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ICU Care for Critically Ill COVID-19

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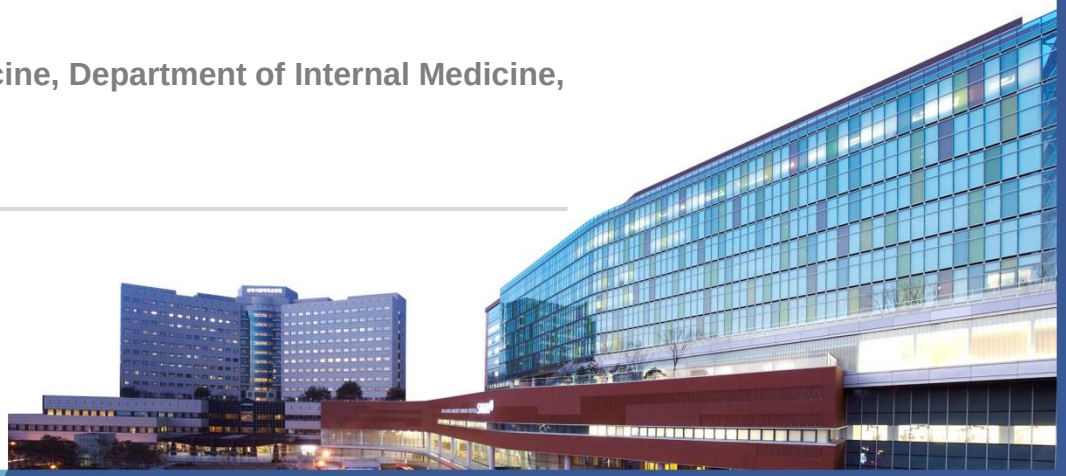

Disclosures

- No conflicts of interest or financial disclosures

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Contents

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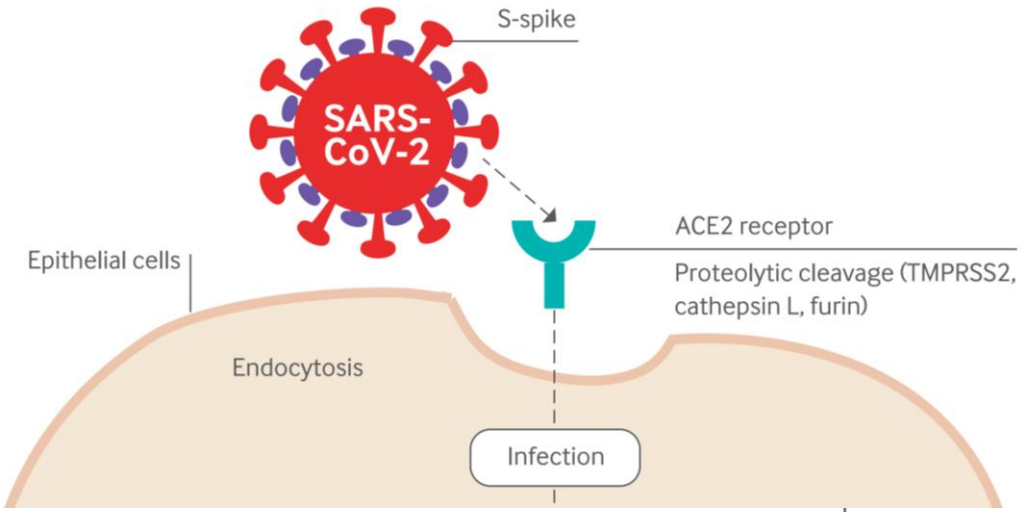
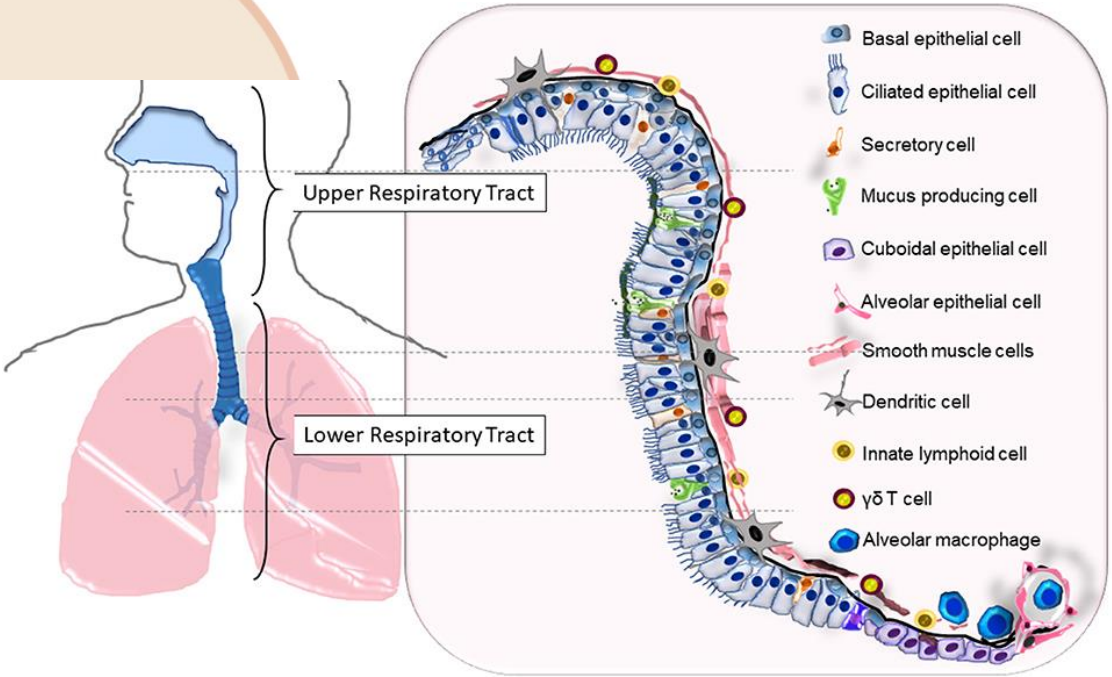
- Ventilatory Support
- Pharmacologic Therapy

SARS-CoV-2 Infection





BMJ . 2021 Mar 10;372:n436.

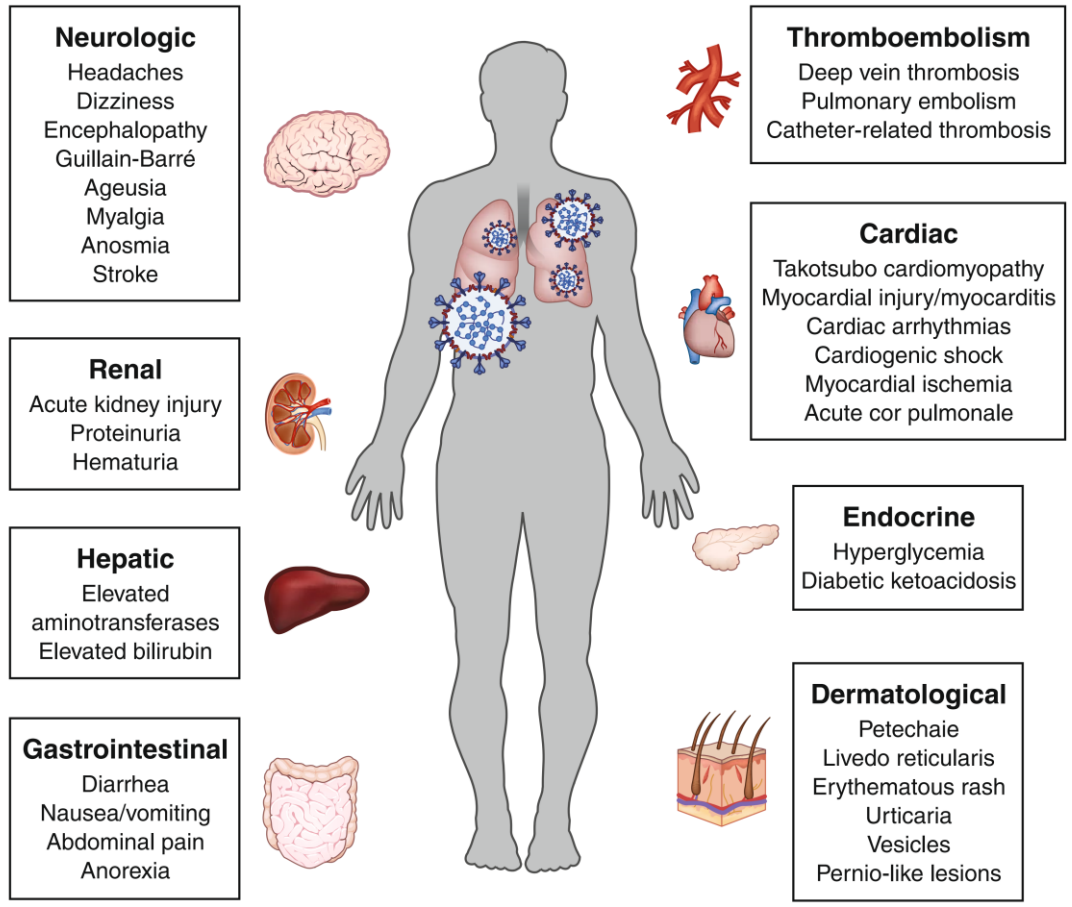
Severe COVID-19 Pneumonia

- **SpO2 <94% on room air**, **PF ratio <300**, RR > 30, lung infiltrates >50%

- Risk Factors: **Older age, male** sex, and **comorbidities** (hypertension, diabetes, cardiovascular disease, chronic pulmonary disease, chronic kidney disease, cancer, and chronic liver disease)

COVID-19 associated ARDS

- **one third of patients** hospitalized with SARS-CoV-2 infection



Nature Medicine volume 26, pages1017–1032(2020)

