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Abstract *Objective:* To investigate the accuracy of eight different prognostic scores (Stiehm, Niklasson, Leclerc, Garlund, the MOC score, Tesero, the Glasgow Meningococcal Septicaemia Prognostic Score (GMSPS) and Tüyzüs) in the prediction of fatal outcome in meningococcal disease.
Design: Combined prospective and retrospective study.
Setting: A 175-bed pediatric department of a university hospital providing secondary care to ± 180,000 inhabitants and serving as a referral center. The Pediatric Intensive Care (14 beds) is one of the six PICUs in the Netherlands and provides tertiary care for children under 18 years.
Patients: During an 8-year period (1986–1994) 125 children (mean age 4 years, 10 months) with culture-proven meningococcal disease were studied: 34 patients presenting with meningitis, 33 patients with septic shock and 58 patients with meningitis and septic shock.
Main results: All eight scores discriminated above average between survivors and non-survivors, as expressed by the corresponding Receiver Operator Characteristic (ROC) curves. The area under the ROC curve (AUC) ranged from 0.74 for the Garlund score to 0.93 for the GMSPS. The GMSPS performed significantly better than its competitors, even after exclusion of the base deficit as one of the score components (AUC = 0.92). It showed above average calibration when logistically transformed into a probability of mortality, and accurately identified a subgroup of patients with no mortality. None of the scores correctly identified non-survivors.
Conclusion: The GMSPS is a simple score that can be reliably used for risk classification and the identification of low-risk patients.

Key words Meningococcal disease · Meningococcal meningitis · Meningococcal septic shock · Sepsis · Severity of illness index · Mortality rate · Prognostication

Introduction

Systemic meningococcal disease can present as septic shock, meningitis or the combination of septic shock and meningitis. Meningococcal meningitis is characterised by nuchal rigidity and the presence of Gram-negative diplococci in the cerebrospinal fluid (CSF). Meningococcal septic shock can be diagnosed rapidly by the demonstration of hypotension and/or signs of 'poor end-organ perfusion', such as metabolic acidosis, oliguria and an altered level of consciousness in the

presence of the characteristic petechiae, purpurae or ecchymoses. In particular in meningococcal septic shock the fatality rate is high and outcome is heavily influenced by early recognition and the immediate start of treatment.

In the last decades several scoring systems have been developed aiming to predict the outcome of patients admitted to the intensive care unit (ICU). These include mortality risk prediction scores, such as the Acute Physiology and Chronic Health Evaluation (APACHE) for adults and the Pediatric Risk of Mortality (PRISM) score for children [1, 2]. Both scores are complicated and consist of an extensive list of vital signs and laboratory tests and do not allow for immediate scoring. The initial APACHE score, as well as the refined APACHE II and III, are validated in adults only and include variables concerning the prior health status of the patient [3–8].

Scoring systems that are specific for sepsis have been developed and the performance of some of these scores has recently been reviewed [9]. These scores have been designed for several purposes, such as the need for making balanced comparisons across centers and treatment alternatives in order to judge treatment outcome. Severity scores can also be used to define treatment allocation rules and the selection of intensive treatment for patients with the worst prospects. Finally, in designing clinical trials, patients at low risk could be safely excluded from studies designed to estimate treatment effects, as they are likely to survive anyway.

In contrast to the sepsis syndrome, meningococcal disease is a rapidly recognisable disease and therefore several simple scores have been developed which aim to predict outcome directly after admittance [10–20]. Unfortunately, most meningococcal disease scoring systems have been developed based on the analysis of small, and heterogenous, patient populations. Moreover, few of these scoring systems have been validated in a separate data set. As a result, their accuracy and usability for the purposes specified remains unknown.

In this study eight published scoring systems suggested for use in predicting mortality in patients with meningococcal disease were compared in a consecutive series of 125 children. The scores were evaluated with respect to their ability to predict fatal outcome based on signs, symptoms and limited laboratory tests available on admission or shortly thereafter.

Methods

Setting

The Emma Children's Hospital at the Academic Medical Center, University of Amsterdam, serves the Southeastern part of Amsterdam and some small surrounding villages, with a population of about 180,000 inhabitants, with secondary care. The pediatric ICU is one of six pediatric ICUs in the Netherlands and provides tertiary care for severely ill children below 18 years.

Patients

All patients under 18 years, admitted to the Children's Academic Center with meningococcal disease, between April 1st, 1986 and April 1st, 1994 were identified from the medical records. To maximize case ascertainment, all medical records of the study hospital with an initial or final diagnosis of (meningococcal) septic shock, sepsis or meningitis were reviewed. In addition, copies were obtained of all the microbiological results and autopsy findings during the study period. All patients meeting the definitions of meningococcal disease (see below) were included.

