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A new prognostic scoring system for meningococcal septic shock in children. Comparison with three other scoring systems

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Abstract *Objective*: To develop a quick and sensitive method for identification of children with presumed meningococcal septic shock at risk of death at admission to the pediatric intensive care unit (PICU) and to compare its performance with three other prognostic systems: Glasgow Meningococcal Septicaemia Prognostic Score (GMSPS), Malley score and the Paediatric Index of Mortality (PIM). *Design*: Multicenter retrospective cohort study. *Setting*: PICUs of 14 tertiary hospitals. *Patients*: The developmental sample included 192 children consecutively admitted to the PICUs with presumed or confirmed meningococcal septic shock from 1983 to 1995. The validation sample included 158 children consecutively admitted from 1996 to 1998. *Interventions*: Clinical and laboratory data gathered during the first 2 h after admission were used to develop the new score and to compute the other scoring systems. Logistic regression was applied to identify the independent predictors of death. *Measurements and results*: Overall mortality was 31.5%. The new score included seven variables: cyanosis (2 points), Glasgow coma scale less than 8 (2 points), refractory hypotension (2 points), oliguria (1 point), leukocytes less than $4000/mm^3$ (1 point), partial thromboplastin time more than 150% of con-

trol value (1 point) and base deficit more than 10 mmol/l (1 point). The new score provided the best discriminative capability, as measured by the area under the ROC curve (SEM) in the validation sample =0.88 (0.03), PIM =0.82 (0.04), Malley I =0.80 (0.04), GMSPS =0.79 (0.04) and Malley II =0.76 (0.04).
Conclusions: A new prognostic score is proposed for therapeutic stratification of children with presumed meningococcal septic shock.

Keywords Pediatrics · *Neisseria meningitidis* · Septic shock · Severity of illness index · Pediatric intensive care units · Prognosis

Introduction

Meningococcal disease remains a major health problem in both developing and industrialized countries. In Spain it is the most important cause of sepsis in children and its incidence ranged from 2.3 to 11.7/100,000 in the period 1982–1998 [1]. Septic shock occurs in about 15% of children with meningococcal infection and includes most of the non-survivors of the disease [2, 3]. The mortality rate remains at 28%–34% despite technological advances in intensive care [4, 5]. On the other hand, meningococcal septic shock is an ideal model for the study of immunotherapy in sepsis associated with marked endotoxemia, because its rapid onset and characteristic skin hemorrhages in a previously healthy patient allow early bedside diagnosis [6]. A well validated scoring system for meningococcal septic shock in children would permit an accurate estimate of the usefulness of new therapies in clinical trials.

Since the introduction of the Stiehm and Damrosch scale in 1966 [7], there has been a steady increase in the number of prognostic scales to quantify severity of patients with presumed meningococcal septic shock. However, imprecision persists with these classification systems regarding clinical outcomes [8, 9]. This low predictive accuracy is mainly related to the heterogeneity and small number of patients from which these scoring systems have been developed. With regard to the generic scores, some studies have shown that the Pediatric Risk of Mortality (PRISM) scores may be useful in children with meningococcal septic shock [4, 8, 10]. However, clinicians are reluctant to use these scores at admission to the PICU as the PRISM was actually designed to be used over 24 h post-admission [11] and the PRISM III between 12 h and 24 h post-admission [12]. Furthermore, the large amount of information required is time-consuming and prone to mistakes being made. To date a simple generic prognostic index derived from data collected at admission to the PICU, the Paediatric Index of Mortality (PIM) [13] has not been validated specifically for meningococcal infection.

The main objective of this study was to develop a rapid and sensitive score for identification of children with presumed meningococcal septic shock at risk of death at admission to the pediatric intensive care unit (PICU) and to compare its performance with the generic PIM and two validated specific scores, the Glasgow Meningococcal Septicaemia Prognostic Score (GMSPS) [14] and Malley score [15], as predictors of mortality. The latter score proposes two models of prediction based on just two and three variables, respectively.

Materials and methods

Patients and setting

A retrospective study of the records of all children aged between 1 month and 14 years admitted to the PICUs of 14 Spanish hospitals with a confirmed or presumed diagnosis of meningococcal septic shock was carried out. The developmental sample included 192 children admitted to four PICUs during a period of 12.5 years (January 1, 1983, to June 30, 1995). The validation sample included 158 children admitted to 10 other PICUs during a period of 3 years (January 1, 1996, to December 31, 1998). All of the hospitals included in the study are third-level teaching hospitals of between 800 and 2000 beds and referral populations ranging from 500,000 to 1,000,000 inhabitants of all ages. The number of PICU beds range from 4 to 18 (median 12).

