Supplementary Material

Biomarker Enhanced Risk Prediction for Adverse Outcomes in Critically Ill Patients Receiving Renal Replacement Therapy

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for the

Biological Markers for Recovery of Kidney (BioMaRK) Study Investigators

Table E1

Characteristics of Participants in the ATN and BioMaRK Study Cohorts

Characteristic	No. (%)	
	BIOMARK (N=817)	ATN (N=1124)
Age, mean (yrs)	60 (15.4)	59.7 (15.3)
Race		
White	626 (76.6)	835 (74)
Black	124 (15.2)	179 (16)
Hispanic	49 (6)	77(7)
Other	18 (2.2)	16 (3)
Male	567 (69.4)	793 (71)
Chronic hypoxemia	80 (9.8)	107 (9.5)
Liver disease	94 (11.5)	131 (11.7)
Cardiovascular disease[a]	309 (37.8)	411 (38.1)
Malignancy[b]	157 (19.2)	225 (20.0)
Immunosuppressive therapy[c]	123 (15.1)	178 (15.8)
Nephrotoxic AKI	198 (24.3)	286 (25)
Sepsis	424 (52)	579 (52)
Ischemic AKI	649 (79.5)	871 (77)
Post-surgery at RRT Initiation	433 (53.0)	558 (49.7)
Heart rate (beats /min)[d]	92 (19.2)	93 (19.4)
Mean arterial pressure, mmHg (SD)	74 (13.9)	74 (14.9)
Urine volume (mL/day)[d, (SD)]	362 (543)	373 (563)
Mechanical ventilation	660 (80.8)	905 (80.6)
Fio2>=60[d]	282 (40.5)	406 (42.3)
Arterial pH	7.3 (0.1)	7.3 (0.1)
Arterial oxygen partial pressure (mmHg)[d,]	107 (45.1)	108 (51.4)
Serum creatinine[e]	1 (0.3)	1 (0.4)

Table 1: Continued

Serum bicarbonate (mmol/L)[d]	22 (5.0)	21 (5.1)
Serum phosphate (mg/dl)[d]	5 (2.0)	5 (2.1)
Serum albumin (g/dl)[d]	2 (0.7)	2 (0.8)
Total bilirubin (mg/dl)[e]	0.7 (1.2)	0.8 (1.2)
INR[d,]	1.8 (0.9)	1.8 (1.6)
Platelet count (k/µl)	139 (114)	138 (114)
Charlson score without age	3 (2.4)	3 (2.5)
Oliguria	654 (80.1)	877 (78)
Apache II[†] score	26 (7.1)	26 (7.3)
Outcome at day 60		
Mortality	415 (50.8)	591 (52.6)
Alive and independent from RRT	298 (36.5)	398 (35.4)

Abbreviations: INR, International Normalized Ratio; RRT, Renal Replacement Therapy; ICU, Intensive Care Unit; APACHE, Acute Physiology and Chronic Health Evaluation; AKI, acute kidney injury.

[†] Acute Physiology and Chronic Health Evaluation II[6] includes initial values of 12 routine physiologic measurements, age, and previous health status ranging from 0 to 71; An increasing score is closely correlated with the subsequent risk of hospital death. All continuous variables were reported as means and standard deviation (SD). Categorical variables were reported as frequencies and percentages.

[a]History of angina, documented myocardial infarction, or congestive heart failure

[b]Solid tumor with or without metastases, leukemia, or lymphoma

[c]Positive HIV status, AIDS, non-renal organ transplantation, or immunosuppressive therapy

[d]Within 24 hrs of RRT initiation

[e]Premorbid serum creatinine taken at screening

[f] Z transformed variable

Table E2

Comparison of Imputed and Non-imputed Parameter Risk Estimates for ATN and BioMaRK Cohorts

