# Race modifies the effect of fluid administration on mortality and long-term functional outcomes after Acute Respiratory Distress Syndrome

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## Abstract

Race modifies the effect of fluid administration on mortality and long- term functional outcomes after Acute Respiratory Distress Syndrome

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**Rationale:** Conservative fluid management in ARDS contributes to more ventilator-free days, but no difference in 60-day mortality. Effects of ICU fluid strategies on longer-term mortality and morbidity in different racial subgroups remain unstudied.

**Objectives:** Determine whether one-year mortality differs by fluid-strategy and race and whether functional dependence after ARDS differs by race.

**Methods/Measurements:** Secondary analysis of data obtained during the ARDS Network Fluid and Catheter Treatment Trial (FACTT) and the Economic Analysis of Pulmonary Artery Catheters (EAPAC) study. Telephone interviews were conducted at 2, 6, 9 and 12 months after ARDS to determine survival and quality of life. Cox proportional hazards regression was used to investigate one-year mortality and logistic regression to investigate race and functional dependence with adjustment for age, sex and severity of illness.

**Main Results:** A total of 582 participants who were enrolled in EAPAC including 475 alive at discharge were included with median follow-up of 336 days. One-year mortality differed significantly by fluid management and race (interaction p = 0.005). Among black participants, compared with conservative fluids, liberal fluids were associated with greater one-year mortality (HR 2.9, 95% CI 1.6-5.2, p=0.001) whereas among white participants, compared with conservative

fluids, liberal fluids was associated with lesser mortality (HR 0.4, 95% CI 0.28-0.62) in adjusted analyses. Post-hospital functional dependence was worse in blacks compared with whites (OR: 2.3, 95% CI: 1.1-4.6, p=0.02).

**Conclusions**: Secondary analysis of participants with one-year follow-up after the FACTT found that there was a significant interaction between liberal fluid administration and race suggesting liberal fluid administration may be harmful to black patients yet beneficial to white patients with ARDS.

## Introduction

Optimal fluid management strategies for critically ill patients remain uncertain. Recent data from the Fluid Expansion as Supportive Therapy (FEAST) trial [1] raise concerns that aggressive bolus fluid resuscitation early in critical illness may be harmful. In the National Heart, Lung and Blood Institute (NHLBI) Acute Respiratory Distress Syndrome (ARDS) Network's Fluid and Catheter Treatment Trial (FACTT) a conservative fluid strategy resulted in no difference in 60-day mortality, but more ventilator-free days, less organ dysfunction and shorter ICU stays [2]. This supported earlier studies demonstrating potential clinical benefits associated with conservative rather than liberal fluid management [3-5] .

It is unclear if the effects of fluids are homogenous among patient subgroups. There are biologically plausible reasons why the effects of alternate fluid management strategies may differ between patients of different racial/ethnic subgroups. Studies suggest that patients who self-identify as black may have less active renin-angiotensin systems [6] and lower bioavailability of nitric oxide than white patients resulting in greater impairments in myocardial and vascular remodeling in response to oxidative stress [6]. Impairment in this response coupled with greater risk of cardiovascular collapse with crystalloid administration as suggested by the FEAST trial, performed exclusively in Sub-Saharan African children, may place black patients at higher risk for poor outcomes after treatment with liberal fluids during the course of critical illness.

While there was no difference in overall 60-day mortality in the FACTT, black participants randomized to the liberal fluid strategy in the FACTT had a higher 60-day mortality compared with white participants. Although there was no evidence of a statistically significant interaction with fluid strategy, short follow-up time may have masked potential mortality effects. The

findings of FACTT, published nearly a decade ago in 2006, are widely adopted today in clinical practice without consideration of racial subgroup. However, the recent findings in FEAST raise concerns about broadly applying any fluid strategy across racial subgroups and questions whether fluid strategies should instead be tailored to the individual patient. Re-evaluation of the FACTT data with longer-term follow-up may better explain the effect of fluid administration on death after ARDS particularly for participants in different racial subgroups. Our aim, therefore, was to determine if race modifies the effect of fluid administration strategy on one-year mortality after ARDS. We hypothesized that there would be a significant interaction between liberal fluid administration and black race with black participants experiencing greater one-year mortality. We also hypothesized that functional dependence would be worse in black participants after ARDS.

## Methods

The manuscript presents new analyses of data collected from a subset of participants who were enrolled in the FACTT trial (2000-2005) and the EAPAC follow-up study, which are described below.

### *FACTT Study Design and Participants*

Details of the study design for the 'parent' trial, FACTT, were published previously [2, 7]. Briefly, participants were randomly assigned using a two-by-two factorial design to one of the two fluid strategies and one of the two catheter strategies via automated concealed allocation in permuted blocks of eight. Participants undergoing mechanical ventilation with clinical evidence of ARDS defined as 1) a ratio of partial pressure of arterial oxygen (PaO2) to the fraction of

inspired oxygen (FiO2) of less than 300, 2) bilateral infiltrates on chest radiography, and 3) no evidence of left atrial hypertension [8] were included. Major exclusion criteria included inability to provide consent, presence of a pulmonary artery catheter after the onset of lung injury, acute lung injury for > 48 hours, other conditions that would independently influence survival, weaning or study procedures, and irreversible conditions with a poor prognosis, such as advanced cancer. The primary outcome investigated was death from any cause at 60 days with secondary outcomes of ventilator-, ICU- and organ-free days along with need for hemodialysis at day 60. FACTT was approved by a protocol-review committee of the NHLBI and the institutional review boards (IRBs) of all participating sites.

