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# Racial and ethnic minority participants in clinical trials of acute respiratory distress syndrome

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## Abstract

**Purpose:** There is growing interest in improving the inclusiveness of racial and ethnic minority participants in trials of acute respiratory distress syndrome (ARDS). With our study we aimed to examine temporal trends of representation and mortality of racial and ethnic minority participants in randomized controlled trials of ARDS.

**Methods:** We performed a secondary analysis of eight ARDS Network and PETAL Network therapeutic clinical trials, published between 2000 and 2019. We classified race/ethnicity into “White”, “Black”, “Hispanic”, or “Other” (including Asian, American Indian or Alaskan Native, Native Hawaiian, or other Pacific Islander participants).

**Results:** Of 5375 participants with ARDS, 1634 (30.4%) were Black, Hispanic, or Other race participants. Representation of racial and ethnic minority participants in trials did not change significantly over time ( $p=0.257$ ). However, among participants with moderate to severe ARDS (i.e., partial pressure of arterial oxygen to fraction of inspired oxygen ratio  $< 150$ ), the difference in mortality between racial and ethnic minority participants and White participants decreased over time. In the five most recent trials, including 2923 participants with ARDS, there were no statistically significant differences in mortality between racial/ethnic groups, even after adjusting for potential confounders. In these five most recent trials, mortality was 31% for White, 31.9% for Black, 30.3% for Hispanic, and 37.1% for Other race participants ( $p=0.633$ ).

**Conclusion:** Representation of racial and ethnic minority participants in ARDS trials from North America, published between 2000 and 2019, did not change over time. Black and Hispanic participants with ARDS may have similar mortality as White participants within trials.

**Keywords:** Acute lung injury, Acute hypoxemic respiratory failure, Intensive care unit, Critical care, Mortality, Epidemiology

## Introduction

Consideration of racial and ethnic diversity groups has been identified as an opportunity for improved clinical trial design [1]. In 2021, the National Institute on Minority Health and Health Disparities set the goal to increase the percentage of participants from diverse populations in clinical trials to 40 percent by the year 2030 in major disease categories [2], such as acute respiratory distress syndrome (ARDS). Indeed, there is growing attention

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toward improving the inclusiveness of racial and ethnic minority participants in future ARDS trials [1, 3]. Despite this increasing interest [1, 4], the last relevant data on the representation and outcomes of racial and ethnic minority participants are based on trials of ARDS, which were published in 2000, 2004, and 2006 [5–7].

Based on previous evidence, racial and ethnic minority patients with ARDS are considered to be at higher risk of mortality than White patients [8]. This consideration may be supported by a secondary analysis (published in 2009 [9]) of data from the first three trials of the ARDS Network (namely, ARMA [5], ALVEOLI [6], and FACTT [7]). In that secondary analysis [9], Black and Hispanic patients with ARDS comprised 27.4% of the study population and were found to have a significantly higher risk of adverse outcomes (including mortality and ventilator-free days) than White patients [9]. Although racial and ethnic minority patients may have a higher risk of developing ARDS [10], updated data on their representation and outcomes in recent therapeutic trials of ARDS do not exist.

Accordingly, we endeavored to determine whether the representation of racial and ethnic minority participants in therapeutic trials of ARDS changed over time and to analyze the mortality of participants with ARDS by race/ethnicity within trials. Part of this work has previously been presented at an international meeting of the European Society of Intensive Care Medicine and published as an abstract [11].

## Methods

### Study design and patient population

We performed a secondary analysis of data from eight ARDS Network and Prevention and Early Treatment of Acute Lung Injury (PETAL) Network prospective therapeutic clinical trials (namely, ARMA [5], ALVEOLI [6], FACTT [7], ALTA [12], EDEN [13], SAILS [14], ROSE [15], and VIOLET [16]). Details on the geographical locations of those trials are provided in the online data supplement (eMethods). Participants from the OMEGA trial [17] were included in this analysis as part of the EDEN trial [13]. Participants from the LaSRS trial [18] were not considered, as they needed to have late-phase ARDS. In those trials [5–7, 12–15], no racial/ethnic group was excluded, and participants had to receive positive-pressure mechanical ventilation through an endotracheal tube, had a partial pressure of arterial oxygen to fraction of inspired oxygen ratio ( $\text{PaO}_2/\text{FiO}_2$ )  $\leq 300$ , and had bilateral infiltrates on chest radiography not fully explained by cardiac failure. Similarly, participants from the VIOLET trial with ARDS at baseline were included in this analysis [16]. As previously described [19, 20], we were granted access to data through the Biologic

## Take-home message

Representation of racial and ethnic minority participants in trials of ARDS did not change significantly over time. Black and Hispanic participants with ARDS may have similar mortality as White participants within trials.

