

Supplemental Table 1. Descriptive Statistics, Subjects Within the ProTECTIII Study

<b>Characteristic</b>	<b>Progesterone (N=383)</b>	<b>Placebo (N=380)</b>	<b>Total (N=763)</b>
Age - Median (Min-Max)	36 (17-94)	35 (17-93)	35 (17-94)
Male - n(%)	280 (73.1)	285 (75.0)	565 (74.1)
Index GCS (as Randomized) - n(%)			
Moderate (iGCS 9-12)	99 (25.9)	100 (26.3)	199 (26.1)
Moderate to Severe (iGCS 6-8/iMotor 4-5)	209 (54.6)	208 (54.7)	417 (54.7)
Most Severe (iGCS 4-5/iMotor 2-3)	75 (19.6)	72 (19.0)	147 (19.3)
Primary Outcome, defined by stratified dichotomy			
Favorable Outcome	188 (49.1)	195 (51.3)	383 (50.2)
Missing	18 (4.7)	19 (5.0)	37 (4.8)
Mortality	53 (13.8)	43 (11.3)	96 (12.6)

**Supplemental Table 2. Mortality according to Proportion of Time Spent in Transgression in Full Cohort**

\*Significant after Holm correction for multiple comparisons.

Transgression Parameter	Simple Models include only one Transgression, Adjusted for Treatment, Severity, Gender, and Age			Full Model Includes all Transgressions EXCEPT CPP, ICP, PbtO2, Temperature; N=752		Final Model after Backward Selection, using $\alpha=0.05$ as criteria for removal	
	N Used*	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)
PaO2	811	0.0018*	0.425 (0.194, 0.928)	0.3573	1.121 (0.401, 3.136)		
			0.426 (0.193, 0.940)		0.735 (0.275, 1.963)		
			0.686 (0.352, 1.335)		0.744 (0.292, 1.897)		
			1.726 (0.955, 3.121)		1.996 (0.776, 5.133)		
Glucose (high)	856	<0.0001*	0.430 (0.143, 1.290)	0.0003*	0.364 (0.100, 1.319)	0.0003*	0.313 (0.091, 1.073)
			0.715 (0.304, 1.681)		0.525 (0.182, 1.520)		0.491 (0.179, 1.345)
			2.644 (1.373, 5.088)		3.046 (1.263, 7.350)		2.064 (0.945, 4.509)
			6.525 (3.574, 11.911)		3.154 (1.284, 7.748)		2.693 (1.284, 5.648)
Glucose (low)	856	0.1563	0.140 (0.019, 1.049)	0.0490	0.100 (0.009, 1.063)		
			0.410 (0.133, 1.262)		0.633 (0.175, 2.291)		
			0.646 (0.216, 1.936)		0.095 (0.015, 0.607)		
			1.151 (0.480, 2.762)		0.719 (0.187, 2.774)		
CPP	457	<0.0001*	0.834 (0.270, 2.575)				
			1.746 (0.656, 4.648)				
			3.630 (1.485, 8.877)				
			7.743 (3.205, 18.704)				
INR	798	<0.0001*	0.593 (0.131, 2.683)	0.0009*	1.075 (0.195, 5.910)	0.0001*	0.858 (0.169, 4.364)
			2.604 (1.027, 6.604)		4.253 (1.307, 13.840)		5.005 (1.695, 14.778)
			5.791 (2.485, 13.494)		3.984 (1.284, 12.361)		3.920 (1.442, 10.653)
			25.903 (11.386, 58.928)		9.693 (2.542, 36.965)		7.735 (2.640, 22.662)
Platelets	856	<0.0001*	0.566 (0.067, 4.805)	0.6942	0.358 (0.027, 4.824)		
			3.929 (1.003, 15.387)		0.939 (0.114, 7.706)		
			3.044 (0.794, 11.670)		1.336 (0.225, 7.937)		
			24.256 (6.574, 89.497)		5.121 (0.375, 69.851)		
O2	862		Quasi-complete separation of data points				
Hemoglobin	855	<0.0001*	0.257 (0.075, 0.877)	0.0018*	0.352 (0.065, 1.900)	0.0006*	0.217 (0.049, 0.975)
			0.458 (0.168, 1.249)		0.395 (0.111, 1.402)		0.407 (0.132, 1.255)

