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Age-, sex-, and race-based differences among patients enrolled versus not enrolled in acute lung injury clinical trials

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Abstract

Objective—Little is known about the participation of racial/ethnic minorities, women, and the elderly into critical care clinical trials. We sought to characterize the representation of racial and ethnic minorities, women and older patients in clinical trials of patients with acute lung injury (ALI) and to determine the reasons for non-enrollment.

Design, Setting, an Patients—We performed a cross-sectional analysis of pooled screening logs from 44 academic hospitals participating in three multi-center, randomized, controlled trials conducted by the Acute Respiratory Distress Syndrome Network (ARDSnet) from 1996 to 2005.

Intervention—None

Measurements and Main Results—We calculated odds ratios (OR) of enrollment for age, sex, racial groups, and the OR for the presence of each exclusion criterion by age, sex, and race adjusted for demographics, ALI risk factor, study, and study center. 10.4% of 17,459 screened patients with ALI were enrolled. The median (range) enrollment by center was 15% (2–88%). Older patients of both sexes were less likely to be enrolled, but older women were more likely to be enrolled than older men. The adjusted OR (95% confidence interval [CI]) for enrollment among men ≥75 years of age was 0.59 (0.45–0.77) and for women ≥75 years of age was 0.45 (0.32–0.62), compared to men <35 years of age. There were no differences in the likelihood of enrollment among all racial/ethnic groups. Older patients and men were less likely to be enrolled because of medical comorbidity. Among all patients who were not enrolled, black patients and their families refused participation more often than white patients.

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Conclusions—Older patients are less likely to be enrolled in ALI clinical trials. There is no evidence that women or racial/ethnic minorities are underrepresented in ALI clinical trials.

Keywords

Critical Illness; Ethics, Research; Healthcare Disparities; Research Methodology; Aged

Introduction

Underrepresentation of women and racial/ethnic minorities among participants in medical research has received prominent attention in part due to the 1993 National Institutes of Health (NIH) Revitalization Act, which mandates inclusion of minorities and women in NIH sponsored research (1). Since its publication the identification and elimination of racial and gender disparities is a stated goal of the NIH and the Institute of Medicine (IOM) (2–4). Despite this mandate, underrepresentation of minorities and women in clinical research remains common in clinical trials of cancer, cardiovascular, and HIV therapies (5–8). Similar NIH guidelines advocating for the inclusion of elderly patients in medical research do not exist despite the consistently reported underrepresention of the elderly in cardiovascular and cancer clinical trials (7, 9).

Racial/ethnic minorities and older patients suffer a disproportionate burden of critical illness. For example, the incidence of sepsis among black Americans is twice that of white Americans (10, 11), and once present, minorities are at greater risk of death (11). The incidence of- and mortality from acute lung injury (ALI) is also greater among racial/ethnic minorities compared to whites (12, 13) and steadily increases with age such that patients older than 75 years of age are at the greatest risk of developing and dying from this disease (14–17). Given the rapidly aging population and the increasing proportions of racial/ethnic minorities in America, the societal burden of these diseases is expected to only increase (18).

Appropriate eligibility and exclusion criteria are essential for the internal validity and safety of efficacy trials. However, inadvertent omission of the elderly, women, and racial/ethnic minorities in critical illness clinical trials may compromise the generalizability of such studies, prevent exploration of necessary subgroup analysis by age, sex, or race/ethnic group, and perpetuate current disparities in equitable access to the latest therapies (19). To date, no study provides a broad characterization of the participation of older patients, women and racial/ethnic minorities in clinical trials in critical care (20).

We sought to determine whether there were differences in enrollment by age, sex, or race/ethnicity in ALI clinical trials. We also examined the reasons for non-enrollment among screened patients in these. We hypothesized that older patients would be less likely to be enrolled than younger patients; black patients would be less likely to be enrolled than white patients; and women would be less likely to be enrolled than men. Some of the results of this study have been previously reported in the form of an abstract (21, 22).

Materials and Methods

The study was approved by the Institutional Review Board (IRB) of the University of Washington. Seven local IRBs at centers where the parent studies were conducted refused the release of patient data for patients that were not enrolled. All patients from these centers were excluded.

Study sample

We performed a cross-sectional analysis of pooled screening logs collected during the three randomized, multi-center clinical trials carried out by the Acute Respiratory Distress Syndrome Network's (ARDSNet). The three included studies were: Ketoconazole and respiratory management in the treatment of ALI and ARDS trial (KARMA) (23); The Assessment of Low tidal Volume and elevated End-expiratory volume to Obviate Lung Injury trial (ALVEOLI) (24); and The Fluid and Catheter Treatment Trial (FACTT) (25, 26). For all studies, patients who were intubated and receiving mechanical ventilation were eligible for enrollment if they met the American-European Consensus Conference (AECC) definition for ALI (27). Specific exclusion criteria and further details about the three studies are in the electronic supplementary material (see Supplemental Digital Content, Appendix A).

