Appendix 1 (as supplied by the authors): Statistical analysis

Adjustment for day 1 PELOD score

The relation between the baseline PELOD score (day 1 PELOD) and outcome (survival versus death) was investigated by a logistic regression. We analyzed the distribution of the day 1 PELOD according to the outcome and identified two cutoff values corresponding to changes in the distribution. Dummy variables were derived from the cutoff values in order to characterize the baseline status (low, medium or high day 1 PELOD score) and a logistic regression was performed to compute the odds ratios corresponding to the medium and high groups.

Method 1: changes in PELOD scores during the first four days

We analyzed the relationship between changes in daily PELOD scores during the first four PICU days and PICU mortality. After adjustment for day 1 PELOD score (low, medium or high day 1 PELOD score), patients were classified into three categories according to whether the delta day 2 – day 1 PELOD score increased, remained unchanged or decreased. Without adjustment for day 1 PELOD score (due to the great number of categories), patients were classified into three categories according to whether the delta day 2 – day 1 PELOD score increased, remained unchanged or decreased and the same process was employed for the delta day 4 – day 2 PELOD score.[2] In each category, the frequency of deaths and the 95% confidence interval were computed using binomial exact method.

Method 2: mean rate of change of PELOD score during the entire PICU stay

As suggested by Doig et al, we compared the daily PELOD score course between survivors and nonsurvivors using the linear mixed model for repeated measurements.[3] This strategy allows handling correlations between repeated measurements and is adapted to situations where the amount of data differs between subjects.[4] In our study, we chose the compound symmetry correlation structure to describe the correlations among the repeated measurements. The choice of the correlation structure was based on the likelihood ratio test.[4] The covariates used in the model were baseline status (defined by dummy variables), outcome and length of PICU stay (days). We considered a model allowing estimation of different intercepts and different slopes according to baseline status and outcome. Because some patients had very prolonged PICU stay, the model was limited to data collected during the first 21 days in PICU. Population-average model according to outcome was obtained by using the estimated coefficients of the linear mixed model analysis (Figure e1).

Method 3: optimal sequence for measuring daily PELOD scores

We studied the influence of daily PELOD score course on outcome while adjusting for baseline value. This analysis was performed using the Cox model, with the delta day i – day 1 PELOD score as a time dependent covariate and the dummy variables as fixed covariates. This method was close to that used by Cook et al.[5]

We used the counting process form of the Cox model to handle time dependent covariates and to compute their associated adequate residuals. The validity of the proportional hazard assumption was verified using the Scale Shonenfeld Residuals (SSR). The proportional hazard assumption was tested for each covariate by correlating the corresponding SSR with the logarithm of time (log(t)) and we analyzed the plots of SSR against log(t) for visualizing the existence and the nature of non proportionality. The plots were increased with a spline smooth and their 95% confidence intervals.[1] When the proportional hazard assumption is true the spline smooth looks like a straight line with a zero slope.

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For the time dependent variable delta day i – day 1 PELOD, the spline smooth revealed that there was a strong relationship between the SSR and log(t). This means that the risk of death varied depending on time.

To determine the times corresponding to a change in the risk of death, we proceeded as follows. First, we analyzed the plots of SSR against log(t) to identify a primary set of time cutoffs. Second, additional time cutoffs were identified by plotting the medians of daily PELOD score versus time after stratification according to baseline status. Finally, some cutoffs were eliminated with the aim to obtain regularly spaced measurements and to decrease time and effort required to complete data collection. The time cutoffs determined different time intervals. We then transformed the model in order to allow the hazard ratio of the delta day i – day 1 PELOD score to vary over time and then for each time interval, a different coefficient for delta day i – day 1 PELOD score was fitted.

Methods (2) and (3) analyzed the entire PICU stay and required an adjustment for centers (the 7 participating sites were considered as a possible confounding variable).

Results

Changes of PELOD scores during the first four days

There were 745 children where day 2-day 1 PELOD and day 4-day 2 PELOD did not both increase. Among these 745 children, those with an increasing delta day 2 – day 1 PELOD or delta day 4 – day 2 PELOD score had a mortality rate of 10% compared to 5% in the others ($p= 0.012$) (table e1). Similar results were observed when considering particular age categories [children < 1 year and adolescents ($\geq$ 13 years)].

Mean rate of change of PELOD score during the entire PICU stay

Figure e1 demonstrates for the three day 1 PELOD groups that there was a difference of day i PELOD score between survivors (continuous line) and non survivors (dotted line); this difference increased with time.

Optimal sequence for measuring daily PELOD scores

In the group with a medium day 1 PELOD score, graphic variations of median daily PELOD score appeared at day 8, 12 and 13 in non-survivors, and at day 5 and 9 in survivors. Finally, in the group with a high day 1 PELOD score, graphic variations of median daily PELOD score appeared at day 2, 8, 12 and 17 in non-survivors and at day 2, 17 and 19 in survivors (Figures e2 and e3).

