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Fluid Management in Patients with Acute Respiratory Distress Syndrome and Diabetes Mellitus

A propensity score matched analysis of the fluid and catheter treatment trial

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Abstract

Diabetes mellitus results in an attenuated inflammatory response, reduces pulmonary microvascular permeability, and may decrease the risk of developing acute respiratory distress syndrome (ARDS). Studies have shown that patients with ARDS are better managed by a conservative as compared to liberal fluid management strategy. However, it is not known if the same fluid management principles hold true for patients with comorbid diabetes mellitus and ARDS.

As diabetes mellitus results in reduced pulmonary microvascular permeability and an attenuated inflammatory response, we hypothesize that in the setting of ARDS, diabetic patients will be able to tolerate a positive fluid balance better than patients without diabetes.

The Fluid and Catheter Treatment Trial (FACTT) randomized patients with ARDS to conservative versus liberal fluid management strategies. In a secondary analysis of this trial, we calculated the interaction of diabetic status and differing fluid strategies on outcomes. Propensity score subclassification matching was used to control for the differing baseline characteristics between patients with and without diabetes.

Nine hundred fifty-six patients were analyzed. In a propensity score matched analysis, the difference in the effect of a conservative as compared to liberal fluid management strategy on ventilator free days was 2.23 days (95% CI: −0.97 to 5.43 days) in diabetic patients, and 2.37 days (95% CI: −0.21 to 4.95 days) in non-diabetic patients. The difference in the effect of a conservative as compared to liberal fluid management on 60 day mortality was 2% (95% CI: −11.8% to 15.8%) in diabetic patients, and −7.9% (95% CI: −21.7% to 5.9%) in non-diabetic patients.

When comparing a conservative fluid management strategy to a liberal fluid management strategy, diabetic patients with ARDS did not have a statistically significant difference in outcomes than non-diabetic patients.

Abbreviations: ARDS = acute respiratory distress syndrome, BMI = body mass index, DM = diabetes mellitus, FACTT = Fluid and Catheter Treatment Trial, FiO2 = fraction of inspired oxygen, ICU = intensive care unit, PaO2 = partial pressure of oxygen.

Keywords: ARDS, diabetes mellitus, fluid and catheters treatment trial, fluid management

1. Introduction

Acute respiratory distress syndrome (ARDS) is characterized by a dysregulated inflammatory response leading to pulmonary epithelial and endothelial injury, increased permeability, and non-cardiogenic pulmonary edema.[1] Improved lung function and an increase in number of ventilator free days was observed in patients with ARDS when a conservative fluid management strategy was used as compared to a liberal fluid management

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The datasets generated and/or analyzed, the FACTT dataset, is available in the BIOLINCC NHLBI repository, available on request.

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strategy in the Fluid and Catheters Treatment Trial (FACTT).[2] The conservative fluid management approach resulted in an even fluid balance over the first week, whereas the liberal fluid management approach resulted in an approximately 7 L positive fluid balance.[2]

Diabetes mellitus is a disorder that is characterized by chronic hyperglycemia due to a failure of insulin production or action, or increased insulin resistance.[3] Several studies have associated diabetes mellitus with a decreased risk of developing acute respiratory distress syndrome, even after controlling for medications for diabetes, glucose levels, and other baseline participant characteristics.[4–6] Filgueiras et al suggest that in a murine model of sepsis, the decreased risk of ARDS conferred by diabetes may be partly explained by impaired macrophage activation; they also noted that diabetic rats developed less pulmonary edema than non-diabetic rats.[7] The protective effect of diabetes may also be partly explained by the diabetic lung's attenuated response to inflammatory stimuli, decreased microvascular permeability, and decreased alveolar recruitment due to systemic microangiopathy.[8–11]

The optimal fluid management strategy for diabetic patients with ARDS is unclear. Due to the decreased pulmonary microvascular permeability and pulmonary edema seen in diabetics with ARDS,[7,9,11] we hypothesize that patients with diabetes will tolerate the positive fluid balance noted in the FACTT liberal fluid strategy arm better than patients without diabetes. Specifically, we hypothesize that patients with diabetes will not benefit as much from active conservative fluid management, and will not have as large an improvement in the number of ventilator free days with a conservative fluid management strategy as compared to liberal fluid management.

