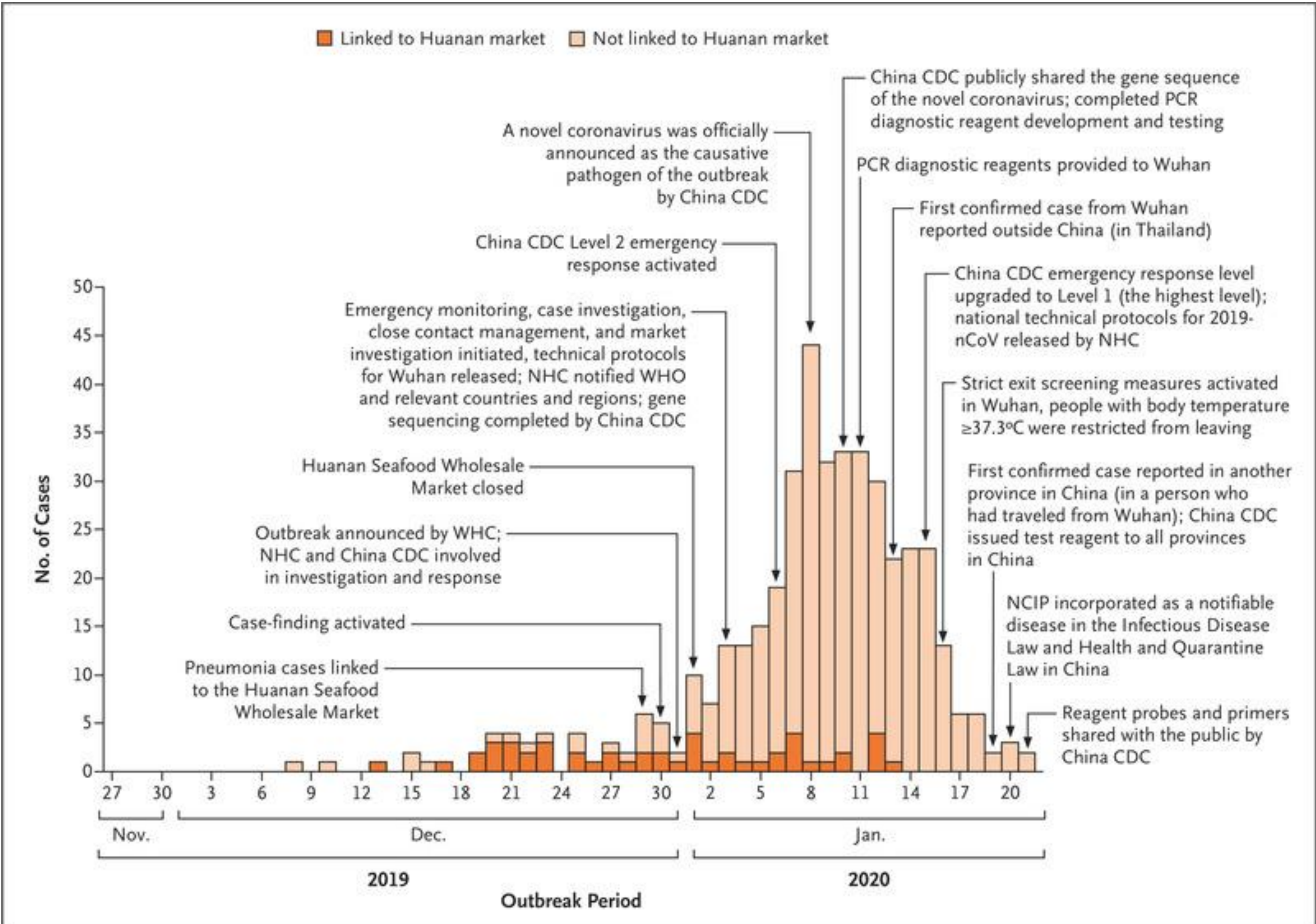
Critically Ill Patients with COVID-19: China Experience

Bin Du, MD
Medical ICU
Peking Union Medical College Hospital

Conflicts of Interest

- None



Linked to Huanan market
Not linked to Huanan market
No. of Cases
0
5
10
15
20
25
30
35
40
45
50
27
30
3
6
9
12
15
18
21
24
27
30
2
5
8
11
14
17
20
Nov.
Dec.
Jan.
2019
2020
Outbreak Period
Pneumonia cases linked to the Huanan Seafood Wholesale Market
Case-finding activated
Outbreak announced by WHC; NHC and China CDC involved in investigation and response
Huanan Seafood Wholesale Market closed
Emergency monitoring, case investigation, close contact management, and market investigation initiated, technical protocols for Wuhan released; NHC notified WHO and relevant countries and regions; gene sequencing completed by China CDC
China CDC Level 2 emergency response activated
A novel coronavirus was officially announced as the causative pathogen of the outbreak by China CDC
China CDC publicly shared the gene sequence of the novel coronavirus; completed PCR diagnostic reagent development and testing
PCR diagnostic reagents provided to Wuhan
First confirmed case from Wuhan reported outside China (in Thailand)
China CDC emergency response level upgraded to Level 1 (the highest level); national technical protocols for 2019-nCoV released by NHC
Strict exit screening measures activated in Wuhan, people with body temperature ≥37.3°C were restricted from leaving
First confirmed case reported in another province in China (in a person who had traveled from Wuhan); China CDC issued test reagent to all provinces in China
NCIP incorporated as a notifiable disease in the Infectious Disease Law and Health and Quarantine Law in China
Reagent probes and primers shared with the public by China CDC