Specimen and Data Repository Information Coordinating Center (BioLINCC) of the National Heart, Lung, and Blood Institute (NHLBI). Because data would be received in de-identified form, the Institutional Review Board of Evangelismos Hospital, Athens, Greece waived the need of informed consent and approved the study (141/05-05-2022).

### Study groups

As previously described [9], we classified race/ethnicity into four mutually exclusive categories: “White” (including only White, non-Hispanic participants), “Black” (including only Black, non-Hispanic participants), “Hispanic”, or “Other” (including non-White, non-Black, non-Hispanic, participants). The “Other” race category was provided in an aggregated form from the original trials (except from VIOLET [16]) and included Asian, American Indian or Alaskan Native, Native Hawaiian, or other Pacific Islander participants. Participants without documented race/ethnicity were only included in sensitivity analyses; the study-level distribution of these participants is available as supplemental Table E1 in the online data supplement. Additional details on the classification of participants into race/ethnicity study groups are available supplementary eMethods.

### Study outcomes

The primary outcomes of the present analysis were the proportion of racial and ethnic minority participants within ARDS therapeutic trials and 90-day mortality, with participants discharged from the hospital prior to 90 days considered to be alive at 90 days. We chose to examine mortality at day 90 because participants in ARDS Network and PETAL Network trials [5–7, 12–16] were followed through day 90 unless they were discharged home earlier. Secondary outcomes were differences in organ failure-free days, ventilator-free days, and intensive care unit (ICU)-free days between racial/ethnic groups through day 28 following enrollment, as previously described [21, 22]. Also, we estimated differences in the occurrence of rapidly improving ARDS (defined as extubation or a  $\text{PaO}_2/\text{FiO}_2 > 300$  on the first study day following enrollment) [23, 24] and prolonged mechanical ventilation (defined as the need of mechanical ventilation after day 21 following enrollment) [25]

between racial/ethnic groups. To better reflect contemporary clinical practice, and given that a similar secondary analysis of the first three trials [5–7] was already published [9], we considered only data from the five most recent trials [12–16] for the analyses of baseline characteristics and outcomes.

### Sensitivity analyses

We performed sensitivity analyses by considering participants without documented race/ethnicity either as a separate category or as part of the Other race category.

Also, to further update our findings by considering trials beyond the ARDS Network and PETAL Network, we performed a sensitivity analysis using data from therapeutic trials, which were published in 2021 and enrolled participants hospitalized with the new coronavirus disease 2019 (COVID-19), namely the Adaptive COVID-19 Treatment Trial (ACTT)-2 [26] and ACTT-3 [27]. For this sensitivity analysis, we only included ACTT-2 and ACTT-3 participants with ARDS, defined as the need for invasive mechanical ventilation and/or extracorporeal membrane oxygenation. We were granted access to those data through the National Institute of Allergy and Infectious Diseases (NIAID).

### Statistical analysis

Continuous variables were presented as median with interquartile range (IQR) and compared using the Kruskal–Wallis test. Categorical variables were presented as percentages and compared using the chi-squared or Fisher's exact test, as appropriate. To estimate the pooled prevalence and pooled 90-day mortality of racial and ethnic minority participants across trials, proportional meta-analyses using inverse variance weights and random-effects models (DerSimonian & Laird) were performed. To stabilize variances, the Freeman–Tukey double arcsine transformation and then back-transformation for ease of interpretation were used [28, 29]. The prevalence of racial and ethnic minority participants was estimated over time via a meta-regression analysis, with time as the independent variable and within-study prevalence of minorities as the dependent variable. Mortality was estimated over time via a meta-regression analysis, with time as the independent variable and the natural logarithm of odds ratio for mortality of minorities compared to the mortality of White participants as the dependent variable. Meta-regression analyses were performed using inverse variance weights and random-effects models.