Parameter	Imputed Estimate ATN (N=1125)	*P* value	Imputed Estimate BioMaRK (N=817)	*P* value	Non-imputed Estimate ATN (N=487)	*P* value	Non-imputed Estimate BioMaRK (N=368)	*P* value
Age	0.04	<0.01	0.04	<0.001	0.04	<0.001	0.03	<0.01
Chronic hypoxemia	0.73	0.07	0.62	0.03	1.27	0.00	1.11	0.01
Cardiovascular disease	0.27	0.03	0.18	0.36	0.01	0.96	0.12	0.67
Malignancy	0.99	<0.01	0.15	0.48	0.37	0.21	0.41	0.22
Immunosuppressive Therapy	-0.44	0.02	-0.37	0.13	-0.43	0.14	-0.63	0.06
Ischemic AKI	0.16	<0.05	-0.05	0.81	0.40	0.22	-0.15	0.67
Post-surgery at RRT Initiation	-0.45	0.08	-0.39	0.03	-0.21	0.36	-0.14	0.60
Heart Rate	0.01	<0.03	0.01	0.01	0.01	0.02	0.01	0.03
Mean arterial pressure	-0.02	<0.02	-0.03	<0.001	-0.02	0.03	-0.03	<0.02
Urine Volume	-0.14	0.02	-0.02	0.11	-0.03	0.04	-0.02	0.21
Mechanical Ventilation	1.03	<0.01	1.02	<0.001	1.13	0.01	1.18	0.01
Fio2>=60	3.07	<0.01	0.42	0.54	0.06	0.95	-0.03	0.98
Interaction of mechanical ventilation and Fio2 >=60	-1.53	<0.01	-0.10	0.89	0.27	0.79	0.24	0.81
Arterial pH	-2.64	0.06	-4.01	<0.001	-2.66	0.06	-3.70	0.02
Arterial oxygen partial pressure	-0.66	<0.05	-0.36	0.12	-0.14	0.63	-0.11	0.74
Serum Creatinine	-0.18	0.01	-0.17	0.51	0.11	0.61	0.48	0.21
Serum Bicarbonate	-0.03	0.02	-0.01	0.73	-0.06	0.02	-0.01	0.72
Serum Phosphate	0.02	0.05	0.03	0.46	-0.03	0.61	-0.04	0.54
Serum Albumin	-0.34	0.02	-0.08	0.53	-0.11	0.44	-0.04	0.81
Total Bilirubin	0.36	<0.01	0.43	<0.001	0.37	0.00	0.29	<0.01
INR	0.54	0.01	0.27	0.29	0.38	0.21	0.11	0.76
Platelet Count	-0.36	<0.01	-0.43	<0.001	-0.36	0.02	-0.44	0.02

