Online Data Supplement

Relationship between Race and the Effect of Fluids on Long-term Mortality after Acute Respiratory Distress Syndrome: Secondary Analysis of the NHLBI Fluid and Catheter Treatment Trial

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Supplemental Digital Content—1: Baseline characteristics of 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[a])	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[b] 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[c] 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[d]	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

[a]SD: standard deviation, [b]HIV: Human Immunodeficiency Virus, AIDS: Acquired Immunodeficiency Syndrome, [c]APACHE: Acute Physiology and Chronic Health Elements Score, [d]PaO2:FiO2: partial pressure of oxygen to fraction of inspired oxygen ratio

Supplemental Digital Content—2: Mortality status for FACTT and EAPAC participants				
	Included in EAPAC Cohort (N=655)		Not Included in EAPAC (N=345)	
	N	%	N	%
Alive with < 330 days of follow up	89	9	226	23
Alive with > 330 days of follow up	350	35		
Died during hospitalization	165	17	119	12
Died after hospitalization	51	5		

Supplemental Digital Content--3:Propensity Score Strata						
	Non-Hispanic White			**Non-Hispanic Black**		
Female	%		N	%		N
Quartile 1	54		204	55		11
Quartile 2	49		185	55		29
Quartile 3	50		158	37		56
Quartile 4	39		94	45		121
Age	Mean	Standard Deviation (SD)		Mean	SD	
Quartile 1	55	16	204	50	19	11
Quartile 2	51	15	185	55	19	29
Quartile 3	50	17	158	52	17	56
Quartile 4	49	14	94	44	14	121
Acute Physiology Score-APACHE						
Quartile 1	74	27	196	78	35	11
Quartile 2	82	27	178	84	22	29
Quartile 3	96	26	154	97	28	55
Quartile 4	86	30	90	90	32	118
Chronic Health Elements Score-APACHE						
Quartile 1	0.53	2.28	196	0.00	0.00	11
Quartile 2	2.50	5.90	179	2.07	6.12	29
Quartile 3	2.89	6.10	155	2.55	5.55	55
Quartile 4	4.53	7.70	90	6.18	9.58	119
PaO2:FiO2						
Quartile 1	153	65	197	117	37	11
Quartile 2	156	72	174	168	71	26
Quartile 3	148	64	155	154	80	53
Quartile 4	161	66	89	163	88	116
Shock	%			%		
Quartile 1	35		203	40		10
Quartile 2	38		182	36		28
Quartile 3	37		158	32		56
Quartile 4	23		94	30		121

Sensitivity Analysis:

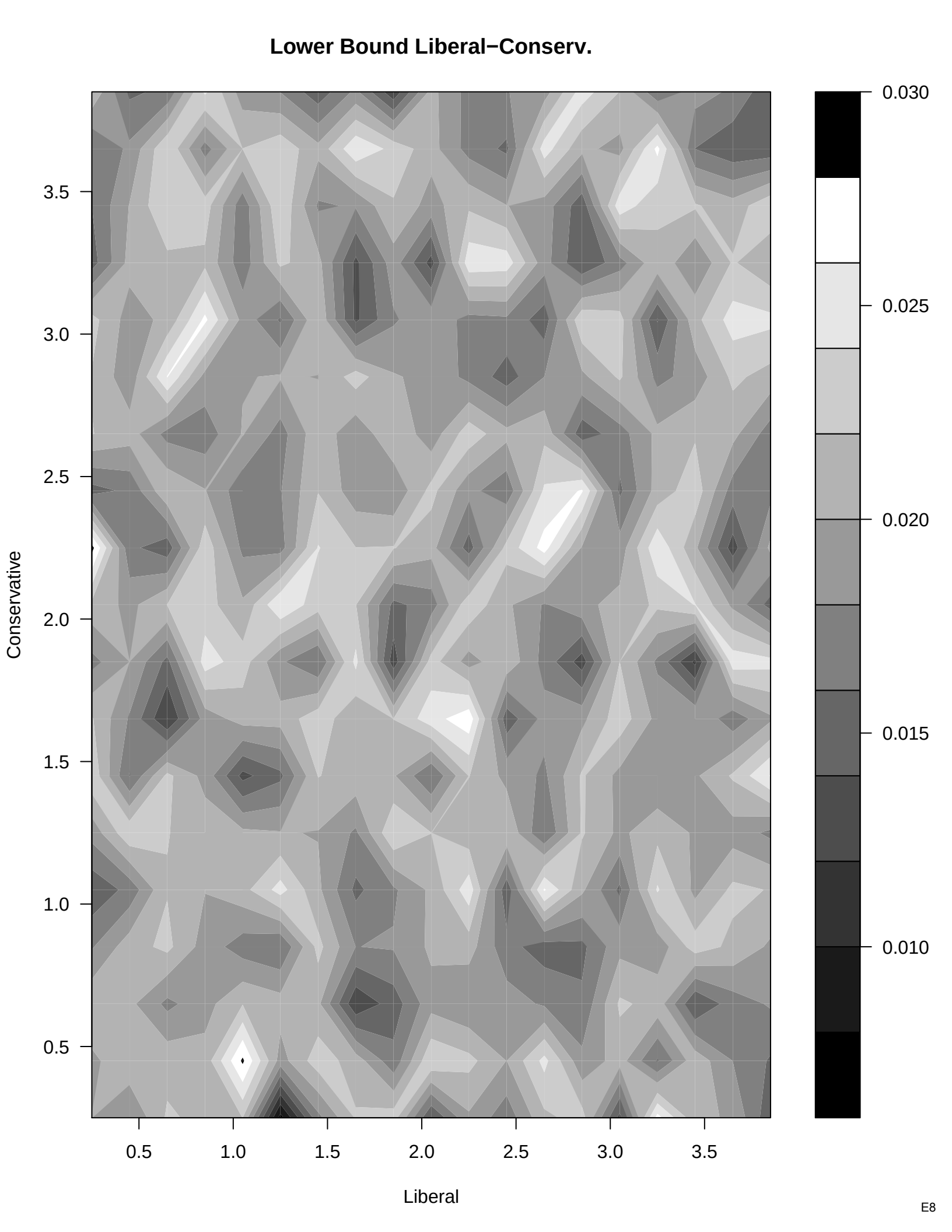
We conducted a sensitivity analysis to determine the effect of missing data on our study findings. We used the method described in http://onlinelibrary.wiley.com/doi/10.1002/sim.6274/abstract but we had to modify it, following the direction of one of the authors, in order to account for the fact that we were using a multi-state model rather than a simple survival model. We used the following approach. First we fit the multi-state model to the data. Then from this model we calculated the probability that each patient would die before one year. For patients who were alive at one year this probability was zero and for those that died it was one. For other patients it was a probability strictly between zero and one. In these cases, we also calculated the standard error of this probability. We focused the sensitivity analysis on the comparison of the treatment groups among black patients because this was the only comparison which was statistically significant. We then conducted a multiple imputation analysis as follows.