Fact Sheet about COVID-19

APRIL

13

23:00 CEST

cumulative
confirmed cases

1,776,867

+84,644

cumulative
deaths

111,828

+6,250

WHO. Coronavirus (COVID-19). Available at https://who.sprinklr.com accessed April 14, 2020

Epidemic of Confirmed COVID-19 Cases

among 44,415 cases

mild cases
81%

Diagnostic Criteria
severe
- **hypoxemia (SpO_2 < 93%) @ RA**

critical
- **hypoxemia requiring NIV/IMV**
- **shock**
- **other organ failure**

severe cases
14%

critical cases
5%

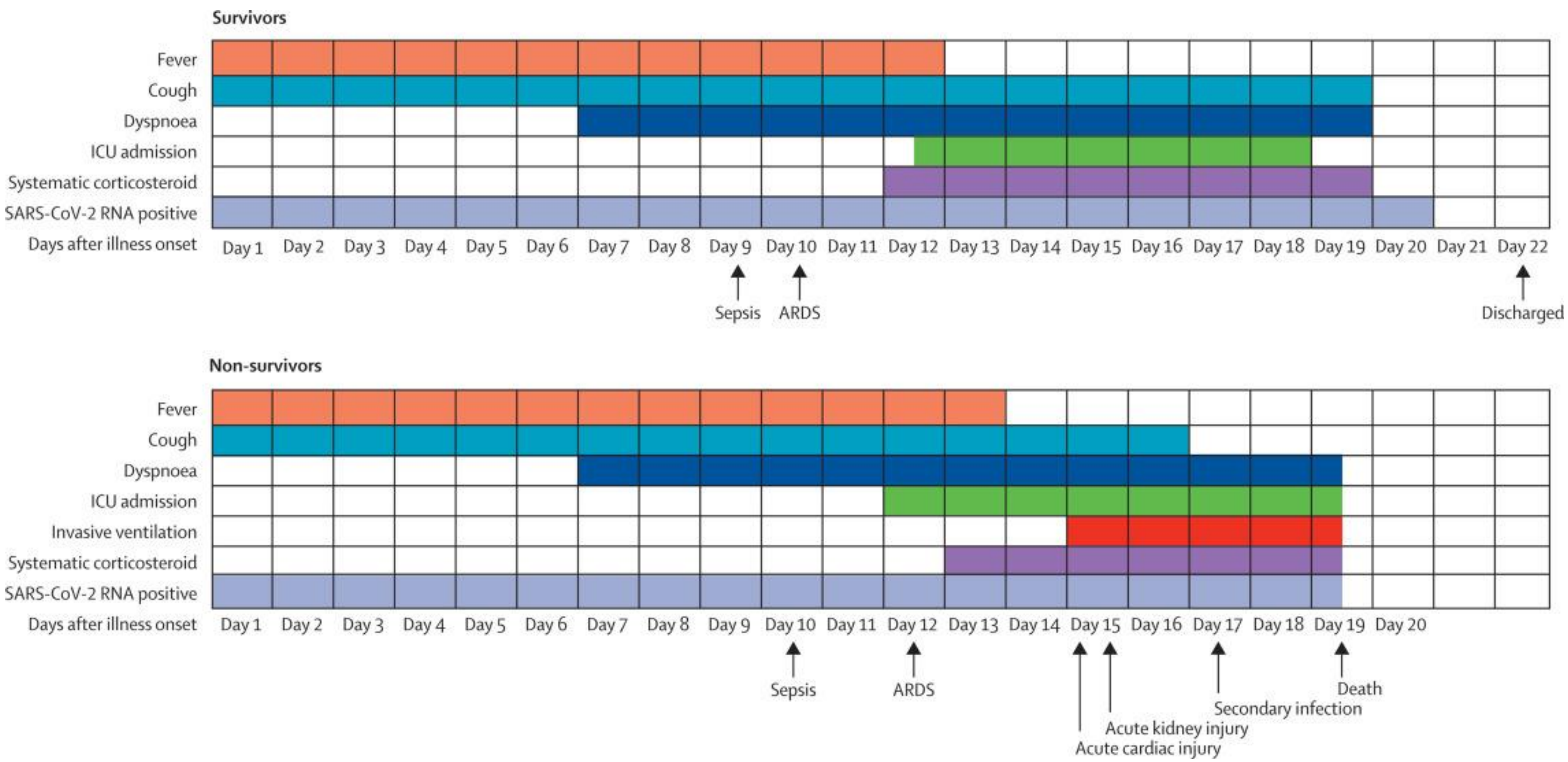
Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020; 323: 1239-1242

Presenting Signs/Symptoms

	Huang et al (n = 41)	Chen et al (n = 99)
Fever	**98%** (40)	**83%** (83)
Cough	**76%** (31)	**82%** (81)
Shortness of breath or dyspnea	**55%** (22/40)	**31%** (31)
Myalgia or fatigue	**44%** (18)	**11%** (11)
Diarrhea	**3%** (1/38)	**2%** (2)

Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506
Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395: 507-513

Clinical Course of Patients with COVID-19

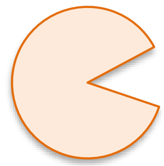


Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020

1591 Critically Ill Patients with COVID-19

Demographics (n = 1591)

63 (56-70)
years

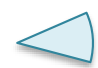


82% (1304)
male

68% (709/1043)
any comorbidity

Respiratory Support (n = 1300)

88% (1150)
IMV



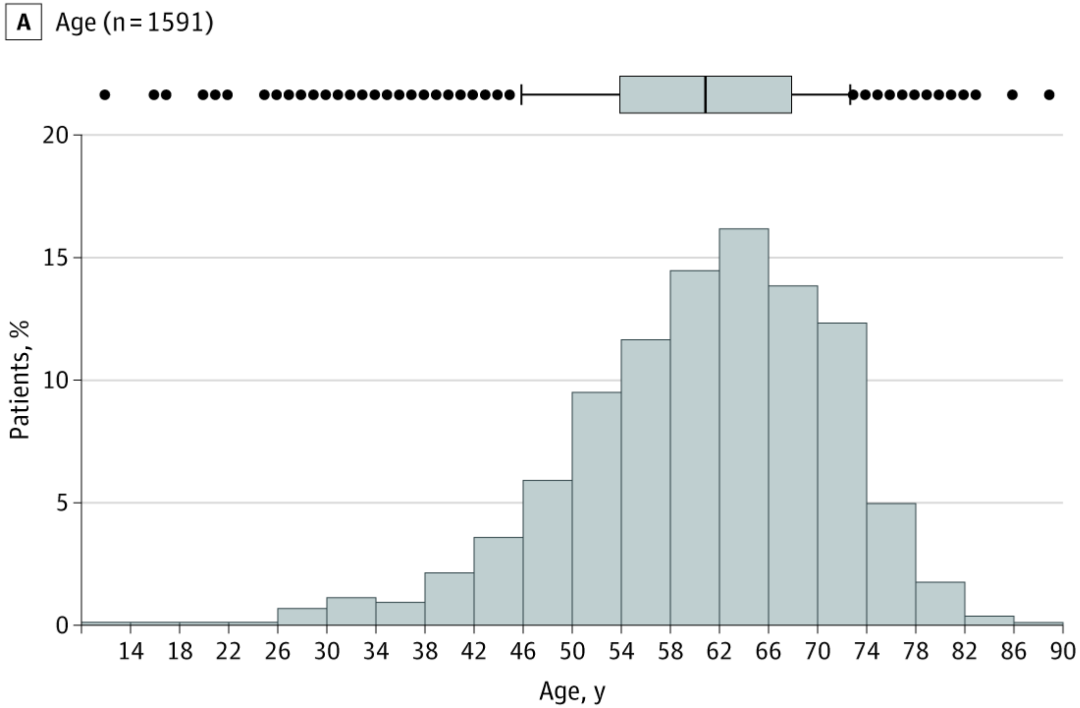
11% (137)
NIV

14 (12-16) cmH_2O
PEEP

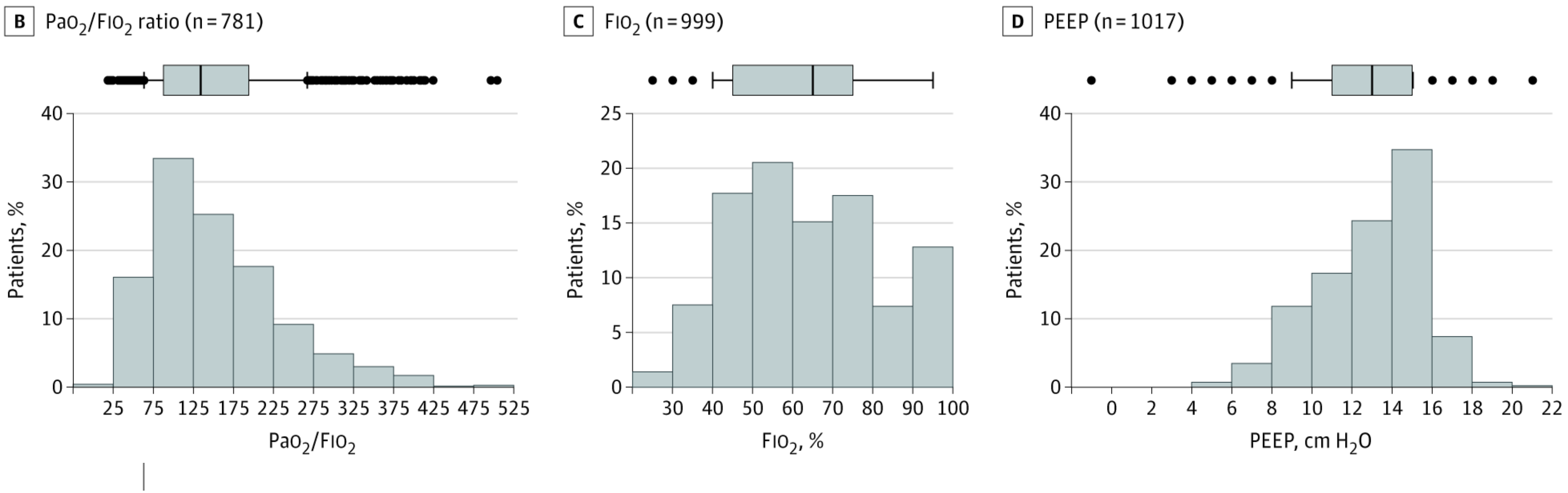
89% (1157)
$FiO_2 > 50\%$

160 (114-220) mmHg
PaO_2/FiO_2

Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA 2020



Retrospective case series of 1591 consecutive patients with laboratory-confirmed COVID-19 referred to the ICUs of the 72 hospitals between February 20 and March 18, 2020.