The standard antibiotic treatment in the study period remained unchanged and consisted of ampicillin and chloramphenicol initially and was changed to penicillin when *N. meningitidis* was cultured. No pharmacological doses of prednisolone were given routinely. All patients with meningococcal septic shock were treated with volume loading as soon as possible. Patients with unstable vital functions were transferred to the pediatric ICU to monitor haemodynamic parameters continuously. In patients with persistent hypotension and/or tachycardia or signs of ongoing organ failure inotropic medication was started: dobutamine, dopamine and, if necessary, epinephrine. If peripheral perfusion remained poor, despite adequate central venous pressure and blood pressure, nitroprusside or prostacyclin was added. All children with meningococcal septic shock or symptoms of cerebral oedema were mechanically ventilated.

Definitions

Patients were categorized on clinical grounds and Gram-stain of blood, CSF and/or skin biopsy shortly after admission. A final diagnosis depended on cultures of *N. meningitidis* or a positive antigen test. The following definitions were used:

Meningococcal meningitis was diagnosed in the presence of nuchal rigidity and a positive isolate of *N. meningitidis* from the CSF or positive CSF bacterial antigen test.

Meningococcal septic shock was defined as the presence of petechiae and/or purpurae, hypotension and/or at least two signs of poor end-organ perfusion and a positive culture for *N. meningitidis* in blood, CSF and/or skin biopsy or a positive antigen test in blood and/or CSF. Hypotension was defined according to age: systolic blood pressure of less than 75 mmHg in children below the age of 1 year, less than 80 mmHg in children aged 1–5 years, less than 85 mmHg in children 6–12 years and less than 100 mmHg in children older than 12 years. The following signs of poor end-organ perfusion were defined: (1) unexplained metabolic acidosis (pH < 7.3, base deficit > 5 or plasma lactate levels > 2 mmol/l); (2) arterial hypoxia ($pO_2 < 75$ mmHg, pO_2/FiO_2 ratio < 250 or TcO_2 sat $< 95\%$ in patients without pre-existing pulmonary problems); (3) oliguria (urine output $< 1/2$ ml/kg/h for at least 2 h despite volume loading in patients without pre-existing renal disease); (4) elevated delta temperature ($T_{rectal} - T_{skin\ lower\ extremity} > 3\,°C$) and (5) mental deterioration.

Children were categorized as having meningococcal septic shock and meningococcal meningitis if they satisfied both of the above definitions.

Meningococcal disease was used as the collective denomer for all systemic infections caused by *N. meningitidis*, e.g. meningococcal meningitis and/or meningococcal septic shock.

Prognostic factors

The following clinical and laboratory data were retrieved from the medical records, or from the notes of the referring hospital.

Clinical data

Age, sex, temperature on entry to the hospital, diarrhoea in the last 24 h prior to admission, blood pressure, delta temperature, cyanosis, time interval between appearance of petechiae and start of treatment, modified coma scale, mental deterioration in the last hour and meningeal signs. In addition, the presence (petechiae and/or ecchymoses and, if ecchymoses were present, the size: 1–5, 6–10, 11–15, > 15 mm) and extent of skin haemorrhages (extensive: confluent, over more than half of any limb or more than 20% of the body surface area; moderate, if ≤ 50% of limb/trunk was involved; and limited, if less than above) were noted.

Laboratory data

The following variables were collected for all patients: haemoglobin, leukocytes, blood platelets, base excess, potassium, activated partial thromboplastin time (APTT), prothrombin time (PT). In CSF: total cell count, WBC, protein, glucose. Cultures were performed of blood and/or CSF and/or skin and in 71 patients also the *N. meningitidis* serogroup was determined.

All variables were obtained prospectively for children admitted to our hospital after January 1st, 1991 (67 patients). Of the patients admitted before this period, the medical records were reviewed. Clinical and laboratory data were extracted from each record independently by two researchers who were blinded for treatment outcome (JvdH, HD). In case of disagreement (< 1% of the data) a decision was made by a third investigator (RB).

Severity scores

The literature was systematically (Medline) searched for articles, published in the last three decades, in which prognostic meningococcal disease severity scores had been discussed. Only scores with well defined variables were included in this study. The following prognostic scores were calculated for all patients: (1) Stiehm (2) Niklasson (3) Leclerc (4) Garlund (5) the MOC score (6) Tesero (7) the GMSPS (8) Tüysüz (Table 1) [10–20].

The scores for each prognostic scoring system were derived according to the definitions given in the original publications for the individual variables. The clinical assessment was made within the first hour after admittance to our hospital. Due to the unavailability of ESR, this variable was replaced by low platelets (< 100 × 10^9/l) in the scoring system proposed by Stiehm. The Leclerc score was only obtained for patients presenting with meningococcal septic shock (± meningococcal meningitis). The cut-off scores for each variable as described in the original papers were applied to our patient population for each score separately. The severity scores were obtained as a research tool and not as a guide for treatment decisions.

