POLITECNICO MILANO 1863

Massachusetts Institute of Technology

Dead Space Monitoring Provides Key Insights for COVID Patients from MargheritaTre EHR

Maximiliano Mollura, Francesca Baroncelli, Giulia Mandelli, Giovanni Tricella, Gary E. Weissman, Daniele Poole, Pietro Caironi, Leo Celi, Riccardo Barbieri and Stefano Finazzi

GiViTI

GRUPPO ITALIANO PER LA VALUTAZIONE DEGLI INTERVENTI IN TERAPIA INTENSIVA

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI - IRCCS

COVID-19 Pandemic

More than 200 mln infected cases worldwide

Case fatality rate ~2%

Average ICU admission rate ~20% (5%-32%)

High in-ICU mortality

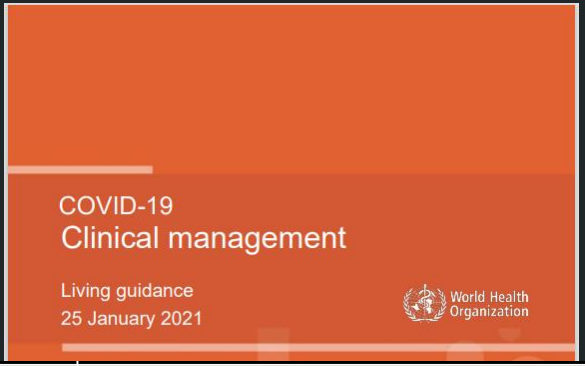
Up to 88% of patients required MV

COVID-19 Disease Severity

Severe Hypoxaemia

PaO_2/FiO_2 plays a key role in assessing COVID-19 disease severity

ARDS is the most common manifestation of COVID-19 (CARDS) observed in 40-96% patients



Critical disease	**Acute respiratory distress syndrome (ARDS)** *(89,90,91)*	**Onset:** within 1 week of a known clinical insult (i.e. pneumonia) or new or worsening respiratory symptoms. **Chest imaging:** (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules. **Origin of pulmonary infiltrates:** respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of infiltrates/oedema if no risk factor present. **Oxygenation impairment in adults** *(89,91)*: • Mild ARDS: 200 mmHg < PaO2/FiO2a ≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH2O).b • Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤ 200 mmHg (with PEEP ≥ 5 cmH2O).b • Severe ARDS: PaO_2/FiO_2 ≤ 100 mmHg (with PEEP ≥ 5 cmH_2O).[b] **Oxygenation impairment in children:** note OI and OSI.[c] Use OI when available. If PaO_2 not available, wean FiO_2 to maintain SpO^2 ≤ 97% to calculate OSI or SpO_2/FiO_2 ratio: • Bilevel (NIV or CPAP) ≥ 5 cmH2O via full face mask: PaO2/FiO2 ≤ 300 mmHg or SpO2/FiO2 ≤ 264. • Mild ARDS (invasively ventilated): 4 ≤ OI < 8 or 5 ≤ OSI < 7.5. • Moderate ARDS (invasively ventilated): 8 ≤ OI < 16 or 7.5 ≤ OSI < 12.3. • Severe ARDS (invasively ventilated): OI ≥ 16 or OSI ≥ 12.3.

WHO. COVID-19 Clinical management. World Health Organization; 2021.

COVID-19 ARDS (CARDS): Not only pneumonia!

"The high incidence of thromboembolic events suggests an important role of COVID-19–induced coagulopathy."

"[...] the presence of platelet–fibrin thrombi in small arterial vessels is consistent with coagulopathy, which appears to be common in patients with COVID-19 [...]"

Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia

Dennis McGonagle, James S O'Donnell, Kassem Sharif, Paul Emery, Charles Bridgewood

Lancet Rheumatol 2020; 2: e437–45 May 7, 2020

Original Research | 18 August 2020

Autopsy Findings and Venous Thromboembolism in Patients With COVID-19

A Prospective Cohort Study

Annals of Internal Medicine

Dominic Wichmann, MD*, Jan-Peter Sperhake, MD*, Marc Lütgehetmann, MD, Stefan Steurer, MD, ... See More