The records of all patients with a primary diagnosis of sepsis, septic shock or meningitis were reviewed. Patients were initially selected if their blood or cerebrospinal fluid (CSF) cultures were positive for *Neisseria meningitidis* or if their clinical illnesses were consistent with acute meningococcal infection (sepsis and purpura of abrupt onset acquired in the community by a previously healthy child), although cultures were negative. Finally, only patients meeting the definitions of septic shock by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference of 1992 [16] were definitely included in the study. Septic shock was defined as the presence of hypotension and/or at least two signs of end organ dysfunction or hypoperfusion despite adequate fluid resuscitation (at least a volume load of 20 ml/kg), needing treatment with more than 5 µg/kg per min dopamine or dobutamine, more than 0.1 µg/kg per min adrenaline or noradrenaline at any time of the disease course. This clinical picture, when associated with purpura, is usually presumed to be caused by *N. meningitidis* [3]. The following signs of organ dysfunction or hypoperfusion were considered: arterial hypoxemia (PaO_2 ≤75 mmHg or PaO_2/FIO_2 ≤250), urine output less than 1 ml/kg per h for at least 1 h, acute alteration of mental status, unexplained metabolic acidosis (base deficit >5 mmol/l) or disseminated intravascular coagulation (platelets <150,000/mm^3, and prothrombin time or partial thromboplastin time >150% of the control value). Hypotension was defined as a systolic blood pressure below 75 mmHg in children below the age of 4 years, or below 85 mmHg in children older than 4 years [14].

The basic treatment was uniform throughout the study period and included appropriate antibiotics, volume replacement with fluids, vasopressors, mechanical ventilation and extrarenal depuration techniques when indicated. Blood exchange, heparin or high doses of corticosteroids were occasionally used.

In both the development and validation samples, patients with a PICU stay of less than 2 h who were either admitted in a state of continuous cardiopulmonary resuscitation or suffered from early irreversible cardiac arrest, as well as those with missing or incomplete medical records, were excluded from the study. Patients with lost cultures or with blood/CSF positive cultures yielding isolates other than *N. meningitidis* were also excluded.

Data collection

Data collection included all the variables necessary for computing the PIM, GMSPS and Malley scores, and a set of new variables that might possibly become part of the new score. The worst values of each variable during the first 2 h in the PICU were selected for the analysis. The following clinical and laboratory data obtained at admission were retrieved from the medical records or from the notes of the referring hospital: (clinical and demographic data) age, sex, interval between the appearance of petechiae and the admission to the PICU, cyanosis, cold skin, meningeal signs, ecchymosis, temperature, heart rate, respiratory rate, blood pressure, oliguria, modified Glasgow coma scale; (laboratory data) leukocytes, blood platelets, pH, PCO_2, PaO_2/FIO_2, bicarbonate, base deficit, potassium, calcium, glucose, blood urea nitrogen (BUN), creatinine, partial thromboplastin time (PTT) and fibrinogen. We included two variables related to therapeutics: use of mechanical ventilation during the first 2 h after admission and refractory hypotension, defined as hypotension not normalized during the first 2 h after admission despite correct treatment with volume infusion and vasopressors. Blood and CSF cultures were also recorded.

The primary outcome used was hospital mortality, defined as death occurring before hospital discharge.

Statistical analysis

Each one of the possible explanatory variables was independently evaluated for its association with hospital mortality. All continuous variables associated with death ($p<0.15$) were dichotomized according to cut-off points of clinical relevance. All dichotomous variables associated with death ($p<0.15$) were entered in a logistic regression model to identify independent predictors of death. Variables with missing data higher than 20% were excluded from the model. The coefficients β were used for factor weighing; points were assigned to each independent prognostic factor, its coefficient being rounded to the nearest integer. Finally, we calculated a prediction score for each patient by summing up the points. Sensitivity (S), specificity (SP), positive and negative predictive values (PPV, NPV) and total correct classification rate were calculated for each score.

The χ^2 test, with the Yates correction when indicated, and Fisher's exact test were used to compare categorical variables. The risk was quantified using relative risks with 95% confidence intervals. The analysis of variance was used for comparison of continuous variables. Data analyses were performed using the BMDP statistical package (BMDP Statistical Software, Cork, Ireland).

Prognostic scoring systems

The performance of the new score obtained from the development sample was compared with three current pediatric prognostic scoring systems, one generic (PIM) and two specific (GMSPS and Malley scores) in the validation sample. The four scores were calculated with the worst values of each variable recorded during the first 2 h on the PICU. The GMSPS was completed according to the criteria used in a previous study [8].

