Supplementary Appendix

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This appendix has been provided by the authors to give readers additional information about the work.

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Early Restrictive Versus Liberal Fluid Management for Sepsis-induced Hypotension

Online Supplement

Contents

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Complete Listing of Study Enrollment Criteria

Inclusion Criteria

1. Age ≥ 18 years
2. A suspected or confirmed infection (broadly defined by administration or planned administration of antibiotics)
3. Sepsis-induced hypotension defined as systolic blood pressure < 100 mmHg or MAP < 65 mmHg or receiving a vasopressor infusion after a minimum of at least 1 liter of fluid

(*Fluids inclusive of pre-hospital fluids; blood pressure must be below any known or reported pre-morbid baseline).

Exclusion Criteria

1. More than 4 hours elapsed since meeting inclusion criteria
2. More than 24 hours elapsed since presentation to the hospital
3. Patient already received more than 3 liters of intravenous fluid (includes prehospital volumes)
4. Unable to obtain informed consent
5. Pregnancy
6. Hypotension suspected to be due to non-sepsis cause (e.g. hemorrhagic shock)
7. Blood pressure is at known or reported baseline level
8. Severe Volume Depletion from an acute condition other than sepsis. In the judgment of the treating physician, the patient has an acute condition other than sepsis causing (or indicative) of *severe volume depletion;

Examples include: Diabetic ketoacidosis, high volume vomiting or diarrhea, hyperosmolar hyperglycemic state, and non-exertional hyperthermia (heat stroke); severe is defined by the need for substantial intravenous fluid administration as part of routine clinical care

9. Pulmonary edema or clinical signs of new fluid overload (e.g. bilateral crackles, new oxygen requirement, new peripheral edema, fluid overload on chest x-ray)
10. Treating physician unwilling to give additional fluids as directed by the liberal protocol*
11. Treating physician unwilling to use vasopressors as directed by the restrictive protocol*.
12. Current or imminent decision to withhold most/all life-sustaining treatment; this does not exclude those patients committed to full support except cardiopulmonary resuscitation
13. Immediate surgical intervention planned such that study procedures could not be followed
14. Patient no longer meets the hypotension inclusion criterion (no available SBP < 100 or MAP < 65 within 30 minutes of randomization or not receiving a vasopressor infusion)
15. Prior enrollment in this study

*Patients will be excluded if the attending physicians believes that either study arm is not good clinical care for his/her patient in their clinical judgement

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Tables

Table S1. Additional baseline characteristics

Characteristic*§	Fluid Restrictive (N = 782)	Fluid Liberal (N = 781)	Overall (N=1563)
Most common Primary sources of infection -- no. (%) §§			
Pneumonia	217 (27.7)	205 (26.2)	422 (27.0)
Urinary tract infection	148 (18.9)	172 (22.0)	320 (20.5)
Skin or soft-tissue infection	97 (12.4)	82 (10.5)	179 (11.5)
Intra-abdominal infection	74 (9.5)	72 (9.2)	146 (9.3)
Other source	76 (9.7)	71 (9.1)	147 (9.4)
Unknown source	170 (21.7)	179 (22.9)	349 (22.3)
Coexisting conditions -- no. (%) ‡			
Cirrhosis	30 (3.9)	33 (4.3)	63 (4.1)
Solid tumors	157 (20.2)	140 (18.1)	297 (19.2)
Hematological malignancy	66 (8.5)	51 (6.6)	117 (7.5)
HIV infection or AIDS	22 (2.8)	35 (4.5)	57 (3.7)
Prehospital level of Care			
Home	83.9% (655/781)	83.2% (650/781)	83.5% (1305/1562)
Homeless or living in temporary shelter	31 (4.0%)	3.5% (27/781)	3.7% (58/1562)
Intermediate care or rehab facility	28 (3.6%)	3.6% (28/781)	3.6% (56/1562)
Nursing facility	61 (7.8%)	9.0% (70/781)	8.4% (131/1562)
Route of pre-randomization vasopressor administration -- no. (%) **			
Central line administration	49 (30.4)	36 (25.2)	85 (28.0)
Peripheral line administration	97 (60.2)	95 (66.4)	192 (63.2)
Both	15 (9.3)	12 (8.4)	27 (8.9)
Pre-randomization vasopressor use -- no. (%)	161 (20.6)	143 (18.3)	304 (19.4)
Vasopressor type at randomization			
Norepinephrine	143 (18.3)	129 (16.5)	272 (17.4)
Epinephrine	6 (0.8)	7 (0.9)	13 (0.8)
Vasopressin	6 (0.8)	6 (0.8)	12 (0.8)
Neosynephrine	1 (0.1)	2 (0.3)	3 (0.2)
Dobutamine	0 (0.0)	1 (0.1)	1 (0.1)
Dopamine	1 (0.1)	0 (0.0)	1 (0.1)
ARDS at time of randomization -- no. (%)‡‡	22 (2.8)	20 (2.6)	42 (2.7)

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Met severe hypotension criteria (Baseline SBP <90 mm Hg or on vasopressor) -- no. (%)£	355 (45.4)	352 (45.1)	707 (45.2)
Pre-randomization invasive mechanical ventilation -- no. (%) ††	53 (6.8)	57 (7.3)	110 (7.1)
Pre-randomization NIPPV -- no. (%) ††	30 (3.8)	33 (4.2)	63 (4.0)
Pre-randomization assisted ventilation (invasive mechanical ventilation or NIPPV) -- no. (%)††	72 (9.3)	73 (9.5)	145 (9.4)
Laboratory Testing			
WBC count -- 1000/mm^3 ¶	13.5±10.5	14.1±11.3	13.8±10.9
Creatinine -- mg/dL ¶	1.8±1.7	1.9±1.9	1.9±1.8
Lactate -- mmol/L ¶	2.9±2.5	2.9±2.4	2.9±2.5

*Unless otherwise indicated, plus–minus values are means ±SD.

§ The protocol includes baseline il6 levels. These were not completed and available at the time of publication. We will report baseline and serial levels in a future publication

§§ 5 patients with 'COVID-19 confirmed by testing' were included in pneumonia. 'Other source' includes vascular catheter-related infection, central nervous system infection, endocarditis or endovascular infection, flu/other virus confirmed by testing, and other source of infection.

** Route of pre-randomization vasopressor administration was assessed in 304 patients.
‡ Coexisting conditions were assessed in 1550 patients except for HIV infection or AIDS. HIV infection or AIDS was assessed in 1548 patients.

† Subjects may have received more than one vasopressor.
‡‡ ARDS at time of randomization was assessed in 1559 patients.

£ Includes patients on vasopressors at the time of randomization, including 17% in Liberal Fluid Group and 19% in Restrictive Fluid Group

†† Pre-randomization invasive mechanical ventilation and NIPPV/CPAP were assessed in 1559 patients. Pre-randomization assisted ventilation was assessed in 1547 patients.

¶ Baseline WBC, Creatinine, and Lactate were assessed in 1552, 1541 and 1390 patients respectively.

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Table S2. Initial consent obtained from the patient or from a surrogate

Variable	Restrictive Fluid Group	Liberal Fluid Group	Overall
Subject	65.5% (512/782)	66.7% (521/781)	66.1% (1033/1563)
Legal Authorized Representatives	34.5% (270/782)	33.3% (260/781)	33.9% (530/1563)

percent (N / available records)

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Table S3: Intravenous Fluid Administration by Study Arm After Protocol Period

Variable	Restrictive Fluid Group	Liberal Fluid Group	Difference (95% CI)*
Day 1	604 [141, 1463] (717)	565 [150, 1481] (739)	39 (-95, 172)
Day 2	782 [200, 1616] (663)	800 [236, 1690] (682)	-18 (-164, 128)
Day 3	525 [70, 1260] (590)	506 [82, 1328] (612)	19 (-117, 155)
Day 4	450 [50, 1360] (489)	480 [50, 1200] (516)	-30 (-173, 113)
Day 5	448 [25, 1293] (421)	470 [50, 1120] (433)	-23 (-162, 117)
Day 6	500 [50, 1336] (359)	500 [95, 1199] (367)	0 (-162, 162)
Day 7	440 [30, 1240] (313)	451 [51, 1263] (313)	-11 (-175, 153)

*Confidence intervals have not been adjusted for multiplicity and may not be used for hypothesis testing.

