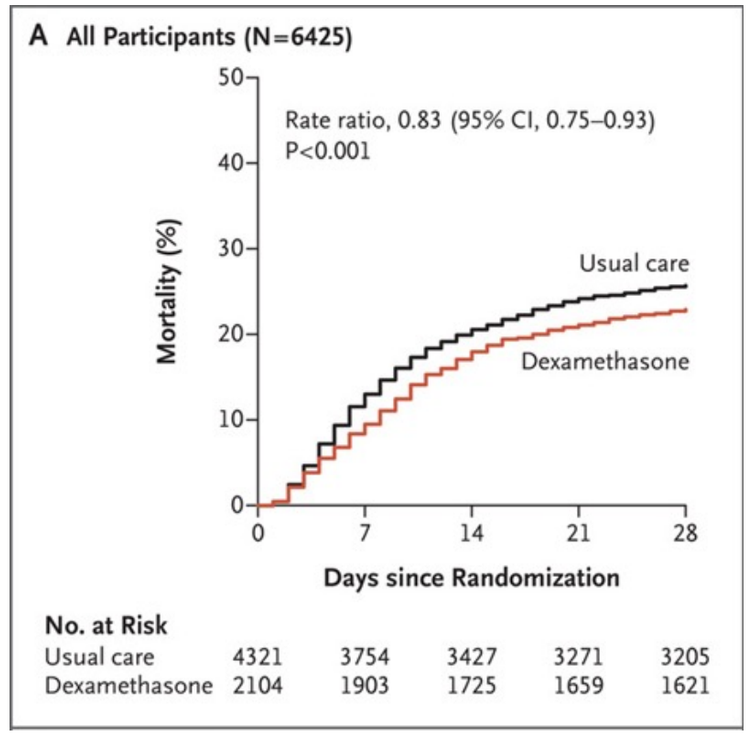
ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

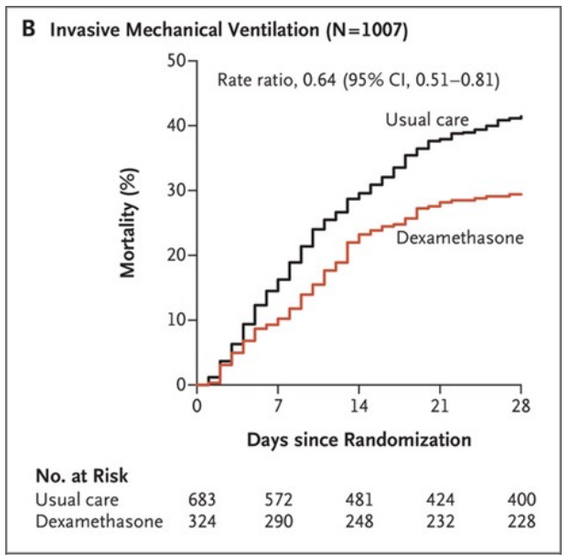
- Randomized – Open label trial
- Low dose dexamethasone 6mg for 10 days
- Hospitalized patients
- Primary Endpoint – Mortality at 28 days
- Patients enrolled
  - Dexamethasone n=2104
  - Usual care N=4321

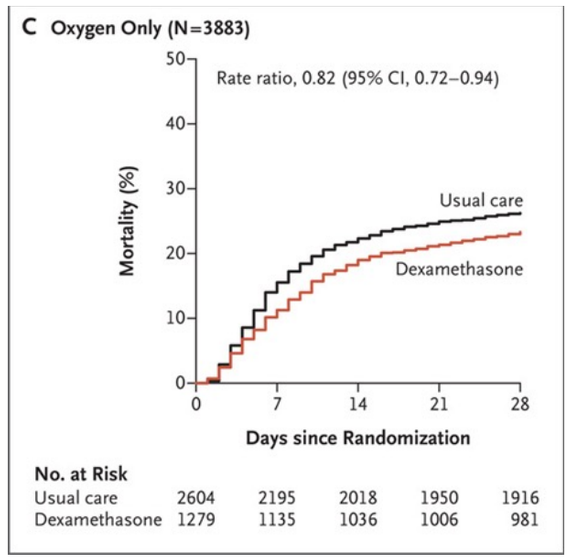
New England Journal of Medicine. doi:10.1056/NEJMoa2021436

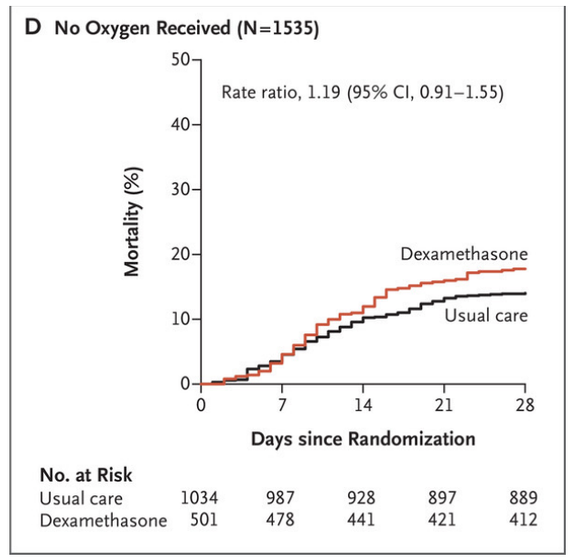


Mortality at 28 Days in All Patients

Mortality at 28 Days According to Respiratory Support at Randomization







The RECOVERY Collaborative Group. N Engl J Med 2020. DOI: 10.1056/NEJMoa2021436

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19
A Meta-analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

