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The New Global Definition of Acute Respiratory Distress Syndrome: Insights from the MIMIC-IV Database

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Declaration of interests

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Dear Editor,

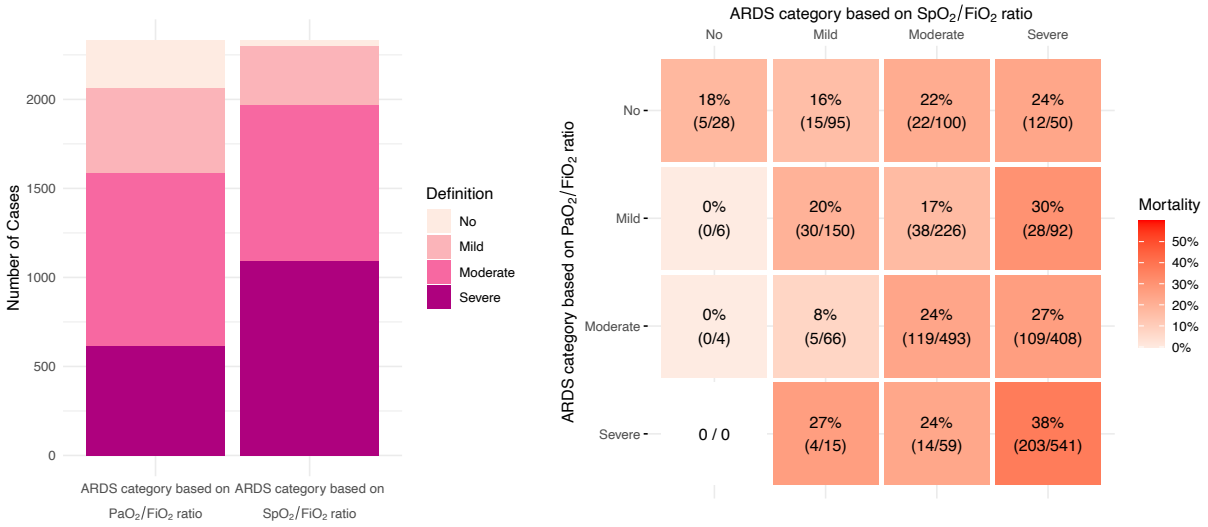
Recently, a new definition of Acute Respiratory Distress Syndrome (ARDS) was proposed [1] which extends and modifies the 2012 Berlin definition [2]. This new global definition integrates pulse oximetry, utilizing peripheral oxygen saturation (SpO_2) as an alternative to blood gas measurement of partial pressure of oxygen (PaO_2), and addresses its applicability in non-intubated patients or resource-limited settings, among other considerations. It aims to rectify limitations identified in expansions that have been proposed for the Berlin definition [3, 4], aligning with the latest evidence and clinical practices. Furthermore, the new global definition is designed to be more accessible in environments with constrained access to diagnostic and therapeutic resources, such as respiratory support devices, chest radiography and blood gas analysis. Nonetheless, there is a need for evaluation of this definition using real-world data.

Using the Medical Information Mart for Intensive Care IV (MIMIC-IV) database, we first conducted a comparative analysis among intubated patients receiving mechanical invasive ventilation with bilateral infiltrates on chest radiograph and positive end-expiratory pressure (PEEP) ≥ 5. They were split into four oxygenation categories relating to ARDS severity: no[1], mild, moderate, and severe. We compared categorization using PaO_2/FiO_2 ratio as per the Berlin definition, where FiO_2 denotes fraction of inspired oxygen, versus using SpO_2/FiO_2 ratio which the new global definition considers in addition to PaO_2/FiO_2 ratio. We compared clinical characteristics and mortality risk among patients categorized according to these ratios. Extraction of the Berlin definition from MIMIC-IV followed previous work on the same database [5] (see the online supplement for further details). We then explored categorization for ARDS in non-intubated patients receiving supplemental oxygen, as introduced by the new global definition, and compared with categories from the Berlin definition. A limitation of the study is that high-flow nasal

[1] The "no" category includes patients who meet the ARDS criteria, except for the requirement of PaO2/FiO2 $\leq$ 300mm Hg for the Berlin definition or $SpO_2/FiO_2 \leq 315$ (if $SpO_2 \leq 97\%$) for the new global definition.

oxygen, non-invasive ventilation cases and lung ultrasound data (which the new global definition considers) are not included due to a lack of data in MIMIC-IV.