Screening data quality

There was no standardized ALI screening practice across ARDSNet centers and the approach to screening in each center was not recorded. Within each study center, local investigators determined which ICUs would be screened, how many days per week screening occurred, and which patients would be written into the screening log. Some centers were given financial compensation for each patient screened while others were not. Although all exclusion criteria for each non-enrolled patient screened during FACTT were collected, investigators only captured one exclusion criterion for patients screened for KARMA and ALVEOLI. When more than one exclusion criterion was present no guidelines were available to facilitate selection of the criterion for log entry. For our analysis, we excluded patients who were included in screening logs but did not have ALI, patients missing data for age, sex, race/ethnicity, and patients who were not enrolled because they were too young.

Definitions and measurements

We defined enrollment fraction as the number of patients who were enrolled in a clinical trial divided by the total patients screened for enrollment. Age and sex were coded by investigators at the time of screening for ALI. To determine race/ethnicity, study personnel examined the patient, reviewed the medical record, and spoke with family. Patients were classified into six mutually exclusive categories: white, non-Hispanic; black, non-Hispanic; Hispanic; Asian or Pacific Islander; and Native American or Alaskan native; or other. With the exception of PaO_2/FiO_2 ratio and predisposing ALI risk factor, no other physiology, laboratory, or outcome data were available on non-enrolled patients.

Statistical analysis

We used χ^2, Fisher's exact, or t-test as appropriate for all bivariate comparisons. We used logistic regression to determine the likelihood of enrollment by age, sex, and race/ethnicity stratified by hospital, adjusting for other potential confounding variables. Age was categorized by decade (<36 to 75+ years) to allow for a non-linear relationship in regression. Given the known wide variation in screening practices, patient populations, and other institutional level factors, we used conditional logistic regression with enrollment as the outcome variable to address confounding by study center after excluding statistical heterogeneity in enrollment by race across sites using the Breslow-Day test of homogeneity (28). We explored multiplicative interactions between age, sex, race/ethnicity and between these three variables and ARDSnet study and retained interactions significant at the $p<0.05$ level. We repeated similar analyses to study the relationship between each reason for non-enrollment and age, sex, and race/ethnicity. A separate model was developed for each of the 24 exclusion criteria with each exclusion criterion serving as the outcome. The coefficient

for age was scaled to represent the ratio in the odds for the presence of the exclusion criterion for each 10 year increment in age. All models included age, sex, race/ethnicity, ALI risk factor, study, and study center. We excluded patients coded as "other" race/ethnicity from regression analyses due to the difficulty in interpreting the meaning of this group.

To determine the influence of moribund status on the reported odds ratios for enrollment among the older patients, we removed patients who were not enrolled because they were not committed to full support (n=611) or who had a terminal illness (n=1507) in a sensitivity analysis.

Results

Pooled screening logs from the three studies at 48 centers identified 23,819 patients of which 23,419 had ALI. Of these, 2452 (10.5%) enrolled in a study. We excluded 5960 (25%) patients because they were too young or were missing data or IRB approval leaving 17,459 patients from 44 centers available for unadjusted analysis (Figure 1).

Patient characteristics

A total of 1,855 (10.6%) of the 17,459 screened patients were enrolled in a clinical trial. On bivariate analysis, enrolled patients were more likely to be younger, female, black or Hispanic, and have pneumonia, sepsis, or aspiration as their predisposing risk factor for ALI, compared to non-enrolled patients (Table 1). In addition, enrolled patients had lower PaO_2 / FiO_2 ratios compared to non-enrolled patients (130 vs. 158, $p<0.001$), and were more often cared for in medical versus surgical ICUs.

Screening log characteristics

There was considerable variability in the number of patients screened for enrollment, the enrollment fraction, and racial makeup of screened patients across the 44 study centers (Table 2). The median (IQR) volume of screened patients was 154 (34–426) and median enrollment fraction was 16% (10–33%). The median percent of screened patients who were white was 74% (54–83%) while the median percent of black patients screened was 14% (3–29%). Variability in the age distribution and other racial/ethnic groups across centers was much smaller.

Adjusted enrollment

For the regression models, we excluded an additional 48 patients from seven centers because enrollment was 100% or 0% for these centers preventing within-center comparisons, leaving 17,411 patients available for regression.

There was no evidence of statistical heterogeneity in enrollment for each race/ethnic group compared to white patients across the study centers (Breslow-Day χ^2 test, $p>0.16$ for all race/ethnicities). There was a statistically significant multiplicative interaction between age and sex in the regression model ($p=0.03$). After adjustment for age, sex, age-sex interaction, ALI risk factor, study, and site, there were no differences in the odds of enrollment for any racial/ethnic group compared to white patients (Table 3).

Age and sex were both significantly associated with enrollment. In general, men were less likely to be enrolled compared to women and as age increased patients among both sexes were less likely to be enrolled in an ARDSnet study (Table 3). Among men and women, each decade beyond 36 years of age showed reductions in the odds of enrollment. Men older than 75 years of age were 41% less likely to be enrolled (OR 0.59, 95% CI 0.45–0.77) and

women older than 75 years of age were 55% less likely to be enrolled (OR 0.45, 95% CI 0.32–0.62), compared to men <36 years of age.