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Table S4. Types and amounts of fluids received during 24-hour protocol period - Restrictive Fluid Group

Fluid Type	Pre-randomization	Hours 0-6	Hours 6-24	Hours 0-24	Pre rand to Hours 24
normal saline	1547±673 (449)	696±564 (182)	667±655 (140)	894±850 (246)	1786±1030 (512)
lactated ringers	1535±610 (412)	905±612 (235)	1213±1155 (177)	1374±1209 (311)	2111±1341 (502)
plasmalyte	1390±725 (30)	807±576 (34)	1004±935 (45)	1297±1123 (56)	1504±1226 (76)
albumin	263±216 (7)	363±211 (6)	458±271 (18)	497±327 (21)	491±377 (25)
IV medications	265±195 (631)	291±249 (573)	565±664 (635)	750±770 (701)	916±801 (756)
blood products	406±168 (15)	437±254 (26)	589±506 (47)	619±499 (63)	626±510 (72)
other	269±278 (30)	265±320 (45)	583±697 (85)	597±781 (103)	575±742 (121)

mean ± standard deviation (N)

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Table S5: Types and amounts of fluids received during 24-hour protocol period - Liberal Fluid Group

Fluid Type	Pre-randomization	Hours 0-6	Hours 6-24	Hours 0-24	Pre rand to Hours 24
normal saline	1558±668 (450)	1582±953 (315)	755±701 (190)	1689±1184 (380)	2437±1560 (551)
lactated ringers	1515±615 (407)	1977±810 (538)	1213±777 (272)	2398±1216 (581)	3253±1568 (618)
plasmalyte	1098±536 (28)	1684±1006 (67)	1205±861 (49)	1791±1094 (96)	2006±1301 (101)
albumin	250±212 (7)	467±606 (9)	375±305 (25)	424±450 (32)	414±472 (37)
IV medications	275±185 (619)	322±315 (564)	526±554 (628)	726±694 (705)	903±732 (756)
blood products	377±289 (10)	552±346 (45)	493±308 (62)	630±422 (88)	651±438 (91)
other	175±217 (33)	233±364 (45)	469±607 (82)	471±638 (104)	456±613 (120)

mean ± standard deviation N

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Table S6. Adherence to study protocol treatment guidance across time *

	1st quarter of records (mean date: 03MAY2018)	2nd quarter of records (mean date: 29JUL2018)	3rd quarter of records (mean date: 28OCT2018)	4th quarter of records (mean date: 26NOV2020)
Restrictive Fluid Group – no./total no. (%)	43/43 (100)	43/44 (98)	52/53 (98)	45/49 (92)
Liberal Fluid Group – no./total no. (%)	49/52 (94)	50/51 (98)	40/42 (95)	45/47 (96)
Overall – no./total no. (%)	92/95 (97)	93/95 (98)	92/95 (97)	90/96 (94)

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Table S7. Description and Impact of Change to Fluid Liberal Protocol in CLOVERS October 2019 Amendment

Item	Description
Description of fluid cessation during 2000 cc infusion component of Protocol Change to Liberal Fluid Arm	In response to correspondence and input from the Office of Human Research Protections, an amendment to the protocol was made that included adding a clinical evaluation at the end of the first 1000 cc with the following instruction: "If blood pressure and heart rate have normalized (SBP ≥ 110 mmHg or MAP ≥ 70 mmHg and HR < 90 bpm) and clinical assessment is patient is volume replete, team may forego second liter and move to 500cc boluses based on fluid triggers… otherwise, continue with second 1000 cc infusion"
Fluid Liberal Arm Patients Enrolled Before and After Amendment	There were 499 patients enrolled in the fluid liberal arm prior to the amendment and 282 patients enrolled in the fluid liberal arm after the amendment.
Number of patients where fluid stopped after first liter	There were 38/282 (13.5%) patients in the fluid liberal arm after implementation of the amendment who had the 2000cc infusion halted after the first 1000cc for being fluid replete.
Overall Change in 6-hour fluid infusion before and after the amendment	The amount of fluids administered to patients in the fluid liberal arm during the initial 6-hours was a mean±SD of 2500 ± 43 cc in the period before the amendment as compared to 2103 ± 45 cc after the period of the amendment.
Clinical Impact on Mortality Prior to Discharge Home at 90 days (primary outcome)	The mortality rate for the restrictive arm was 13.5% versus 14.7% for the liberal arm prior to the protocol amendment with an absolute difference of -1.2% (95% CI: -5.5 to 3.2%), and 14.9% versus 15.4%, respectively, after the amendment with an absolute difference of -0.5% (95% CI: -6.4% to 5.5%). The p-value for interaction between time period (before vs after the protocol amendment) and mortality prior to discharge home at 90 days (primary outcome) was 0.855. (Figure S6)

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Table S8. ICU admission rate for each study arm*

Variable percent (N)	Restrictive Fluid Group	Liberal Fluid Group	Difference (95% CI) ‡
ICU admission hours 0-24£	525 (67.3%)	462 (59.2%)	8.1% (3.3%, 12.8%)
ICU Admission day 0-7££	545 (70.0%)	480 (61.6%)	8.3% (3.7%, 13.0%)

*This is a requested post-hoc analysis

£ Data on ICU admission hours 0-24 were available for 1560 patients (for 780 in the restrictive-fluid group and 780 in the liberal-fluid group).
££ Data on ICU Admission day 0-7 were available for 1558 patients (for 779 in the restrictive-fluid group and 779 in the liberal-fluid group).
‡ Confidence intervals have not been adjusted for multiplicity and may not be used for hypothesis testing.

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Table S9. DSMB Futility Assessment at Second Interim Analysis

Stage	Effective Sample Size	Information Proportion (%)	Efficacy - Lower p-value boundary favoring restrictive fluid group	Futility - Lower p-value boundary favoring restrictive fluid group	Futility - Upper p-value boundary favoring liberal fluid group	Efficacy - Upper p-value boundary favoring liberal fluid group	Observed p-value	Action
1	834	35.96	0.0004182	.	.	0.99958	0.20951	Continue
2	1540	66.39	0.00466	0.27104	0.72896	0.99534	0.21857	Continue
3	2320	100.0	0.02362	0.02362	0.97638	0.97638	.	

Table S10: Mortality Estimate at 2nd Interim

Variable	Liberal Fluid Group	Restrictive Fluid Group	Difference	Overall	P-value
Mortality Estimates	0.150±0.013	0.136±0.012	-.014±0.018	0.143±0.009	0.437

Mortality Estimate ± StdErr
p value is calculated from Wald test

Based on these analyses, the DSMB and NHLBI issued the following statement:

The DSMB unanimously recommended that the CLOVERS study stop. The decision was based on the result that the primary and secondary outcomes did not show any significant difference between the liberal and restrictive arms. The likelihood of showing a significant difference even if a total of 2,320 patients were enrolled is exceedingly small. The additional knowledge to be gained by allowing the study to go to completion did not justify the small risk to participants from continuing the study. The DSMB conclusion was based upon the 90-day mortality estimates, futility analysis, survival curves, secondary analysis, stochastic estimates, and the consent, which states that the objective of the study is to determine whether one approach provides a survival benefit.

NHLBI Determination

- The DSMB recommended that the trial should stop enrollment
- Stop active intervention under the protocol
- Continue follow up of patients already enrolled
- The DSMB had no safety concerns

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Table S11. Patient location and vital status to day 90

Variable	Restrictive Fluid Group	Liberal Fluid Group	Overall
Alive but not home yet	5.8% (45/782)	7.3% (57/781)	6.5% (102/1563)
Arrive home alive	79.7% (623/782)	77.3% (604/781)	78.5% (1227/1563)
Censored	0.6% (5/782)	0.5% (4/781)	0.6% (9/1563)
Dead before arriving home	13.9% (109/782)	14.9% (116/781)	14.4% (225/1563)

percent (N / available records)

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Table S12. Reported Adverse events during hospitalization by organ system and severity*

Organ System	Severity	Restrictive Fluid Group	Liberal Fluid Group	Overall	P-value
Blood And Lymphatic System Disorders	Non-serious	0	3	3	0.763
	Serious	2	0	2	
Cardiac Disorders	Non-serious	1	6	7	0.013
	Serious	3	10	13	
Gastrointestinal Disorders	Serious	2	0	2	0.157
General Disorders And Administration Site Conditions	Serious	2	5	7	0.257
Hepatobiliary Disorders	Serious	1	0	1	0.317
Infections And Infestations	Serious	2	3	5	0.655
Metabolism And Nutrition Disorders	Serious	1	0	1	0.317
Musculoskeletal And Connective Tissue Disorders	Non-serious	1	0	1	0.317
Nervous System Disorders	Non-serious	1	0	1	0.096
	Serious	2	0	2	
Renal And Urinary Disorders	Non-serious	0	1	1	0.317
	Serious	2	0	2	
Respiratory, Thoracic And Mediastinal Disorders	Non-serious	0	4	4	0.480
	Serious	1	0	1	
Skin And Subcutaneous Tissue Disorders	Serious	0	1	1	0.317
Vascular Disorders	Non-serious	1	0	1	0.052
	Serious	3	0	3	

* p values are calculated from weighted Poisson regression. Weight for 'serious' adverse event is 2, weight for 'non-serious' adverse event is 1. unit of the analysis is adverse event.

