

Supplementary material

Plasma and Urinary Biomarkers Improve Prediction of Mortality through 1 Year in Intensive Care Patients: An Analysis from FROG-ICU

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Table S1a. Continuous covariates considered for inclusion in the prognostic models.

	N	Missing (%)	Mean	SD	Min	Q1	Median	Q3	Max
Demographics									
Age (year)	2087	0.0	61	16	18	51	63	74	98
Vitals at Inclusion									
Systolic BP (mmHg)	2037	2.4	124	23	40	108	122	139	220
Diastolic BP (mmHg)	1967	5.7	63	14	10	53	61	70	149
Heart Rate (bpm)	2009	3.7	93	21	42	78	92	106	190
Respiratory Rate (/min)	1546	25.9	21	7	8	16	20	25	51
Temperature (Celsius)	2040	2.3	37.2	1.0	27.0	36.7	37.2	37.8	40.9
Oxygen Saturation (%)	1976	5.3	97	3	70	96	98	100	100
Weight (Kg)	1750	16.1	79	19	30	65	78	90	212
Positive End-Expiratory Pressure (cmH2O)	1843	11.7	6	3	1	5	5	8	28
Expired volume (ml)	1558	25.3	484	118	60	410	470	534	1000
Fraction of inspired oxygen (%)	1920	8.0	43	17	21	30	40	50	100
PaO2/FiO2 Ratio	1770	15.2	224.8	140.9	2.0	123.3	220.0	316.7	709.5
Partial pressure of carbon dioxide (mmHg)	1894	9.2	39	9	20	34	38	43	126
Partial pressure of oxygen (mmHg)	1912	8.4	106	53	30	76	92	120	600
Local Laboratory at Inclusion									
White blood cell count (/mm3)	1938	7.1	12374	7496	500	7600	10900	16100	65100
Hemoglobin (g/dL)	1983	5.0	10.2	1.9	3.4	8.9	10.0	11.4	19.9
Platelets (/mm3)	1958	6.2	185750	120760	3000	99000	164000	243000	860000
Total protein (g/L)	1835	12.1	54	10	20	48	54	60	112
Urea (mmol/L)	1936	7.2	10.7	8.3	0.3	5.3	8.4	14.0	78.3
eGFR (ml/min/1.73 m2)	2087	0.0	80.4	44.9	6.0	40.0	77.5	117.6	150.0
Uric acid (μmol/L)	1984	4.9	217.0	139.4	30.0	116.5	183.0	288.6	1175.8
Sodium (mmol/L)	2030	2.7	140	5	116	137	140	143	158
Potassium (mmol/L)	2008	3.8	3.9	0.6	2.6	3.6	3.9	4.3	7.0
Chloride (mmol/L)	2077	0.5	102	7	70	99	103	107	129
Glycemia (mmol/L)	1958	6.2	7.9	2.7	0.1	6.2	7.4	9.1	26.9
Lactate (mmol/L)	1647	21.1	1.71	1.51	0.06	0.98	1.30	1.90	16.00
Arterial pH	1905	8.7	7.41	0.08	7.00	7.36	7.42	7.46	7.84
Bicarbonates (mmol/L)	1758	15.8	24	5	6	21	24	26	50
Diuresis of 24 hours (ml/24h)	1690	19.0	1652	1254	1	800	1388	2200	10000
Central Laboratory/Biomarkers at Inclusion									