In the MIMIC-IV database, 2,333 patients had data to verify ARDS criteria with both PaO_2/FiO_2 and SpO_2/FiO_2 ratio available. Figure 1 illustrates the distribution of the categories in intubated patients according to these two ratios. Despite significant differences in the distribution of the categories (Chi-square test, $p < 10^{-15}$)[2], the mortality risk within each category is similar across both ratios, indicating that they are complementary rather than interchangeable. Additional findings in the online supplement include: (i) category-specific mortality for patients on supplemental oxygen was substantially lower than for intubated cases; (ii) SpO_2/FiO_2 ratio's categorization did not show racial bias of pulse oximetry in a comparison between Caucasian and African-American patients.



(a) **(b)**

Figure 1: Distribution of oxygenation categories relating to ARDS severity based on PaO_2/FiO_2 ratio and SpO_2/FiO_2 ratio in intubated patients

Panel (a) visualises the counts of patients within each category for each ratio. The "no" category includes patients who meet the ARDS criteria, except for the requirement of PaO2/FiO2 ≤ 300mm Hg or SpO_2/FiO_2 ≤ 315 (if SpO_2 ≤ 97%). Panel (b) presents a heat map of the 30-day hospital mortality rates for combinations of the two categorizations. For example, in the top right square, 50 patients were simultaneously categorized as "no" based on PaO_2/FiO_2 ratio and as having severe ARDS based on SpO_2/FiO_2 ratio. Of these 50 patients, 12 succumbed, corresponding to a mortality rate of 24%.

[2] The result $p < 10^{-15}$ is obtained both when including and when excluding the "no" category for the Chi-square test.

References

1. Matthay MA, Arabi Y, Arroliga AC, Bernard G, Bersten AD, Brochard LJ, Calfee CS, Combes A, Daniel BM, Ferguson ND (2024) A new global definition of acute respiratory distress syndrome. American Journal of Respiratory and Critical Care Medicine 209:37-47. https://doi.org/10.1164/rccm.202303-0558WS

2. The ARDS Definition Task Force (2012) Acute respiratory distress syndrome: the Berlin Definition. JAMA 307:2526-2533. https://doi.org/10.1001/jama.2012.5669

3. Riviello ED, Kiviri W, Twagirumugabe T, Mueller A, Banner-Goodspeed VM, Officer L, Novack V, Mutumwinka M, Talmor DS, Fowler RA (2016) Hospital incidence and outcomes of the acute respiratory distress syndrome using the Kigali modification of the Berlin definition. American Journal of Respiratory and Critical Care Medicine 193:52-59. https://doi.org/10.1164/rccm.201503-0584OC

4. Grasselli G, Calfee CS, Camporota L, Poole D, Amato MB, Antonelli M, Arabi YM, Baroncelli F, Beitler JR, Bellani G (2023) ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. Intensive Care Medicine 49:727-759. https://doi.org/10.1007/s00134-023-07050-7

5. Wang Z, Zhang L, Huang T, Yang R, Cheng H, Wang H, Yin H, Lyu J (2023) Developing an explainable machine learning model to predict the mechanical ventilation duration of patients with ARDS in intensive care units. Heart & Lung 58:74-81. https://doi.org/10.1016/j.hrtlng.2022.11.005

Supplementary Information to:

The New Global Definition of Acute Respiratory Distress Syndrome: Insights from the MIMIC-IV Database

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Data description

We collected data from the Medical Information Mart for Intensive Care (MIMIC)-IV database version 2.2 [1] in accordance with the ethical standards of the institutional review board of the Massachusetts Institute of Technology (no. 0403000206) and with the 1964 Helsinki declaration and its later amendments. MIMIC-IV comprises 73,181 ICU admissions between 2008 and 2019 for 50,920 patients at the Beth Israel Deaconess Medical Centre in Boston, MA, USA. The database is maintained by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology. It includes hourly physiologic readings from bedside monitors, demographics, diagnoses via International Classification of Diseases, Ninth/Tenth Revision (ICD-9/10) codes and other clinical data, collected during routine medical care. The database has extensive documentation and public code from a community of users.

Methodology

We used the following inclusion criteria to subset the MIMIC-IV database:

(a) initiation of invasive mechanical ventilation [2, 3];
(b) a positive end-expiratory pressure (PEEP) ≥ 5;
(c) Evidence of bilateral infiltrates as suggested by:
    - chest radiology reports with keywords 'edema' or both 'bilateral' and 'infiltrates' in free-text notes[1] [2, 4] or
    - ARDS evidence based on ICD-9 code (518.82) and ICD-10 codes (J80) [4].

Additionally, as in [3], we excluded patients if:

(i) ICD-9/10 codes indicated that concurrent acute heart failure was present, to rule out bilateral infiltration due to hydrostatic edema or
(ii) the patients underwent extracorporeal membrane oxygenation (ECMO) during their ICU stay.