The performance of all scores was assessed by evaluating calibration and discrimination in the validation study sample. Calibration evaluates the degree of correspondence between predicted and observed mortality and was assessed using the Hosmer-Lemeshow goodness-of-fit χ^2 test [17], which compares the number of observed and predicted deaths in risk categories covering the entire range of probabilities of death. Patients were stratified in quintiles of risk. The new score, GMSPS and Malley scores were converted into a probability model using logistic regression equations to calculate the predicted mortality.

For assessing the models' discrimination between survivors and non-survivors, the area under the receiver operating characteristic (ROC) curve, and its 95% confidence interval, was used [18]. The comparison of the areas under ROC curves was carried out using the Hanley-McNeil's non-parametric method [19].

Results

Developmental sample

The developmental sample has been described in a previous study [8]. The records of 1398 patients admitted consecutively during the study period with sepsis and/or meningitis were reviewed, 229 children fulfilled the criteria of presumed meningococcal septic shock. A total of 37 cases (16%) were excluded from the study, 26 of them were non-survivors. Twenty-two patients were excluded due to missing records or missing values on key variables, 15 of them died before 2 h of admission in the PICU. Eleven patients (4 deaths) with lost cultures and four additional cases (1 death) with positive cultures in blood or CSF other than *N. meningitidis* were also excluded. Most of the exclusions were patients referred from other hospitals. The subjects of the sample were 192 children (108 boys and 84 girls) ranging in age from 1 month to 14 years (median 18.5 months). There were 66 deaths. Relevant demographic data are shown in Table 1.

The results of the univariate analysis for clinical and biological variables are shown in Table 2 and Table 3, respectively. Non-survivors were younger than survivors and had greater degrees of coagulation derangements, larger decreases in pH and more severe abnormalities in hemodynamics and kidney function. In contrast, respiratory function appeared not to be severely affected at shock onset. Of the 30 variables collected to build the new score, only five were unrelated to mortality ($p>0.15$) and were excluded from multivariate analysis: temperature, respiratory rate, PCO_2, calcium and glucose. More than 20% of the data on creatinine was missing, and this variable was also deleted from further analysis. Only four variables had missing data higher than 5%: calcium (18%), interval between petechiae appearance and PICU admission (10%), glucose (7%) and BUN (6%).

The logistic regression analysis provided seven independent predictors of death at admission that were included in the new score: cyanosis, coma (Glasgow Coma

Table 1 Differences between developmental and validation samples (*SBP* systolic blood pressure, *DIC* disseminated intravascular coagulation, *ARDS* acute respiratory distress syndrome, *PIM* Pediatric Index of Mortality, *GMSPS* Glasgow Meningococcal Septicaemia Prognostic Score)

Variable	Developmental sample *n*=192	Validation sample *n*=158	*p* value
Age (months)	30.89±2.27	33.28±3.04	0.52
Male sex	108 (56%)	69 (44%)	0.02
Deaths	66 (34%)	46 (29%)	0.35
Hours petechiae-admission	3.88±0.24	2.35±0.21	<0.001
Positive culture	141 (74%)	119 (75%)	0.83
N. meningitidis B	98 (69%)	35 (29%)	
N. meningitidis C	25 (18%)	69 (58%)	<0.001
SBP (mmHg)	74.52±1.49	71.68±1.36	0.16
Glasgow Coma Scale	10.67±0.22	10.21 ±0.23	0.14
DIC	150 (78.12%)	120 (75.9%)	0.72
ARDS	45 (23.4%)	39 (25%)	0.88
Meningitis	89/171 (52%)	49/128 (38%)	0.02
Mechanical ventilation	92 (48%)	104 (69%)	0.001
Skin graft/ minor amputation	17 (9%)	25 (16%)	0.06
Risk of death % (PIM)	14.6±0.8	14.3±0.9	0.65
Malley (model I)	1.7±0.1	1.6±0.1	0.72
Malley (model II)	1.2±0.1	1.1±0.1	0.57
GMPS	7.45±0.27	9.13±0.27	<0.01

Results of the continuous variables are expressed as mean ± standard error of the mean

Scale score <8), refractory hypotension, oliguria, leukocytes less than 4000/mm^3, PTT more than 150% of control and base deficit higher than 10 mmol/l. Points assigned on the basis of the logistic regression coefficients for each variable varied from 1 to 2. The maximun score was 10 points (Table 4).

A second logistic regression analysis including the 15 cases excluded because of lost or other cultures different from *N. meningitidis* provided the same predictors of death selected by the previous one (data not shown).

