Prediction of impending septic shock in children with sepsis

Supplementary Materials

Authors: Ran Liu, BS[1,2], Joseph L. Greenstein, PhD[1,2], James C. Fackler, MD[3], Jules Bergmann, MD[3], Melania M. Bembea, MD, MPH, PhD[3,4], Raimond L. Winslow, PhD[1,2]

Affiliations:

[1]Institute for Computational Medicine, The Johns Hopkins University

[2]Department of Biomedical Engineering, The Johns Hopkins University School of Medicine & Whiting School of Engineering

[3]Department of Anesthesiology and Critical Care Medicine, and [4]Department of Pediatrics, The Johns Hopkins University School of Medicine

Materials and Methods:

Labeling Clinical States

We applied four sets of criteria for determining sepsis and septic shock in pediatric patients: the Sepsis-2-based Goldstein criteria[1], and three sets of Sepsis-3 criteria adapted for sepsis patients. The Goldstein criteria define sepsis as the presence of suspected infection with concurrent fulfillment of 2 or more SIRS criteria[1]. A full list of age-adjusted criteria for variables used in determining SIRS is given in Table S5. For SIRS, septic shock is defined as sepsis occurring with cardiovascular dysfunction. Cardiovascular dysfunction is defined as hypotension, which is determined as a mean arterial pressure (MAP) below the 5th percentile for age, computed as 1.5 × (age in years) + 40 mmHg[2], or the administration of vasopressors, or a lactate concentration of 2.5 mmol/L and urine output <0.5 mL/kg/hr[1].

Sepsis-3[3] defines sepsis as organ dysfunction consequent to suspected infection. Our three sets of Sepsis-3 criteria are defined by the different methods by which we determine the presence of organ dysfunction. The first is using age-adjusted SOFA score[4,5], where organ dysfunction is determined by a 2-point increase in age-adjusted SOFA score. Age-adjusted SOFA score, as suggested by Matics et al., uses the PELOD-2 age cutoffs for MAP and creatinine[5]. A full list of age cutoffs for variables used in calculating age-adjusted SOFA score is given in Table S6. The second and third Sepsis-3 criteria determine organ dysfunction using PELOD-2 score, where either a 2-point increase or a 6-point increase in PELOD-2 score indicates organ dysfunction[6,7]. Septic shock patients are those that have sepsis, have received adequate fluid resuscitation, require vasopressors to maintain MAP of at least the 5th percentile by age, and have a serum lactate concentration >2 mmol/L. Adequate fluid resuscitation was determined using the 2020 Pediatric SSC guidelines[8,9]: adequate fluid resuscitation is defined as having received 40 mL/kg of fluids, or having attained fluid resuscitation targets of MAP of at least the 5th percentile by age.

Results in an Independent Cohort

We applied the same methodology for data extraction and applied the same criteria for generating clinical state labels to EHR data from PIC[10]. Mean blood pressure values were computed from systolic and diastolic blood pressure values as 1/3 systolic BP + 2/3 diastolic BP. Items ids corresponding to each queried clinical feature are given in Table S12. For external testing of our septic shock risk models and methodology for early prediction, models for risk score, structural timeseries models, and mean values for imputation were fitted on data from the Johns Hopkins PICU, and then evaluated on data from PIC.

Discussion:

Spectral Clustering

In the spectral clustering approach to patient stratification used in this analysis, the eigengap heuristic is used to determine the optimal number of clusters. This procedure selects k (i.e. the number of clusters) such that the gap between the k-th and (k+1)-th eigenvalues of the graph Laplacian is relatively large compared with gaps between all other consecutive pairs of eigenvalues. Geometrically, by the Davis-Kahan theorem, this guarantees that the eigenvectors of the graph Laplacian are robust to small perturbations in the data[11]. Intuitively, this means that the results of spectral clustering for a selected value of k will be robust to small changes in the data, which is one common measure of goodness of fit for clustering algorithms[12].

Using this method, we infer that the optimal number of clusters in our dataset is 2, as the gap between the 2nd and 3rd eigenvalues of the graph Laplacian is largest (Figure S2). We find that higher risk clusters have higher mortality, prevalence of septic shock, and fewer patients who are adequately fluid resuscitated at time of early prediction, trends that are consistent with our previous observations in adult patients[13]. However, we did not find a statistically significant difference in median EWT or in the proportion of patients receiving vasopressors.