Acute Respiratory Distress Syndrome

Table 1. Berlin Definition of the Acute Respiratory Distress Syndrome (ARDS).*

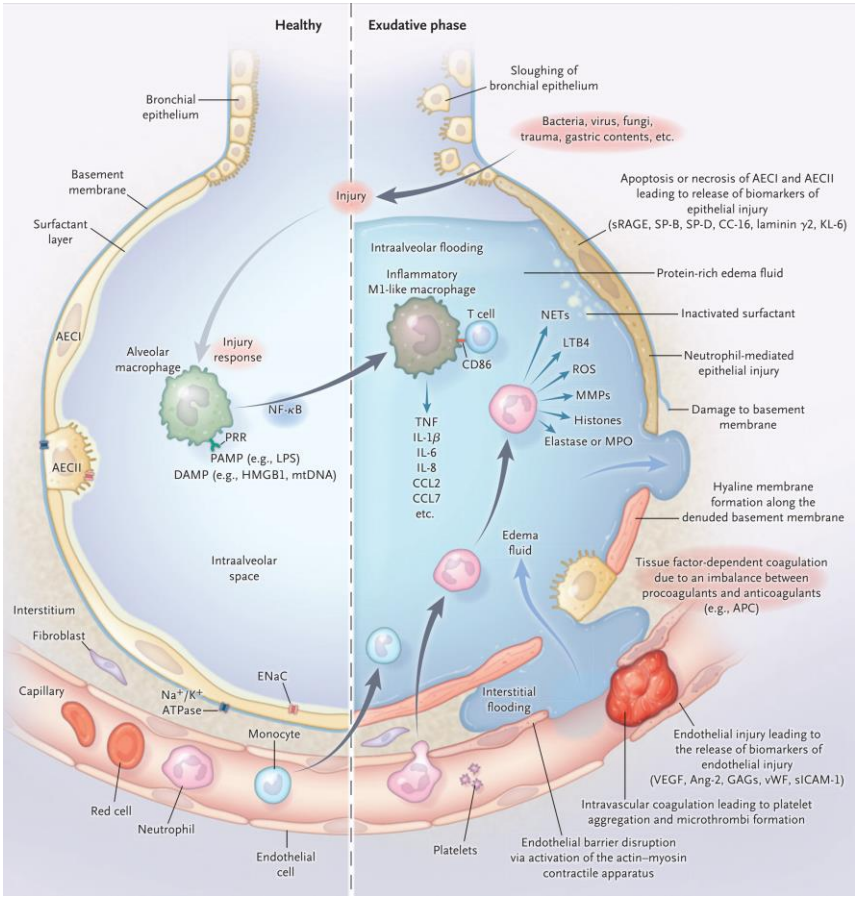
Criteria	Rationale
Onset within 7 days after a known clinical insult or new or worsening respiratory symptoms	Observational data suggest that ARDS will develop within 72 hr in the majority of patients at risk for the syndrome and within 1 wk in nearly all patients at risk
Bilateral opacities that are "consistent with pulmonary edema" on chest radiographs or chest CT	There is poor interobserver reliability in interpreting the chest radiograph for the presence of edema. To address this issue, the Berlin definition offers more explicit criteria (e.g., opacities should not be fully explained by effusions, lobar or lung atelectasis, or nodules or masses), with illustrative radiographs provided
Categorization of ARDS severity	A patient-level meta-analysis validated three thresholds for hypoxemia, all consisting of a Pao_2:FIo_2 ratio ≤300 mm Hg
Mild	Pao_2:FIo_2, 201 to 300 mm Hg; mortality, 27% (95% CI, 24–30)
Moderate	Pao_2:FIo_2, 101 to 200 mm Hg; mortality, 32% (95% CI, 29–34)
Severe	Pao_2:FIo_2, ≤100 mm Hg; mortality, 45% (95% CI, 42–48)
Minimum PEEP setting or CPAP, 5 cm of water; Pao_2:FIo_2 assessed on invasive mechanical ventilation (CPAP criterion used for the diagnosis of mild ARDS)	Estimates of FIo_2 are not accurate with oxygen-delivery systems other than invasive or noninvasive ventilation (with a tight-fitting mask), with the exception of nasal high-flow oxygen delivery systems (at flow rates ≥45 liters per minute); requiring higher PEEP settings does not increase predictive validity of the Berlin severity strata and adds complexity

* The definition and the quotation about opacities are from Ferguson et al.[6] CI denotes confidence interval, CPAP continuous positive airway pressure, Pao_2:FIo_2 ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, and PEEP positive end-expiratory pressure.

N Engl J Med 2017;377:562-72.

Pathophysiology

- Hypoxemia due to shunt
- Low compliance correlates to PF ratio



N Engl J Med 2017;377:562-72.

COVID-19 associated ARDS (CARDS)

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REVIEW Open Access

Acute respiratory failure in COVID-19: is it "typical" ARDS?

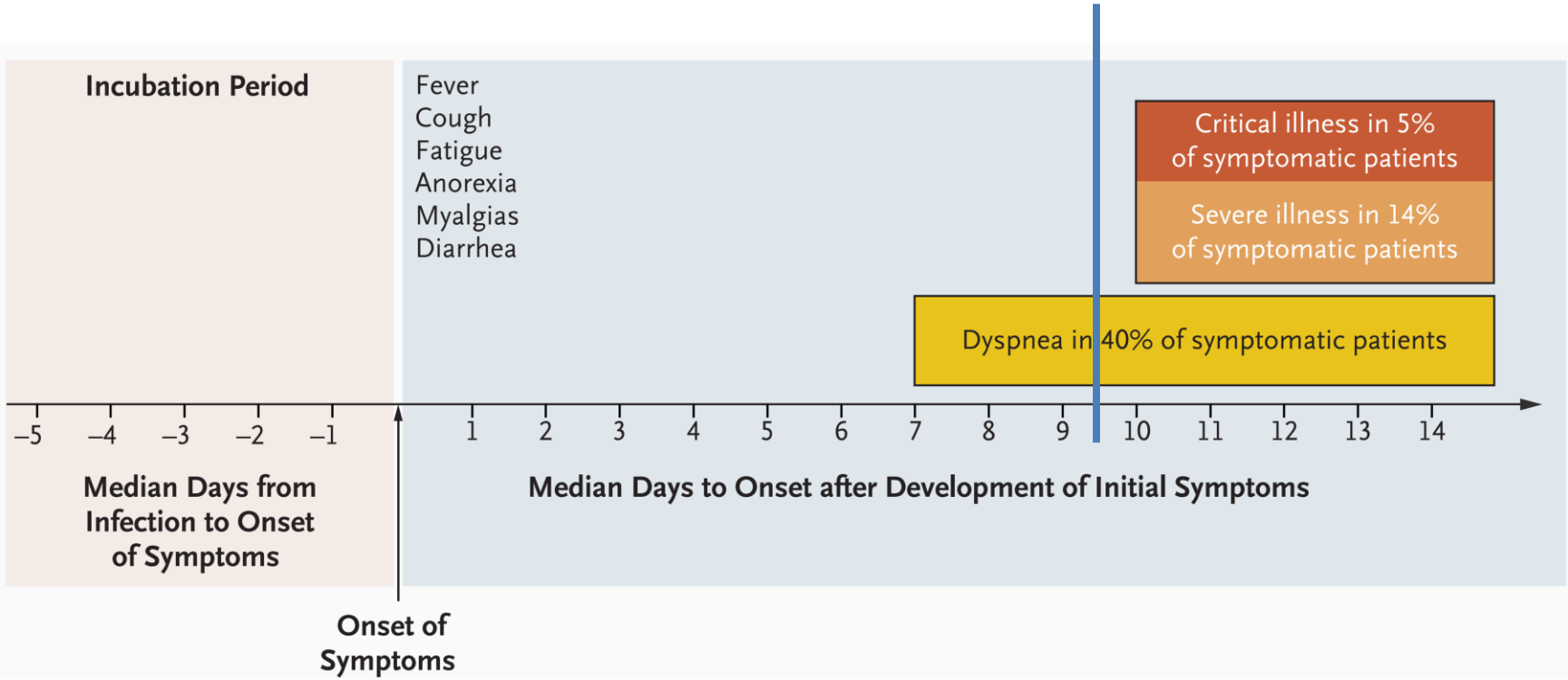
Check for updates

Xu Li and Xiaochun Ma*

- **Timing of onset**
  - 8-12 days
- **Respiratory system compliance**
  - Lung compliance might be relatively normal in some COVID-19-related ARDS patients

- **Specificity of clinical features**
  - Clinical symptoms were inconsistent with the severity of laboratory and imaging findings
  - Clinical manifestations were relatively mild

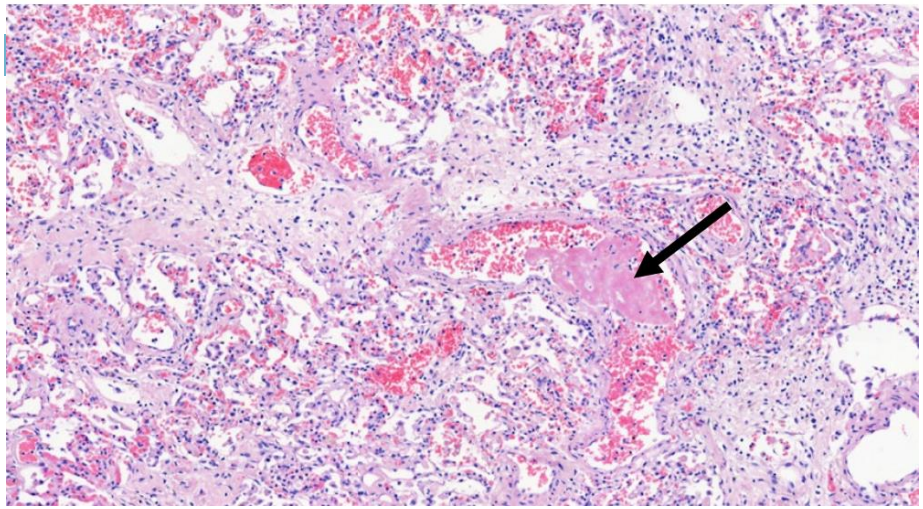
Timeline of CARDS

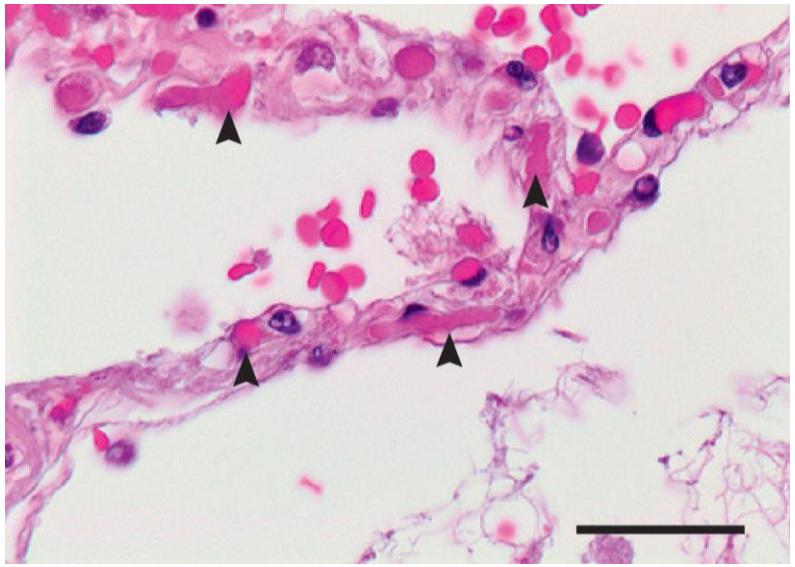


N Engl J Med. 2020 Dec 17;383(25):2451-2460.

Pathophysiology of CARDS

- Diffuse Alveolar damage along **with pulmonary vasculature involvement**
- **Severe endothelial injury**
- **Widespread thrombosis with microangiopathy** (Nine times than influenza)





N Engl J Med 2020;383:120-8

Intensive Care Med. 2021 Jan 22 : 1–2.

Aims: Whole blood from 24 patients admitted at the intensive care unit because of COVID-19 was collected and evaluated with thromboelastography by the TEG point-of-care device on a single occasion and six underwent repeated measurements on two consecutive days for a total of 30 observations. Plasma was evaluated for the other parameters of hemostasis.

Results: TEG parameters are consistent with a state of hypercoagulability as shown by decreased values, and increased values of K angle and MA. Platelet count was normal or increased, prothrombin time and activated partial thromboplastin time were near(normal). Fibrinogen was increased and D-dimer was dramatically increased. C-reactive protein was

J ThrombHaemost 2020; 18:1738–1742

- higher D-dimer levels (median 1880 ng/mL) and correlated with increased dead space ventilation and higher mortality

- Out of 3334 hospitalized patients, 16% at least one thrombotic event (6.2% venous vs 11.1% arterial)

- 829 ICU patients, 29.4% (13.6% venous vs 18.6% arterial)

JAMA 2020;324:799–801.