These criteria are shared by the Berlin and the new global definition of acute respiratory distress syndrome (ARDS). The data extraction described above follows established practice [2–4]. Note that this use of radiology reports implies the assumption that the reports accurately record whether bilateral infiltrates are visible in the chest radiographs.

Our investigation focuses on aspects of the new global definition concerning SpO2/FiO2 (as a surrogate for PaO2/FiO2) and supplemental oxygen, as a result of the scope of data available in the MIMIC-IV database. Specifically, MIMIC-IV includes a paucity of ARDS cases involving patients on high-flow nasal oxygen (HFNO) and non-invasive ventilation

[1] We excluded the patients when negative expressions like 'no', 'without', 'there is no' or 'there is no evidence' appear with those keywords.

(NIV). Moreover, lung ultrasound data are absent. The new global definition enables inclusion of such data, which can lead to additional detection of bilateral infiltrates compared to using only chest X-ray [5]. As a result, our analysis might underestimate the prevalence of ARDS under the new global definition.

Figure S1 depicts our process of selecting ICU stays from MIMIC-IV. We only used data from the first ICU admission during the first hospitalization, as in [2]. Table S1 presents the count of patients in various ARDS categories based on the PaO_2/FiO_2 and SpO_2/FiO_2 ratios . Here, 'intubated' denotes patients classified as ARDS during invasive mechanical ventilation. Measurements for both ratios were obtained from the MIMIC-IV database, as outlined in the GitHub repository at https://github.com/MIT-LCP/mimic-iv. These measurements are calculated by utilizing pairs of FiO_2 and PaO_2 or SpO_2 values, each pair recorded no more than 4 hours apart. For the ARDS classification, we used the lowest ratio values measured within the first 24 hours following intubation as detailed in [2]. Source code for the analyses can be found at https://github.com/Qianxiaoxie917/ARDS-definitions.

The categories are 'no' ($PaO_2/FIO_2 > 300$ mm Hg or $SpO_2/FiO_2 > 315$, if $SpO_2 \leq 97\%$), 'mild' (200 mm Hg $< PaO_2/FiO_2 \leq 300$ mm Hg or $235 < SpO_2/FiO_2 \leq 315$, if $SpO_2 \leq 97\%$), 'moderate' (100 mm Hg $< PaO_2/FiO_2 \leq 200$ mm Hg or $148 < SpO_2/FiO_2 \leq 235$, if $SpO_2 \leq 97\%$), and 'severe' ($PaO_2/FiO_2 \leq 100$ mm Hg or $SpO_2/FiO_2 \leq 148$, if $SpO_2 \leq 97\%$) as in [6]. Furthermore, 'supplemental oxygen' applies to patients on supplemental oxygen, a classification unique to the new global definition.

For supplemental oxygen cases, the MIMIC-IV database provides chart values for FiO2. See for instance ref. [7] which uses these values for patients on supplemental oxygen. We do so too. Because of the availability of the FiO2 chart values, we do not also estimate FiO2, e.g. as is sometimes done using oxygen flow rate [6].

