Science Translational Medicine
AAAS

stm.sciencemag.org/cgi/content/full/11/518/eaax9000/DC1

Supplementary Materials for

Prospective clinical testing and experimental validation of the Pediatric Sepsis Biomarker Risk Model

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Published 13 November 2019, *Sci. Transl. Med.* **11**, eaax9000 (2019)
DOI: 10.1126/scitranslmed.aax9000

This PDF file includes:

Fig. S1

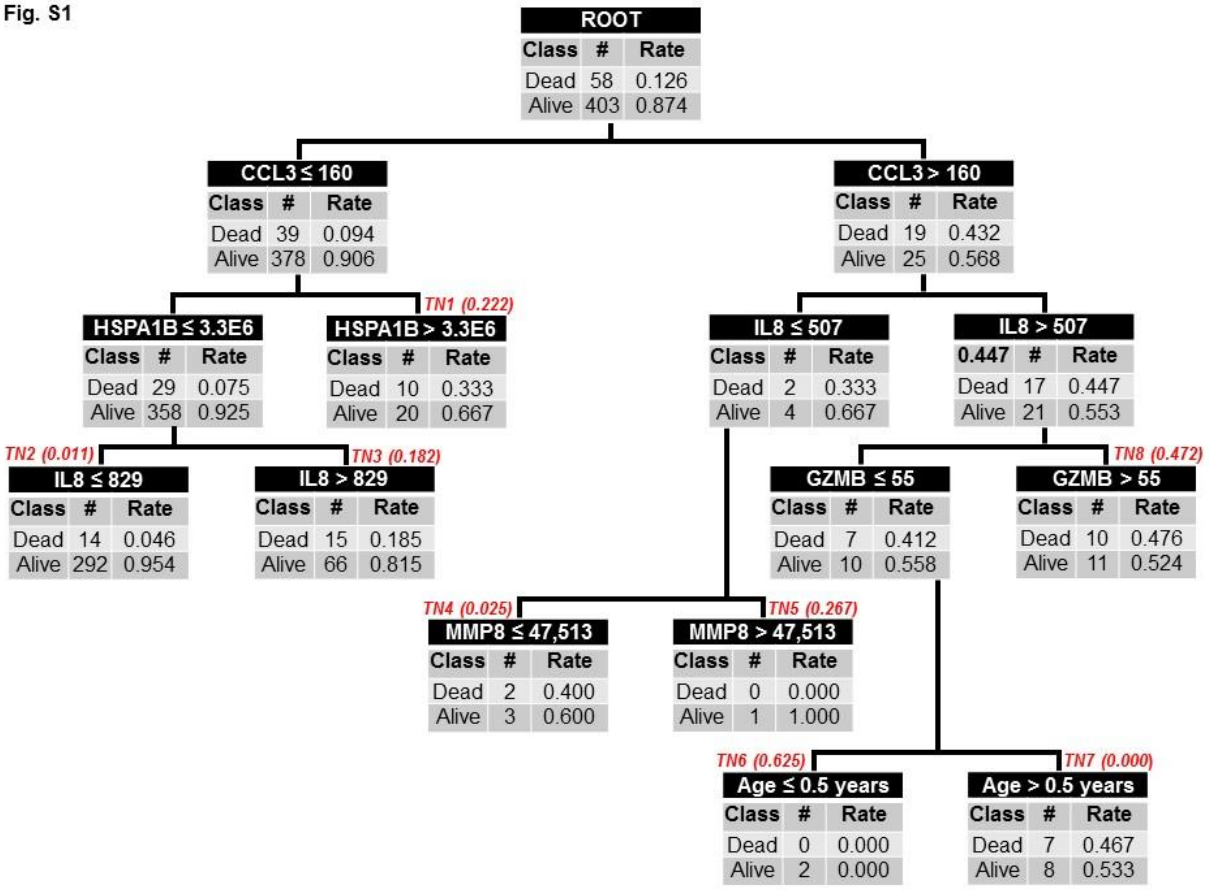

Fig. S1. Classification of the test cohort patients according to PERSEVERE. All patients (n = 461) are included in the root node at the top of the figure, with the corresponding numbers of 28-day survivors and non-survivors, and the respective rates. Patients are subsequently allocated to daughter nodes using a biomarker-based criterion as indicated at the top row of each node. All biomarker data are shown as pg/ml. Each daughter node provides the number of survivors and non-survivors allocated to that node, and the respective rates. Subsequent daughter nodes are generated, ending in terminal nodes (TN) indicated by red, italic font. The terminal nodes are used to assign a baseline mortality risk to a patient classified to a given terminal node. The baseline mortality risk corresponding to each terminal node is indicated in parentheses next to the TN and is derived from the published PERSEVERE model (*6*). These baseline mortality risks are used for construction of the AUROC. For calculation of the other test characteristics, the mortality probability is dichotomized into those who are predicted to survive and those who are predicted to not survive by 28 days. Patients allocated to TN2, TN4, and TN7 (mortality risk 0.000 to 0.025) are classified as predicted survivors. Patients allocated to TN1, TN3, TN5, TN6, and TN8 are classified as predicted non-survivors (mortality risk 0.182 to 0.625).