- Prospective meta-analysis; 7 randomized trials
- 1703 Patients total
  - 678 Corticosteroids
  - 1025 Usual Care
- Endpoint
  - 28 Day all cause mortality

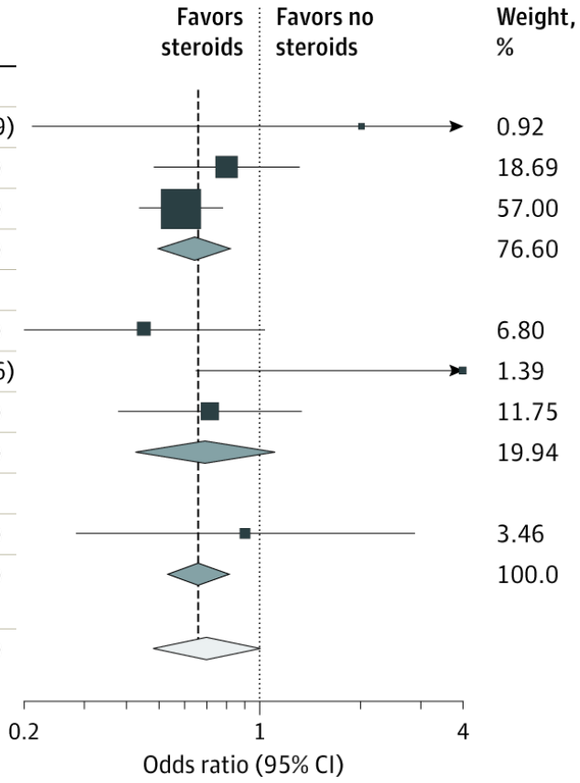
Table 1. Characteristics of Included Trials

	DEXA-COVID 19	CoDEX	RECOVERY	CAPE COVID	COVID STEROID	REMAP-CAP	Steroids-SARI[a]
ClinicalTrials.gov identifier	NCT04325061	NCT04327401	NCT04381936	NCT02517489	NCT04348305	NCT02735707	NCT04244591
Planned sample size	200	350	NA	290	1000	NA[b]	80
Eligibility criteria	• Intubation • Mechanical ventilation • Moderate to severe ARDS per Berlin criteria[9] • Confirmed COVID-19	• Intubation • Mechanical ventilation • Moderate to severe ARDS per Berlin criteria[9] • Onset of ARDS <48 h before randomization • Probable or confirmed COVID-19	Criteria[c] used for this meta-analysis: Intubation Suspected or confirmed COVID-19	• Minimal severity • Admitted to ICU or intermediate care unit • Oxygen (≥6 L/min) • Probable or confirmed COVID-19	• Oxygen (≥10 L/min) • Confirmed COVID-19	• Admitted to ICU receiving high-flow nasal oxygen with Fio_2 ≥0.4 at ≥30 L/min, noninvasive or invasive ventilatory support, or receiving vasopressors • Probable or confirmed COVID-19	• Admitted to ICU with Pao_2:Fio_2 <200 mm Hg on positive pressure ventilation (invasive or noninvasive) or high-flow nasal canulae >45 L/min • Confirmed COVID-19
Corticosteroid							
Drug name	Dexamethasone	Dexamethasone	Dexamethasone	Hydrocortisone	Hydrocortisone	Hydrocortisone	Methylprednisolone

JAMA. 2020;324(13):1330-1341. doi:10.1001/jama.2020.17023

Mortality

Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of deaths/total No. of patients: Steroids	No. of deaths/total No. of patients: No steroids	Odds ratio (95% CI)	Weight, %
Dexamethasone						
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)	0.92
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)	18.69
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)	57.00
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)	76.60
Hydrocortisone						
CAPE COVID	NCT02517489	Low: 200 mg/d intravenously	11/75	20/73	0.46 (0.20-1.04)	6.80
COVID STEROID	NCT04348305	Low: 200 mg/d intravenously	6/15	2/14	4.00 (0.65-24.66)	1.39
REMAP-CAP	NCT02735707	Low: 50 mg every 6 h intravenously	26/105	29/92	0.71 (0.38-1.33)	11.75
Subgroup fixed effect			43/195	51/179	0.69 (0.43-1.12)	19.94
Methylprednisolone						
Steroids-SARI	NCT04244591	High: 40 mg every 12 h intravenously	13/24	13/23	0.91 (0.29-2.87)	3.46
Overall (fixed effect) $P = .31$ for heterogeneity; $I^2 = 15.6\%$			222/678	425/1025	0.66 (0.53-0.82)	100.0
Overall (random effects[a])			222/678	425/1025	0.70 (0.48-1.01)	



JAMA. 2020;324(13):1330-1341. doi:10.1001/jama.2020.17023

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Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19
A Meta-analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

- 28 Day mortality lower in patients randomized to steroids
- Class effect
  - No difference between Dexamethasone and Hydrocortisone
- No signal that higher dose is better
  - Estimates imprecise
- Benefit whether on MV or not