2. Statistical methods

2.1. Data

The Partners Healthcare Institutional Review Board has reviewed this study and determined it does not meet the criteria for human subjects research and is exempted from further continuing review. We used the de-identified FACTT data.[2] FACTT was a randomized controlled multicenter trial that was conducted across 20 healthcare institutions in North America and enrolled 1000 patients with acute lung injury between 2000 and 2005; the study size of our analysis is limited by the number of patients enrolled in FACTT.[2] FACTT evaluated the difference between conservative and liberal fluid management strategies for the following primary and secondary outcomes: 60 day mortality, ventilator free days, intensive care init (ICU) free days, and non-pulmonary organ failure free days. Diabetes mellitus status was collected as a part of the background assessment for patients enrolled in the Fluid and Catheter Treatment trial. For the purposes of our analysis, we excluded participants whose diabetic status was unknown, or were missing information about primary or secondary outcomes.

2.2. Propensity score

To control for differences in baseline comorbidities between patients with and without diabetes, patients were subclassified into 4 strata defined by a propensity score for diabetic status.[12] Within each stratum, the average propensity score and the baseline characteristics of participants are similar – in essence, controlling for likely confounders. The strata were sized such that there would be an equal number of participants with diabetes within each stratum.[13] We pre-defined the covariates of the propensity score model by including likely confounding variables.[12,14] The following variables were identified as likely confounders for the interaction of diabetes on ARDS outcomes: age, gender, body mass index (BMI), and ethnicity.[15–17] The additional covariates included in the propensity score model were: the primary cause of ARDS, whether the patient was immediately post-operative, AIDS status, if the patient had leukemia, lymphoma, solid tumor with metastasis, immunosuppression, cirrhosis, underlying chronic pulmonary disease, if the patient needed vasopressors in the last 24 hours, hematocrit, highest white blood cell count, platelets, mean arterial pressure, pulmonary artery carbon dioxide, pulmonary artery pH, albumin levels, bilirubin levels, bicarbonate levels, fluid intake and output over the past 24 hours before randomization, partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FiO2) ratio, and fluid management strategy. The following covariates, which could mediate the effect pathway of the interaction of diabetes on ARDS, were excluded from the propensity score: diagnosis of hypertension, myocardial infarction, congestive heart disease, peripheral vascular disease, stroke, if the participant was on dialysis at baseline, highest baseline creatinine, lowest baseline creatinine, highest baseline glucose, edema, and lowest baseline glucose.

The balance achieved by the propensity score matching is measured by comparing the standardized mean difference of baseline variables before and after propensity score matching. The standardized mean difference is calculated by subtracting the mean value of a variable in the diabetic population by the mean value of the variable in the non-diabetic population, and then dividing this difference in values by the standard deviation of the variable; the standardized mean differences in this analysis were calculated using the R TableOne and R MATCH IT packages.[18–20]

2.3. Missing baseline data – multiple imputation

To replace missing data, we used multivariate imputation by chained equations.[21] Multiple imputation is an appropriate choice to replace missing data, as data was plausibly missing at random and all baseline variables were missing less than 40% of data.[22] Multivariate imputation was conducted by regressing the observed values of baseline variables, such as comorbidities and laboratory values, on each of the other variables in the dataset, creating a model which would then be used to predict the missing values. Based on simulations of the model, the missing values were replaced.[23–25] We created 5 imputed data sets for the purposes of our analysis to create variability in the replaced missing values. The missing variables for diabetic and non-diabetic participants were imputed separately.[26]

2.4. Calculation of outcomes

Our primary outcomes are 60 day hospital mortality and ventilator free days to day 28, as defined by the Fluid and Catheter Treatment Trial.[2] Our secondary outcomes are non-pulmonary organ failure free days; these variables were measured from days 1 to 7, and also from days 1 to 28. For each outcome, within in each of the 4 propensity score based strata, we calculated the mean outcome result for every combination of fluid

Table 1

Baseline variables before propensity score matching.