When patients that were not enrolled either due to the presence of a terminal illness or because they were not committed to full support were removed from the above models, results were unchanged for all coefficients (results not shown).

Exclusion criteria

Of the 15,604 patients not enrolled, 91% had one recorded exclusion criterion, 8% had two, and 1% had three or more exclusions. The percent of patients with each reason for exclusion across age, sex, and racial/ethnic groups are shown in the electronic supplementary material (see Supplemental Digital Content, Appendix B).

Age and Sex—After adjusting for confounding variables, older patients were less likely to be enrolled due to the presence of a comorbid condition (Figure 2). Exclusion criteria present more frequently in older patients included: the presence of an acute myocardial infarction, chronic lung diseases, not committed to full support, presence of a PAC since ALI onset, and presence of a terminal illness. In contrast, older patients were less likely to be excluded due to physician refusal, neuromuscular disease, co-enrollment in other studies, patient inability to consent and surrogate not available, acute or chronic liver disease, morbid obesity, burns, and bone marrow or lung transplant. Statistically significant adjusted ORs for the presence of each exclusion for women compared to men are shown in Figure 3. We identified no consistent patterns

Race—Black patients (OR 1.49, 95% CI 1.24–1.79), Hispanic patients (OR 2.15, 95% CI 1.65–2.79), and American Indian/Alaskan Native patients (OR 1.82, 95% CI 1.11–2.98), were more likely than white patients to be excluded due to patient inability to consent or absence of a surrogate (Figure 4).

Discussion

Utilizing study screening data from over 17,000 patients evaluated for enrollment in three multi-center, randomized trials conducted by the ARDSnet, we determined that there was considerable variability in the number of patients screened for enrollment, the enrollment fraction, and racial/ethnic makeup of screened patients across the study center. Significant differences in enrollment in ALI clinical trials exist across age and sex groups, but not among racial/ethnic groups. Men were enrolled less often than women across all age groups while older men and women were enrolled less often than their younger counterparts. Among excluded patients all racial/ethnic minorities were more likely to be excluded due to an inability to consent and lack of a surrogate, and black patients were more likely to be excluded due to patient or family refusal, compared to white patients. The presence of comorbid disease was a more common reason for trial exclusion among older patients.

There is a long history of investigators excluding older patients from clinical trials (9, 29). Government efforts (30) and the publication of stricter reporting standards for exclusion criteria in clinical trials (31) have modestly reduced the exclusion of older adults from research (9); explicit age limits are now less likely found in contemporary clinical trials (32). The ARDSnet places no upper limit on age for eligible patients. Yet despite the absence of age exclusions in ARDSnet studies, patients over 75 years of age were almost half as likely to be enrolled compared to younger patients. Older patients were underrepresented because they were more likely to have exclusion criteria, which included a lack of commitment to full support or a comorbid condition.

Selecting inclusion and exclusion criteria for clinical studies requires balancing the internal validity of the study and generalizability of its results (19). By narrowing enrollment criteria, efficacy studies seek to identify a sample of patients who have the greatest likelihood of producing a clinically meaningful and statistically significant benefit from the studied intervention and have the least likelihood of suffering harm (9). Unfortunately, these studies often fail to address the effectiveness of the treatment in actual practice where patients with ALI are frequently older and have more comorbidities (16). These issues are particularly important given the increasing incidence of ALI with age and the aging US population (15, 33–35).

The literature documenting sex and racial/ethnic disparities in clinical trial enrollment in other areas of medicine is extensive with little evidence that national efforts to improve diversity in enrollment have been effective (5–7). Thus, we were surprised to determine that neither women nor racial/ethnic minorities were underrepresented in ALI clinical trials. In fact, our results indicate that women are more likely to be enrolled than men. One possible explanation for these findings is that the ARDS network made a concerted effort to include centers serving diverse populations to ensure that women and minorities were adequately represented in its clinical trials. Sex-based differences in enrollment were not attributable to patient or family preferences or physician refusal to enroll, but rather a function of differing prevalence of comorbidities and other exclusion criteria between men and women. Although our best estimates suggest that no racial/ethnic enrollment differences exist, readers should note that the 95% confidence intervals for the enrollment estimates among minority groups do not exclude the possibility that meaningful differences in enrollment exist.

While the ARDSnet achieved equivalent enrollment fractions among age, sex and racial/ethnic groups it is unclear if enrollment rate is the best measure of “appropriate” enrollment. One arguably better measure of enrollment appropriateness is proportionality – the extent to which the distribution of age, sex and race/ethnicity in ARDSnet studies reflects the distribution of ALI in the general population (7). Men and women over 64 years-old represent approximately 11% and 15% of the population, respectively (18). Our results indicate that men and women were enrolled in ALI trials at rates of approximately 17% and 16% which is considerably lower than would be expected because the incidence of ALI peaks in this age group (16). Recent population-based data suggests black patients may have twice the incidence of ALI compared to white patients (12). Given these figures, it is important to note that the proportion of participants identified as black within each ARDSNet study used in our analysis ranged from 14% to 22% (23, 24, 26) which exceeds the 13% of Americans who are black (18). This suggests that even when using proportionality as a measure of appropriate enrollment, ARDSNet has succeeded in adequately representing racial/ethnic minorities. Perhaps the ideal measure of proportionality would compare enrollment rates across groups to the population of patients served by each ARDSnet center. We were unable to conduct these analyses because study center was deidentified in our data.