***FACTT Study Procedures***

Ventilation according to the ARDS Network protocol was initiated within one hour of enrollment and continued to day 28. The fluid management strategy was initiated within 6 hours of enrollment and continued for seven days or until 12 hours after a participant was able to breathe without assistance. Participants in the liberal fluid group were monitored by either a central venous catheter (CVC) or a pulmonary artery catheter (PAC) with administration of fluids to maintain a central venous pressure (CVP) of 10-12 mmHg or a pulmonary artery occlusion pressure (PAOP) of 14-18 mmHg while participant in the conservative fluid management group received diuretic medication or restriction of intravenous fluids to maintain a CVP of <4 mmHg or PAOP of <8 mmHg. Catheter readings and clinical signs were evaluated at least every 4 hours; protocols did not specify the type of intravenous fluid to administer and the protocol could be suspended when a participant was in shock.

Detailed baseline and clinical data were collected in the trial as previously described [2]. Race was assigned as non-Hispanic white or non-Hispanic black by study coordinators following interview with the patient and/or family.

***EAPAC sub-study design and participants***

Details of the study design for the EAPAC study were published previously [9]. Briefly, for participants consenting to long-term follow-up, we conducted interviews at 2, 6, 9 and 12 months. During the interview, trained interviewers administered the Health Utilities Index Mark 2 and Mark 3 questionnaires (Health Utilities Inc., Dundas, Ontario,, Canada) to assess quality of life and health utility [10, 11]. Study participants were interviewed preferentially if available with a proxy administration if a study participant was unable to participate. We did not administer the HUI questionnaire at to trial participants or proxies at FACTT trial enrollment. Death was adjudicated using the fall 2006 National Death Index.

***Racial Subgroup Analyses***

For these analyses, we restricted the EAPAC study participants to those who were black and white to test hypotheses related to mortality and functional dependence.

*Survival*

We performed survival analysis for the one-year follow-up cohort. Cohort entry was the time of enrollment into FACTT and observations were censored at the end of the one-year follow-up period. Cox proportional hazards models were used to estimate hazard curves with log-rank testing to assess for differences in survival between conservative and liberal fluid strategies by race (white vs. black). We tested effect modification of fluid effect by race using an interaction term between race and fluid arm. We adjusted for other potential confounders including age, sex, and severity of illness using an adjusted Cox proportional hazards model. Schoenfeld's test was performed to assess for violation of the proportional hazards assumption.

We also performed one-year survival analysis on the subset who survived until discharge.

*Functional Outcomes*

We explored the associated between race and HUI-2 mobility score at 6 months post-hospitalization. The HUI-2 attribute score was dichotomized into a binary variable collapsing levels 1 and 2[*functional independence (able to walk, bend, lift, jump and run normally for age* or *walks, bends, lifts, jumps or runs with some limitations but does not require help*)] vs. levels 3, 4, and 5 [*functional dependence (requires mechanical equipment (such as canes, crutches, braces or wheelchair)*] *to get around independently* or *requires the help of another person to walk or get around and requires mechanical equipment as well* or *unable to move arms or legs*). This dichotomization represents a clinically relevant division between independence and the requirement of help (mechanical or person-to-person) for mobility. A multivariable logistic regression model adjusting for age, sex, and severity of illness was used to explore the association between black race and functional dependence.

## Results

### *Cohort Derivation*

There were 1000 participants analyzed in FACTT; 774 (77%) were enrolled at sites and during time periods for which IRB approval was granted for the EAPAC long-term follow-up study (Figure 1). Of these 774 FACTT participants, 655 (85%) agreed to participate in EAPAC. Rates of recruitment into the follow-up study were similar across study treatment arms (E1). Median duration of follow-up was 336 days [IQR 32-352] and did not differ by treatment arm

(p=0.98). FACTT participants opting not to participate in EAPAC were less likely to be white (57% vs. 68%, p=0.0005) and more likely to have HIV infection or AIDS (10% vs. 6%). They also received higher tidal volumes (490 vs. 452 cc, p<0.0001) and a higher cardiac index (4.4 vs. 4.1 L/min) at time of enrollment in FACTT, but were otherwise similar.

***Follow-up Analysis***

Among the 582 participants, 21% (n=136) identified as black (Table 1). Black participants were more likely to receive care in a medical ICU (74% vs. 61%, p=0.005), have co-existing illness (44% vs. 28%, p=0.003) and be infected with HIV/AIDS (12% vs. 4%, p=0.002). APACHE III scores were higher, on average, for black participants (mean 99 vs. 91, p=0.01). A greater proportion of black participants assigned to the liberal fluid arm had sepsis (46% vs. 31%, p=0.07) although this was not a statistically significant difference (Table 2). There were significantly more white participants with solid tumors (3% conservative vs. 1% liberal, p=0.04) in the conservative fluid strategy arm. Otherwise, baseline characteristics for EAPAC participants were similar between those assigned to the liberal and conservative fluid strategies. Among the 582 participants enrolled in EAPAC, a total of 475 survived to hospital discharge and 384 were alive at one-year post-hospitalization.