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Table S13. Specific adverse events during hospitalization and severity*

Organ System	Events	Severity	Restrictive Fluid Group	Liberal Fluid Group	Overall	P-value
Blood And Lymphatic System Disorders	Anemia	Non-serious	0	2	2	1.000
		Serious	1	0	1	
	Coagulopathy	Non-serious	0	1	1	0.317
	Thrombocytopenia	Serious	1	0	1	0.317
Cardiac Disorders	Bradycardia	Non-serious	0	1	1	0.317
	Cardiac Arrest	Serious	1	2	3	0.564
	Chest Pain	Non-serious	1	0	1	0.317
	Flash Pulmonary Edema	Serious	0	1	1	0.317
	Fluid Overload	Non-serious	0	3	3	0.020
		Serious	0	3	3	
	Myocardial Ischemia, Elevated Troponin	Serious	0	1	1	0.317
	Polymorphic Vt	Serious	1	0	1	0.317
	Pulmonary Edema	Non-serious	0	1	1	0.096
		Serious	0	2	2	
	Supraventricular Tachycardia	Serious	1	0	1	0.317
	Tachycardia	Serious	0	1	1	0.317
	Transfusion Associated Circulatory Overload	Non-serious	0	1	1	0.317
Gastrointestinal Disorders	Gastrointestinal Bleeding	Serious	2	0	2	0.157
General Disorders And Administration Site Conditions	Death	Serious	1	4	5	0.180
	Multiple Organ Dysfunction Syndrome	Serious	1	0	1	0.317
	Readmit	Serious	0	1	1	0.317
Hepatobiliary Disorders	Cholangitis	Serious	1	0	1	0.317

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Organ System	Events	Severity	Restrictive Fluid Group	Liberal Fluid Group	Overall	P-value
Infections And Infestations	Cellulitis	Serious	0	1	1	0.317
	Pneumonia	Serious	1	0	1	0.317
	Sepsis	Serious	0	2	2	0.157
	Septic Shock	Serious	1	0	1	0.317
Metabolism And Nutrition Disorders	Lactic Acidosis	Serious	1	0	1	0.317
Musculoskeletal And Connective Tissue Disorders	Rhabdomyolysis	Non-serious	1	0	1	0.317
Nervous System Disorders	Cerebral Infarct	Serious	1	0	1	0.317
	Seizure	Serious	1	0	1	0.317
	Seizure Vs Syncope Vasovagal	Non-serious	1	0	1	0.317
Renal And Urinary Disorders	Hematuria	Serious	1	0	1	0.317
	Renal Calculus	Non-serious	0	1	1	0.317
	Worsening Kidney Failure	Serious	1	0	1	0.317
Respiratory, Thoracic And Mediastinal Disorders	Hypoxia	Non-serious	0	1	1	0.317
	Pneumothorax	Serious	1	0	1	0.317
	Respiratory Failure	Non-serious	0	1	1	0.317
	Shortness Of Breath	Non-serious	0	1	1	0.317
	Worsening Hypoxia	Non-serious	0	1	1	0.317
Skin And Subcutaneous Tissue Disorders	Blisters	Serious	0	1	1	0.317
Vascular Disorders	Hypotension	Serious	1	0	1	0.317
	Peripheral Ischemia	Serious	2	0	2	0.157
	Thrombosis Venous Deep	Non-serious	1	0	1	0.317

* p values are calculated from weighted Poisson regression. Weight for 'serious' adverse event is 2, weight for 'non-serious' adverse event is 1. unit of the analysis is adverse event.

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Table S14. Listing of adverse events during hospitalization - Restrictive Fluid Group

Organ	Events	Severity	Event Day	Unexpected	Study Related	AE Status When Reported	Final Outcome
Blood And Lymphatic System Disorders	Anemia	Serious	7	Yes	Definitely not related	AE present, being treated	Residual effect / being treated
	Thrombocytopenia	Serious	2	No	Definitely not related	Recovered	Recovered
Cardiac Disorders	Cardiac Arrest	Serious	2	No	Definitely not related	Residual effect / being treated	Residual effect / being treated
	Chest Pain	Non-serious	1	No	Probably or possibly related	Recovered	Recovered
	Polymorphic Vt	Serious	1	Yes	Probably not related	Recovered	Recovered
	Supraventricular Tachycardia	Serious	1	No	Probably or possibly related	Recovered	Recovered
Gastrointestinal Disorders	Gastrointestinal Bleeding	Serious	2	No	Definitely not related	Recovered	Recovered
		Serious	2	Yes	Definitely not related	AE present, being treated	Recovered
General Disorders And Administration Site Conditions	Death	Serious	4	No	Probably not related	Deceased as a result of the AE	Deceased as a result of the AE
	Multiple Organ Dysfunction Syndrome	Serious	3	No	Definitely not related	AE present, being treated	Recovered

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Organ	Events	Severity	Event Day	Unexpected	Study Related	AE Status When Reported	Final Outcome
Hepatobiliary Disorders	Cholangitis	Serious	3	No	Definitely not related	AE present, being treated	Recovered
Infections And Infestations	Pneumonia	Serious	5	No	Definitely not related	Deceased as a result of the AE	Deceased as a result of the AE
	Septic Shock	Serious	0	No	Probably not related	Deceased as a result of the AE	Deceased as a result of the AE
Metabolism And Nutrition Disorders	Lactic Acidosis	Serious	1	No	Probably not related	Deceased as a result of the AE	Deceased as a result of the AE
Musculoskeletal And Connective Tissue Disorders	Rhabdomyolysis	Non-serious	1	No	Probably or possibly related	Recovered	Recovered
Nervous System Disorders	Cerebral Infarct	Serious	9	No	Probably not related	Residual effect / no treatment	Residual effect / no treatment
	Seizure	Serious	0	Yes	Definitely not related	Recovered	Recovered
	Seizure Vs Syncope Vasovagal	Non-serious	0	Yes	Probably not related	Recovered	Recovered
Renal And Urinary Disorders	Hematuria	Serious	12	Yes	Definitely not related	AE present, being treated	AE present, being treated
	Worsening Kidney Failure	Serious	2	Yes	Probably not related	AE present, being treated	AE present, being treated
Respiratory, Thoracic And Mediastinal Disorders	Pneumothorax	Serious	1	No	Probably not related	Recovered	Recovered
Vascular Disorders	Hypotension	Serious	5	No	Definitely not related	Recovered	Recovered

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Organ	Events	Severity	Event Day	Unexpected	Study Related	AE Status When Reported	Final Outcome
	Peripheral Ischemia	Serious	1	No	Probably or possibly related	AE present, no treatment	Residual effect / being treated
		Serious	3	No	Probably not related	AE present, being treated	AE present, being treated
	Thrombosis Venous Deep	Non-serious	3	Yes	Definitely not related	AE present, no treatment	AE present, no treatment

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Table S15. Listing of Adverse events during hospitalization - Liberal Fluid Group

Organ	Events	Severity	Event Day	Unexpected	Study Related	AE Status When Reported	Final Outcome
Blood And Lymphatic System Disorders	Anemia	Non-serious	0	No	Probably or possibly related	AE present, no treatment	AE present, no treatment
		Non-serious	1	No	Probably or possibly related	AE present, being treated	AE present, being treated
	Coagulopathy	Non-serious	2	Yes	Definitely not related	Recovered	Recovered
Cardiac Disorders	Bradycardia	Non-serious	1	No	Probably not related	Recovered	Recovered
	Cardiac Arrest	Serious	0	Yes	Definitely not related	Deceased as a result of the AE	Deceased as a result of the AE
		Serious	0	Yes	Definitely not related	Recovered	Recovered
	Flash Pulmonary Edema	Serious	3	No	Probably not related	Recovered	Recovered
	Fluid Overload	Serious	3	No	Probably not related	Recovered	Recovered
		Non-serious	0	No	Probably or possibly related	Recovered	Recovered
		Non-serious	3	No	Probably not related	Recovered	Recovered
		Non-serious	6	No	Probably or possibly related	AE present, being treated	Residual effect / being treated
		Serious	1	No	Probably or possibly related	Deceased as a result of the AE	Deceased as a result of the AE
		Serious	0	No	Probably or possibly related	Recovered	Recovered