Despite no differences in overall enrollment fractions, black compared to white patients were more likely to have patient or family refusal as the reason for study exclusion. This may reflect existing mistrust of the research environment held by many black patients (36–39), potentially exacerbated by an aversion to technology, an inescapable feature of the ICU (40). Additional hypotheses for these differences include a lack of research staff diversity potentially undermining trust between patients and staff (37, 41). Other well described socioeconomic barriers to participation more commonly found among black patients, such as poor access to care (39), a greater perceived economic burden of research (42), and barriers to communication (39) are potential explanations that require further study in ICU

populations. While important to investigate further, readers should note the absolute difference in rates between white and black patients for this exclusion were small.

We recognize several limitations to our analysis. First, our data derived from the study screening logs collected at each study site. Screening practices and the collection of exclusion criteria were not standardized across centers and only a single exclusion criterion was collected for each individual in two of the three studies. Variability in screening practice may influence the crude estimates of the enrollment fraction. However, these differences should not influence our adjusted enrollment comparisons unless screening occurred in a biased fashion based on age, sex, or race within a given center because our conditional analysis performs all comparisons within a given center. The absence of differential enrollment for black versus white patients that we report could have occurred if black patients were selectively under-screened, but this would have had to occur across all centers. Although it is highly unlikely that all centers actively or inadvertently differentially screened based on age, sex, or race, in the same way the lack of available information on screening practice prevented exploration of this possibility. Second, race/ethnicity of the patient was determined by the investigator without a protocol which may not accurately represent a patient's true race. Nevertheless, this is the same data reported to the NIH for study monitoring purposes and is similar to how race is determined in most studies in the ICU. If present, it is likely that misclassification of race within a center did not differ based upon a patients enrolled status. Third, we excluded over 24% of the screened patient population in sites whose local IRBs did not allow release of data for non-enrolled patients. Variation in IRB decisions is common; however, it is difficult to understand the privacy or ethical concerns raised by analysis of de-identified screening data for clinical trials. Unfortunately, this IRB practice serves only to increase the difficulty in answering research questions about enrollment disparities in a valid manner. Finally, we were unable to explore the cause of heterogeneity in enrollment and distribution of race by center because we did not have details about the participating study centers. This is an important area of future research as characterizing and exporting the center level factors that explain greater fractions of study enrollment is one approach to improve research participation in low enrollment centers.