ORIGINAL ARTICLE

Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia

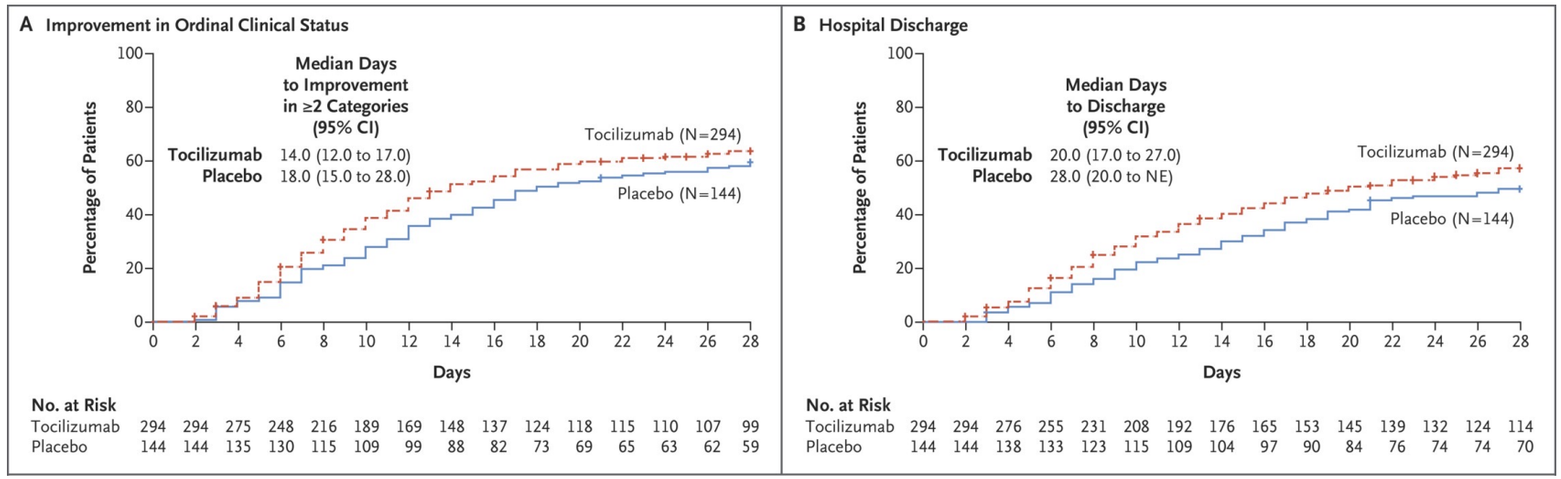
I.O. Rosas, N. Bräu, M. Waters, R.C. Go, B.D. Hunter, S. Bhagani, D. Skiest, M.S. Aziz, N. Cooper, I.S. Douglas, S. Savic, T. Youngstein, L. Del Sorbo, A. Cubillo Gracian, D.J. De La Zerda, A. Ustianowski, M. Bao, S. Dimonaco, E. Graham, B. Matharu, H. Spotswood, L. Tsai, and A. Malhotra

- IL- 6 Receptor Antibody
- Phase 3
- Randomized, Placebo Controlled
- International - 62 hospitals in 9 countries
- 452 Patients
- SpO2 <=93% or P/F <300
- Primary outcome – Improvement in 7 point ordinal scale at Day 28.

COVACTA – Primary and Secondary Outcomes

Table 2. Primary and Secondary Efficacy Outcomes.*

Outcome	Tocilizumab (N=294)	Placebo (N=144)	Difference or Hazard Ratio (95% CI)	P Value
Primary outcome				
Median value for clinical status on 7-category ordinal scale at day 28 (95% CI)	1.0 (1.0 to 1.0)	2.0 (1.0 to 4.0)	−1.0 (−2.5 to 0.0)	0.31†
Secondary outcomes				
Median value for clinical status at day 14 on 7-category ordinal scale (95% CI)‡	3.0 (2.0 to 4.0)	4.0 (3.0 to 5.0)	−1.0 (−2.0 to 0.5)	
Death at day 28 — no. (%)	58 (19.7)	28 (19.4)	0.3 (−7.6 to 8.2)§	0.94
Median no. of days until hospital discharge or readiness for discharge (95% CI)	20.0 (17.0 to 27.0)	28.0 (20.0 to NE)	1.35 (1.02 to 1.79)¶	



