

Best Practices for the Management of Severe COVID-19 Pneumonia

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- Clinical focus: Critical care
- Research focus: Quantitative imaging

Disclosures

- Related to this presentation:
 - None
- Other:
 - Quantitative Imaging Solutions – owner/equity
 - Vertex Pharmaceuticals – consulting

Objectives

- Brief review of the key aspects of critical care for patients with severe COVID-19 pneumonia:
 - That is the same as other patients with similar illnesses
 - That is different from other patients with similar illnesses
- Review COVID-19 pneumonia specific therapies

Outline

- General principles
- Background
- Respiratory Failure
- Thrombosis
- COVID Specific Therapy
- Summary
- References

General Principles



General Principles

- The key tenets of the care of patients with severe COVID-19 pneumonia are the same as those for the care of all patients with severe respiratory illnesses
- Carefully consider study design, analysis and context prior to modifying standards of care
- Ongoing developments in COVID specific therapies continue to refine guidelines and improve outcomes

General Principles

- While the role of COVID specific therapy is increasing, a patient's COVID status does not change the management of their:
 - Sepsis
 - Shock
 - Acute kidney injury
 - Gastrointestinal bleed
 - Stroke
 - Hyperglycemia/DKA
 - Acute coronary syndrome
 - Myocarditis
 - And others...



Background

Image: https://www.who.int/health-topics/coronavirus#tab=tab_1

Background

Disease Severity Categories

Severity Category	Description
Asymptomatic or presymptomatic	Individuals who test positive for SARS-CoV-2 using a virologic test but have no symptoms consistent with COVID-19
Mild illness	Individuals who have any of the various signs and symptoms of COVID-19 but do not have shortness of breath, dyspnea, or abnormal chest imaging
Moderate illness	Individuals who have SpO ₂ <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO ₂ /FiO ₂) <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%
Severe illness	Individuals who have SpO ₂ <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO ₂ /FiO ₂) <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%
Critical illness	Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction

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Background

Disease Severity Categories

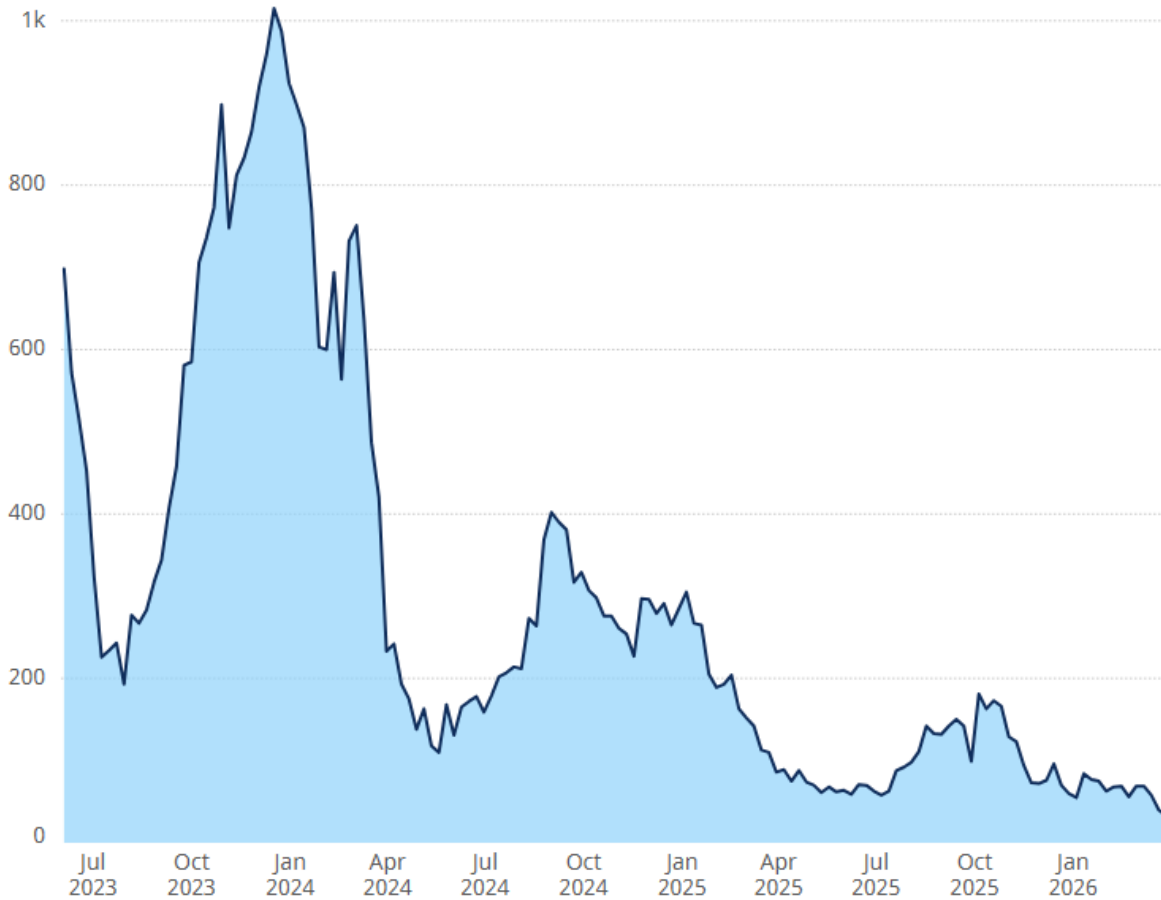
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Background

ICU Admission

New ICU admissions reported to WHO (weekly)

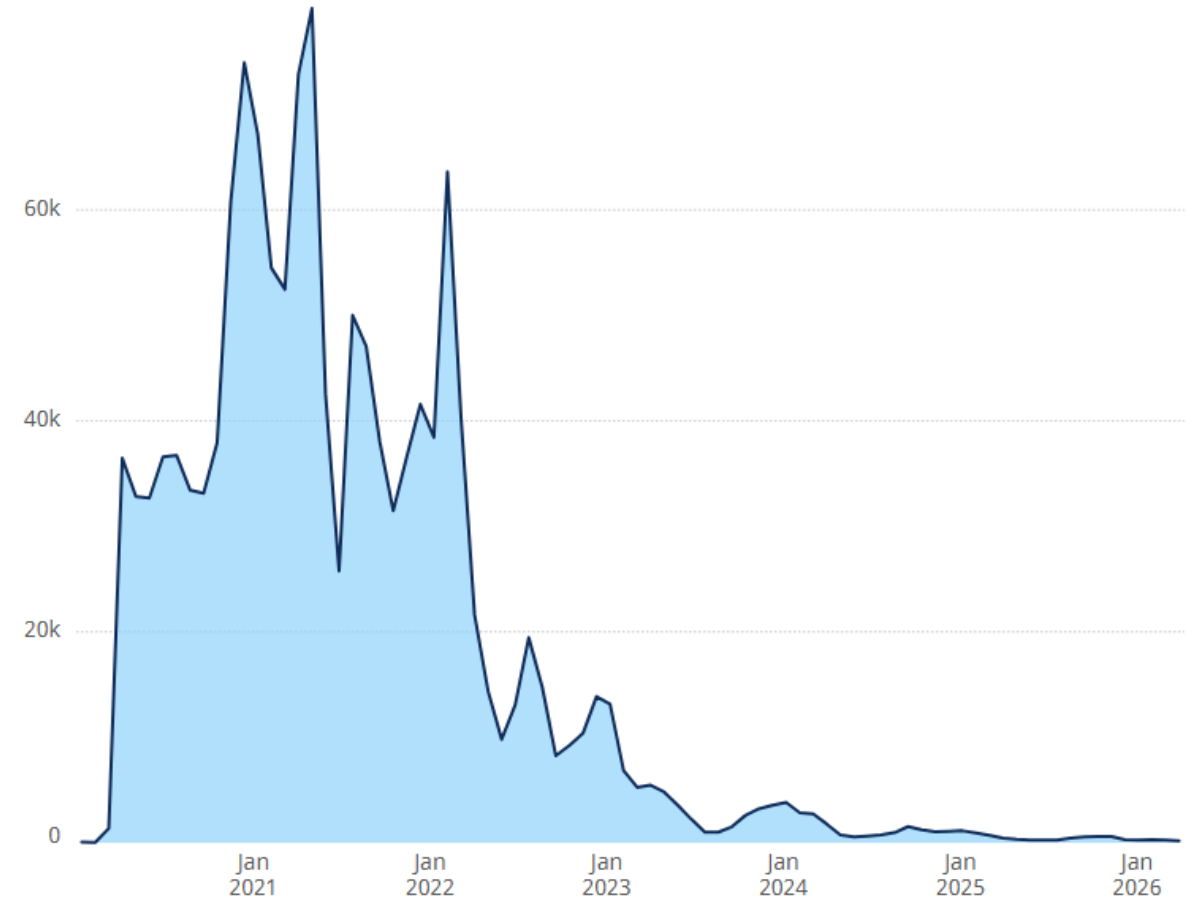
World, July 2023 - present



Source: World Health Organization

New ICU admissions reported to WHO (28 days)

World, January 2020 - present



Source: World Health Organization

<https://data.who.int/dashboards/covid19/hospitalizations>

Background

Causes of Death

2020

- Respiratory failure alone, 53%
- Circulatory failure alone, 7%
- Mixed respiratory and circulatory failure, 33%
- Unknown cause, 7%

Yang, Lancet Repir Med, 2020
Arentz, JAMA, 2020
Phua, Lancet Respir Med, 2020
Wu, JAMA, 2020
Cummings, Lancet, 2020
Ruan, Intensive Care Med, 2020
Butt, Int J Inf Dis, 2023

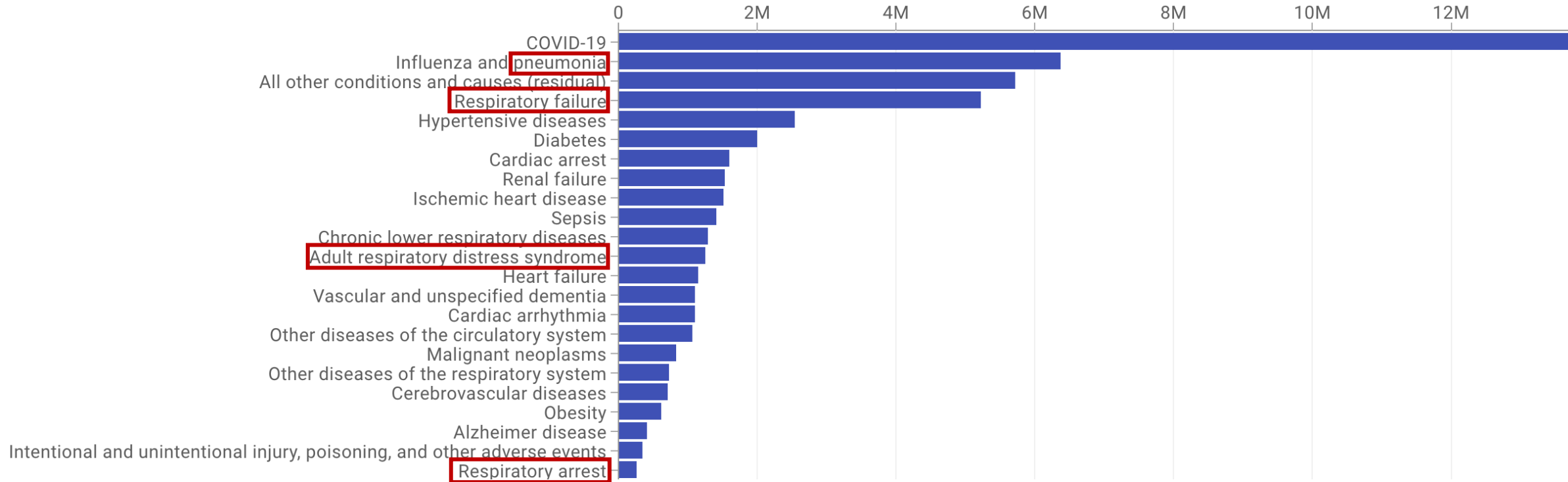
2023

Table 3. Cause of death, by location.