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Organ	Events	Severity	Event Day	Unexpected	Study Related	AE Status When Reported	Final Outcome
	Myocardial Ischemia, Elevated Troponin	Serious	0	Yes	Probably not related	AE present, being treated	AE present, being treated
	Pulmonary Edema	Serious	0	No	Probably or possibly related	AE present, being treated	AE present, being treated
		Serious	0	No	Probably or possibly related	AE present, being treated	AE present, being treated
		Non-serious	0	No	Probably or possibly related	Recovered	Recovered
	Tachycardia	Serious	0	No	Probably not related	Recovered	Recovered
	Transfusion Associated Circulatory Overload	Non-serious	0	No	Probably or possibly related	Recovered	Recovered
General Disorders And Administration Site Conditions	Death	Serious	5	No	Definitely not related	Deceased as a result of the AE	Deceased as a result of the AE
		Serious	4	Yes	Definitely not related	Deceased as a result of the AE	Deceased as a result of the AE
		Serious	2	No	Definitely not related	Deceased as a result of the AE	Deceased as a result of the AE
		Serious	7	No	Definitely not related	Residual effect / no treatment	Residual effect / no treatment
	Readmit	Serious	5	No	Definitely not related	AE present, being treated	AE present, being treated
Infections And Infestations	Cellulitis	Serious	35	Yes	Probably not related	AE present, being treated	AE present, being treated
	Sepsis	Serious	2	No	Probably not related	Recovered	Recovered

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Organ	Events	Severity	Event Day	Unexpected	Study Related	AE Status When Reported	Final Outcome
		Serious	4	No	Probably not related	Deceased as a result of the AE	Deceased as a result of the AE
Renal And Urinary Disorders	Renal Calculus	Non-serious	1	Yes	Definitely not related	Recovered	Recovered
Respiratory, Thoracic And Mediastinal Disorders	Hypoxia	Non-serious	0	No	Probably or possibly related	Recovered	Recovered
	Respiratory Failure	Non-serious	1	No	Probably or possibly related	Residual effect / no treatment	Residual effect / being treated
	Shortness Of Breath	Non-serious	0	No	Probably or possibly related	Recovered	Recovered
	Worsening Hypoxia	Non-serious	0	No	Probably or possibly related	Recovered	Recovered
Skin And Subcutaneous Tissue Disorders	Blisters	Serious	2	Yes	Probably not related	AE present, being treated	AE present, no treatment

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Table S16. New ventilation and oxygen use prior to and during the 24-hour protocol period

New ventilation and oxygen use – no. (%)	N		Fluid Restrictive (N = 782)	Fluid Liberal (N = 781)	Difference (95% CI)*
High Flow O_2 (Before Randomization)	1559	Yes	37 (4.7)	41 (5.3)	-0.5% (-2.7%, 1.6%)
NIPPV/CPAP (Before Randomization)	1559	Yes	30 (3.8)	33 (4.2)	-0.4% (-2.3%, 1.6%)
Invasive Ventilation (Before Randomization)	1559	Yes	53 (6.8)	57 (7.3)	-0.5% (-3.1%, 2.0%)
New High Flow O_2 (0-6 Hours)	1481	Yes	18 (2.4)	32 (4.3)	-1.9% (-3.8%, -0.1%)
New NIPPV/CPAP (0-6 Hours)	1496	Yes	7 (0.9)	12 (1.6)	-0.7% (-1.8%, 0.5%)
New Invasive Ventilation (0-6 Hours)	1449	Yes	24 (3.3)	19 (2.6)	0.7% (-1.1%, 2.4%)
New High Flow O_2 (0-24 Hours)	1481	Yes	24 (3.2)	41 (5.6)	-2.3% (-4.4%, -0.2%)
New NIPPV/CPAP (0-24 Hours)	1496	Yes	17 (2.3)	25 (3.4)	-1.1% (-2.8%, 0.6%)
New Invasive Ventilation (0-24 Hours)	1449	Yes	45 (6.2)	49 (6.8)	-0.6% (-3.1%, 1.9%)

*Confidence intervals have not been adjusted for multiplicity and may not be used for hypothesis testing.

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Table S17. Line complications during hospitalization related to central venous catheter placement among patients who had a central venous line inserted between randomization and 72 hours

Complications *		Fluid Restrictive (N=208)	Fluid Liberal (N=155)	Difference (95% CI)	P-value
Any line complications of central venous catheter placement †	Yes	8 (3.8)	6 (3.9)	0.0% (-4.8%, 4.1%)	1.000
Catheter-related bloodstream infection	Yes	0 (0.0)	0 (0.0)		.
Catheter-related deep vein thrombosis	Yes	1 (0.5)	3 (1.9)	-1.5% (-5.1%, 1.0%)	0.317
Pneumothorax	Yes	1 (0.5)	0 (0.0)	0.5% (-1.9%, 2.7%)	1.000
Arterial injury	Yes	0 (0.0)	0 (0.0)		.
Venous injury	Yes	0 (0.0)	0 (0.0)		.
Post-procedural hemorrhage	Yes	0 (0.0)	0 (0.0)		.
Post-procedural hematoma	Yes	1 (0.5)	0 (0.0)	0.5% (-1.9%, 2.7%)	1.000
Ventricular arrhythmia	Yes	2 (1.0)	1 (0.6)	0.3% (-2.7%, 2.9%)	1.000
Atrial arrhythmia	Yes	5 (2.4)	2 (1.3)	1.1% (-2.4%, 4.4%)	0.703
Infusion site extravasation	Yes	0 (0.0)	0 (0.0)		.
Air embolism	Yes	0 (0.0)	0 (0.0)		

* Significance test is Fisher's Exact Test. Confidence Intervals are estimated by Miettinen-Nurminen method.

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Table S18: Additional outcomes

Outcome *	N	Fluid Restrictive (N = 782)	Fluid Liberal (N = 781)	Difference (95% CI) ‡
Central venous line insertion between randomization and 72 hours	1559	208 (26.7)	155 (19.9)	6.8% (2.6%, 11.0%)
Vasopressor infusion through peripheral venous catheter between randomization and 72 hours	1559	310 (39.7)	190 (24.4)	15.4% (10.8%, 19.9%)

* The percentage and mean were calculated from the non-missing records.
† Significance test is Fisher's Exact Test. Confidence Intervals are estimated by Miettinen-Nurminen method.
‡ Confidence intervals have not been adjusted for multiplicity and may not be used for hypothesis testing.

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Table S19. Complications of peripheral venous catheter vasopressor infusion to day 28 among patients who received vasopressors through a peripheral catheter inserted between randomization and 72 hours

Complications *		Fluid Restrictive (N=310)	Fluid Liberal (N=190)	Difference (95% CI) ‡	P-value
Site extravasation	Yes	3 (1.0)	0 (0.0)	1.0% (-1.0%, 2.8%)	0.292

* Significance test is Fisher's Exact Test. Confidence Intervals are estimated by Miettinen-Nurminen method.

‡ Confidence intervals have not been adjusted for multiplicity and may not be used for hypothesis testing.

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Table S20. Representativeness of study participants in the CLOVERS trial.

Category	Description
Disease under investigation	Sepsis with hypotension; a serious infection with low blood pressure treated at a hospital
Special considerations related to:	
Sex and gender	In the CLOVERS trial, 47% of participants were female. This is consistent with the epidemiology of sepsis, in which approximately half of sepsis cases occur in females and half occur in males. [1-3] During conduct of the trial, we collected sex based on information reported in the hospital medical record system, which usually reflects biological sex assigned at birth. We did not collect information on gender.
Age	In the CLOVERS trial, we enrolled adults (aged ≥18 years old). We did not enroll children because the approach to intravenous fluids and vasopressors is different between adults and children, and in the United States, children and adults are often treated in different hospital settings (e.g., children's hospitals versus adult hospitals). Among adults, sepsis is more common in older people, especially those over 65 years old. Median age for participants in the CLOVERS trial was 59.5 years. This age distribution is similar to estimates for patient with sepsis presenting to the emergency department in the United States. Ranging from 62.7 years[1] to 65.1 years.[3] Table S21
Race or ethnic group	Sepsis affects adults of all races and ethnicities. We sought for the CLOVERS population to closely resemble the race and ethnicity distribution of the adult population in the United States. The race and ethnicity distribution of participants in the CLOVERS trial included White 71%, Black 16%, Asian 4%, and Hispanic 15%. The adult population in the 2020 US census (US Census Bureau, www.census.gov) included: White 64%, Black 12%, Asian 6%, and Hispanic 17%. These data suggest that compared to the overall adult US population, the CLOVERS trial included slightly more people of White and Black race and slightly fewer people of Asian race and Hispanic ethnicity. Further, these race and ethnicity distributions mirror frequencies amongst patient presenting to emergency departments and admitted for sepsis in the USA. [1-3] Table S21
Geography	This trial was conducted in the United States only. While the results likely generalize well to sepsis care in the United States, they may not generalize to other settings, particularly those in more resource-limited areas without widespread access to advanced critical care medicine. In the CLOVERS trial, we found that use of a restrictive fluids strategy and liberal fluids strategy resulted in similar mortality prior to discharge before day 90 for adults hospitalized with sepsis-induced hypotension. Overall, results of this trial were similar those reported from the CLASSIC 2 trial which was conducted in Europe. [4] However, the results from CLOVERS and CLASSIC 2 were different from recent trials evaluating intravenous fluid volume for sepsis patients in sub-Saharan Africa, including the FEAST trial[5] and the Simplified Severe Sepsis Protocol 2 Trial.[6] Both of these sub-Saharan African trials reported better outcomes for patients treated with a restrictive fluid protocol compared to a liberal fluid protocol.
Overall representativeness of this trial	The distributions of sex, age, race, and ethnicity among participants in the CLOVERS trial were similar to those expected for a population of adults in the United States hospitalized with sepsis. Trial results are expected to generalize to the adult population in the United States. The trial did not attempt to enroll children or patients outside the United States, and results may not generalize well to these populations.