Statistical analysis

The predictive abilities of the scores were evaluated by plotting the sensitivity against the specificity for each value of the score, thereby making a series of dichotomisations. Areas under the resulting receiver operator characteristic (ROC) curves were calculated as a measure of a score's ability to discriminate between survivors and non-survivors [21–23]. The area under the ROC curve (AUC) takes values between 0 and 1; an AUC of 0.5 means that a set does not discriminate, an AUC of 1.0 means that perfect discrimination can be achieved. Areas under the curve were calculated using the trapezoidal rule [24]. The AUC was compared between scores using a chi-squared test statistic for homogeneity, followed by tests of pairwise differences, calculating standard errors and correlations according to the methods described by Hanley & MacNeil [24].

Results

Demographic features

During the study period, 132 children fulfilled the criteria of meningococcal disease. Seven patients were excluded due to missing records or missing values on key variables (one of these patients died and six recovered without sequelae). In the remaining 125 children (72 boys, 53 girls; mean age 4 years 10 months, range 24 days–16.5 years) nearly all data could be obtained. Fifty-two patients were directly admitted to our hospital, while 73 patients were referred from other hospitals.

Only 5% of the data in the retrospective analysis were missing, most commonly the delta temperature and the modified coma scale in patients with minor illness. If no delta temperature was mentioned it was scored as elevated (> 3 °C) if 'cold extremities' or 'weak peripheral pulsations' was noted in the chart. In patients with an adequate verbal response in whom no modified coma scale was scored, a score was imputed based on the median value in comparable patients. Using these methods only 0.75% of the data items could not be used. For scoring purposes these missing items were assumed to be normal.

Clinical picture

In the first hour after admission patients suspected of meningococcal disease were categorised on clinical grounds and Gram-staining of CSF and/or skin biopsy as having meningococcal meningitis, meningococcal septic shock, or both. Meningococcal disease was definitely diagnosed after *N. meningitidis* was cultured. Thirty-three patients had meningococcal septic shock, 34 meningococcal meningitis and 58 patients had meningococcal septic shock and meningococcal meningitis. Most of these patients were under 5 years (*n* = 83).

Mortality

The overall case mortality rate from meningococcal disease was 20.8% (26/125 patients): 2 of the 34 patients

Table 1 Clinical and laboratory variables of eight prognostic scoring systems for meningococcal disease

	Stiehm & Damrosch	Niklasson	Leclerc[a]	Garlund	MOC score	Tesoro	GMSPS	Tüysüz
General features								
age < 1 yr			1					
1–2 yr			2					
> 2 yr			3					
diarrhoea (b)					1			
T-rectal		1 (if ≥ 40 °C)		1 (if > 39 °C)	1			
deterioration (c)							2	
Haemodynamic features								
shock	1 (if RRsys ≤ 70)	1 (if RRsys ≤ 70 (≤ 14 yr) if RRsys ≤ 100 (> 14 yr)		1 (if RRsys < 100)	1 (if age adjusted RR sys < 100)	1 (d)	3 (if RRsys < 75 in pat < 4 yr or < 85 in > 4 yr)	3 (if < 5th percentile)
T-delta > 3 °C							3	
cold extremities					1			
Skin haemorrhages								
petechiae present	1 (e)	1 (e)		1 (if extensive) (h)	1	1		2 (e)
ecchymosis					1			
extensive rash (f)							1	
cyanosis					1			
Neurologic features								
meningitis clinically present			1					
meningitis clinically absent					1		2	1
modified coma scale (g)							3 (if < 8 or deterioration ³3 in 1 h)	
altered mental status						1		1
Laboratory data								
leukocytes	1 (if < 10 × 10⁹/l)	1 (if < 15 × 10⁹/l)	1 (if < 10 × 10⁹/l)			1 (if < 5 × 10⁹/l)		2 (if < 5 × 10⁹/l)
platelets		1 (if < 100 × 10⁹/l)	1 (if < 100 × 10⁹/l)	1 (if < 125 × 10⁹/l) (h)			1	
Base deficit (> 8)								
kaliaemia			1 (if > 5 mmol/l)					
ESR (< 10 mm/h)	1							
WBC in CSF	1 (if < 20/mm³)	1 (if < 100/mm³)						