The association between race/ethnicity and 90-day mortality (primary outcome) was tested with a Cox proportional hazards regression analysis taking into consideration trial, age, sex, comorbidities (presence versus absence), PaO<sub>2</sub>/FiO<sub>2</sub>, and non-pulmonary organ failures

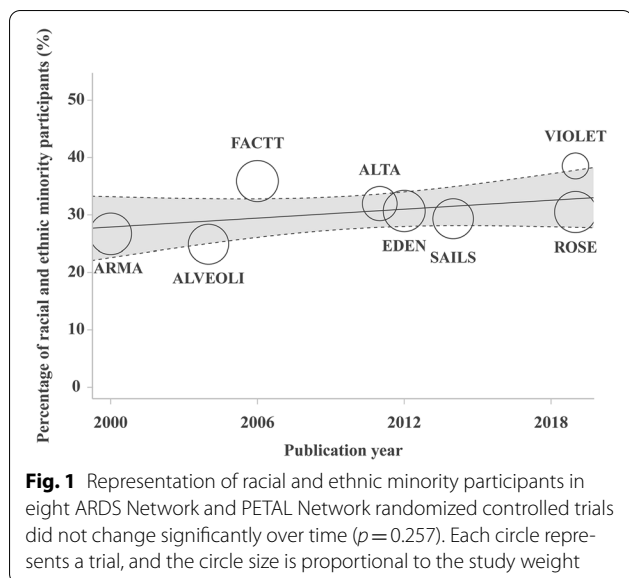
on the day of enrollment, as previously described in the literature [9]. Potential violations of the proportional hazards assumption were assessed using scaled Schoenfeld residuals for each covariate [30] and were addressed by bootstrap techniques using 2000 resamples with 95% confidence intervals (CI) being estimated using the bias-corrected accelerated method [31]. Also, the linearity of the continuous covariates (namely, age and PaO<sub>2</sub>/FiO<sub>2</sub> at the day of enrollment) was assessed and confirmed using Martingale residuals [30]. To further evaluate the association between race/ethnicity and 90-day mortality, a sensitivity Cox proportional hazards regression analysis with participants discharged from the hospital prior to 90 days considered to be dead at 90 days was performed. To construct the Cox proportional hazards regression model, all available information on mortality and the included variables were used. Missing data on outcomes were below 4% (supplementary Table E2 in the online data supplement). All p values were two-sided, and statistical significance was considered at an  $\alpha$  level of 0.05. All statistical analyses were conducted using SPSS software version 28.0 (SPSS, Inc., Chicago, IL, USA) and R software version 4.2.1 (R Foundation for Statistical Computing).

## Results

### Temporal trends of representation and mortality of racial and ethnic minority participants

Out of 5375 participants with ARDS enrolled in eight ARDS Network and PETAL Network randomized controlled trials [5–7, 12–16], 1634 (30.4%) were racial and ethnic minority participants (namely, Black, Hispanic or Other race). Baseline characteristics by race/ethnicity are presented in supplementary Table E3. In all eight trials [5–7, 12–16], the pooled prevalence of racial and ethnic minority participants was 30.4% (95% CI 27.7–33.2%) ranging from 24.9% in the ALVEOLI trial [6] to 38.5% in VIOLET trial [16] (supplementary Fig. E1). Representation of racial and ethnic minority participants in therapeutic clinical trials of ARDS did not change significantly over time ( $p = 0.257$ ) (Fig. 1).

In all eight trials [5–7, 12–16], the pooled 90-day mortality of racial and ethnic minority participants was 33% (95% CI 27.8–38.5%) (supplementary Fig. E2). To assess temporal trends of mortality, we focused our analysis on participants with moderate to severe ARDS (defined as PaO<sub>2</sub>/FiO<sub>2</sub> < 150) [32] because the ROSE trial only included such participants [15]. A total of 3244 participants had moderate to severe ARDS and were included in this analysis. In the first three ARDS Network trials (namely, ARMA [5], ALVEOLI [6], and FACTT [7]), the mortality rate of racial and ethnic minority participants was higher than the mortality rate of White participants. However, in the five most recent trials (namely, ALTA



[12], EDEN [13], SAILS [14], ROSE [15], and VIOLET [16]), the difference in mortality between racial and ethnic minority participants and White participants with moderate to severe ARDS decreased (Fig. 2A). Meta-regression analysis found a significant effect of time on the difference in mortality between racial and ethnic minority participants and White participants with moderate to severe ARDS ( $p=0.021$ ) (Fig. 2B). As detailed in supplementary Table E4, the mortality rate changed from 35.7% for White and 44.2% for racial and ethnic minority participants in the ARMA trial [5] ( $p=0.072$ ) to 47.2% for White and 46.7% for racial and ethnic minority