	ICU deaths n=648		Non-ICU deaths n=101	
	N	%	N	%
COVID-19 pneumonia	426	65.7%	70	69.3%
Major adverse cardiac event	45	6.9%	8	7.9%
Hospital-associated pneumonia	44	6.8%	7	6.9%
Bacteremia	42	6.5%	5	5.0%
Disseminated fungal infection	37	5.7%	2	2.0%
Thromboembolism	31	4.8%	3	3.0%
Acute ischemia or bleeding	11	1.7%	0	0.0%
Metastatic cancer	6	0.9%	2	2.0%
No consensus	4	0.6%	5	5.0%
Trauma	2	0.3%	0	0.0%

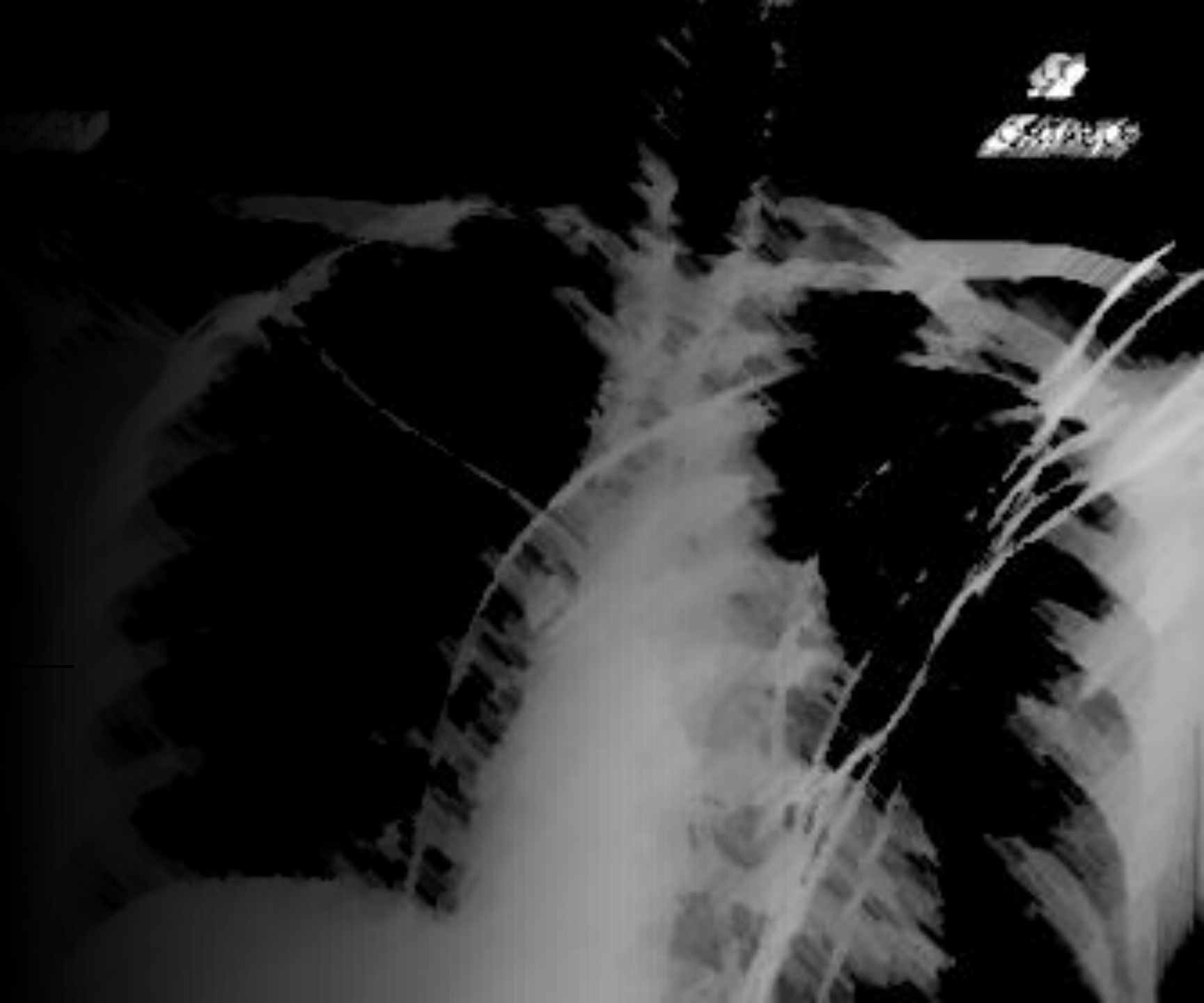
Background

Causes of Death





Respiratory Failure



Respiratory Failure

Pre-intubation

- Primary challenges:
 - Hypoxemia
 - Infection control/prevention
 - Goals of care
- Oxygen delivery options:
 - Nasal cannula
 - Oxymizer
 - Venturi mask
 - Non-rebreather mask
 - High flow nasal cannula
 - Non-invasive positive pressure ventilation (CPAP/BiPAP)



Respiratory Failure

Pre-intubation

Nonmechanically Ventilated Adults With Acute Hypoxemic Respiratory Failure

High-Flow Nasal Cannula Oxygen and Noninvasive Ventilation

Recommendations

- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends starting therapy with HFNC oxygen; if patients fail to respond, NIV or intubation and mechanical ventilation should be initiated ([BIIa](#)).
- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy who do not have an indication for endotracheal intubation and for whom HFNC oxygen is not available, the Panel recommends performing a closely monitored trial of NIV ([BIIa](#)).

Respiratory Failure

High flow nasal cannula (HFNC)

- Should be used as in non-COVID-19 patients — same indications apply
 - Acute hypoxemic respiratory failure
 - Immunocompromised
 - Need for inhaled pulmonary vasodilator
- RCT evidence supports reduction in intubation rate vs. conventional oxygen; HFNC preferred first-line over standard oxygen in moderate-severe COVID AHRF

Respiratory Failure

High flow nasal cannula (HFNC)

JAMA

QUESTION In patients with respiratory failure due to COVID-19, does the use of high-flow nasal cannula oxygen reduce the risk of mortality compared with standard oxygen therapy?

CONCLUSION This randomized clinical trial found that high-flow nasal cannula oxygen did not significantly reduce mortality at day 28 compared with standard oxygen therapy among patients with respiratory failure due to COVID-19.

POPULATION

497 Men
214 Women



Adults with respiratory failure due to COVID-19

Mean age: **61** years

LOCATIONS

34 ICUs
in France



INTERVENTION



782 Patients randomized
711 Patients analyzed

357

High-flow oxygen

Oxygen continuously delivered via large bore binasal prongs with gas flow of ≥ 50 L/min



354

Standard oxygen

Oxygen continuously delivered through a nonrebreathing mask, with oxygen flow set at ≥ 10 L/min

PRIMARY OUTCOMES

Proportion of patients who died within 28 days following randomization

FINDINGS

Mortality rate at day 28

High-flow oxygen
36 of 357 patients



Standard oxygen
40 of 354 patients



The results were not significant:

Absolute difference, **-1.2%**
(95% CI, -5.8% to 3.4%); $P = .60$

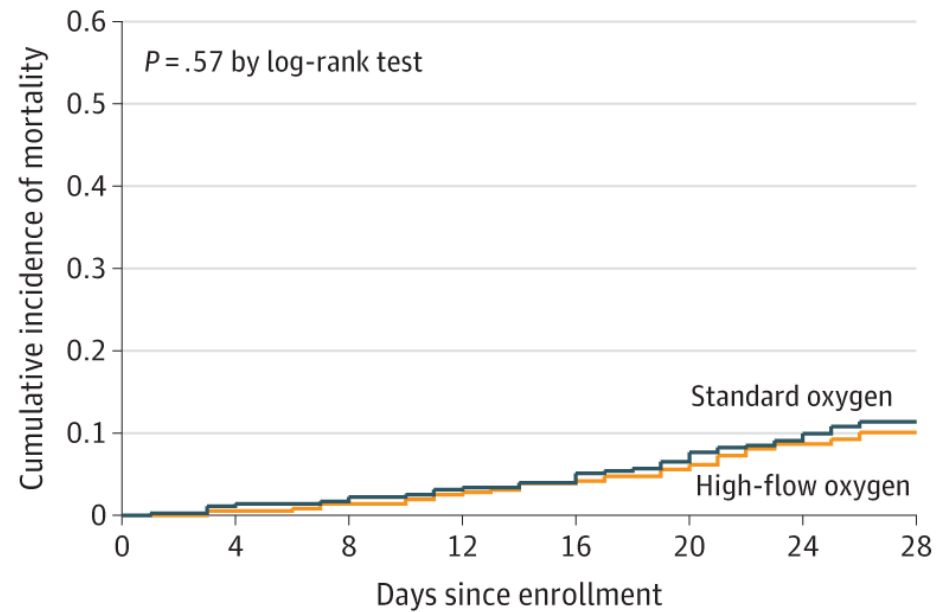
© AMA

Frat JP, Quenot JP, Badie J, et al; SOHO-COVID Study Group; REVA Network. Effect of high-flow nasal cannula oxygen vs standard oxygen therapy on mortality in patients with respiratory failure due to COVID-19: the SOHO-COVID randomized clinical trial. *JAMA*. Published September 27, 2022. doi:10.1001/jama.2022.15613

Respiratory Failure

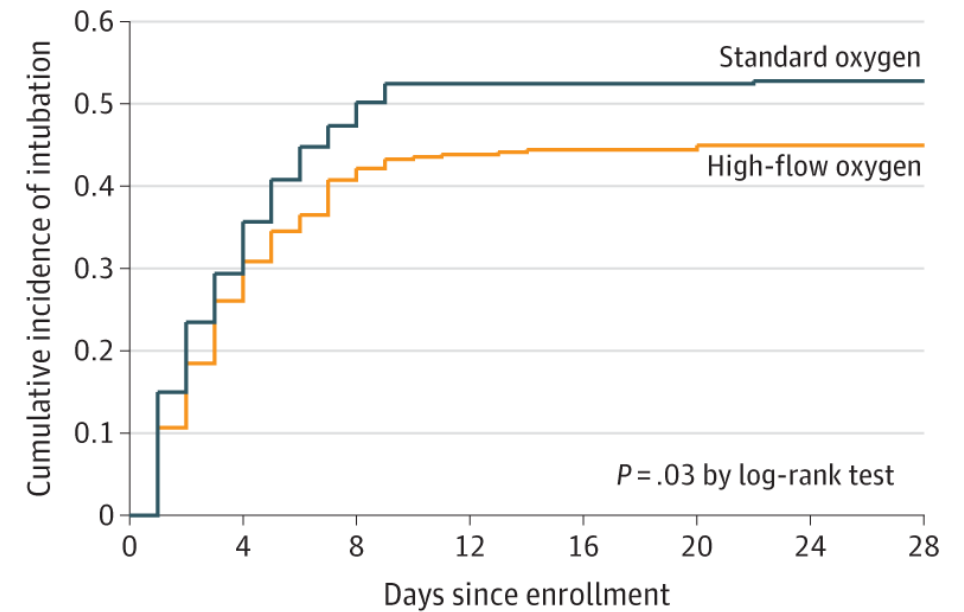
High flow nasal cannula (HFNC)

A Cumulative incidence of mortality (primary outcome)



No. at risk								
High-flow oxygen	357	355	352	348	343	337	326	321
Standard oxygen	354	349	347	342	337	328	319	311