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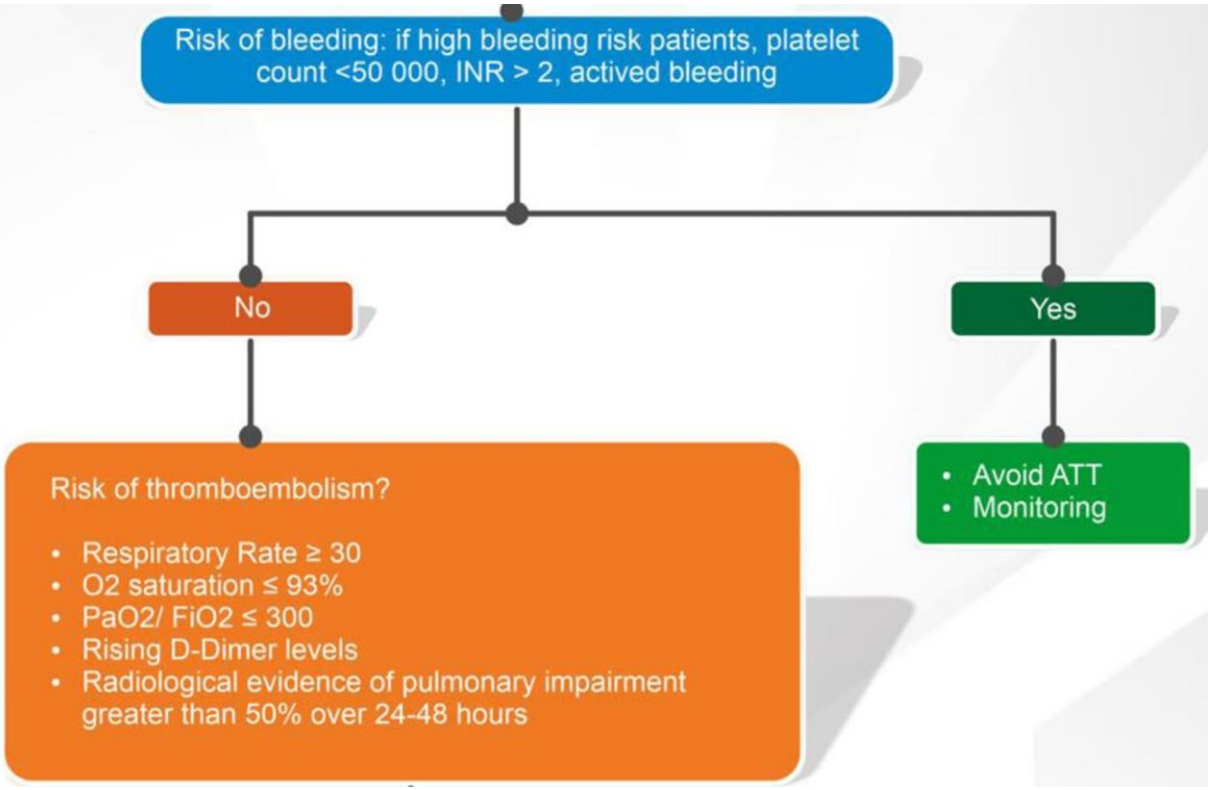
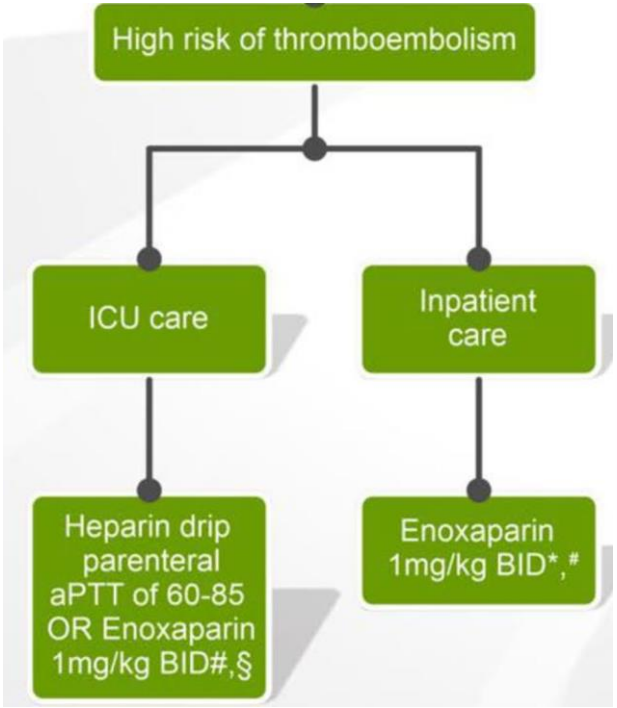
Algorithm for the management of antithrombotic therapy in CARDS

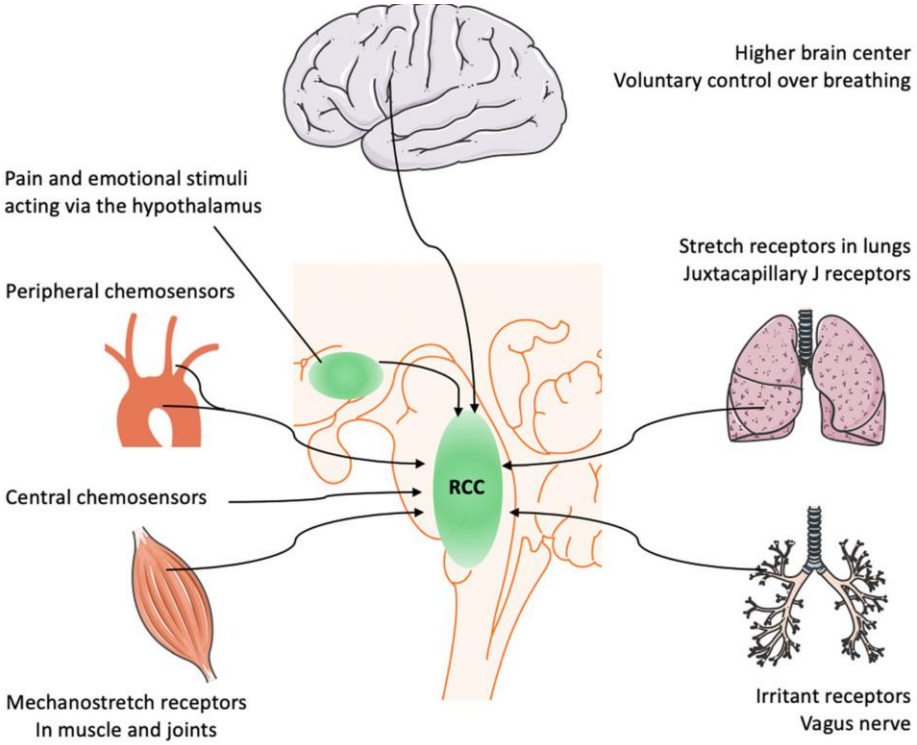


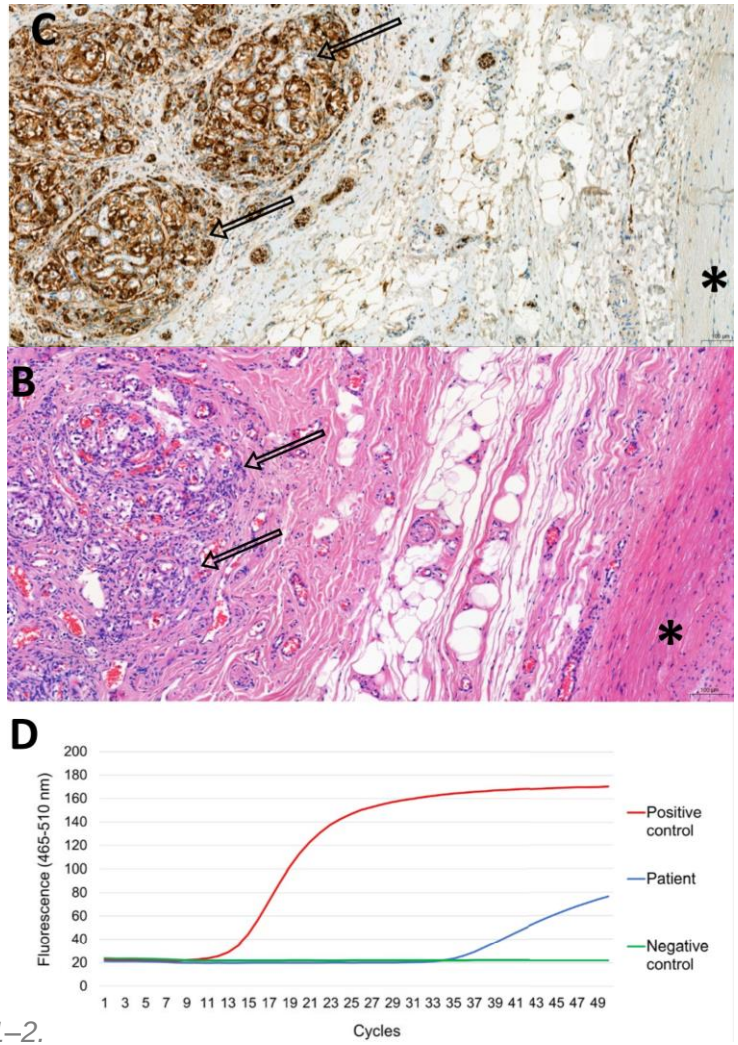


#perform point of care ultrasound, if negative enoxaparin 40mg BID, if positive mantain full dose. §Prefer use of heparina in patients with instatability or creatinin clearence < 40ml/m. *Adjusted enoxaparin dose for renal failure. ATT, antithrombotic

Ann Intensive Care. 2021 Feb 18;11(1):36.

“Silent Hypoxemia”



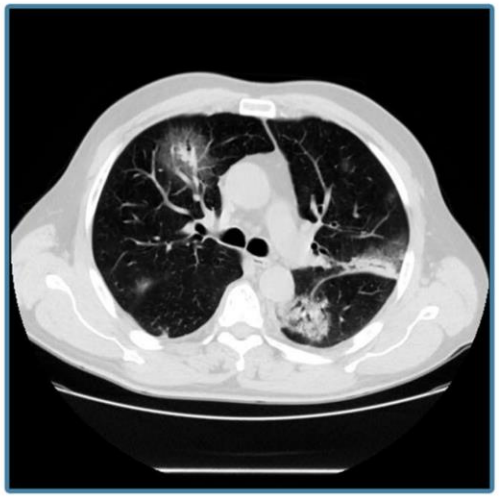


Respir Res . 2020 Jul 28;21(1):198.

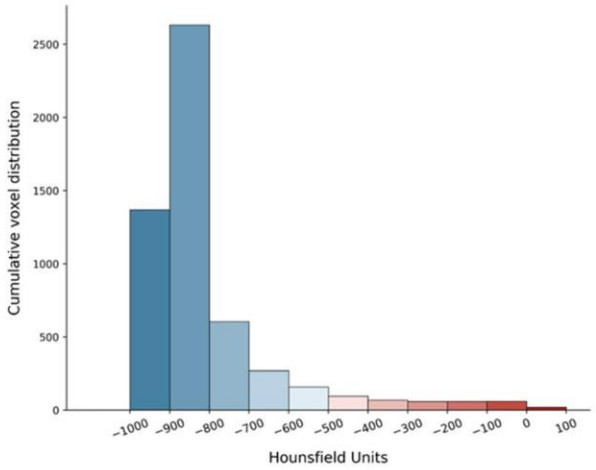
Intensive Care Med. 2021 Jan 22 : 1–2.