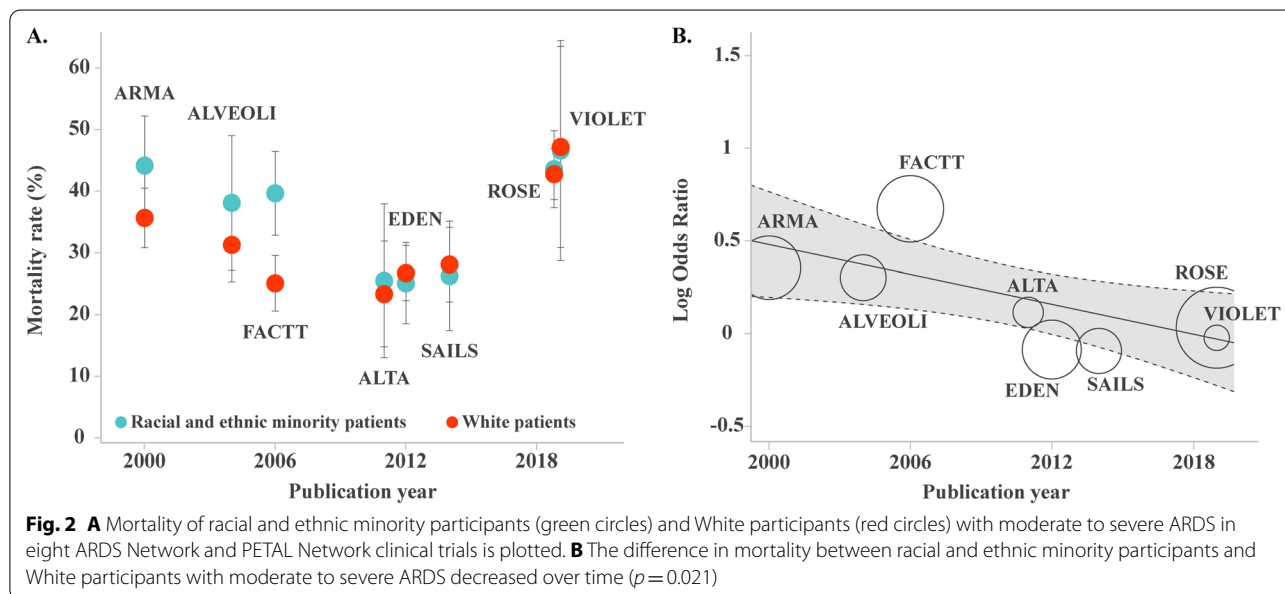
participants in VIOLET trial [16] ( $p=0.964$ ). Additional details on temporal trends of mortality rates per racial/ethnic group (namely, White, Black, Hispanic, or Other race) are available in supplementary Table E5. Temporal trends of mortality in the total population, regardless of ARDS severity, are presented in supplementary Fig. E3 and Table E6.

To better reflect contemporary clinical practice, the remainder of our analyses considered only data from the five most recently published clinical trials; namely, ALTA [12], EDEN [13], SAILS [14], ROSE [15], and VIOLET [16] (all published after 2010). The latter trials [12–16] enrolled a total of 2923 participants with ARDS; i.e., 2026 (69.3%) White, 448 (15.3%) Black, 360 (12.3%) Hispanic, and 89 (3%) Other race participants.

#### Baseline characteristics of participants by race/ethnicity

Table 1 depicts baseline characteristics of participants by race/ethnicity. The median (IQR) age of White, Black, Hispanic, and Other race participants was 56 (44–67), 52.5 (41–62), 51 (40–60), and 57 (41–69.5) years, respectively. There were no substantial differences between racial/ethnic groups in terms of sex, primary risk factor of ARDS, and usage of steroids. There were differences between groups in terms of comorbidities (Table 1). Renal failure was more common in Black (34.2%) and Hispanic (29.4%) participants compared to White (26%) and Other race (24.7%) participants.