Soluble-ST2 (ng/mL)	2063	1.1	520.0	455.5	3.5	182.3	345.6	765.1	2321.1
Proenkephalin (pmol/L)	2075	0.6	100.4	116.1	11.5	36.5	61.2	116.2	1398.6
Bioactive-adrenomedullin (pg/mL)	2074	0.6	116.1	156.1	4.0	34.7	66.6	135.2	1926.1
Galectin-3 (ng/mL)	2076	0.5	27.4	20.1	5.2	14.2	21.0	33.0	114.0
PCT (ng/mL)	2075	0.6	8.3	20.9	0.0	0.3	1.1	5.8	186.7
IL-6 (pg/mL)	2076	0.5	678.2	3622.4	1.5	43.5	100.9	261.7	50000.0
CRP (mg/L)	2077	0.5	159.1	102.2	0.6	78.6	143.7	219.8	547.3
NT-proBNP (pg/mL)	2076	0.5	4828	8486	5	293	1202	4516	35000
Troponin T (pg/mL)	2076	0.5	306.6	1001.6	3.0	17.5	45.7	143.1	10000.0
Cystatin-C (mg/L)	2077	0.5	1.7	1.1	0.0	0.9	1.3	2.1	9.5
NGAL (ng/mL)	2041	2.2	428	613	1	97	209	509	7668
Urinary Albumin (mg/L)	2077	0.5	1088	1473	84	300	384	478	4000
Urinary Cystatin-C (mg/L)	1926	7.7	2.6	5.7	0.0	0.1	0.3	1.9	50.1
Urinary NGAL (ng/mL)	1927	7.7	454.9	564.5	0.9	38.8	135.4	740.8	1500.0
Urinary L-FABP (ng/mL)	1916	8.2	450.4	3160.2	0.1	10.3	31.6	92.0	64800.0
Disease Severity Scores at Admission									
APACHE II	971	53.5	22.29	7.67	3	17	23	28	42
SOFA score	1518	27.3	8	4	0	5	8	10	22
SAPS II	2086	0.0	50	19	0	36	49	63	110
Glasgow Coma Scale	1696	18.7	11	5	3	5	14	15	15
Charlson Comorbidity Index	1736	16.8	4	2	1	2	4	5	12
Novel Urinary Biomarker at Inclusion									
HF1-classifier	1649	21.0	-0.09	0.95	-3.38	-0.75	-0.09	0.64	2.53
HF2-classifier	1649	21.0	-0.06	0.59	-2.21	-0.45	-0.06	0.33	2.22
CAD238-classifier	1649	21.0	-0.34	0.26	-1.06	-0.51	-0.39	-0.21	0.95
CKD273-classifier	1686	19.2	0.44	0.39	-1.11	0.21	0.56	0.73	1.19
ACM128-classifier	1624	22.2	-0.27	0.69	-1.98	-0.76	-0.35	0.16	2.39

Table S1b. Categorical variables considered for inclusion in the prognostic models.

	Missing (%)	n	N	%
Demographics				
Male gender	0	1361	2087	65.2
Diagnosis at Admission	0			
Cardiac disease		325	2086	15.6
Acute neurological disorder		286	2086	13.7
Acute respiratory failure		394	2086	18.9
Sepsis		536	2086	25.7
Trauma		199	2086	9.5
Other		346	2086	16.6
Admission Unit	0			
Cardiac Ward		91	2087	4.4
Emergency Room		563	2087	27
Home		206	2087	9.9
Medical		9	2087	0.4
Medical ICU		95	2087	4.6
Medical Ward		274	2087	13.1
Operating Room		187	2087	9
Scheduled Surgical		51	2087	2.4
Surgical ICU		168	2087	8
Surgical Ward		219	2087	10.5
Unscheduled Surgical		47	2087	2.3
Trauma		47	2087	2.3
Other		130	2087	6.2
Status at Admission				
Cardiac arrest before admission	0.2	178	2082	8.5
Kidney Disease Improvement Global Outcome	4.3			
0		1485	1998	74.3
1		309	1998	15.5
2		133	1998	6.7
3		71	1998	3.6
Chronic treatments				
Oxygen at home	0.9	29	2068	1.4
Aldosterone antagonists	0.9	14	2068	0.7
Diuretics	0.9	449	2068	21.7
Antiplatelets	0.9	533	2068	25.8
Calcium antagonist	0.9	285	2068	13.8
Inhaled steroids	0.9	82	2068	4
Psychiatric treatment	0.9	457	2068	22.1
Morphine	0.9	53	2068	2.6
Insulin	0.9	118	2068	5.7