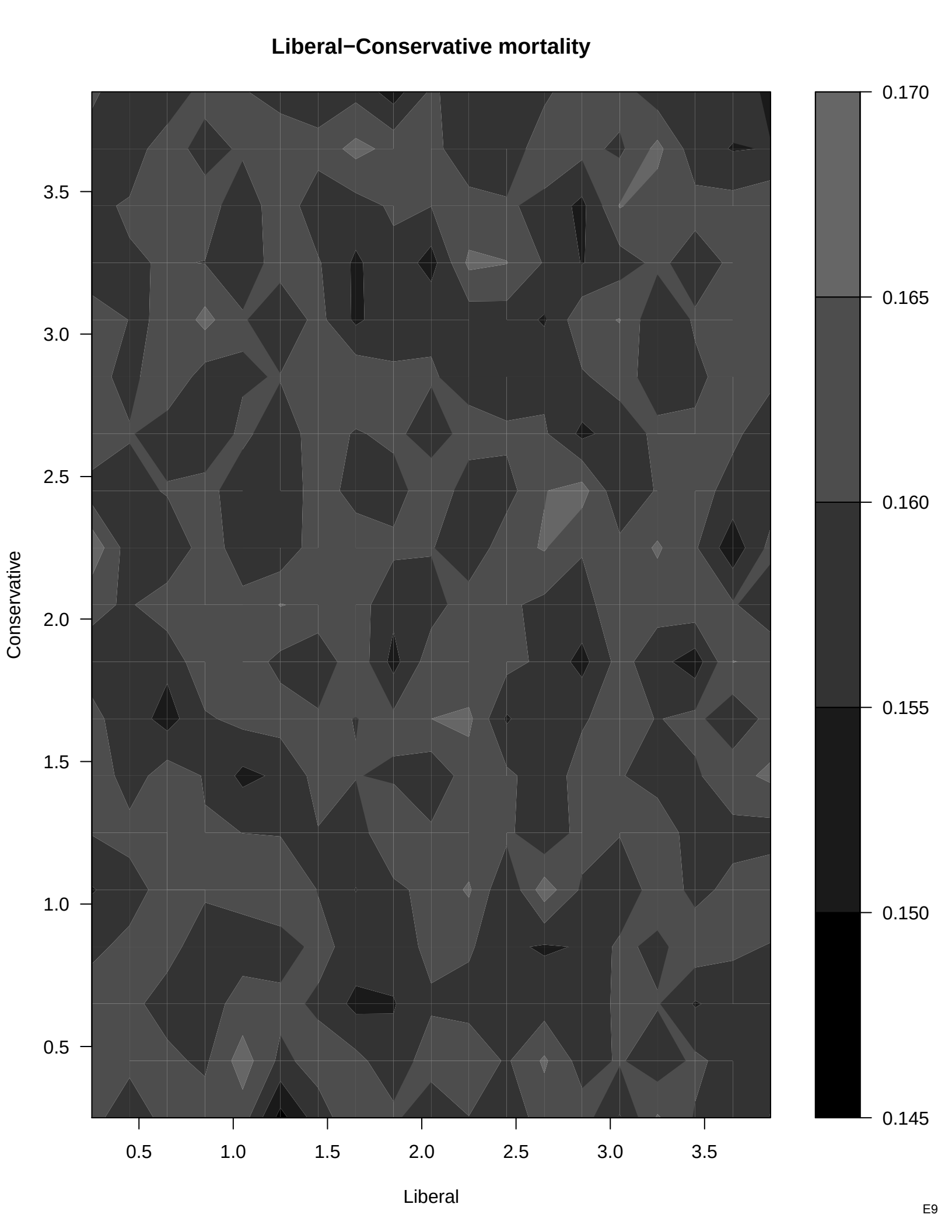
We imputed 100 samples of the binary variable of whether or not the patient died before one year under the assumption of dependent censorship as follows: First we fit a beta distribution to their estimated of probability of death and its standard error. Next, we drew their probability of death from this beta distribution (in order to have a proper imputation, see Rubin) for patients eligible for EAPAC. We then converted these probabilities to odds and multiplied the odds by a factor DL or DC depending on whether they were in the Liberal or Conservative Group respectively. These factors DL and DC ranged from 0.25 to 4, and represent the proportional increase in the odds of death that might occur for a patient after being censored based on their treatment group. When DL and DC equal one the data is *missing at random*. These new odds were then converted back into a probability. No modification was done on the patients who were not eligible for EAPAC (the study had not started when they accrued) because these patients were missing data at random. Finally we used these probabilities to generate binomial random variables as to whether these patients died or not. We then used Rubin's rule to calculate the estimated difference between the treatment groups and its lower 97.5% confidence bound.

Results: The two contour plots show the results of this analysis. Note that even for a differential four fold change in the odds of death the inference is largely unchanged. This is because there are only

15 blacks in the liberal group who were eligible for EAPAC and were missing 1 year follow up. The chance of death in this group ranged from 11% to 26% with a median of 22%. The corresponding conservative group had 12 patients with a range of probabilities from 3% to 9%. Thus even a quite large change in the odds of death had quite a small effect on the inference. The variation in the graph is due to the fact that the multiple imputation was repeated for each choice of DL and DC, so much of the variation is random.

Rubin, D.B. (1976), “Inference and Missing Data,” *Biometrika*, 63, 581–592.


Lower Bound Liberal−Conserv.
Conservative
Liberal
0.5
1.0
1.5
2.0
2.5
3.0
3.5
0.030
0.025
0.020
0.015
0.010


Liberal−Conservative mortality
Conservative
Liberal
0.5
1.0
1.5
2.0
2.5
3.0
3.5
0.170
0.165
0.160
0.155
0.150
0.145