Supplemental Table 1. Patient Populations.

	PETROS	MESSI	iSPAAR Cases	iSPAAR Controls
Study Design	Prospective Cohort	Prospective Cohort	Case Control Study	
Study Site	Penn Medicine	Penn Medicine	NIH ARDSNet Studies Mass General Hospital	Mass General Hospital
Population	Trauma	Sepsis	Sepsis	
Inclusion Criteria	- acute traumatic injury (<24 hours) - injury severity score >15	- Sepsis-2 criteria for severe sepsis or septic shock	- ARDS by American European Consensus Criteria - Sepsis -2 criteria	- Sepsis-2 criteria
Exclusion Criteria	- die or discharge within 24 hours - isolated head trauma - incarceration	- admitted from a long-term acute care facility - do not intubate order	* see specific ARDSNet study exclusion criteria	- ARDS risk factor other than sepsis
Genotyping Platform	Affymetrix AxionTxv1 Array		Illumina Human610-Quad Bead Array	

Supplemental Table 2. Single nucleotide polymorphisms utilized to infer ABO blood type alleles in PETROS, MESSI, and iSPAAR.

ABO Allele – PETROS/MESSI	Single Nucleotide Polymorphism in the *ABO* gene		
	rs8176719	rs1053878	rs8176746
A1	G	G	C
A2	G	A	C
B	G	G	A
O	-	G	G
ABO Allele - iSPAAR	rs505922	rs8176704	rs8176746
A1	C	G	C
A2	C	A	C
B	C	G	A
O	T	G	C

Supplemental Table 3. Concordance of genetically determined blood type and ABO blood type by chart review in PETROS and MESSI

PETROS	ABO BLOOD TYPE				
	A	**B**	**AB**	**O**	Total
A1A1	23	0	0	2	23
A1A2	20	0	0	1	15
A1O	173	3	1	20	173
A2A2	7	0	0	0	3
A2O	132	6	0	14	128
BB	0	15	0	1	13
BO	13	164	1	7	162
A1B	1	1	30	0	31
A2B	1	0	18	2	20
OO	22	8	2	524	464
Total	392	197	52	571	1,212
MESSI	ABO BLOOD TYPE				
	A	**B**	**AB**	**O**	Total
A1A1	24	0	0	0	24
A1A2	27	0	0	1	28
A1O	179	0	0	19	198
A2A2	10	0	0	0	10
A2O	107	0	0	3	110
BB	0	14	0	1	15
BO	5	116	0	1	122
A1B	2	4	29	1	36
A2B	0	1	18	0	19
OO	6	0	0	450	456
Total	360	135	47	476	1,018

Nine subjects do not have a blood type available in MESSI (96% concordance in MESSI, 91% in Trauma).

Supplemental Table 4. Unadjusted Distributions of moderate or severe ARDS risk by ABO genotype among the prospective cohort studies PETROS, MESSI overall population, and MESSI non-pulmonary sepsis.

	PETROS		MESSI		MESSI Non-Pulmonary	
	No.	% ARDS	No.	% ARDS	No.	% ARDS
A1A1	25	32%	24	54%	14	36%
A1A2	21	19%	28	43%	16	31%
A1O	197	25%	198	39%	120	35%
A2A2	7	14%	10	40%	8	38%
A2O	152	20%	111	43%	57	28%
BB	16	31%	15	40%	9	0%
BO	185	21%	125	34%	65	22%
A1B	32	9%	36	39%	18	28%
A2B	21	14%	19	32%	10	30%
OO	556	16%	461	34%	233	21%
Total	1,212	19%	1,027	37%	550	26%

Supplemental Table 5. Adjusted association of the ABO blood type A1 allele versus O with moderate or severe ARDS risk, excluding patients enrolled in our previous non-genetic study of ABO blood type and ARDS, and adjusted association of ABO blood type A1 allele versus all other blood types in overall population.

Population – Excluding previous patients		No.	OR (95% CI) A1 vs. O[A]	p
PETROS[B]	Overall	739	1.83 (1.06, 3.16)	0.031
MESSI[C]	Overall	605	1.38 (0.89, 2.15)	0.149
	Pulmonary	280	1.16 (0.61, 2.18)	0.649
	Non-Pulmonary	325	1.71 (0.91, 3.22)	0.095
Population – Comparing A1 vs. not A1		No.	OR (95% CI) A1 vs. not[C]	p
PETROS[B]	Overall	1212	1.44 (1.01, 2.05)	0.043
MESSI[C]	Overall	1027	1.37 (1.01, 1.86)	0.045
	Pulmonary	550	1.05 (0.68, 1.64)	0.820
	Non-Pulmonary	477	1.70 (1.11, 2.60)	0.015

[A]Odds ratios and 95% confidence intervals were obtained via multivariable logistic regression with the primary comparison between subjects with an A1 allele to subjects with the OO genotype. [B]The PETROS cohort analysis was adjusted for age, sex, injury severity score, mechanism of trauma, and population stratification. [C]The MESSI cohort analysis was adjusted for age, sex, transfusions, history of diabetes, history of cancer, source of sepsis, and population stratification. [C]Odds ratios and 95% confidence intervals were obtained via multivariable logistic regression with the primary comparison between subjects with an A1 allele to all other subjects without an A1 allele.