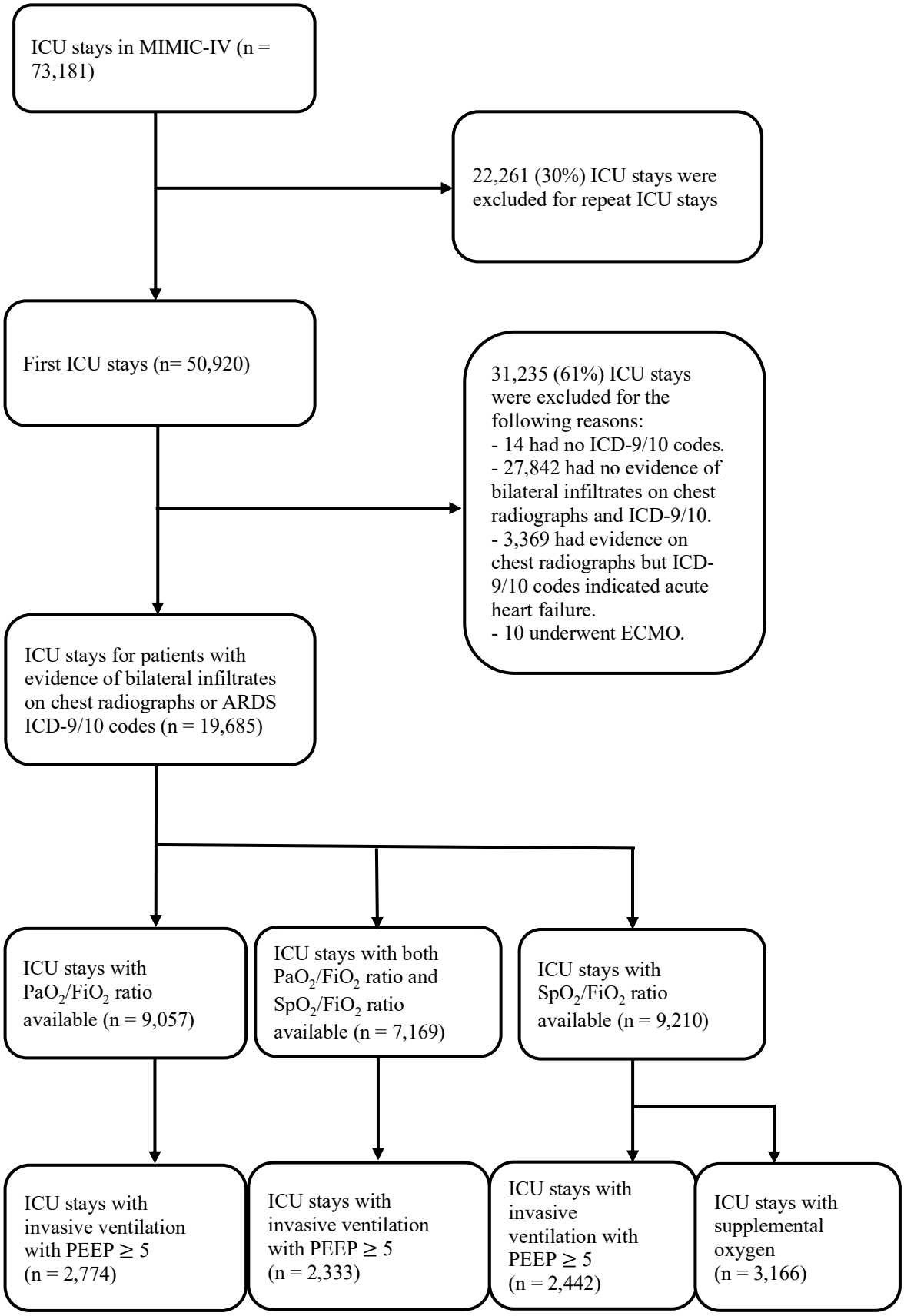


Figure S1: Case inclusion flowchart
Visual representation of how the patients were selected from MIMIC-IV.

Table S1: Patient counts in ARDS categories as defined by the two definitions

ARDS category	Total	No	Mild	Moderate	Severe
Intubated based on PaO_2/FiO_2 ratio:	2774	494	602	1039	639
Intubated based on SpO_2/FiO_2 ratio:	2442	40	352	934	116
Supplemental oxygen:	3166	39	416	1116	1595

Statistical Analysis

For our comparative analysis, we selected the intubated subset that has data available for ARDS diagnosis based on both the PaO_2/FiO_2 and SpO_2/FiO_2 ratios, as detailed in the flowchart. We refer to this subset as the *intersection subset* (i.e. the subset with n = 2,333 in Figure S1). In contrast, subsets with data available for only one ratio are referred to as the *separate subsets* (i.e. the subsets with n = 2,774 and n = 2,442 in Figure S1). Table S2 outlines the characteristics of patients identified as ARDS, either by one or by both definitions. This comparison highlights the clinical similarities between ARDS cases defined using the PaO_2/FiO_2 ratio and those defined using the SpO_2/FiO_2 ratio, which has also been observed in [8]. Table S3 illustrates the characteristics of patients with supplemental oxygen ARDS versus those without ARDS, as per the new global definition. Notably, the number of patients not diagnosed with ARDS is significantly lower compared to those categorized as having ARDS.

We analysed mortality rates within ARDS categories, assessing whether the rates differed between the two ratios. Figure S2 displays the results for: (i) separate subsets, which include 2,774 patients classified based on PaO_2/FiO_2 ratio and 2,442 patients based on SpO_2/FiO_2 ratio ; (ii) the intersection subset of 2,333 patients. We used the Cochran-Mantel-Haenszel (CMH) test [9] with the different ARDS categories as strata to test for differences in mortality rates between ratios. The findings do not show highly statistically significant differences in mortality risk within ARDS categories between the two ratios, with *p*-values of 0.06 for the separate subsets and 0.02 for the intersection subset. We also conducted the CMH test on subsets excluding the "no" category, yielding a p-value of 0.07 for separate subsets (2280 patients for PaO_2/FiO_2 ratio and 2402 for SpO_2/FiO_2 ratio) and a p-value of 0.05 for the intersecting subset (2050 patients), indicating consistent results. On the other hand, Figure S3 presents a comparison between intubated patients and patients on supplemental oxygen, categorized based on SpO_2/FiO_2, with 2,442 and 3,166 patients, respectively. The findings indicate that the new global definition tends to overestimate severity in patients receiving supplemental oxygen compared to those who are intubated.