Equation 1

Finding the Optimal Biomarker Cutoff Value

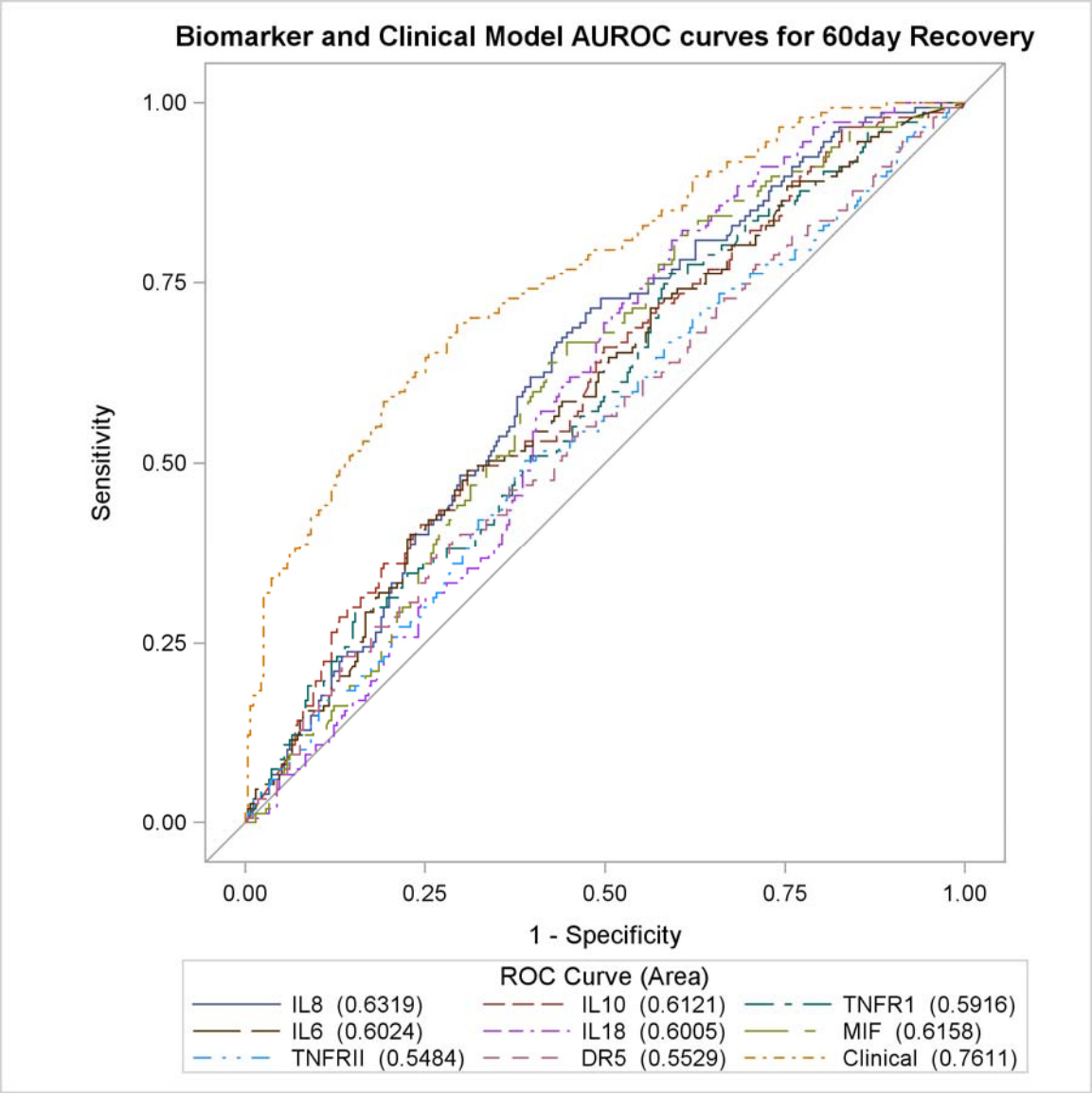
Youden's Index is given as J=Sensitivity+Specificity-1.The optimal biomarker cutoff is found by using the fitted probability p_{maxJ}, associated with the maximum value of Youden's Index (J_{MAX}) from a univariate biomarker logistic model, along with the fitted intercept and slope as follows:

$$CUTOFF_{optimal} = \left(\frac{\log\left(\frac{p_{\max J}}{1 - p_{\max J}} \right) - \hat{\beta}_{\text{int}}}{\hat{\beta}_{slope}} \right)$$