Regarding baseline lung mechanics, there were no substantial differences between groups in terms of tidal volume per predicted body weight and positive end-expiratory pressure. However, median  $\text{PaO}_2/\text{FiO}_2$  was



**Table 1 Baseline characteristics of participants by race/ethnicity in the five most recent ARDS Network and PETAL Network trials**

	All (n = 2923)	White (n = 2026)	Black (n = 448)	Hispanic (n = 360)	Other race (n = 89)	p value
Age	55 (43–65)	56 (44–67)	52.5 (41–62)	51 (40–60)	57 (41–69.5)	<0.001
Female sex	1396 (47.8)	964 (47.6)	222 (49.6)	172 (47.8)	38 (42.7)	0.678
BMI	29.3 (24.2–35)	29.4 (24.5–35)	28.7 (23.7–35.3)	29.8 (24.8–35.2)	27.1 (22.6–32.4)	0.046
<b>Comorbidities</b>						
Hypertension	1347 (48.2)	910 (46.9)	239 (56)	159 (47.2)	39 (44.8)	0.007
Diabetes mellitus	792 (27.5)	486 (24.3)	155 (35)	130 (36.6)	21 (23.9)	<0.001
Chronic pulmonary disease	464 (16.1)	352 (17.6)	57 (12.9)	44 (12.4)	11 (12.5)	0.010
End-stage renal disease	86 (3.1)	36 (1.9)	32 (7.5)	15 (4.4)	3 (3.4)	<0.001
Liver disease	216 (7.5)	140 (7)	22 (5)	47 (13.3)	7 (8)	<0.001
AIDS	57 (2.2)	20 (1.1)	24 (6)	12 (3.7)	1 (1.3)	<0.001
Leukemia	119 (4.1)	92 (4.6)	12 (2.7)	11 (3.1)	4 (4.5)	0.224
Non-Hodgkin Lymphoma	32 (1.1)	19 (1)	8 (1.8)	4 (1.1)	1 (1.1)	0.389
Solid tumor with metastasis	103 (3.6)	77 (3.9)	13 (2.9)	11 (3.1)	2 (2.3)	0.650
Prior myocardial infarction	161 (5.6)	130 (6.5)	19 (4.3)	9 (2.5)	3 (3.4)	0.009
Congestive heart failure	205 (7.1)	133 (6.7)	46 (10.4)	21 (5.9)	5 (5.7)	0.031
<b>Primary risk factor of ARDS</b>						
Pneumonia	1801 (61.6)	1226 (60.5)	293 (65.4)	234 (65)	48 (53.9)	0.052
Sepsis	480 (16.4)	345 (17)	55 (12.3)	63 (17.5)	17 (19.1)	0.074
Aspiration	348 (11.9)	256 (12.6)	46 (10.3)	31 (8.6)	15 (16.9)	0.046
Trauma	101 (3.6)	74 (3.8)	16 (3.7)	8 (2.3)	3 (3.4)	0.631
Multiple transfusions	43 (1.5)	26 (1.3)	9 (2.1)	4 (1.2)	4 (4.5)	0.069
Other	131 (4.6)	87 (4.4)	23 (5.3)	19 (5.6)	2 (2.3)	0.481
<b>Organ failure at enrollment</b>						
Cardiovascular	2094 (71.6)	1472 (72.7)	299 (66.7)	259 (71.9)	64 (71.9)	0.096
Renal	807 (27.6)	526 (26)	153 (34.2)	106 (29.4)	22 (24.7)	0.004
Liver	446 (15.3)	283 (14)	74 (16.5)	69 (19.2)	20 (22.5)	0.012
Coagulation	546 (18.7)	368 (18.2)	84 (18.8)	76 (21.1)	18 (20.2)	0.594
Usage of steroids	973 (34.5)	682 (34.8)	134 (31.2)	128 (37.5)	29 (33)	0.298
<b>Lung mechanics at enrollment</b>						
PaO <sub>2</sub> /FiO <sub>2</sub>	128.3 (95–175)	130 (97.1–176)	126.3 (91.9–175.8)	117.5 (84–162)	133 (103.1–191.3)	0.002
Tidal volume per predicted body weight	6.2 (6–7.1)	6.2 (6–7)	6.2 (5.9–7)	6.2 (6–7.3)	6.1 (5.9–7.1)	0.738
PEEP	10 (8–12)	10 (8–12)	10 (8–12)	10 (8–14)	10 (8–13.5)	0.150
Driving pressure	14 (11–17)	13 (10–17)	15 (12–18.8)	14 (11–18)	15 (10.8–18.3)	<0.001

Other race patients include Asian, American Indian or Alaskan Native, Native Hawaiian, or other Pacific Islander patients

The VIOLET trial recruited 1358 participants that had one or more acute risk factors for death or lung injury. Of those, 103 participants had ARDS at baseline. Of the latter participants with ARDS, 96 patients also had a documented race/ethnicity and, therefore, were included in this secondary analysis

Data on usage of steroids, tidal volume, and driving pressure were not available for the VIOLET trial

ARDS acute respiratory distress syndrome, *n* number, BMI body mass index, AIDS Acquired Immune Deficiency Syndrome, PaO<sub>2</sub>/FiO<sub>2</sub> partial pressure of arterial oxygen to fraction of inspired oxygen ratio, PEEP positive end-expiratory pressure

lower in Hispanic participants [117.5 (84–162)], while median driving pressure was higher in Black [15 (12–18.8) cmH<sub>2</sub>O] and Other race [(15 (10.8–18.3) cmH<sub>2</sub>O] participants than comparators.