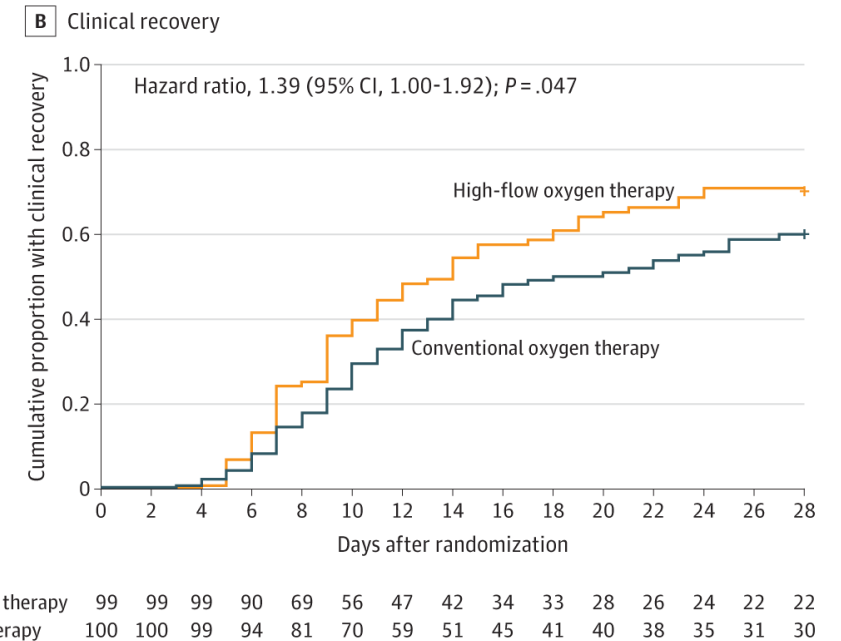
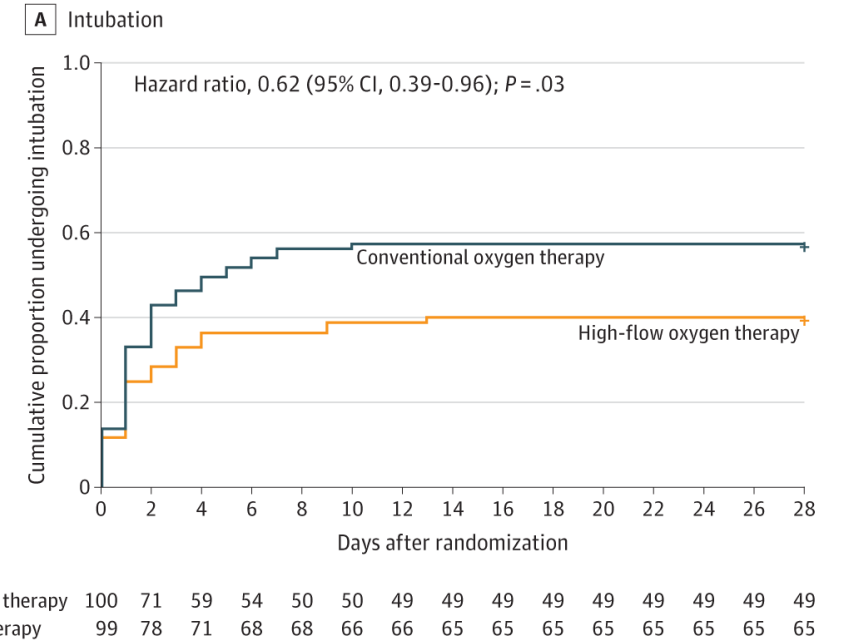
B Cumulative incidence of intubation (secondary outcome)



No. at risk								
High-flow oxygen	357	262	210	199	197	195	193	193
Standard oxygen	354	248	185	165	164	164	163	163

High flow nasal cannula (HFNC)

- RCT of 220 patients with severe COVID-19
- HFNC vs conventional oxygen therapy
- Reduced rate of intubation and time to clinical recovery



Respiratory Failure

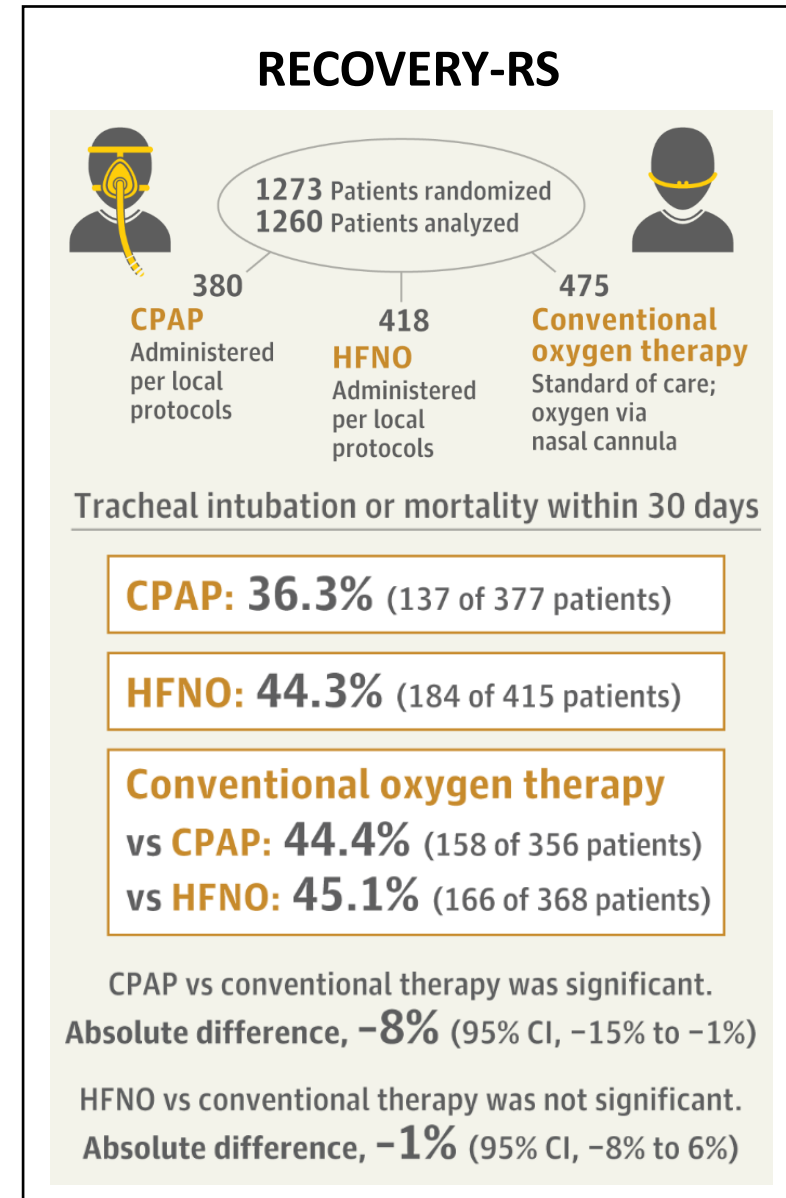
Non-invasive positive pressure

- Should be used for the same indications as COVID-19 negative patients
 - Continuation of home use (e.g., OSA)
 - Acute pulmonary edema
 - COPD exacerbation
- If used
 - It should be considered aerosol generating procedure
 - If possible, use dual limb machine with HEPA filter and mask without anti-asphyxia valve
 - Ensure proper mask fit

Hui, Eur Respir J, 2019

Brusasco, Eur Respir J, 2021

Perkins, JAMA, 2022



Respiratory Failure

Pre-intubation

Self-proning

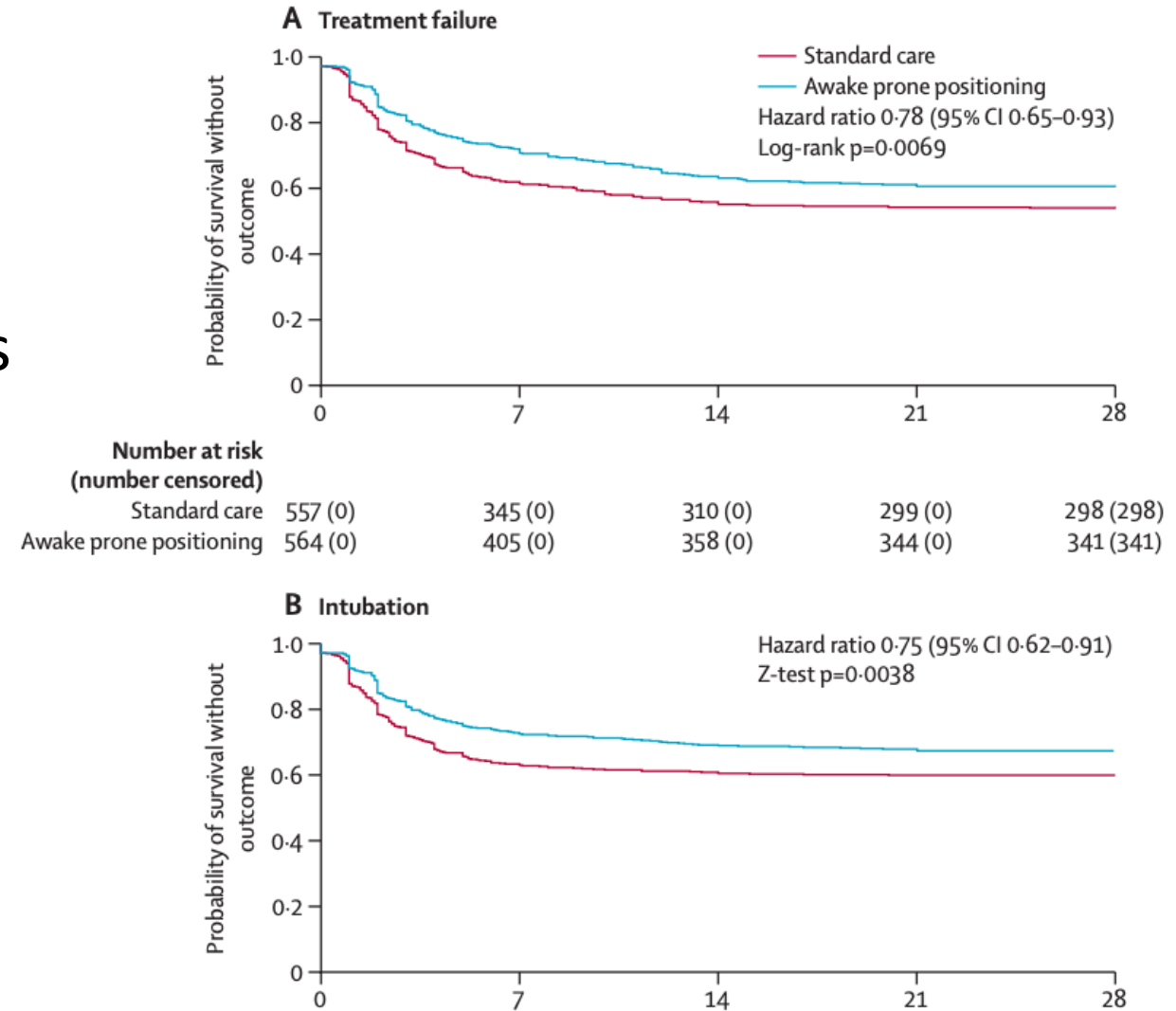
- Improves oxygenation and reduces need for intubation
- Best evidence when combined with HFNC or NIV
- Patient must be able to move independently
- Goal: ≥ 10 hours per 24 hours; greatest benefit when sustained ≥ 3 days

Scaravilli, J of Critical Care, 2015

Ehrmann, Lancet Respir Med, 2021

Qin et al., BMC Pulm Med, 2023 (meta-analysis, 10 RCTs)