ACE Inhibitors or ARB	0.9	553	2068	26.7
Cardiac glycosides	0.9	30	2068	1.5
Nitrates	0.9	15	2068	0.7
Vitamin K Antagonists	0.9	173	2068	8.4
Statins	0.9	497	2068	24
Beta-2 mimetics	0.9	104	2068	5
Antidiabetics	0.9	222	2068	10.7
Beta Blocker Non cardio selective	0.9	155	2068	7.5
Beta Blocker Cardio selective	0.9	370	2068	17.9
Amiodarone	0.9	109	2068	5.3
Immunosuppressive agents	0.9	60	2068	2.9
Hydrocortisone	0.9	163	2068	7.9
CV Comorbidities				
Chronic heart failure	0.2	153	2083	7.3
Diabetes mellitus	0.2	384	2083	18.4
Hypertension	0.2	902	2083	43.3
Prior myocardial infarction	0.2	83	2083	4
Severe valvular disease or previous valvular surgery	0.2	82	2083	3.9
Prior stroke	0.2	92	2083	4.4
Peripheral vascular disease including carotid artery disease	0.2	209	2083	10
Pulmonary embolism	0.2	58	2083	2.8
Dyslipidemia	0.2	412	2083	19.8
Obesity	0.2	227	2083	10.9
Coronary artery disease	0.2	188	2083	9
Atrial fibrillation flutter	0.2	221	2083	10.6
Pulmonary hypertension	0.2	33	2083	1.6
Congenital heart defect	0.2	11	2083	0.5
Pacemaker	0.2	54	2083	2.6
Cardiac resynchronization therapy	0.2	11	2083	0.5
Prior Coronary Revascularization	0.2	126	2083	6
Cardiac Defibrillator	0.2	16	2083	0.8
Non-CV Comorbidities				
COPD	0.2	273	2083	13.1
Chronic liver disease	0.2	158	2083	7.6
Depression	0.2	261	2083	12.5
Dysthyroidism	0.2	140	2083	6.7
Cognitive dysfunction	0.2	33	2083	1.6
Smoking	0.2	570	2083	27.4
Alcohol	0.2	365	2083	17.5
Hemodialysis	0.2	28	2083	1.3
Chronic renal disease	0.2	241	2083	11.6
Active recent malignant tumors	0.2	281	2083	13.5
Asthma	0.2	93	2083	4.5

Anemia	0.2	33	2083	1.6
Chronic inflammatory disease	0.2	77	2083	3.7
Loss of autonomy	0.2	78	2083	3.7
HIV	0.2	53	2083	2.5
Medications (Admission to Inclusion)				
Stockings compression	0.3	521	2080	25
Inotrope/vasopressor	0.3	1490	2080	71.6
RBC Transfusion	0.3	476	2080	22.9
Feeding Enteral	0.3	1032	2080	49.6
Hydrocortisone	0.3	581	2080	27.9
Renal Replacement Therapy	0.3	219	2080	10.5
ECMO	0.3	28	2080	1.3
Feeding Parenteral	0.3	363	2080	17.5
Coronary revascularization	0.3	37	2080	1.8
Heparin	0.3	1577	2080	75.8
Other device	0.3	442	2080	21.2
Vasodilator	0.3	196	2080	9.4
Morphine	0.3	1539	2080	74
Benzodiazepine	0.3	1028	2080	49.4
Neuromuscular blocking agents (curare)	0.3	720	2080	34.6
Amiodarone	0.3	334	2080	16.1

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; HIV, human immunodeficiency virus; ICU, intensive care unit, RBC, red blood cells.

Table S2. Centrally measured biomarkers at study inclusion considered in prognostic models.