The separation between the two clusters, either for risk score or any individual physiological variable, can be quantified by the Kullback-Leibler divergence[14] (Figure S3) between their distributions. We find that clusters are more separable by risk score than by any single physiological variable, and that clusters are indistinguishable prior to time of early prediction (time of threshold crossing). The evolution of physiological variable clusters is similar to that of risk score clusters (Figure S4), as distributions of lactate and GCS are indistinguishable between the two clusters prior to entry into pre-shock, but diverge after time of threshold crossing. Cluster 1 has a higher risk score than cluster 2, and has correspondingly higher values of lactate, and lower values of GCS, reflecting the more severe state of the patients.

Supplementary Figures:

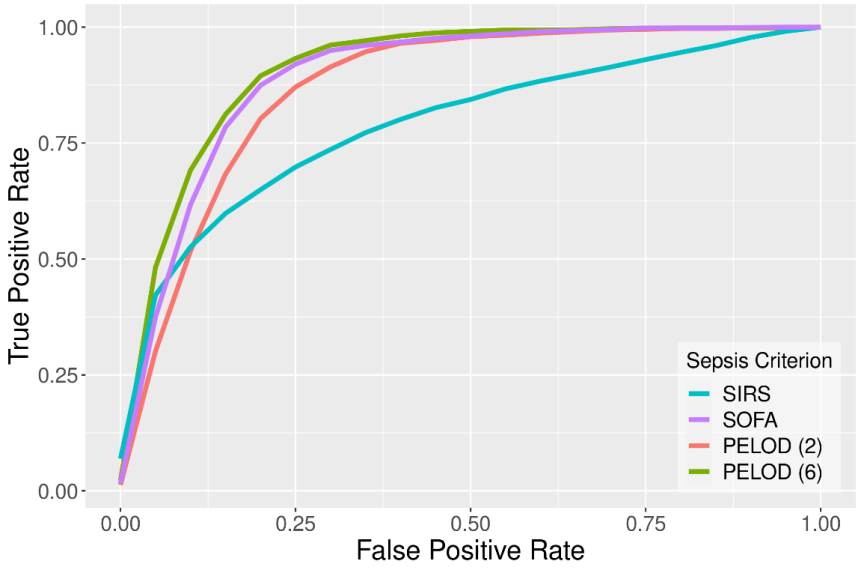

Figure S1: Average ROC curves for early prediction using different clinical criteria for labeling of sepsis and septic shock patients.

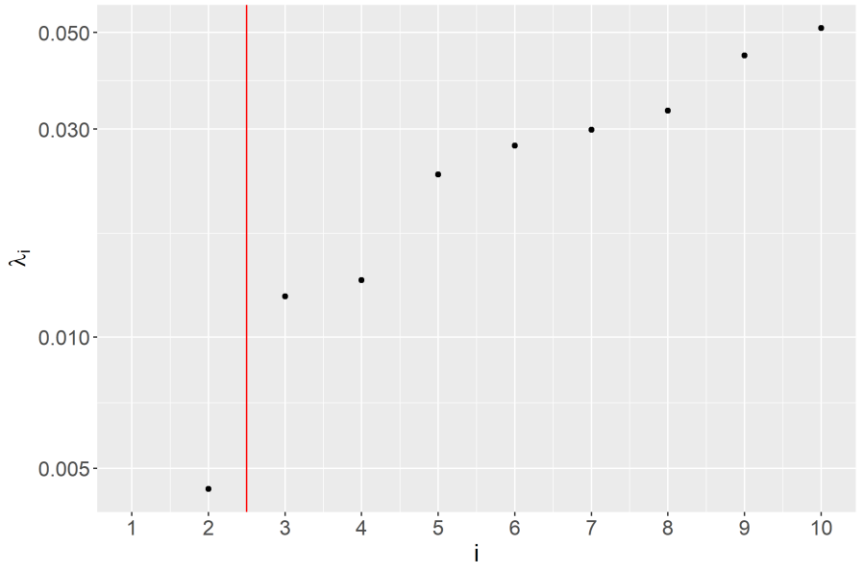

Figure S2: Eigenvalues of Graph Laplacian of risk trajectories following time of early prediction.