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

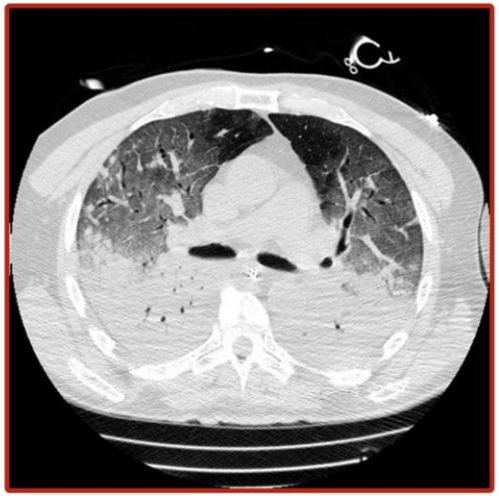
A



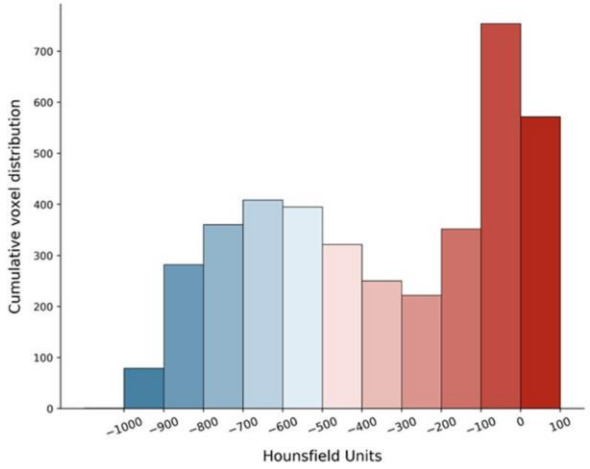
PaO_2/FiO_2
95 mmHg

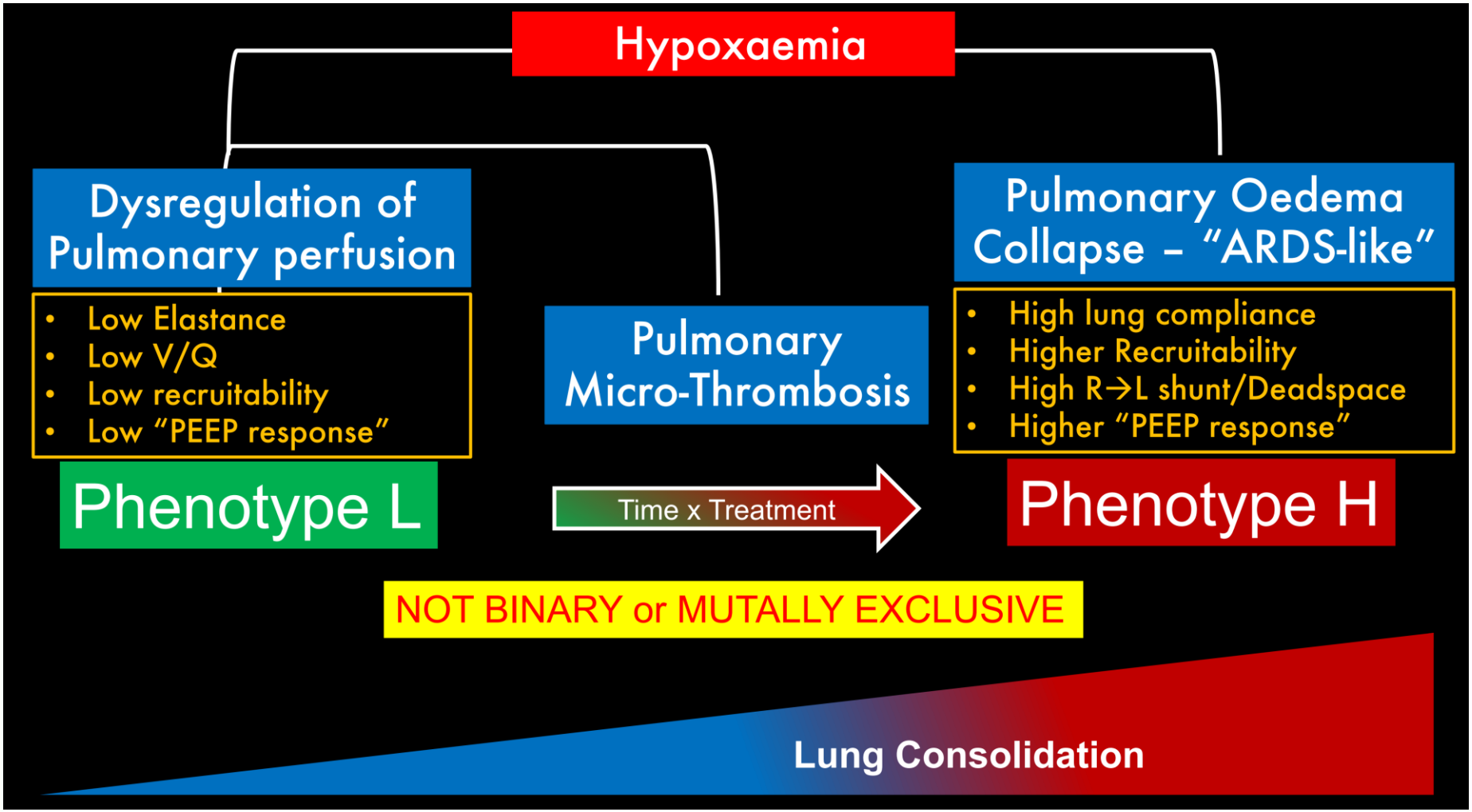


B



PaO_2/FiO_2
84 mmHg



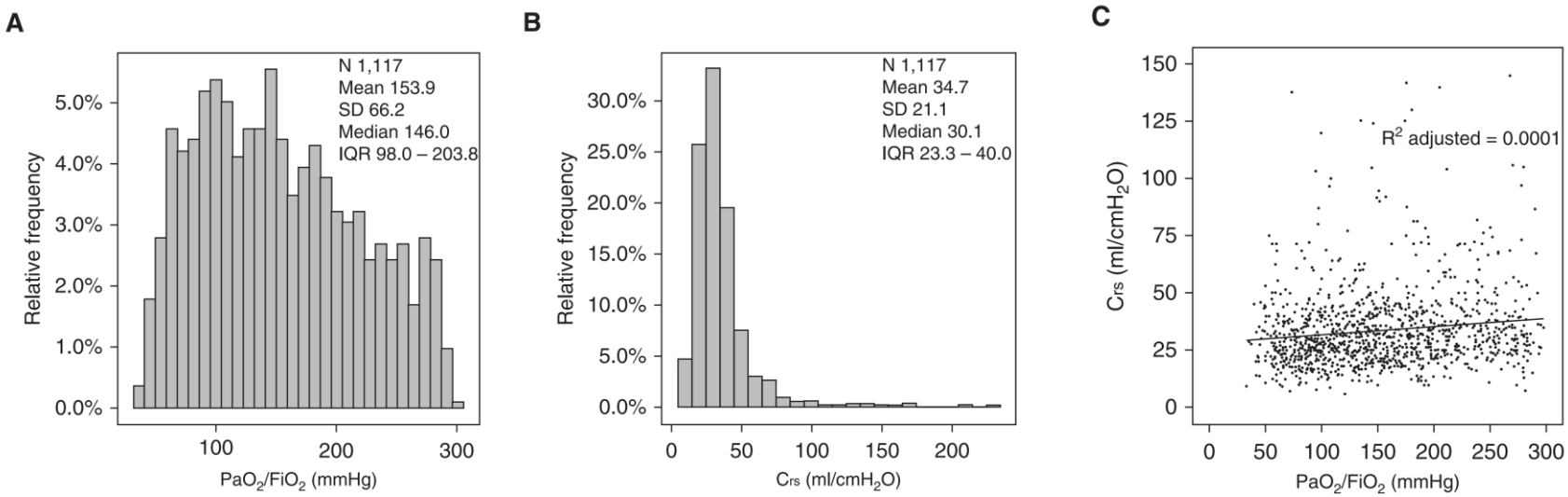


Camporota-ESICM-Webinar-2020.

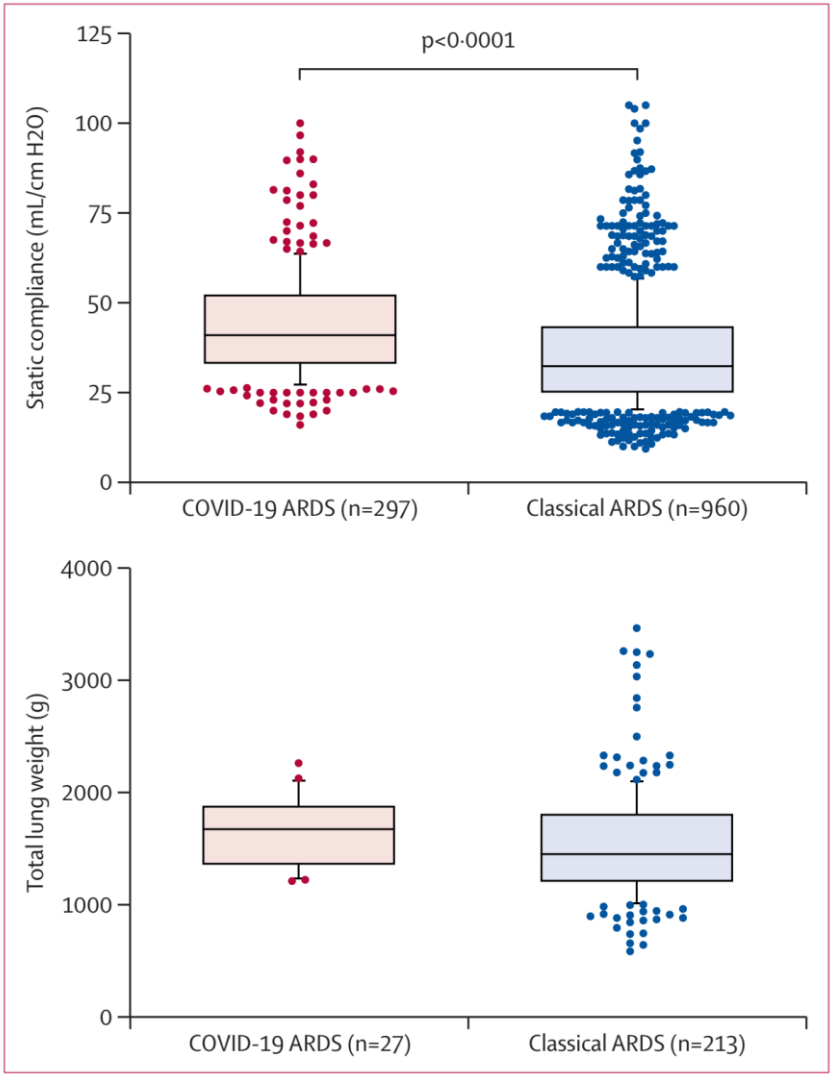
ORIGINAL ARTICLE

Compliance Phenotypes in Early Acute Respiratory Distress Syndrome before the COVID-19 Pandemic

Rakshit Panwar[1,2], Fabiana Madotto[3], John G. Laffey[4,5,6*], and Frank M. P. van Haren[7,8,9*]; on behalf of the LUNG SAFE Investigators and the ESICM Trials Group



Am J Respir Crit Care Med Vol 202, Iss 9, pp 1244–1252, Nov 1, 2020



	Hazard ratio (95% CI)
Class	
High D-dimers, low compliance	1 (ref)
High D-dimers, high compliance	0·448 (0·230–0·873)
Low D-dimers, high compliance	0·420 (0·215–0·818)
Low D-dimers, low compliance	0·386 (0·152–0·985)
Sex	
Female	1 (ref)
Male	1·803 (0·679–4·788)
Age	1·048 (1·002–1·095)*
PaO_2/FiO_2	0·996 (0·992–1·000)*

PaO_2/FiO_2=ratio of partial pressure of arterial oxygen to fractional concentration of oxygen in inspired air. *Change in risk of death per one unit increase (years for age and mm Hg for PaO_2/FiO_2).

Table 2: **Cox proportional risk analysis for mortality**

Am J Respir Crit Care Med Vol 202, Iss 9, pp 1244–1252, Nov 1, 2020

Intensive Care Med
https://doi.org/10.1007/s00134-020-06320-y

EDITORIAL

Is severe COVID-19 pneumonia a typical or atypical form of ARDS? And does it matter?