			0.901 (0.390, 2.081)		1.173 (0.358, 3.844)		0.725 (0.248, 2.120)
			4.906 (2.727, 8.826)		4.730 (1.846, 12.123)		3.348 (1.515, 7.396)
ICP	460	<0.0001*	0.529 (0.194, 1.444)				
			1.227 (0.501, 3.004)				
			1.735 (0.711, 4.235)				
			7.119 (3.179, 15.941)				
MAP (65)	853	<0.0001*	0.477 (0.228, 0.998)	0.1312	0.583 (0.219, 1.552)		
			0.233 (0.092, 0.589)		0.223 (0.068, 0.733)		
			1.087 (0.579, 2.039)		0.621 (0.229, 1.684)		
			1.796 (1.000, 3.224)		0.389 (0.137, 1.109)		
PbtO2	152						
SBP (high)	863	0.0031*	0.198 (0.075, 0.527)	0.1101	0.216 (0.063, 0.735)		
			0.302 (0.121, 0.753)		0.494 (0.149, 1.640)		
			0.619 (0.311, 1.233)		1.005 (0.400, 2.527)		
			0.791 (0.416, 1.503)		1.002 (0.402, 2.495)		
SBP (low, 90)	863	<0.0001*	0.141 (0.032, 0.616)	0.0007*	0.181 (0.037, 0.883)	<0.0001*	0.187 (0.041, 0.852)
			0.426 (0.177, 1.025)		0.396 (0.130, 1.209)		0.322 (0.118, 0.876)
			0.874 (0.432, 1.768)		0.573 (0.201, 1.639)		0.645 (0.274, 1.519)
			5.523 (3.189, 9.567)		3.591 (1.346, 9.580)		3.072 (1.470, 6.421)
Temp (high)	862	0.0001*	0.198 (0.079, 0.499)				
			0.391 (0.193, 0.793)				
			0.714 (0.371, 1.375)				
			1.345 (0.751, 2.409)				
Temp (low)	862		Quasi-complete separation of data points				

**Supplemental Table 3. Mortality according to Proportion of Time Spent in Transgression tICP cohort**

\*Significant after Holm correction for multiple comparisons.

Transgression Parameter	Full Model Includes all Transgressions EXCEPT PbtO2, Temperature; N=428		Final Model after Backward Selection, using $\alpha=0.05$ as criteria for removal	
	p-value	OR (95% CI)	p-value	OR (95% CI)
PaO2	0.4226	0.344 (0.083, 1.425)		
		0.351 (0.088, 1.407)		
		0.307 (0.079, 1.201)		
		0.538 (0.138, 2.094)		
Glucose (high)	0.0283	0.638 (0.148, 2.740)	0.0293*	0.549 (0.142, 2.126)
		0.438 (0.112, 1.703)		0.603 (0.187, 1.945)
		2.959 (0.904, 9.692)		2.258 (0.832, 6.126)
		3.317 (0.823, 13.367)		2.843 (0.948, 8.529)
Glucose (low)	0.2229	0.116 (0.010, 1.284)		
		0.601 (0.091, 3.965)		
		0.147 (0.014, 1.513)		
		0.501 (0.074, 3.408)		
CPP	0.0290	2.970 (0.493, 17.895)		
		6.332 (1.289, 31.113)		
		13.284 (2.203, 80.087)		
		23.430 (3.164, 173.485)		
INR	0.2551	1.547 (0.213, 11.215)		
		3.451 (0.746, 15.957)		
		3.895 (0.883, 17.171)		
		2.220 (0.330, 14.914)		
Platelets	0.8005	2.310 (0.119, 44.763)		
		1.846 (0.106, 32.175)		
		1.042 (0.097, 11.141)		
		6.939 (0.201, 239.457)		
O2				
Hemoglobin	0.0372	0.332 (0.045, 2.457)	0.0220*	0.265 (0.049, 1.427)
		0.557 (0.129, 2.397)		0.454 (0.124, 1.654)