Rosas IO et al. N Engl J Med 2021;384:1503-1516

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 22, 2021 VOL. 384 NO. 16

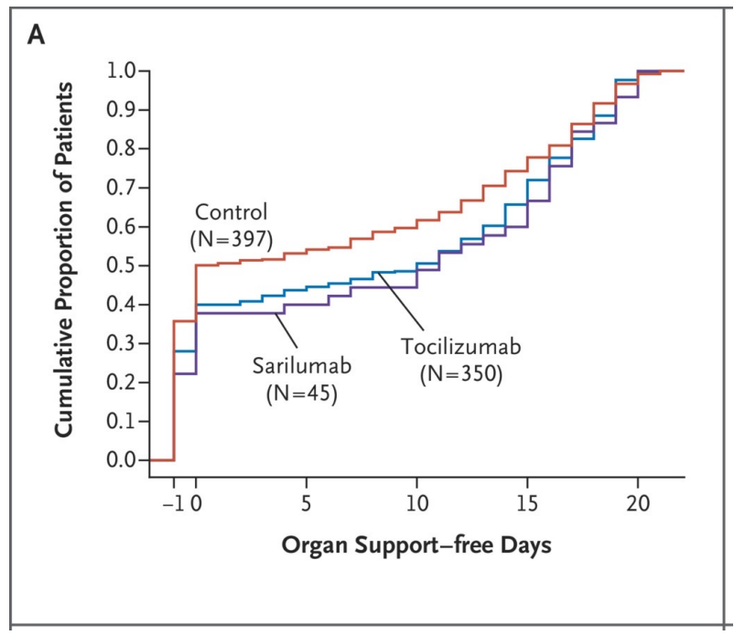
Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19

The REMAP-CAP Investigators*

- Tocilizumab or sarilumab versus standard care
- IL-6 Receptor Antibody
- International, multifactorial, adaptive platform trial
- Open label
- 803 Patients
- Enrollment within 24 hours of organ support (respiratory or cardiovascular)
- Primary outcome - Respiratory and cardiovascular organ support–free days
- Bayesian Statistical Model

Organ Support Free Days

	Tocilizumab	Sarilumab	Control
	N=353	N=48	N=402
Primary Outcome			
Median (IQR)	10 (-1-5)	11 (0 to 16)	0 (-1 to 15)
Adjusted odds ratio			
Mean	1.65+0.23	1.83+0.44	1
Median (95% credible interval)	1.64 (1.25 to 2.14)	1.76 (1.17-2.91)	1
Probability of superiority to control	>99.9%	99.5	

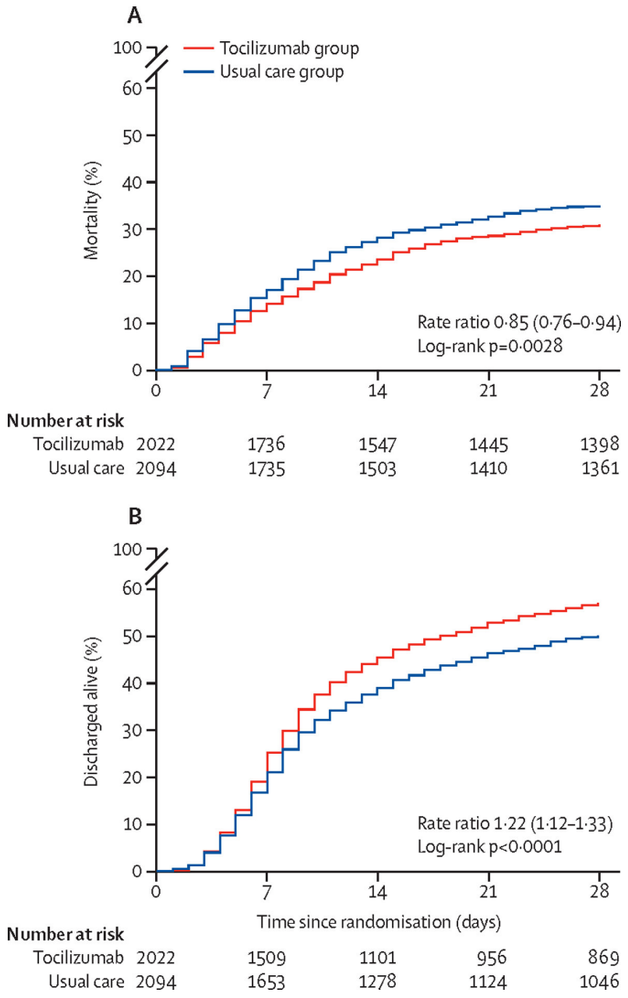


The REMAP-CAP Investigators. N Engl J Med 2021;384:1491-1502

Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

RECOVERY Collaborative Group*

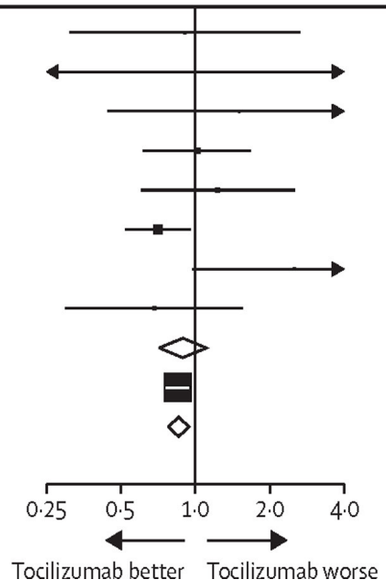
- Randomized, controlled, open label platform trial.
- SpO2<92% or on O2 with CRP>75mg/L
- 4116 patients
- Primary outcome – All cause mortality 28 days
- Secondary outcome –
  - Time to hospital discharge
  - Initiation of invasive mechanical ventilation



The Lancet 2021 3971637-1645DOI: (10.1016/S0140-6736(21)00676-0)