The independent validation sample

The independent validation sample included 158 children (69 boys and 89 girls). The median age was 20 months (range 25 days–14 years). *N. meningitidis* was isolated in 119 cases (75%). In contrast to the developmental sample, serogroup C was predominant (68% of isolations). Twenty-four cases with negative cultures had been treated with antibiotics before admission. A total of 18 cases (11%) were excluded from the sample. Eleven patients were excluded due to missing values on key variables, four of them died before 2 h of admission in the PICU. Four patients with lost cultures and three additional cases with positive cultures in blood or CSF other than *N. meningitidis* were also excluded. There were 46 deaths (29%), all on the PICU. Twenty-five children (16%) needed skin graft or minor amputations. The comparison of the developmental with the validation sample is shown in Table 1. The mortality rates and severity were not significantly different. The interval between the onset of petechiae and admission to the PICU was shorter in the validation sample whereas meningitis and male sex were more frequent in the developmental sample.

Data were not missing for any of the variables of the new score in the validation sample. After examining the scores (Table 5), the best total correct classification rate (84.8%) corresponded to a score of 6 or more. This cut-off achieved the next figures: S =73.9%, SP =89.3%, PPV =73.9% and NPV =85.9%. The new scoring system was able to define three risk groups of mortality (Fig. 1): a low risk group (score ≤3), an intermediate risk group (scores of 4–5) and a high risk group (score ≥6), with mortality rates of 2.7% (2/74), 26.3% (10/38) and 73.9% (34/46), respectively.

The PIM, GMSPS and Malley scores were computed for each patient in the validation sample. All four scoring systems were clear predictors of death, with highly significant differences in the comparison of the scores between survivors and non-survivors (Table 6). However, none of the scoring systems was able to define a risk group with 100% mortality. All children with an estimated probability of death less than 4% according to the PIM (29 cases), all children with Malley (model I) =0 (24 cases), and all children with GMSPS less than 5 (13 cases), survived. Figure 1 shows the distribution of both survivors and non-survivors according to the scores of each scoring system and the risks estimated by the PIM. The positive predictive values of the scores were: Malley (model I) 2 or higher: 48.7%, Malley (model II) =2: 53% and GMSPS 11 or higher: 56%. The best total correct classification rate for the PIM was achieved with a cut-off of 0.29: 81.4%.

The ROC curve analysis is illustrated in Fig. 2. The areas under the ROC curve (SEM) for the new score were 0.91 (0.02) in the developmental sample and 0.88 (0.03) in the validation sample (p=0.10). The other three scores yielded lower ROC areas: PIM =0.82 (0.03), Malley (model I) =0.80 (0.04), GMSPS =0.79 (0.04)

Table 2 Univariate analysis for clinical variables in the developmental sample

Variable	Non-survivors *n*=66	Survivors *n*=126	Relative risk	Confidence Interval (95%)	*p* value
Age (months)					
Mean	24.9±2.7	33.9±3.9			0.059
< 12	31 (51.6)	29(48.4)	1.95	1.34–2.83	<0.001
≥ 12	35 (26.5)	97 (73.5)			
Sex					
Male	43 (39.8)	65 (60.2)	1.45	0.96–2.21	0.072
Female	23 (27.4)	61(72.6)			
Petechiae interval (h)					
Mean	3.5±0.3	4±0.3			0.31
Mechanical ventilation					
Admission	29 (80.6)	7 (19.4)	3.40	2.46–4.70	<0.001
Post admission	37 (66.1)	19 (33.9)			
Not used	0 (0)	100 (100)			
Cold skin					
Yes	59 (43.4)	77 (56.6)	3.16	1.55–6.46	<0.001
No	7(13.7)	44 (86.3)			
Cyanosis					
Yes	63 (50.4)	62 (49.6)	10.25	3.35–31.22	<0.001
No	3 (4.9)	58 (95.1)			
Meningeal signs					
Yes	7 (14.3)	42 (85.7)			
No	53 (39.6)	81 (60.4)	2.77	1.35–5.67	<0.001
Ecchymosis					
Yes	50 (45)	61 (55)	2.28	1.4–3.7	<0.001
No	16 (19.8)	65 (80.2)			
Systolic blood pressure (mmHg)					
Mean	64.4±1.4	79.8±3			<0.001
< 70	42 (47.7)	46 (52.3)	2.07	1.37–3.13	<0.001
≥ 70	24 (23.1)	80 (76.9)			
Refractory hypotension					
Yes	30 (85.7)	5 (14.3)	3.74	2.72–5.13	0.001
No	36 (22.9)	121 (77.1)			
Heart rate (beats/min)					
Mean	178.5±3.8	169.4±2.2			0.029
> 180	33 (47.8)	36 (52.2)	1.78	1.22–2.61	0.003
≤ 180	33 (26.8)	90 (73.2)			
Respiratory rate (breaths/min)					
Mean	49.32±2	48.95±1.1			0.865
Rectal temperature (°C)					
Mean	38.7±1.4	38.8±1			0.517
Glasgow Coma Scale score					
Mean	8.8±0.3	11.6±0.2			<0.001
< 8	45 (26.9)	122 (73.1)	3.12	2.30–4.22	<0.001
≥ 8	21 (84)	4 (16)			
Oliguria					
Yes	60 (46.2)	70 (53.8)	4.77	2.18–10.43	<0.001
No	6 (9.7)	56 (90.3)			