THE LANCET Infectious Diseases

Volume 20, Issue 10, October 2020, Pages 1135-1140

Articles

Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study

Luca Carsana MD [a], Aurelio Sonzogni MD [d], Ahmed Nasr MD [d, e], Roberta Simona Rossi MD [a], Alessandro Pellegrinelli MD [a], Pietro Zerbi MD [a, f], Roberto Rech MD [b], Riccardo Colombo MD [b], Prof Spinello Antinori MD [c, f], Mario Corbellino MD [c], Prof Massimo Galli MD [c, f], Emanuele Catena MD [b], Antonella Tosoni BSc [a], Andrea Gianatti MD [a], Prof Manuela Nebuloni MD [a, f]

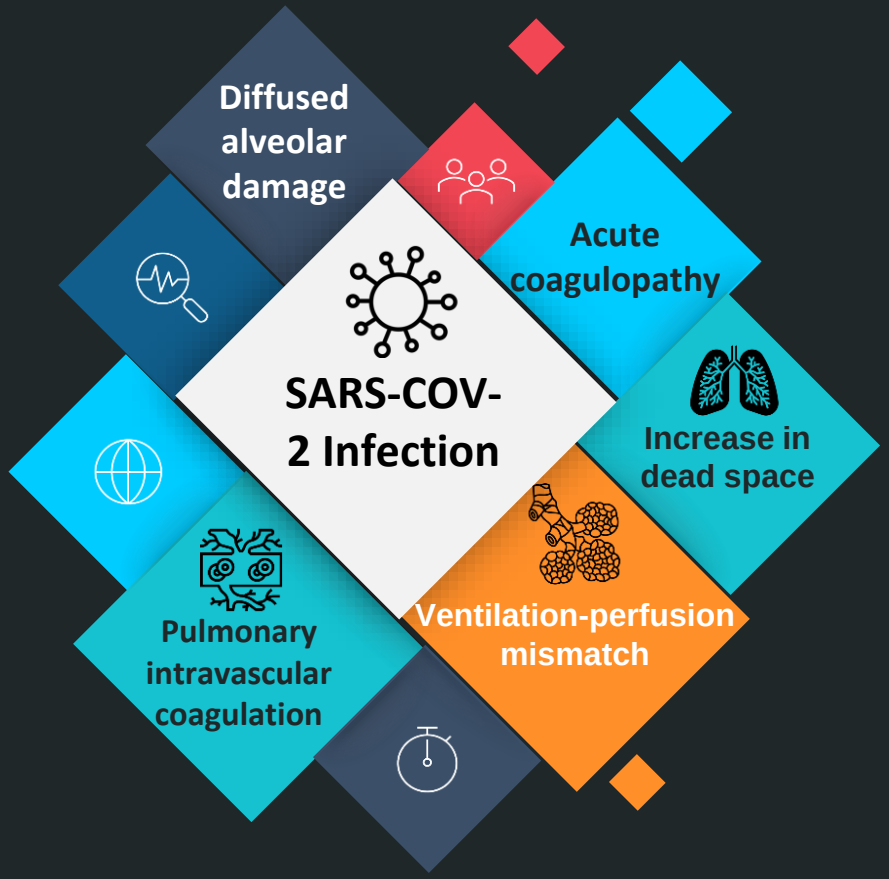
Perspective | Published: 06 April 2021

Endothelial dysfunction and immunothrombosis as key pathogenic mechanisms in COVID-19

Aldo Bonaventura, Alessandra Vecchié, Lorenzo Dagna, Kimberly Martinod, Dave L. Dixon, Benjamin W. Van Tassell, Francesco Dentali, Fabrizio Montecucco, Steffen Massberg, Marcel Levi & Antonio Abbate

Nature Reviews Immunology **21**, 319–329 (2021) | Cite this article

Can dead space improve patients' monitoring strategies?

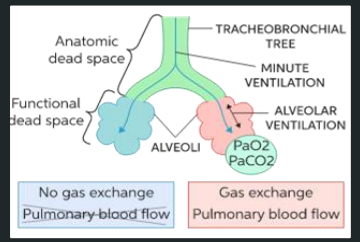


"Increased dead-space fraction is a feature of the early phase of the acute respiratory distress syndrome. **Elevated values are associated with an increased risk of death**"

Nuckton TJ et al., 2002, NEJM

Dead space is the volume of inhaled air that does not take part in the gas exchange, because it either remains in the conducting airways (Anatomical) or reaches alveoli (Alveolar) that are not perfused or poorly perfused.