Clinical Features of Patients with COVID-19

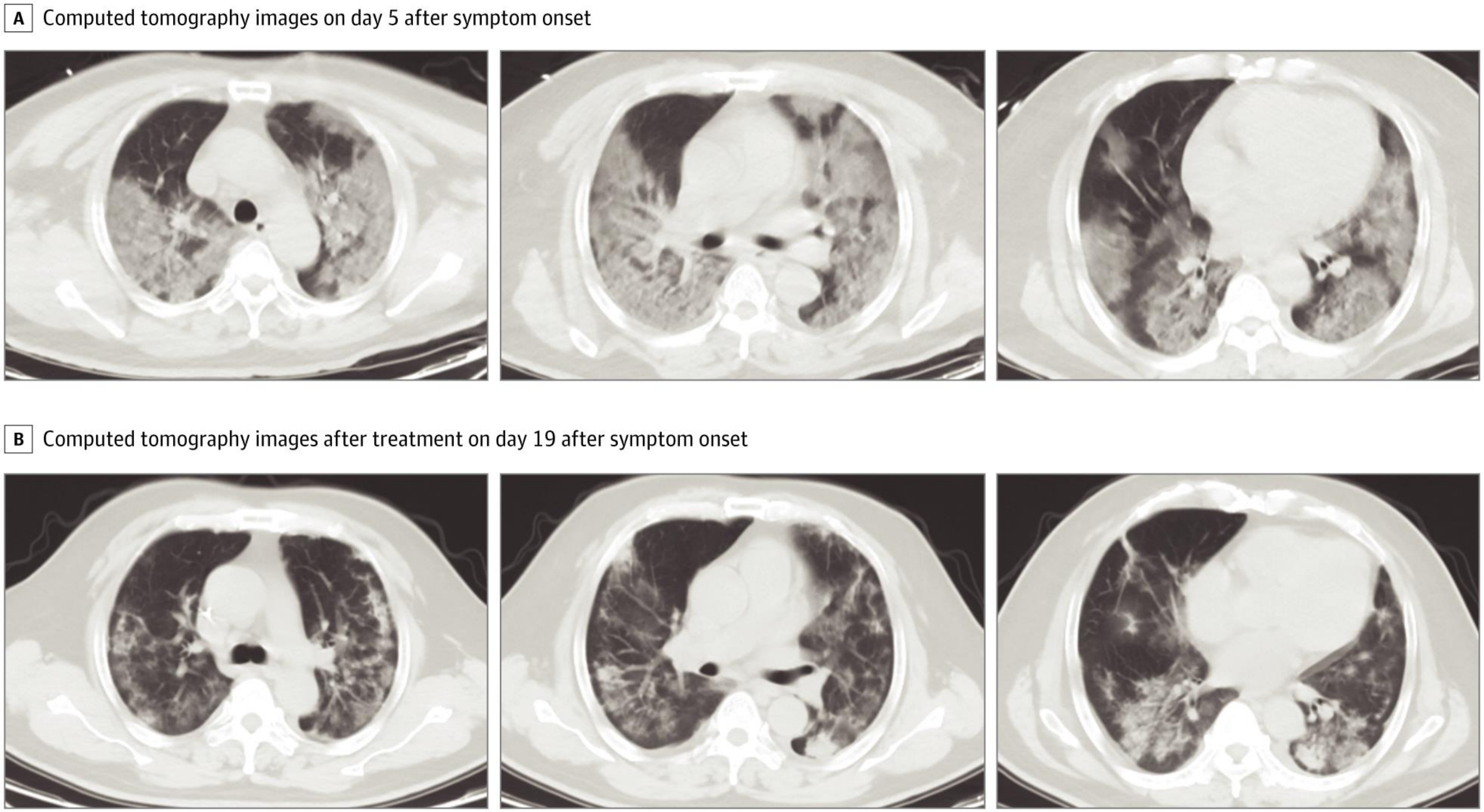
Study	No.	ICU adm	Cardiac injury	Shock	NIV	IMV	CFR
Huang	41	32%	12%	7%	24%	5%	15%
Chen	99	23%		4%	13%	4%	11%
Wang	138	26%	7%	9%	11%	12%	
Guan	1099			1%	5.1%	2.3%	1%
Yang	52	100%	23%	35%	55.8%	42.3%	62%
Zhou	191	26%	17%	20%	14%	17%	28%
Chen	274		44%	17%	37%	6%	41%

