Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

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Acetaminophen and Ascorbate in Sepsis: Targeted Therapy to Enhance Recovery (ASTER)

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II. Supplemental Tables

eTable 1. Plasma biomarker levels at baseline and study day 2 and day 3 by treatment group

Analyte		Acetaminophen	Placebo	Change from Baseline		
				Acetaminophen	Placebo	p value
Interleukin-6 (pg/mL)	Baseline	31.8 [15.5, 170.0] 219	37.2 [14.9, 103.3] 213			
	Day 2	13.9 [6.6 40.0] 195	18.7 [7.3, 45.1] 188	-19.1 [-127.3, -1.7] 190	-16.2 [-76.2, 0.0] 186	0.27
	Day 3	11.5 [5.3, 24.3] 180	13.7 [6.3, 31.4] 174	-22.8 [-130.5, -3.9] 175	-18.3 [-82.1, -0.9] 171	0.20
Angiopoietin-2 (pg/mL)	Baseline	9144 [5518, 15877] 219	9521 [5513, 19963] 212			
	Day 2	7467 [4838 13151] 195	8006 [4930, 14610] 187	-1519 [-6215, 2339] 190	-1696 [-6162, 1367] 184	0.56
	Day 3	6420 [4291, 10952] 180	7024 [4230, 10504] 174	-2218 [-6961, 1135] 175	-2775 [-8990, -24] 170	0.23
TNF Receptor-1 (pg/mL)	Baseline	5379 [3567, 10064] 218	6520 [3441, 10630] 211			
	Day 2	4626 [2923, 7626] 195	5273 [3031, 8850] 187	-537 [-2147, 787] 190	-669 [-2535, 474] 183	0.31
	Day 3	4630 [2741, 7431] 179	4825 [3280, 8537] 173	-735 [-2336, 410] 174	-956 [-3509, 323] 169	0.30
Syndecan-1 (ng/mL)	Baseline	150.0 [99.0, 285.0] 219	144.5 [97.3, 245.2] 213			
	Day 2	150.9 [100.7, 329.5] 192	132.9 [94.4, 269.1] 188	3.9 [-56.1, 92.5] 187	-6.4 [-57.1, 69.3] 186	0.41
	Day 3	171.7 [109.5, 414.2] 179	141.9 [98.2, 274.1] 172	21.5 [-66.2, 138.3] 174	3.6 [-42.8, 66.4] 169	0.42

Analyte				Change from Baseline		
		Acetaminophen	Placebo	Acetaminophen	Placebo	p value
Cell-free DNA (ng/uL)	Baseline	1.17 [0.94, 1.61] 218	1.16 [0.92, 1.65] 213			
	Day 2	1.05 [0.89, 1.40] 193	1.08 [0.93, 1.48] 187	-0.09 [-0.43, 0.18] 187	-0.04 [-0.29, 0.28] 185	0.05
	Day 3	1.07 [0.86, 1.47] 178	1.11 [0.90, 1.45] 171	-0.05 [-0.39, 0.20] 173	-0.08 [-0.37, 0.22] 168	0.97
Cell-free Hemoglobin (mg/dL)	Baseline	8.3 [4.4, 17.0] 218	8.5 [4.6, 18.6] 212			
	Day 2	7.0 [4.1, 13.1] 191	6.7 [4.3, 10.9] 187	-1.2 [-8.9, 4.4] 185	-1.2 [-8.4, 3.2] 184	0.87
	Day 3	6.3 [4.2, 13.3] 177	6.7 [3.8, 12.5] 171	-1.0 [-10.0, 3.8] 171	-2.2 [-9.7, 5.0] 167	0.99

Median [q1, q3] N

p-value is from Wilcoxon Rank-Sum Test

eTable 2. Daily AST, ALT and Bilirubin levels in acetaminophen and matched placebo*

		Acetaminophen	Placebo	Difference (95% CI)	P-value
AST (U/L)	Baseline	45.5 (35.0), 227	40.4 (37.2), 199	5.1 (-1.8, 11.9)	0.15
	Day 1	68.7 (208.9), 176	48.1 (52.6), 144	20.6 (-14.5, 55.7)	0.25
	Day 2	54.5 (198.9), 211	54.0 (224.0), 189	0.5 (-41.1, 42.0)	0.98
	Day 3	44.0 (50.3), 191	43.2 (111.5), 178	0.7 (-16.8, 18.2)	0.93
	Day 4	56.3 (111.8), 178	49.2 (119.8), 164	7.1 (-17.6, 31.7)	0.57
	Day 5	51.7 (101.4), 161	169.9 (1571.5), 145	-118.2 (-362.4, 126.0)	0.34
	Day 6	51.7 (67.7), 102	210.0 (1667.5), 95	-158.3 (-484.2, 167.5)	0.34
	Day 7	40.4 (40.0), 116	35.2 (38.7), 98	5.3 (-5.4, 15.9)	0.33
ALT (U/L)	Baseline	30.9 (26.6), 227	31.0 (34.2), 199	-0.1 (-5.9, 5.7)	0.97
	Day 1	44.6 (101.9), 178	36.7 (46.4), 145	7.9 (-10.1, 25.9)	0.39
	Day 2	44.0 (149.1), 211	42.0 (140.0), 188	2.0 (-26.6, 30.6)	0.89
	Day 3	39.2 (67.9), 191	38.5 (120.5), 178	0.7 (-19.1, 20.6)	0.94
	Day 4	46.3 (84.1), 178	41.8 (129.2), 164	4.6 (-18.5, 27.6)	0.70
	Day 5	45.3 (92.3), 162	70.8 (474.5), 146	-25.5 (-100.4, 49.3)	0.50
	Day 6	46.9 (75.3), 102	88.6 (542.7), 95	-41.7 (-148.7, 65.3)	0.44
	Day 7	36.3 (37.8), 117	29.4 (29.2), 98	6.9 (-2.3, 16.1)	0.14
Bilirubin (mg/dL)	Baseline	0.9 (0.9), 225	0.9 (1.0), 197	0.0 (-0.2, 0.2)	0.82
	Day 1	0.9 (1.1), 169	0.9 (1.0), 138	0.1 (-0.2, 0.3)	0.60
	Day 2	0.8 (1.1), 187	0.7 (0.9), 175	0.0 (-0.2, 0.2)	0.65
	Day 3	0.7 (0.9), 175	0.7 (0.9), 159	-0.0 (-0.2, 0.2)	0.88
	Day 4	0.7 (1.0), 162	0.7 (0.9), 150	-0.0 (-0.2, 0.2)	0.78
	Day 5	0.7 (0.9), 146	0.8 (0.9), 137	-0.0 (-0.2, 0.2)	0.82
	Day 6	0.7 (0.7), 101	0.8 (0.9), 90	-0.1 (-0.3, 0.2)	0.57
	Day 7	0.7 (0.8), 109	0.8 (1.2), 88	-0.1 (-0.4, 0.2)	0.38