		0.721 (0.172, 3.018)		0.646 (0.184, 2.276)
		4.783 (1.301, 17.590)		3.160 (1.103, 9.048)
ICP	0.1152	0.205 (0.039, 1.081)	<0.0001*	0.518 (0.136, 1.969)
		0.422 (0.091, 1.943)		1.273 (0.375, 4.319)
		0.506 (0.094, 2.734)		2.190 (0.656, 7.310)
		1.315 (0.281, 6.146)		8.511 (2.846, 25.452)
MAP (65)	0.0045*	0.433 (0.123, 1.519)	0.0133*	0.579 (0.202, 1.657)
		0.042 (0.008, 0.229)		0.122 (0.031, 0.475)
		0.240 (0.049, 1.188)		0.815 (0.230, 2.886)
		0.100 (0.019, 0.533)		0.285 (0.080, 1.022)
PbtO2				
SBP (high)	0.0190	0.061 (0.011, 0.348)	0.0071*	0.073 (0.015, 0.350)
		0.239 (0.052, 1.105)		0.223 (0.060, 0.827)
		0.399 (0.119, 1.336)		0.406 (0.150, 1.095)
		0.511 (0.137, 1.904)		0.473 (0.159, 1.411)
SBP (low, 90)	0.0649	0.527 (0.088, 3.161)	0.0114*	0.399 (0.077, 2.073)
		0.797 (0.186, 3.412)		0.770 (0.226, 2.620)
		2.019 (0.522, 7.800)		1.721 (0.565, 5.241)
		5.563 (1.423, 21.739)		6.147 (1.847, 20.452)
Temp (high)				
Temp (low)				

**Supplemental Table 4. Mortality according to Transgression Occurrence in tICP cohort**

\*Significant after Holm correction for multiple comparisons.

Transgression Parameter	Full Model Includes all Transgressions EXCEPT CPP, ICP, PbtO2, Temperature; N=428		Final Model after Backward Selection, using $\alpha=0.05$ as criteria for removal	
	p-value	OR (95% CI)	p-value	OR (95% CI)
PaO2	0.0985	0.555 (0.276, 1.116)		
Glucose (high)	0.5503	1.238 (0.614, 2.498)		
Glucose (low)	0.1830	0.594 (0.276, 1.278)		
CPP	0.0018*	5.024 (1.822, 13.855)	0.0038*	3.815 (1.540, 9.451)
INR	0.0032*	2.838 (1.419, 5.676)	0.0009*	2.833 (1.528, 5.251)
Platelets	0.0694	2.575 (0.928, 7.148)		
O2	0.6795	0.876 (0.468, 1.641)		
Hemoglobin	0.0764	0.543 (0.276, 1.067)		
ICP	0.8887	1.063 (0.454, 2.486)		
MAP (65)	0.0188	0.357 (0.151, 0.843)	0.0051*	0.344 (0.163, 0.726)
PbtO2				
SBP (high)	0.0014*	0.346 (0.180, 0.665)	0.0002*	0.309 (0.168, 0.569)
SBP (low, 90)	0.3928	1.354 (0.676, 2.714)		
Temp (high)				
Temp (low)				

**Supplemental Table 5. Poor Outcome according to Proportion of Time Spent in Transgression in Full Cohort**

\*Significant after Holm correction for multiple comparisons.

Transgression Parameter	Simple Models include only one Transgression, Adjusted for Treatment, Severity, Gender, and Age			Full Model Includes all Transgressions EXCEPT CPP, ICP, PbtO2, Temperature; N=726		Final Model after Backward Selection, using $\alpha=0.05$ as criteria for removal	
	N Used*	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)
PaO2	782	0.0062*	1.550 (0.986, 2.439)	0.1941	1.495 (0.866, 2.583)		
			1.989 (1.252, 3.159)		1.822 (1.059, 3.135)		
			1.414 (0.908, 2.203)		1.164 (0.686, 1.974)		
			2.182 (1.334, 3.569)		1.643 (0.887, 3.042)		
Glucose (high)	823	<0.0001*	1.363 (0.865, 2.148)	0.0015*	1.116 (0.661, 1.884)	<0.0001*	1.273 (0.780, 2.076)
			1.368 (0.855, 2.190)		1.121 (0.646, 1.946)		1.221 (0.735, 2.029)
			2.459 (1.535, 3.937)		2.022 (1.151, 3.552)		1.998 (1.203, 3.317)
			5.260 (3.028, 9.137)		3.399 (1.787, 6.466)		3.970 (2.203, 7.155)
Glucose (low)	823	0.7973	0.879 (0.475, 1.627)	0.4888	0.617 (0.304, 1.251)		
			1.152 (0.618, 2.147)		1.031 (0.501, 2.124)		
			1.208 (0.642, 2.270)		1.057 (0.500, 2.234)		
			0.744 (0.394, 1.407)		0.590 (0.268, 1.300)		
CPP	444	0.0096	0.866 (0.461, 1.627)				
			1.846 (0.971, 3.511)				
			1.886 (1.008, 3.529)				
			2.409 (1.250, 4.644)				
INR	769	0.0011*	1.248 (0.633, 2.463)	0.5129	1.040 (0.456, 2.373)		
			1.954 (0.982, 3.885)		1.310 (0.616, 2.787)		
			2.000 (1.027, 3.893)		1.620 (0.725, 3.622)		
			4.093 (1.871, 8.953)		1.967 (0.758, 5.102)		
Platelets	823	0.2342	0.402 (0.106, 1.530)	0.0329	0.135 (0.030, 0.599)		
			2.235 (0.661, 7.559)		0.941 (0.235, 3.763)		
			0.614 (0.174, 2.168)		0.272 (0.071, 1.042)		
			2.297 (0.592, 8.909)		0.448 (0.067, 2.989)		
O2	829	0.0010*	0.699 (0.415, 1.179)	0.0012*	0.449 (0.243, 0.831)	0.0031*	0.546 (0.308, 0.968)
			0.756 (0.451, 1.266)		0.447 (0.244, 0.816)		0.537 (0.304, 0.946)
			1.535 (0.915, 2.575)		0.934 (0.508, 1.715)		1.038 (0.589, 1.829)