***One-year mortality***

Among the 91 (19%) participants who died during the one-year follow-up period 25 identified as black and 66 identified as white. One-year mortality differed significantly by fluid management and race (interaction p = 0.001). Among black participants, compared with conservative fluids, liberal fluids were associated with greater one-year mortality (HR 2.5, 95% CI 1.4-4.5) whereas among white participants, compared with conservative fluids, liberal fluids was

associated with lesser mortality (HR 0.7, 95% CI 0.5-1.0) in adjusted analyses (Figure 2, Panel A). Similar effects were observed restricting the cohort to hospital survivors (n = 384). Overall, black survivors had an increased hazard of death compared with white survivors (HR 1.6, 95% CI 1.0-2.5, p=0.05) and one-year mortality differed significantly by fluid management and race (interaction p = 0.005). Among black survivors, compared with conservative fluids, liberal fluids were associated with greater one-year mortality (HR 3.3, 95% CI 1.17-9.12) whereas among white survivors, compared with conservative fluids, liberal fluids was associated with lesser mortality (HR 0.6, 95% CI 0.4-1.0) in adjusted analyses (Figure 2, Panel B). We did not detect non-proportional hazards over time.

***Long-Term Functional Outcomes***

Among the 582 participants in the one-year mortality analysis, 300 (52%) participants were alive and participated in 6 month functional testing. A significantly greater proportion of black participants reported HUI-2 mobility scores > 2 compared with white participants (43% vs. 25%, p=0.02) (Figure 3). In multivariable logistic regression analysis, black race was independently associated with the odds of reporting a HUI-2 mobility score >2 at 6 months after controlling for age, sex and severity of illness (adjusted OR 2.3, 95% CI 1.1-4.6, p=0.02).

**Discussion**

There are several important observations from this follow-up study of participants enrolled in the NHLBI ARDS Network FACTT. Consistent with previous studies, hospital survivors remained at risk for a number of important sequelae, including significant risk of death and long-term functional dependence after ARDS [12-15]. However, our secondary analyses of a

subgroup of FACTT participants suggest that blacks may greater mortality and more functionald dependence following ARDS compared with white survivors and that this effect appears to be modified in part by liberal fluid administration during the course of critical illness. This finding is of particular interest as previous reports suggest that race is not associated with outcome for critical illness after adjustment for risk factors and systemic effects [16-18] and few studies have identified modifiable factors such as fluid strategy that may explain racial/ethnic disparities.

In these analyses, there was strong, observational evidence of greater long-term mortality for blacks compared to whites. Early separation of the hazard curves in hospital survivors likely results from residual effects of acute illness and its treatments. In the FACTT, black participants had higher in-hospital mortality and, while there was a trend towards worse outcomes in blacks with liberal fluid administration, the interaction failed to achieve statistical significance (mortality: blacks, 37% liberal vs. 31% conservative, whites 23% liberal vs. 24% p=0.002, interaction 0.10) [2]. With longer follow-up, we found that there was evidence of effect modification by race in the liberal fluid treatment arm. The relationship between fluid strategy and race became more detectable with increased follow-up time suggesting that the short-term follow-up from the original clinical trial may have been inadequate to assess the full effect.

These results are of particular importance as recent studies have questioned the benefit and in some cases demonstrated potential harm with liberal fluid administration in black patients. The FEAST study, for example, reported excess mortality in children receiving bolus fluid administration in sub-Saharan Africa [1] suggesting that a universal fluid management approach may not be appropriate.

There may well be a mechanistic explanation for worse outcomes in blacks as polymorphisms in cytokine genotypes found to be more common in blacks are consistently associated with up-regulation of the inflammatory response. Such evidence was presented for IL-1beta, IL-6 and IL-10 [19]. More recently, specific genetic polymorphisms in the *Darc* gene in African American patients resulted in over-expression of IL-8 and was associated with greater mortality and fewer ventilator-free days [20]. The lung, as a target organ to inflammation, may be particularly vulnerable to fluid status. Therefore, associations between race and outcome, based on inflammatory genotype, may be worth reexamining in data from prior trials involving lung sparing strategies in the context of inflammatory challenges.

Although the hazard curves in our study diverged early in the follow-up period, there was also a persistent increased hazard of death over the year after ARDS hospitalization for black compared with white participants. This suggests that differences in post-hospital factors may additionally contribute to ongoing risk for black participants. Our study is the first, to our knowledge, to address racial/ethnic disparities in recovery after ARDS. Prior studies have focused on disparities in development and severity of in-hospital ARDS amongst patients of non-white race/ethnicity [21-25]. We found that significant racial disparities in long-term functional outcomes exist after ARDS. Estimates obtained in our cohort potentially underestimate the magnitude of the associations between race and long-term outcomes as a result of differential hospital survivorship amongst black participants. Additionally, survivors in our cohort likely represent a less extreme phenotype as a result of informative censoring resulting from differential mortality by race.