Alhazzani W, Møller MH, Arabi YM, et al. Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Intensive Care Med 2020

Respiratory Failure in Patients with COVID-19

	All Patients	ICU Patients
Prevalence of ARDS	**17%** to **41%**	**61%** to **85%**
HFNC	**21%** to **27%**	**63.5%**
NIV	**10.9%** to **34%**	**41.7%** to **62%**
IMV	**4%** to **17%**	**30%** to **47.2%**
Prone positioning	**2%**	**11.5%**
ECMO	**2.9%** to **5%**	**11.1%** to **15%**

Acute Respiratory Failure in COVID-19



Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; 323; 1061-1069

High Failure Rate of NIV/HFNC Trial

- Prolonged NIV/HFNC failure associated with high fatality
  - Even after invasive mechanical ventilation
- Criteria of NIV failure
  - Refractory hypoxemia
  - High tidal volume (> 9 ml/kg IBW) or inspiratory effort
  - Overt respiratory distress
- Prompt initiation of invasive mechanical ventilation highly recommended by WHO Interim Guidance
  - Within 2 hours vs. 1 to 2 days

WHO Interim Guidance on NIV/HFNC

- HFNO or NIV should only be used in selected patients with hypoxemic respiratory failure
- The risk of treatment failure is high in patients with MERS treated with NIV, and patients treated with either HFNO or NIV should be closely monitored for clinical deterioration

Severe Hypoxemia in COVID-19

- Refractory hypoxemia ($PaO_2/FiO_2 < 100$ mmHg) very common
  - Possibly due to delay of invasive mechanical ventilation
- Lung protective ventilation strategy
  - Heavy sedation and/or neuromuscular blockade necessary
  - Low tidal volume
  - PEEP with a double-edged sword effect
    - Improved PaO_2 at the cost of alveolar overdistention
    - 5 to 10 cmH_2O?

Severe Hypoxemia in COVID-19

- Rescue therapy
  - Recruitment maneuver
    - Effective in 80% of patients at early stage
    - Ineffective at late stage?
  - Prone positioning
    - Effective in almost all patients?
    - Even in patients with NIV/HFNC

Refractory Hypercapnia in COVID-19

- A finding at late stage?
  - Usually after the third week after symptom onset
  - $PaCO_2$ up to > 150 mmHg
- A sign of poor prognosis?
- Potential mechanism
  - Dead space ventilation
- Management
  - Partially resolved by adjusting minute ventilation, or prone positioning
  - Improved with disease resolution

COVID-19 vs. ARDS

	COVID-19	ARDS
Etiology	SARS-CoV-2	Infectious and noninfectious etiologies
Radiology	Ground glass opacity	Consolidation in dependent regions
Pathophysiology		
Hypoxemia	?	Intrapulmonary shunt
Hypercapnia	Dead space ventilation	Low tidal volume ventilation
Treatment		
Tidal volume	Low	Low
PEEP	< 5 (?) due to alveolar overdistention	High
Proning	Highly effective	Effective
RM	Effective only at early stage	Depending on etiology, radiographic features

Cardiac Injury in Patients with COVID-19

Prevalence of Cardiac Injury*

All Patients	ICU Patients
7% to **17%**	**22%** to **31%**

*defined as elevated biomarkers of cardiac injury

Hypersensitive cardiac troponin I (hscTnI)

up to **20,000⁺** pg/mL

Result of Viral Myocarditis?

Cardiac Injury in Patients with COVID-19

	Survivors (n = 137)	Nonsurvivors (n = 54)
hscTnI (pg/mL)	**3,000** (1,100 – 5,500)	**22,200** (560 – 83,100)
		P < 0.0001
hscTnI > 28,000 pg/mL	**1%** (1/95)	**46%** (23/50)
		P < 0.0001