	No diabetes	Diabetes	Standardized mean difference	Missing values (n)
n	784	172		
Age (mean (SD))	48.7 (16.1)	54.8 (14.2)	**0.40**	0
Male (%)	428 (54.6%)	80 (46.5%)	**0.16**	0
Female (%)	356 (45.4%)	92 (53.5%)	**0.16**	0
Body mass index, kg/m^2 (mean (SD))	28.0 (7.0)	31.8 (9.2)	**0.47**	77
Race (%)			**0.27**	0
White	522 (66.6%)	92 (53.5%)		
Black	164 (20.9%)	48 (27.9%)		
Primary cause of ARDS (n(%))				
Trauma	65 (8.3%)	1 (0.6%)	**0.38**	0
Sepsis	173 (22.1%)	51 (29.7%)	**0.18**	0
Multiple transfusion ALI	7 (0.9%)	1 (0.6%)	**0.16**	0
Aspiration	120 (15.3%)	20 (11.6%)	**0.16**	0
Pneumonia	372 (47.4%)	84 (48.8%)	0.03	0
Baseline comorbidities				
Patient is immediately post-operative (n(%))	37 (4.7%)	9 (5.2%)	0.02	0
Acute physiology and chronic health evaluation (APACHE) 3 (mean (SD))	93.2 (31.1)	99.6 (30.1)	**0.21**	4
Intensive care unit readmission (n(%))	34 (4.3%)	11 (6.4%)	0.09	0
On dialysis (mean (SD)) (n(%))	1 (0.1%)	0 (0.0%)	0.05	0
Acquired immunodeficiency syndrome (AIDS) (n(%))	70 (8.9%)	1 (0.6%)	**0.4**	0
Leukemia (n(%))	19 (2.4%)	3 (1.7%)	0.05	0
Non-Hodgkins lymphoma (n(%))	11 (1.4%)	2 (1.2%)	0.02	0
Solid tumor with metastasis (n(%))	10 (1.3%)	5 (2.9%)	**0.11**	0
Immunosuppression (n(%))	64 (8.2%)	13 (7.6%)	0.02	0
Hepatic failure with encephalopathy (n(%))	6 (0.8%)	3 (1.7%)	0.09	0
Cirrhosis (n(%))	27 (3.4%)	6 (3.5%)	0.00	0
Hypertension (n(%))	141 (21.2%)	97 (64.7%)	**0.98**	140
Prior MI (n(%))	17 (2.5%)	19 (12.7%)	**0.39**	139
Congestive heart failure (n(%))	12 (1.8%)	15 (10.0%)	**0.35**	138
Peripheral vascular disease (n(%))	11 (1.6%)	21 (14.0%)	**0.47**	139
Prior stroke (n(%))	15 (2.2%)	18 (12.0%)	**0.39**	139
Dementia (n(%))	12 (1.8%)	6 (4.0%)	**0.13**	139
Chronic pulmonary disease (n(%))	42 (6.3%)	20 (13.3%)	**0.24**	139
Arthritis (n(%))	42 (6.3%)	21 (14.0%)	**0.26**	139
Ulcer (n(%))	27 (4.0%)	9 (6.0%)	0.09	139
Vasopressor use in the last 24 h (n(%))	257 (32.8%)	67 (39.0%)	**0.13**	1
Protocol defined alcohol use (n(%))	81 (11.4%)	9 (5.8%)	**0.20**	92
Baseline lab values (24 h preceding randomization by fluid management strategy)				
Lowest hematocrit (mean (SD))	29.7 (6.7)	29.9 (5.5)	0.03	5
Highest WBC in 1000 s (mean (SD))	14.9 (13.7)	14.2 (11.2)	0.06	8
Platelets in 1000 s (mean (SD))	190.5 (124.7)	214.6 (118.4)	**0.20**	8
Highest glucose, mg/dL (mean (SD))	153.4 (81.5)	207.6 (115.8)	**0.54**	19
Lowest glucose, mg/dL (mean (SD))	120.3 (50.6)	145.5 (86.5)	**0.36**	17
Highest creatinine, mg/dL (mean (SD))	1.3 (0.9)	1.67 (1.1)	**0.37**	5
Lowest albumin, g/dL (mean (SD))	2.2 (0.68)	2.3 (0.8)	0.09	204
Bilirubin, mg/dL (mean (SD))	1.7 (3.8)	1.6 (3.6)	0.03	245
Lowest serum bicarbonate, mEq/L (mean (SD))	21.4 (5.5)	20.4 (5.8)	**0.19**	13
Anasarca on physical exam (n(%))	126 (16.1%)	44 (25.6%)	**0.24**	0
Mean arterial pressure, mm Hg (mean (SD))	77.3 (13.9)	75.6 (15.2)	**0.12**	5
Central venous pressure, mm Hg (mean (SD))	11.9 (4.7)	12.3 (4.9)	0.072	74
Fluid intake in liters over last 24 h (mean (SD))	5.0 (3.8)	4.6 (3.4)	**0.13**	26
Fluid output in liters over last 24 h (mean (SD))	2.3 (1.8)	1.9 (1.4)	**0.23**	32
Pulmonary artery CO2 (mean (SD))	41.1 (10.3)	39.7 (10.2)	**0.13**	11
Pulmonary artery pH (mean (SD))	7.4 (0.1)	7.4 (0.1)	0.03	11
PaO2/FiO2 ratio (mean (SD))	142.0 (60.3)	138.5 (59.5)	0.06	11
Conservative fluid management	394 (50.3%)	88 (51.2%)	0.02	0
Liberal fluid management	390 (49.7%)	84 (48.8%)	0.02	0