Table 3 Univariate analysis for biological variables in the developmental sample (*PTT* partial thromboplastin time)

Variable	Non-survivors *n*=66	Survivors *n*=126	Relative risk	Confidence interval (95%)	*p* value
Glucose (mg/dl)					
Mean	111.5±11.5	112.1±3.9			0.95
Potassium (meq/l)					
Mean	4.1±0.1	3.7±0.05			0.001
> 5	9 (69.2)	4 (30.8)	2.20	1.44–3.36	0.01
≤ 5	56 (31.5)	122 (68.5)			
Calcium (mg/dl)					
Mean	7.8±0.1	7.9±0.1			0.62
pH					
Mean	7.30±0.01	7.37±0.007			<0.001
< 7.30	19 (65.5)	10 (34.5)	2.27	1.59–3.25	<0.001
≥ 7.30	47 (28.8)	116 (71.2)			
Bicarbonate (mmol/l)					
Mean	12.9±0.4	16.1±0.3			<0.001
< 15	46 (51.7)	43 (48.3)	2.66	1.71–4.14	<0.001
≥ 15	20 (19.4)	83 (80.6)			
Base deficit (mmol/l)					
Mean	11.1±0.6	7.2±0.3			<0.001
> 10	31 (22.3)	108 (77.7)	2.96	2.05–4.27	<0.001
≥ 10	35 (66)	18 (34)			
PCO_2					
Mean	27.4±1.3	28.0±0.6			0.66
PaO_2/FIO_2					
Mean	347.8±13.4	390.6±10.7			0.11
≥ 150	46 (29.9)	108 (70.1)			
< 150	20 (52.6)	18 (47.4)	1.76	1.20–2.59	0.01
BUN (mg/dl)					
Mean	23.7±1	20.1±0.7			0.005
> 15	55 (37.4)	92 (62.6)	1.76	0.88–3.52	0.11
≤ 15	7 (21.2)	26 (78.8)			
Creatinine (mg/dl)					
Mean	1.1±0.1	0.8±0.05			0.005
PTT (s)					
Mean	106.7±9.9	49±2			<0.001
> 150% of control value	50 (56.2)	39 (43.8)	3.62	2.22–5.88	<0.001
≤ 150% of control value	16 (15.5)	87 (84.5)			
Platelets (1000 cells/mm^3)					
Mean	129.0±11.6	180.3±7.8			<0.001
< 100,000	33 (24.3)	23 (41.1)	2.43	1.68–3.51	<0.001
≥ 100,000	33 (58.9)	103 (75.7)			
Fibrinogen (mg/dl)					
Mean	154.7±13.6	297.2±13.1			<0.001
< 150	35 (67.3)	17 (32.7)	3.04	2.10–4.34	<0.001
≥ 150	31 (22.3)	108 (77.7)			
Leukocytes (cells/mm^3)					
Mean	5501.3±596.8	6916.6±592.2			0.12
< 4000	36 (42.4)	49 (57.6)	1.51	1.02–2.24	0.038
≥ 4000	30 (28)	77 (72)			

Table 4 Independent predictors of death at admission in 192 children with presumed meningococcal septic shock (*CI* confidence interval, *PTT* partial thromboplastin time)

Variable	β	Standard error β	Odds ratio	(95% CI)	Score
Refractory hypotension	1.957	0.668	3.30	2.44–4.47	2
Base deficit > 10 mmol/l	1.004	0.503	2.92	2.10–4.06	1
Glasgow Coma Scale < 8	2.041	0.714	3.15	2.41–4.12	2
Leukocytes < 4000 mm^3	1.071	0.462	1.55	1.10–2.22	1
PTT > 150% of control	1.277	0.466	3.82	2.42–6.01	1
Cyanosis	2.030	0.620	7.40	3.13–17.48	2
Oliguria	1.185	0.587	5.04	2.44–10.38	1