There are several potential explanations for why functional outcomes may be differential in non-white ARDS survivors. First, studies suggest that black patients experience greater in-hospital severity of ARDS [23, 25]. This may result in longer periods of immobility leading to a greater in-hospital decline in muscle mass and longer-term weakness [26]. Second, greater severity of ARDS may put black patients at greater risk for ICU acquired weakness [27, 28]. Studies are needed to understand whether neuromuscular changes differ amongst racial/ethnic groups. Third, black patients often have a higher burden of chronic co-morbid disease upon ICU presentation. Review of data collected during the Cardiovascular Heart Study reported a four-fold increase in frailty among African Americans compared to white patients of similar age and sex [29]. This baseline frailty places African American patients at high risk of longer-term weakness and death after critical illness [30]. Finally, little is known regarding access to post-rehabilitative care in black ARDS survivors. Studies of patients surviving traumatic brain injury and spinal cord injuries report decreased acceptance into inpatient and outpatient rehab programs for black patients resulting in worse long-term outcomes [31, 32]. Studies are needed to understand current practice around provision of post-ICU care to non-white ARDS survivors.

There is a strong case to be made for examining the combined clinical consequences of interventions in critically ill patients, and to extend this observation well beyond the initial hospitalization. Mortality and functional dependence after critical illness extends well beyond the acute episode and therefore an impact on long-term quality-adjusted survival may be demonstrable in the absence of significant short-term benefits. The real impact of an ICU intervention, therefore, especially if the episode of illness extends beyond a standard follow-up

period such as hospital discharge may not be properly measured by short-term clinical metrics, as early benefit or harm may or may not be confirmed by a broader evaluation.

There are some notable limitations to our study. The number of black patients enrolled in the trial was low with greater loss to follow-up amongst black patients. Retention of minority research participants represents a common problem across all areas of biomedical research. A cross-sectional analysis of screening logs from the 44 ARDS Net participating sites from three randomized trials, demonstrated no differences in likelihood of enrollment by racial/ethnic group [33]. Developing observational cohorts with over-representation of racial/ethnic minority survivors with targeted sampling of potential participants may aid in further studies aimed at understanding racial/ethnic disparities in recovery after critical illness. Black patients enrolled in the ARDS Network randomized trials, additionally, may not be representative of the overall population of black survivors given their selection for inclusion in a randomized controlled trial and may actually represent a less sick phenotype. Similarly, excess in-hospital mortality amongst blacks resulted in differential survivorship limiting the generalizability of our inferences on functional outcomes. We did not adjust for potential clustering of non-Hispanic black patients in hospitals where outcomes may be worse. Such a bias is less likely given that systematic differences in outcome have not previously been reported across ARDS Network sites. Additionally, the Health Utilities Index-2 has not undergone rigorous validation in survivors of critical illness, despite being validated in large cohorts of patients with similar functional disabilities. The HUI-2 has a potential benefit over other measures of health related quality of life, namely its high proxy-patient agreement [34]. This may be of particular interest in critically ill patients who often require surrogates for participation in clinical trials. Further psychometric

testing around validity, test-retest reliability and proxy-patient agreement is needed in cohorts of critically ill patients. Finally, our study of effects in racial subgroups was limited to non-Hispanic black and white participants given concerns that this may be particularly high risk group in light of the recent FEAST trial findings. It is highly likely that differential effects of fluid strategies on other racial subgroups including Hispanic, Asian, Native American and Pacific Islander subgroups exist. Further study is necessary to understand the effect of liberal and conservative fluid administration in the subgroups to appropriately tailor fluid management strategies for optimized patient outcomes.

**Conclusions**

Secondary analysis of patients with one-year follow-up after the FACTT found that there was a significant interaction between liberal fluid administration and race suggesting liberal fluid administration may be harmful to black patients yet beneficial to white patients with ARDS. Our findings provide further support that mortality and functional dependence outcomes are worse in black than white patients with ARDS and that approaches to fluid management may need to incorporate race into decision-making.