Ewan C. Goligher[1,2,3], V. Marco Ranieri[4] and Arthur S. Slutsky[1,5*]

RESEARCH **Open Access**

Expert consensus statements for the management of COVID-19-related acute respiratory failure using a Delphi method

Table 1 Consensus and stability analysis of the clinical statements on the respiratory management of C-ARF

	Agree. (%)	Neutral (%)	Disagree. (%)	Median (IQR)	χ^2 p-value
Section-1: Non-invasive respiratory interventions					
1. The pathophysiology of C-ARF is similar to that of ARDS	86.5	0	13.5	5 (0)	0.05

EDITORIAL

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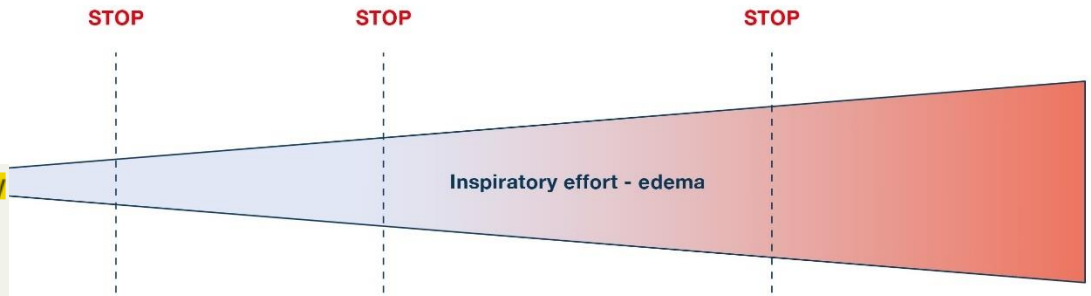
COVID-19 pneumonia: different respiratory treatments for different phenotypes?

Luciano Gattinoni[1*], Davide Chiumello[2], Pietro Caironi[3,4], Mattia Busana[1], Federica Romitti[1], Luca Brazzi[5] and Luigi Camporota[6]

Lung damage progression
(Virus + P-SILI)

Type L[a]: use lower PEEP (<10 cm H_2O)
Use more liberal tidal volume (7-9 mL/kg) as needed
Reduce O_2 demand
Consider prone positioning

Lower tidal volumes are unnecessary
Higher PEEP is ineffective, creates dead space, and adversely redirects blood flow



Type L

Low elastance
Low VA/Q mismatch
Low lung weight
Low reclutability

Non invasive support

- HFNC
- CPAP
- NIV

Early intubation

- PEEP (5-10 cmH_2O)
- Sedation
- NMBA

Late intubation

- Higher PEEP (10-15 cmH_2O)
- Prone position
- (ECMO)

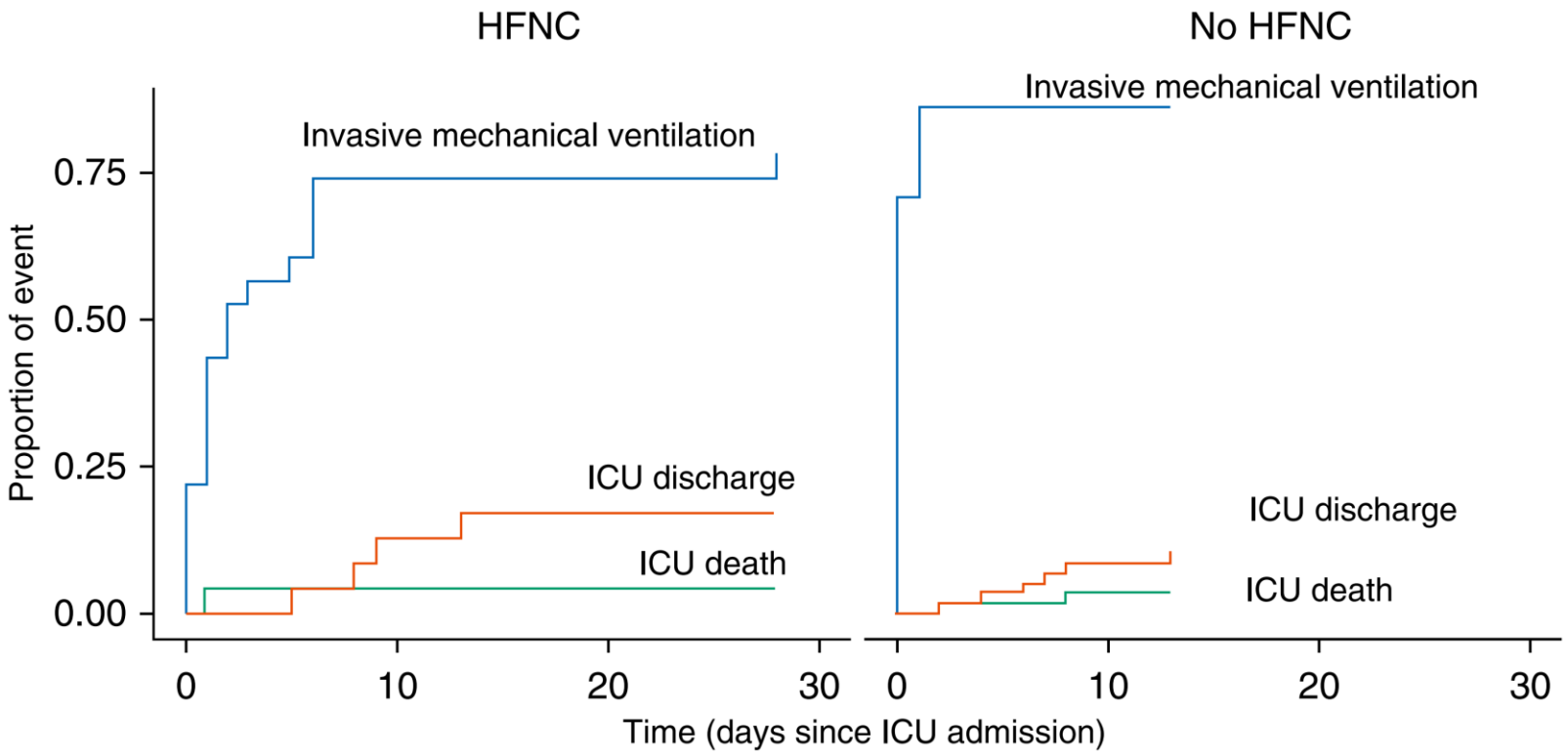
Type H

High elastance
High R-L shunt
High lung weight
High reclutability

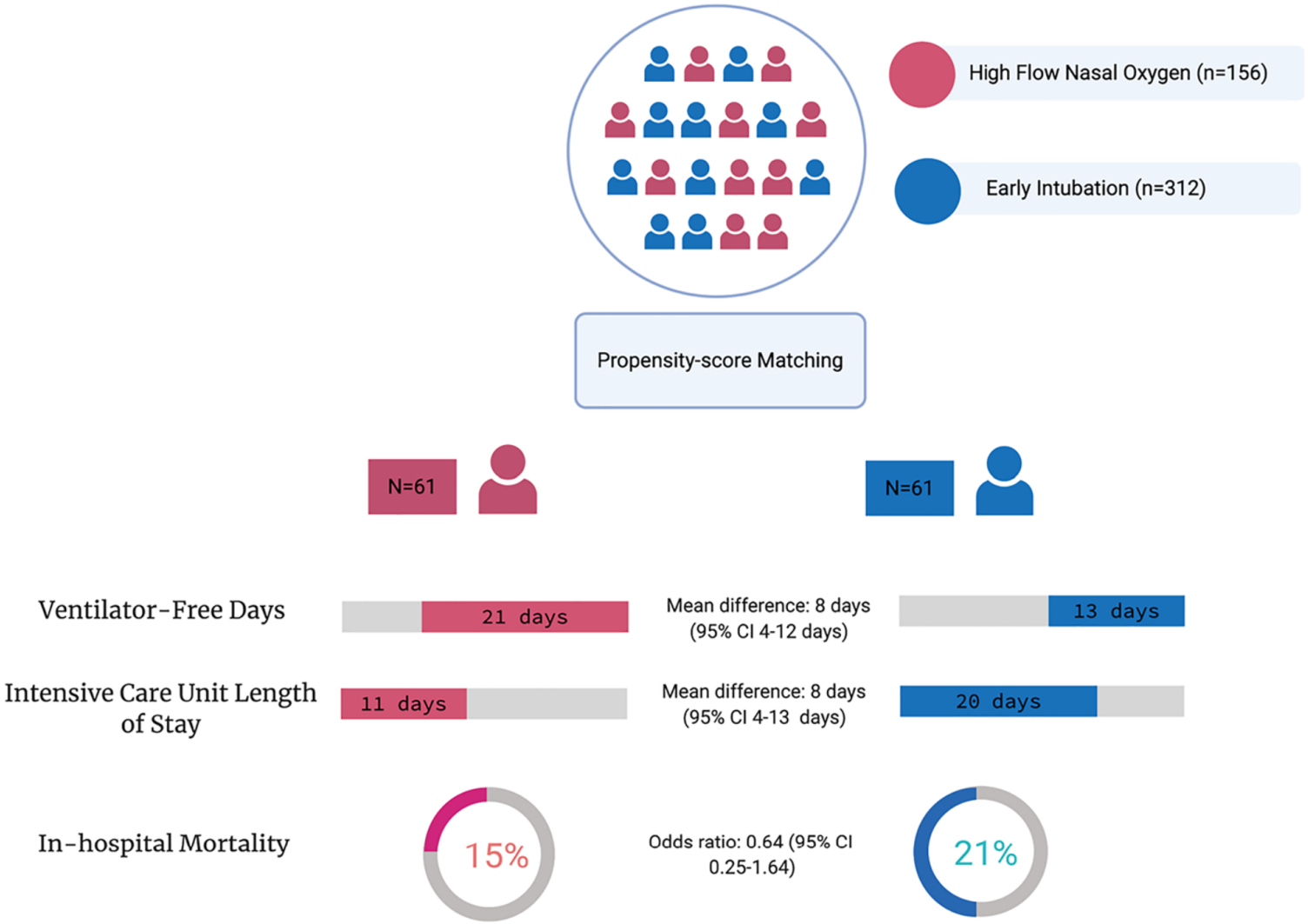
Ventilatory Support

- High Flow Nasal Cannula
- Self Prone Positioning
- Mechanical Ventilator Strategy
- ECMO

High flow nasal cannula (HFNC) reduce intubation



HFNC vs Early intubation



Failure of high-flow nasal cannula therapy may delay intubation and increase mortality

Abstract *Purpose:* Intubation in patients with respiratory failure can be avoided by high-flow nasal cannula (HFNC) use. However, it is unclear whether waiting until HFNC fails, which would delay intubation, has adverse effects. The present retrospective observational study assessed overall ICU mortality and other hospital outcomes of patients who received HFNC therapy that failed. *Methods:* All consecutive patients in one tertiary hospital who received HFNC therapy that failed and who then required intubation between January 2013 and March 2014 were enrolled and classified according to whether intubation started early (within 48 h) or late (at least 48 h) after commencing HFNC. *Results:* Of the 175 enrolled patients, 130 (74.3 %) and 45 (25.7 %) were intubated before and after 48 h of HFNC, respectively. The groups were similar in terms of most baseline characteristics. The early intubated patients had better overall ICU mortality (39.2 vs. 66.7 %; $P = 0.001$) than late intubated patients. A similar pattern was seen with extubation success (37.7 vs. 15.6 %; $P = 0.006$), ventilator weaning (55.4 vs. 28.9 %; $P = 0.002$), and ventilator-free days (8.6 ± 10.1 vs. 3.6 ± 7.5; $P = 0.011$). In propensity-adjusted and -matched analysis, early intubation was also associated with better overall ICU mortality [adjusted odds ratio (OR) = 0.317, $P = 0.005$; matched OR = 0.369, $P = 0.046$]. *Conclusions:* Failure of HFNC might cause delayed intubation and worse clinical outcomes in patients

Intensive Care Med. 2015 Apr;41(4):623-32.