Meta-analysis of Mortality in Randomized Tocilizumab Trials

	Deaths/patients randomly assigned (%)		Observed minus expected deaths*		Ratio of death rates, rate ratio (95% CI)
	Tocilizumab group	Usual care group	(O–E)	Var (O–E)	
CORIMUNO-TOCI[10]	7/64 (11%)	8/67 (12%)	−0·3	3·3	0·91 (0·31–2·65)
RCT-TCZ-COVID-19[11]	2/60 (3%)	1/66 (2%)	0·6	0·7	2·17 (0·22–21·3)
BACC Bay[12]	9/161 (6%)	(3/82) ×2† (4%)	1·0	2·6	1·51 (0·44–5·13)
COVACTA[9]	58/294 (20%)	(28/144) ×2† (19%)	0·3	15·3	1·02 (0·62–1·68)
EMPACTA[13]	26/249 (10%)	(11/128) ×2† (9%)	1·6	7·5	1·23 (0·60–2·52)
REMAP-CAP[15]	98/353 (28%)	142/402 (35%)	−14·2	40·8	0·71 (0·52–0·96)
TOCIBRAS[8]	14/65 (22%)	6/64 (9%)	3·9	4·3	2·51 (0·97–6·50)
COVINTOC[14]	11/91 (12%)	15/89 (17%)	−2·1	5·6	0·68 (0·30–1·56)
Subtotal: eight trials	**225/1337 (17%)**	**256/1396 (18%)**	**−9·3**	**80·1**	**0·89 (0·72–1·11)**
RECOVERY	621/2022 (31%)	729/2094 (35%)	−54·4	330·6	0·85 (0·76–0·94)
All trials	**846/3359 (25%)**	**985/3490 (28%)**	**−63·7**	**410·7**	**0·86 (0·78–0·94)**
					p=0·0017



The Lancet 2021 3971637-1645DOI: (10.1016/S0140-6736(21)00676-0)

IL-6 Receptor Antibody in Covid-19

- Why the difference in COVACTA?
  - Percentage of patients receiving steroids
    - Toci – 19.4%
    - Placebo 28.5%
  - REMAP-CAP – 93%
  - RECOVERY - 82%

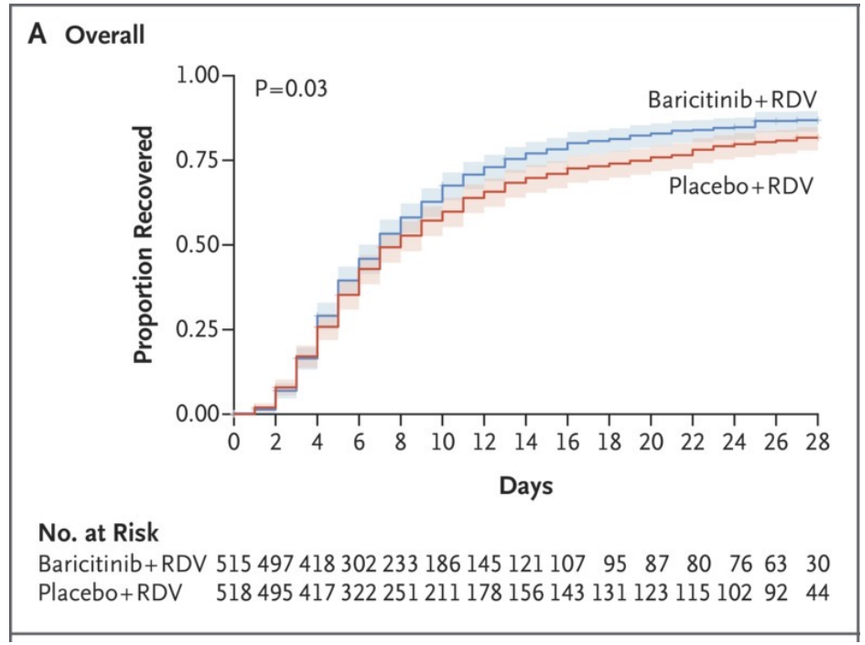
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 4, 2021 VOL. 384 NO. 9

Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19

ACTT-2 Adaptive Covid-19 Treatment Trial

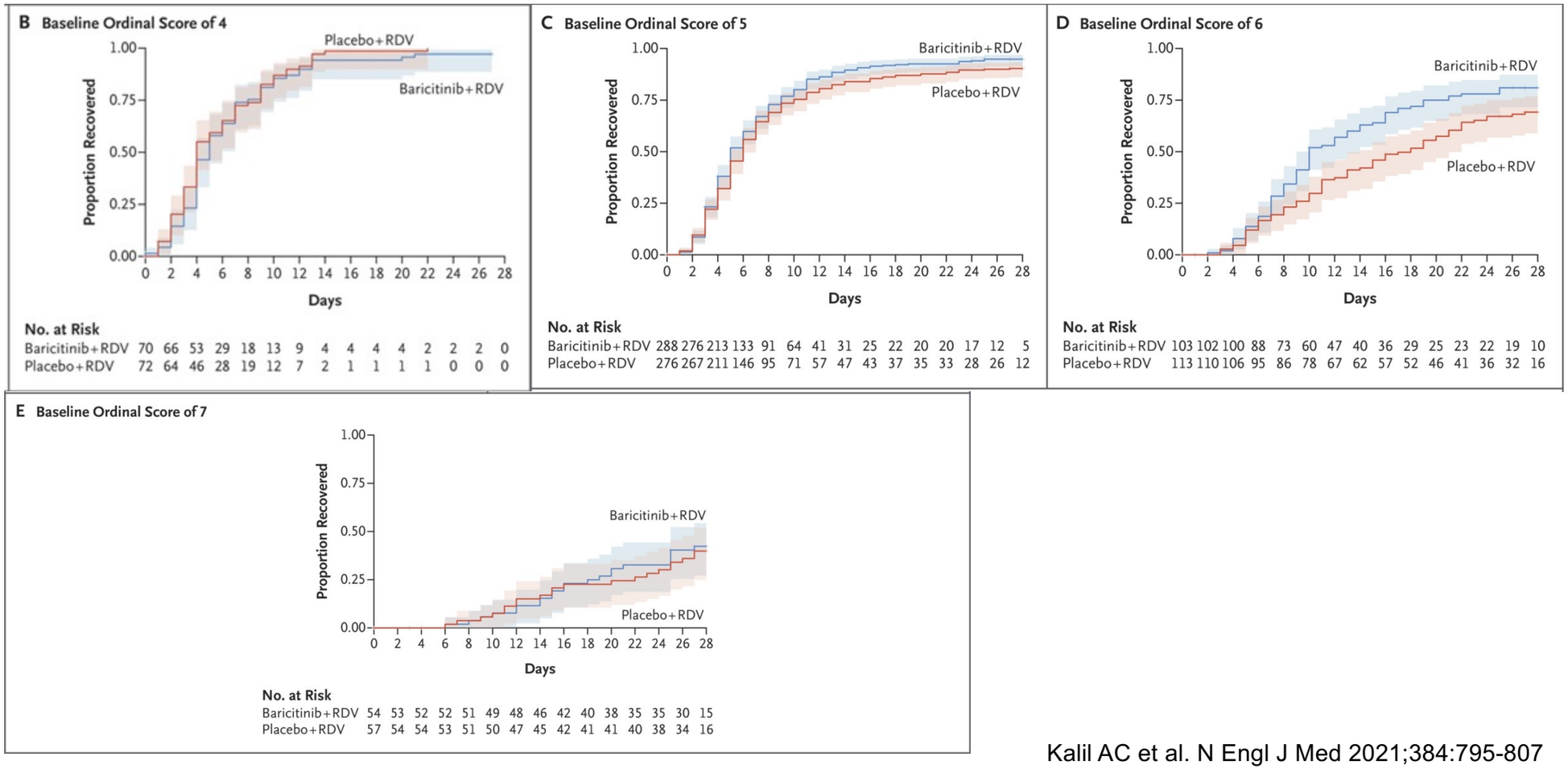
- Janus kinase inhibitor
- Double blind, randomized, control
- Remdesivir plus baricitinib vs. remdesivir plus placebo
- 1033 patients
- 67 Sites; 8 countries
- Primary Outcome: Time to Recovery
- Glucocorticoids for standard indications only



Median time to recovery:
Bariticinib: 7 days (95% confidence interval [CI], 6 to 8)
Control: 8 days (95% CI, 7 to 9)
Rate ratio for recovery, 1.16; 95% CI, 1.01 to 1.32; P = 0.03),

Kalil AC et al. N Engl J Med 2021;384:795-807

Cumulative Recovery Based on Ordinal Score at Study Entry



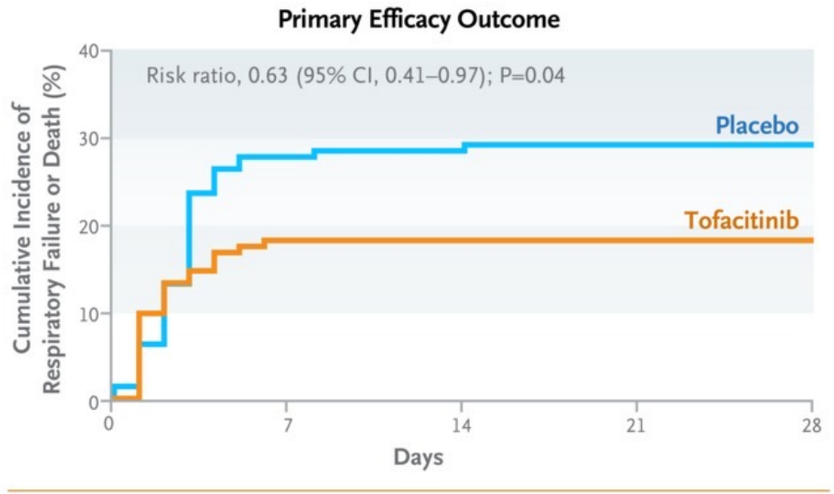
Kalil AC et al. N Engl J Med 2021;384:795-807