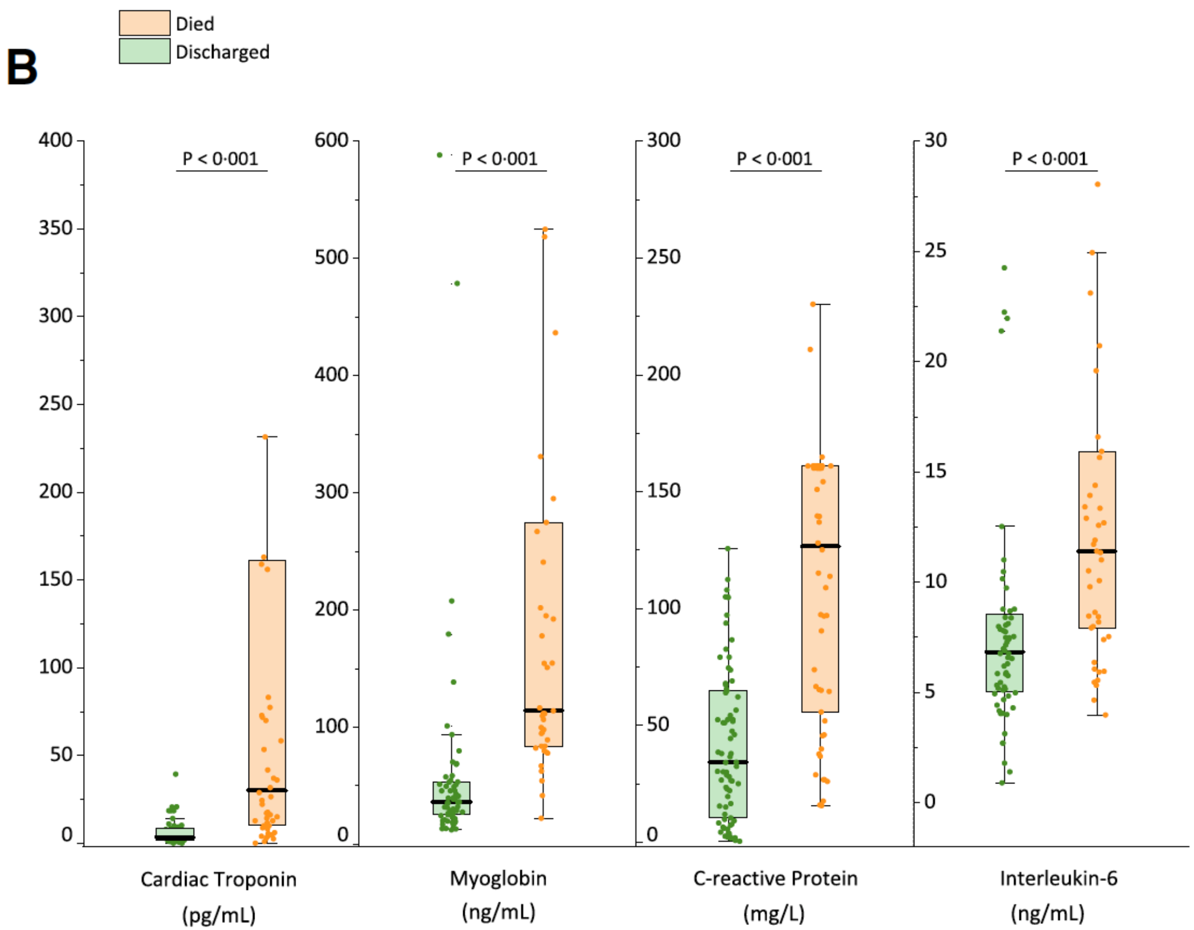
Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020

Cardiac Injury in Patients with COVID-19

	Survivors (n = 161)	Nonsurvivors (n = 113)
hscTnI (pg/mL)	**3.3** (1.9 – 7.0)	**40.8** (14.7 –157.8)
> 15.6 pg/mL	**14%** (15/109)	**72%** (68/94)
NT-proBNP (pg/mL)	**72.0** (20.0 – 185.0)	**800.0** (389.8 – 1817.5)
> 285 pg/mL	**18%** (17/93)	**85%** (68/80)

Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020; 368: m1091

Predictors of COVID-19 Hospital Mortality



Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020

Causes of Death in Patients with COVID-19

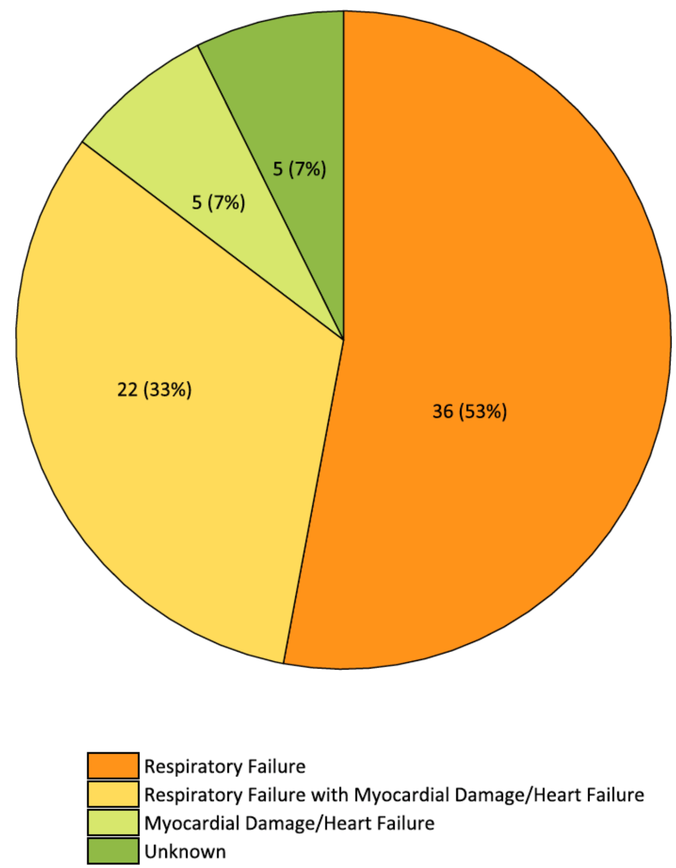
Prevalence of Shock

All Patients

4% to 20%

ICU Patients

23% to 31%

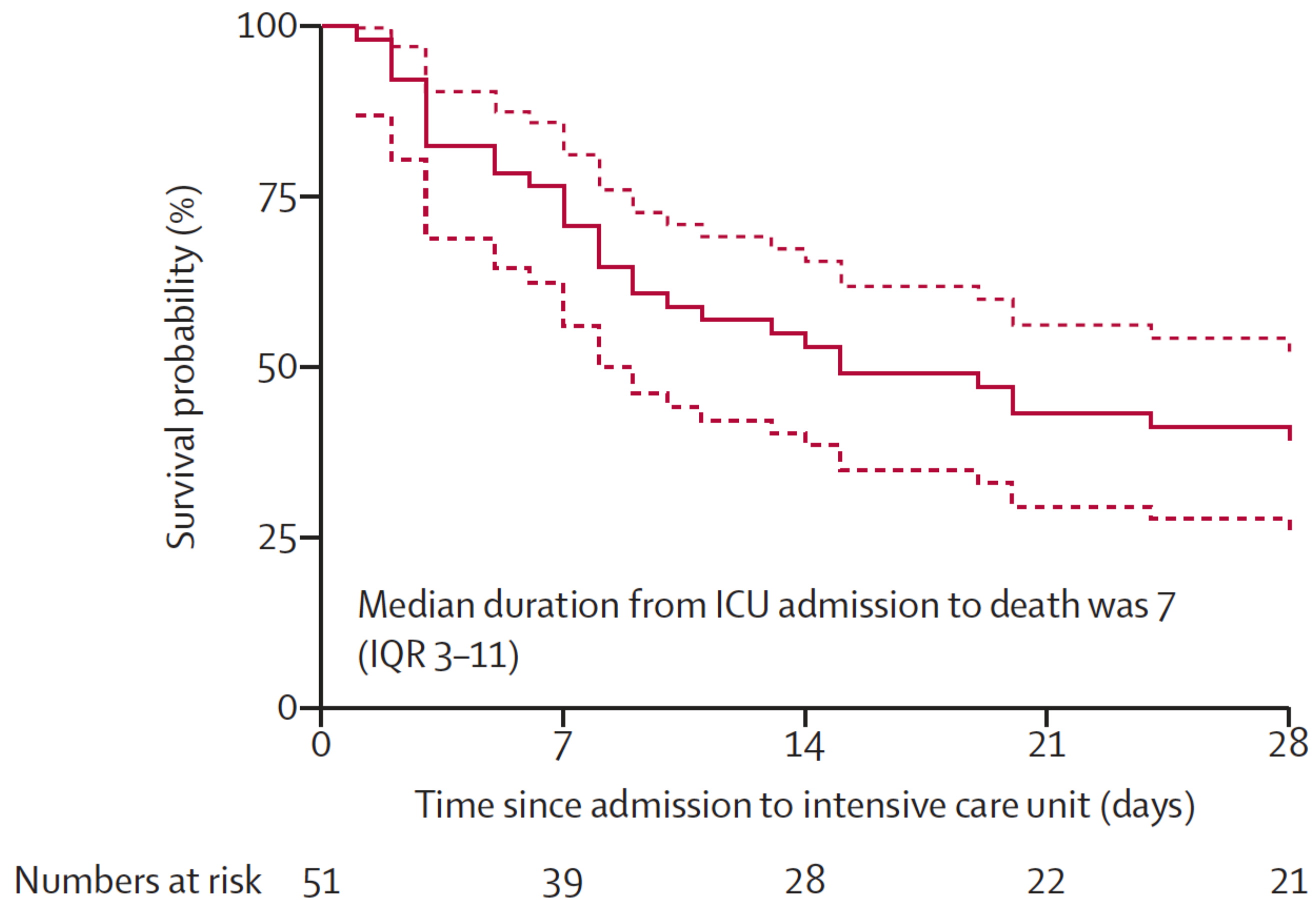


Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020

Acute Renal Injury in Patients with COVID-19

	All Patients	ICU Patients
Prevalence of AKI	3% to 15%	8.3% to 29%
CRRT	1.5% to 9%	5.6% to 23%

Critically Ill Patients with COVID-19



Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020

Risk Factors for Mortality in COVID-19

	Univariate OR	Multivariate OR
Age, per year increase	**1.14** (1.09 – 1.18) < 0.0001	**1.10** (1.03 – 1.17) 0.0043
SOFA score, per 1 unit increase	**6.14** (3.48 – 10.85) < 0.0001	**5.65** (2.61 – 12.23) < 0.0001
D-dimer ≤ 0.5 μg/L	1 (Ref)	1 (Ref)
D-dimer > 0.5 μg/L	**1.96** (0.52 – 7.43) 0.32	**2.14** (0.21 – 21.39) 0.52
D-dimer > 1.0 μg/L	**20.04** (6.52 – 61.56) < 0.0001	**18.42** (2.64 – 128.55) 0.0033

Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020

Critical Appraisal of Prediction Models

Table 2 | Risk of bias assessment (using PROBAST) based on four domains across 27 studies that created prediction models for coronavirus disease 2019

Authors	Risk of bias: Participants	Predictors	Outcome	Analysis
Hospital admission in general population				
DeCaprio et al[8]	High	Low	High	High
Diagnosis				
Feng et al[10]	Low	Unclear	High	High
Lopez-Rincon et al[35]	Unclear	Low	Low	High
Meng et al[12]	High	Low	High	High
Song et al[30]	High	Unclear	Low	High
Prognosis				
Bai et al[9]	Low	Unclear	Unclear	High
Caramelo et al[18]	High	High	High	High
Gong et al[32]	Low	Unclear	Unclear	High
Lu et al[19]	Low	Low	Low	High
Qi et al[20]	Unclear	Low	Low	High
Shi et al[37]	High	High	High	High
Xie et al[7]	Low	Low	Low	High
Yan et al[21]	Low	High	Low	High
Yuan et al[22]	Low	High	Low	High

PROBAST=prediction model risk of bias assessment tool.
*Risk of bias high owing to calibration not being evaluated. If this criterion is not taken into account, analysis risk of bias would have been unclear.
†Risk of bias high owing to calibration not being evaluated. If this criterion is not taken into account, analysis risk of bias would have been low.