Predictors of HFNC failure
ROX index

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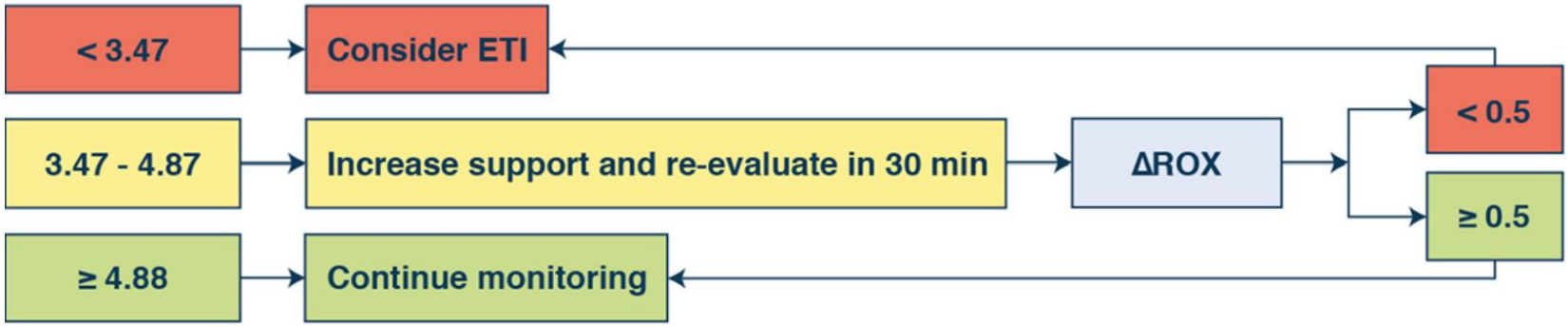
$$\text{ROX index} = \frac{SpO_2/F_iO_2}{RR}$$

Positive association with HFNC success

Positive association with HFNC Failure

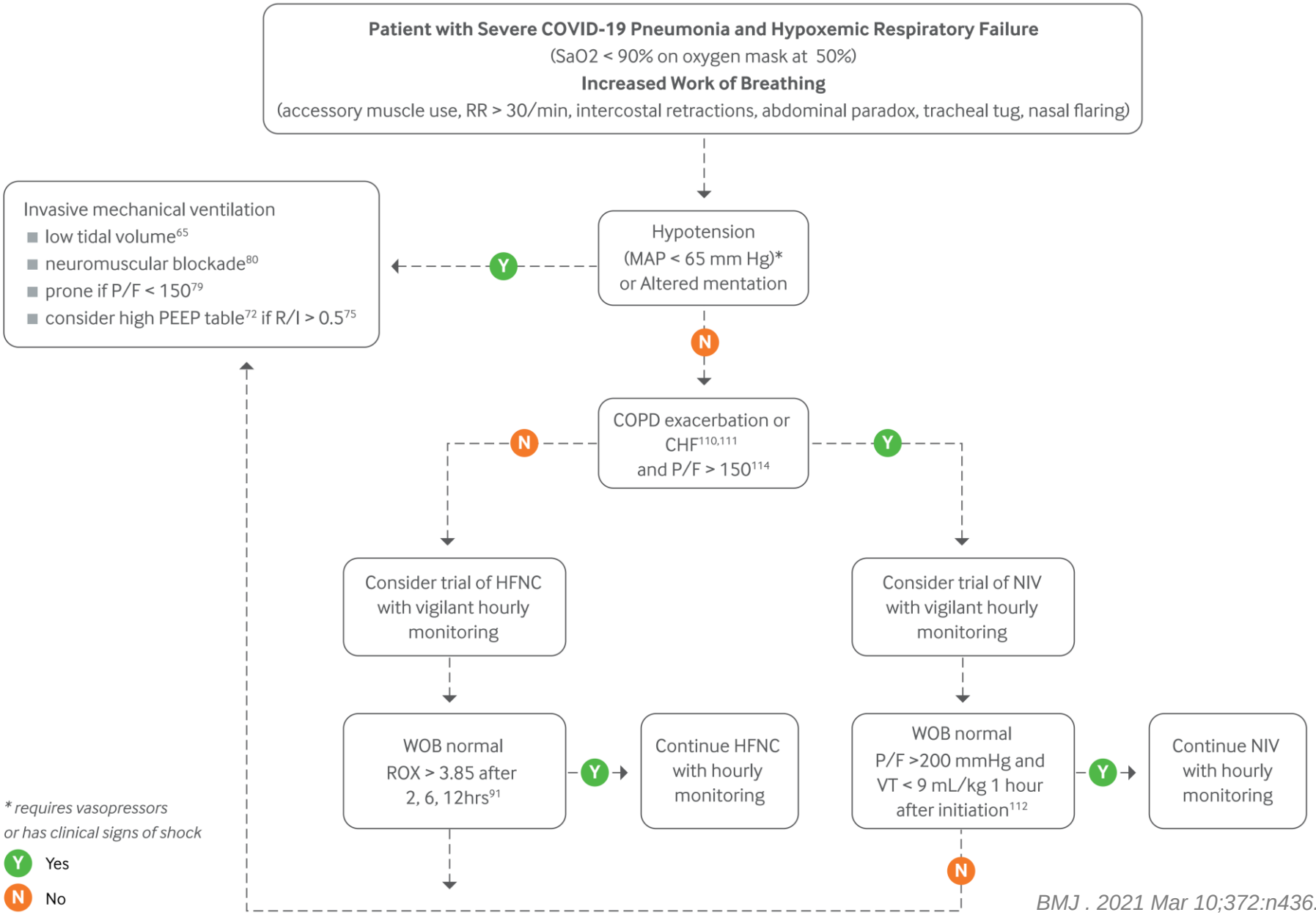
The lower, the higher rate of HFNC Failure



Intensive Care Med. 2015 Apr;41(4):623-32.

- ROX index ≥5.37 within 4 h of initiation of HFNO predicted a lower risk of intubation

Intensive Care Med 46:1924–1926.



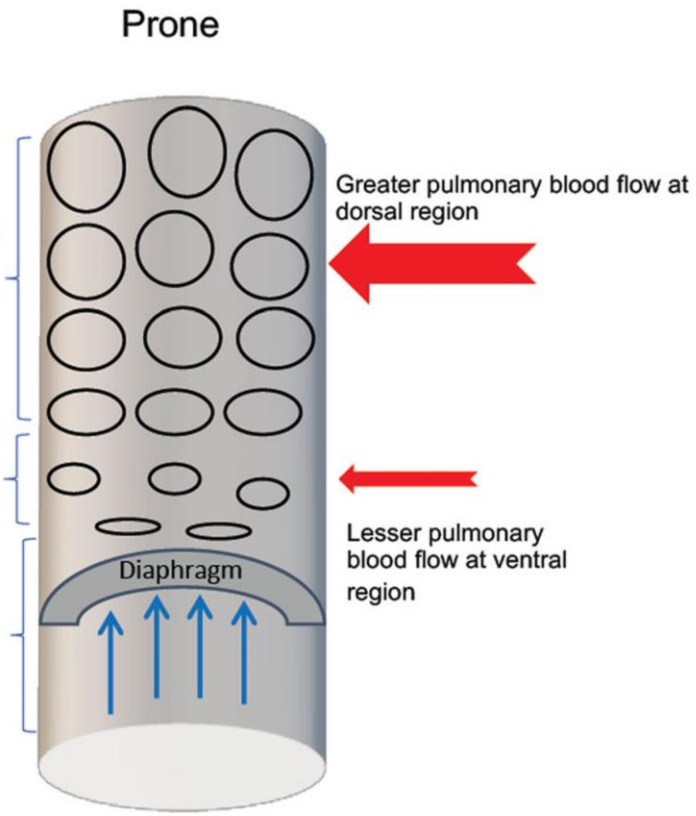
BMJ . 2021 Mar 10;372:n436.

Prone position

Prone positioning

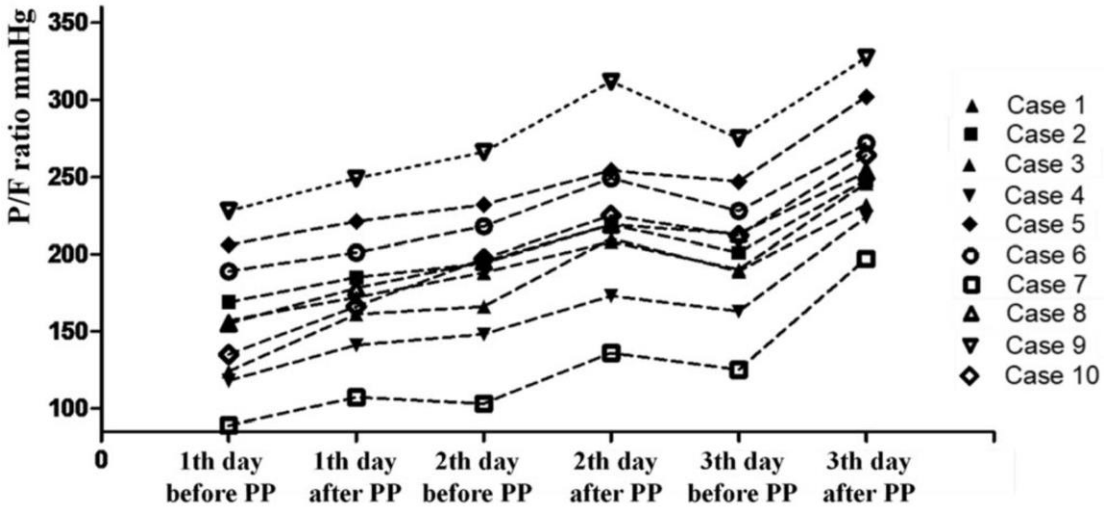
Current standards

Prone positioning is one of the most effective strategies in patients with moderately-severe ARDS ($PaO_2/FiO_2 < 150$ mmHg) and is the cornerstone of adjunctive therapies in these patients as it improves survival [64]. Prone positioning frequently leads to an improvement of gas exchange but the improved survival does not depend on improved oxygenation [65, 66]. This improved survival is likely mediated through a decrease in ventilator-induced lung injury due to a more uniform distribution of volume and distending forces across the lung. Several clinical trials have convincingly demonstrated that prone positioning applied early and for at least 16 h/day in ARDS patients with P/F < 150 mmHg reduces mortality

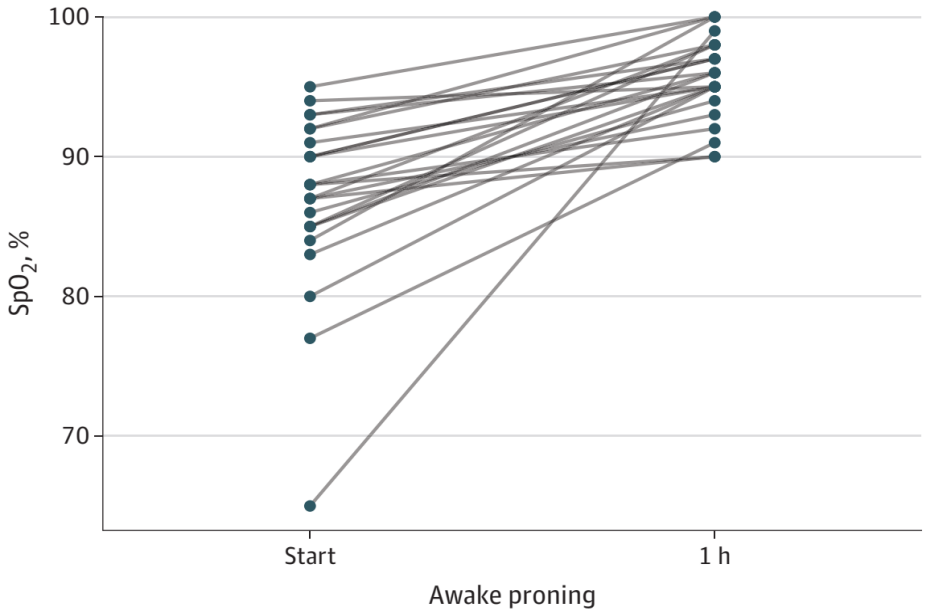


Pulm Ther (2020) 6:233–246

Ann Intensive Care. 2019 Jun 13;9(1):69.