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Table S21. Comparison of CLOVERS with Other Studies

	Wang [1] 2009–2011	Ramgopal [2] 2016-2018	Chan [3] 2016-2019	CLOVERS 2018-2022
Variable				
Age (Mean ± SD)	62.7±19.8	Not reported.	65.1±17.1	59.5±15.9
Male sex (%)	44.7	53.2	52.7	52.8
Race (% of total)				
White	79.6	79.5	67.2	70.7
Black	17.2	16.7	18.1	15.8
Other	3.2	**	3.3	13.8
Non-Hispanic ethnicity[a]	93.1	89.5		81.5

Table S21 includes demographics for ED Sepsis visits amongst adults ≥ 18 years old

Methods:

To determine the representativeness of the enrolled CLOVERS patient population, we performed a PubMed search focusing on the contemporaneous epidemiology of septic shock amongst adults in North America. We identified 3 studies covering the period of 2011-2019 describing the epidemiology of the adult septic shock population. The overall representativeness of the CLOVERS trial was established by comparing the distributions of sex, age, race, and ethnicity among participants in the CLOVERS trial with those expected for a population of adults predominantly evaluated and managed for sepsis related hypotension and shock in United States.

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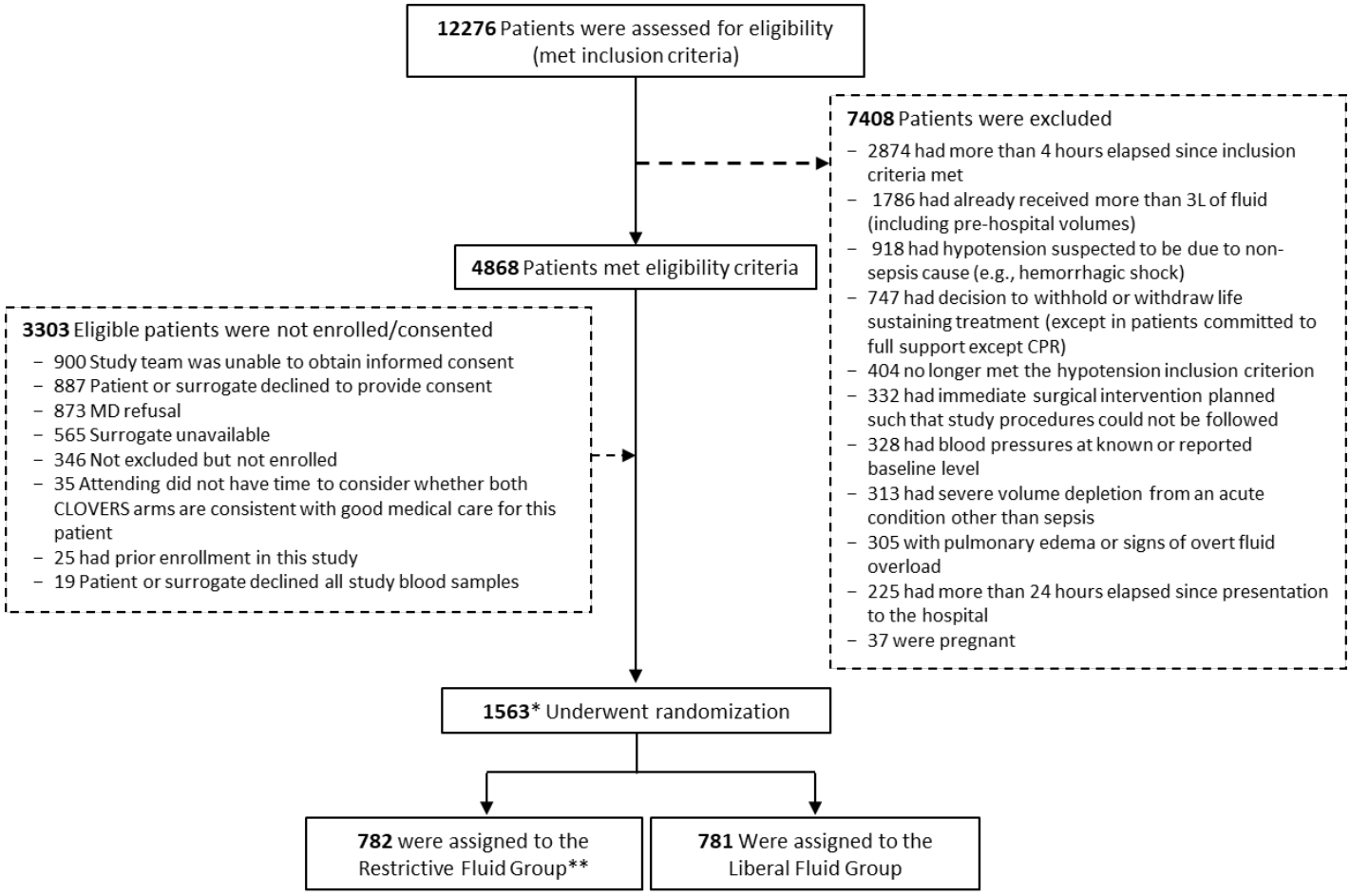
Figures

Figure S1. CONSORT flow diagram.



**One participant was randomized to restrictive and 4 months later randomized to liberal fluid.*
***One participant was randomized to restrictive but received liberal fluid.*

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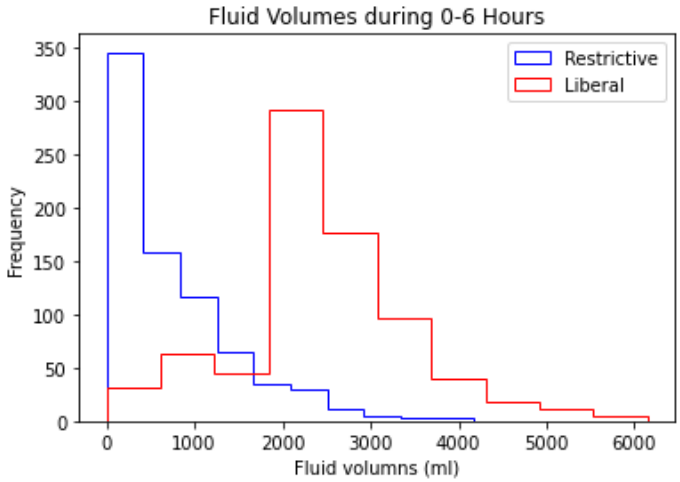
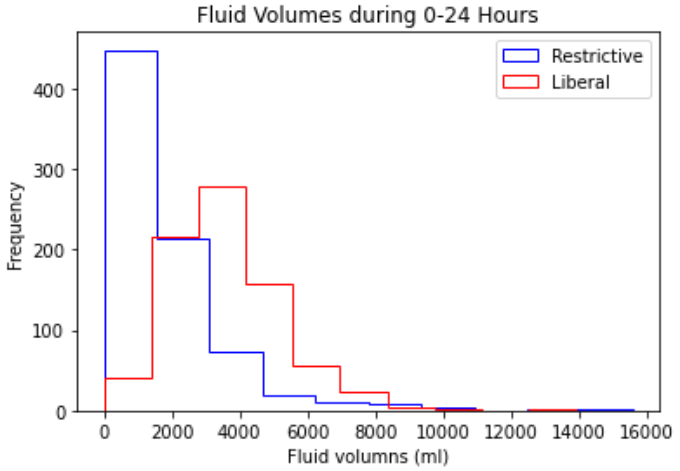
Figure S2. Fluid volumes and vasopressor hours stratified by treatment groups. (a) Fluid volumes during 0-6 hours, (b) fluid volumes during 0-24 hour, (c) total vasopressor hours.