Fig. S2

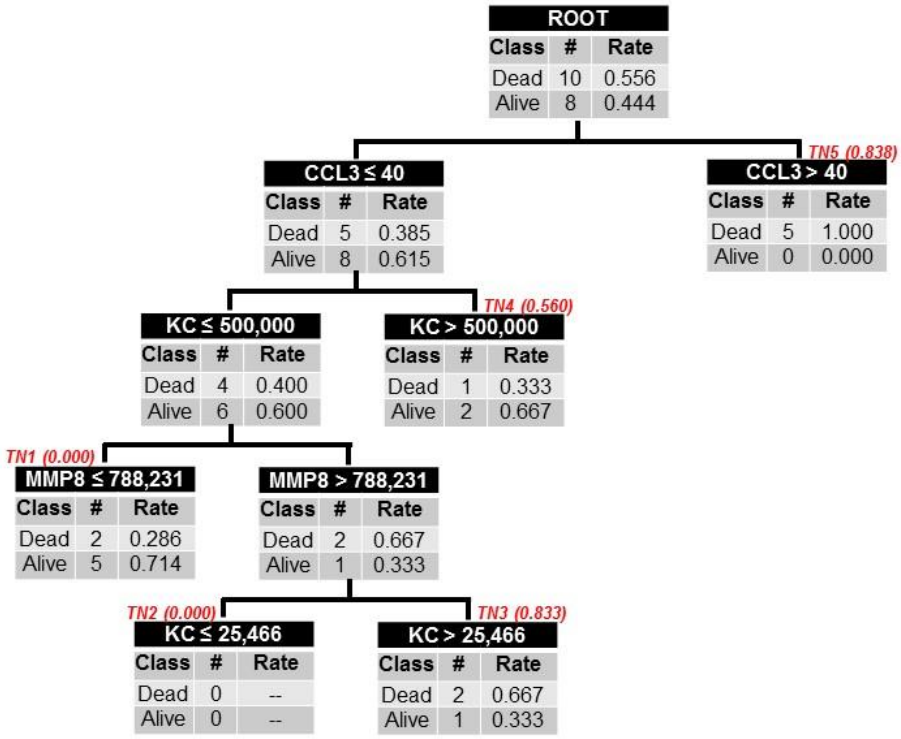

Fig. S2. Classification of the test cohort mice according to the derived mPERSEVERE. All mice (n = 18) are included in the root node at the top of the figure, with the corresponding numbers of 10-day survivors and non-survivors, and the respective rates. Mice are subsequently allocated to daughter nodes using a biomarker-based criterion as indicated at the top row of each node. All biomarker data are shown as pg/ml. Each daughter node provides the number of survivors and non-survivors allocated to that node, and the respective rates. Subsequent daughter nodes are generated, ending in terminal nodes (TN) indicated by red, italic font. The terminal nodes are used to assign a baseline mortality risk to a mouse classified to a given terminal node. The baseline mortality risk corresponding to each terminal node is indicated in parentheses next to the TN, and is derived from the derived mPERSEVERE model (Fig. 4). These baseline mortality risks are used for construction of the AUROC. For calculation of diagnostic test characteristics, the mortality probability is dichotomized into mice that are predicted to survive and those that are predicted to not survive by 10 days. Mice allocated to TN1 and TN2 (mortality risk 0.000) are classified as predicted survivors. Mice allocated to TN3, TN4, and TN5 are classified as predicted non-survivors (mortality risk 0.560 to 0.838).