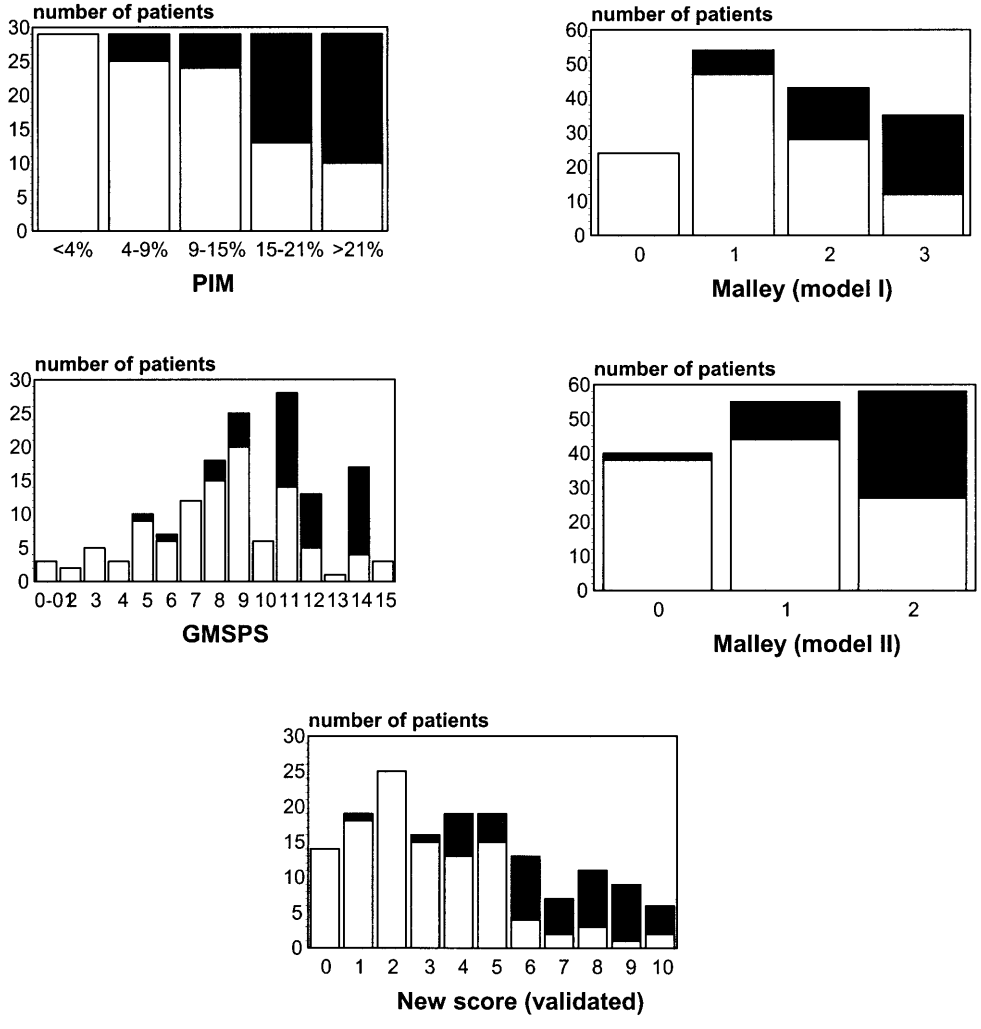

Fig. 1 Distribution of the survivors (*in white*) and non-survivors (*in black*) according to the scores of each scoring system. Patients are grouped by quintiles of risk in the Pediatric Index of Mortality (*PIM*) (*GMSPS* Glasgow Meningococcal Septicaemia Prognostic Score)

and Malley (model II) =0.76 (0.04). There was a significant difference between the new score and Malley (model I, p=0.04; model II, p<0.01) and GMSPS ROC curves (p<0.01), but not between the new score and the PIM (p=0.10). There were also no significant differences between the PIM and Malley (model I, p=0.34; model II, p=0.11), and between PIM and GMSPS (p=0.27).

The new score also presented good calibration in both the developmental and validation data set with no significant differences between the observed and predicted mortality as evaluated by the Hosmer-Lemeshow test: p=0.55 and p=0.47, respectively. Apart from the PIM, the remaining scores of the other scoring systems also showed good calibration in the validation sample: Malley (model I, p=0.62) and GMSPS (p=0.33). The

Table 5 Predictive values of the new score in both the developmental sample and the validation sample (*PPV* positive predictive value (probability of death), *NPV* negative predictive value (probability of not dying), *Overall accuracy* total correct classification rate)

Score	Developmental sample					Validation sample				
	Sensitivity	Specificity	PPV	NPV	Overall accuracy	Sensitivity	Specificity	PPV	NPV	Overall accuracy
0	100	0	35.5	100	35.5	100	0	29.1	100	29.1
≥1	100	4.2	36.5	100	38.2	100	12.5	31.9	97	37.9
≥2	100	16.7	39.8	100	46.2	97.8	28.6	36	98.2	48.7
≥3	100	35.8	46.2	97.2	58.6	97.8	50.9	45	97.3	65.2
≥4	97	75.8	56.1	92.9	72	95.7	64.3	52.4	91.4	73.4
≥5	89.3	89.2	67	83.6	80.6	82.6	75.9	58.5	89.3	77.8
≥6	68.2	98.3	80.4	77.1	81.7	73.9	89.3	73.9	85.9	84.8
≥7	47	100	93.9	71.4	80	54.3	92.9	75.7	80.3	81.6
≥8	27.3	100	100	67.8	74.2	43.5	94.7	76.9	76.2	79.7
≥9	13.7	100	100	65.6	69.4	26.1	97.3	80	72.3	76.6
≥10	4.6	100	100	64.5	66.1	8.7	98.2	66.6	70.8	73