			2.630 (1.513, 4.571)		2.024 (0.995, 4.118)		2.124 (1.135, 3.972)
Hemoglobin	822	<0.0001*	1.049 (0.622, 1.769)	0.0043*	1.050 (0.571, 1.929)	0.0035*	0.970 (0.554, 1.699)
			1.902 (1.116, 3.241)		1.797 (0.976, 3.307)		1.698 (0.975, 2.958)
			1.839 (1.105, 3.062)		1.917 (1.008, 3.646)		1.530 (0.872, 2.687)
			3.452 (1.979, 6.021)		3.275 (1.655, 6.479)		2.927 (1.605, 5.335)
ICP	448	0.0001*	1.798 (0.942, 3.430)				
			2.181 (1.133, 4.200)				
			2.068 (1.069, 4.001)				
			5.507 (2.743, 11.056)				
MAP (65)	821	0.4288	1.181 (0.758, 1.838)	0.0184	0.979 (0.574, 1.669)		
			0.870 (0.559, 1.354)		0.591 (0.338, 1.031)		
			0.934 (0.597, 1.461)		0.404 (0.223, 0.731)		
			1.335 (0.847, 2.103)		0.657 (0.356, 1.212)		
PbtO2							
SBP (high)	830	0.1032	1.756 (1.093, 2.822)	0.6631	1.484 (0.850, 2.589)		
			1.167 (0.718, 1.896)		0.997 (0.567, 1.754)		
			1.317 (0.817, 2.124)		1.026 (0.587, 1.796)		
			1.628 (0.988, 2.682 )		1.244 (0.689, 2.247)		
SBP (low, 90)	830	0.0272	1.102 (0.700, 1.734)	0.1865	0.895 (0.521, 1.540)		
			1.358 (0.855, 2.158)		1.632 (0.909, 2.932)		
			1.290 (0.815, 2.041)		1.495 (0.837, 2.669)		
			2.265 (1.375, 3.732)		1.795 (0.898, 3.587)		
Temp (high)	829	<0.0001*	1.063 (0.673, 1.678)				
			1.605 (1.015, 2.536)				
			1.853 (1.167, 2.941)				
			3.643 (2.272, 5.842)				
Temp (low)	829	<0.0001*	0.928 (0.548, 1.574)				
			1.414 (0.842, 2.372)				
			1.252 (0.744, 2.107)				
			4.337 (2.429, 7.742)				



**Supplemental Table 6. Poor Outcome according to Proportion of Time Spent in Transgression in tICP cohort**

\*Significant after Holm correction for multiple comparisons.