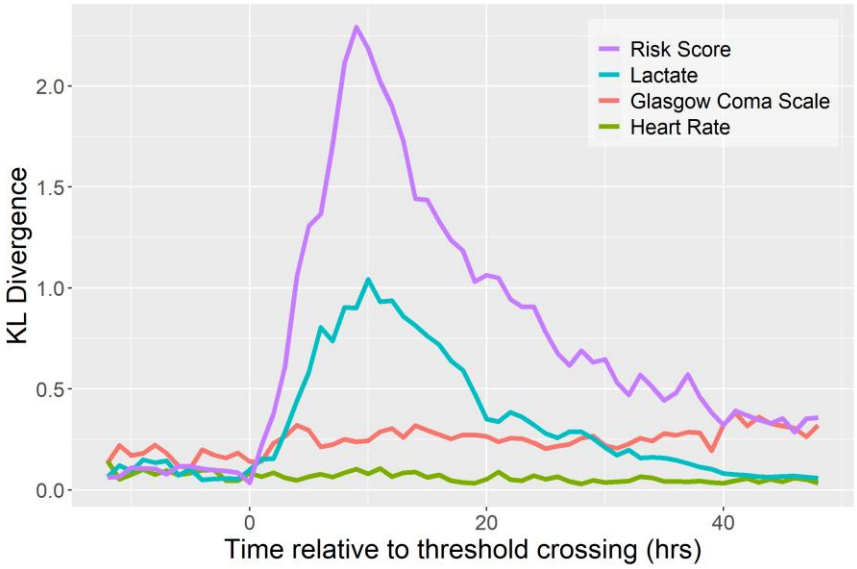

Figure S3: Kullback-Leibler divergences of risk score, heart rate, lactate, and MAP in the pediatric dataset.

Figure S4: Trajectories of lactate (A) and GCS (B) for the 2 clusters of patients illustrated in Figure 3. Solid lines indicate the mean value of each feature within each cluster. Shaded areas indicate an interval of 1 standard deviation from the mean.

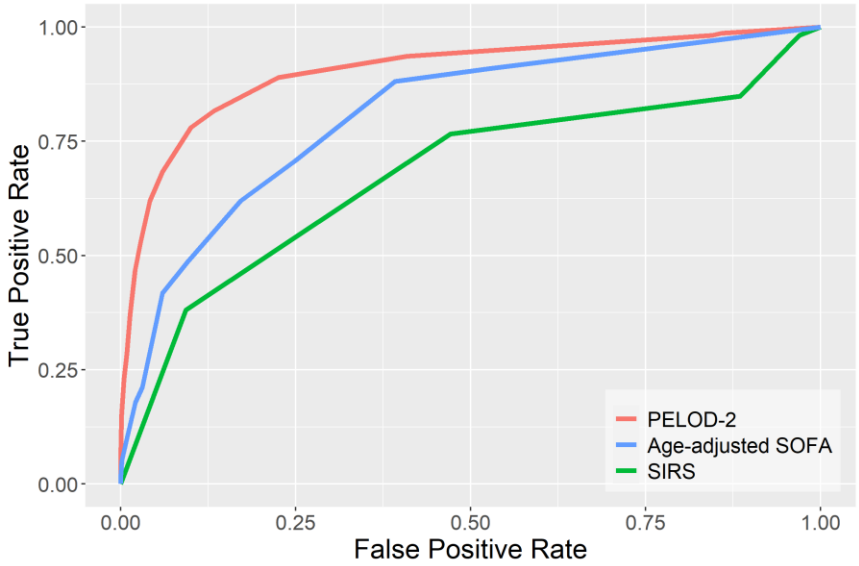

Figure S5: ROC curves for prediction of mortality using most severe value of PELOD-2, age-adjusted SOFA, and SIRS.