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Table e1: Changes in PELOD score in relation to mortality for children in PICU for at least four days

day 1 to day 2 PELOD score					day 2 to day 4 PELOD score				
Evolution	Number at risk	Number of deaths	(%)	[95% CI]	Evolution	Number at risk	Number of deaths	(%)	[95% CI]
Increased	173	23	(13)	[8.6-19.3]	Increased	14	7	**(50)**	[23.0-77.0]
					Unchanged	30	3	**(10)**	[2.1-26.5]
					Decreased	129	13	**(10)**	[5.5-16.7]
Unchanged	342	15	(4)	[2.5-7.1]	Increased	35	3	**(9)**	[1.8-23.1]
					Unchanged	164	4	**(2)**	[0.7-6.1]
					Decreased	143	8	**(6)**	[2.5-10.7]
Decreased	244	18	(7)	[4.4-11.4]	Increased	50	5	**(10)**	[3.3-21.8]
					Unchanged	89	6	**(7)**	[2.5-14.1]
					Decreased	105	7	**(7)**	[2.7-13.3]

CI = confidence interval.

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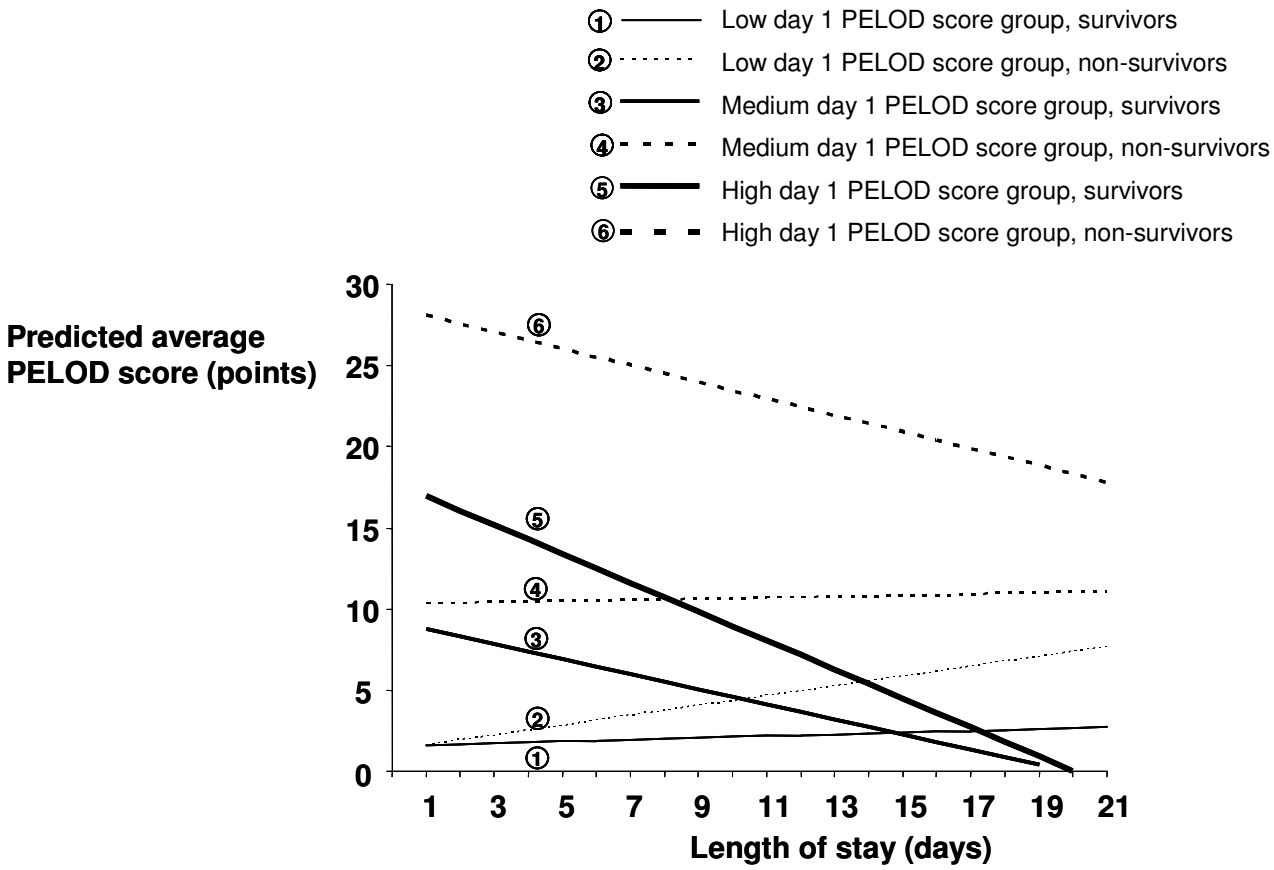

Figure e1: Predicted average PELOD score with the different intercepts and slopes estimated from the linear mixed model stratified by the day 1 PELOD score and the PICU discharge status (See "Mean rate of change of PELOD score during the entire PICU stay").
Note: Because the values of the day 1 PELOD scores depicted in the figure are predicted average values, they can be different than those of the 6 categories defined in label; this is the case for groups 5 and 3. Low day 1 PELOD score group: <10 points; medium day 1 PELOD score group: 10–19 points; high day 1 PELOD score group: ≥ 20 points.