Dead space can be estimated with the Bohr Equation:



$$DS = \frac{PaCO_2 - EtCO_2}{PaCO_2}$$

Methods - Study Design

MargheritaTre Electronic Health Records

- Adult patients (older than 17 years old) with CARDS and admitted to 22 ICUs from different Italian hospitals before March 31st, 2021, i.e., within 1-year after COVID-19 presentation
- Collected Data: tidal volume, PEEP, PaO_2/FiO_2, $PaCO_2$, $EtCO_2$, systolic arterial pressure, age, comorbidities

Cohort Selection

1765 → 364: Not required MV

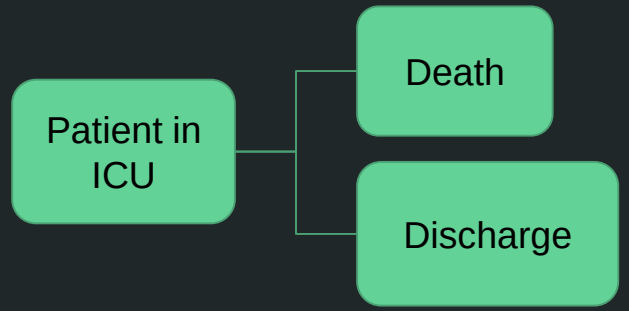
1401 → 675: $EtCO_2$ Not recorded

726 → 76: No dead space estimates

650 → 183: No contemporaneous recordings

467

Competing risk modelling approach



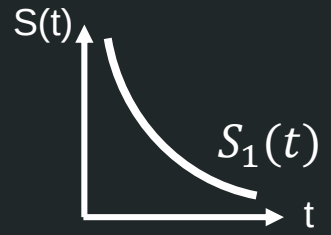
Cox Proportional Hazard Model

Methods - Cox Model

The general goal of survival analysis is to derive a survival function S(t), i.e. the probability that an event has not occurred before time t

$$S(t) = P(T \geq t) = e^{-\int_0^t h(u)du}$$

HAZARD function



$$h(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t | T \geq t)}{\Delta t}$$

Probability of having an event in a specific time window (t,t+Δt) divided by the duration of the window (Δt)

Cox Model:

$$h(t, X) = h_0(t) e^{\sum_{i=1}^{p} \beta_i X_i(t)}$$

These are the clinical variables

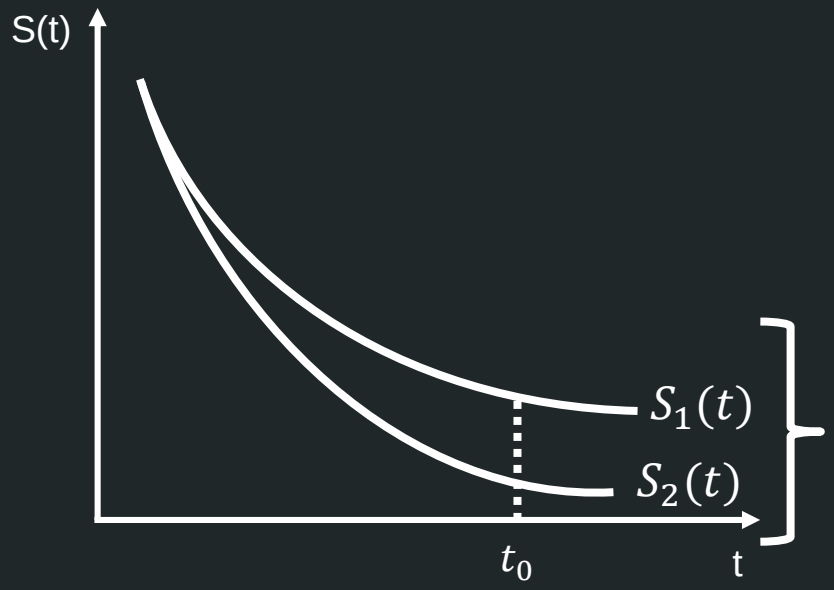
Methods - Cox Model

If we compare two observations the hazard ratio (HR) is defined as follows:

$$\frac{h(t,X^*)}{h(t,X)} = HR = \frac{e^{\sum_{i=1}^{p} \beta_i X_i^*(t)}}{e^{\sum_{i=1}^{p} \beta_i X_i(t)}}$$

$$HR = e^{\beta(1-0)} = e^{\beta}$$

Hazard Ratio (HR) is linked to a model coefficient while correcting for the others, and it estimates the change in the hazard function for an increase of that model coefficient.
HR=1 : No changes in Hazard
HR<1 : Reduced Hazard
HR>1 : Increased Hazard



$$h_2(t_0) > h_1(t_0)$$
$$S_2(t_0) < S_1(t_0)$$
$$HR = \frac{h_2(t_0)}{h_1(t_0)} > 1$$