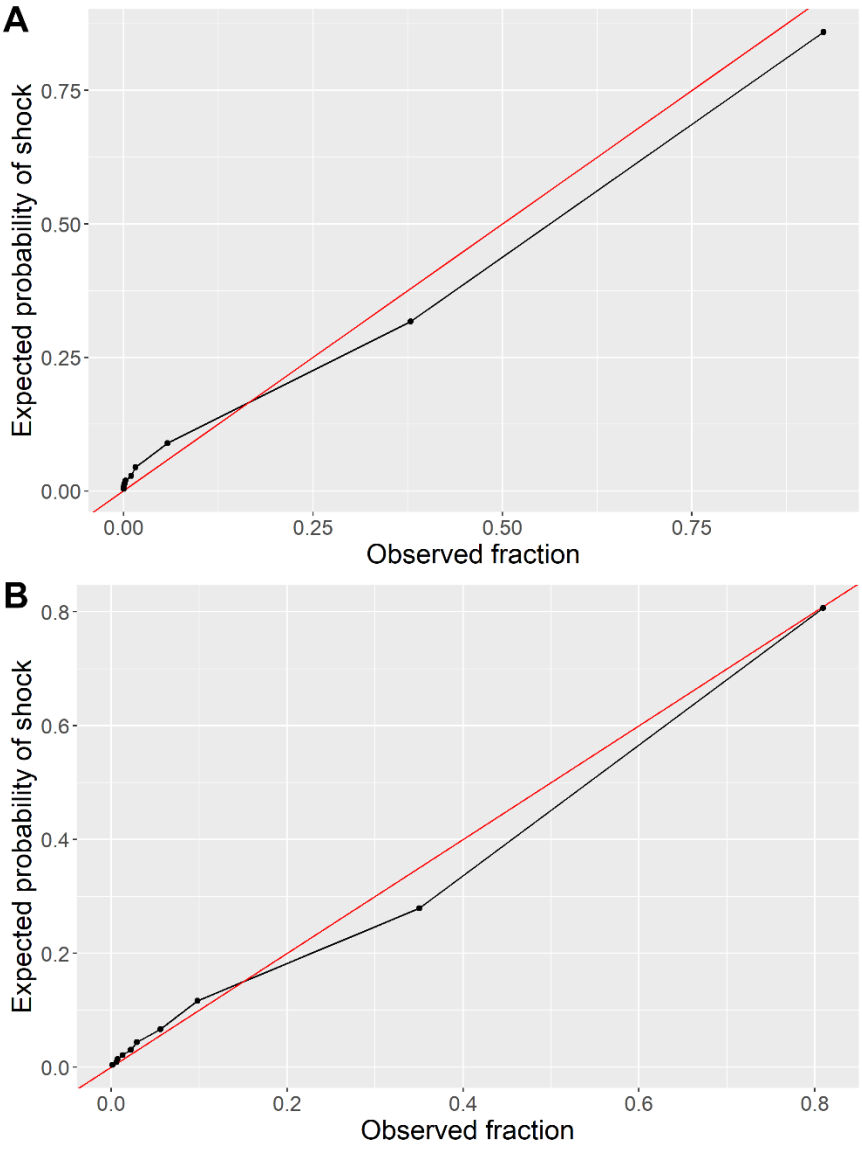

Figure S6: Calibration curves for (A) XGBoost and (B) GLM models, giving average risk score (which is equivalent to the expected probability of septic shock) vs observed fraction of septic shock in each decile of risk. The line $y = x$ is indicated in red.

Supplementary Tables:

Table S1: Pediatric Complex Chronic Conditions

Comorbidity	Non-sepsis	Sepsis without shock	Shock	Overall
Neurological/neuromuscular	20.72%	31.92%	34.08%	22.77%
Cardiovascular	20.16%	39.07%	60.51%	24.26%
Respiratory	9.39%	18.70%	23.57%	11.21%
Renal and urologic	6.28%	13.72%	17.83%	7.74%
Gastrointestinal	18.63%	38.65%	39.49%	22.18%
Hematological/immunological	4.18%	13.05%	19.11%	5.96%
Metabolic	11.60%	23.77%	39.81%	14.32%
Congenital/genetic	9.67%	16.13%	19.43%	10.93%
Malignancy	3.78%	8.56%	7.64%	4.59%
Premature and neonatal	5.75%	23.44%	37.26%	9.36%
Technology dependence	24.01%	43.64%	48.73%	27.65%
Transplant	0.90%	2.66%	7.01%	1.37%

Table S2: Age-adjusted SIRS criteria.

Age Range	Temperature (°C)	Heart Rate (beats/min)	Respiratory Rate (breaths/min)	WBC Count (k/mm^3)
0-1 week	<36 or >38.5	>180 or <100	>50	>34
1 week-1 month	<36 or >38.5	>180 or <100	>40	>19.5 or <5
1 month-1 year	<36 or >38.5	>180 or <90	>34	>17.5 or <5
2-5 years	<36 or >38.5	>140	>22	>15.5 or <6
6-12 years	<36 or >38.5	>130	>18	>13.5 or <4.5
13-17 years	<36 or >38.5	>110	>14	>11 or <4.5