#### Outcomes of participants by race/ethnicity

Table 2 depicts the outcomes of participants by race/ethnicity. There were no statistically significant differences

between racial/ethnic groups in terms of 90-day mortality; the mortality rate was 31% (628 of 2026) for White, 31.9% (143 of 448) for Black, 30.3% (109 of 360) for Hispanic, and 37.1% (33 of 89) for Other race participants ( $p=0.633$ ). Supplementary Table E7 depicts outcomes by race/ethnicity with Black, Hispanic, and Other race participants combined as one group. Consistently, in a Cox regression analysis shown in Table 3, race/ethnicity

**Table 2 Outcomes of participants by race/ethnicity in the five most recent ARDS Network and PETAL Network trials**

	All (n = 2923)	White (n = 2026)	Black (n = 448)	Hispanic (n = 360)	Other race (n = 89)	p value
90-day mortality	913 (31.2)	628 (31)	143 (31.9)	109 (30.3)	33 (37.1)	0.633
Organ failure-free days	15 (0–25)	15 (0–25)	14 (0–24)	14 (0–24)	11.5 (0–21.8)	0.059
Ventilator-free days	17 (0–24)	18 (0–24)	17 (0–23)	16.5 (0–23)	10 (0–23)	0.083
ICU-free days	15 (0–22)	16 (0–23)	15 (0–22)	14 (0–21)	9 (0–19)	0.040
Rapidly improving ARDS	389 (13.3)	281 (13.9)	66 (14.7)	34 (9.4)	8 (9)	0.059
Prolonged mechanical ventilation	415 (14.2)	264 (13)	78 (17.4)	60 (16.7)	13 (14.6)	0.049

Rapidly improving ARDS was defined as a partial pressure of arterial oxygen to fraction of inspired oxygen ratio ( $\text{PaO}_2/\text{FiO}_2$ ) > 300 on the first study day following enrollment; and/or achieving unassisted breathing on the first study day following enrollment

Prolonged mechanical ventilation was defined as the need of mechanical ventilation after day 21 following enrollment

Organ failure-free days and ICU-free days were not available in the VIOLET trial

n number, ARDS acute respiratory distress syndrome, ICU intensive care unit

**Table 3 Cox regression analysis to isolate the contribution of trial, age, sex, comorbidities,  $\text{PaO}_2/\text{FiO}_2$ , and non-pulmonary organ failures at day of enrollment, and race/ethnicity (independent variables) to the 90-day mortality (dependent variable)**

	Univariable analysis			Multivariable analysis		
	Hazard ratio	95% confidence intervals	p value	Hazard ratio	95% confidence intervals	p value
ALTA trial	Ref	Ref		Ref	Ref	
EDEN trial	1.007	0.753–1.345	0.965	1.069	0.799–1.430	0.653
SAILS trial	1.234	0.916–1.661	0.167	1.227	0.909–1.656	0.182
ROSE trial	2.154	1.632–2.843	< 0.001	1.621	1.222–2.151	< 0.001
VIOLET trial	2.419	1.636–3.576	< 0.001	2.581	1.725–3.860	< 0.001
Age (increments of 1 year)	1.030	1.026–1.035	< 0.001	1.031	1.026–1.036	< 0.001
Female sex	0.884	0.776–1.007	0.063	0.920	0.805–1.051	0.221
Comorbidities (presence versus absence)	2.433	2.127–2.782	< 0.001	1.962	1.705–2.259	< 0.001
$\text{PaO}_2/\text{FiO}_2$ (increments of 10)	0.964	0.953–0.975	< 0.001	0.968	0.956–0.980	< 0.001
No non-pulmonary organ failure at baseline	Ref	Ref		Ref	Ref	
One non-pulmonary organ failure at baseline	1.441	1.149–1.808	0.002	1.391	1.100–1.758	0.006
Two non-pulmonary organ failures at baseline	2.440	1.933–3.079	< 0.001	2.174	1.706–2.770	< 0.001
Three non-pulmonary organ failures at baseline	3.610	2.789–4.674	< 0.001	3.078	2.345–4.041	< 0.001
Four non-pulmonary organ failures at baseline	5.184	3.604–7.457	< 0.001	4.051	2.770–5.923	< 0.001
White participants	Ref	Ref		Ref	Ref	
Black participants	1.026	0.855–1.230	0.785	1.133	0.941–1.364	0.188
Hispanic participants	0.984	0.803–1.206	0.875	0.973	0.788–1.202	0.800
Other race participants	1.230	0.867–1.746	0.246	1.148	0.804–1.640	0.448