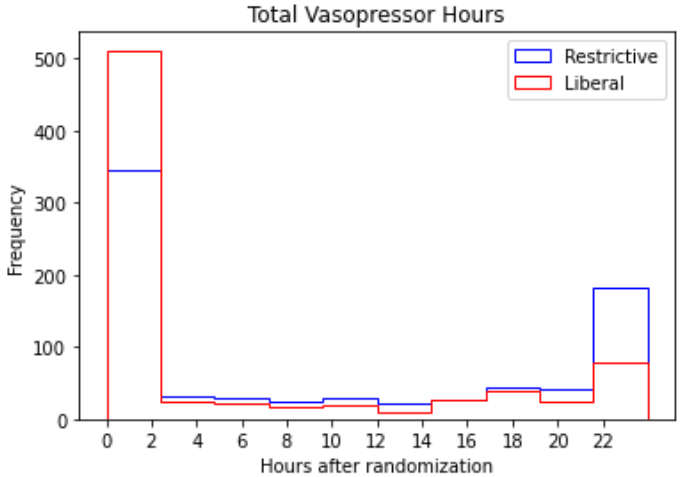


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Figure S3. Total fluid volume stratified by treatment groups

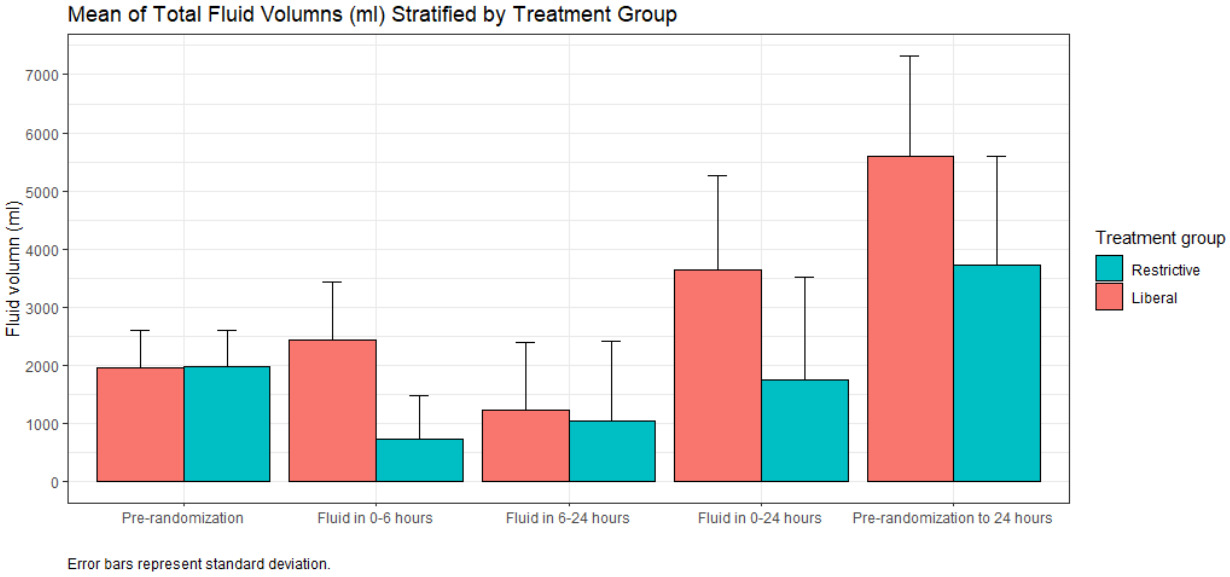

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Figure S4. Survival curve: patients who survived to discharge home during the first 90 days after randomization.