Values are highlighted if standardized mean difference is >.1, which is a sign of imbalance. FiO2 = fraction of inspired oxygen, PaO2 = partial pressure of oxygen

management strategy and diabetes status. Across each strata, the estimates for the outcomes were then averaged, leaving us with outcome estimates for 4 groups: conservative fluid management with diabetes, conservative fluid management without diabetes, liberal fluid management with diabetes, and liberal fluid management without diabetes. A contrast between conservative and liberal fluid management strategy in participants with diabetes and without diabetes was calculated, resulting in 2 outcome contrasts. These 2 outcome estimates were then subtracted to determine the effect modification of diabetic status on fluid management strategy for our primary and secondary outcomes. We tested the statistical significance of this effect modification with a 2-tailed *t* test. We pooled the results of our analysis across the multiple imputations together using Rubin's Rules to calculate the final interaction term effect per outcome.[26] Statistical significance was defined as $P < .05$.

2.5. Software used

The multiple multivariate imputation by chained equations were created using the R MICE package (R version 3.5.1, R Foundation for Statistical Computing, Vienna, Austria).[27] The propensity score stratification was done using the R MATCH IT package.[18]

3. Results

Of the 1000 participants included in the Fluid and Catheter Treatment Trial, 44 participants were excluded because they were missing either the diabetes variable or outcome variables, leaving 956 participants for the analysis. One hundred seventy-two participants had the diagnosis of diabetes preceding participation in the study (Table 1 and Fig. 1).