Comorbidities include AIDS, leukemia, lymphoma, solid tumor with metastasis, immunosuppression and liver disease. AIDS was not available in ALTA trial, and immunosuppression was not available in VIOLET trial

Non-pulmonary organ failures include cardiovascular, renal, liver, or coagulation failure

Other race patients include Asian, American Indian or Alaskan Native, Native Hawaiian, or other Pacific Islander patients

$\text{PaO}_2/\text{FiO}_2$  partial pressure of arterial oxygen to fraction of inspired oxygen ratio, Ref reference

was not independently associated with 90-day mortality after controlling for trial, age, sex, comorbidities,  $\text{PaO}_2/\text{FiO}_2$  and non-pulmonary organ failures at day

of enrollment [with White participants being the reference category; Hazard ratio (HR)=1.133; 95% CI 0.941–1.364 for Black participants; HR=0.973; 95% CI

0.788–1.202 for Hispanic participants; and HR = 1.148; 95% CI 0.804–1.640 for Other race participants]. Even after utilizing bootstrap techniques, race/ethnicity was not independently associated with 90-day mortality (supplementary Table E8). This was also the case for the sensitivity Cox regression analyses by adding the effect of intervention/control per each trial in the model (supplementary Table E9), and by considering participants discharged from the hospital prior to 90 days as dead at 90 days. With regard to secondary outcomes, Other race participants had fewer ICU-free days than comparators (Table 2).

### Sensitivity analyses

In the sensitivity analyses by considering participants without documented race/ethnicity either as a separate category or as part of the Other race category, race/ethnicity was again not independently associated with mortality. Relevant results are presented in supplementary Tables E10 and E11, respectively.

Consistently, this was also the case for the sensitivity analysis of data from the ACTT-2 [26] and ACTT-3 [27] randomized controlled trials (supplementary Table E12). In this sensitivity analysis, Black and Hispanic participants with ARDS did not have higher mortality than White participants. Details are provided as eResults in the online data supplement.

### Discussion

This secondary analysis of data from 5375 participants with ARDS included in eight ARDS Network and PETAL Network therapeutic trials suggests that the representation of racial and ethnic minority participants did not change significantly over time. However, the difference in mortality between racial and ethnic minority participants and White participants in trials of ARDS decreased. In the five most recently published trials, there were no statistically significant differences in mortality between White, Black, Hispanic, and Other race participants, even after adjusting for confounders.

The results of the present secondary analysis may be useful to ARDS clinical trialists. Clinical trialists have identified as a primary strategy to improve the design of ARDS trials the increase in the representativeness of clinical trial populations [1]. We found that the representation of racial and ethnic minority participants in therapeutic trials of ARDS did not change from 2000 to 2019. Therefore, given that the National Institute on Minority Health and Health Disparities aimed to increase the percentage of participants from diverse populations in clinical research to 40 percent by 2030, there is still potential for improvement. That being said, the representation of Black participants within ARDS Network and PETAL

Network trials was found to be 16.7%, while their estimated representation in the US population is 12.6% [4], probably due to their higher risk of developing ARDS [10]. Taken together, our findings (in accordance with previous evidence [33]) suggest that the problem of not sufficiently reporting [4] or including racially and ethnically marginalized communities may not be as large in ARDS as in other fields, such as heart failure [34] or cancer [35].

The present secondary analysis found that the difference in mortality between racial and ethnic minority participants and White participants with ARDS decreased. Also, the prevalence of rapidly improving ARDS, that has been associated with better outcomes compared to ARDS > 1 day [23], did not differ between racial/ethnic groups. Exploring the cause of these intriguing findings was beyond the scope of this analysis. However, one could make the conjecture that changes in mortality over 20 years may be reflective of altered comorbidity burdens, staffing burdens of institutions, and/or growing expertise in the management of patients with ARDS, regardless of race/ethnicity [5, 23, 32, 36]. Our findings might be an indication of ever-increasing awareness among clinicians to provide optimal management of racial and ethnic minority patients with ARDS.