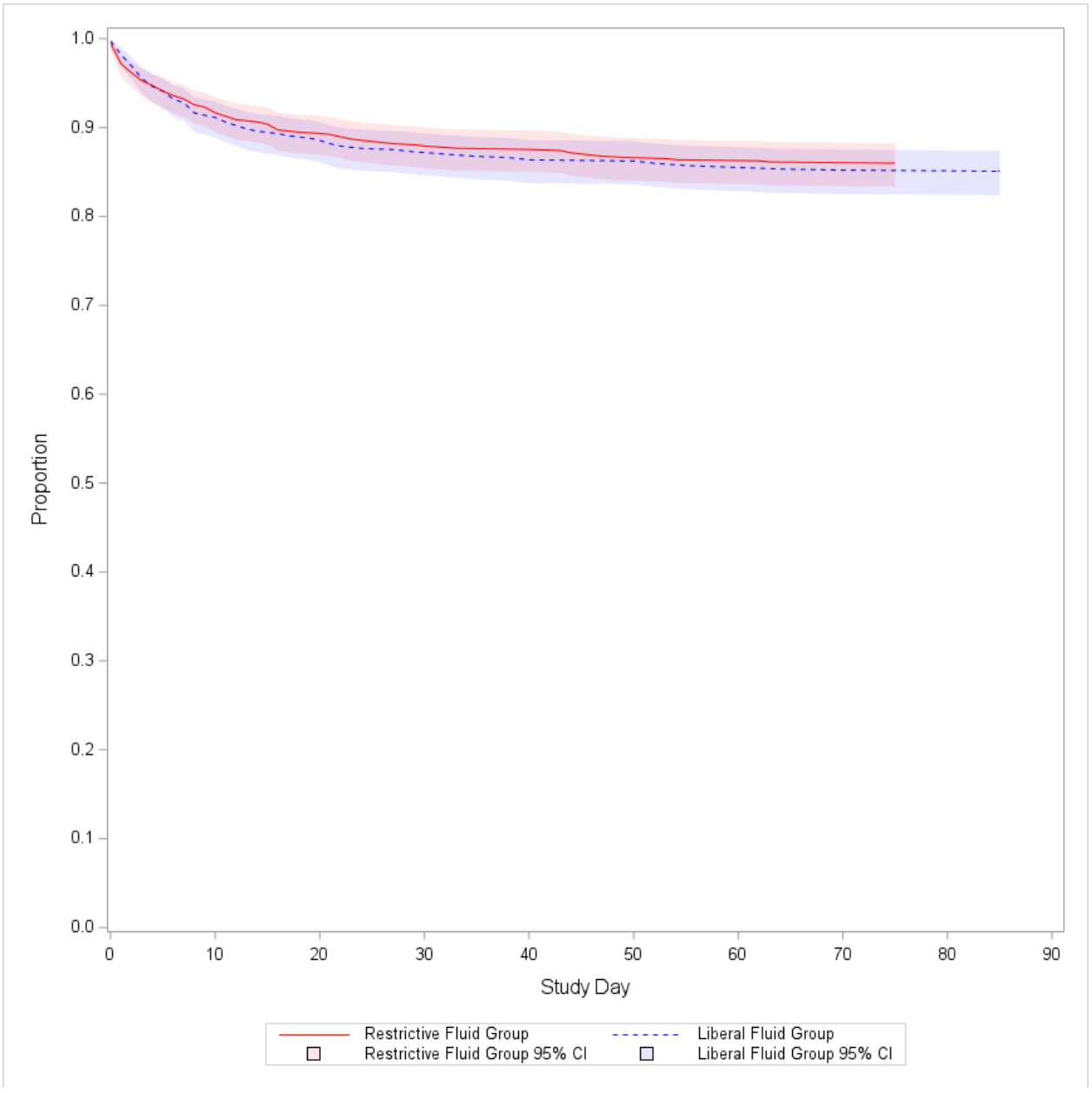

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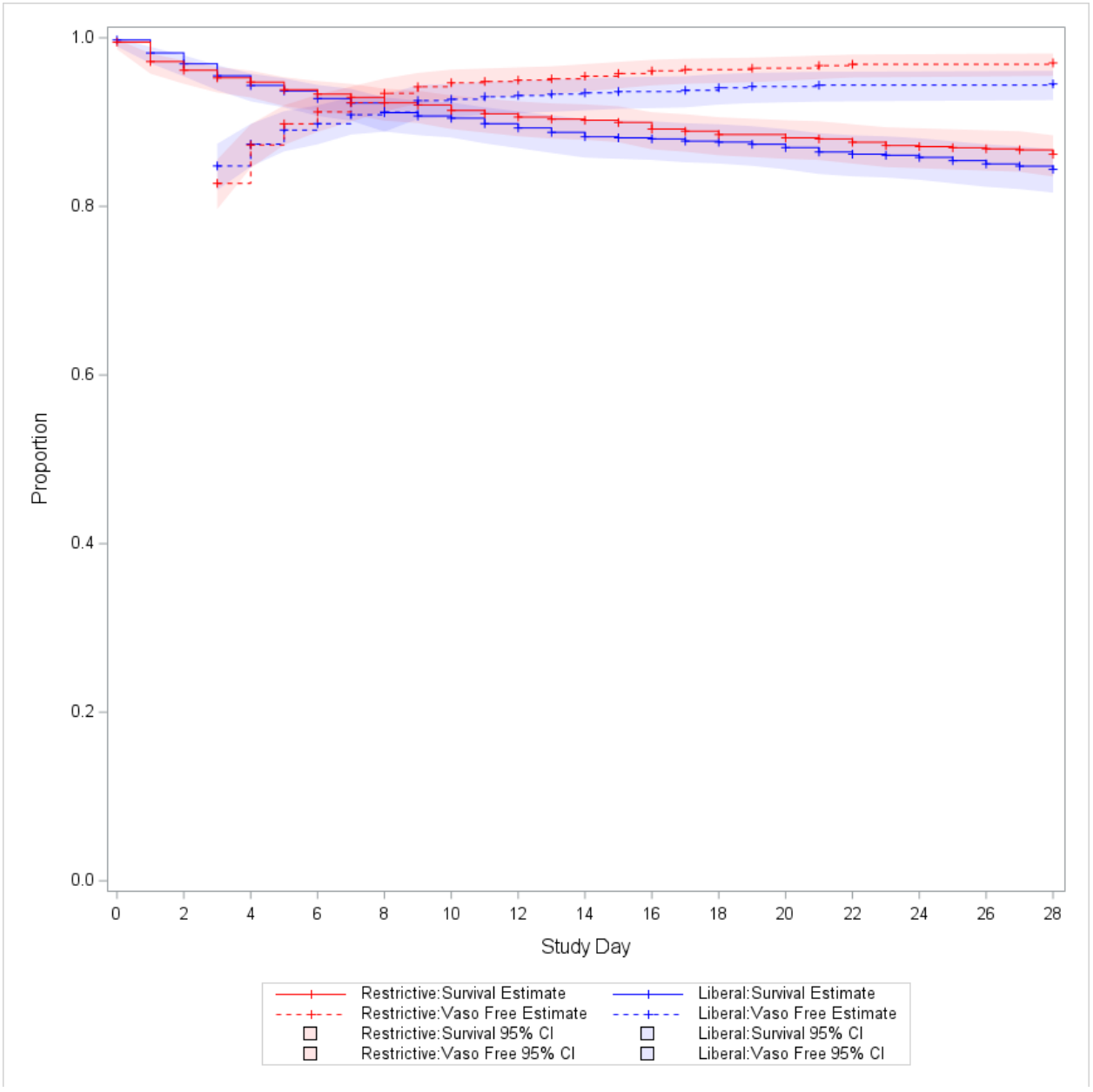
Figure S5. Patients who survived to 28-day and were (a) vasopressor-free, (b) ventilator-free and (c) support-free (ventilator-free, vasopressor-free and RRT-free).

(a) Curves for survival and vasopressor freedom.



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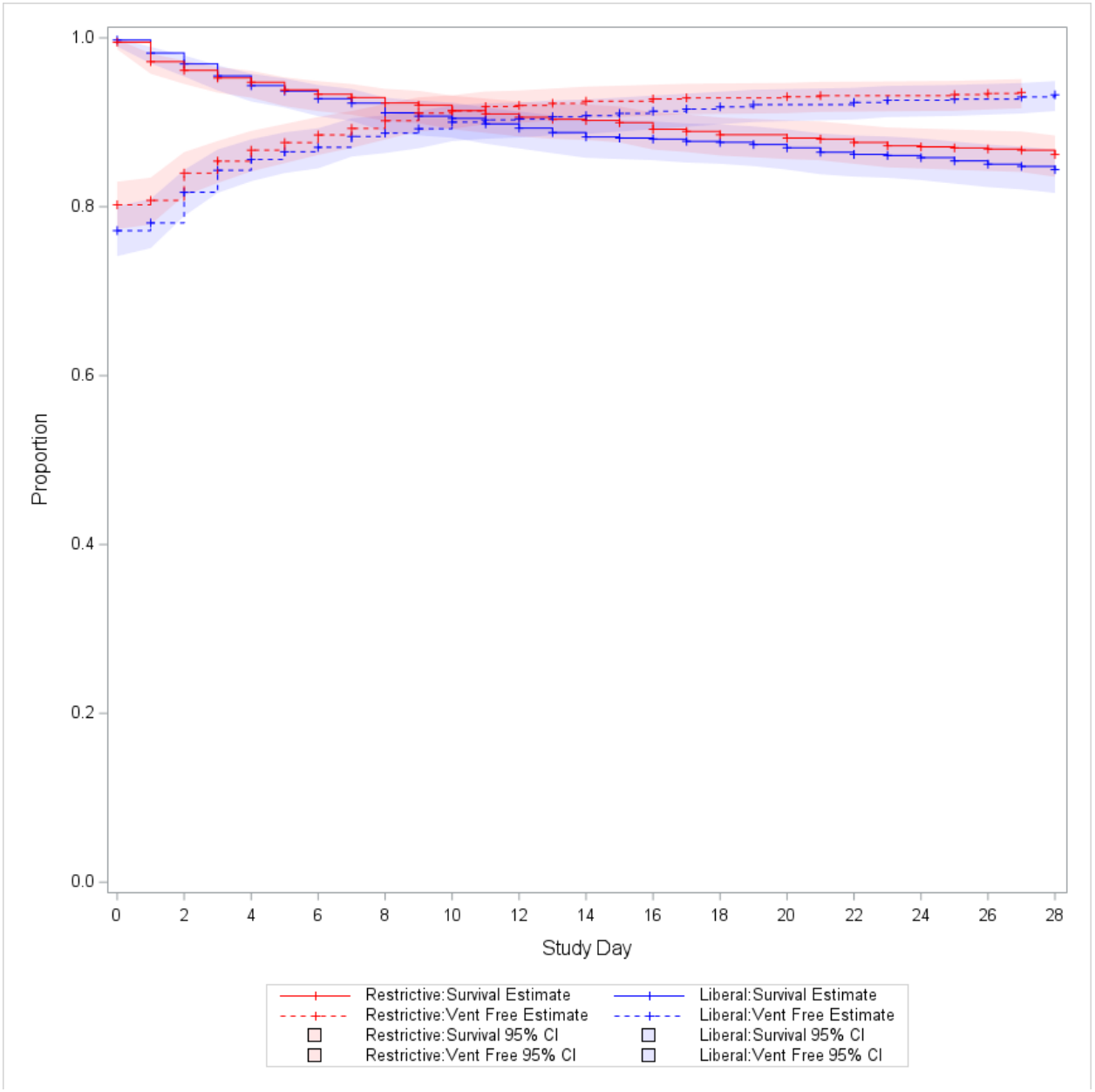
(b) Curves for survival to 28-days and ventilator freedom.