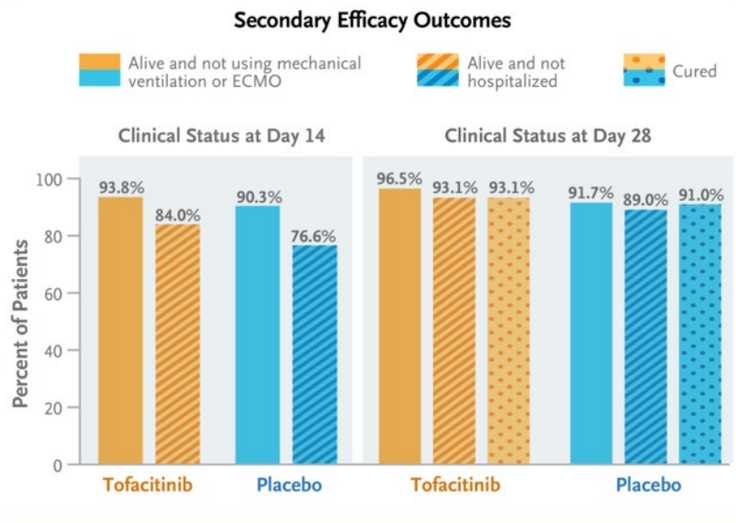
Tofacitinib in Patients Hospitalized with Covid-19 Pneumonia

Patrícia O. Guimarães, M.D., Ph.D., Daniel Quirk, M.D., M.P.H.,

STOP-COVID Trial Investigators

- Janus Kinase Inhibitor
- Randomized, double blind, placebo
- 289 Patients
  - Excludes noninvasive or invasive ventilation
- 15 Sites, Brazil
- Primary Outcome: Incidence of death or respiratory failure
- 89.3% Glucocorticoids





Guimarães PO et al. N Engl J Med 2021;385:406-415

Immunomodulatory therapy

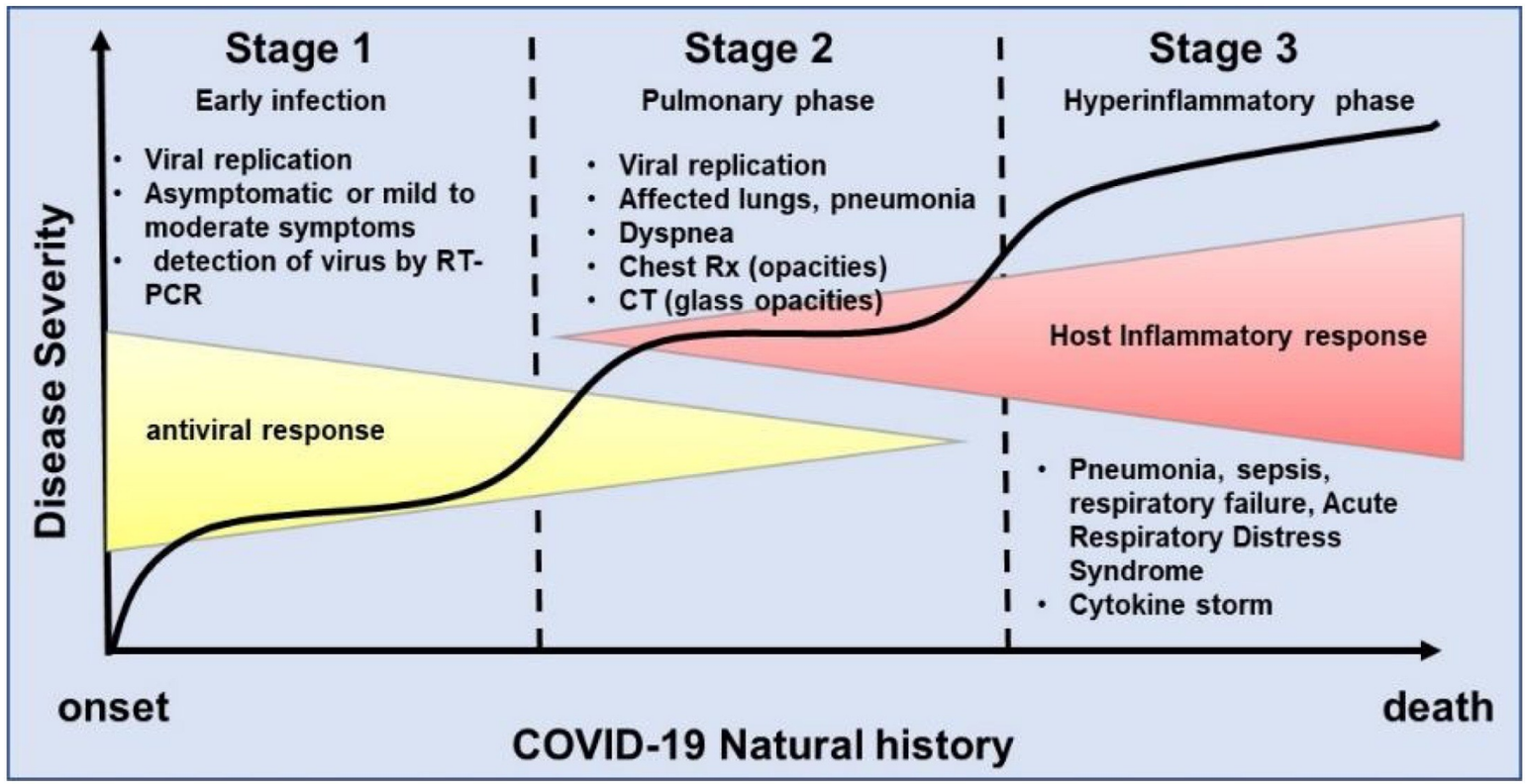
- Corticosteroids
  - Use for patients with supplemental O2, HFNC, NIV, IMV - RECOVERY
- IL-6 Receptor Antibodies
  - Use for HFN, NIV, IMV
  - Use early (within 24 hours) –REMAP-CAP
  - Use with steroids – REMAP-CAP, RECOVERY
  - Contraindications
    - Concomitant uncontrolled fungal or bacterial infection
    - ANC <500
    - Risk of GI perforation
    - Elevated LFTs
- Janus Kinase Inhibitors
  - Hospitalized patients – O2, HFNC, NIV -Benefit if steroids cannot be used.
  - Use with steroids
- Unclear IL-6 RA vs. JAK Inhibition
- Unclear benefit of using both together