**Table 1. Baseline characteristics and hospital outcomes stratified by race**

| | Non-Hispanic Black | Non-Hispanic White | All | p-value |
|---|---|---|---|---|
| N | 136 | 446 | 582 | |
| Age, mean (SD) | 49 (16) | 51 (15) | 51 (16) | 0.23 |
| Sex, female, n (%) | 59 (43) | 224 (50) | 283 (49) | 0.16 |
| Liberal fluid randomization arm, n (%) | 74 (54) | 215 (48) | 289 (50) | 0.21 |
| Primary lung injury, n (%) | | | | |
| Pneumonia | 82 (60) | 261 (59) | 343 (59) | 0.71 |
| Sepsis | 53 (39) | 180 (40) | 233 (40) | 0.77 |
| Aspiration | 26 (19) | 99 (22) | 125 (21) | 0.44 |
| Trauma | 11 (8) | 38 (9) | 49 (8) | 0.87 |
| Multiple transfusions | 3 (2) | 10 (2) | 13 (2) | 0.64 |
| Co-existing conditions, n (%) | | | | |
| None | 76 (56) | 322 (72) | 398 (56) | 0.003 |
| Diabetes | 28 (21) | 66 (15) | 94 (17) | 0.14 |
| HIV infection or AIDS | 16 (12) | 15 (4) | 31 (6) | 0.002 |
| Cirrhosis | 6 (4) | 17 (4) | 23 (4) | 0.79 |
| Solid tumors | 3 (2) | 7 (2) | 10 (2) | 0.71 |
| Leukemia | 1 (1) | 8 (2) | 9 (2) | 0.69 |
| Lymphoma | 0 (0) | 5 (1) | 5 (1) | 0.60 |
| Immunosuppression | 13 (10) | 33 (8) | 46 (8) | 0.47 |
| Apache III score, mean (SD) | 99 (32) | 91 (31) | 93 (31) | 0.01 |
| Medical ICU, n (%) | 101 (74) | 273 (61) | 374 (64) | 0.005 |
| Cardiorespiratory variables, mean (SD) | | | | |
| Mean arterial pressure, mm/Hg | 78 (13) | 77 (15) | 77 (14) | 0.40 |
| Cardiac index, L/min/$m^2$ | 4 (1) | 4 (1) | 4 (1) | 0.62 |
| Vasopressor use, n (%) | 52 (39) | 167 (38) | 219 (38) | 0.83 |
| Pre-randomization fluid balance, L | 2.7 (3.6) | 3.0 (3.7) | 2.9 (3.7) | 0.40 |
| $PaO_2$:$FiO_2$ ratio | 129 (62) | 127 (55) | 127 (56) | 0.71 |
| Tidal volume (ml) | 453 (93) | 452 (102) | 453 (100) | 0.94 |
| Length of stay (LOS), med [IQR] | | | | |
| ICU LOS (days) | 12 [7-19] | 11 [7-17] | 11 [7-18] | 0.72 |
| Hospital LOS (days) | 15 [7-27] | 16 [9-26] | 15 [9-26] | 0.63 |

SD= standard deviation

**Table 2. Fluid strategy assignment stratified by race**

| | Non-Hispanic Black | | | Non-Hispanic White | | |
|---|---|---|---|---|---|---|
| | Liberal fluid strategy | Conservative fluid strategy | p-value | Liberal fluid strategy | Conservative fluid strategy | |
| N | 74 | 62 | | 215 | 231 | |
| Age, mean (SD) | 48 (15) | 50 (17) | 0.31 | 50 (15) | 52 (15) | 0.34 |
| Sex, female, n (%) | 32 (43) | 27 (44) | 0.97 | 103 (48) | 121 (52) | 0.35 |
| Primary lung injury, n (%) | | | | | | |
| Pneumonia | 49 (66) | 33 (53) | 0.12 | 126 (59) | 135 (58) | 0.97 |
| Sepsis | 34 (46) | 19 (31) | 0.07 | 94 (44) | 86 (37) | 0.16 |
| Aspiration | 12 (16) | 14 (23) | 0.35 | 43 (20) | 56 (24) | 0.28 |
| Trauma | 4 (5) | 7 (11) | 0.21 | 16 (7) | 22 (10) | 0.43 |
| Multiple transfusions | 2 (3) | 1 (2) | 0.57 | 3 (1) | 7 (3) | 0.34 |
| Co-existing conditions, n (%) | | | | | | |
| None | 33 (45) | 27 (44) | 0.90 | 59 (27) | 65 (28) | 0.87 |
| Diabetes | 17 (24) | 11 (18) | 0.40 | 29 (14) | 37 (17) | 0.47 |
| HIV infection or AIDS | 10 (14) | 6 (10) | 0.45 | 9 (4) | 6 (3) | 0.34 |
| Cirrhosis | 3 (4) | 3 (5) | 0.85 | 9 (4) | 8 (4) | 0.68 |
| Solid tumors | 1 (2) | 2 (3) | 0.65 | 1 (1) | 6 (3) | 0.04 |
| Leukemia | 0 (0) | 1 (2) | 0.28 | 1 (1) | 7 (3) | 0.07 |
| Lymphoma | 0 (0) | 0 (0) | | 4 (2) | 1 (1) | 0.20 |
| Immunosuppression | 4 (6) | 9 (15) | 0.14 | 17 (8) | 16 (7) | 0.72 |
| Apache III score, mean (SD) | 103 (33) | 95 (31) | 0.18 | 92 (30) | 90 (32) | 0.55 |
| Medical ICU, n (%) | 56 (76) | 45 (73) | 0.68 | 131 (61) | 142 (62) | 0.91 |
| Cardiorespiratory variables, mean (SD) | | | | | | |
| Mean arterial pressure, mm/Hg | 78 (11) | 78 (16) | 0.80 | 77 (15) | 77 (14) | 0.73 |
| Cardiac index, L/min/$m^2$ | 4 (2) | 4 (1) | 0.74 | 4 (1) | 4 (1) | 0.76 |
| Vasopressor use, n (%) | 27 (38) | 25 (40) | 0.79 | 85 (40) | 82 (36) | 0.35 |
| Pre-randomization fluid balance, L | 2.7 (3.3) | 2.6 (3.9) | 0.97 | 3.1 (3.9) | 2.9 (3.4) | 0.56 |
| $PaO_2$:$FiO_2$ ratio | 130 (64) | 128 (59) | 0.86 | 127 (54) | 126 (55) | 0.84 |
| Tidal volume (ml) | 455 (95) | 451 (92) | 0.84 | 453 (104) | 452 (101) | 0.88 |