Our finding that there was no statistically significant difference in outcomes between racial/ethnic groups seems to be at odds with evidence outside ARDS Network and PETAL Network trials. It is thought that Black and Hispanic patients with ARDS are at higher risk of mortality than White patients [8, 37], and this has been partially attributed to the fact that pulse oximetry might overestimate oxygenation of patients of color [8]. Although pulse oximetry-derived overestimation of oxygenation in patients of color indeed affects the administration of supplemental oxygen [38, 39], this might have been inconsequential in the ARDS Network and PETAL Network trials where the management of patients was primarily based on PaO<sub>2</sub> rather than the saturation of peripheral oxygen (SpO<sub>2</sub>). Beyond pulse oximetry, it is possible that the overall protocolized nature of randomized controlled trials might improve care for racial and ethnic minority patients as compared to “real life” situations where unconscious and conscious biases may be less mitigated by highly protocolized and idealized care that occurs within trials.

Our study has limitations. First, the “Other” race category was provided in an aggregated form from the original ARDS Network and PETAL Network trials (except from VIOLET [16]) and included Asian, American Indian or Alaskan Native, Native Hawaiian, or other Pacific Islander participants. Thus, due to the subsequent heterogeneity of this race category, the observed differences

in organ failure-free days, ventilator-free days, and ICU-free days between the “Other” race participants and comparators were difficult to interpret and need further evaluation. Accordingly, we suggest that all trials collect and report disaggregated granular data on race/ethnicity to allow for future research on outcomes of Asian, American Indian or Alaskan Native, Native Hawaiian, or other Pacific Islander participants. Second, it is a post hoc secondary analysis. However, we designed the statistical plan prospectively in our study protocol, which was given to BioLINCC. Third, recruitment for these clinical trials often occurs at large academic centers and thus our findings may not represent nonacademic hospitals that provide the majority of care to racial and ethnic minority patients.

Fourth, the ARDS Network and PETAL Network trials exclusively enrolled participants from North America and thus their conclusions may not be generalizable to other continents. However, we performed a sensitivity analysis of data from the ACTT-2 [26] and ACTT-3 [27] trials, which did not limit their enrollment to sites in North America; rather they also enrolled participants from Asia and Europe. In this sensitivity analysis of ACTT trials, we again found that Black and Hispanic participants with ARDS did not have higher mortality than White participants. Fifth, there were no available data on the consent rates in racial/ethnic groups. A relevant secondary analysis of the first three ARDS Network trials [5–7] found that racial and ethnic minority patients were more likely than White patients to be excluded due to lack of consent [33]. Sixth, there are other diversity groups, such as those based on sex [40, 41] that may influence outcomes of patients with ARDS. Nevertheless, the assessment of the effect of such diversity groups on the outcomes of ARDS was out of the scope of the current study. Seventh, due to the limited number of events in the “Other” race category, we included comorbidities in a simplified (presence versus absence) manner rather than a detailed (each comorbidity) manner in the Cox regression analysis. Finally, we did not have information on the social demographics of health variables, including the socioeconomic status of participants, which are important confounders when assessing race and ethnicity-based disparities [42].

## Conclusions

In conclusion, we found that the representation of racial and ethnic minority participants in ARDS trials from North America, published between 2000 and 2019, did not change significantly over time. Black and Hispanic participants with ARDS may have similar mortality as White participants within trials.

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1007/s00134-023-07238-x>.

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## Author contributions

EP and IIS had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. EP and IIS contributed to the concept and design of the study. EP, PK, VT, AK, CR, AK, and IIS were responsible for data acquisition and/or interpretation of the data. EP undertook statistical analyses and drafted the manuscript. PK, VT, AK, CR, AK, and IIS critically revised the manuscript for intellectual content and gave final approval of the manuscript. IIS supervised the study. All authors read and approved the final manuscript.

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## Data availability

Data which this secondary analysis was based on are available through the Biologic Specimen and Data Repository Information Coordinating Center of the National Heart, Lung, and Blood Institute (<https://biolincc.nhlbi.nih.gov/home/>).

## Declarations

## Conflicts of interest

The authors declare no conflict of interest in relation to this manuscript.

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