Table S3: Age-adjusted SOFA Score

A. Mean Arterial Pressure Age Cutoffs for Cardiovascular SOFA Score

Age \ Cardiovascular SOFA Score	0	1
<1 month	MAP <46 mmHg	MAP ≥46 mmHg
1 - <12 months	MAP <55 mmHg	MAP ≥55 mmHg
12 - <24 months	MAP <60 mmHg	MAP ≥60 mmHg
24 - <60 months	MAP <62 mmHg	MAP ≥62 mmHg
60 - <144 months	MAP <65 mmHg	MAP ≥65 mmHg
≥144 months	MAP <67 mmHg	MAP ≥67 mmHg

B. Creatinine Age Cutoffs for Kidney SOFA Score

Age \ Kidney SOFA Score	0	2
<1 month	Creatinine ≤69 µmol/L	Creatinine >69 µmol/L
1 - <12 months	Creatinine ≤22 µmol/L	Creatinine >22 µmol/L
12 - <24 months	Creatinine ≤34 µmol/L	Creatinine >34 µmol/L
24 - <60 months	Creatinine ≤50 µmol/L	Creatinine >50 µmol/L
60 - <144 months	Creatinine ≤58 µmol/L	Creatinine >58 µmol/L
≥144 months	Creatinine ≤92 µmol/L	Creatinine >92 µmol/L

Table S4: Availability of EHR data

Feature	**% of Patients with at least 1 entry**	**Average time (hrs) between observations (mean/median)**	**Observations per admission (mean/median)**
Risk Score	100.00	1.83/1.00	190.50/53
Heart Rate	100.00	1.20/1.00	132.50/34
Systolic Blood Pressure	99.85	2.36/2.00	67.17/20
Diastolic Blood Pressure	99.85	2.36/2.00	67.17/20
Mean Arterial Pressure	99.92	1.63/1.00	95.99/19
Respiratory Rate	99.98	1.28/1.00	123.87/33
Temperature	99.98	2.34/2.00	68.06/13
Central Venous Pressure	11.11	0.99/0.50	14.42/0
PaO_2	27.24	10.63/3.53	6.58/0
FiO_2	73.59	1.62/1.00	61.04/0
GCS	50.15	2.45/2.00	20.66/0
Bilirubin	51.36	43.96/23.83	3.98/1
Platelets	67.44	33.02/22.18	6.35/1
Lactate	36.77	18.18/4.28	5.07/0
BUN	74.65	28.28/22.32	7.91/2
Arterial pH	24.84	8.28/3.63	5.77/0
WBC	28.52	131.33/27.43	0.66/0
$PaCO_2$	27.24	10.58/3.53	6.59/0
Hemoglobin	32.98	25.44/4.10	3.20/0
Hematocrit	68.24	33.21/22.43	6.41/2
Potassium	71.68	29.10/22.53	7.60/2

Table S5: Central Tendency Measures of Patient Physiological Data

Feature	**Mean**	**Median**
Heart Rate (bpm)	124.52	126.00
Systolic BP (mmHg)	97.30	97.00
Diastolic BP (mmHg)	55.46	54.00
MAP (mmHg)	69.74	68.00
Respiratory Rate (bpm)	35.68	33.00
Temperature (°F)	98.18	98.20
CVP (mmHg)	13.37	11.00
PaO_2 (mmHg)	119.87	97.00
FiO_2 (%)	53.21	40.00
GCS	12.08	14.00
Bilirubin (mg/dL)	2.34	0.60
Platelets (1000/µL)	219.78	182.00
Lactate (mmol/L)	2.10	1.50
BUN (mg/dL)	17.16	12.00
Arterial pH	7.36	7.37
WBC (1000/µL)	72.15	6.00
$PaCO_2$ (mmHg)	47.49	45.00
Hemoglobin (g/dL)	11.27	11.10
Hematocrit (%)	31.51	30.70
Potassium (mmol/L)	4.18	4.10

Table S6: Queried items in the pediatric dataset

Feature	Table	Items
Heart Rate	Flowsheet	8
Systolic/Diastolic BP	Flowsheet	5
Mean Arterial Pressure	Flowsheet	301250,301360
Respiratory Rate	Flowsheet	9
Temperature	Flowsheet	6
CVP	Flowsheet	301370
PaO_2	Labs	2000000122
FiO2	Flowsheet	301550,1601063025,3040019917,304064870
GCS	Flowsheet	30440104971,30440104966
Bilirubin	Labs	2000000107
Platelets	Labs	2000000008
Lactate	Labs	2000000900
BUN	Labs	2000000100
pH	Labs	2000000120
WBC	Labs	2000000722
$PaCO_2$	Labs	2000000121
Hemoglobin	Labs	2000000897
Hematocrit	Labs	2000000003
Potassium	Labs	2000000096