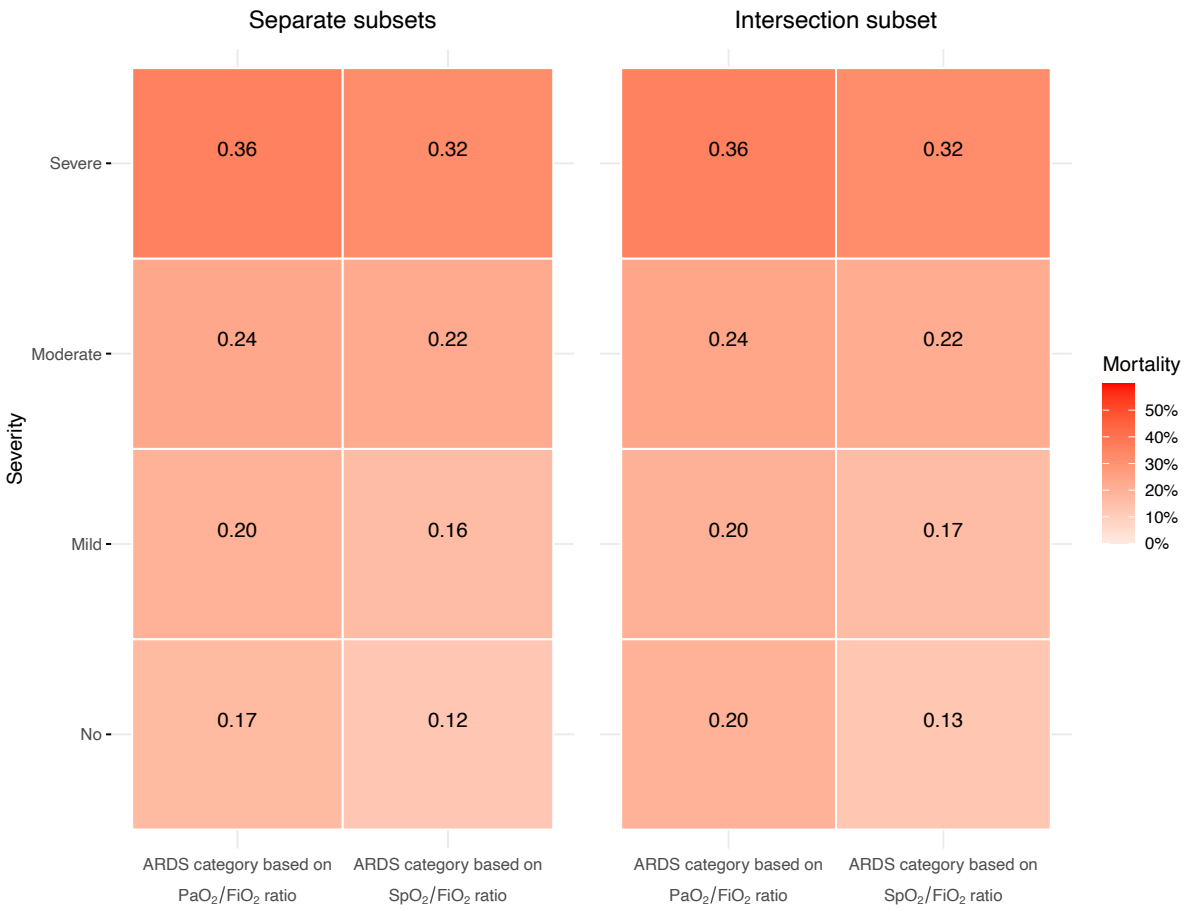
To investigate potential racial bias in ARDS patients, e.g. due to pulse oximetry and skin pigmentation [10], we focused on the two largest racial groups in our data set: Caucasian and African-American. Figure S4 compares the distribution of intubated ARDS categories between these groups under the new global definition, where no statistically significant difference was observed (Chi-square test, $p = 0.31$). Additionally, the mortality rates in these racial groups were similar, as seen in Figures S5 and S6.