The developmental sample included 192 children with presumed meningococcal septic shock. The validation sample included 158 children with presumed meningococcal septic shock

Table 6 Descriptive analysis of the five scoring systems applied in the validation sample (*GMSPS* Glasgow Meningococcal Septicaemia Prognostic Score, *PIM* Pediatric Index of Mortality, *m* mean, *SEM* standard error of the mean)

Score	*n*	Non-survivors m ± SEM (range)	*n*	Survivors m ± SEM (range)	*p*
New score	46	6.80±0.31(1–10)	112	2.95±0.21(0–10)	<0.001
GMSPS	45	11.37±0.33(14–5)	108	8.19±0.22(0–15)	<0.001
PIM (risk of death)	44	23.2±0.02	101	10.5±0.1	<0.001
Malley (model I)	45	2.4±0.1	111	1.3±0.1	<0.001
Malley (model I)	44	1.7±0.1	109	0.9±0.1	<0.001

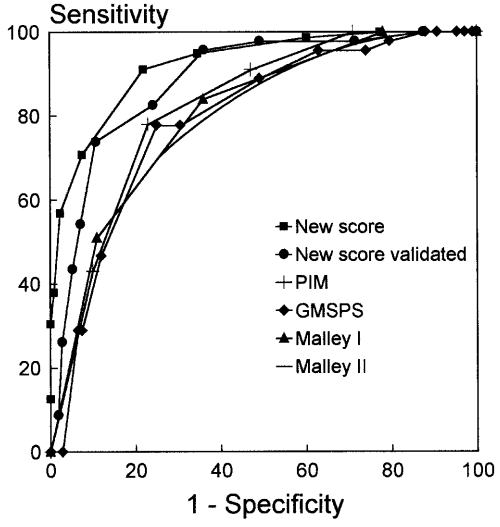

Fig. 2 Receiver operating characteristics (ROC) curves drawn at different cut-off values for the new score, new score validated, Pediatric Index of Mortality (*PIM*), Glasgow Meningococcal Septicaemia Prognostic Score (*GMSPS*) and Malley scores (model I and model II)

mortality rate predicted by the PIM in the intermediate and high risk strata was significantly lower than observed ($p<0.001$).

Discussion

Therapeutic trials must be carefully designed to ensure that treatment and control groups are at an equivalent risk of death. An accurate prognostic system allows the stratification of patients according to risk-of-death categories before randomization and the evaluation of the efficacy of therapy, comparing observed and expected outcome in the different risk strata of the two groups.

This retrospective study presents a new scoring system to assess severity of illness at admission to the PICU in children with presumed meningococcal septic shock. Death was reliably predicted by the presence of a combination of the following factors: cyanosis, coma, refractory hypotension, oliguria, leukocytes below 4000/mm^3, PTT more than 150% of control and base deficit higher than 10 mmol/l. The worst value during the first 2 h in the PICU is taken into account. All these variables are either routinely measured or easily available in hospital laboratories and reflect the importance of the severity of shock, disseminated intravascular coagulation and co-

ma, which are the main determinants of the outcome in meningococcal septic shock. Most of the independent predictors selected have been previously associated with death in this situation [3, 14, 20, 21, 22, 23, 24], except refractory hypotension, which has not been studied before.

Some criticism can arise from the inclusion in the scoring system of a subjective variable (cyanosis) and a therapeutic variable (refractory hypotension). However, the former has been significantly associated with mortality in other studies [21, 23, 24] and highlights the importance of clinical observation in contrast to an evaluation based exclusively on laboratory data. As regards blood pressure, it is largely used as a predictor of death in shock. It is included in most of the current scoring systems for children and adults. However, the time course of blood pressure under treatment seems much more informative. Metrangolo et al. [25] observed that an early increase in mean arterial pressure was the most significant finding in adult survivors of septic shock of different etiologies. Otherwise, other authors, as in our study, have found that a poor response of blood pressure to therapy is an early indicator of mortality [26, 27]. Regarding coagulation performance, PTT would be an earlier prognostic indicator of coagulation disorders than other parameters (platelets and fibrinogen) more frequently quoted in medical literature [28, 29].