Take Home

- Significant knowledge gained since 12/2019
- Maintain SpO2 92-96%
- Intervene on excessive work of breathing
- HFNC may reduce need for mechanical ventilation
  - More research needed on actual MV reduction and impact on mortality
- Noninvasive ventilation in select clinical conditions
- Key lessons regarding mechanical ventilation of Non Covid -ARDS apply
  - Low tidal volume
  - Prone Ventilation
  - NMB
- Pharmacologic and biologic interventions should be informed by the clinical phase of Covid-19 Illness
- Immunomodulatory Therapy for hospitalized patients on supplemental oxygen or ventilation reduces mortality
  - Steroids
  - IL-6 receptor antagonists or JAK inhibitors may be additive
  - More research needed

Appendix

Covid – 19 Clinical Patterns and Treatment Targets



Dos Santos WG. Natural history of COVID-19 and current knowledge on treatment therapeutic options. Biomed Pharmacother. 2020 Sep;129:110493.

Different Respiratory Strategies ?

- Type L patients
  - An early intubation may avert the transition to Type H phenotype
  - If hypercapnic, ventilate with tidal volumes greater than 6 ml/kg (up to 8–9 ml/kg)
  - The PEEP should be reduced to 8–10 cmH2O
    - recruitability is low and minimize hemodynamic consequences
  - Prone positioning should be used only as a rescue maneuver

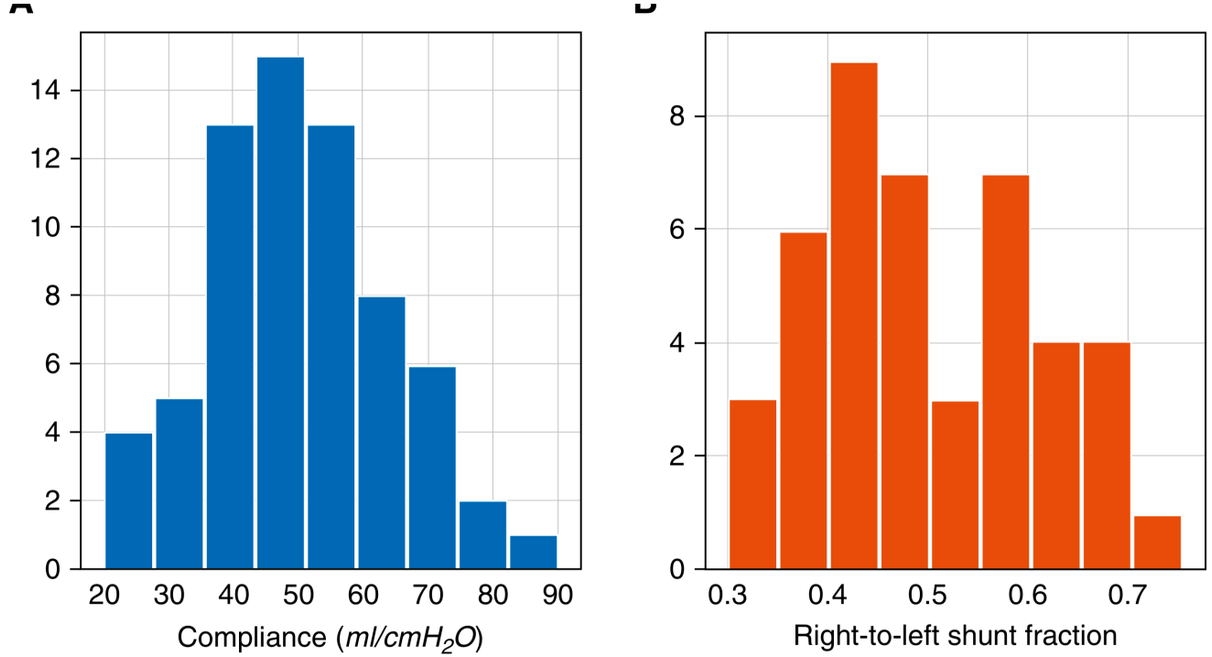
Gattinoni, L. *et al.* COVID-19 pneumonia: different respiratory treatments for different phenotypes?. *Intensive Care Med* (2020). https://doi.org/10.1007/s00134-020-06033-2

Ventilator Management in Covid-19 ARDS (CARDS) 9?

COVID-19 Does Not Lead to a “Typical” Acute Respiratory Distress Syndrome

16 Patients

Compliance 50.2 + 1.6 ml/ cm H20
Shunt fraction 0.50+ 0.11



Gattinoni, L. et al.. COVID-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome. *AJRCCM, 201*(10), 1299-1300.