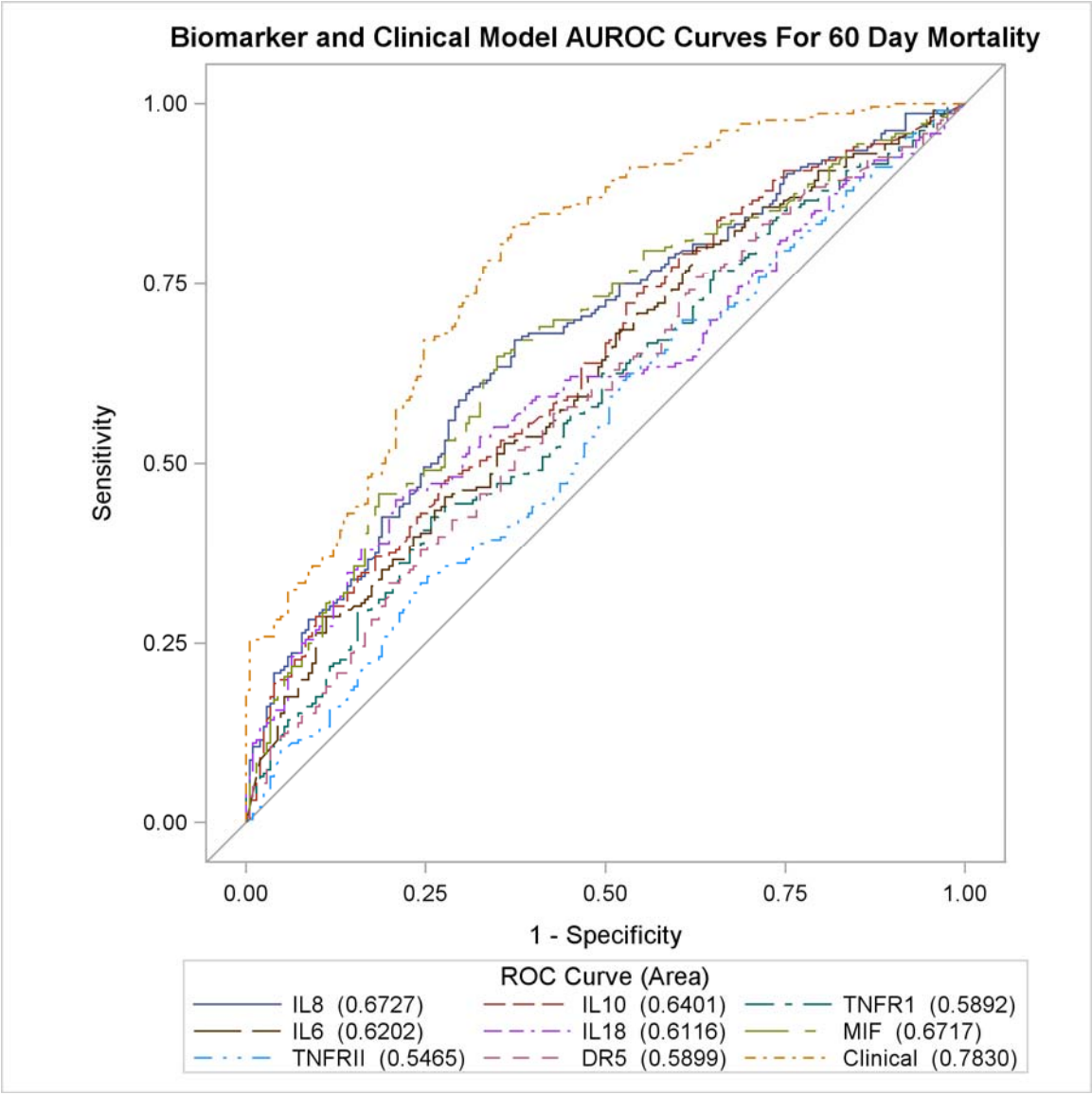
Where $\hat{\beta}_{\text{int}}$ and $\hat{\beta}_{slope}$ are the fitted intercept and slope from a univariate logistic mortality or recovery model with a continuous biomarker as the only predictor.

$$\log\left(\frac{p}{1 - p} \right) = \beta_{\text{int}} + \beta_{slope}\left(\text{Marker} \right)$$