Table S2: Patients characteristic for intubated ARDS

Patient characteristics	ARDS based on both ratios (N = 2050)	ARDS only based on PaO_2/FiO_2 ratio but not based on SpO_2/FiO_2 ratio (N = 10)	ARDS only based on SpO_2/FiO_2 ratio but not based on PaO_2/FiO_2 ratio (N = 245)	No ARDS based on both ratios (N = 28)
30-day hospital mortality, n (%)	550 (26.8)	0 (0)	49 (20.0)	5 (17.9)
Male gender, n (%)	1248 (60.9)	3 (30)	146 (59.6)	22 (78.6)
African-American, n (%)	166 (8.1)	1 (10)	24 (9.8)	2 (7.1)
Age (years), median (mean) [IQR]	64 (62.6) [52–75]	70 (68.5) [63–77.8]	67 (64.3) [52–80]	71 (63.0) [48–77.5]
BMI (kg/m^2), median (mean) [IQR]	29.61 (31.50) [25.63–35.72]	30.94 (33.99) [26.46–34.72]	26.03 (26.93) [22.55–29.98]	25.32 (25.95) [23.70–27.38]
SOFA score, median (mean) [IQR]	5 (5.8) [3–8]	3 (3.5) [1.5–3.8]	3 (3.7) [1–5]	3 (3.8) [2–5.3]
Number of FiO2 measurements, median (mean) [IQR]	15.5 (30.0) [6-38]	6.5 (8.1) [2.3–13]	8 (25.8) [4–27]	16.5 (26.6) [7–32.3]
Median FiO2, median (mean) [IQR]	50 (51.0) [40–50]	32.5 (45) [30–50]	40 (43.1) [40–50]	30 (34.5) [30–40]
Number of SpO2 measurements, median (mean) [IQR]	65 (125.5) [24–160]	29.5 (36.8) [13.3–61]	33 (104.5) [17–104]	78 (106.7) [24.8–130.3]
Median SpO2, median (mean) [IQR]	98 (97.2) [96–99]	100 (99.4) [98.6–100]	99 (98.9) [98–100]	99 (98.6) [97.8–100]
Duration of ventilation, median (mean) [IQR]	46.5 (83.5) [18–106]	12 (25.5) [8–35.5]	23 (67.0) [13–72]	37.5 (54.7) [13.3–73]

Table S3: Patients characteristic for supplemental oxygen ARDS

Patient characteristics	ARDS (N = 3127)	No ARDS (N = 39)
30-day hospital mortality, n (%)	464 (14.8)	5 (12.8)
Male gender, n (%)	1718 (54.9)	25 (64.1)
African-American, n (%)	217 (6.9)	9 (23.1)
Age (years), median (mean) [IQR]	69 (68.4) [59–80]	69 (66.7) [60–78]
BMI (kg/m^2), median (mean) [IQR]	28.34 (29.60) [24.49–33.03]	30.50 (29.79) [26.75–32.39]
SOFA score, median (mean) [IQR]	3 (3.7) [1–5]	4 (4.3) [2–5]
Number of FiO2 measurements, median (mean) [IQR]	3 (5.9) [1–7]	1.5 (2.4) [1–2]
Median FiO2, median (mean) [IQR]	50 (63.0) [45–80]	30 (31.6) [26–33.8]
Number of SpO2 measurements, median (mean) [IQR]	29 (44.6) [14–60]	21 (34.1) [11–49]
Median SpO2, median (mean) [IQR]	96 (95.5) [94–97]	96 (96.1) [95–97]
Duration of ventilation, median (mean) [IQR]	24 (35.9) [12–48]	20 (27.6) [8.5–37]



(a) **(b)**

Figure S2: Comparison of mortality rates for intubated ARDS

Panel (a) presents mortality rates in separate subsets: 2,774 patients based on PaO_2/FiO_2 ratio and 2,442 based on SpO_2/FiO_2 ratio, with p-value = 0.06 of the CMH test for a difference in mortality rates. Panel (b) focuses on the intersection subset of 2,333 patients with p-value = 0.02 of the CMH test.