Conclusion

We demonstrated that older patients are underrepresented in clinical trials of ALI. Contrary to our hypotheses, women were not underrepresented and were even more likely to be enrolled than men while racial/ethnic minorities were equally represented compared to white patients. Ensuring age, gender, and racial/ethnic diversity in clinical trials improves the power of sub-group analysis in high-risk patients, establishes equity in access to the benefits of, and in the distribution of burden from clinical research, and most importantly, reduces threats to a trial's external validity. With each passing year the typical critically ill patient becomes older and has a greater number of comorbidities. As a result, the need for studies testing therapies in older patients has never been greater and will only increase.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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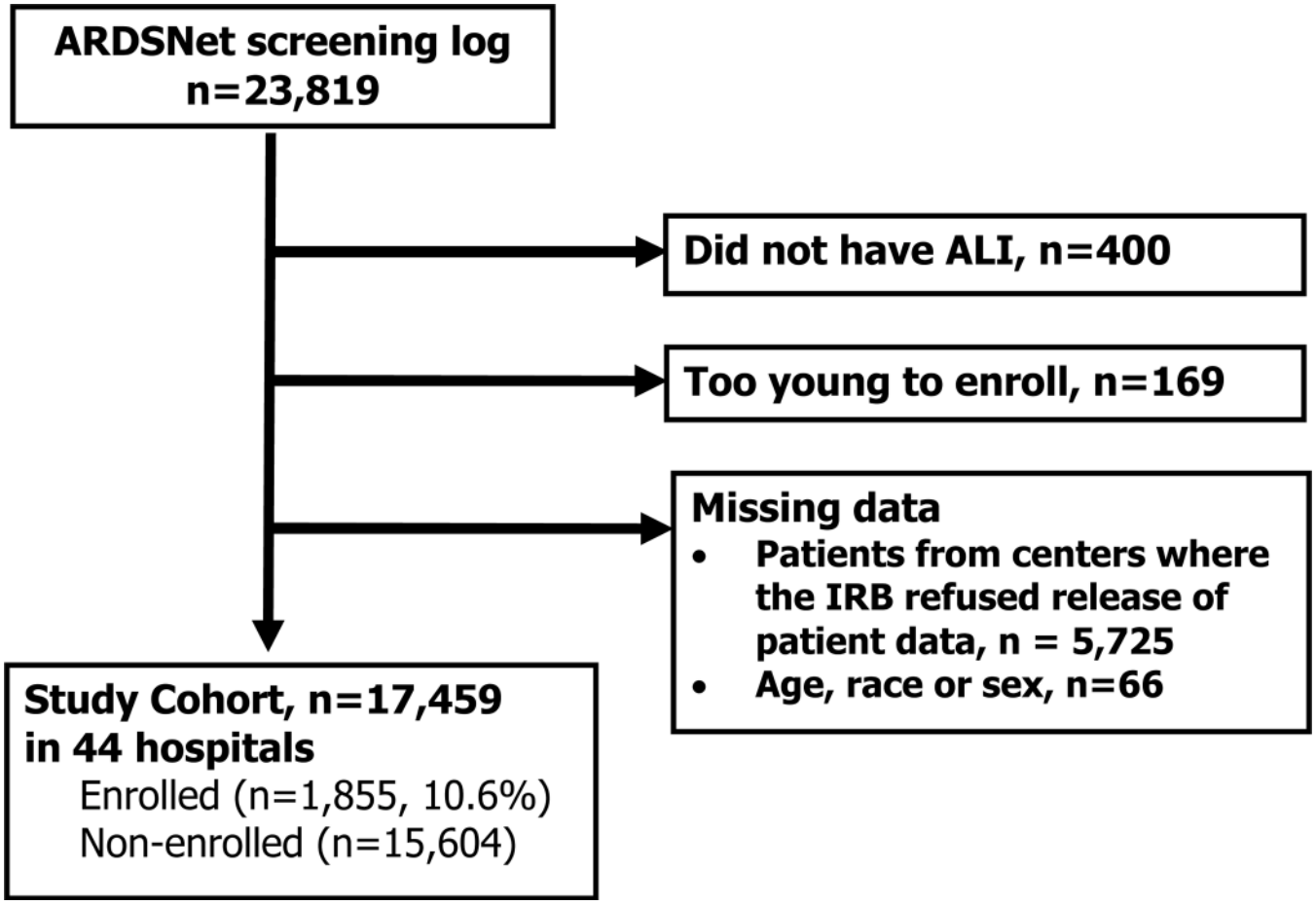