In our study, the specific new score was the most useful for early detection of children with presumed meningococcal septic shock at risk of death. It provided the greatest area under the curve (0.88) and also presented good calibration with no significant differences between observed and predicted mortality. It was the only scoring system that included an important number of patients in both low and high risk groups with a survival rate very close to 100% (score ≤3) and a mortality rate close to 100% (score ≥6), respectively. This classification system would be very valuable to clinicians in the decision making process related to the identification of patients who could benefit from aggressive or high risk treatments such as plasmapheresis [30], blood exchange [31] or extracorporeal membrane oxygenator [32]. It would be also useful in clinical trials with anticoagulant therapies [33, 34] or immunomodulator agents [5, 35]. These studies should be targeted to those patients at a reversible stage who are most likely to respond to therapy (intermediate risk group) by excluding the less severely ill patients, who would quickly recover after conventional therapy and the most severe patients, for whom no therapy would achieve a positive outcome.

The new score kept good discriminative capability in the validation sample despite this being somewhat different from the developmental sample with respect to the study period and bacteriological isolations. *N. meningitidis* serogroup C, which has been associated with more severe disease than serogroup B infection [36], was predominant in the validation sample. We found a lower mortality (albeit not statistically different) with no differences in severity as measured by severity scores in the developmental sample. An earlier admission to the PICU, earlier use of mechanical ventilation and improvements in basic management could explain the more favorable results in the validation sample. Since the independent predictors of death did not change when children with lost cultures or with blood/CSF positive cultures yielding isolates other than *N. meningitidis* were included in the multivariate analysis, the new scoring system could be used for early risk stratification of children with a clinical picture of purpura and septic shock, although the culture results are not available.

The generic prognostic system PIM used a logistic regression equation to compute the probability of death for each patient. It showed fairly good discriminative performance (area under the curve =0.82). However calibration was poor, the PIM failed to classify correctly children in the intermediate and high risk strata, underestimating significantly the mortality rate in these groups. These results are not surprising since two of the variables included in PIM are extreme. None of the children in the validation sample had fixed pupils at admission and the FIO_2/PaO_2 rate was normal in most of them. A decrease in performance of PIM has been showed when patients are categorized by diagnostic groups [13]. The inclusion of disease-specific physiological corrections could improve the performance of the generic prognostic systems.

The specific prognostic scores proposed by Malley et al. [15] were developed by multivariable analysis from a sample of 153 patients with invasive meningococcal disease. The model II based on just two variables (neutropenia and hypofibrinogenemia) was inferior to model I based on three variables (hypoperfusion, thrombocytopenia and neutropenia). The latter was able to define a relatively broad group with no mortality (score =0) and discriminated well (area under the curve =0.80). Although the area under the curve was statistically inferior to the new score, this decrease in performance could be outweighed by the improved clinical acceptability achieved by a substantial reduction of the number of variables. However, the positive predictive value of a score of 2 or higher was only 45%. Many patients of the sample it was developed from were unlikely to be in septic shock since poor perfusion and hypotension were present in only 14% and 18% of the patients, respectively, and the mortality rate was low (8%). Furthermore, half of them had not had coagulation studies performed at admission to the hospital. Therefore, it could be more valuable as a criterium of admission to the PICU than for stratifying patients in septic shock.

With regard to the GMSPS, it was created as an indicator of severity to determine the most appropriate place for a child to be cared for. However, it has been used as a predictor of mortality for therapeutic stratification in at least two recent important trials [5, 35]. The new scoring system shares some similarities with the GMSPS. Both

are based on a reduced number of clinical and laboratory parameters that weight mainly the presence of shock and coma. However, the new scoring system is a little more objective, provides a more detailed evaluation of the physiological instability status and, in our study, showed a significantly higher performance. The mortality rate of the high risk group (GMSPS ≥11) was 56%, lower than that found in our previous study [8] and similar to that reported by Derkx et al. [9]. A loss of positive predictive value has been observed in several studies [9, 37, 38, 39, 40], it could be due to the heterogeneity of the samples and the subjectivity in the interpretation of some of its items. Our results should also be interpreted with caution because the criteria used to apply the score to our children were somewhat different to the originals in one item [8].

We propose a score based entirely on clinical signs and basic routine laboratory parameters. It is time-saving, universally applicable and easy to compute and compare, in addition to being able to measure clinically relevant factors. The performance of the GMSPS and Malley scores, as assessed by ROC analysis was statistically inferior to the new scoring system. The PIM showed fairly good discriminative performance but significantly underestimated the risk of hospital death.

In conclusion, if our results are supported by other studies, the new scoring system would be an appropriate tool with which to assess severity of illness in children with presumed meningococcal septic shock at admission to the PICU, with applications in clinical practice and clinical research.

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