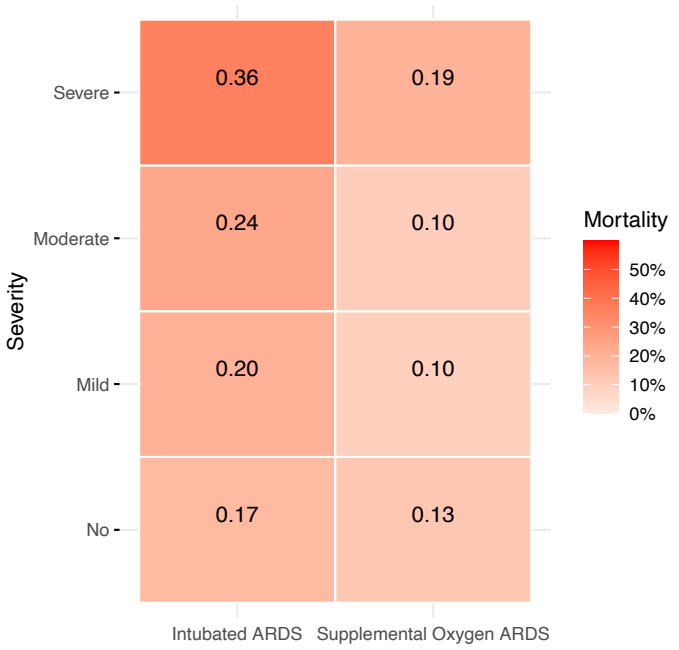


Figure S3: Comparison of mortality rates for supplemental oxygen ARDS
The comparison is among patients with intubated ARDS (2,774) as classified under the Berlin definition and those with supplemental oxygen ARDS (3,166) as classified under the new global definition with p-value $< 10^{-15}$ of the CMH test for a difference in mortality rates.

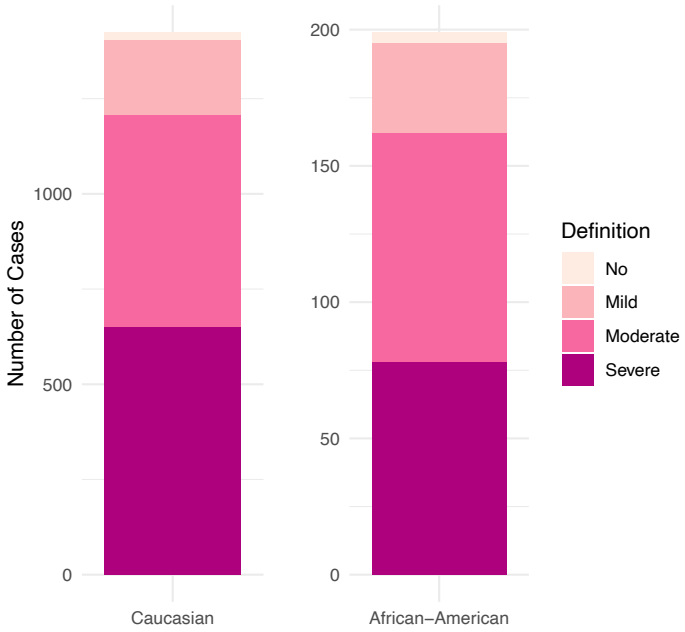
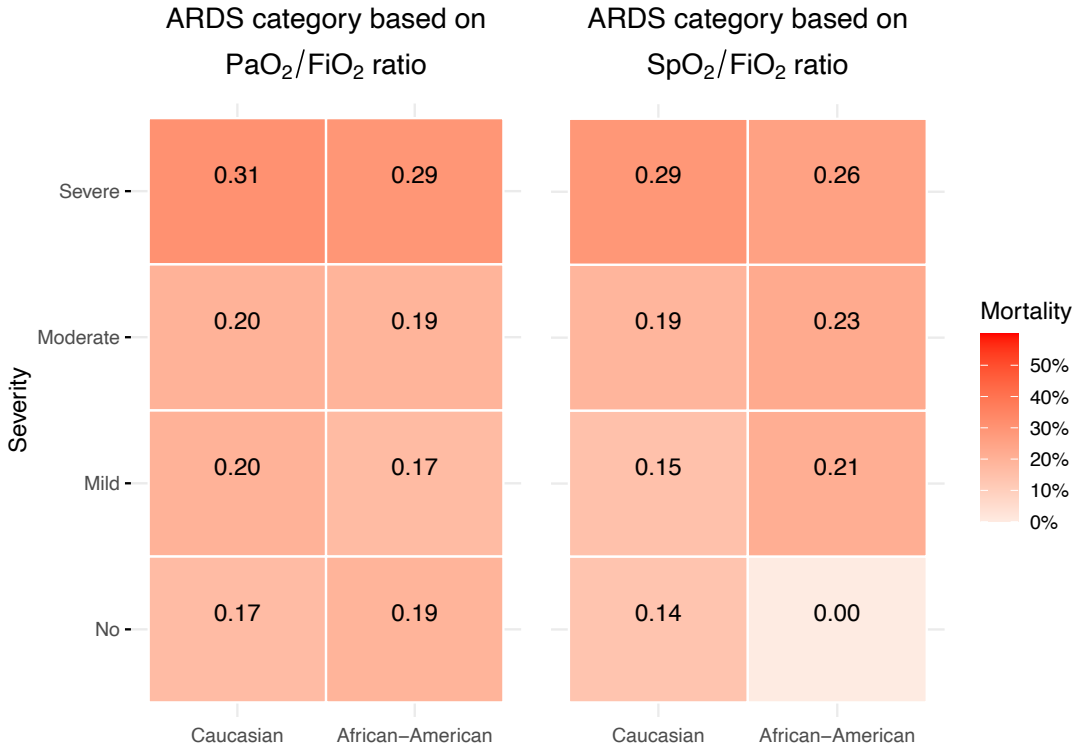


Figure S4: Distribution of intubated ARDS categories in Caucasian and African-American patients under the new global definition
The comparison of ARDS category distributions is among the separate subsets: 1,424 Caucasian patients and 199 African-American patients under the new global definitions.