Box 2: Common causes of risk of bias in the 19 reported prediction models

Models to predict hospital admission for coronavirus disease 2019 (covid-19) pneumonia in general population

These models were based on Medicare claims data, and used proxy outcomes to predict hospital admission for covid-19 pneumonia, in the absence of patients with covid-19.[8]

Diagnostic models

People without covid-19 (or a proportion of them) were excluded, altering the disease prevalence.[30] Controls had viral pneumonia, which is not representative of the target ...

... specifically designed, without benchmarking the used architecture against others.

Prognostic models

Study participants were often excluded because they did not develop the outcome at the end of the study period but were still in follow-up (that is, they were in hospital but had not recovered or died), yielding a highly selected study sample.[7 20-22] Additionally, only one study accounted for censoring by using Cox regression.[19] One study developed a model to predict future severity using cross sectional data (some participants were severely ill at inclusion)[37]; this implies that the timing of the measurement of the predictors is not appropriate and the (uncleanly defined) outcome might have been influenced by the predictor values. Other studies used highly subjective predictors,[22] or the last available predictor measurement from electronic health records (rather than measuring the predictor value at the time when the model was intended for use).[21]

Proposed models are poorly reported, at high risk of bias, and their reported performance is probably optimistic. The predictors identified in included studies could be considered as candidate predictors for new models.

Wynants L, van Claster B, Bonten M, et al. Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal. BMJ 2020; 369: m1328

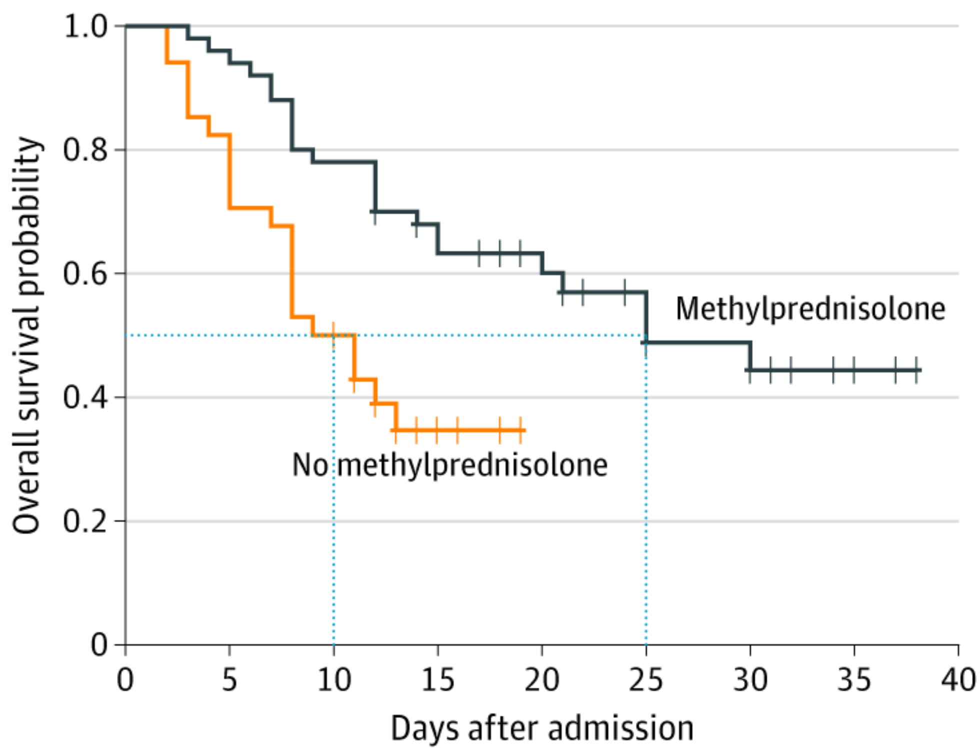
Corticosteroids in COVID-19

- Widely used in critically ill patients
  - Without systematic evaluation

All Patients	ICU Patients
19% to 45%	**46% to 72%**

- Prolonged corticosteroid therapy associated with prolonged viral shedding
  - Delayed but more severe deterioration (e.g. hypoxemia)?
- Short-term corticosteroid therapy beneficial?

Corticosteroids in COVID-19



No. at risk

No methylprednisolone	34	28	17	4	0	0	0	0	0
Methylprednisolone	50	48	39	29	20	14	11	4	0

Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020

Take Home Message

- Global outbreak of COVID-19
- Critically ill patients characterized by acute respiratory failure, cardiac injury/shock, and acute kidney injury
- Supportive therapies as cornerstone in patient management
- High mortality rate associated with organ injury