- with an SpO2 of 95% or greater after 1 hour of the prone position was associated with a lower rate of intubation



Spo_2 before and 1 h after initiation of the prone position in awake, nonintubated patients with COVID-19 severe hypoxemic respiratory failure (n = 25).

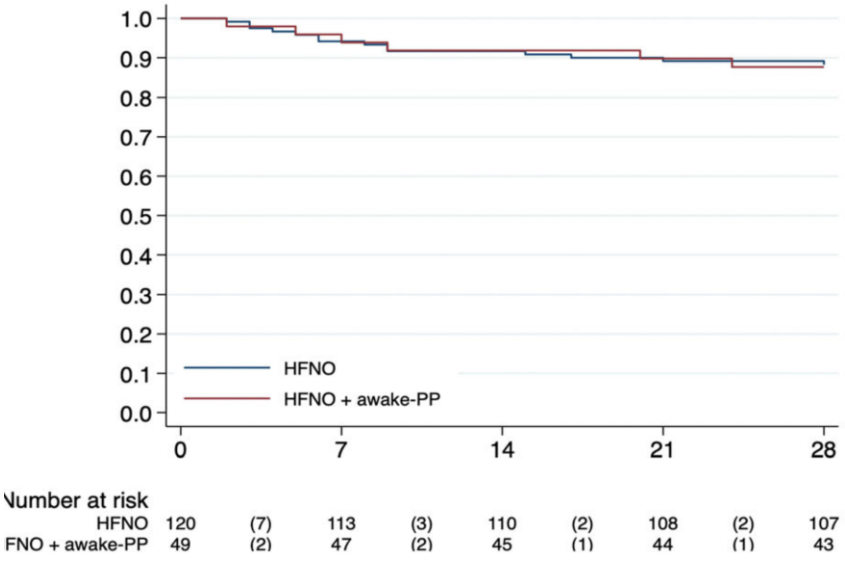
Crit Care. 2020 May 26;24(1):256.

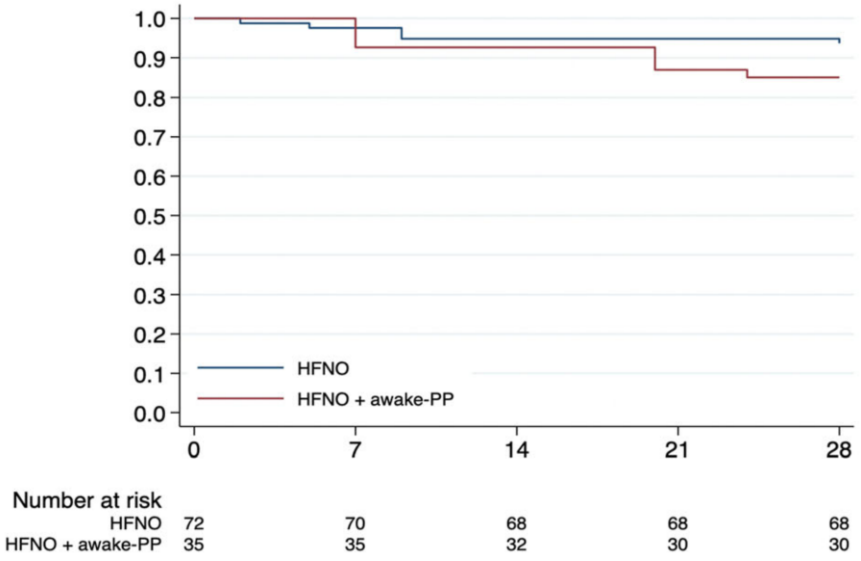
JAMA Intern Med . 2020 Jun 17;180(11):1537-1539.

Awake prone with HFNC

Analysis	Hazard ratio (95% CI); *p* value
Intubation	
Crude analysis	0.879 (0.538, 1.435); $p = 0.60$
Inverse probability weighting analysis	1.002 (0.531, 1.890); $p = 0.99$
28-day mortality	
Crude analysis	1.046 (0.402, 2.722); $p = 0.92$
Inverse probability weighting analysis	2.411 (0.556, 10.442); $p = 0.23$

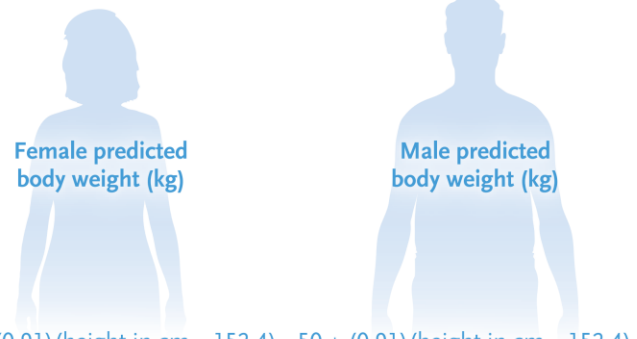
Crit Care. 2020 Oct 6;24(1):597.





Mechanical Ventilator Strategy

Measure height and calculate predicted body weight



45.5 + (0.91) (height in cm – 152.4)

50 + (0.91) (height in cm – 152.4)

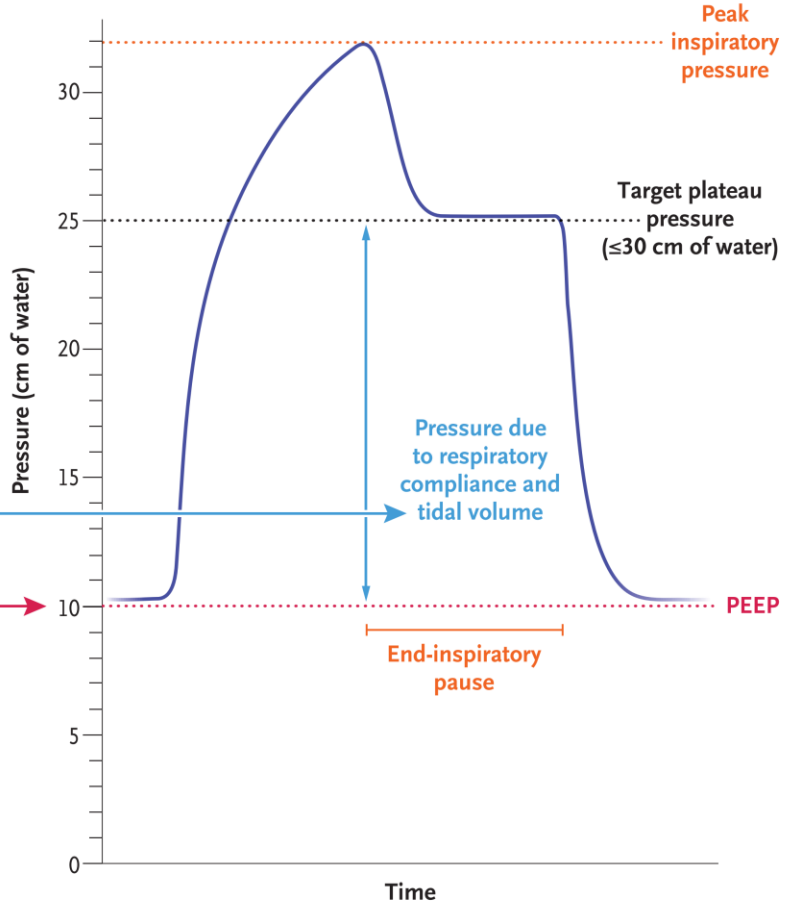
Target tidal volume, 6–8 ml/kg of predicted body weight

Set PEEP to prevent lung derecruitment

Monitor hemodynamics, respiratory compliance, and gas exchange at each PEEP setting

If plateau pressure >30 cm of water, consider:

- Reducing tidal volume (minimum, 4 ml/kg of predicted body weight)
- Reducing PEEP
- Allowing higher plateau pressures in patients with obesity or reduced chest-wall compliance



N Engl J Med. 2020 Dec 17;383(25):2451-2460.

ECMO for CARDS

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Methods This retrospective cohort study was done in the Paris–Sorbonne University Hospital Network, comprising five intensive care units (ICUs) and included patients who received ECMO for COVID-19 associated ARDS. Patient demographics and daily pre-ECMO and on-ECMO data and outcomes were collected. Possible outcomes over time were categorised into four different states (states 1–4): on ECMO, in the ICU and weaned off ECMO, alive and out of ICU, or death. Daily probabilities of occupation in each state and of transitions between these states until day 90 post-ECMO onset were estimated with use of a multi-state Cox model stratified for each possible transition. Follow-up was right-censored on July 10, 2020.

Findings From March 8 to May 2, 2020, 492 patients with COVID-19 were treated in our ICUs. Complete day-60 follow-up was available for 83 patients (median age 49 [IQR 41–56] years and 61 [73%] men) who received ECMO. Pre-ECMO, 78 (94%) patients had been prone-positioned; their median driving pressure was 18 (IQR 16–21) cm H_2O and PaO_2/FiO_2 was 60 (54–68) mm Hg. At 60 days post-ECMO initiation, the estimated probabilities of occupation in each state were 6% (95% CI 3–14) for state 1, 18% (11–28) for state 2, 45% (35–56) for state 3, and 31% (22–42) for state 4. 35 (42%) patients had major bleeding and four (5%) had a haemorrhagic stroke. 30 patients died.

Interpretation The estimated 60-day survival of ECMO-rescued patients with COVID-19 was similar to that of studies published in the past 2 years on ECMO for severe ARDS. If another COVID-19 outbreak occurs, ECMO should be considered for patients developing refractory respiratory failure despite optimised care.

Lancet Respir Med 2020;8: 1121–31

Pharmacological Therpay

- **Corticosteroid**
- **Remdesvir**
- **Tocilizumab**
- **Convalescent plasma**

Dexamethasone

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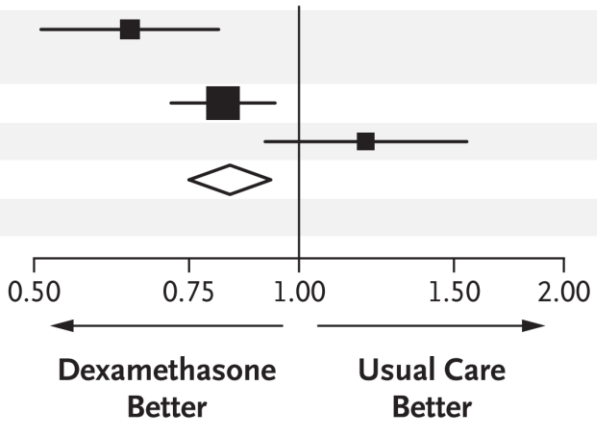
Table 2. Primary and Secondary Outcomes and Prespecified Subsidiary Clinical Outcomes.