Biomarker	Assay	Function and clinical implication
<i>Plasma biomarkers included in model(s)</i>		
Bioactive-adrenomedullin (pg/mL)	Adrenomed GmbH, Hennigsdorf, Germany	vasodilatation, induction of angiogenesis, protection against oxidative stress and hypoxic injury: marker of myocyte stress
Galectin-3 (ng/mL)	Abbott, Abbott Park, IL, USA	involve in inflammation, fibrosis and neoplastic transformation: marker of heart failure
Interleukin-6 (pg/mL)	Roche, Penzberg, Germany	pro-inflammation and anti-inflammation cytokine: marker of inflammation/infection
Procalcitonin (ng/mL)	Adrenomed GmbH, Hennigsdorf, Germany	precursor of calcitonin: marker of infection, mostly bacterial
Soluble-ST2 (ng/mL)	Eurobio, Critical Diagnostics, San Diego, CA, USA	involve in inflammation, fibrosis, and cardiac stress: marker of myocyte stress
<i>Plasma biomarkers also considered</i>		
C-reactive protein (mg/L)	Abbott, Abbott Park, IL, USA	acute-phase protein: marker of inflammation/infection
Cystatin-C (mg/L)	Abbott, Abbott Park, IL, USA	protein derived by all nucleated cells, reabsorbed by proximal tubular cells: marker of decrease glomerular filtration rate
NGAL (ng/mL)	Abbott, Abbott Park, IL, USA	involve in innate immunity: marker of renal tubular injury
NT-proBNP (pg/mL)	Roche Diagnostics GmbH, Mannheim, Germany	biologically inactive segment of BNP: marker of myocyte stress
Proenkephalin (pmol/L)	Sphingotec GmbH, Hennigsdorf, Germany	endogenous opioid polypeptide hormone: marker of cardiovascular and cerebrovascular disease
Troponin T (pg/mL)	Abbott, Abbott Park, IL, USA	part of troponin complex, heart contraction: marker of myocyte injury
<i>Urinary biomarkers included in model(s)</i>		
Proteomic Classifier: ACM128	Mosaiques Diagnostics, Hanover, Germany	consist of 128 urinary peptide fragments
Proteomic Classifier: CKD273	Mosaiques Diagnostics, Hanover, Germany	consist of 273 urinary peptide fragments: marker of early fibrosis of the kidney
Proteomic Classifier: HF1	Mosaiques Diagnostics, Hanover, Germany	consist of 85 urinary peptide fragments: marker of left ventricular dysfunction
<i>Urinary biomarkers also considered</i>		
Urinary Albumin (mg/L)	Abbott, Abbott Park, IL, USA	involve in glomerular injury: marker of renal glomerular injury
Urinary Cystatin-C (mg/L)	Abbott, Abbott Park, IL, USA	protein derived by all nucleated cells, reabsorbed by proximal tubular cells: marker of renal tubular injury
Urinary L-FABP (ng/mL)	Nordia L-FABP; Sekisui Medical Co., Ltd., Tokyo, Japan	involve in renal tubulointerstitial damage: marker of renal tubular injury
Urinary NGAL (ng/mL)	Abbott, Abbott Park, IL, USA	involve in innate immunity: marker of renal tubular injury
Proteomic Classifier: CAD238	Mosaiques Diagnostics, Hanover, Germany	consist of 238 urinary peptide fragments: marker of cardiovascular disease
Proteomic Classifier: HF2	Mosaiques Diagnostics, Hanover, Germany	consists of 671 urinary peptide fragments: marker of left ventricular dysfunction

Figure S1. Calibration Plots for Multivariable Logistic Regression and Cox Proportional Hazards Models for A) In-ICU Mortality, B) In-Hospital Mortality, and C) 1-Year Survival. Results are presented for the first multiple imputation dataset.