AST, aspartate aminotransferase; ALT, alanine aminotransferase
*Mean (SD), N. P-value is calculated from two sample t-test.

eTable 3. Fluid balance (ml) by study day*

	Acetaminophen (N=227)	Placebo (N=220)	Difference (95% CI)	P-value
Day 1	612.3 (1616.3), 215	732.9 (3370.0), 209	-120.6 (-622.9, 381.8)	0.64
Day 2	277.3 (1808.5), 174	246.9 (1464.2), 172	30.4 (-317.8, 378.6)	0.86
Day 3	125.7 (1705.7), 124	-8.1 (1535.0), 136	133.8 (-262.0, 529.5)	0.51
Day 4	131.7 (1610.7), 99	39.0 (1760.3), 107	92.7 (-372.0, 557.4)	0.70
Day 5	-304.4 (1600.5), 81	-209.4 (1607.6), 92	-95.0 (-577.5, 387.5)	0.70
Day 6	-154.5 (1563.0), 70	57.5 (1098.8), 75	-212.0 (-653.1, 229.2)	0.34
Day 7	-258.4 (1754.8), 53	90.1 (1479.6), 62	-348.5 (-946.0, 248.9)	0.25

*Mean (SD), N

P-value is calculated from two-sample t-test

eTable 4a. Adverse events by organ system and severity in acetaminophen and matched placebo

Organ	Severity	Acetaminophen (N=227)	Placebo (N=199)	Overall (N=426)	P-value
Blood And Lymphatic System Disorders	Non-severe	1 (0.44%)	3 (1.51%)	4 (0.94%)	0.34
Cardiac Disorders	Non-severe	1 (0.44%)	1 (0.5%)	2 (0.47%)	1.00
	Severe	2 (0.88%)	3 (1.51%)	5 (1.17%)	0.67
Endocrine Disorders	Non-severe	1 (0.44%)	0 (0%)	1 (0.23%)	1.00
Gastrointestinal Disorders	Non-severe	1 (0.44%)	0 (0%)	1 (0.23%)	1.00
	Severe	1 (0.44%)	0 (0%)	1 (0.23%)	1.00
General Disorders and Administration Site Condition	Non-severe	0 (0%)	1 (0.5%)	1 (0.23%)	0.47
	Severe	0 (0%)	1 (0.5%)	1 (0.23%)	0.47
Hepatobiliary Disorders	Non-severe	1 (0.44%)	0 (0%)	1 (0.23%)	1.00
Infections And Infestations	Non-severe	0 (0%)	1 (0.5%)	1 (0.23%)	0.47
	Severe	2 (0.88%)	1 (0.5%)	3 (0.7%)	1.00
Investigations	Non-severe	4 (1.76%)	0 (0%)	4 (0.94%)	0.13
	Severe	8 (3.52%)	5 (2.51%)	13 (3.05%)	0.59
Metabolism And Nutrition Disorders	Non-severe	1 (0.44%)	1 (0.5%)	2 (0.47%)	1.00
Musculoskeletal And Connective Tissue Disorders	Severe	1 (0.44%)	0 (0%)	1 (0.23%)	1.00
Renal And Urinary Disorders	Non-severe	1 (0.44%)	0 (0%)	1 (0.23%)	1.00
Respiratory, Thoracic And Mediastinal Disorders	Non-severe	2 (0.88%)	1 (0.5%)	3 (0.7%)	1.00
	Severe	1 (0.44%)	3 (1.51%)	4 (0.94%)	0.34

Skin And Subcutaneous Tissue Disorders	Non-severe	1 (0.44%)	0 (0%)	1 (0.23%)	1.00
Surgical And Medical Procedures	Non-severe	1 (0.44%)	0 (0%)	1 (0.23%)	1.00
Vascular Disorders	Non-severe	1 (0.44%)	0 (0%)	1 (0.23%)	1.00
	Severe	5 (2.2%)	9 (4.52%)	14 (3.29%)	0.28
Any (Total number of events)*	Non-severe	16	8	24	0.10
	Severe	20	24	44	0.55

N (%)
Unit of the analysis is patient except for the total number of events analysis by severity status
*For the total number of severe/non-severe events, p values are calculated from Poisson regression
Other p values are calculated from Fisher's exact test.

eTable 4b. Listings of all adverse events in acetaminophen group

Organ	Events	Severity	Event Day	Unexpected for Acetaminophen	Related to study procedures?	AE Status When Reported	Final Outcome
Blood And Lymphatic System Disorders	Acute Blood Loss Anemia	Non-severe	1	Yes	Definitely not related	AE present, being treated	Recovered
Cardiac Disorders	Heart Failure (Nos)	Severe	2	Yes	Definitely not related	AE present, no treatment	AE present, no treatment
	Paroxysmal Atrial Fibrillation	Non-severe	1	Yes	Definitely not related	AE present, being treated	Recovered
	Supraventricular Tachycardia	Severe	1	Yes	Definitely not related	Recovered	Recovered
Endocrine Disorders	Diabetes Mellitus	Non-severe	1	Yes	Probably not related	AE present, being treated	AE present, being treated
Gastrointestinal Disorders	Bowel Obstruction	Severe	3	Yes	Probably not related	Residual effect / being treated	Recovered
	Dyspepsia	Non-severe	1	Yes	Definitely not related	AE present, being treated	Recovered
Hepatobiliary Disorders	Hepatocellular Damage	Non-severe	3	No	Definitely not related	Residual effect / no treatment	Residual effect / no treatment
Infections And Infestations	Sepsis	Severe	6	No	Definitely not related	Deceased as a result of the AE	Deceased as a result of the AE
	Ventilator Associated Pneumonia	Severe	3	Yes	Definitely not related	AE present, being treated	Deceased as a result of the AE
Investigations	Alanine Aminotransferase Increase, Aspartate Aminotransferase Increased	Non-severe	7	No	Probably not related	Recovered	Recovered