Transgression Parameter	Full Model Includes all Transgressions EXCEPT PbtO2, Temperature; N=416		Final Model after Backward Selection, using $\alpha=0.05$ as criteria for removal	
	p-value	OR (95% CI)	p-value	OR (95% CI)
PaO2	0.3578	1.146 (0.510, 2.574)		
		1.133 (0.497, 2.583)		
		1.104 (0.465, 2.618)		
		0.474 (0.179, 1.255)		
Glucose (high)	0.0214	1.176 (0.565, 2.446)	0.0167*	1.060 (0.556, 2.019)
		0.921 (0.414, 2.049)		1.068 (0.540, 2.113)
		2.364 (1.037, 5.391)		1.811 (0.908, 3.610)
		4.190 (1.520, 11.552)		4.306 (1.722, 10.769)
Glucose (low)	0.7923	0.677 (0.272, 1.686)		
		1.229 (0.370, 4.080)		
		1.688 (0.489, 5.831)		
		0.863 (0.228, 3.268)		
CPP	0.3444	0.746 (0.306, 1.818)		
		1.669 (0.650, 4.289)		
		1.449 (0.529, 3.969)		
		1.945 (0.580, 6.523)		
INR	0.1840	0.453 (0.149, 1.376)		
		2.371 (0.792, 7.101)		
		0.653 (0.207, 2.060)		
		0.516 (0.146, 1.824)		
Platelets	0.2935	0.108 (0.013, 0.899)		
		1.033 (0.131, 8.120)		
		0.327 (0.034, 3.130)		
		>999 (<0.001, >999)		
O2	0.0207	0.537 (0.239, 1.203)	0.0180*	0.497 (0.243, 1.016)
		0.446 (0.176, 1.132)		0.609 (0.271, 1.370)
		0.893 (0.356, 2.242)		1.073 (0.487, 2.365)

		3.226 (1.143, 9.099)		3.007 (1.228, 7.365)
Hemoglobin	0.0294	1.094 (0.477, 2.507)		
		1.368 (0.606, 3.089)		
		2.063 (0.856, 4.972)		
		6.008 (1.927, 18.733)		
ICP	0.1252	1.347 (0.588, 3.089)	0.0075*	1.471 (0.710, 3.047)
		2.041 (0.828, 5.035)		1.984 (0.938, 4.196)
		2.020 (0.796, 5.127)		1.912 (0.915, 3.994)
		4.188 (1.407, 12.462)		4.407 (1.979, 9.816)
MAP (65)	<0.0001*	0.555 (0.244, 1.263)	0.0047*	0.783 (0.390, 1.5730)
		0.103 (0.040, 0.270)		0.262 (0.124, 0.553)
		0.221 (0.078, 0.626)		0.671 (0.311, 1.448)
		0.214 (0.069, 0.662)		0.741 (0.320, 1.718)
PbtO2				
SBP (high)	0.3541	1.380 (0.594, 3.208)		
		0.909 (0.401, 2.064)		
		0.512 (0.229, 1.143)		
		0.806 (0.333, 1.952)		
SBP (low, 90)	0.1638	1.146 (0.532, 2.466)		
		2.505 (1.075, 5.836)		
		2.074 (0.854, 5.035)		
		2.350 (0.829, 6.660)		
Temp (high)				
Temp (low)				

**Supplemental Table 7. Poor Outcome according to Transgression Occurrence in tICP cohort**

\*Significant after Holm correction for multiple comparisons.

Transgression Parameter	Full Model Includes all Transgressions PbtO2, Temperature; N=416		Final Model after Backward Selection, using $\alpha=0.05$ as criteria for removal	
	p-value	OR (95% CI)	p-value	OR (95% CI)
PaO2	0.5207	1.198 (0.690, 2.079)		
Glucose (high)	0.2385	1.339 (0.824, 2.175)		
Glucose (low)	0.9287	1.024 (0.603, 1.739)		
CPP	0.7800	1.094 (0.584, 2.048)		
INR	0.3206	1.315 (0.766, 2.258)		
Platelets	0.1380	0.501 (0.201, 1.249)		
O2	0.6137	0.889 (0.563, 1.404)		
Hemoglobin	0.3028	1.293 (0.793, 2.110)		
ICP	0.0379	1.932 (1.037, 3.596)	0.0064*	2.143 (1.239, 3.708)
MAP (65)	0.0074	0.416 (0.219, 0.790)	0.0185*	0.488 (0.268, 0.886)
PbtO2				
SBP (high)	0.5831	0.875 (0.543, 1.409)		
SBP (low, 90)	0.0780	1.563 (0.951, 2.568)	0.0286*	1.702 (1.057, 2.739)
Temp (high)				
Temp (low)				

Supplemental Figure 1. The relationship between the proportion of time spent in transgression and predicted probability of poor functional outcome by severity of initial injury (iGCS) categories and transgression types