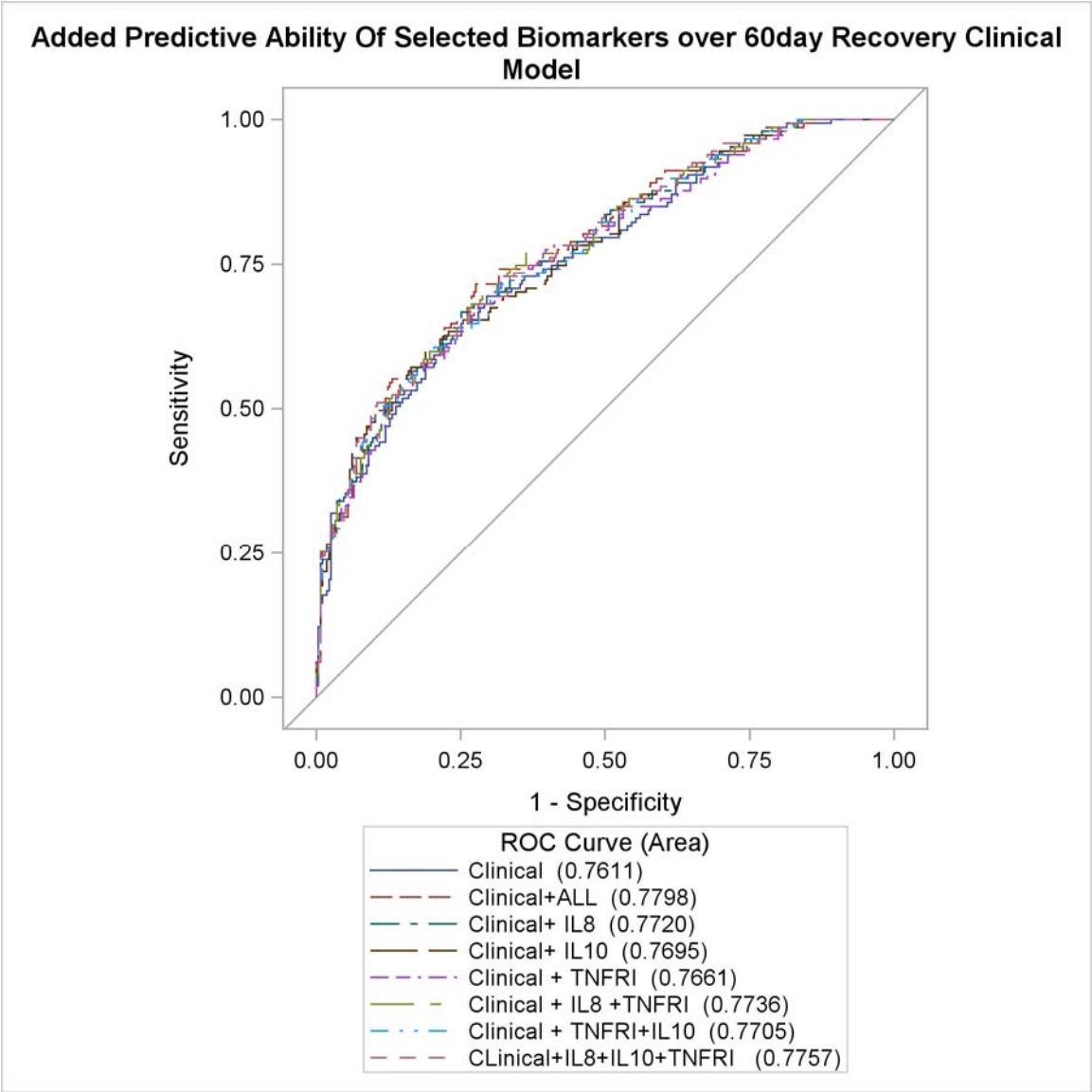
eFigure 1


Biomarker and Clinical Model AUROC curves for 60day Recovery
Sensitivity
1.00
0.75
0.50
0.25
0.00
0.00
0.25
0.50
0.75
1.00
1 - Specificity
ROC Curve (Area)
IL8 (0.6319)
IL6 (0.6024)
TNFRII (0.5484)
IL10 (0.6121)
IL18 (0.6005)
DR5 (0.5529)
TNFR1 (0.5916)
MIF (0.6158)
Clinical (0.7611)