Outcome	Dexamethasone (N=2104)	Usual Care (N=4321)	Rate or Risk Ratio (95% CI)*
		no./total no. of patients (%)	
Primary outcome			
Death at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)

Respiratory Support at Randomization	Dexamethasone	Usual Care	Rate Ratio (95% CI)
	no. of events/total no. (%)		
Invasive mechanical ventilation	95/324 (29.3)	283/683 (41.4)	0.64 (0.51–0.81)
Oxygen only	298/1279 (23.3)	682/2604 (26.2)	0.82 (0.72–0.94)
No oxygen received	89/501 (17.8)	145/1034 (14.0)	1.19 (0.92–1.55)
All Patients	**482/2104 (22.9)**	**1110/4321 (25.7)**	**0.83 (0.75–0.93)**
			P<0.001

Chi-square trend across three categories: 11.6



N Engl J Med 2021;384:693-704.

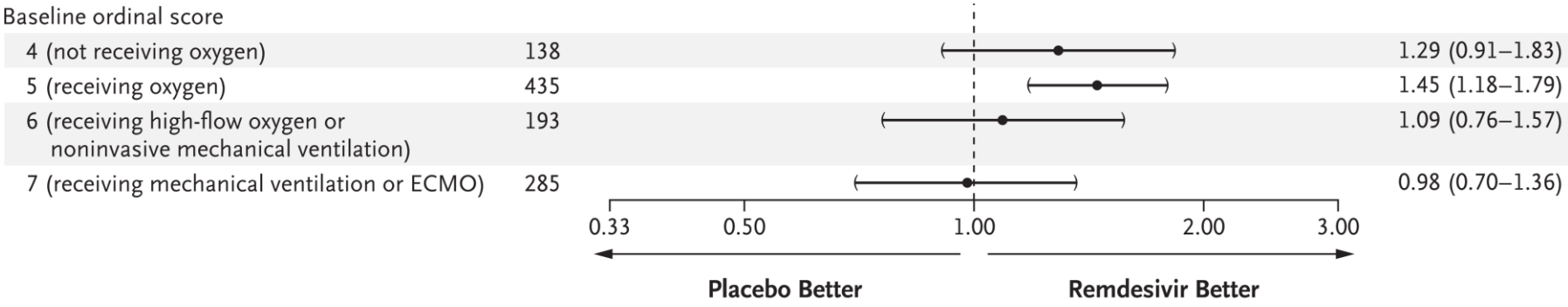
Remdesivir

METHODS

We conducted a double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection. Patients were randomly assigned to receive either remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) or placebo for up to 10 days. The primary outcome was the time to recovery, defined by either discharge from the hospital or hospitalization for infection-control purposes only.

RESULTS

A total of 1062 patients underwent randomization (with 541 assigned to remdesivir and 521 to placebo). Those who received remdesivir had a median recovery time of 10 days (95% confidence interval [CI], 9 to 11), as compared with 15 days (95% CI, 13 to 18) among those who received placebo (rate ratio for recovery, 1.29; 95% CI, 1.12 to 1.49; P<0.001, by a log-rank test). In an analysis that used a proportion-



N Engl J Med 2020;383:1813-26.

Tocilizumab

METHODS

We performed a randomized, double-blind, placebo-controlled trial involving patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, hyperinflammatory states, and at least two of the following signs: fever (body temperature >38°C), pulmonary infiltrates, or the need for supplemental oxygen in order to maintain an oxygen saturation greater than 92%. Patients were randomly assigned in a 2:1 ratio to receive standard care plus a single dose of either tocilizumab (8 mg per kilogram of body weight) or placebo. The primary outcome was intubation or death, assessed in a time-to-event analysis. The secondary efficacy outcomes were clinical worsening and discontinuation of supplemental oxygen among patients who had been receiving it at baseline, both assessed in time-to-event analyses.

Table 2. Time-to-Event Outcomes in the Modified Intention-to-Treat Population.*

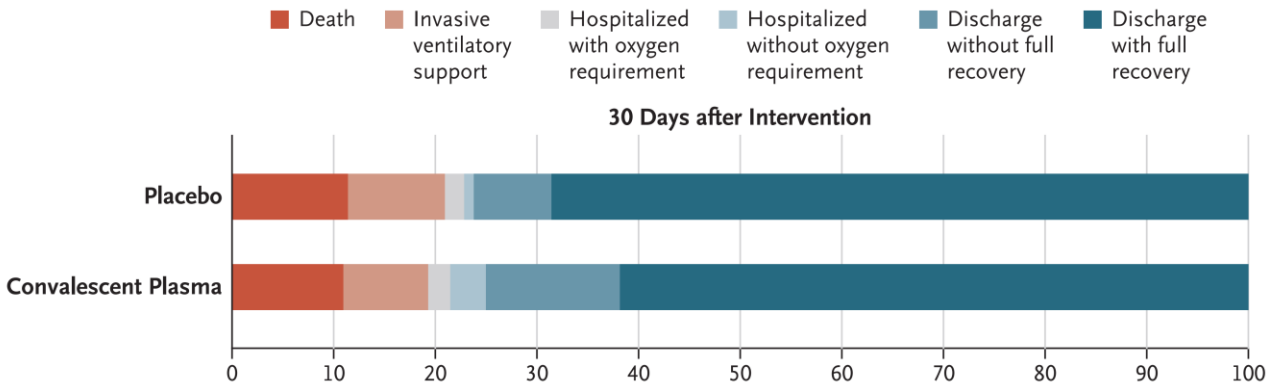
Outcome	No. of Patients with Event within 28 Days	Percentage of Patients with Event (95% CI)†		Median No. of Days to Event (95% CI)	Hazard Ratio (95% CI)	Log-Rank P Value‡
		Day 14	Day 28			
Measures of worsening						
Primary outcome: mechanical ventilation or death						
Tocilizumab	17	9.9 (6.2–15.7)	10.6 (6.7–16.6)	NR	0.83 (0.38–1.81)	0.64
Placebo	10	10.0 (5.1–18.9)	12.5 (6.9–22.0)	NR		
Secondary outcome: clinical worsening on ordinal scale§						
Tocilizumab	31	18.0 (12.9–24.9)	19.3 (14.0–26.2)	NR	1.11 (0.59–2.10)	0.73
Placebo	14	14.9 (8.7–24.7)	17.4 (10.7–27.7)	NR		

N Engl J Med 2020;383:2333-44.

Convalescent plasma

Table 2. Clinical Outcomes in Patients Who Received Convalescent Plasma as Compared with Placebo.*

Outcomes	Convalescent Plasma (N = 228)	Placebo (N = 105)	Odds Ratio or Hazard Ratio (95% CI)	P value
Primary outcome, clinical status at 30 days — no. of patients (%)			Odds ratio, 0.81 (0.50–1.31)	0.396
Death	25 (11)	12 (11.4)		
Invasive ventilatory support	19 (8.3)	10 (9.5)		
Hospitalized with supplemental oxygen requirement	5 (2.2)	2 (1.9)		
Hospitalized without supplemental oxygen requirement	8 (3.5)	1 (1)]		
Discharged without full return to baseline physical function	30 (13.2)	8 (7.6)		
Discharged with full return to baseline physical function	141 (61.8)	72 (68.6)		



N Engl J Med 2021;384:619-29.

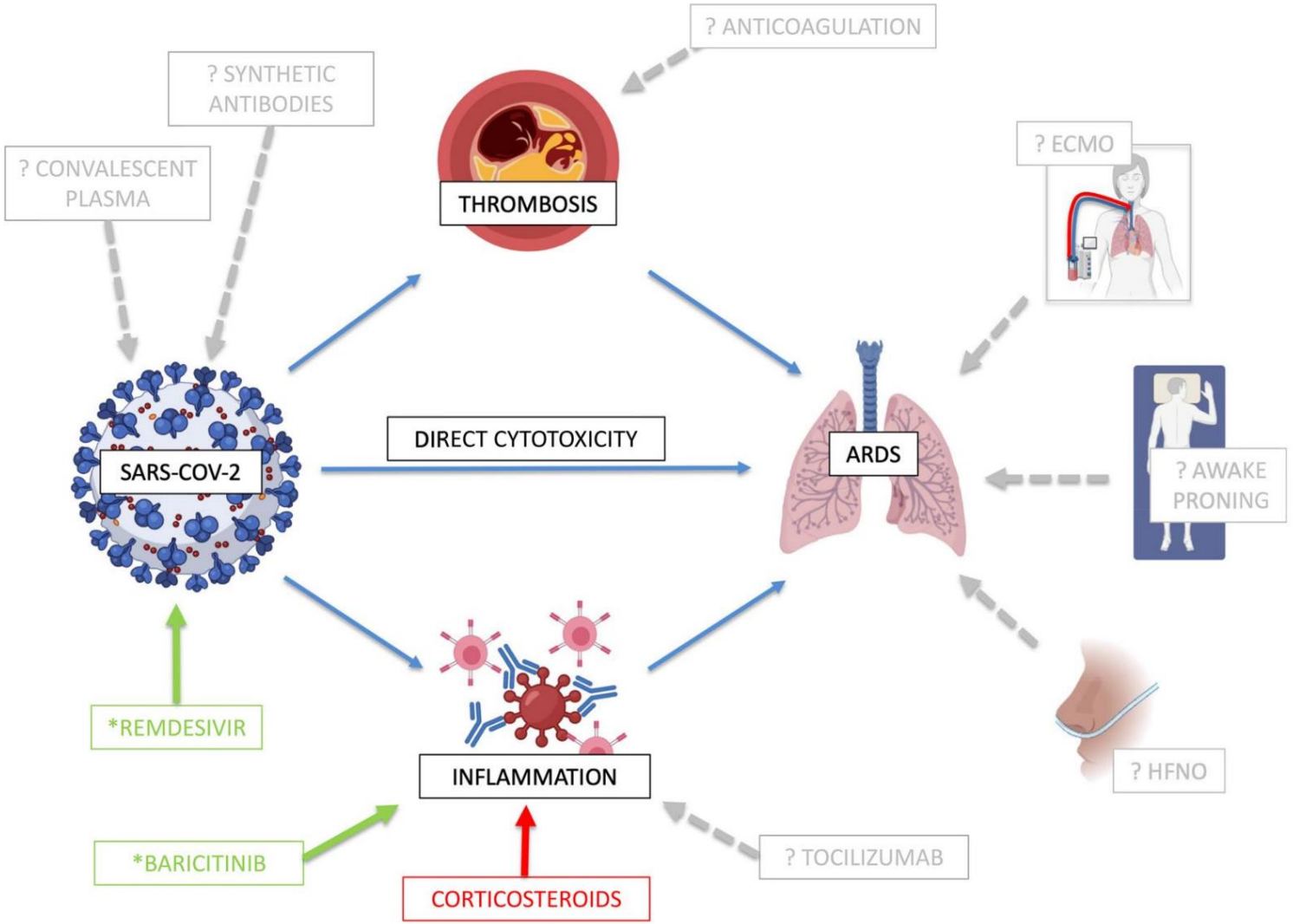
Pharmacological Therpay

Table 2 | Therapeutic considerations for acute covid-19 by clinical syndrome/disease severity

Clinical scenario	Pharmacologic interventions
Hospitalized for mild to moderate covid-19 (not hypoxemic)	• Supportive care • No clear benefit for remdesivir or convalescent plasma • Steroids have no demonstrated benefit and may cause harm
Hospitalized for severe covid-19, but not critical (hypoxemic needing low flow supplemental oxygen)	• Supportive care • Corticosteroids (dexamethasone 6 mg/day × 10 days or until discharge or an equivalent dose of hydrocortisone or methylprednisolone) • May consider remdesivir • May benefit from use of tocilizumab.
Hospitalized for covid-19 and critically ill (needing HFNC, NIV, IMV, or ECMO)	• Supportive care • Corticosteroids (dexamethasone 6 mg/day × 10 days or until discharge or an equivalent dose of hydrocortisone or methylprednisolone) • May consider remdesivir • May benefit from use of tocilizumab.

BMJ . 2021 Mar 10;372:n436.

Summary



BMJ . 2021 Mar 10;372:n436.