Advantages:

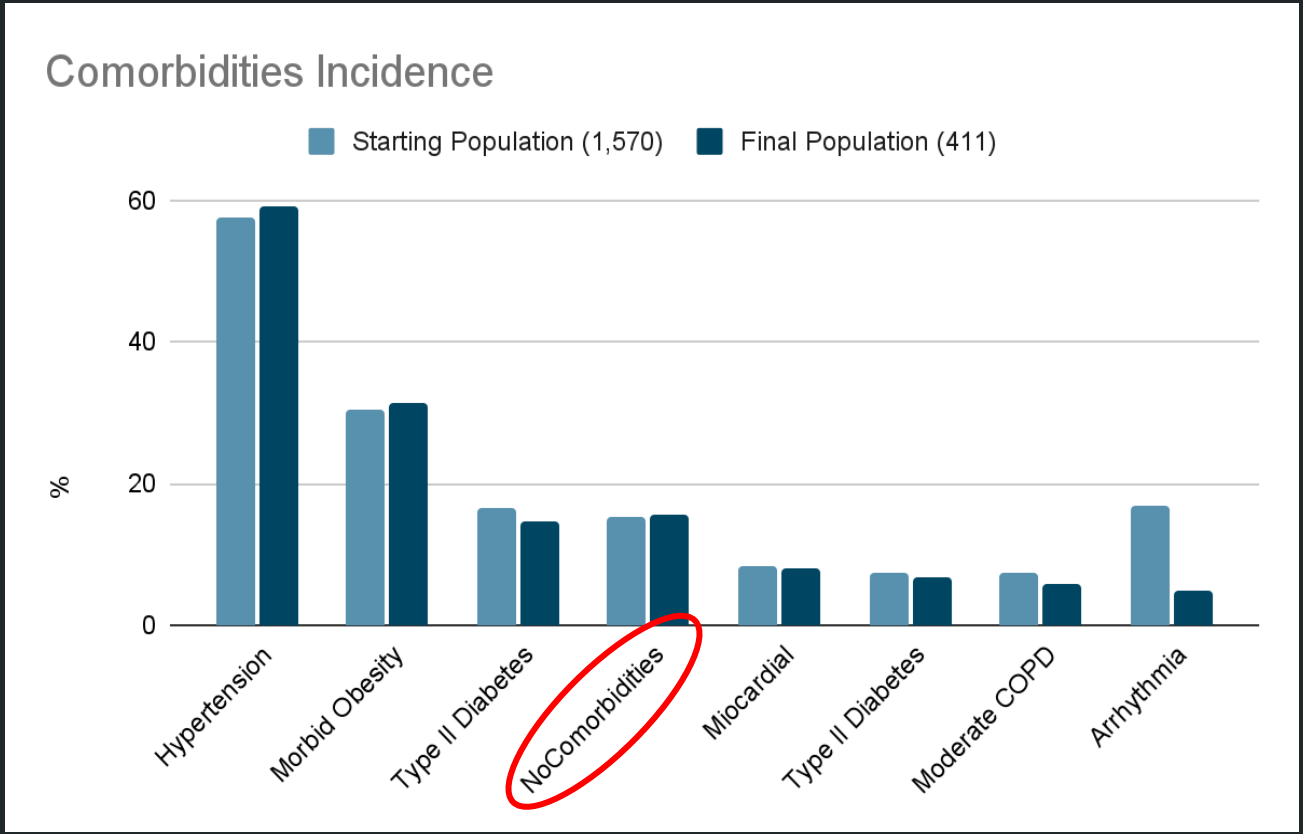
- ✓ Time-Dependence
- ✓ Include censored observations
- ✓ Take into account different outcomes at the same time