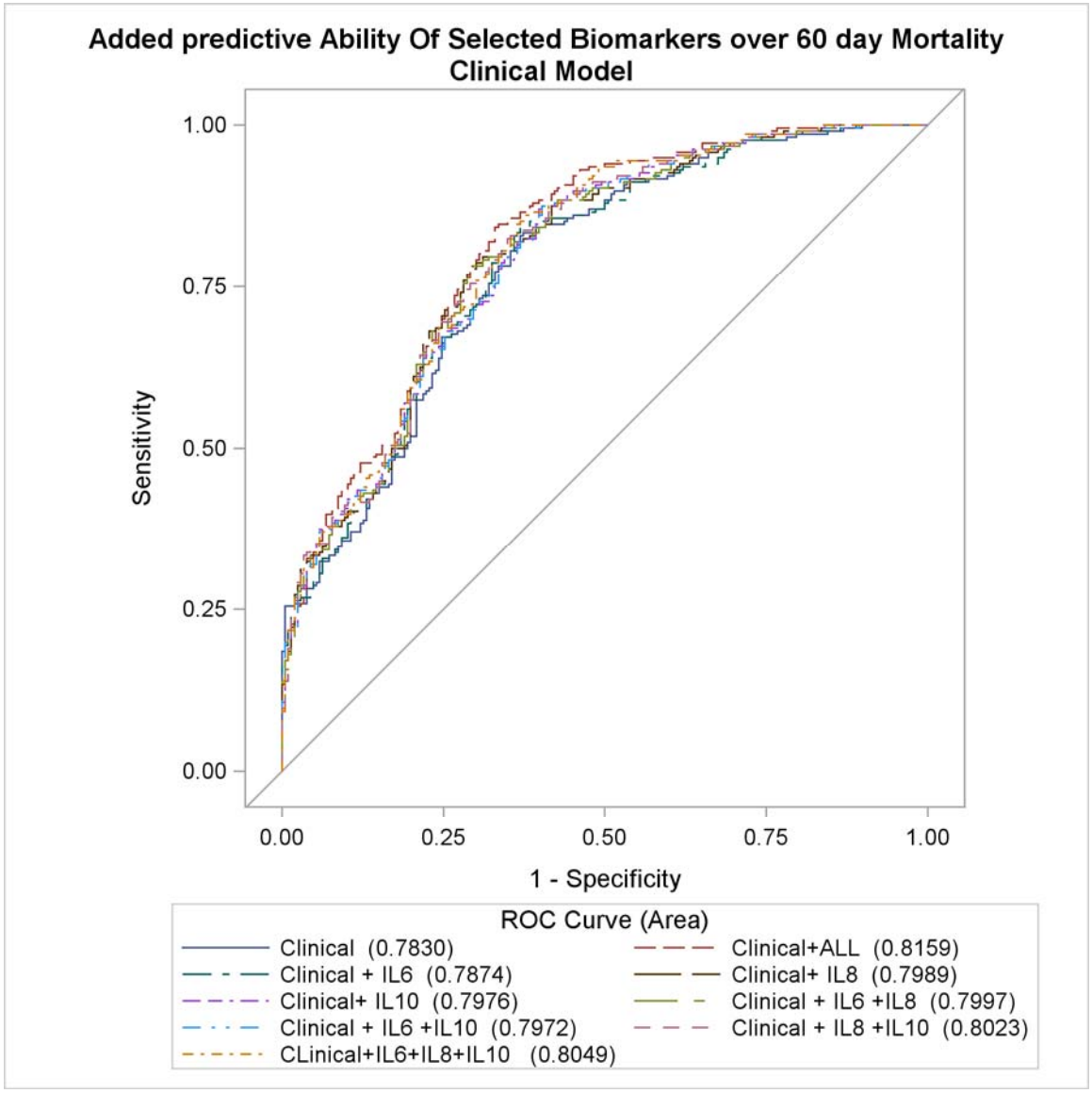
eFigure 2


Biomarker and Clinical Model AUROC Curves For 60 Day Mortality
Sensitivity
1.00
0.75
0.50
0.25
0.00
0.00
0.25
0.50
0.75
1.00
1 - Specificity
ROC Curve (Area)
IL8 (0.6727)
IL6 (0.6202)
TNFRII (0.5465)
IL10 (0.6401)
IL18 (0.6116)
DR5 (0.5899)
TNFR1 (0.5892)
MIF (0.6717)
Clinical (0.7830)

eFigure 3


Added Predictive Ability Of Selected Biomarkers over 60day Recovery Clinical Model
Sensitivity
1.00
0.75
0.50
0.25
0.00
0.00
0.25
0.50
0.75
1.00
1 - Specificity
ROC Curve (Area)
Clinical (0.7611)
Clinical+ALL (0.7798)
Clinical+ IL8 (0.7720)
Clinical+ IL10 (0.7695)
Clinical + TNFRI (0.7661)
Clinical + IL8 +TNFRI (0.7736)
Clinical + TNFRI+IL10 (0.7705)
CLinical+IL8+IL10+TNFRI (0.7757)

eFigure 4


Added predictive Ability Of Selected Biomarkers over 60 day Mortality
Clinical Model
Sensitivity
1.00
0.75
0.50
0.25
0.00
0.00
0.25
0.50
0.75
1.00
1 - Specificity
ROC Curve (Area)
Clinical (0.7830)
Clinical + IL6 (0.7874)
Clinical+ IL10 (0.7976)
Clinical + IL6 +IL10 (0.7972)
CLinical+IL6+IL8+IL10 (0.8049)
Clinical+ALL (0.8159)
Clinical+ IL8 (0.7989)
Clinical + IL6 +IL8 (0.7997)
Clinical + IL8 +IL10 (0.8023)

Item S1: Biomarker Assay

Interleukin-6, IL-8, IL-10, IL-1β, TNF, GM-CSF, TNFR-I, TNFR-II, and DR-5 were assayed utilizing Life Technologies Invitrogen™ Luminex® assays (Grand Island NY, USA). Plasma MIF and IL-18 were assayed utilizing Bio-Rad Bio-Plex® Luminex® assays (Hercules CA, USA). All assays were measured on the Bio-Rad Bio-Plex® 200 System with Bio-Plex Manager™ 4.0 software.