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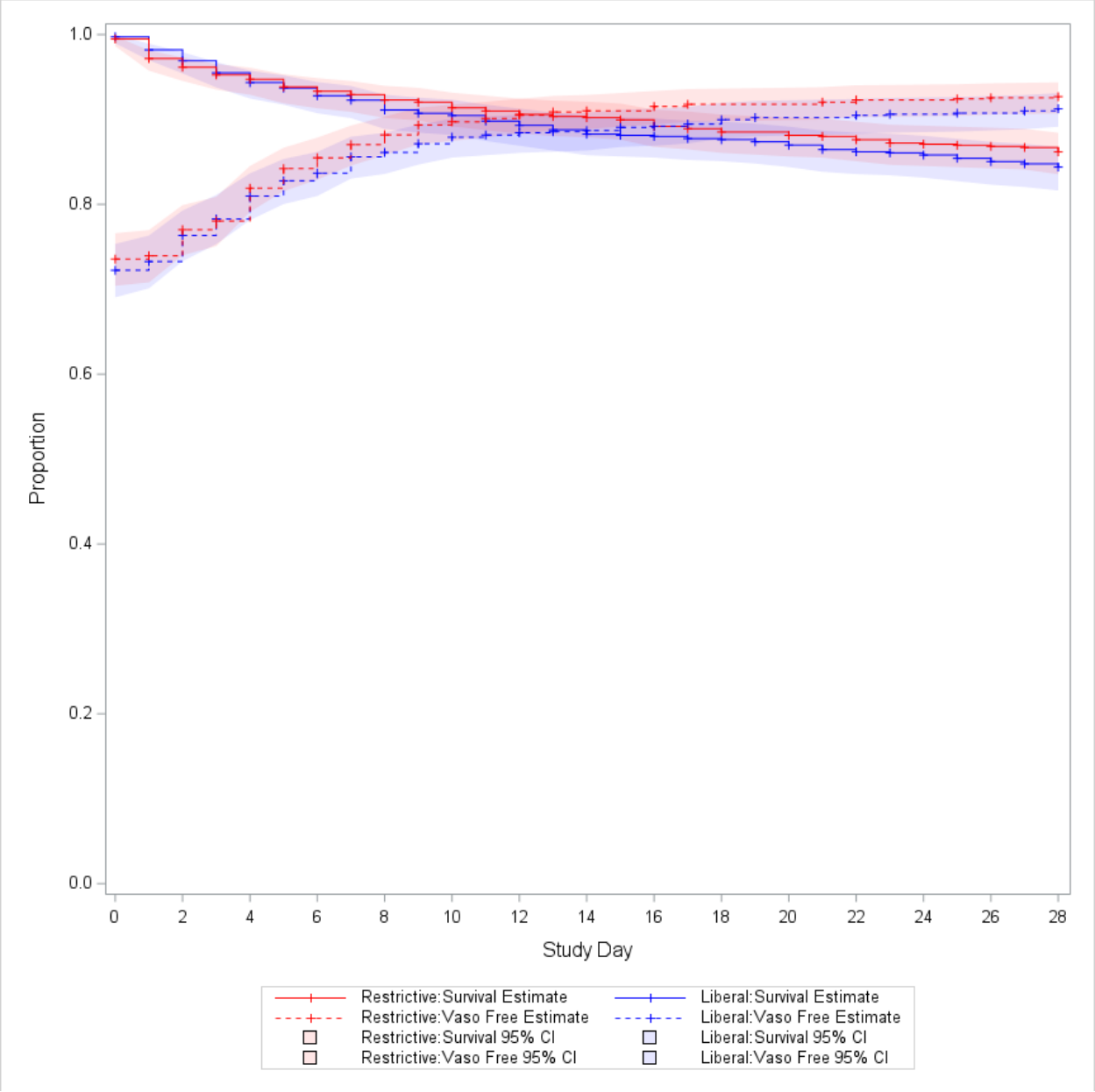
(c) Curves for survival to 28-days and combined vasopressor, ventilator, and renal replacement freedom.



The support-free curves above can cross the survival curves because patients can be free of support and still die prior to Day 28.

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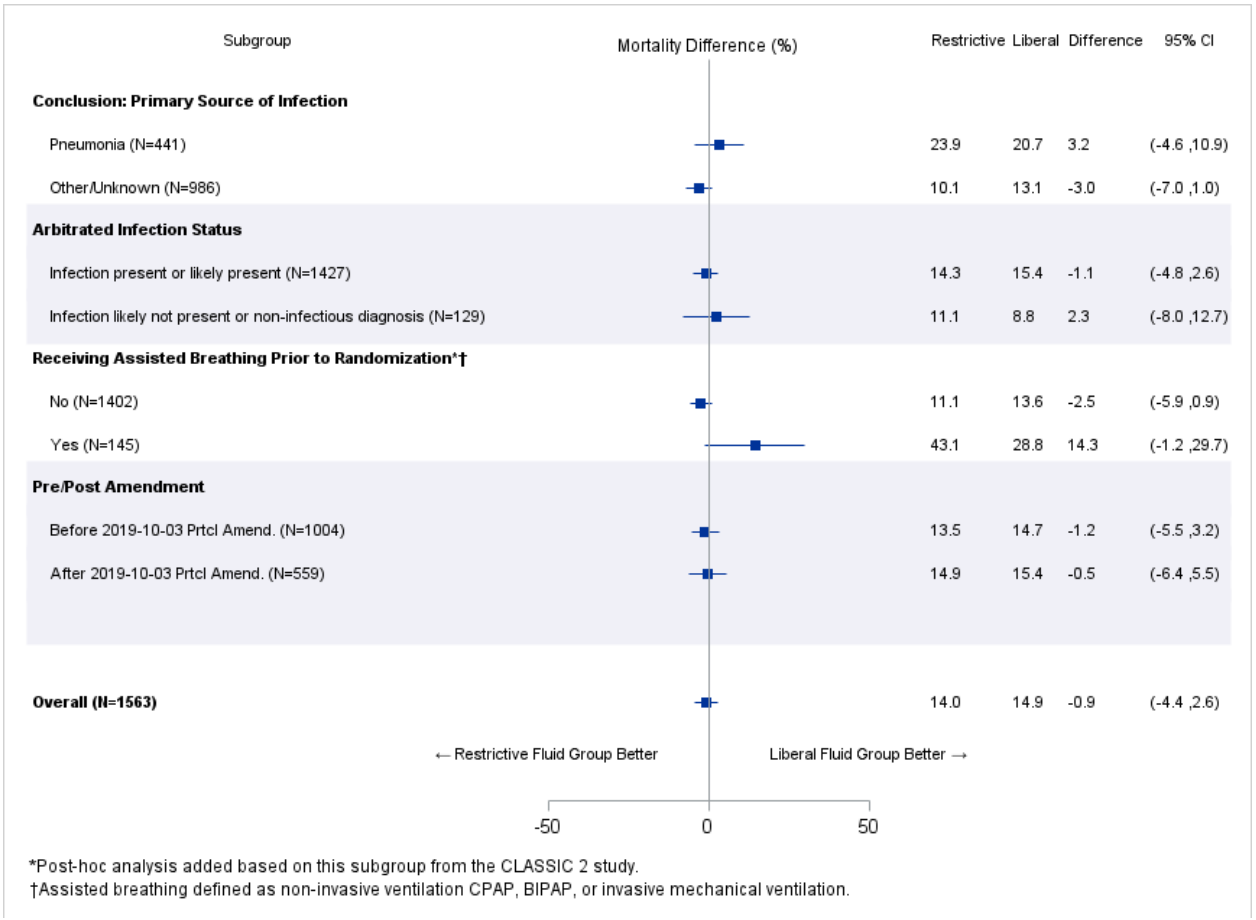
Figure S6. Additional subgroup analysis‡.



‡Confidence intervals have not been adjusted for multiplicity and may not be used for hypothesis testing.

Based on results from the CLASSIC II trial[15], we added an assessment of those receiving assisted breathing (non-invasive or invasive ventilation) at randomization. This subgroup demonstrated a 14.3% (1.2% to 29.7%) absolute difference in mortality prior to discharge home before day 90, favoring the liberal fluid group. This difference is the opposite direction of the CLASSIC II findings which favored their restrictive fluid group receiving assisted ventilation at randomization. Given the findings in differing directions, post-hoc nature in our study, and low power, the data do not currently support a particular approach for this subgroup.

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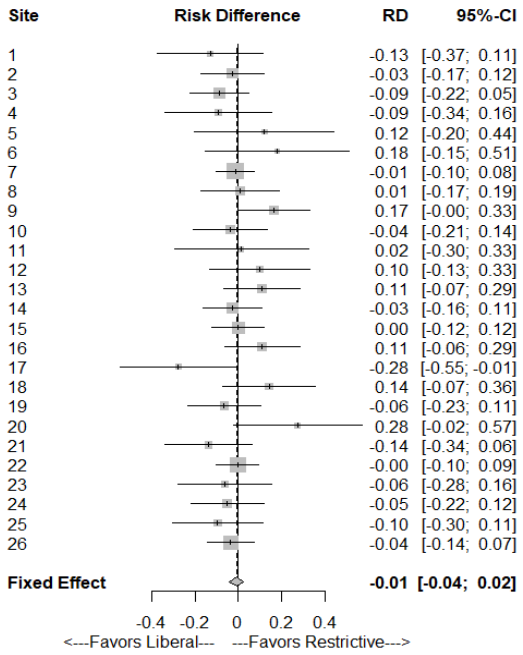
Figure S7: Risk Difference Stratified by Site‡



‡Confidence intervals have not been adjusted for multiplicity and may not be used for hypothesis testing.

Methods

Meta-analysis for the primary endpoint by site was performed using the fixed effect model. We excluded 9 censored subjects leaving a total 225 deaths out of 1554 subjects for analysis. We pooled 26 sites with fewer than 20 subjects each into a single site. The pooled risk difference between Restrictive and Liberal groups was estimated by the inverse-variance (IV) method. Cochran's Q statistic was used to test the heterogeneity by site. Results produced with the R statistical package meta, version 6.0-0.

Meta-analysis interpretation

Overall pooled risk difference with 95% confidence interval is -0.0077 (-0.0398, 0.0243). Cochran's Q statistic is 25.97, we fail to reject the null hypothesis that the true treatment effect is the same across sites

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Supplement References

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2. Ramgopal S, Horvat CM, Adler MD. Varying Estimates of Sepsis among Adults Presenting to US Emergency Departments: Estimates from a National Dataset from 2002-2018. J Intensive Care Med 2022;37(11):1451-1459. DOI: 10.1177/08850666221080060.
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