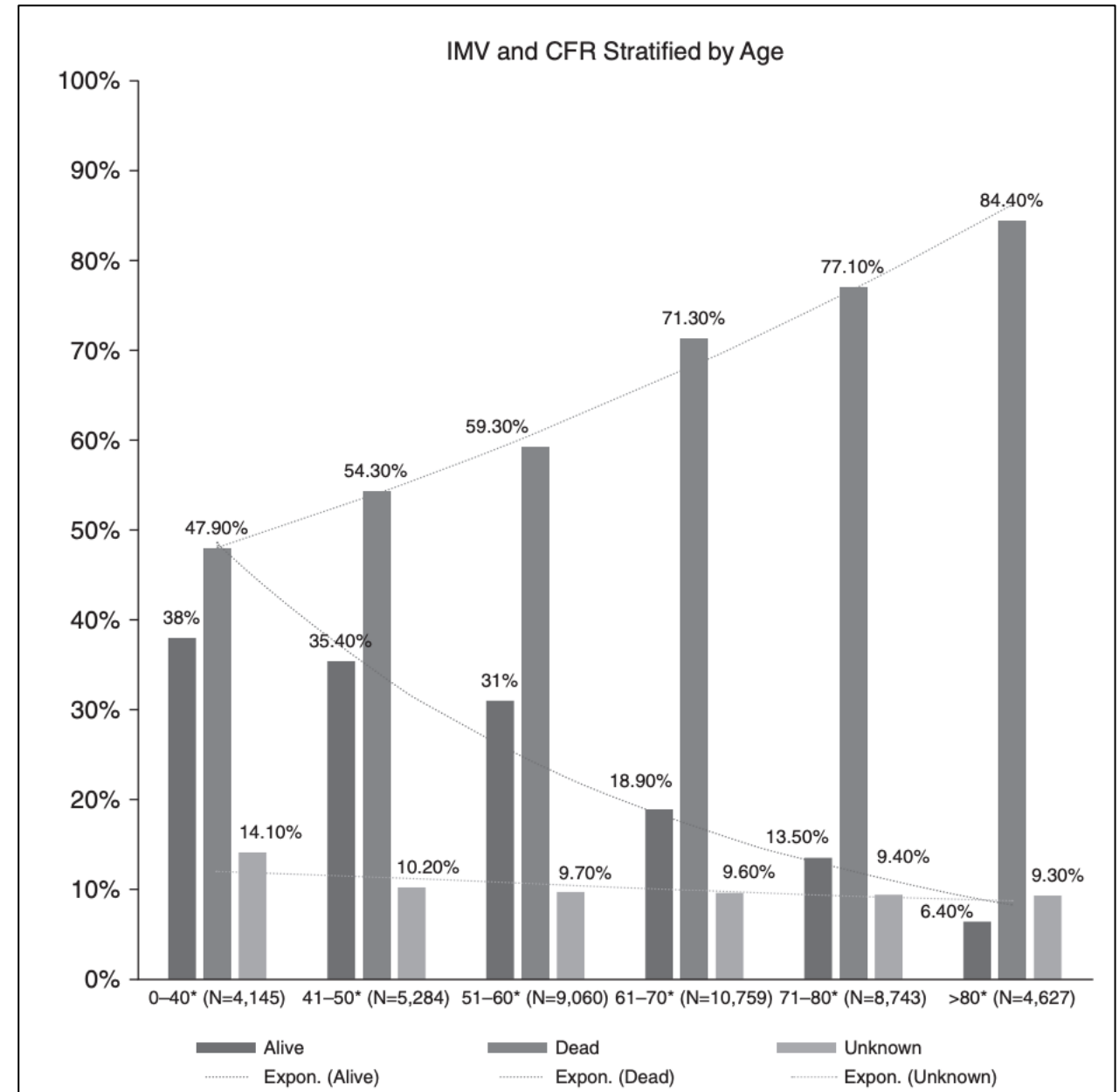
ACP Hospitalist, Mar 2025 (meta-analysis, 14 RCTs)



Respiratory Failure

Intubation

- Preparation
 - Goals of care discussion*
 - Airborne isolation if possible
 - Proper PPE and equipment
- Procedure
 - Limit personnel in room
 - Pre-oxygenation
 - RSI with video-laryngoscopy
 - Connect directly to ventilator



Respiratory Failure

Mechanical Ventilation



Mechanically Ventilated Adults

General Considerations

Recommendations

For mechanically ventilated adults with COVID-19 and ARDS:

- The Panel recommends using low tidal volume (VT) ventilation (VT 4–8 mL/kg of predicted body weight) over higher VT ventilation (VT >8 mL/kg) ([A1](#)).
- The Panel recommends targeting plateau pressures of <30 cm H₂O ([A1a](#)).
- The Panel recommends using a conservative fluid strategy over a liberal fluid strategy ([B1a](#)).
- The Panel **recommends against** the routine use of inhaled nitric oxide ([A1a](#)).

Rationale

There is no evidence that the ventilator management of patients with hypoxemic respiratory failure due to COVID-19 should differ from the ventilator management of patients with hypoxemic respiratory failure due to other causes.

Authors	PMID	Specimen type	No. of cases	Main findings	DAD	Thrombi
Xu et al. [38]	32,085,846	Post-mortem biopsies of lung, liver, and heart	1	DAD	Yes	None mentioned
Tian et al. [39]	32,114,094	Lobectomies	2	DAD and mononuclear inflammatory cells	Yes (early DAD pattern in 1 of 2)	None mentioned
Barton et al. [40]	32,275,742	Complete autopsies	2	DAD and chronic airway inflammation	Yes (1 case)	Few (lung, case 1)
Karami et al. [41]	32,283,217	Autopsy of the lungs	1	Hyaline membranes and viral cytopathic effect	Yes (hyaline membrane noted)	None mentioned
Tian et al. [42]	32,291,399	Post-mortem biopsies of lung, liver, and heart	4	DAD	Yes	None mentioned
Magro et al. [43]	32,299,776	Limited autopsies (2) and skin biopsies (3)	5	"Hemorrhagic pneumonitis" (lung), and "thrombogenic vasculopathy" (skin)	Yes (hyaline membranes in 1 of 2 cases in which lungs were examined)	Yes (skin)
Barnes et al. [44]	32,302,401	Autopsies (brief mention)	3	"Neutrophil extracellular traps"	Not mentioned	None mentioned
Varga et al. [45]	32,325,026	Autopsies (2) and small intestine resection (1)	3	"Endothelitis, DAD, and viral inclusions in the endothelial cells of kidney"	Yes	"Only scattered fibrin thrombi"
Konopka et al. [46]	32,360,729	Autopsy	1	"Fibrinous pneumonia"	Yes	"Rare fibrin thrombi were also identified within small vessels and a small muscular pulmonary artery"
Menter et al. [27]	32,364,264	Autopsy	21	DAD (exudative in 16, proliferative in 8); superimposed bronchopneumonia in 10/21	Yes	Pulmonary embolism in 4/21; microthrombi of alveolar capillaries in 5/11
Wichmann et al. [47]	32,374,815	Complete autopsies	12	DAD (8/12; "focal bronchopneumonia" (no DAD) in 4/12)	Yes	"Massive pulmonary embolism" (4/12); deep vein thrombosis in 3; fresh thrombosis in prostatic venous plexus (6/9 men)
Lax et al. [48]	32,422,076	Autopsies	11	DAD (11/11); bronchopneumonia (6/11); Fibrinous adhesions (7/11)	Yes	Thrombosis of small and mid-sized pulmonary arteries (11/11)
Yan et al. [49]	32,422,081	Complete autopsy	1	DAD	Yes	Pulmonary infarction
Buja et al. [50]	32,434,133	Complete autopsies	3	DAD	Yes	Pulmonary embolism in 1/3
Martinez et al. [51]	32,437,316	Complete autopsies	8	DAD	Yes	Fibrinous thrombi in 1/8
Schaller et al. [52]	32,437,497	Complete autopsies	10	DAD	Yes	—
Duarte-Neto et al. [53]	32,443,177	Post-mortem "biopsies"	10	DAD	Yes	Fibrinous thrombi in 8/10; small thrombi in kidneys (glomeruli) and other organs
Sekulic et al. [54]	32,451,533	Complete (1) and partial(1) autopsy	2	DAD	Yes	—
Aguiar et al. [55]	32,458,044	Complete autopsy	1	DAD, superimposed pneumonia	Yes	—
Schaefer et al. [56]	32,561,849	Autopsies	7	Acute DAD (5/7), organizing DAD (5/7)	Yes	Pulmonary thromboembolism (5/7)
Beigmohammadi et al. [57]	32,552,178	Post-mortem biopsies from Lung, Heart and Liver	7	DAD (5/7), Acute pneumonia (2/7)	Yes	None mentioned
Konopka et al. [58]	32,542,743	Limited autopsies	8	DAD (8/8)	Yes	Fibrin thrombi (5/8)
Escher et al. [59]	32,529,795	Endomyocardial biopsy	5	Myocardial necrosis, small arterial obliteration	Not applicable	None mentioned

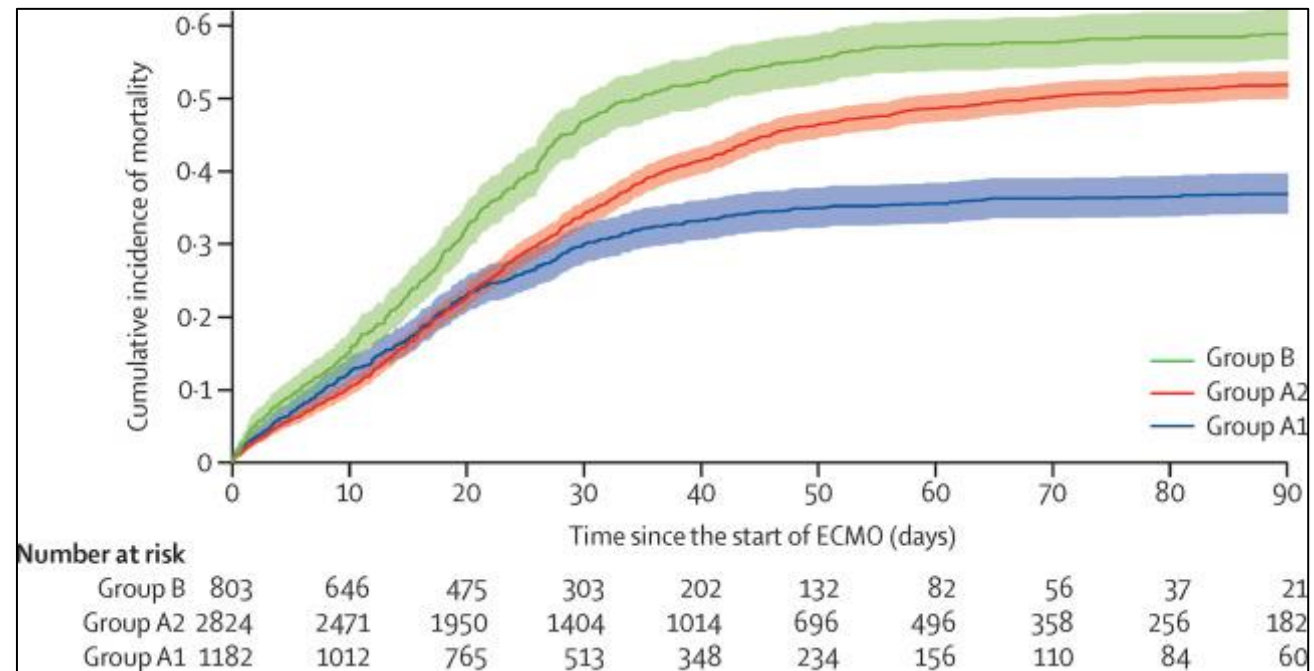
Respiratory Failure

Refractory Hypoxemia - ECMO

Contraindications

- Advanced age (center-specific; no universal cutoff per ATS/ESICM 2024)
- Multiorgan failure (excluding cardiopulmonary)
- Active, uncontrollable hemorrhage
- Prolonged mechanical ventilation (7-10 days)
- Irreversible neurologic injury or unknown neurologic status
- Significant baseline comorbidities