	Alt Increased, AST Increased	Non-severe	5	No	Probably or possibly related	AE present, being treated	AE present, being treated
	AST Increased	Severe	1	No	Probably not related	AE present, being treated	AE present, no treatment
		Severe	3	No	Probably not related	AE present, being treated	Recovered
	Elevated LFTs	Non-severe	1	No	Probably or possibly related	Recovered	Recovered
	Function Liver Abnormal	Severe	1	No	Definitely not related	AE present, no treatment	Recovered
	Hepatic Function Abnormal	Severe	2	No	Probably or possibly related	AE present, being treated	AE present, no treatment
	Liver Enzyme Abnormal	Severe	4	No	Probably or possibly related	Recovered	Recovered
		Severe	1	No	Probably or possibly related	AE present, being treated	Recovered
	Liver Function Tests Multiple Abnormal	Non-severe	7	No	Probably not related	AE present, no treatment	Recovered
		Severe	4	Yes	Probably or possibly related	AE present, no treatment	Recovered
		Severe	0	No	Probably not related	Recovered	Recovered
Metabolism And Nutrition Disorders	Hypokalemia	Non-severe	0	Yes	Probably not related	AE present, being treated	Recovered
Musculoskeletal And Connective Tissue Disorders	Myopathy	Severe	9	Yes	Definitely not related	Residual effect / being treated	Residual effect / being treated
Renal And Urinary Disorders	Kidney Failure Acute	Non-severe	0	Yes	Definitely not related	AE present, no treatment	AE present, being treated
eTable 4c. Listings of all adverse events in matching placebo group	Embolism Pulmonary	Severe	1	Yes	Probably not related	AE present, being treated	Recovered
Respiratory, Thoracic And Mediastinal Disorders	Hypoxia	Non-severe	3	Yes	Definitely not related	Residual effect / no treatment	Residual effect / being treated

	Pneumothorax	Non-severe	3	Yes	Definitely not related	AE present, being treated	AE present, being treated
Skin And Subcutaneous Tissue Disorders	Dermatitis Contact	Non-severe	3	No	Probably or possibly related	AE present, being treated	AE present, being treated
Surgical And Medical Procedures	Transfer Back To ICU	Non-severe	5	No	Definitely not related	AE present, being treated	Recovered
Vascular Disorders	Acute Bilateral Popliteal Arterial Occlusion	Severe	3	Yes	Definitely not related	AE present, being treated	AE present, being treated
	Hypotension	Non-severe	2	No	Definitely not related	Recovered	Recovered
		Severe	1	No	Probably not related	AE present, being treated	Recovered
		Severe	5	No	Probably or possibly related	AE present, being treated	AE present, no treatment
	Infarct Cerebral	Severe	1	No	Definitely not related	AE present, no treatment	AE present, no treatment
	Shock	Severe	5	Yes	Definitely not related	AE present, being treated	Recovered

Organ	Events	Severity	Event Day	Unexpected for Acetaminophen	Related to study procedures?	AE Status When Reported	Final Outcome
Blood And Lymphatic System Disorders	Anemia	Non-severe	2	Yes	Probably not related	AE present, being treated	AE present, being treated
	Thrombocytopenia	Non-severe	1	No	Probably or possibly related	Recovered	Recovered
		Non-severe	1	No	Probably not related	Recovered	Recovered
Cardiac Disorders	Bradycardia	Non-severe	0	Yes	Definitely not related	Recovered	Recovered
	Cardiac Arrest	Severe	5	Yes	Definitely not related	Residual effect / being treated	Deceased as a result of the AE
	Cardiogenic Shock	Severe	1	Yes	Definitely not related	AE present, being treated	AE present, being treated
	Cardiomyopathy	Severe	4	Yes	Definitely not related	Recovered	Recovered
	Coronary Artery Disease	Severe	1	No	Definitely not related	AE present, being treated	AE present, being treated
General Disorders And Administration Site Conditions	Edema Left Leg	Non-severe	5	Yes	Definitely not related	Recovered	Recovered
	Multiple Organ Failure	Severe	9	Yes	Definitely not related	Deceased as a result of the AE	Deceased as a result of the AE
Infections And Infestations	Infection Bacterial	Non-severe	8	Yes	Definitely not related	AE present, being treated	AE present, being treated
	Worsening Infection	Severe	1	Yes	Probably not related	Recovered	Recovered

Investigations	Alt Increased, AST Increased	Severe	7	No	Probably not related	Deceased as a result of the AE	Deceased as a result of the AE
	Aspartate Aminotransferase Increased, Alanine Aminotransferase Increased	Severe	2	No	Probably not related	AE present, no treatment	Recovered
	AST Increased	Severe	4	No	Probably or possibly related	AE present, being treated	AE present, no treatment
	AST Increased; Alt Increased	Severe	4	No	Probably not related	AE present, being treated	AE present, being treated
	Hepatic Function Abnormal	Severe	1	No	Definitely not related	AE present, no treatment	AE present, no treatment
Metabolism And Nutrition Disorders	Hypokalemia	Non-severe	3	Yes	Definitely not related	Recovered	Recovered
Respiratory, Thoracic And Mediastinal Disorders	Coughing	Non-severe	2	Yes	Definitely not related	AE present, no treatment	Recovered
	Pneumothorax	Severe	5	Yes	Definitely not related	Recovered	Recovered
		Severe	1	Yes	Definitely not related	AE present, being treated	AE present, being treated
	Respiratory Failure	Severe	2	No	Definitely not related	Recovered	Recovered
Vascular Disorders	Deep Vein Thrombosis	Severe	4	Yes	Definitely not related	AE present, being treated	AE present, no treatment
	Hypertension	Severe	1	No	Probably not related	AE present, being treated	Recovered
		Severe	3	No	Probably not related	AE present, being treated	Recovered
	Hypotension	Severe	1	No	Probably or possibly related	AE present, being treated	AE present, being treated
		Severe	0	No	Probably not related	AE present, being treated	Recovered

VIII

		Severe	0	No	Probably or possibly related	AE present, being treated	AE present, being treated
		Severe	0	No	Probably not related	Recovered	Recovered
	Left MCA Stroke	Severe	1	Yes	Probably not related	Residual effect / being treated	Residual effect / no treatment
	Retroperitoneal Hemorrhage Grade 4	Severe	5	Yes	Definitely not related	Recovered	Recovered
	Thrombosis Venous Deep	Severe	1	Yes	Definitely not related	AE present, being treated	AE present, being treated

eTable 5. Comparison of baseline patient characteristics between the higher and lower cell-free hemoglobin groups