Figure 1. Cohort flow diagram

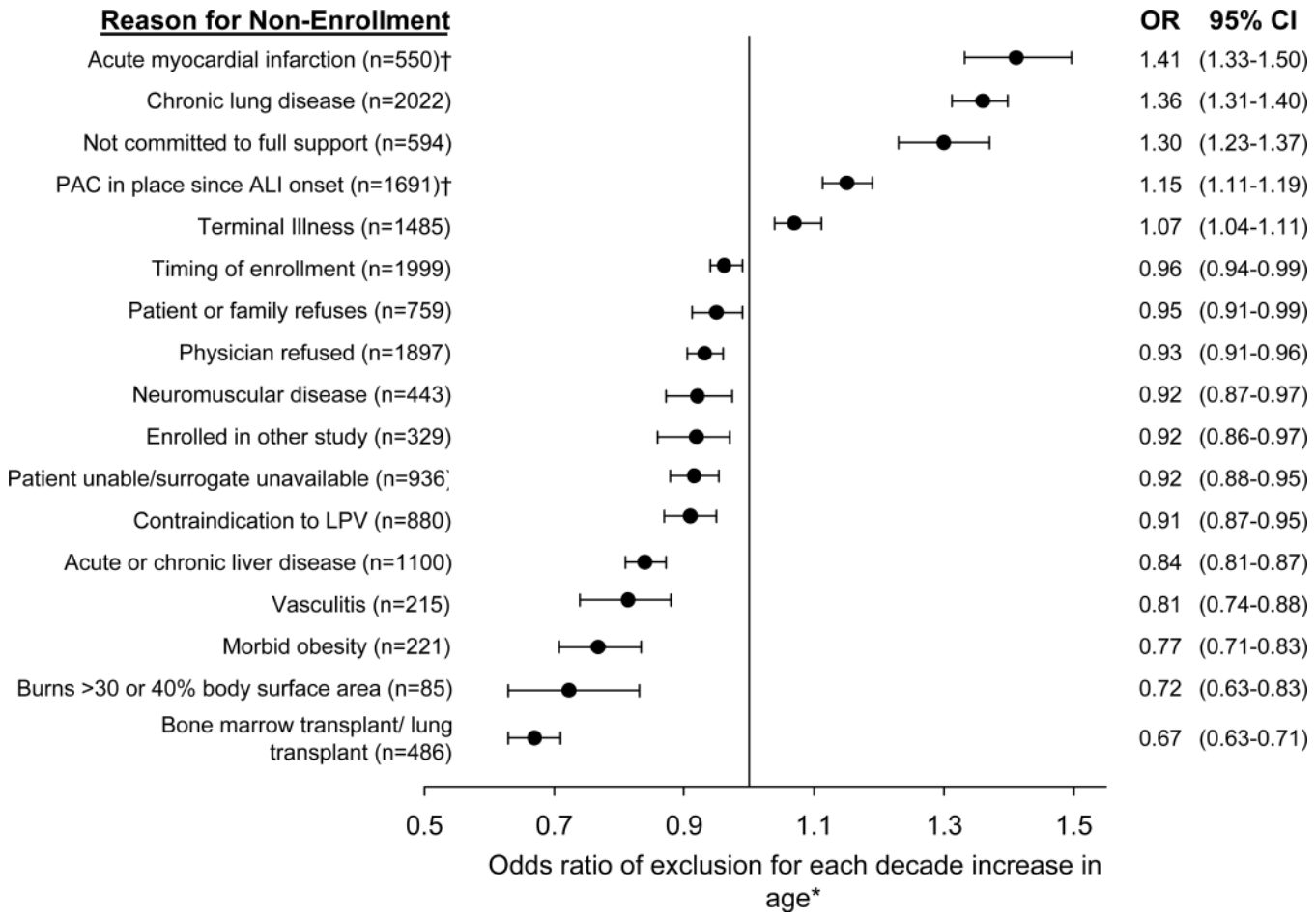

Figure 2. Reason for exclusion by age

For each exclusion criterion a separate logistic regression model was fit with exclusion as the outcome and age as a linear explanatory variable. Models were adjusted for sex, race/ethnicity, study center, study, and acute lung injury risk factor. Reported odds ratios (OR) are scaled per 10 year increase in age. Criteria marked with a symbol (†) were available only for the Fluid and Catheter Treatment Trial.