Outcomes



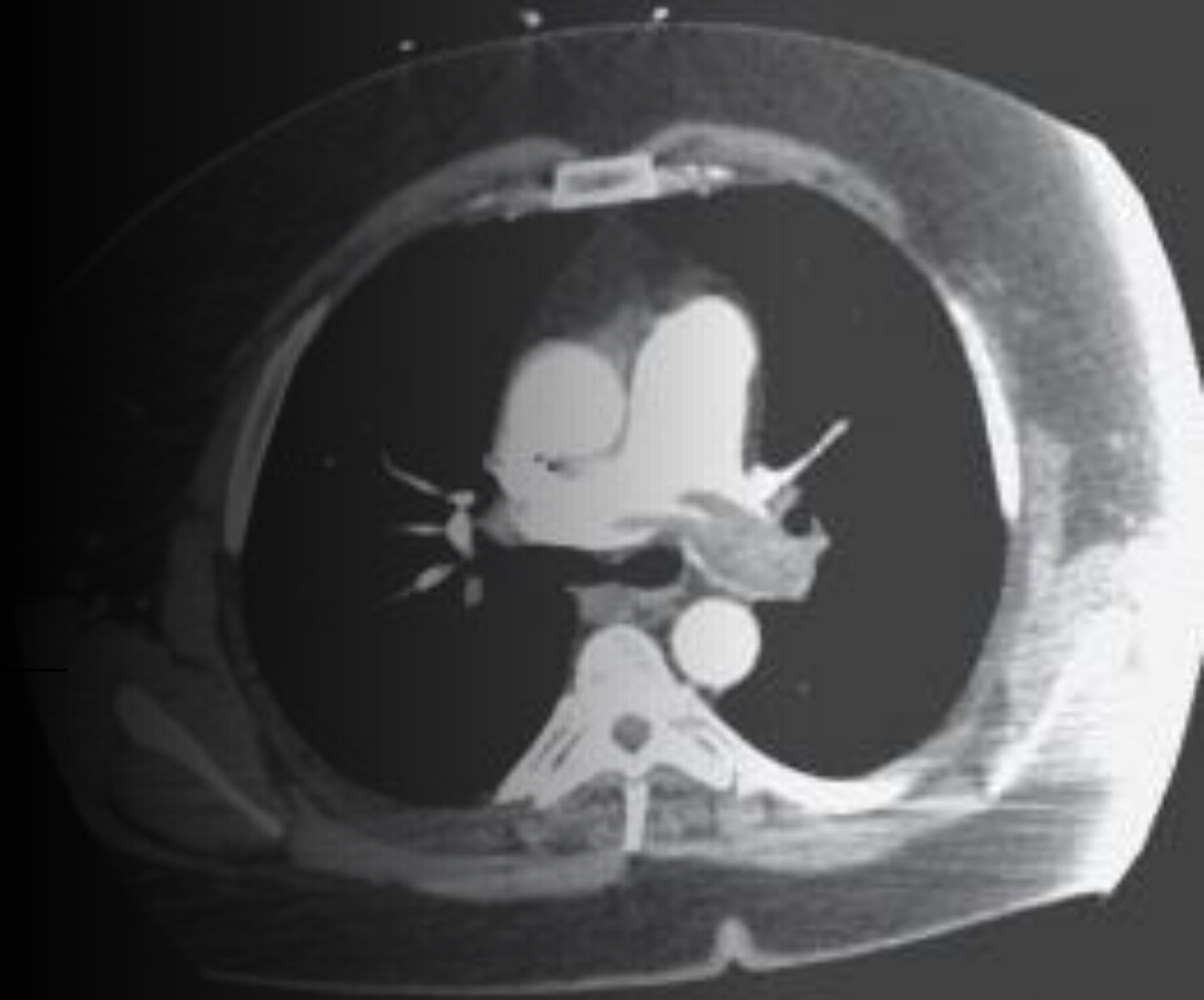
Respiratory Failure

Ventilator Weaning, Extubation and Tracheostomy

- Weaning as per usual protocol with daily SAT/SBT when appropriate
- Extubation
 - Ensure appropriate PPE
 - Limit personnel in room
 - If possible, limit entry into room for 45-60 minutes after procedure
- Tracheostomy
 - Goals of care
 - In general ICU population, 60% 1-year mortality for those ventilator dependent at discharge
 - Guidelines evolving
 - Previous guidance suggested until waiting until day 21 or COVID PCR negative
 - Attempt to limit healthcare worker exposure as much as practical
 - PPE
 - Limited/essential staff
 - Paralysis
 - Mouth packing



Thrombosis



Thrombosis

A 52 year old male, non-obese patient with a history of hypertension is admitted to the ICU for COVID-19 pneumonia. He has no other chronic or acute indications for anticoagulation. He should:

- a) Be placed on therapeutic anticoagulation with a heparin drip
- b) Be placed on therapeutic anticoagulation with a bivalirudin drip
- c) Be placed on intermediate dose anticoagulation (i.e., higher than standard prophylactic dosing but not “therapeutic”)
- d) Be placed on standard prophylactic dose anticoagulation

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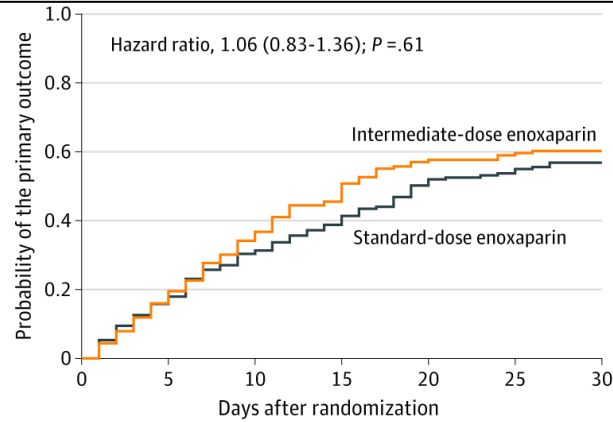
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Thrombosis

Studies of therapeutic and intermediate anticoagulation have had mixed results but in general:

- 1) They do NOT support increased intensity of anticoagulation for **CRITICALLY ILL** COVID-19 patients
- 2) They MAY support increased intensity of anticoagulation for severe but **NON-CRITICALLY ILL** COVID-19 patients

Thrombosis



No. of patients at risk							
Intermediate dose							
Total	276	235	196	175	156	154	150
Primary outcome	0	41	39	21	19	2	4
All-cause mortality	0	37	41 ^a	20	16	2	2
VTE	0	4	1	1	2	0	0
Ischemic stroke	0	0	0	0	1	0	0
Standard dose							
Total	286	244	211	194	173	167	160
Primary outcome	0	42	33	17	21	6	7
All-cause mortality	0	38	29	17 ^a	21 ^a	6	6
VTE	0	3	4	1	2 ^b	0	1
Ischemic stroke	0	1	0	0	0	0	0

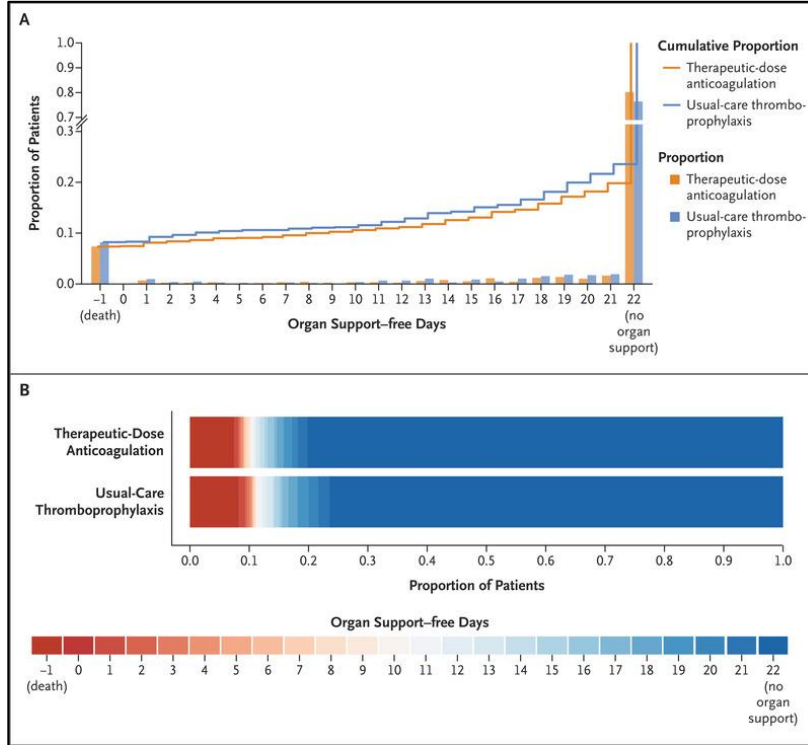
INSPIRATION, JAMA, 2021

Intervention: Intermediate vs. standard dose enoxaparin

Patient population: Unselected ICU population

Outcome: Composite thrombosis, ECMO, mortality

Result: No benefit



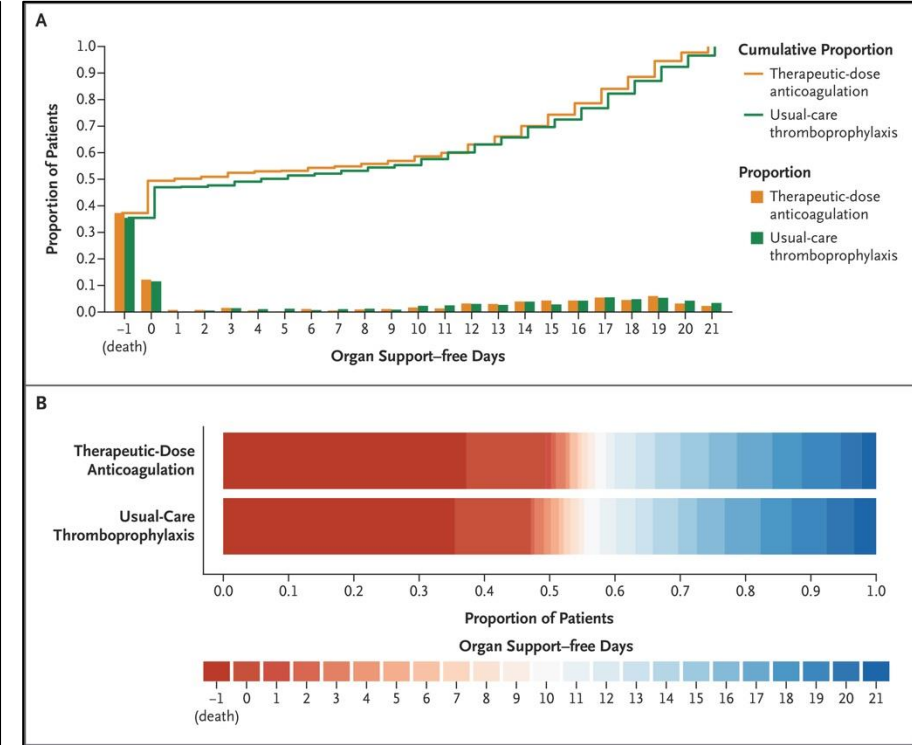
Critically Ill REMAP-CAP, ACTIV-4a, and ATTACC, NEJM, 2021

Intervention: Therapeutic vs. standard dose enoxaparin

Patient population: Patients requiring ICU level support

Outcome: Organ support-free days

Result: No benefit



Non-Critically Ill REMAP-CAP, ACTIV-4a, and ATTACC, NEJM, 2021

Intervention: Therapeutic vs. standard dose enoxaparin

Patient population: Hospitalized but non-critically ill

Outcome: Organ support-free days

Result: Probability of increased organ support free days = 98% (OR 1.27)