	Higher Baseline Cell-free Hemoglobin (> 10 mg/dl)			Lower baseline Cell-free Hemoglobin (≤ 10 mg/dl)		
Characteristic	Acetaminophen N=93	Placebo N=97	Overall N=190	Acetaminophen N=125	Placebo N=115	Overall N=240
Age (yr)	64.4 (15.6)	65.5 (15.5)	65.0 (15.5)	63.3 (16.0)	63.3 (14.5)	63.3 (15.3)
Sex no. (%)						
Male	54 (58.1)	44 (45.4)	98 (51.6)	57 (45.6)	60 (52.2)	117 (48.8)
Female	39 (41.9)	53 (54.6)	92 (48.4)	68 (54.4)	55 (47.8)	123 (51.3)
Ethnicity no. (%)						
Hispanic or Latino	14 (15.1)	12 (12.4)	26 (13.7)	17 (13.6)	15 (13.0)	32 (13.3)
Not Hispanic or Latino	79 (84.9)	83 (85.6)	162 (85.3)	103 (82.4)	96 (83.5)	199 (82.9)
Not reported	0 (0.0)	2 (2.1)	2 (1.1)	5 (4.0)	4 (3.5)	9 (3.8)
Race no. (%)						
White	64 (68.8)	66 (68.0)	130 (68.4)	81 (64.8)	76 (66.1)	157 (65.4)
Black	16 (17.2)	15 (15.5)	31 (16.3)	28 (22.4)	16 (13.9)	44 (18.3)
Asian	1 (1.1)	3 (3.1)	4 (2.1)	5 (4.0)	9 (7.8)	14 (5.8)
American Indian or Alaskan Native	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.6)	0 (0.0)	2 (0.8)
Native Hawaiian or other Pacific Islander	1 (1.1)	1 (1.0)	2 (1.1)	3 (2.4)	2 (1.7)	5 (2.1)
Not reported	11 (11.8)	12 (12.4)	23 (12.1)	6 (4.8)	12 (10.4)	18 (7.5)
BMI (kg/m^2)	28.6 (8.1)	28.7 (10.0)	28.7 (9.1)	30.0 (11.5)	29.2 (8.8)	29.6 (10.3)
Vasopressors at baseline no. (%)	62 (66.7)	73 (75.3)	135 (71.1)	105 (84.0)	89 (77.4)	194 (80.8)

	Higher Baseline Cell-free Hemoglobin (> 10 mg/dl)			Lower baseline Cell-free Hemoglobin (≤ 10 mg/dl)		
Characteristic	Acetaminophen N=93	Placebo N=97	Overall N=190	Acetaminophen N=125	Placebo N=115	Overall N=240
Assisted ventilation at baseline no. /total no. (%)	42/93 (45.2)	40/96 (41.7)	82/189 (43.4)	56/125 (44.8)	45/115 (39.1)	101/240 (42.1)
HFNO at baseline no. /total no. (%)	19/93 (20.4)	14/96 (14.6)	33/189 (17.5)	12/125 (9.6)	22/115 (19.1)	34/240 (14.2)
ARDS at baseline no. /total no. (%)	19/93 (20.4)	15/96 (15.6)	34/189 (18.0)	22/125 (17.6)	13/115 (11.3)	35/240 (14.6)
Time from inclusion to randomization (hours), Median (q1-q3)	10.7 (5.8-20.9)	9.2 (2.1-18.4)	10.1 (2.9-18.9)	8.6 (1.8-19.0)	11.3 (4.1-20.2)	9.5 (2.6-19.7)
Screening hospital location no. (%)						
ED	48 (51.6)	41 (42.3)	89 (46.8)	42 (33.6)	38 (33.0)	80 (33.3)
ICU	43 (46.2)	55 (56.7)	98 (51.6)	81 (64.8)	76 (66.1)	157 (65.4)
Hospital floor	2 (2.2)	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Stepdown/intermediate unit	0 (0.0)	1 (1.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.6)	1 (0.9)	3 (1.3)
Site of infection no. (%)						
Pneumonia	50 (53.8)	41 (42.3)	91 (47.9)	45 (36.0)	51 (44.3)	96 (40.0)
Urinary tract infection	15 (16.1)	28 (28.9)	43 (22.6)	21 (16.8)	24 (20.9)	45 (18.8)
Intra-abdominal infection	10 (10.8)	7 (7.2)	17 (8.9)	14 (11.2)	9 (7.8)	23 (9.6)

	Higher Baseline Cell-free Hemoglobin (> 10 mg/dl)			Lower baseline Cell-free Hemoglobin (≤ 10 mg/dl)		
Characteristic	Acetaminophen N=93	Placebo N=97	Overall N=190	Acetaminophen N=125	Placebo N=115	Overall N=240
Skin or soft-tissue infection	5 (5.4)	4 (4.1)	9 (4.7)	12 (9.6)	12 (10.4)	24 (10.0)
Vascular catheter- related infection	0 (0.0)	1 (1.0)	1 (0.5)	0 (0.0)	1 (0.9)	1 (0.4)
Central nervous system infection	1 (1.1)	2 (2.1)	3 (1.6)	1 (0.8)	2 (1.7)	3 (1.3)
Endocarditis or endovascular infection	0 (0.0)	1 (1.0)	1 (0.5)	1 (0.8)	0 (0.0)	1 (0.4)
Flu/other virus confirmed by testing	4 (4.3)	1 (1.0)	5 (2.6)	4 (3.2)	2 (1.7)	6 (2.5)
Other source of infection	4 (4.3)	4 (4.1)	8 (4.2)	10 (8.0)	2 (1.7)	12 (5.0)
Unknown	4 (4.3)	8 (8.2)	12 (6.3)	17 (13.6)	12 (10.4)	29 (12.1)
COVID-19 status in 3 weeks prior to admission no. (%)						
Positive test within 3 weeks prior to admission	8 (8.6)	11 (11.3)	19 (10.0)	9 (7.2)	11 (9.6)	20 (8.3)
Negative (only negative tests with 3 weeks prior to admission)	69 (74.2)	71 (73.2)	140 (73.7)	86 (68.8)	91 (79.1)	177 (73.8)
Unknown (no test within 3 weeks prior to admission)	16 (17.2)	15 (15.5)	31 (16.3)	30 (24.0)	13 (11.3)	43 (17.9)