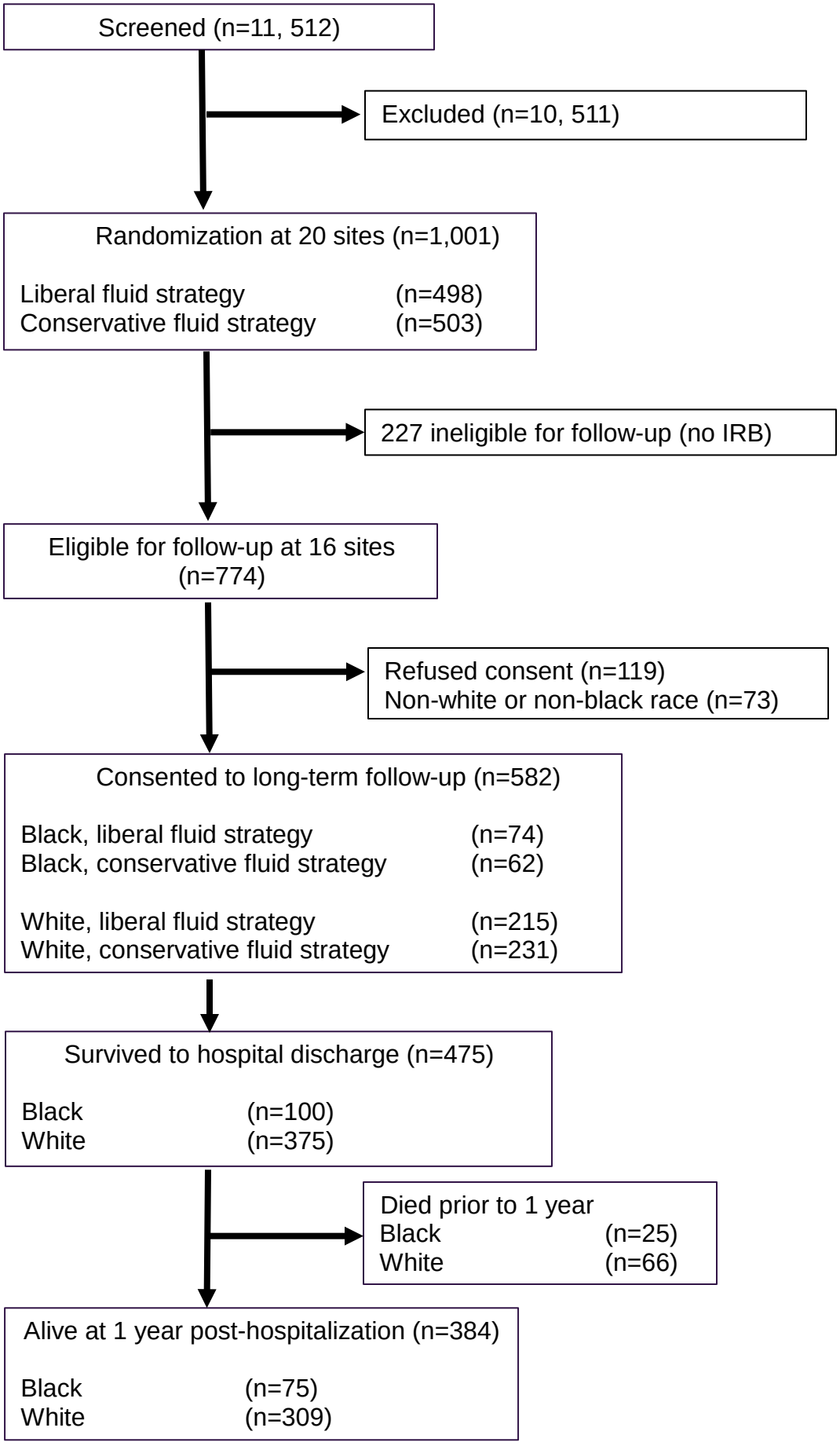
SD= standard deviation

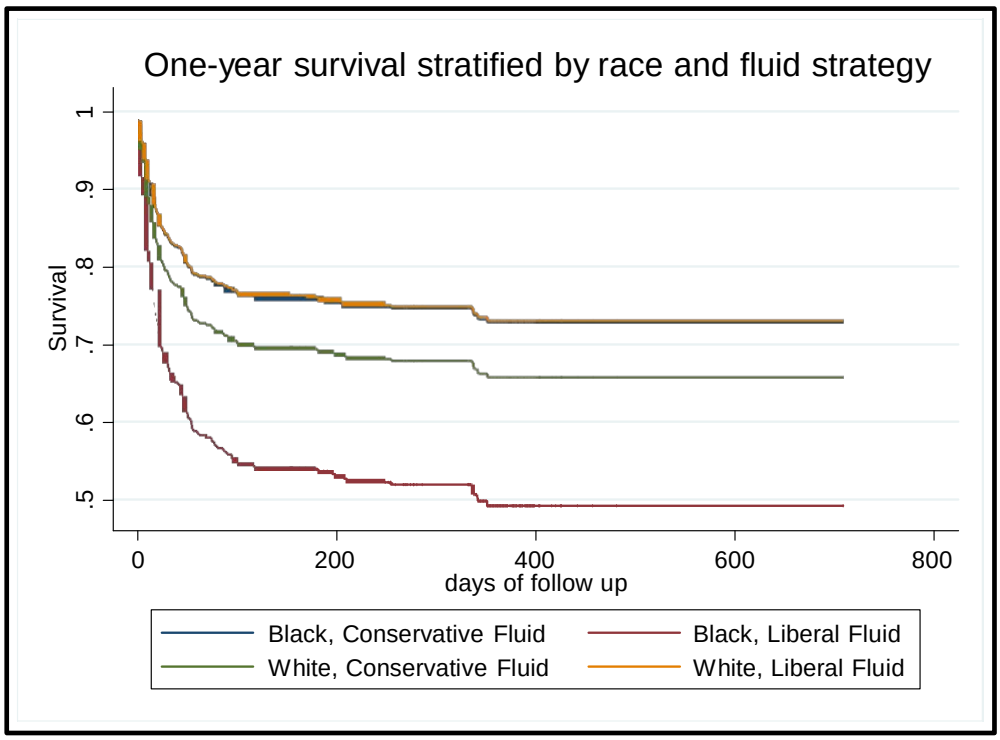
## FIGURE LEGENDS

**Figure 1. – Quorum chart of the EAPAC one-year follow-up cohort**

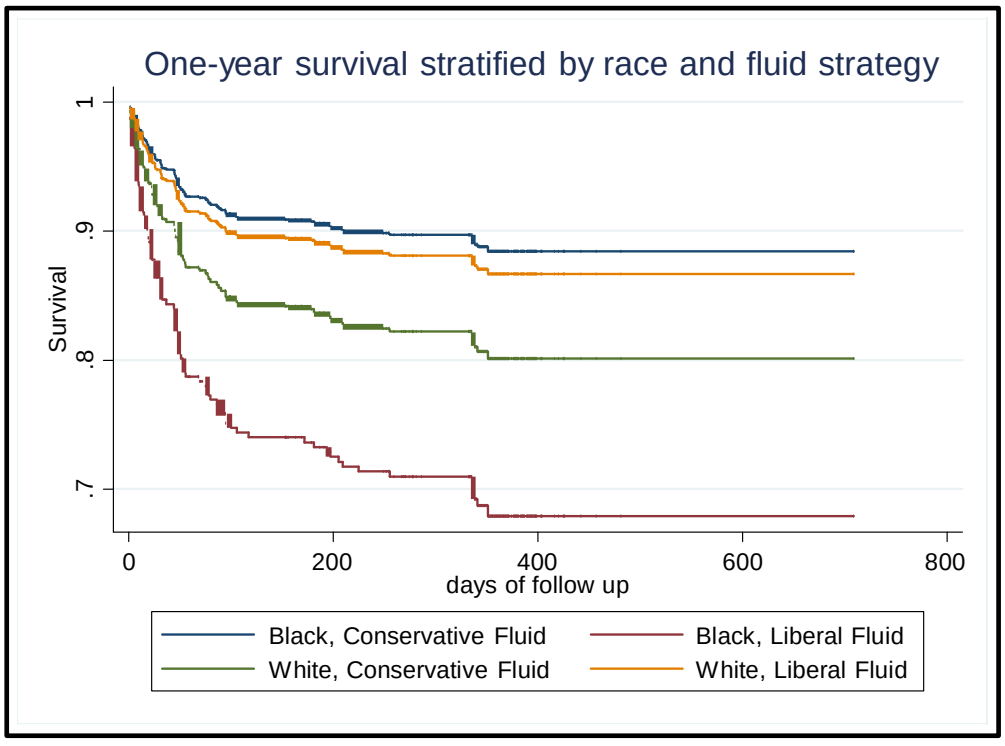
**Figure 2. –Cox proportional hazard curves of death stratified by fluid strategy and race.** Panel A: Stratified cox proportional hazard curves for the EAPAC study cohort. Liberal fluids compared with conservative fluids was associated with greater mortality among black patients (HR 2.5, 95% CI 1.4-4.5). Panel B: Stratified cox proportional hazard curves for EAPAC study hospital survivors. Liberal fluids compared with conservative fluids was associated with greater mortality among black hospital survivors (HR 3.3, 95% CI 1.17-9.12).

**Figure 3. Distribution of functional dependence stratified by race.** HUI-2 mobility scores >2 were more frequently reported by non-Hispanic black participants compared with non-Hispanic white participants (OR 2.1, 95% CI 1.1-4.2, p=0.02).


Screened (n=11, 512)
Excluded (n=10, 511)
Randomization at 20 sites (n=1,001)
Liberal fluid strategy (n=498)
Conservative fluid strategy (n=503)
227 ineligible for follow-up (no IRB)
Eligible for follow-up at 16 sites (n=774)
Refused consent (n=119)
Non-white or non-black race (n=73)
Consented to long-term follow-up (n=582)
Black, liberal fluid strategy (n=74)
Black, conservative fluid strategy (n=62)
White, liberal fluid strategy (n=215)
White, conservative fluid strategy (n=231)
Survived to hospital discharge (n=475)
Black (n=100)
White (n=375)
Died prior to 1 year
Black (n=25)
White (n=66)
Alive at 1 year post-hospitalization (n=384)
Black (n=75)
White (n=309)