COVID Specific Therapy

COVID Directed Therapy

- There are no FDA-approved therapeutics for COVID-19
- Remdesivir:
 - May improve time to recovery
 - Especially in severe disease
- Consider clinical trial if available:
 - Convalescent plasma
 - Ravulizumab
 - Sarilumab
- If not available, then consider:
 - Tocilizumab
 - Anakinra

Histogram of on



Disease Severity Scale:

- 1, not hospitalized, no limitations
- 2, not hospitalized, limitations
- 3, hospitalized, not requiring
- 4, hospitalized, not requiring
- 5, hospitalized, requiring
- 6, hospitalized, requiring

COVID Specific Therapy

You are called to evaluate a 62 year old female patient with a history of hyperlipidemia and osteoporosis on the general medical floor. She was admitted with COVID-19 pneumonia 12 hours ago and her oxygen requirement has increased from 2 LPM by nasal cannula in the emergency department to 15 LPM by non-rebreather mask. She has received her first doses of dexamethasone and remdesivir, and you elect to transfer her to the ICU for oxygen administration by high flow nasal cannula. The best additional intervention at this time is:

- A) Administer high titer convalescent plasma
- B) Administer baricitinib
- C) Increase the dexamethasone dose to 12mg daily
- D) Administer inhaled epoprostonol via the high flow nasal cannula

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COVID Specific Therapy

Hospitalized Severe, NOT Critical — Hypoxemic (Low-Flow Supplemental Oxygen)

Care Location / Disease Severity	Pharmacologic Treatments (United States)	Notes
Hospitalized severe, NOT critical (Hypoxemic — low-flow supplemental oxygen)	Corticosteroids (dexamethasone 6 mg/d × 10 days or until discharge, or equivalent dose of another agent). Remdesivir × 5 days.	Core regimen
	Tocilizumab or sarilumab — progressive disease with elevated inflammatory markers <i>OR</i> Baricitinib or tofacitinib — elevated inflammatory markers.	Add immunomodulator if deteriorating
	No benefit in RCTs: convalescent plasma, hydroxychloroquine, azithromycin, lopinavir/ritonavir, ivermectin.	 Do NOT use

Notes: Immunomodulators should NOT be combined with each other. If already on remdesivir and disease progresses, complete the full course.
IDSA 2025 (Oct): baricitinib and tocilizumab are equivalent (conditional recommendation, very low certainty). No clear superiority of either agent.

COVID Specific Therapy

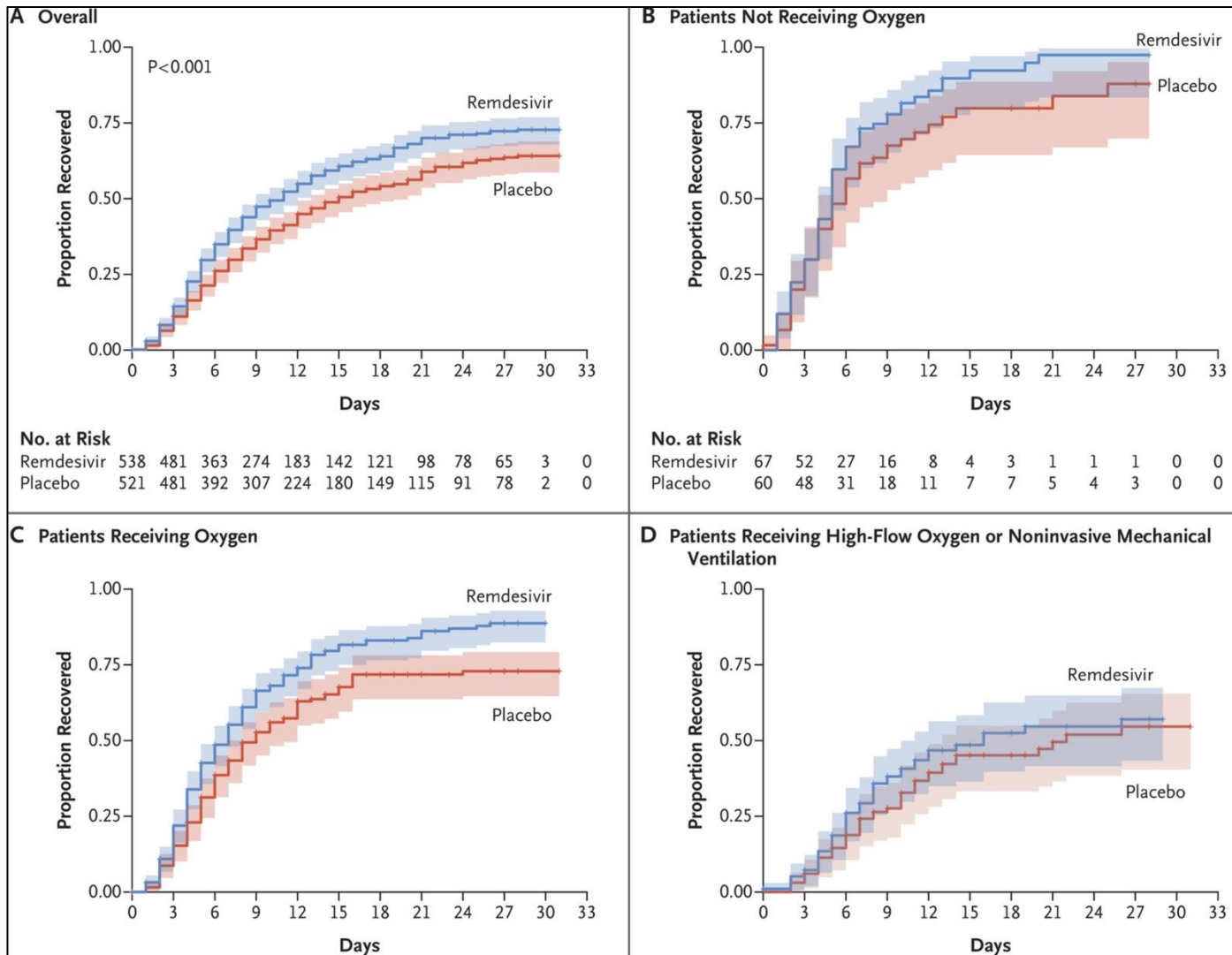
Hospitalized Critically Ill — NIV / High-Flow O₂ and Invasive MV / ECMO

Care Location / Disease Severity	Pharmacologic Treatments (United States)	Notes
Critically ill Non-invasive ventilation or High-Flow O ₂	Corticosteroids (dexamethasone 6 mg/d × 10 days or until discharge; or equivalent dose of hydrocortisone or methylprednisolone).	Core regimen
	Tocilizumab or sarilumab — elevated inflammatory markers. <i>OR</i> Baricitinib or tofacitinib — elevated inflammatory markers.	Add immunomodulator (either/or; see †)
Critically ill Invasive mechanical ventilation or ECMO	Corticosteroids (dexamethasone 6 mg/d × 10 days or until discharge; or equivalent dose of hydrocortisone or methylprednisolone).	Core regimen
	Tocilizumab or sarilumab — elevated inflammatory markers. <i>OR</i> Baricitinib or tofacitinib — elevated inflammatory markers.	Add immunomodulator (either/or; see †)
	No benefit in RCTs: remdesivir, convalescent plasma, hydroxychloroquine, azithromycin, lopinavir/ritonavir, ivermectin.	 Do NOT use

† **IDSA 2025 (Oct)**: baricitinib and tocilizumab are equivalent for severe/critical COVID-19 (conditional recommendation, very low certainty). No clear superiority. Abatacept or infliximab: IDSA 2025 conditional recommendation as second-line when baricitinib AND tocilizumab are both unavailable. Immunomodulators should NOT be combined with each other. Complete the full remdesivir course if already started when disease progresses.