x

	Higher Baseline Cell-free Hemoglobin (> 10 mg/dl)			Lower baseline Cell-free Hemoglobin (≤ 10 mg/dl)		
Characteristic	Acetaminophen N=93	Placebo N=97	Overall N=190	Acetaminophen N=125	Placebo N=115	Overall N=240
Baseline creatinine (mg/dL)	1.6 (1.1)	1.6 (1.2)	1.6 (1.2)	1.6 (1.2)	1.8 (1.4)	1.7 (1.3)
Baseline outpatient creatinine in 365 days prior to admission (mg/d)*	1.1 (0.9)	1.2 (1.1)	1.2 (1.0)	1.1 (0.8)	1.3 (1.0)	1.2 (0.9)
Baseline AST (U/L)	40.7 (31.9)	41.5 (42.0)	41.1 (37.3)	49.6 (37.5)	41.0 (32.2)	45.5 (35.3)
Baseline ALT (U/L)	28.9 (25.0)	31.3 (36.7)	30.1 (31.4)	32.5 (27.7)	31.6 (33.2)	32.1 (30.4)
Baseline bilirubin (mg/dL)	0.9 (0.7)	0.9 (1.2)	0.9 (1.0)	1.0 (1.0)	0.9 (1.0)	1.0 (1.0)
Baseline platelets (×1000/mm³)	206.1 (115.1)	228.6 (140.4)	217.6 (128.8)	225.0 (134.0)	215.7 (126.8)	220.5 (130.5)
Baseline total SOFA score (excludes GCS)	5.2 (2.5)	5.1 (2.5)	5.2 (2.5)	5.7 (2.5)	5.3 (2.5)	5.5 (2.5)
Baseline Plasma cell-free hemoglobin (mg/dL)	49.7 (86.1)	44.9 (91.5)	47.3 (88.7)	5.1 (2.3)	5.0 (2.3)	5.1 (2.3)
Baseline Acetaminophen no. (%)	54 (58.1)	41 (42.3)	95 (50.0)	49 (39.2)	47 (40.9)	96 (40.0)

Data as mean (SD) or N (%) unless otherwise indicated. BMI, body mass index; HFNO, high flow nasal oxygen; ARDS, acute respiratory distress syndrome; ED, emergency department; ICU, intensive care unit; COVID-19, coronavirus-associated infectious disease 2019; AST, aspartate aminotransferase; ALT, alanine aminotransferase; SOFA, sequential organ failure assessment; ranges 0-20; 20 is most severe; GCS, Glasgow coma score.

*Available 66 and 63 in higher cell-free Hb Acetaminophen and Placebo, 90 and 88 in lower cell-free Hb Acetaminophen and Placebo

eTable 6. Secondary outcomes by treatment in higher (>10 mg/dl) and lower (≤10 mg/dl) baseline cell-free hemoglobin level groups

	Baseline Cell-free Hemoglobin	Acetaminophen (N=218)		Placebo (N=212)		Acetaminophen vs. Placebo		High vs Low Baseline Cell- free Hemoglobin (Difference in difference)	
Outcome* †		N	Mean (95% CI)	N	Mean (95% CI)	Difference (95% CI)	P-value	Difference (95% CI)	Interaction P-value
Ventilator free days to day 28	High	92	22.3 (20.0, 24.7)	96	19.7 (17.4, 22.0)	2.6 (-0.6, 5.9)	0.12	1.8 (-2.6, 6.2)	0.42
	Low	124	19.7 (17.7, 21.8)	115	18.9 (16.8, 21.0)	0.8 (-2.1, 3.7)	0.58		
Vasopressor free days to day 28	High	92	23.0 (20.8, 25.3)	96	20.1 (17.9, 22.3)	3.0 (-0.2, 6.1)	0.06	2.1 (-2.1, 6.3)	0.33
	Low	124	20.3 (18.4, 22.3)	115	19.4 (17.4, 21.4)	0.9 (-1.9, 3.7)	0.53		
New renal replacement therapy to day 28	High	92	23.7 (21.4, 26.0)	96	22.1 (19.8, 24.4)	1.6 (-1.7, 4.9)	0.34	0.9 (-3.5, 5.2)	0.70
	Low	124	21.4 (19.4, 23.4)	115	20.6 (18.5, 22.7)	0.7 (-2.2, 3.6)	0.62		
28-day hospital mortality – %	High	93	10.8 (4.5, 17.0)	96	20.8 (12.7, 29.0)	-10.1 (-20.4, 0.2)	0.06	-7.6 (-22.3, 7.2)	0.31
	Low	124	21.0 (13.8, 28.1)	115	23.5 (15.7, 31.2)	-2.5 (-13.1, 8.0)	0.64		
ICU free days to day 28	High	92	20.5 (18.4, 22.5)	96	18.9 (16.8, 20.9)	1.6 (-1.3, 4.5)	0.27	1.9 (-1.9, 5.7)	0.33
	Low	124	18.6 (16.8, 20.3)	115	18.8 (17.0, 20.7)	-0.3 (-2.8, 2.3)	0.83		
Hospital free days to day 28	High	92	13.5 (11.3, 15.7)	96	11.2 (9.0, 13.3)	2.4 (-0.7, 5.5)	0.13	3.1 (-1.0, 7.3)	0.14
	Low	124	10.0 (8.1, 11.9)	115	10.8 (8.8, 12.7)	-0.8 (-3.5, 2.0)	0.59		
ICU days to day 28	High	92	5.3 (4.0, 6.6)	96	5.1 (3.9, 6.4)	0.1 (-1.6, 1.9)	0.87	-0.2 (-2.5, 2.2)	0.89
	Low	123	5.3 (4.2, 6.4)	114	5.0 (3.9, 6.1)	0.3 (-1.3, 1.9)	0.70		
Initiation of assisted ventilation to day 28 – %	High	50	8.0 (0.5, 15.5)	56	23.2 (12.2, 34.3)	-15.2 (-28.6, -1.8)	0.03	-22.6 (-40.8, -4.5)	0.02
	Low	69	20.3 (10.8, 29.8)	70	12.9 (5.0, 20.7)	7.4 (-4.9, 19.7)	0.24		
	High	92	12.0 (5.3, 18.6)	96	7.3 (2.1, 12.5)	4.7 (-3.8, 13.1)	0.28	6.2 (-4.9, 17.3)	0.28