(a) **(b)**

Figure S5: Comparison of the mortality rates for intubated ARDS among Caucasian and African-American patients

Panel (a) displays the mortality rates among 1,364 Caucasian patients within the intersection subset of the two definitions. Panel (b) details the same for 193 African-American patients.



(a) **(b)**

Figure S6: Comparison of mortality rates for intubated ARDS between Caucasian and African-American patients with statistical significance

Panel (a) shows the comparison of mortality rates for categories based on PaO_2/FiO_2 ratio within the separate subsets of the ratios with p value = 0.89 of the CMH test. Panel (b) presents analogous information for categories based on SpO_2/FiO_2 ratio, with p value = 0.81 of the CMH test for a difference in mortality rates.

References

1. Johnson AE, Bulgarelli L, Shen L, Gayles A, Shammout A, Horng S, Pollard TJ, Hao S, Moody B, Gow B, (2023) MIMIC-IV, a freely accessible electronic health record dataset. Scientific data 10:1. https://doi.org/10.1038/s41597-022-01899-x
2. Serpa Neto A, Deliberato RO, Johnson AE, Bos LD, Amorim P, Pereira SM, Cazati DC, Cordioli RL, Correa TD, Pollard TJ, (2018) Mechanical power of ventilation is associated with mortality in critically ill patients: an analysis of patients in two observational cohorts. Intensive care medicine 44:1914-1922. https://doi.org/10.1007/s00134-018-5375-6
3. Toal CM, Fowler AJ, Patel BV, Puthucheary Z, Prowle JR, (2023) Hypoxemia Trajectory of Non-COVID-19 Acute Respiratory Distress Syndrome Patients. An Observational Study Focusing on Hypoxemia Resolver Status. Critical Care Explorations 5:e0985. https://doi.org/10.1097/CCE.0000000000000985
4. Wang Z, Zhang L, Huang T, Yang R, Cheng H, Wang H, Yin H, Lyu J, (2023) Developing an explainable machine learning model to predict the mechanical ventilation duration of patients with ARDS in intensive care units. Heart & Lung 58:74-81. https://doi.org/10.1016/j.hrtlng.2022.11.005
5. See KC, Ong V, Tan YL, Sahagun J, Taculod J, (2018) Chest radiography versus lung ultrasound for identification of acute respiratory distress syndrome: a retrospective observational study. Critical Care 22:203. https://doi.org/10.1186/s13054-018-2105-y
6. Matthay MA, Arabi Y, Arroliga AC, Bernard G, Bersten AD, Brochard LJ, Calfee CS, Combes A, Daniel BM, Ferguson ND, (2024) A new global definition of acute respiratory distress syndrome. American journal of respiratory and critical care medicine 209:37-47. https://doi.org/10.1164/rccm.202303-0558WS
7. Yarnell CJ, Angriman F, Ferreyro BL, Liu K, De Grooth HJ, Burry L, Munshi L, Mehta S, Celi L, Elbers P, Thoral P, Brochard L, Wunsch H, Fowler RA, Sung L, Tomlinson G, (2023) Oxygenation thresholds for invasive ventilation in hypoxemic respiratory failure: a target trial emulation in two cohorts. Critical Care 27:67. https://doi.org/10.1186/s13054-023-04307-x
8. Chen W, Janz DR, Shaver CM, Bernard GR, Bastarache JA, Ware LB, (2015) Clinical characteristics and outcomes are similar in ARDS diagnosed by oxygen saturation/Fio2 ratio compared with Pao2/Fio2 ratio. Chest 148:1477-1483. https://doi.org/10.1378/chest.15-0169
9. Agresti A (2019) An Introduction to Categorical Data Analysis. Wiley
10. Cabanas AM, Fuentes-Guajardo M, Latorre K, León D, Martín-Escudero P, (2022) Skin pigmentation influence on pulse oximetry accuracy: a systematic review and bibliometric analysis. Sensors 22:3402. https://doi.org/10.3390/s22093402