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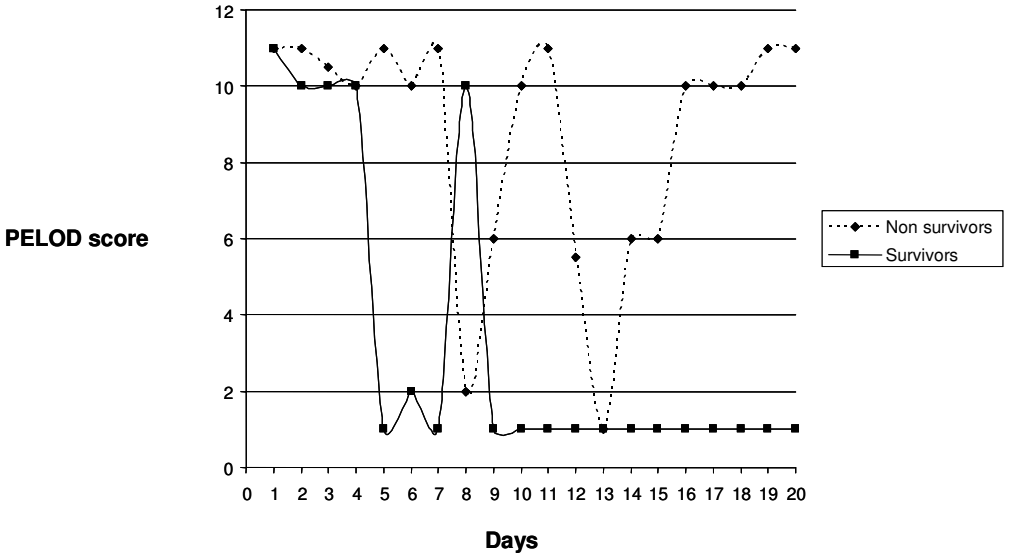

Figure e2: Plot of the medians of daily PELOD score versus time in the group with a medium day 1 PELOD score (10–19 points).

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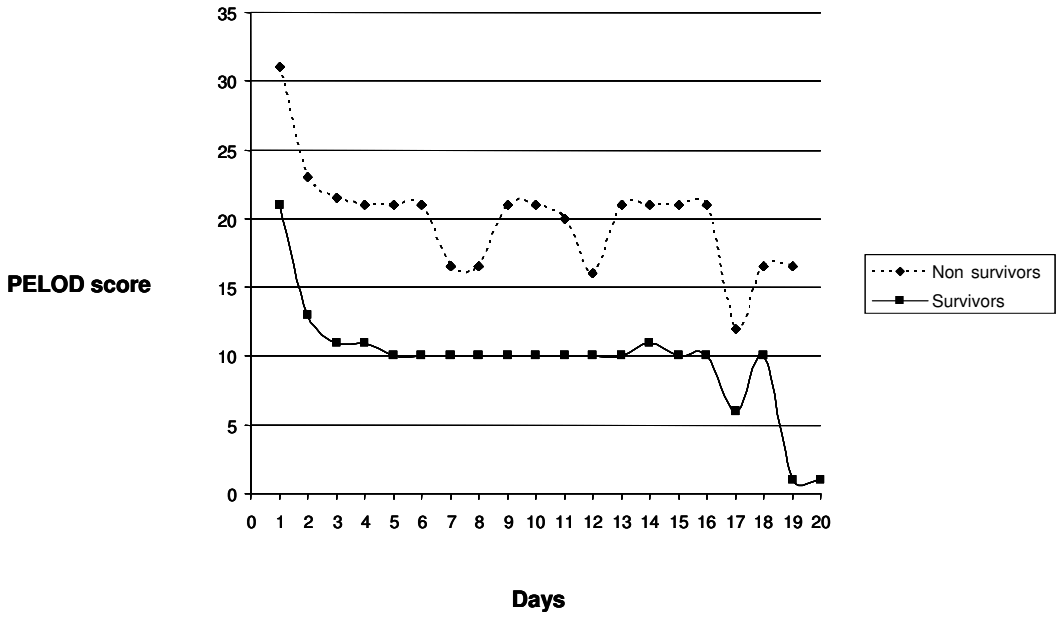

Figure e3: Plot of the medians of daily PELOD score versus time in the group with a high day 1 PELOD score (≥ 20 points).

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