Supplemental Table 6. Unadjusted distribution of ABO genotypes in the overall iSPAAR case control study, and ISPAAR patients with non-pulmonary sepsis separated by ARDS cases and controls.

	iSPAAR		iSPAAR non-pulmonary	
	NO ARDS	**ARDS**	**NO ARDS**	**ARDS**
A1A1	26 (2%)	9 (5%)	13 (2%)	9 (5%)
A1A2	27 (2%)	7 (4%)	12 (2%)	6 (3%)
A1O	315 (25%)	60 (30%)	163 (25%)	56 (31%)
A2A2	4 (<1%)	0 (0%)	2 (<1%)	0 (0%)
A2O	103 (8%)	16 (8%)	51 (8%)	14 (8%)
BB	14 (1%)	1 (1%)	10 (2%)	1 (1%)
BO	135 (11%)	14 (7%)	65 (10%)	13 (7%)
A1B	36 (3%)	4 (2%)	16 (2%)	4 (2%)
A2B	58(1%)	0 (0%)	4 (1%)	0 (0%)
OO	605 (47%)	87 (44%)	315 (48%)	75 (42%)
Total	1,273	198	651	178

Supplemental Table 7. Association of possession of an A1 allele versus O and moderate or severe ARDS risk among "non-secretors" in MESSI and PETROS.

Population		No.	OR (95% CI) A1 vs. O[A]	p
PETROS[B]	Overall	305	2.84 (1.27, 6.34)	0.011
MESSI[C]	Overall	245	1.41 (0.66, 2.49)	0.369
	Non-Pulmonary	127	2.37 (0.75, 7.55)	0.143
	Pulmonary	118	1.10 (0.35, 3.43)	0.867
Combined PETROS & Non-pulmonary MESSI[D]		432	2.15 (1.18, 3.92)	0.012

[A]Odds ratios and 95% confidence intervals were obtained via multivariable logistic regression with the primary comparison between subjects with an A1 allele to subjects with the OO genotype. [B]The PETROS cohort analysis was adjusted for age, sex, injury severity score, mechanism of trauma, and population stratification. [C]The MESSI cohort analysis was adjusted for age, sex, source of sepsis, and population stratification. [D]The combine cohort was adjusted for age, sex, sepsis versus trauma, and population stratification.

Supplemental Table 8. Correlation Matrix for Endothelial Derived Glycoproteins

Biomarker	vWF	sTM	sICAM-1	E-selectin
vWF	XXXX	0.48	0.35	0.30
sTM		XXXX	0.53	0.45
sICAM-1			XXXX	0.45
E-selectin				XXXX

Values represent the Spearman Rho. All correlations are statistically significant with a p-value <0.01.

Supplemental Table 9. Endothelial Plasma Biomarkers by Clinically Determined ABO Blood Type.

Biomarker	ABO Blood Type	MESSI – Sepsis			PETROS – Trauma		
		N	Median (IQR)	p	N	Median (IQR)	p
sICAM-1	Overall	553	358 (198, 599)	0.015	559	181 (131, 238)	0.099
	A	195	395 (213, 731)		182	186 (136, 250)	
	B	75	345 (207, 599)		91	180 (138, 237)	
	AB	24	406 (233, 595)		19	191 (131, 282)	
	O	259	336 (184, 543)		267	175 (125, 231)	
vWF	Overall	569	327 (240, 464)	0.018	560	196 (145, 274)	0.008
	A	199	339 (259, 483)		182	201 (153, 274)	
	B	80	359 (280, 470)		91	217 (153, 309)	
	AB	24	350 (261, 506)		19	305 (182, 333)	
	O	266	304 (210, 444)		268	185 (129, 251)	
sTM	Overall	569	7.6 (5.3, 12.0)	0.234	560	3.8 (2.9, 5.0)	0.031
	A	200	8.0 (5.4, 12.4)		183	3.9 (3.0, 5.1)	
	B	80	7.7 (5.2, 12.0)		91	3.9 (3.2, 5.0)	
	AB	24	8.8 (5.9, 11.4)		18	5.4 (3.8, 6.8)	
	O	265	7.1 (5.3, 12.0)		268	3.6 (2.7, 4.8)	
sE-selectin	Overall	554	58.2 (29.9, 103.1)	0.001	561	20.9 (3.8, 33.1)	0.001
	A	194	50.3 (25.3, 85.8)		183	16.0 (3.4, 26.6)	
	B	77	60.0 (31.8, 93.5)		91	18.1 (3.6, 34.5)	
	AB	24	61.1 (35.8, 121.4)		19	13.9 (3.7, 23.3)	
	O	259	64.9 (35.1, 117.0)		268	26.8 (4.4, 36.9)	

P-values are for the comparison of ABO blood type A versus O using the Wilcoxon Rank-sum test separately for MESSI and PETROS. Concentrations of sICAM-1, sTM, and sE-selectin are in ng/mL. Concentrations of vWF are represented as percentage of control specimen.