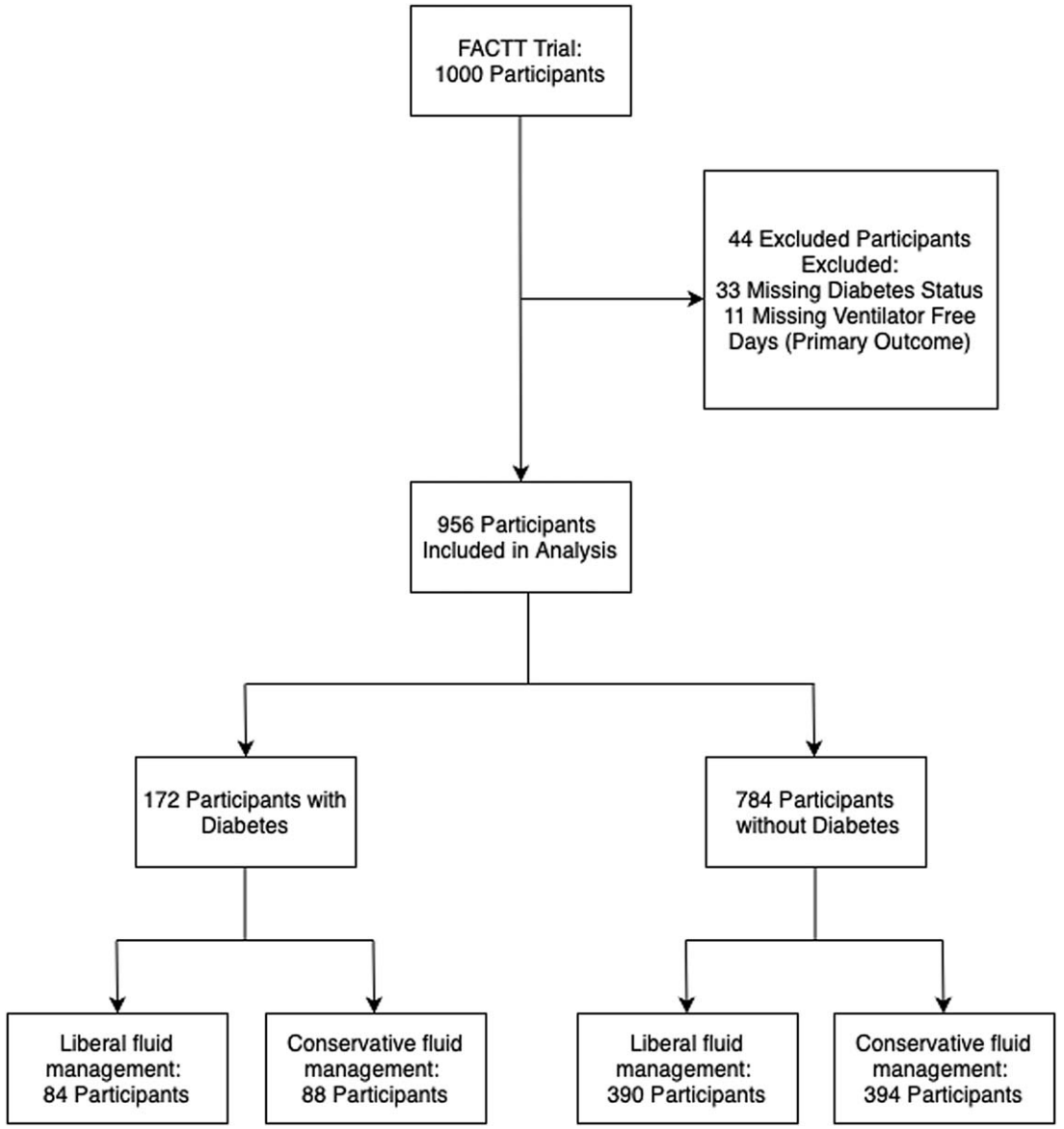

Figure 1. Data from the FACTT (Fluid and Catheter Treatment Trial) was used for this secondary analysis. Participant data was excluded if diabetic status prior to the trial was not recorded, or if ventilator free days after randomization was missing.

Table 2

Baseline Variables and Randomization Status After Propensity Score Matching.

	Mean values for non-diabetic patients after matching	Mean values for diabetic patients after matching	Absolute mean difference (Min–Max across imputations)	Standardized mean difference (min–max over imputations)
n	784	172		
Age	54.3	54.8	0.50 (0.4, 0.6)	**0.11 (0.11, 0.12)**
Male (%)	396 (50.6%)	80 (46.5%)	4% (4%, 5%)	0.08 (0.06, 0.09)
Female (%)	388 (49.4%)	92 (53.5%)	4% (4%, 5%)	
Body mass index, kg/m^2	30.9	31.8	0.9 (0.7, 1.2)	**0.12 (0.10, 0.13)**
White	408 (52.0%)	92 (53.5%)	1% (1%, 2%)	0.08 (0.08, 0.09)
Black	214 (27.3%)	48 (27.9%)	1% (−1%, 2%)	0.06 (0.05, 0.09)
Primary cause of ARDS (n(%))				
Trauma	27 (3.4%)	1 (0.6%)	−3% (−3%, −3%)	**0.37 (0.36, 0.38)**
Sepsis	200 (25.5%)	51 (29.7%)	4% (4%, 5%)	0.10 (0.08, 0.14)
Multiple Transfusion ALI	4 (0.5%)	1 (0.6%)	0% (0%, 0%)	0.05 (0.04, 0.07)
Aspiration	108 (13.7%)	20 (11.6%)	−2% (−3%, −2%)	**0.11 (0.09, 0.13)**
Pneumonia	387 (49.4%)	84 (48.8%)	−1% (−1%, 0%)	0.08 (0.04, 0.10)
Baseline comorbidities				
Patient is immediately post-operative (n(%))	39 (4.9%)	9 (5.2%)	0% (−1%, 0%)	0.05 (0.04, 0.09)
Acute physiology and chronic health evaluation (APACHE) 3 (mean (SD))	95.8	99.6	3.9 (3.2, 4.9)	0.10 (0.08, 0.11)
Intensive care unit readmission (n(%))	38 (4.8%)	11 (6.4%)	−2% (−2%, −1%)	0.08 (0.04, 0.12)
On dialysis (mean (SD)) (n(%))	1 (0.0%)	0 (0.0%)	0% (0%, 0%)	
Acquired immunodeficiency syndrome (AIDS) (n(%))	29 (3.7%)	1 (0.6%)	3% (3%, 3%)	**0.41 (0.40, 0.41)**
Leukemia (n(%))	14 (1.7%)	3 (1.7%)	0% (0%, 0%)	0.08 (0.07, 0.09)
Non-Hodgkin's lymphoma (n(%))	8 (1.0%)	2 (1.2%)	0% (0%, 0%)	0.04 (0.03, 0.05)
Solid tumor with metastasis (n(%))	17 (2.1%)	5 (2.9%)	−1% (−1%, 0%)	0.09 (0.05, 0.16)
Immunosuppression (n(%))	58 (7.4%)	13 (7.6%)	0% (0%, 0%)	0.09 (0.07, 0.11)
Hepatic failure with encephalopathy (n(%))	20 (2.6%)	3 (1.7%)	1% (0%, 2%)	**0.19 (0.14, 0.26)**
Cirrhosis (n(%))	33 (4.2%)	6 (3.5%)	1% (1%, 1%)	**0.15 (0.12, 0.20)**
Hypertension (n(%))	245 (31.3%)	109 (63.3%)	−32% (−33%, −30%)	**0.33 (0.32, 0.35)**