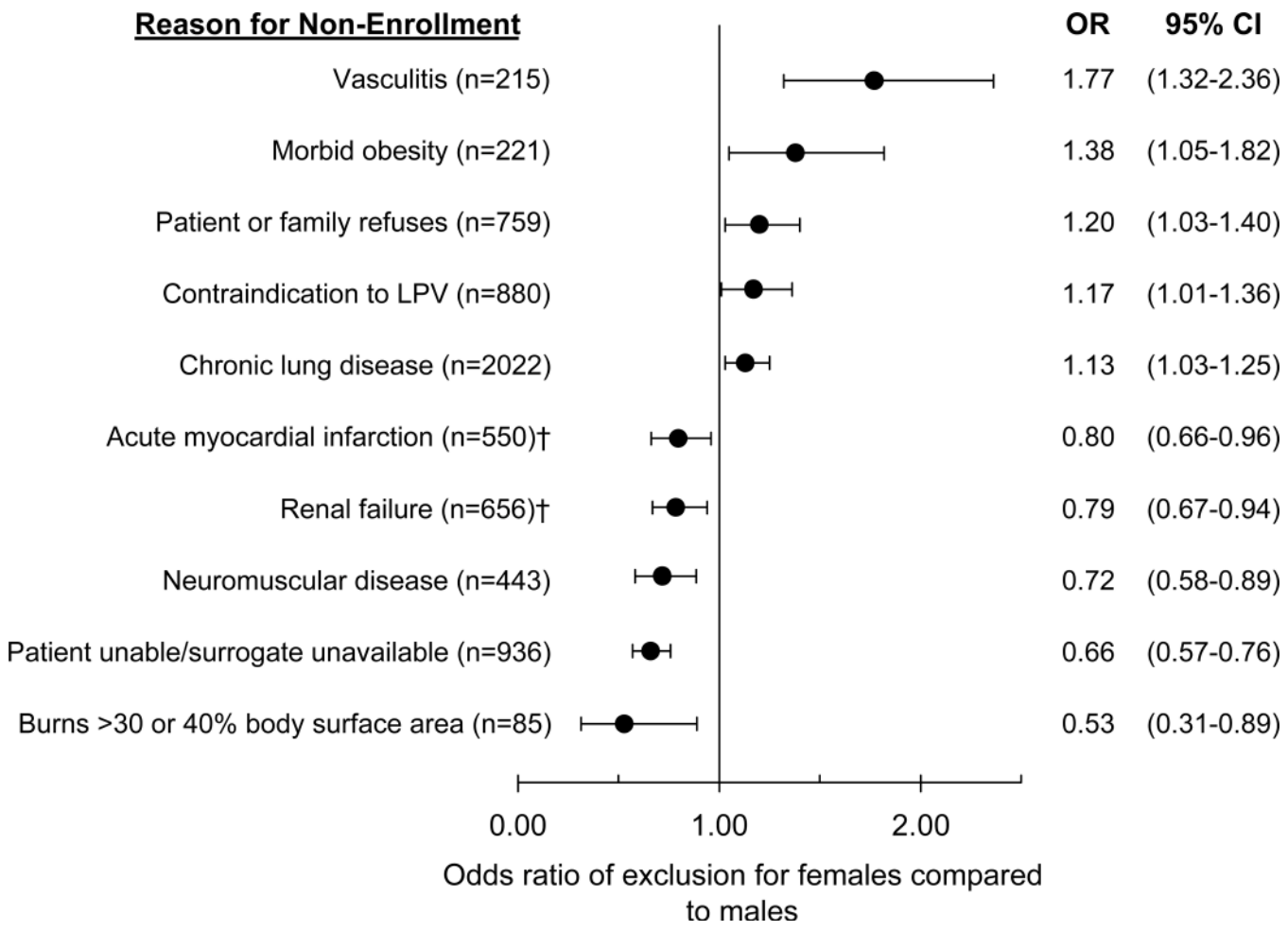

Figure 3. Reason for exclusion by sex

For each exclusion criterion a separate logistic regression model was fit with exclusion as the outcome and sex as a linear explanatory variable. Models were adjusted for age, race/ethnicity, study center, study, and acute lung injury risk factor. Reported odds ratios (OR) are for females compared to males. Criteria marked with a symbol (†) were available only for the Fluid and Catheter Treatment Trial.

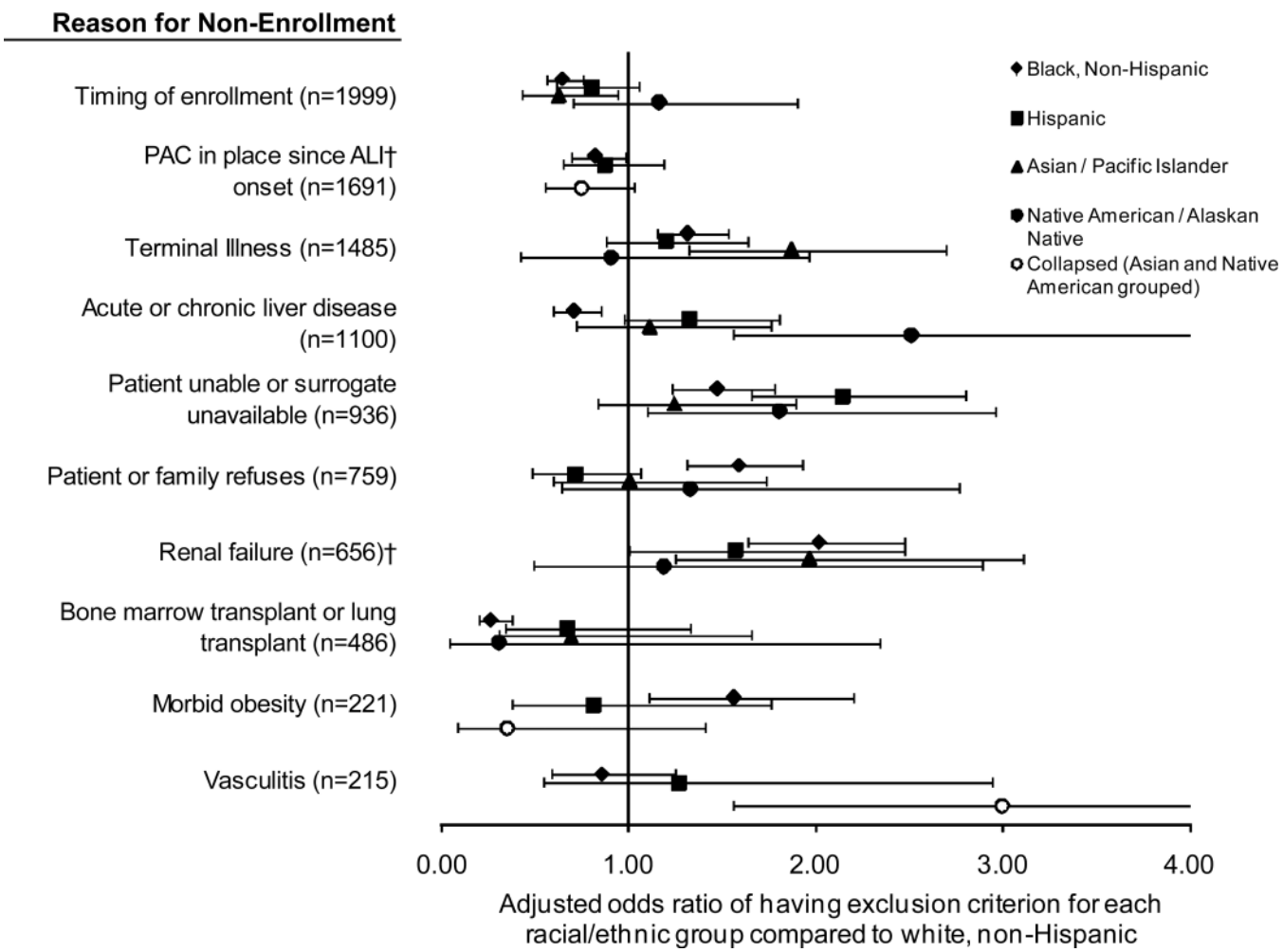

Figure 4. Reason for exclusion by race/ethnicity

For each exclusion criterion, point estimates and 95% confidence intervals for the odds ratio of having the exclusion criterion for each racial/ethnic group are presented. White, non-Hispanic patients that did not enroll serve as the referent category and are not presented. Odds ratios are adjusted for age, sex, primary risk factor for acute lung injury, study, and study center. Exclusion criteria that have a statistically significant association with race/ethnicity ($p<0.05$) are shown. Missing racial/ethnic categories represent analyses that required collapsing of Asian/Pacific Islander and Native American/Alaskan Native into a single group represented by "collapsed". Criteria marked with a symbol (†) were available only for the Fluid and Catheter Treatment Trial. PAC, pulmonary artery catheter; ALI, acute lung injury.