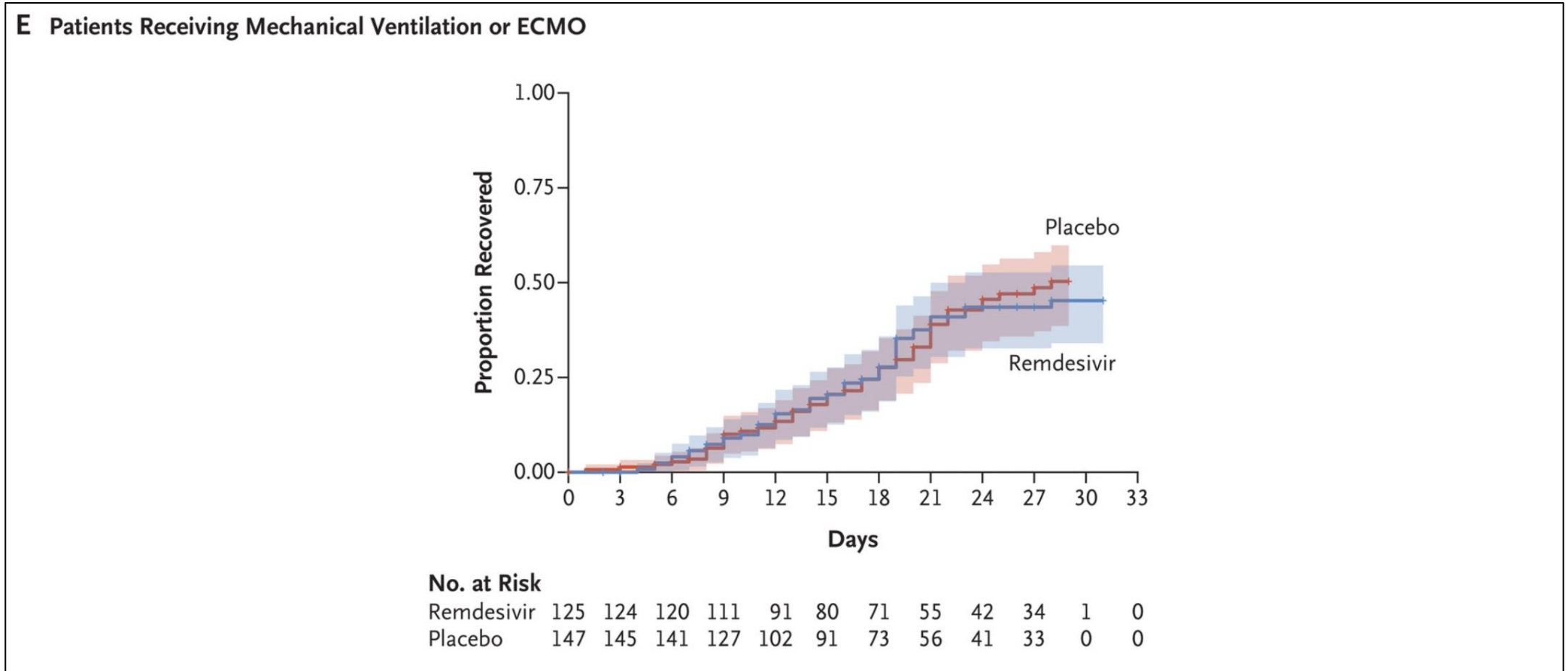
COVID Specific Therapy

Remdesivir



COVID Specific Therapy

Remdesivir



COVID Specific Therapy

Steroids

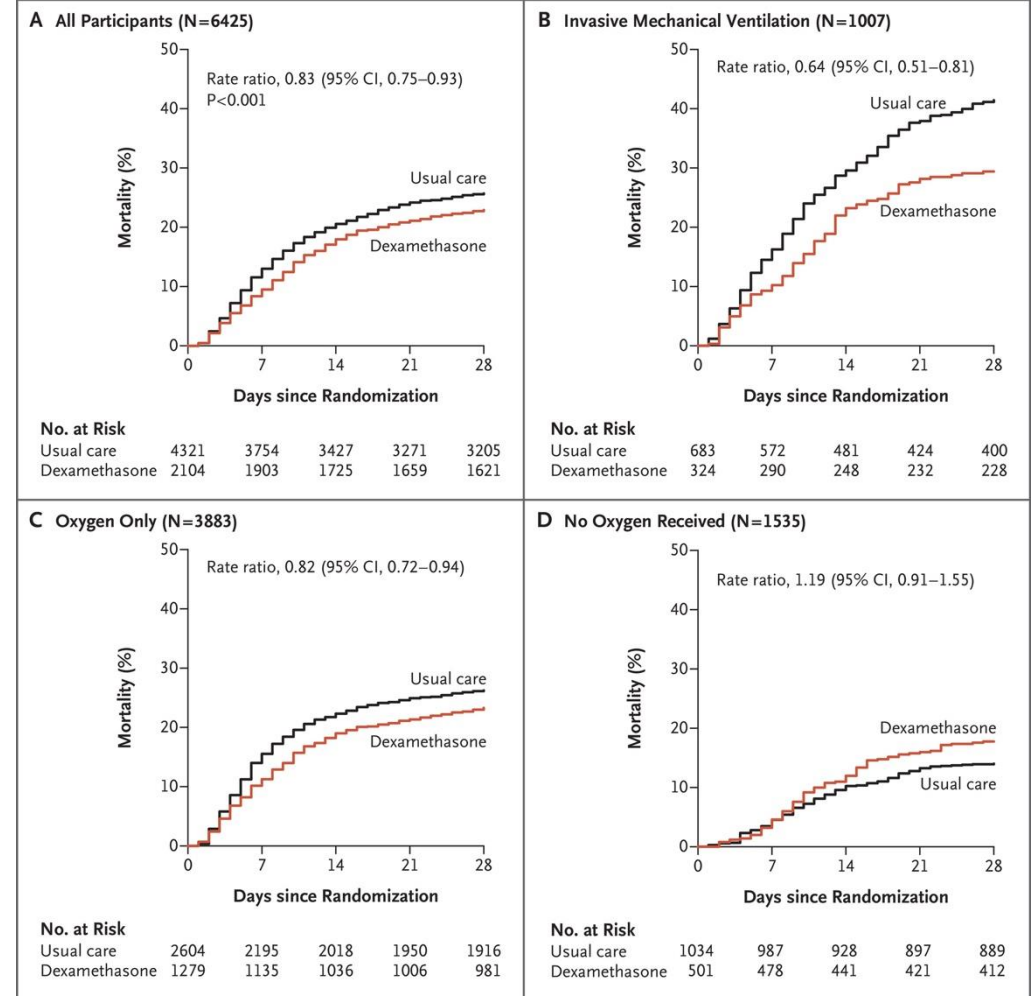
- Dexamethasone preferred
- 6mg daily x 10 days*
 - *possibly until hospital discharge

Table 2. Primary and Secondary Outcomes.

Outcome	Dexamethasone (N=2104)	Usual Care (N=4321)	Rate or Risk Ratio (95% CI)*
<i>no./total no. of patients (%)</i>			
Primary outcome			
Mortality at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)
Secondary outcomes			
Discharged from hospital within 28 days	1413/2104 (67.2)	2745/4321 (63.5)	1.10 (1.03–1.17)
Invasive mechanical ventilation or death†	456/1780 (25.6)	994/3638 (27.3)	0.92 (0.84–1.01)
Invasive mechanical ventilation	102/1780 (5.7)	285/3638 (7.8)	0.77 (0.62–0.95)
Death	387/1780 (21.7)	827/3638 (22.7)	0.93 (0.84–1.03)

* Rate ratios have been adjusted for age with respect to the outcomes of 28-day mortality and hospital discharge. Risk ratios have been adjusted for age with respect to the outcome of receipt of invasive mechanical ventilation or death and its subcomponents.

† Excluded from this category are patients who were receiving invasive mechanical ventilation at randomization.



COVID Specific Therapy

Tocilizumab

- Interleukin 6 Inhibitor
- 8mg/kg up to 800mg once
- Likely most beneficial early in disease course or in those who are most “inflamed”

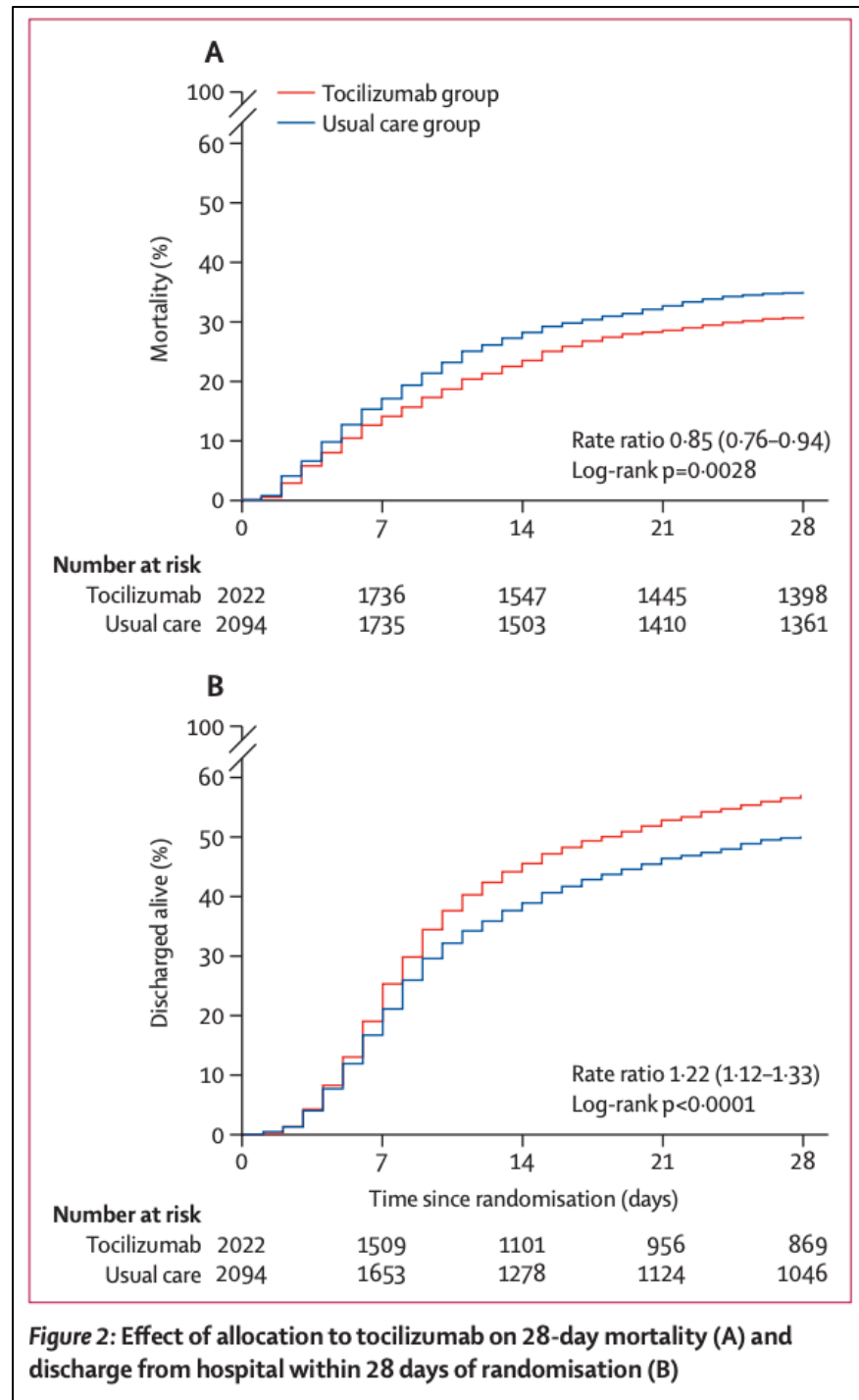
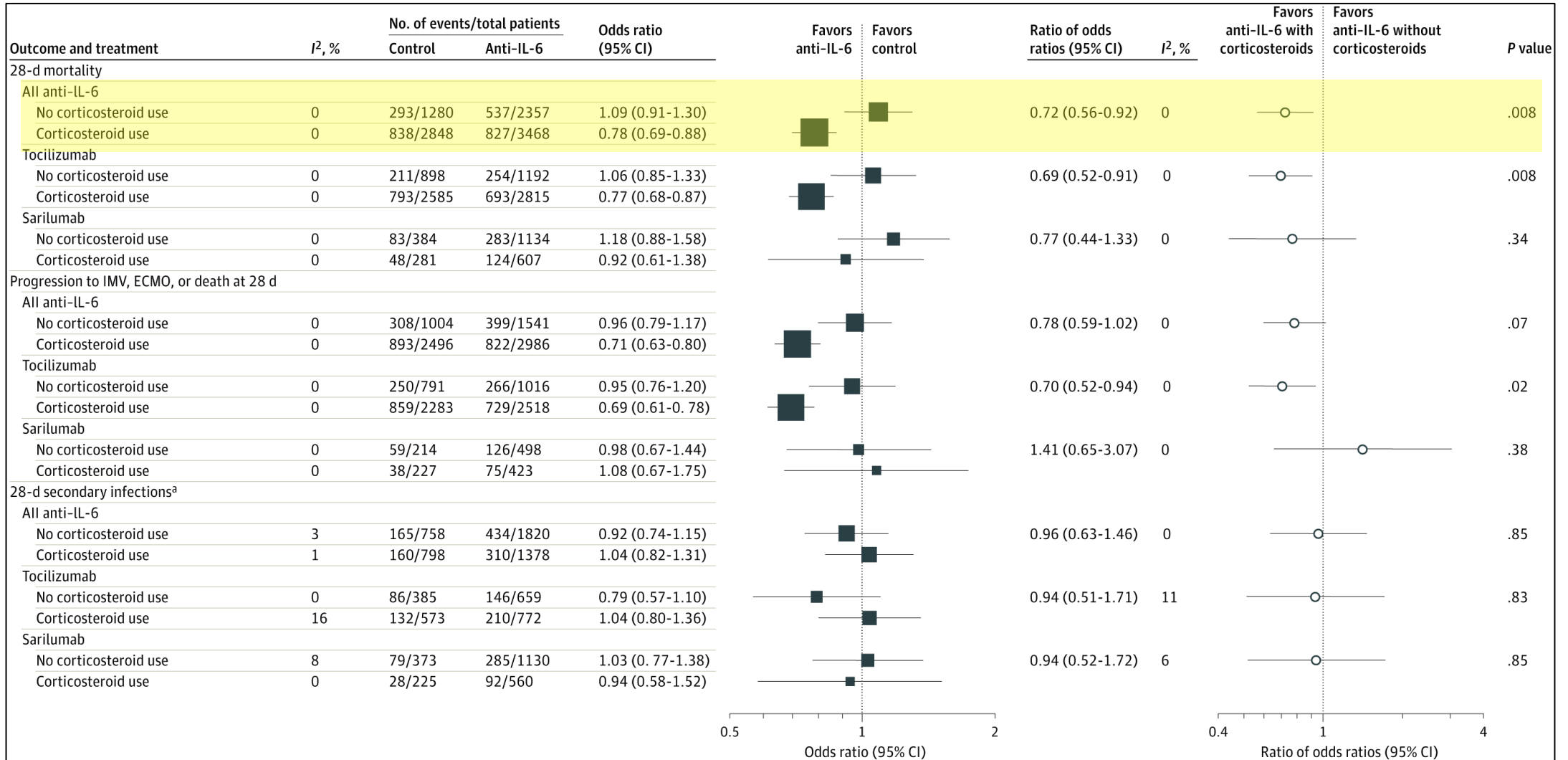


Figure 2: Effect of allocation to tocilizumab on 28-day mortality (A) and discharge from hospital within 28 days of randomisation (B)