Prior MI (n(%))	29 (3.8%)	29 (17.1%)	−13% (−15%, −12%)	**0.18 (0.17, 0.19)**
Congestive heart failure (n(%))	22 (2.9%)	20 (11.4%)	−9% (−10%, −6%)	**0.16 (0.14, 0.17)**
Peripheral vascular disease (n(%))	25 (3.1%)	25 (14.5%)	−11% (−13%, −10%)	**0.19 (0.18, 0.19)**
Prior stroke (n(%))	14 (1.7%)	24 (14.2%)	−12% (−14%, −12%)	**0.18 (0.17, 0.20)**
Dementia (n(%))	24 (3.1%)	10 (5.7%)	−3% (−3%, −2%)	**0.11 (0.09, 0.12)**
Chronic pulmonary disease (n(%))	81 (10.3%)	24 (13.8%)	−4% (−5%, −3%)	**0.16 (0.13, 0.19)**
Arthritis (n(%))	73 (9.4%)	27 (15.9%)	−7% (−10%, −4%)	**0.12 (0.08, 0.16)**
Ulcer (n(%))	35 (4.5%)	12 (6.9%)	−2% (−4%, −1%)	0.07 (0.05, 0.09)
Vasopressor use in the last 24 h (n(%))	302 (38.5%)	67 (39.0%)	0% (−1%, 0%)	0.06 (0.03, 0.09)
Protocol defined alcohol use (n(%))	59 (7.5%)	12 (7.1%)	0% (0%, 1%)	0.06 (0.03, 0.07)
Baseline lab values (24 h preceding randomization by fluid management strategy)				
Lowest hematocrit	29.7	29.9	0.2 (0.2, 0.4)	0.07 (0.04, 0.10)
Highest WBC (in 1000 s)	14.3	14.2	−0.1 (−0.3, 0.1)	0.05 (0.04, 0.08)
Platelets (in 1000 s)	219.5	213.4	−6.1 (−10.3, −2.8)	**0.11 (0.07, 0.18)**
Highest glucose, mg/dL	161.8	207.0	45.2 (42.0, 46.6)	**0.23 (0.22, 0.23)**
Lowest glucose, mg/dL	125.5	146.0	20.6 (18.3, 22.6)	**0.15 (0.14, 0.18)**
Highest creatinine, mg/dL	1.4	1.7	0.2 (0.2, 0.3)	**0.14 (0.11, 0.15)**
Lowest albumin, g/dL	2.3	2.3	0.0 (−0.1, 0.0)	**0.11 (0.07, 0.15)**
Bilirubin, mg/dL	1.6	1.7	0.2 (0.0, 0.3)	0.06 (0.04, 0.09)
Lowest serum bicarbonate, mEq/L	20.4	20.4	0.0 (−0.1, 0.1)	0.06 (0.05, 0.07)
Anasarca on physical exam (n(%))	155 (19.8%)	44 (25.6%)	−6% (−7%, −4%)	0.08 (0.08, 0.10)
Mean arterial pressure, mm Hg	75.7	75.5	−0.2 (−0.5, 0.0)	0.04 (0.02, 0.07)
Central venous pressure, mm Hg	12.0	12.2	0.2 (0.0, 0.4)	0.07 (0.04, 0.12)
Fluid intake in liters over last 24 h	4.7	4.6	0.0 (−0.1, 0.0)	0.05 (0.02, 0.07)
Fluid output in liters over last 24 h	2.0	1.9	0.0 (−0.1, 0.0)	0.09 (0.08, 0.11)
Pulmonary artery CO2	39.7	39.7	0.0 (−0.2, 0.2)	0.07 (0.05, 0.10)
Pulmonary artery pH	7.4	7.4	0.0 (0.0, 0.0)	0.05 (0.03, 0.10)
PaO2/FiO2 ratio	129	127.4	−1.3 (−2.2, −0.1)	0.09 (0.06, 0.14)
Conservative fluid management	418 (53.3%)	88 (51.2%)	2% (2%, 3%)	0.08 (0.06, 0.13)
Liberal fluid management	366 (46.7%)	84 (48.8%)	2% (2%, 3%)	0.08 (0.06, 0.13)