Initiation of renal replacement therapy to day 28 – %	Low	124	8.1 (3.3, 12.9)	115	9.6 (4.2, 14.9)	-1.5 (-8.7, 5.7)	0.68		
Change in SOFA score from baseline to day 7	High	61	-3.2 (-4.0, -2.4)	66	-2.5 (-3.3, -1.8)	-0.7 (-1.7, 0.4)	0.25	-0.7 (-2.1, 0.8)	0.37
	Low	81	-3.3 (-3.9, -2.6)	81	-3.3 (-4.0, -2.6)	0.0 (-1.0, 1.0)	0.98		
90-day hospital mortality – %	High	93	16.1 (8.7, 23.6)	96	25.0 (16.3, 33.7)	-8.9 (-20.3, 2.6)	0.13	-9.5 (-25.4, 6.5)	0.24
	Low	124	25.8 (18.1, 33.5)	115	25.2 (17.3, 33.2)	0.6 (-10.5, 11.6)	0.92		
Development of ARDS within 7 Days of Randomization – %	High	74	2.7 (-1.0, 6.4)	81	8.6 (2.5, 14.8)	-5.9 (-13.1, 1.2)	0.10	0.9 (-8.5, 10.3)	0.85
	Low	102	2.0 (-0.7, 4.7)	102	8.8 (3.3, 14.3)	-6.9 (-13.0, -0.7)	0.03		
Change in serum creatinine from enrollment to discharge, death, initiation of dialysis or 28 days, whichever occurs first	High	79	-0.2 (-0.4, 0.0)	89	-0.2 (-0.4, -0.0)	0.0 (-0.2, 0.3)	0.74	0.1 (-0.2, 0.5)	0.53
	Low	113	-0.3 (-0.5, -0.1)	104	-0.2 (-0.4, -0.0)	-0.1 (-0.3, 0.2)	0.57		
90-day all-cause all-location mortality– %	High	92	21.7 (13.3, 30.2)	96	30.2 (21.0, 39.4)	-8.5 (-20.9, 4.0)	0.18	-4.5 (-21.6, 12.5)	0.60
	Low	124	28.2 (20.3, 36.1)	115	32.2 (23.6, 40.7)	-3.9 (-15.6, 7.7)	0.51		

* Unless otherwise indicated, values are mean (95% Confidence intervals)

† The percentage and mean were calculated from the non-missing records.

III. Supplemental Figures

eFigure 1. Change in individual component Sequential Organ Failure Assessment (SOFA) scores from enrollment to day 7 by treatment arm.

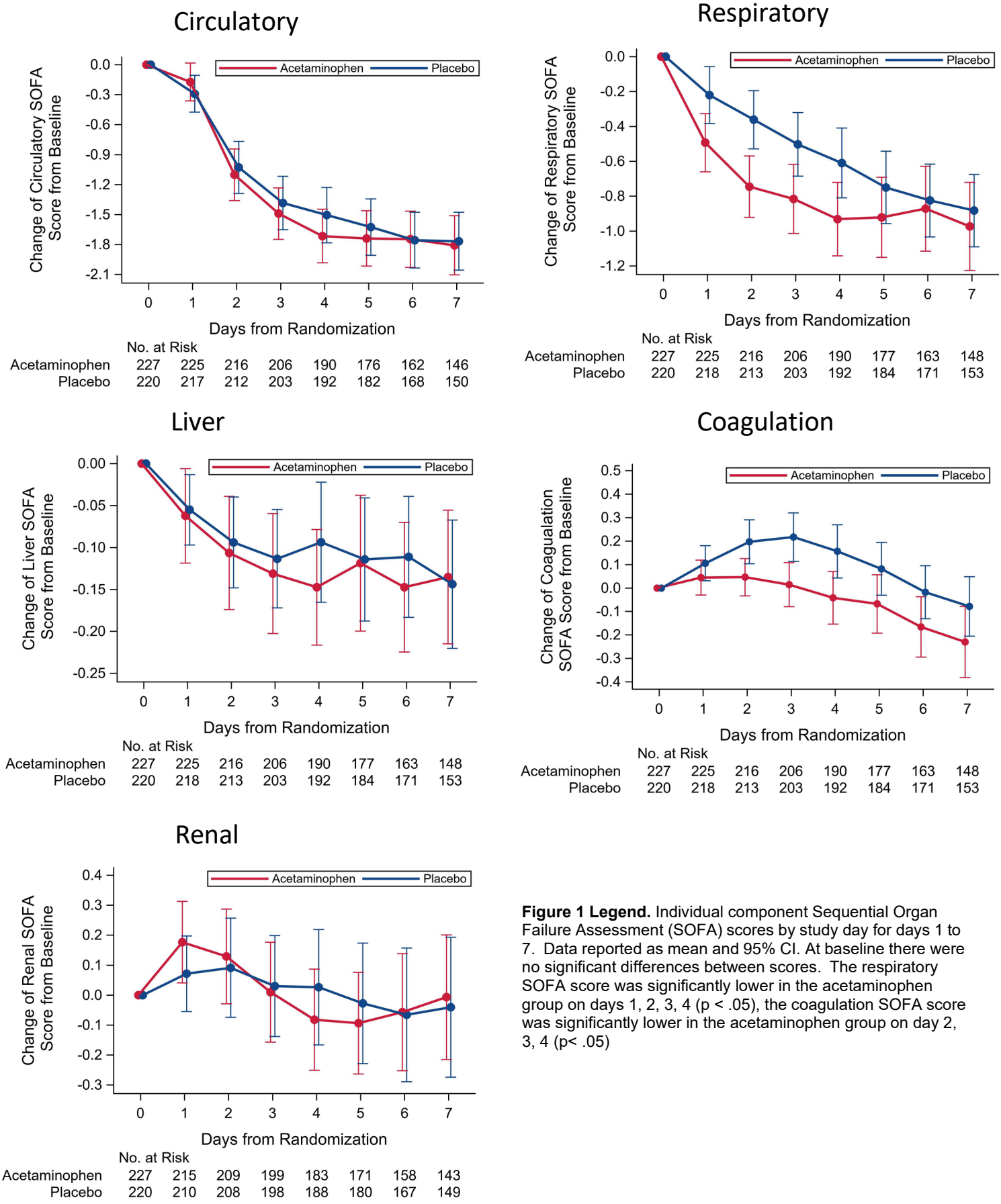
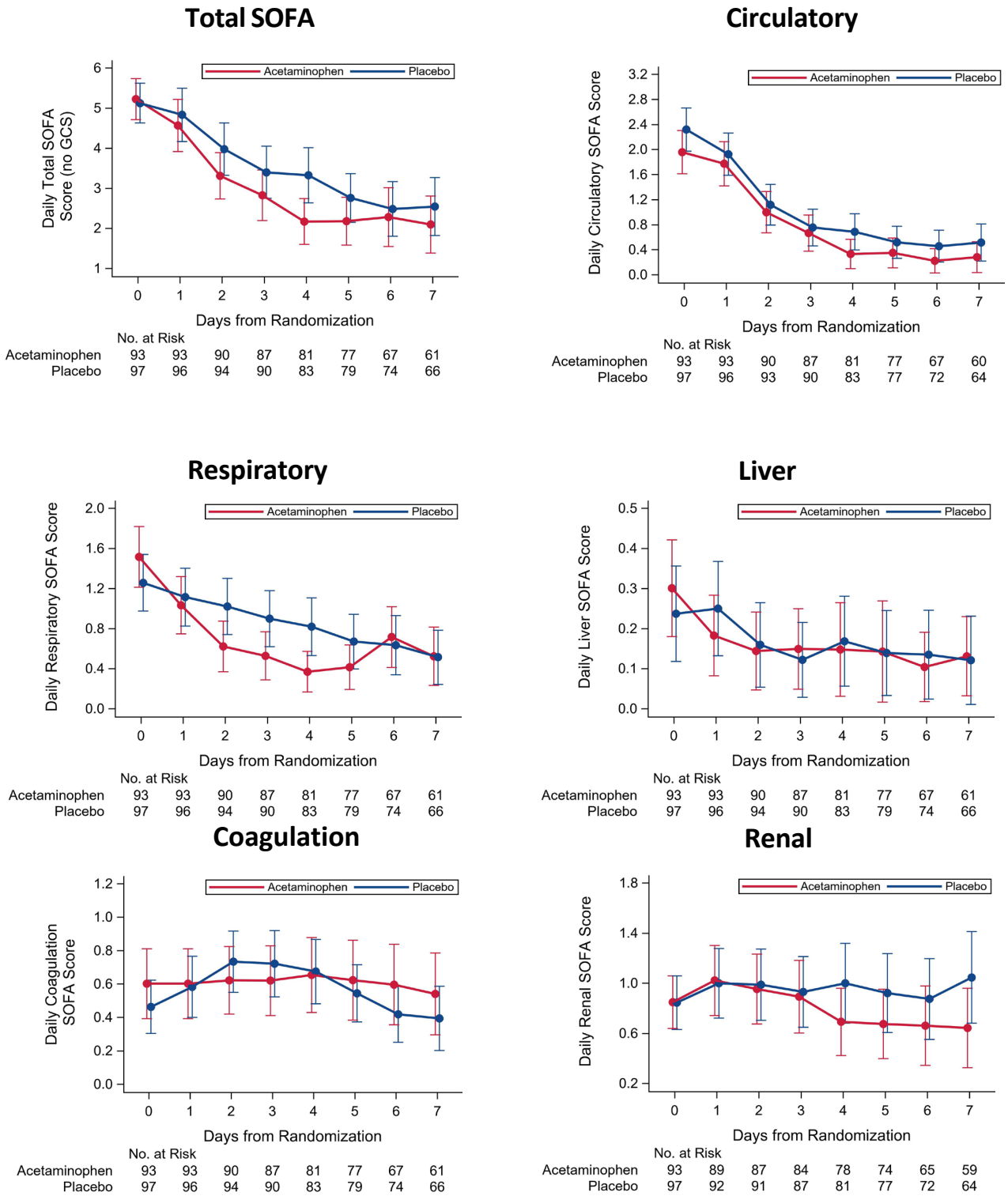