Fig. S1

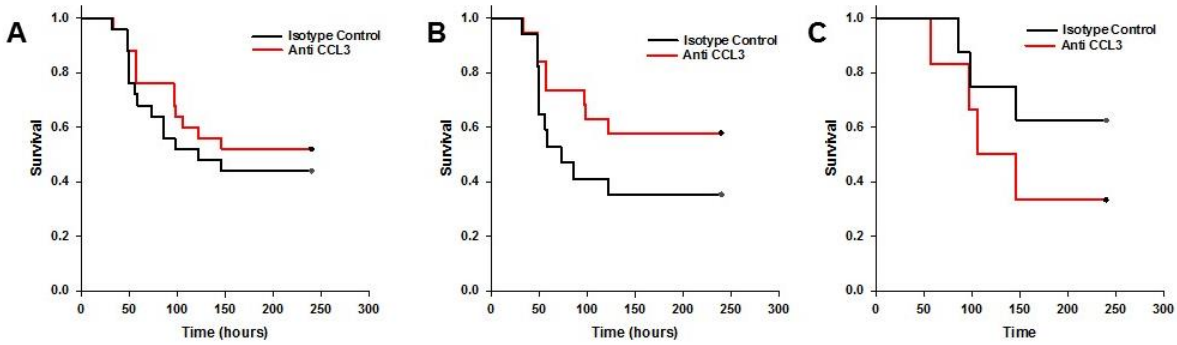

Fig. S3. Ten-day survival curves of mice challenged with CLP and then randomized to treatment with an anti-CCL3 antibody or an isotype control antibody. (A) All mice, un-stratified; n = 25 in each group, p = 0.472, log rank test. **(B)** High risk mice as defined by mPERSEVERE stratification. Isotype control antibody, n = 17. Anti-CCL3 antibody, n = 19, p = 0.149, log rank test. **(C)** Low risk mice as defined by mPERSEVERE stratification. Isotype control antibody, n = 8. Anti-CCL3 antibody, n = 6, p = 0.287, log rank test.

Table S1. Demographic and clinical characteristics of the study cohort according to 28-day survival.

	Survivors	Non-survivors
N	403	58
Median age, yrs (IQR)	7.2 (2.3 to 13.8)	6.4 (1.7 to 12.9)
Males, n (%)	209 (52)	29 (50)
Median PRISM, (IQR)	10 (6 to 14)	16 (10 to 25)[1]
Gram positive bacteria, n (%)	85 (21)	13 (22)
Gram negative bacteria, n (%)	104 (26)	18 (31)
Other organism, n (%)	38 (9)	8 (14)
Culture negative, n (%)	176 (44)	19 (33)
Comorbidity, n (%)	281 (70)	44 (76)
Malignancy, n (%)	54 (13)	13 (22)
Immune suppression, n (%)	86 (21)	27 (47)[2]
Bone marrow transplantation, n (%)	24 (6)	15 (26)[2]
Received corticosteroids, n (%)	173 (43)	42 (72)[2]

[1]$p < 0.05$ vs. survivors, Rank Sum Test
[2]$p < 0.05$ vs. survivors, Chi Square Test

Table S2. Comparison of illness severity measures among true-negative and false-positive subjects.

Variable	True Negatives	False Positives	P value
N	278	125	--
PRISM III score	9 (6 to 12)[1]	13 (9 to 18)	<0.001
Maximum # of organ failures	2 (1 to 2)	2 (2 to 3)	<0.001
Persistent multi-organ failure, n (%)[2]	37 (13)	28 (22)	0.032
PICU length of stay, days	6 (2 to 12)	8 (3 to 17)	0.062
PICU free days	22 (16 to 26)	20 (12 to 25)	0.059

[1]All data shown as medians (intra-quartile range) unless otherwise noted.
[2]Defined as ≥2 organ failures at day seven of septic shock.

Table S3. Calculation of the NNT.

Effect Size	Absolute Risk Reduction	NNT
100%	45%	2
90%	41%	2
80%	36%	3
70%	32%	3
60%	27%	4
50%	23%	4
40%	18%	6
30%	14%	7
20%	9%	11
10%	5%	22

Calculations are based on a theoretical range reflecting the percentage of high risk patients rescued by high dose antibiotics (effect size) and a mortality rate of 45%.