The values for the propensity score analysis were calculated by averaging across 5 imputed datasets. Values are highlighted if standardized mean difference is >.1, which is a sign of imbalance. FiO2 = fraction of inspired oxygen, PaO2 = partial pressure of oxygen.

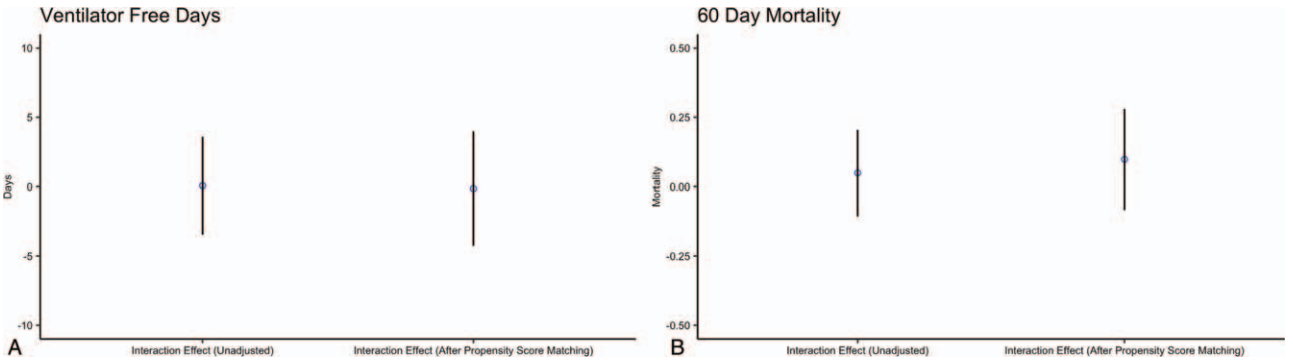

Figure 2. Mean (with 95% confidence interval) interaction effect of diabetic status on a conservative fluid management strategy as compared to a liberal fluid management strategy, on the primary outcomes of ventilator free days (A) and 60 day mortality (B).

3.1. Missing values

Of the 956 participants, only 236 participants had completely documented baseline variables data. Of the 58 baseline variables, 22 were completely documented (Table 1). Of all the baseline data, bilirubin had the least complete data, with 25.6% of participants missing baseline bilirubin levels (Table 1).

3.2. Unadjusted group comparison – before imputation of missing data or stratification matching by propensity score

Without stratification matching by propensity score, on average, participants with diabetes were older (54.78 years old) than those without diabetes (48.68 years old). 53.5% of participants with diabetes were female; 45.4% of participants without diabetes were female. 27.9% of participants with diabetes were black; 20.9% of participants without diabetes were black. On average, participants with diabetes also had a higher BMI (31.8 kg/m^2) than participants without diabetes (28.0 kg/m^2) (Tables 1 and 2). Without controlling for these potential confounders, the unadjusted group comparison did not show a statistically significant interaction of diabetes on the effect of the conservative fluid management strategy on the primary outcomes (Supplemental Appendix Table 5, http://links.lww.com/MD/E898, Supplemental Appendix Table 6, http://links.lww.com/MD/E899).

3.3. Propensity score stratification

After matching participants by the 4 propensity score strata (Supplemental Appendix: Table 7, http://links.lww.com/MD/E900), the balance of baseline variables between participants with diabetes and without diabetes is greatly improved as noted when comparing the standardized mean differences of the baseline variables in the unadjusted analysis and the propensity score adjusted analysis, which was calculated as an average over the 5 imputations (Tables 1 and 2). In the propensity score adjusted analysis, the average age of participants with diabetes was 54.8 years old, and the average age of participants without diabetes was 54.3 years. 53.5% of participants with diabetes were female; 49.4% of participants without diabetes are female. 27.9% of participants with diabetes identified as black; 27.3% of participants without diabetes identified as black. The average BMI of participants with diabetes was 31.8 kg/m^2, and the average BMI of participants without diabetes was 30.9 kg/m^2 (Tables 1 and 2).

In the propensity score adjusted analysis, the standardized mean difference for the confounders of gender and race is less than 0.1. While the standardized mean differences for the confounders of age and BMI are 0.11 and 0.12, the absolute mean differences are 0.5 years and 0.9 kg/m^2, respectively, which are not clinically meaningful differences in age or BMI. All measured confounders achieved an improved balance in the propensity score analysis as compared to the unadjusted analysis (Tables 1 and 2).

3.4. Contrast analysis

In the propensity matched analysis, in diabetic patients, the mean difference in the effect of a conservative as compared to liberal fluid management strategy on the number of ventilator free days was 2.23 days (95% confidence interval: −0.97 to 5.43 ventilator free days), and in non-diabetic patients the difference was 2.37 days (95% CI: −0.21 to 4.95 days). Furthermore, in diabetic patients, the mean difference in the effect of a conservative as compared to a liberal fluid management on the probability of 60 day mortality was 2% (confidence interval: −11.8% to 15.8%), and in non-diabetic patients the mean difference was −7.9% (95% CI: −21.7% to 5.9%). The numerical difference in ventilator free days due to the interaction of diabetic status on the effect of a conservative as compared to liberal fluid management strategy is −0.14 days (95% CI: −4.26 days to 3.98 days, Fig. 2 and Table 3). The numerical difference in probability of 60 day mortality due to the interaction of diabetic status on the effect of a

Table 3

Ventilator free days results with matching to control for confounders.