Figure 1 Legend. Individual component Sequential Organ Failure Assessment (SOFA) scores by study day for days 1 to 7. Data reported as mean and 95% CI. At baseline there were no significant differences between scores. The respiratory SOFA score was significantly lower in the acetaminophen group on days 1, 2, 3, 4 ($p < .05$), the coagulation SOFA score was significantly lower in the acetaminophen group on day 2, 3, 4 ($p < .05$)

eFigure 2a. Total and component SOFA scores from enrollment to Day 7 by treatment arm in the higher cell-free hemoglobin group (>l0 mg/dL).



eFigure 2b. Total and component SOFA scores from enrollment to Day 7 by treatment arm in the lower cell-free hemoglobin group (≤10 mg/dL).

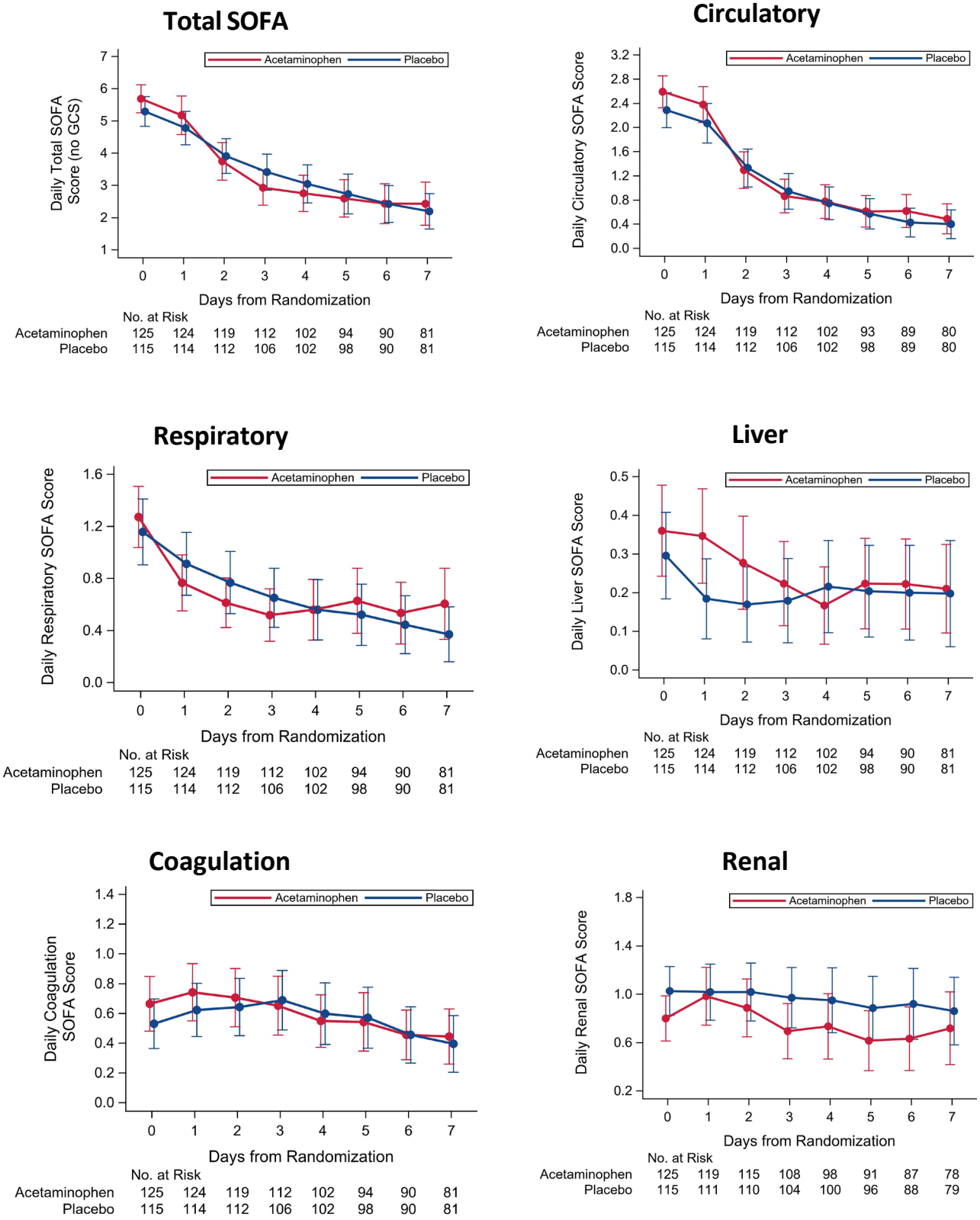
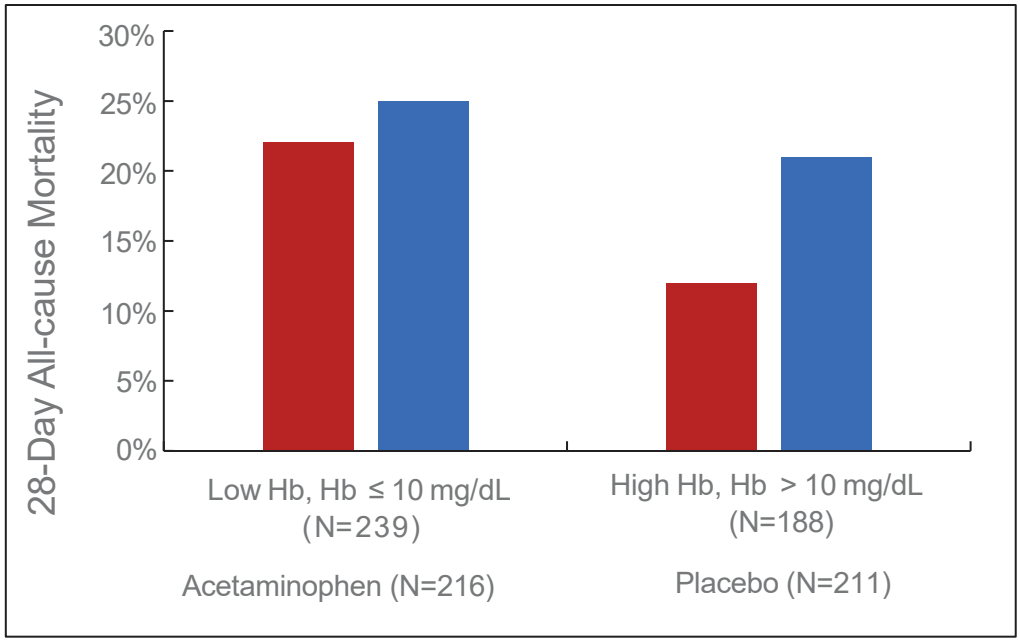