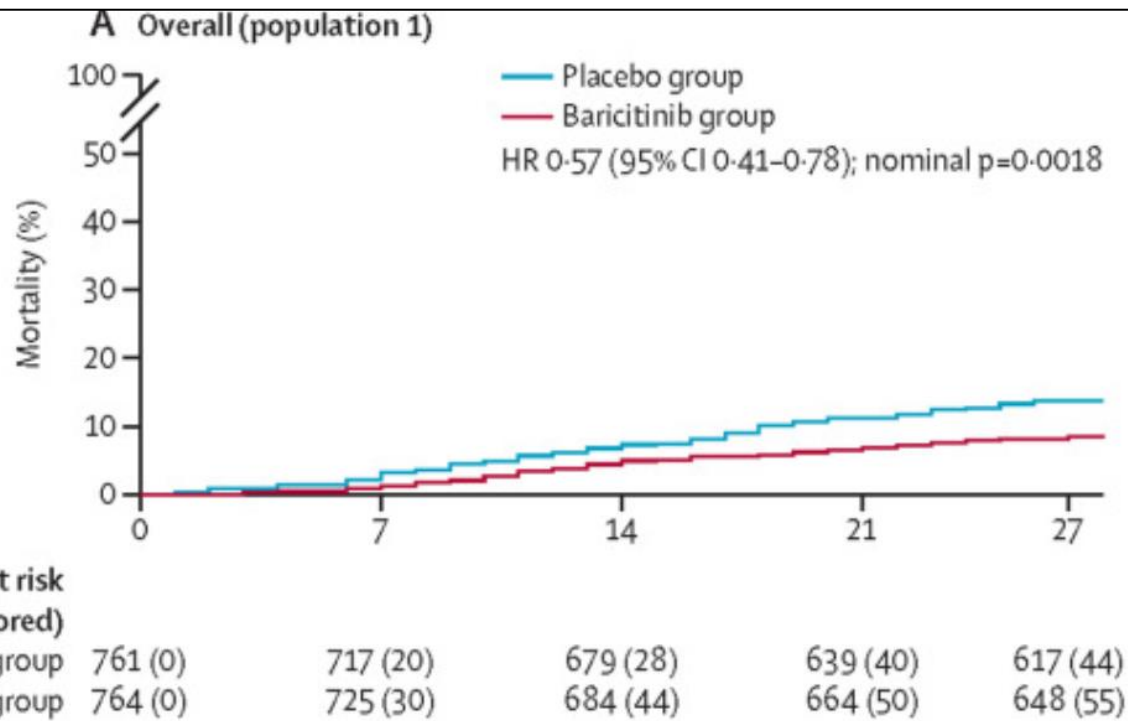
COVID Specific Therapy

Anti-IL-6

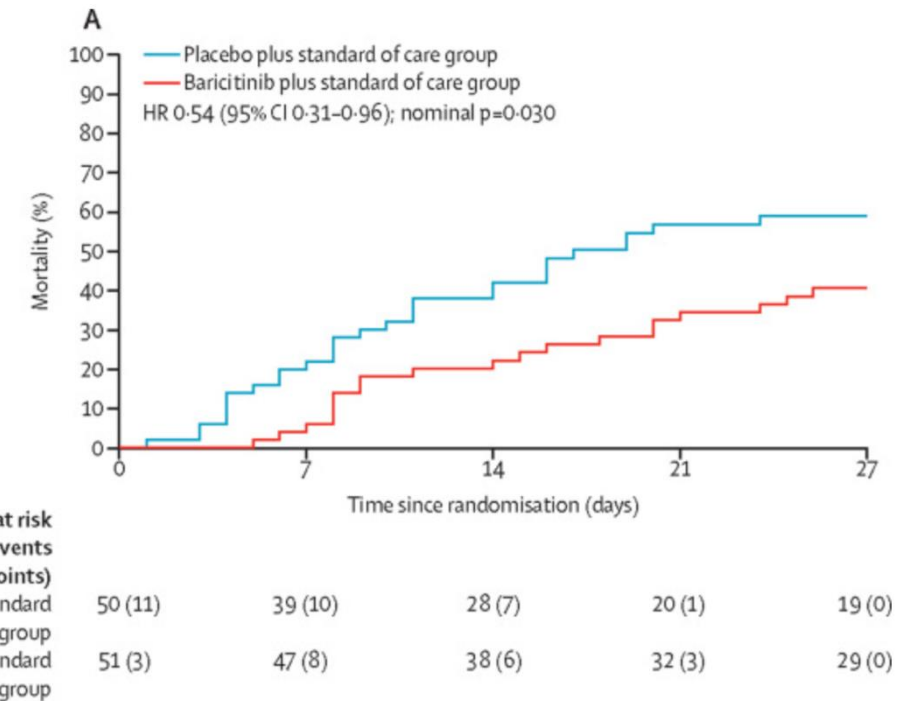


COVID Specific Therapy

Baricitinib



Hospitalized Adults
(No mechanical ventilation or ECMO)



Mechanical Ventilation or ECMO

COVID Specific Therapy

Steroid Dosing

- Patients with hypoxia requiring simple oxygen only
- May 2021 - May 2022
- Dexamethasone 6mg daily vs Dexamethasone 20mg x 5 days and then 10mg x 5 days

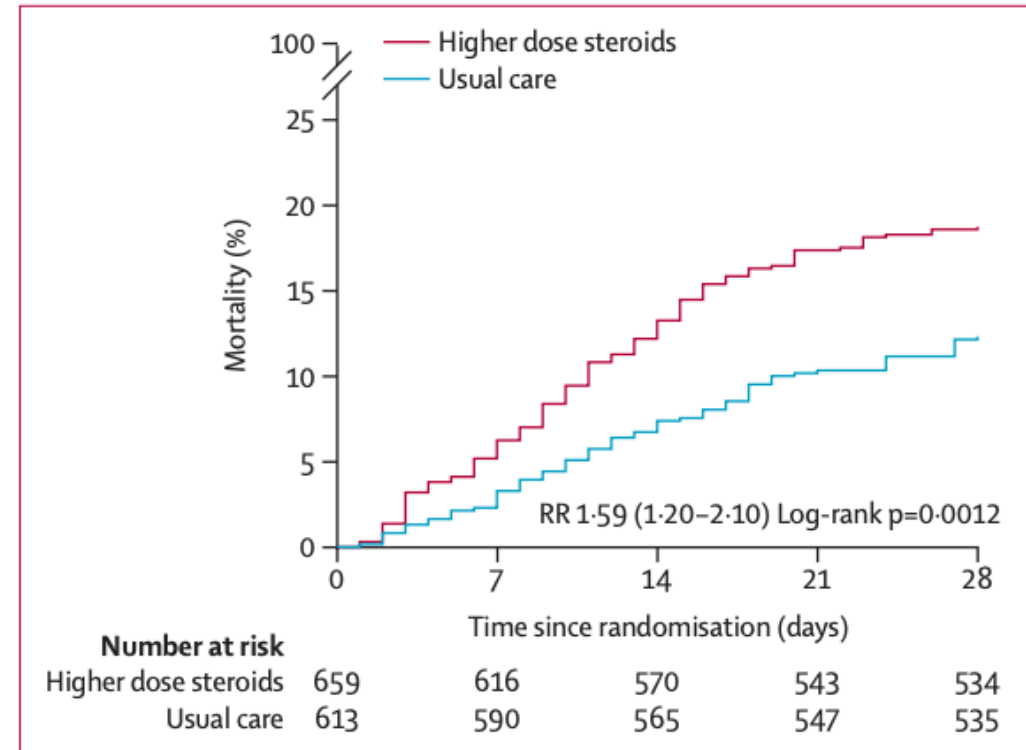


Figure 2: Effect of allocation to higher dose corticosteroids or usual care (lower dose corticosteroids) on 28-day mortality in patients receiving no oxygen or simple oxygen only
RR=rate ratio.

Summary/MOC Reflective Statements

- The key tenets of the critical care of patients with COVID-19 are the same as those for the care of all critically ill patients and departures from general standards of care should be based only on specific evidence
- The primary driver of adverse outcomes is respiratory failure, and the proper management of ARDS is critical for the care of critically ill COVID-19 patients
- Current evidence does not support the routine use of intermediate or therapeutic anticoagulation in critically ill COVID-19 patients
- Multiple COVID specific therapies are available, and their selection is based on the severity of disease



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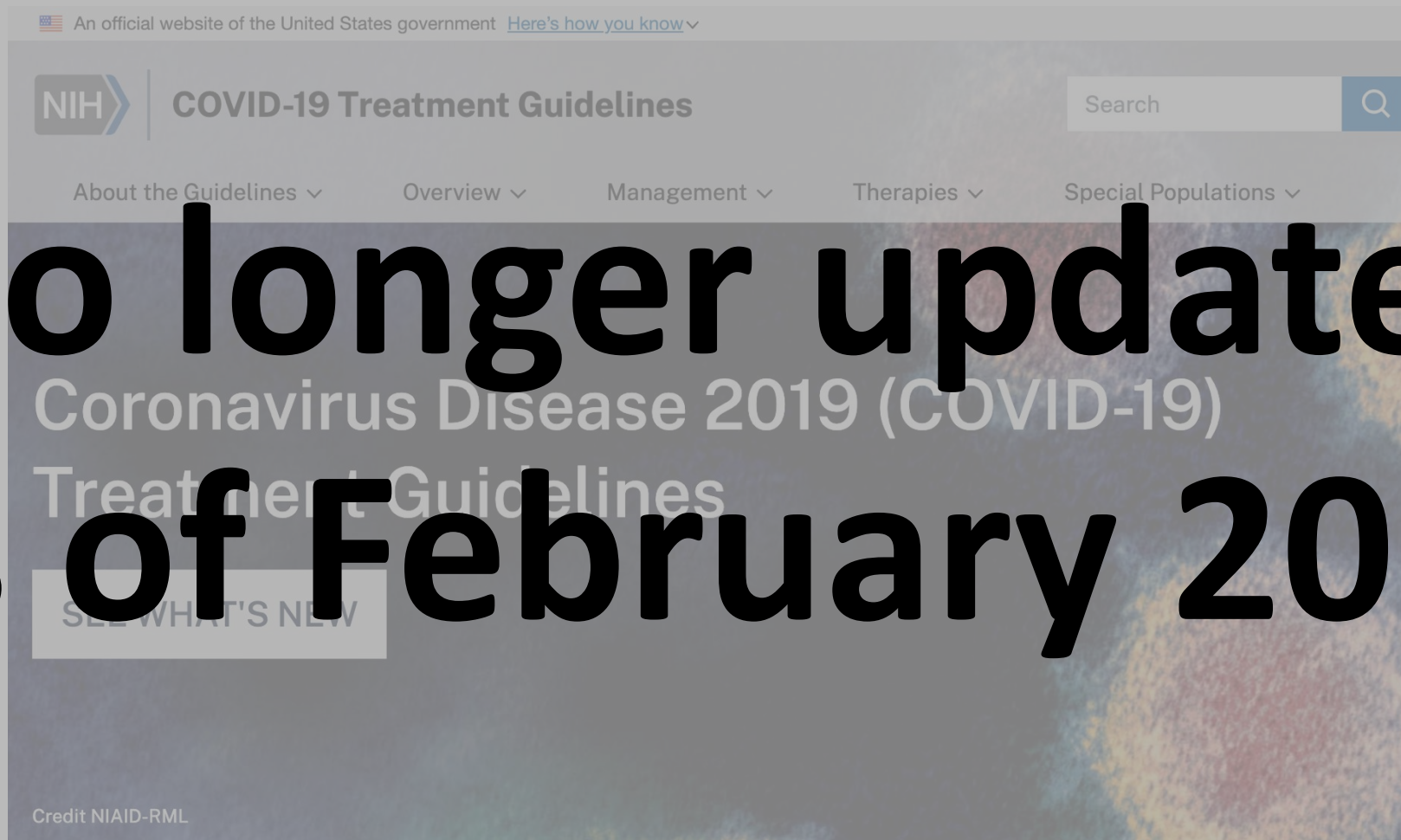
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