Table 1

Characteristics of patients evaluated for enrollment into ARDSnet clinical trials

Characteristic*	Not enrolled (n=15,604)	Enrolled (n=1,855)	P value
Age, years (%)			<0.001
<35	18	20	
36–45	16	22	
46–55	21	22	
56–65	17	16	
66–75	16	13	
> 75	12	9	
Male (%)	60	55	<0.001
Race/Ethnicity (%)			<0.001
White, non-Hispanic	74	71	
Black, non-Hispanic	16	19	
Hispanic	4	7	
Asian/Pacific Islander	2	2	
Native American/Alaskan Native	1	1	
Other	1	1	
Primary risk factor for ALI (%)			
Pneumonia	28	40	<0.001
Sepsis	19	23	<0.001
Trauma	20	11	<0.001
Aspiration	12	15	<0.001
Multiple transfusion	3	2	
Other/none	18	9	
PaO_2 / FiO_2	158 (69)	130 (61)	<0.001
Location of patient			<0.001
MICU	41	57	
SICU	16	14	
MICU/SICU	8	11	
CCU	6	3	
Neuro ICU	4	1	
Burn ICU	4	2	
Cardiac SICU	1	1	
Other	20	11	

*Data missing for PaO2/FiO2 in 49 patients; ALI risk factor in two patients.

ALI, acute lung injury; PaO2, partial pressure of arterial oxygen; FiO2, fractional inspired oxygen; MICU, medical intensive care unit; SICU, surgical intensive care unit; CCU, coronary care unit.

Table 2

Aggregate characteristics of screening logs for centers participating in ARDSnet

Characteristic*	Median	IQR
Screening logs	n=44	
Number of screened patients per screening log	154	(34–426)
Enrollment fraction (%)	16	(10–33)
Age, years (%)		
< 36	17	(10–20)
36 – 45	16	(13–19)
46–55	21	(17–24)
56–65	17	(13–20)
66–75	17	(12–23)
> 75	11	(8–17)
Male (%)	58	(52–66)
Race/ethnicity (%)		
White, non-Hispanic	74	(54–83)
Black, non-Hispanic	14	(3–29)
Hispanic	2	(1–8)
Asian/Pacific Islander	1	(<1–2)
Native American/Alaskan Native	0	(0–0.4)
Other	0.2	(0–1)
ALI risk factor (%)		
Pneumonia	33	(22–47)
Sepsis	24	(17–30)
Aspiration	12	(8–18)
Multiple Transfusion	2	(<1–5)
Trauma	1	(0–15)
Other/none	7	(3–13)
PaO2/FiO2	140	(124–167)

Table 3

Trial enrollment by age, sex, and race*

Patient characteristic	No. of patients screened	Crude enrollment fraction, %	Adjusted Odds Ratio (point, 95% CI)†		P value
Age (years)					
Male					
< 35	1,832	11	1.00	Referent	
36–45	1,707	12	0.97	(0.78–1.21)	0.77
46–55	2,109	9	0.67	(0.54–0.84)	<0.001
56–65	1,724	9	0.64	(0.51–0.82)	<0.001
66–75	1,637	8	0.58	(0.45–0.74)	<0.001
75+	1,146	5	0.59	(0.45–0.77)	<0.001
Female					
< 35	1,205	13	1.02	(0.81–1.30)	0.85
36–45	1,205	15	1.07	(0.85–1.35)	0.57
46–55	1,466	14	1.01	(0.81–1.27)	0.92
56–65	1,228	10	0.73	(0.57–0.94)	0.02
66–75	1,108	9	0.63	(0.48–0.82)	<0.001
75+	810	7	0.45	(0.32–0.62)	<0.001
Racial/Ethnic group					
White, non-Hispanic	12,915	10	1.00	Referent	
Black, non-Hispanic	2,915	12	0.97	(0.84–1.13)	0.72
Hispanic	784	15	0.96	(0.75–1.22)	0.72
Asian / Pacific Islander	394	8	1.00	(0.68–1.49)	0.98
Native American / Alaskan Native	169	6	0.85	(0.43–1.66)	0.63

*Excludes all patients identified as “other” race/ethnicity (n=234), and 48 patients from 7 centers with 100% or 0% enrollment.

†Adjusted for clinical trial, study center, and risk factor for acute lung injury.