Panel A




Panel B

**Health Utilities Index-2 Score by Race (%)**

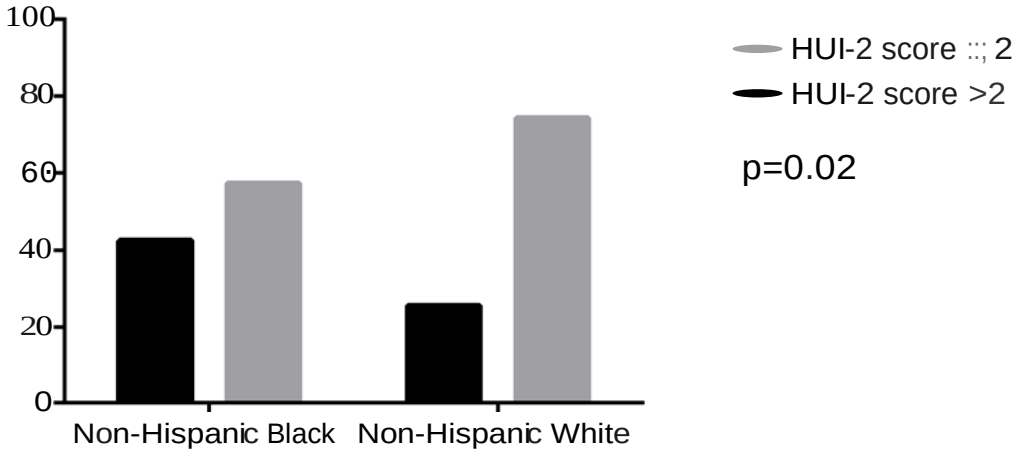


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**Table E1. Baseline characteristics of the FACTT and EA-PAC cohorts**

| Variable | EA-PAC Cohort | FACTT Cohort that was not part of EA-PAC | Total FACTT cohort | p-value |
|---|---|---|---|---|
| N | 655 | 345 | 1000 | |
| Age, mean (SD) | 50.10 (16.00) | 49.09 (16.72) | 49.75 (16.00) | .3423 |
| Sex, female, n (%) | 308 (47%) | 158 (49%) | 466 (47%) | .7390 |
| Race, n (%) | | | | |
| White non-Hispanic | 445 (68%) | 196 (57%) | 641 (64%) | .0005 |
| Black non-Hispanic | 136 (21%) | 81 (23%) | 217 (22%) | .3334 |
| Other | 74 (11%) | 68 (20%) | 142 (14%) | .0004 |
| Primary Lung injury, n (%) | | | | |
| Pneumonia | 299 (46%) | 172 (50%) | 471 (47%) | .2564 |
| Sepsis | 145 (22%) | 88 (26%) | 233 (24%) | .2707 |
| Aspiration | 103 (16%) | 46 (13%) | 149 (15%) | .3060 |
| Trauma | 50 (8%) | 24 (7%) | 74 (7%) | .7056 |
| Multiple transfusions | 6 (1%) | 3 (1%) | 9 (1%) | .9999 |
| Other | 46 (7%) | 11 (3%) | 57 (6%) | .0141 |
| Co-existing Conditions, n (%) | | | | |
| None | 444 (68%) | 216 (63%) | 660 (66%) | .1065 |
| Diabetes | 110 (17%) | 63 (19%) | 173 (18%) | .6608 |
| HIV Infection or AIDS | 36 (6%) | 35 (10%) | 71 (7%) | .0098 |
| Cirrhosis | 24 (4%) | 9 (3%) | 33 (3%) | .4578 |
| Solid Tumors | 12 (2%) | 3 (1%) | 15 (2%) | .2823 |
| Leukemia | 12 (2%) | 10 (3%) | 22 (2%) | .3657 |
| Lymphoma | 6 (1%) | 7 (2%) | 13 (1%) | .1561 |
| Immunosuppression | 51 (8%) | 27 (8%) | 78 (8%) | .9999 |
| Apache III score, mean (SD) | 93.67 (31.29) | 95.04 (30.15) | 94.15 (30.89) | .5103 |
| Medical ICU, n (%) | 421 (64%) | 242 (70%) | 663 (66%) | .0674 |
| Cardiorespiratory Variables, mean (SD) | | | | |
| Mean arterial pressure (mm Hg) | 77.31 (14.28) | 76.83 (13.97) | 77.15 (14.16) | .6101 |
| Cardiac index (liters/min/m2) | 4.12 (1.36) | 4.42 (1.54) | 4.23 (1.43) | .0427 |
| Vasopressor use, n (%) | 248 (39%) | 150 (44%) | 398 (40%) | .1012 |
| Pre-randomization fluid balance (mL) | 2875.34 (3590.32) | 2552.95 (3417.14) | 2763.99 (3533.02) | .1774 |

| | | | | |
|---|---|---|---|---|
| PaO2:FiO2 | 126.69 (57.03) | 127.40 (61.63) | 126.93 (58.61) | .8589 |
| Tidal volume (mL), mean (SD) | 451.99 (98.69) | 490.40 (122.36) | 465.19 (108.88) | <.0001 |
| Tidal volume (mL/kg of PBW), mean (SD) | 6.31 (2.74) | 6.82 (3.08) | 6.49 (2.87) | <.0001 |

SD= standard deviation