Ventilator free days	Conservative fluid management (mean ± SE)	Liberal fluid management	Difference	*T*-statistic	*P*
Diabetes	12.26 ± 1.11	10.03 ± 1.15	2.23 ± 1.60	1.39	.16
Without diabetes	13.46 ± 0.86	11.09 ± 0.95	2.37 ± 1.29	1.84	.07
Interaction			−0.14 ± 2.06	−0.07	.94

Table 4

60 day mortality results with matching to control for confounders.

60 day mortality results	Conservative fluid management	Liberal fluid management	Difference	*T*-statistic	*P*
Diabetes	34.6% ± 4.9%	32.6% ± 4.9%	2.0% ± 6.9%	0.28	.78
Without diabetes	26.5% ± 3.8%	34.3% ± 4.5%	−7.9% ± 6.0%	−1.31	.19
Interaction			9.8% ± 9.1%	1.08	.28

conservative as compared to a liberal fluid management strategy is 9.8% (95% CI: −8.4% to 28%, Fig. 2 and Table 4). There were no statistically significant results for the interaction of diabetic status on the effect of conservative versus a liberal fluid management strategy on non-pulmonary organ failure free days in the first 28 days, or on the number of intensive care unit free days in the first 28 days.

4. Discussion

ARDS and diabetes mellitus (DM) are both complex heterogeneous disease processes which exert widespread effects on multiple organ systems. While the biological hallmark of ARDS is increased pulmonary vascular permeability and fluid overload, comorbid diabetes mellitus has been associated with attenuated inflammation and decreased pulmonary vascular permeability.[8–10]

In our secondary analysis of the FACTT data, we found that diabetes mellitus has no interaction on measured primary outcomes in ARDS (ventilator free days and 60 day mortality) when a conservative fluid management strategy is utilized as compared to a liberal fluid management strategy. Our analysis suggests that fluid management of patients with ARDS should not differ based on diabetic status.

While diabetes attenuates inflammation and decreases pulmonary microvascular permeability,[8,9] these effects may be too small to necessitate a change in the fluid management of diabetic patients with ARDS. Another possible biological explanation is that although diabetes mellitus leads to protective immunomodulatory effects in the setting of ARDS,[8] the harmful metabolic changes, such as an inappropriate stress response, seen in long-standing diabetes may negate these protective effects.[28] The findings of our study are consistent with a recent secondary analysis of the LUNG SAFE database and a meta-analysis by Ji that suggest that diabetic status may not affect the risk of developing of ARDS, and may also not affect ARDS outcomes.[29,30]

It is important to note that ARDS and diabetes mellitus are heterogenous syndromes. In the Fluid and Catheter Treatment Trial, specific details about patients' diabetic histories were not recorded: the type of DM, duration of disease, and the extent of microvascular complications. Notable pulmonary microvascular alterations may have only been present in patients with long-standing, uncontrolled diabetes mellitus. As more specific data describing patients' diabetes mellitus status is collected, and as our knowledge of how to best characterize ARDS sub-phenotypes evolves,[31] this interaction could be further elucidated.

The key strengths of this secondary analysis are the randomized comparison of 2 fluid management approaches in FACTT, and the balance of baseline variables that was achieved through propensity score matching.

Our study has several limitations. First, our sample size (n = 956; diabetic patients n = 172; non-diabetic patients n = 784) is limited by the size of the FACTT dataset and our objective to study the interaction of diabetes mellitus on fluid management strategies in the treatment of ARDS. Second, the propensity score model could not control for unmeasured confounders such as medications used to treat diabetes. Angiotensin converting enzyme inhibitors, statins, and insulin have been shown to limit inflammatory response in pneumonia, sepsis, and ARDS in animal models.[7] Third, many of the outcomes that were reported did not have a normal distribution. However, the 2 sample *t* test is quite robust with respect to variables with non-normal distributions at the sample sizes we are using.[32–34] Fourth, the FACTT data de-identification process changed the age and race variables. For any participant older than 89 years old, their age was truncated to 89 years old. The race of participants who did not identify as "black" or "white" were assigned to the category of "other." As the de-identification process modified age and race values, this may have slightly affected the assignment of propensity score values but is unlikely to have significantly changed the results of the final analysis. Larger sample sizes with more granular data would be required to further study this interaction.

5. Conclusion

In this secondary analysis of the Fluid and Catheter Treatment Trial, diabetic participants with ARDS did not have a statistically significant difference in outcomes than non-diabetic participants, when a conservative fluid management strategy was compared to a liberal fluid management strategy. These findings support other recent studies that suggest diabetic status may not be a protective factor in the development of ARDS, or affect ARDS outcomes. Further study is needed to understand how the interplay of the pulmonary effects of diabetes should modify clinical management pathway of lung disease in patients with diabetes, if at all.

Author contributions

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