$$h^{(r)}(t,X) = h_0^{(r)}(t) e^{\sum_{i=1}^{p} \beta_i^{(r)} X_i(t)}$$

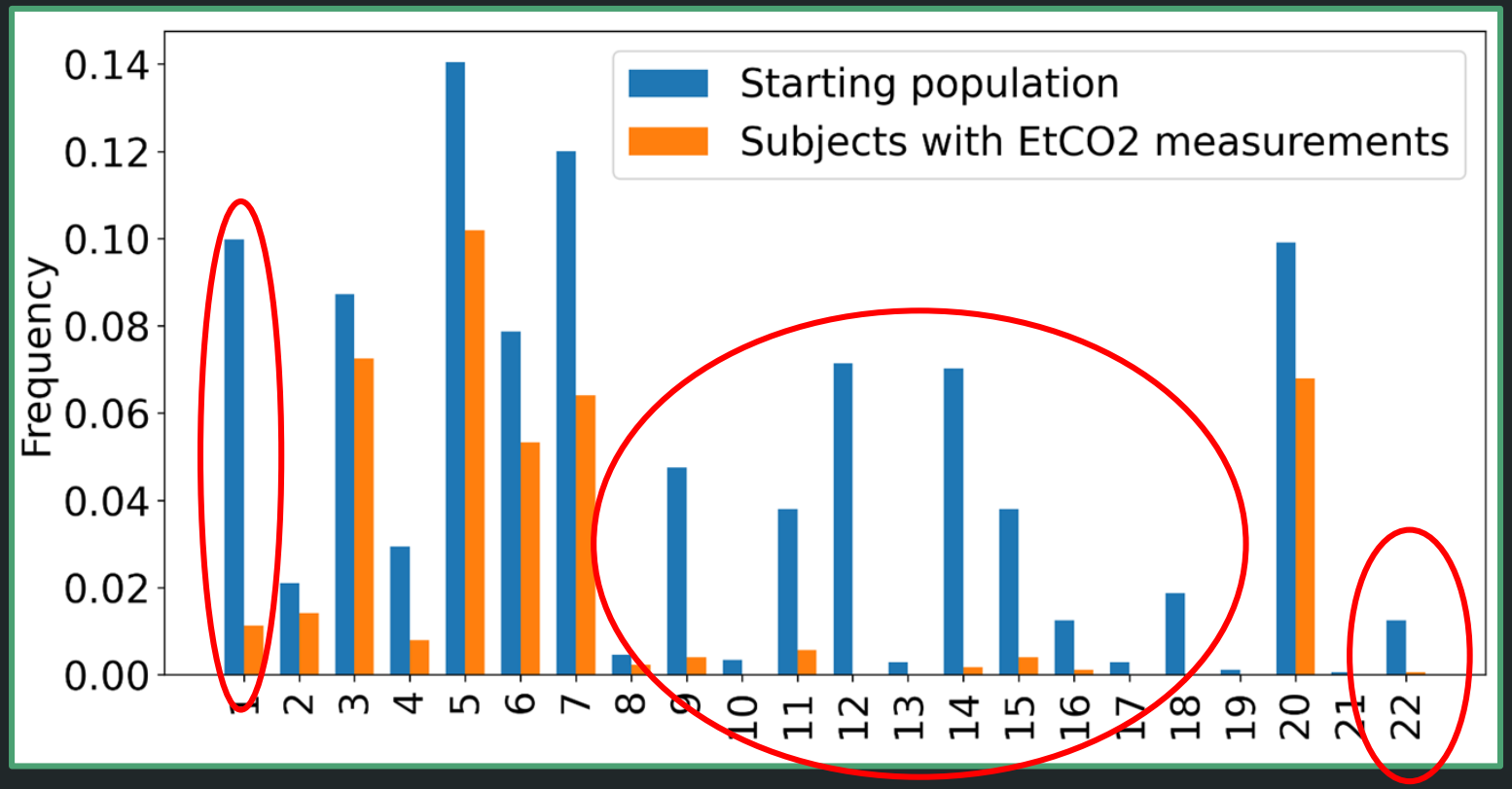
Results - Population Statistics

	Starting Population	Intubated	Never Intubated	No Recordings	Final Population
Patients	1,765	1,401	364	934	467
Mortality	586 (33%)	553 (39%)	33 (9%)	378 (40%)	175 (37%)
Discharged	868 (49%)	575 (41%)	293 (80%)	387 (41%)	188 (40%)
Censored	311 (18%)	273 (20%)	38 (11%)	169 (19%)	104 (23%)
Age [y.o.]	66 (58-73)	67 (59-73)	64 (54-72)	67 (60-74)	65 (58-71)
Length of stay [days]	10 (5-19)	13 (7-23)	4 (2-7)	12 (6-20)	18 (11-29)
Sex (%F)	26%	25%	28%	19%	23%