Table S7: Performance metrics

Model	AUC	Sensitivity	Specificity	PPV	Median EWT (hrs)
XGBoost	0.90	0.84	0.82	0.43	8.9
GLM	0.87	0.83	0.75	0.35	12.0
Cox	0.82	0.76	0.76	0.34	14.9
SOFA	0.72	0.61	0.67	0.24	29.2

Table S8: Feature importance using (A) XGBoost and (B) GLM for top 10 selected features, sorted in descending order of relative importance.

A. XGBoost

Feature	Gain	Cover	Frequency
Lactate	0.451	0.243	0.156
Respiratory SOFA	0.133	0.083	0.052
GCS	0.095	0.129	0.089
FiO_2	0.037	0.066	0.083
Liver SOFA	0.036	0.044	0.026
Heart Rate	0.028	0.057	0.057
Platelets	0.027	0.038	0.057
Temperature	0.020	0.031	0.036
Urine Output	0.019	0.034	0.042
BUN	0.016	0.033	0.031

B. GLM

Feature	Coefficient	SE	Odds Ratio
Lactate	1.758	0.012	5.799
GCS	-1.350	0.018	0.259
Respiratory SOFA	0.684	0.021	1.983
HR	0.675	0.009	1.963
Urine Output	-0.672	0.012	0.511
MAP	0.583	0.020	1.791
DBP	-0.512	0.029	0.600
Normalized MBP	-0.482	0.013	0.618
Platelets	-0.415	0.023	0.660
Nervous SOFA	-0.333	0.014	0.717

Table S9: Stratification of patients by first post-threshold crossing value of risk score.

Percentiles	False Positives (1-PPV)	True Positives (PPV)
0-20	66 (58.41%)	47 (41.59%)
21-40	70 (61.40%)	44 (38.60%)
41-60	58 (51.33%)	55 (48.67%)
61-80	61 (53.98%)	52 (46.02%)
81-100	43 (38.05%)	70 (61.95%)

Table S10: Outcome characteristics of clusters in Figure 3. An asterisk denotes a statistic which is significantly different between the clusters at the $p<0.01$ confidence level (Fisher's exact test for binary variables (shock prevalence, mortality, fluid resuscitation, vasopressor administration), Wilcoxon rank-sum test for continuous variables (median EWT)).

Cluster	**Size**	**Shock Prevalence***	**Mortality***	**Median EWT**	**% Patients Adequately Fluid Resuscitated***	**% Patients Treated with Vasopressors**
1	385	200 (51.95%)	79 (20.52%)	7.49 hrs	76.88%	54.81%
2	179	67 (37.43%)	18 (10.06%)	5.37 hrs	87.15%	50.28%

Table S11: Baseline statistics in the PIC database. Sepsis cohorts are determined using age-adjusted SOFA scores[6].

Most severe clinical state reached	**No sepsis**	**Sepsis without septic shock**	**Sepsis leading to septic shock**	**Overall**
Admissions	11,415 (84.88%)	1,682 (12.51%)	352 (2.62%)	13,449 (100%)
Patients	10,887 (84.52%)	1,643 (12.76%)	351 (2.72%)	12,881 (100%)
PICU Stays	11,692 (83.87%)	1,805 (12.95%)	444 (3.18%)	13,941 (100%)
In-hospital mortality	885 (7.75%)	29 (1.72%)	57 (16.19%)	971 (7.22%)
Gender	57.65% Male, 42.35% Female	54.53% Male, 45.47% Female	55.27% Male, 44.73% Female	57.19% Male, 42.81% Female
Median ICU stay length, days (IQR)	2.91 (1.46, 9.41)	4.40 (1.48, 12.65)	7.57 (3.61, 21.53)	3.44 (1.46, 9.64)
Mean age, years (SD)	2.53 (3.63)	2.26 (3.45)	2.40 (3.84)	2.49 (3.61)

Table S12: Availability of EHR data in the PIC database.