Figure 2a, b Legend. Total and individual component Sequential Organ Failure Assessment (SOFA) scores by study day for days 1 to 7 for the higher (> 10 mg/dL, Panel A) and lower (≤ 10 mg/dL, Panel B) baseline cell-free hemoglobin (Hb) groups. Data reported as mean and 95% CI. At baseline there were no significant differences between scores. In the higher hemoglobin group, the respiratory SOFA score was significantly lower in the acetaminophen group on days 2, 3, 4 ($p < .05$) and in the low hemoglobin group, the liver SOFA score was significantly higher in the acetaminophen group on day 1.

eFigure 3a. 28-day all-cause Mortality Categorized by Cell-Free Hemoglobin Level



P-values given by Wald Chi-squared test. P value=0.10 in patients with High-Hb level; P value=0.53 in patients with low-Hb level. No interaction between study treatment and Hb level (P=0.48)

eFigure 3b. Non-linear relationship between cell-free hemoglobin and 28-day all- cause Mortality by treatment arm

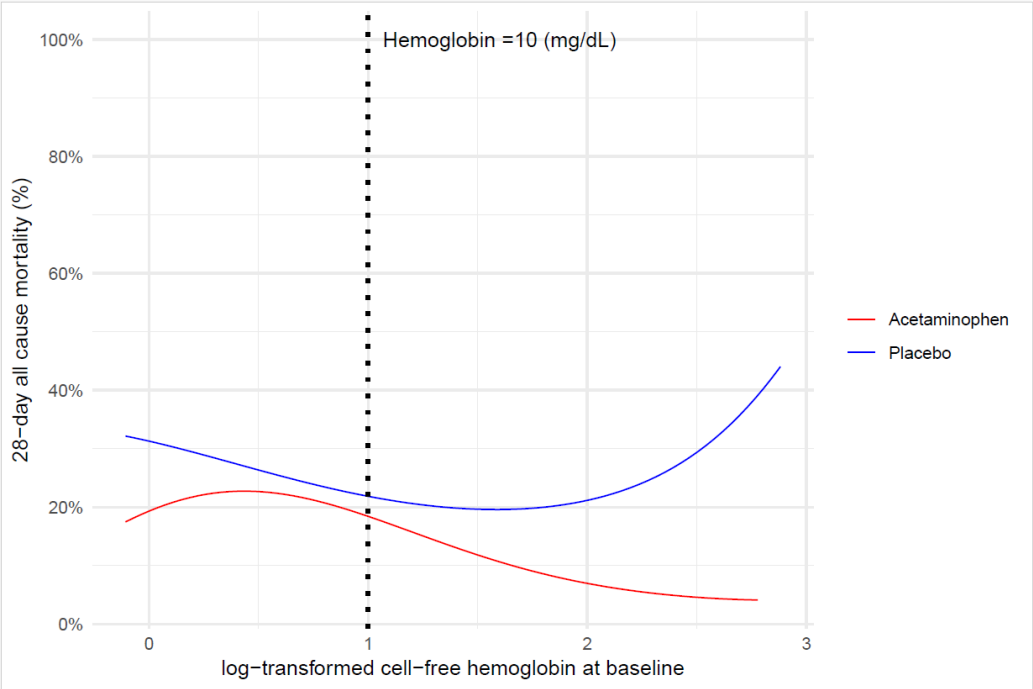


Figure 3 legend. Panel A. Comparison of 28-day all-cause mortality in the acetaminophen and placebo groups for the higher and lower baseline cell-free hemoglobin groups. The higher cell-free hemoglobin group had baseline levels > 10 mg/dl. The lower cell-free hemoglobin group had baseline levels ≤ 10 mg/dl. P value for interaction 0.48. **Panel B.** Non-linear relationship between baseline cell-free hemoglobin and 28-day all-cause mortality by treatment arm.