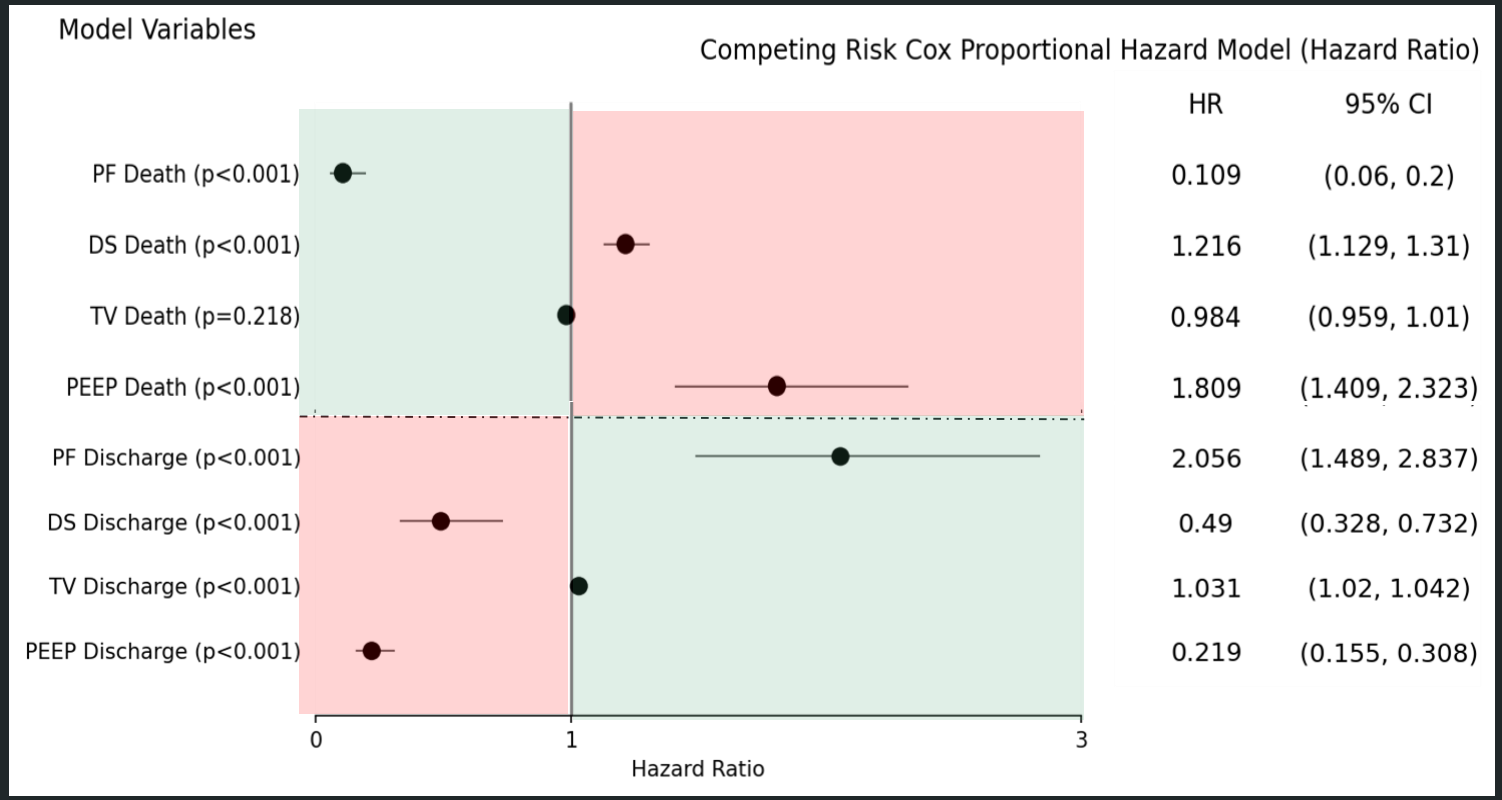
Results - Population Statistics



Results - $EtCO_2$ availability in different ICUs



Results - Correction for ventilation

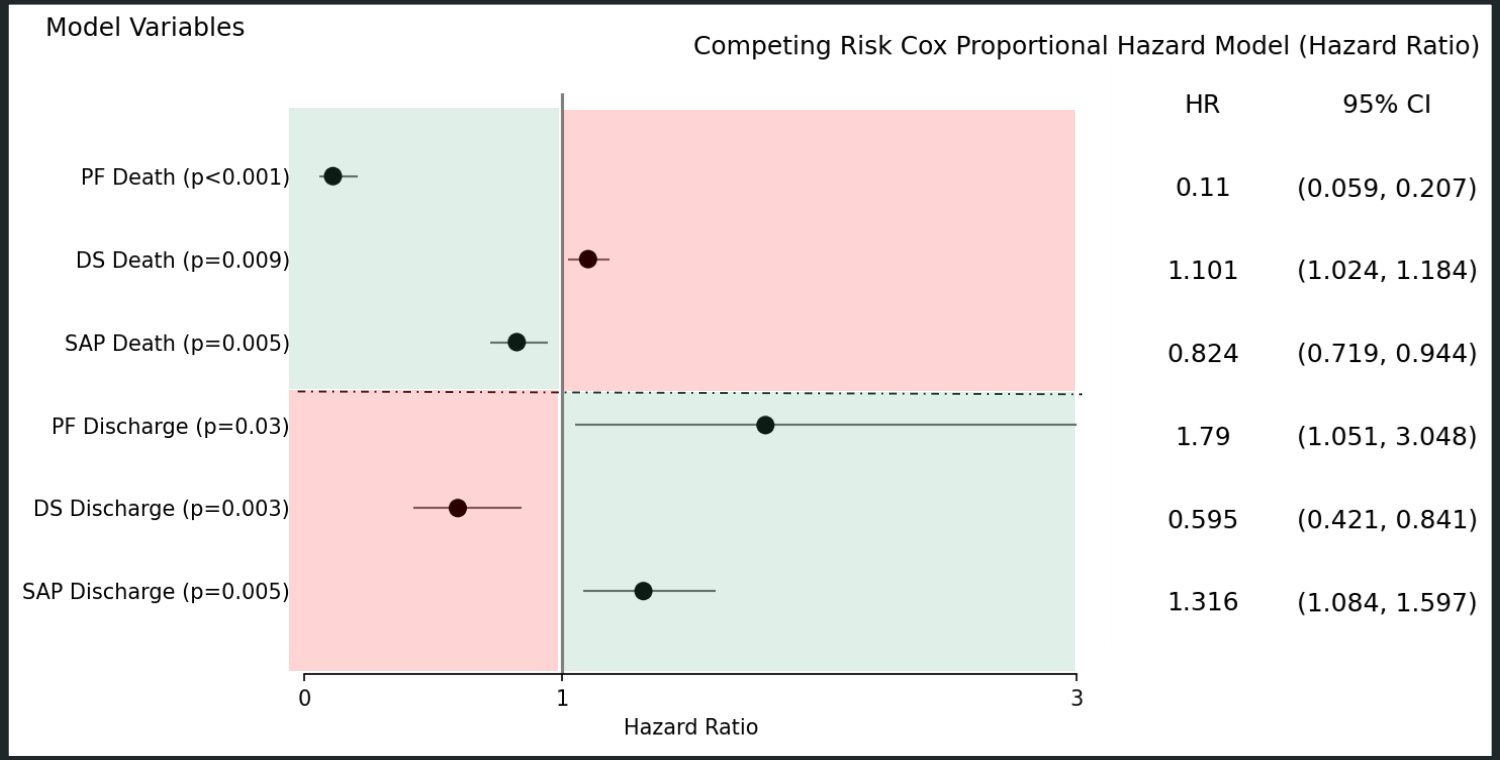


Lower Mortality

Higher Mortality

Hazard Ratios (HR) are computed for an increase of the corresponding feature

Results - Correcting for cardiovascular state



Lower Mortality

Higher Mortality

Hazard Ratios (HR) are computed for an increase of the corresponding feature

★ Similar results were found also when correcting for AGE and Comorbidities

Summary

- ★ Population statistics during the first two waves were similar to previously published studies
- ★ PF ratio plays a key role in assessing state of COVID patients
- ★ **Dead space estimation adds key information in estimating patients' risk of death after correcting for confoundings**

Final Messages:

- ★ To collect $EtCO_2$ and $PaCO_2$ data more often
- ★ To implement Dead Space calculation in monitors

Thanks !

Contacts:

Maximiliano Mollura

maximiliano.mollura@polimi.it