Feature	**% of Patients with at least 1 entry**	**Average time (hrs) between observations (mean/median)**	**Observations per admission (mean/median)**
Risk Score	96.37	51.44/24	11.37/7
Heart Rate	76.46	43.77/24	7.43/4
Systolic Blood Pressure	68.54	74.18/24	3.10/2
Diastolic Blood Pressure	68.54	74.18/24	3.10/2
Respiratory Rate	78.22	37.78/24	9.93/7
Temperature	78.24	36.86/24	10.26/7
PaO_2	92.70	47.33/24	6.72/4
FiO_2	17.12	40.29/24	1.37/0
Bilirubin	91.29	86.63/48	4.30/3
Platelets	93.02	67.68/24	8.04/5
Lactate	92.65	47.17/24	6.66/4
BUN	92.11	116.51/72	3.41/3
Arterial pH	92.70	47.36/24	6.71/4
WBC	93.02	67.70/24	8.04/5
$PaCO_2$	92.70	47.33/24	6.72/4
Hemoglobin	93.38	59.63/24	9.15/6
Hematocrit	93.38	59.61/24	9.15/6
Potassium	92.71	47.61/24	6.73/4

Table S13: Queried items in the PIC database

Feature	Table	Items
Heart Rate	Chartevents	1003
Systolic BP	Chartevents	1016
Diastolic BP	Chartevents	1015
Respiratory Rate	Chartevents	1004
Temperature	Chartevents	1001
Weight	Chartevents	1014
Bilirubin	Labevents	5225, 5075
PaO_2	Labevents	5239, 5244
FiO_2	Labevents	5222
Creatinine	Labevents	5032, 5041, 6954
Lactate	Labevents	5227
White Blood Cell Count	Labevents	5141
Platelets	Labevents	5129
Arterial pH	Labevents	5237, 5374
BUN	Labevents	6477, 5033
$PaCO_2$	Labevents	5235
Hemoglobin	Labevents	5099, 5257
Hematocrit	Labevents	5097, 5225
Potassium	Labevents	5226

Table S14: Performance metrics in the PIC database

Model	AUC	Sensitivity	Specificity	PPV	Median EWT (hrs)
XGBoost	0.82	0.79	0.71	0.22	48
GLM	0.72	0.64	0.71	0.19	108
Cox	0.63	0.67	0.55	0.13	231
SOFA	0.66	0.47	0.77	0.17	248

References:

1. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics*. *Pediatric Critical Care Medicine.* 2005;6(1):2-8.
2. Haque IU, Zaritsky AL. Analysis of the evidence for the lower limit of systolic and mean arterial pressure in children. *Pediatric Critical Care Medicine.* 2007;8(2):138-144.
3. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *Jama.* 2016;315(8):801.
4. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med.* 1996;22(7):707-710.
5. Matics TJ, Sanchez-Pinto LN. Adaptation and Validation of a Pediatric Sequential Organ Failure Assessment Score and Evaluation of the Sepsis-3 Definitions in Critically Ill Children. *JAMA Pediatrics.* 2017;171(10):e172352.
6. Schlapbach LJ, Straney L, Bellomo R, MacLaren G, Pilcher D. Prognostic accuracy of age-adapted SOFA, SIRS, PELOD-2, and qSOFA for in-hospital mortality among children with suspected infection admitted to the intensive care unit. *Intensive Care Medicine.* 2017;44(2):179-188.
7. Leteurtre S, Duhamel A, Salleron J, Grandbastien B, Lacroix J, Leclerc F. Pelod-2. *Critical Care Medicine.* 2013;41(7):1761-1773.
8. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children. *Pediatric Critical Care Medicine.* 2020;21(2):e52-e106.
9. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Medicine.* 2017;43(3):304-377.
10. Zeng X, Yu G, Lu Y, et al. PIC, a paediatric-specific intensive care database. *Scientific Data.* 2020;7(1).
11. Davis C, Kahan WM. The Rotation of Eigenvectors by a Perturbation. III. *SIAM Journal on Numerical Analysis.* 1970;7(1):1-46.
12. Ng AY, Jordan MI, Weiss Y. On spectral clustering: Analysis and an algorithm. Paper presented at: Advances in neural information processing systems2002.
13. Liu R, Greenstein JL, Fackler JC, Bembea MM, Winslow RL. Spectral clustering of risk score trajectories stratifies sepsis patients by clinical outcome and interventions received. *eLife.* 2020;9.
14. Kullback S, Leibler RA. On Information and Sufficiency. *The Annals of Mathematical Statistics.* 1951;22(1):79-86.