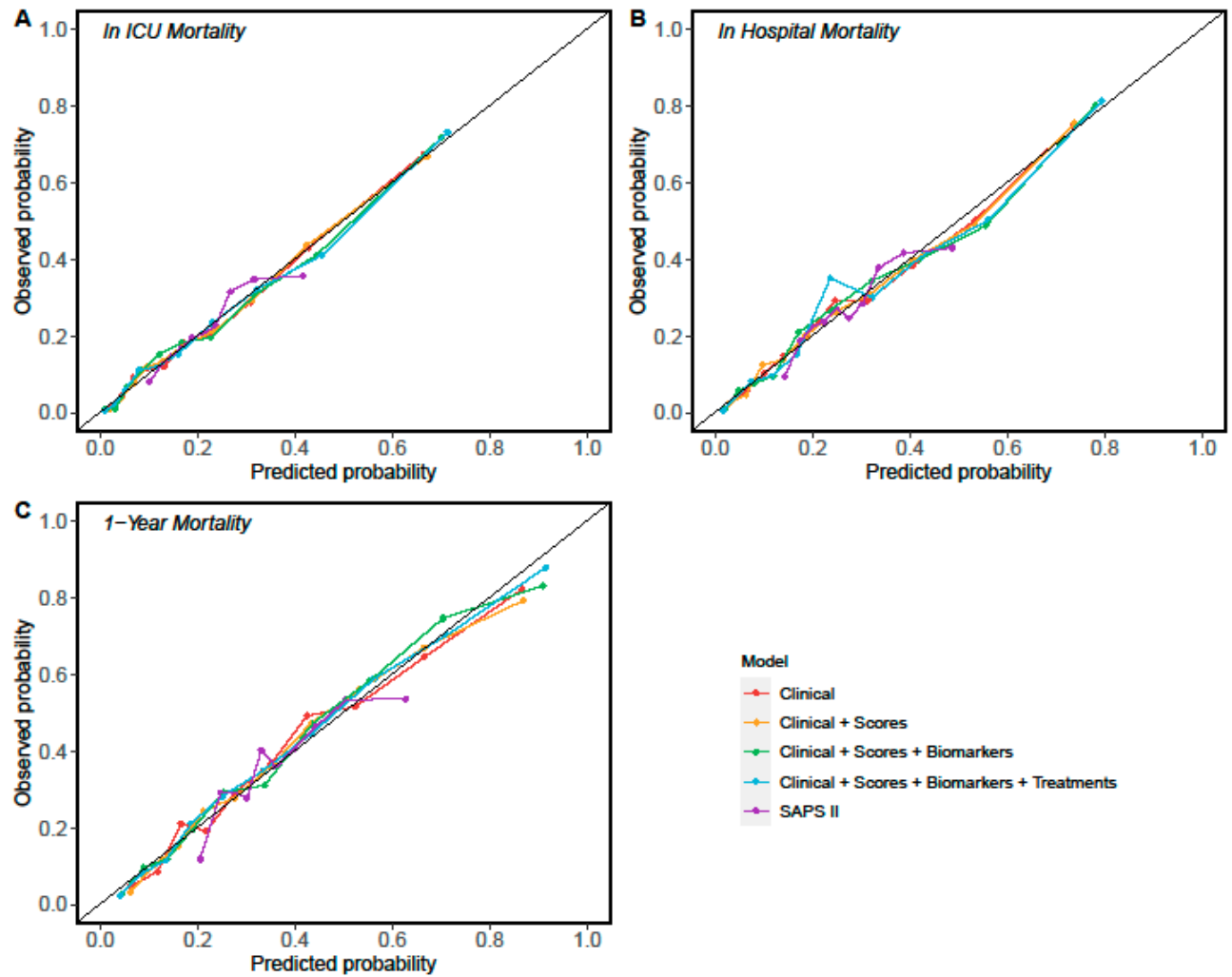


Figure S2. Receiver Operating Characteristic Curves for Multivariable Logistic Regression Models for A) In-ICU Mortality, B) In-Hospital Mortality, and C) 1-Year Survival. Results are presented for the first multiple imputation dataset.