a. Formula: −1(age) + 1.7(kaliaemia) + 0.7(WBC) − 1.3(meningism) + 1(platelets) + 1.9; b. before or on admission; c. deterioration in hour before scoring; d. not defined; e. presence of petechiae for less than 12 h prior to admission; f. extending purpuric rash or widespread ecchymoses; g. modified coma scale (1. eyes open: spontaneously (4), to speech (3), to pain (2), none (1); 2. best verbal response: orientated (6), words (4), vocal sounds (3), cries (2), none (1); 3. best motor response: obeys commands (6), localizes pain (4), moves to pain (1), none (0); h. low platelets and petechiae can substitute one another

with meningococcal meningitis (5.9%), 16 of the 33 patients with meningococcal septic shock (48.5%) and 8 of the 58 patients with meningitis and septic shock (13.8%). Seven patients died within 5 h after admission, one from cerebral oedema and subsequent cerebral herniation complicating meningococcal meningitis. The other six patients had irreversible shock and severe disseminated intravascular coagulation unresponsive to therapy. Twenty-one of the 26 non-survivors died within 48 h after admission. All patients with fatal meningococcal septic shock had severe disseminated intravascular coagulation and extensive skin haemor-rhages. Twenty-four children were below 1 year of age at the onset of symptoms, 8 of whom died (33.3%). Of six infants younger than 3 months of age, four died. Strain typing was performed in 71 cases. Serogroup B was found in 58 patients, C in 10, A in 2 and Y in one patient. No significant association between serogroup and outcome was observed.

Severity scores

As no systematic differences in discriminatory performance were observed in prognostic scores based on retrospectively ($n = 58$) versus prospectively ($n = 67$) collected data, all data were pooled. The range and median of the scores are presented in Table 2. Figure 1 shows the distribution of the scores within the study group, stratified for survivors (in white) and non-survivors (in black). All scores show zero mortality in the lowest scores.

Each score's ability to predict mortality, as expressed by the area under the ROC curve (AUC), can be found in Table 2. All scores predicted above average – with the AUC ranging from 0.74 for the Garlund score to 0.93 for the GMSPS – but failed to achieve a perfect classification of survivors and non-survivors. When the base deficit was left out as a scoring factor for the GMSPS, the AUC for this score remained nearly the same (0.92). When the modified coma scale was left out of the scoring system as well, the AUC became 0.87. In the following, only the original GMSPS score will be referred to, including base deficit and modified coma scale. Homogeneity had to be rejected for the AUCs of the different scoring systems, based on the chi-squared test statistic ($p < 0.01$). Pairwise tests of contrasts revealed that the GMSPS performed significantly better than all of its competitors ($p < 0.01$ to $p = 0.03$) except for Gedde-Dahl's MOC score (pairwise contrast $p = 0.19$). Figure 2 shows the ROC curve for the GMSPS. All patients with GMSPS scores of 5 or lower survived.

For illustration purposes, we also looked at the level of calibration of the GMSPS scores. The level of calibration expresses the degree to which a prognostic score correctly predicts the probability of survival in a group of patients [25]. A well calibrated test yields accurate probabilities. The evaluation of calibration is based on a comparison of the predicted probability of mortality in particular subgroups of patients with the number of patients who actually died. With a well calibrated test, a subgroup with a predicted probability of mortality of 0.20 would show 20% mortality.

The GMSPS scores were transformed into predicted probabilities of mortality, using logistic regression applied to our own set of data. The resulting logistic model had an estimated intercept of -7.1 and a scale factor of 0.55, yielding predicted probabilities that ranged from 0 (for a score of 0) to 0.78 (for a maximum score of 15). Subsequently, all patients were ranked, based on their GMSPS score, and classified into five groups of equal size, based on their ranking. Within each group, the average predicted probability of mortality was calculated, as obtained from the logistic regression on the GMSPS scores, and compared with the observed mortality rate within that subgroup. The results of this comparison are plotted in Fig. 3. The differences between the predicted probabilities of mortality and the observed fatality rate are small, with a maximum of 6% difference in the stratum with the highest severity scores corresponding to the highest probability of mortality. All average predicted probabilities fall well within the 95% confidence interval of the estimated probability of mortality, based on the relative frequency of mortality within each subgroup. These data suggest that the GMSPS not only shows good discrimination – as measured by the AUC – but also shows reasonable calibration.

Discussion

In this study, eight meningococcal disease outcome prediction scoring systems were compared with regard to their ability to classify correctly patients with meningococcal septic shock and/or meningococcal meningitis into hospital survivors and non-survivors. Of the scores studied, the GMSPS performed significantly better than most of its competitors, with an area under the ROC curve of 0.93, and accurately identified a substantial number of survivors. The second best system was the MOC, that only includes variables that can be obtained at the bedside.

The present study was based on a series of 125 patients in one center. Although the restriction to one center may limit the extent to which the actual distribution of the scores within each system can be generalized, the comparison of eight scoring systems in a single group of children guarantees a high internal validity of the comparison of the scoring systems, which have been
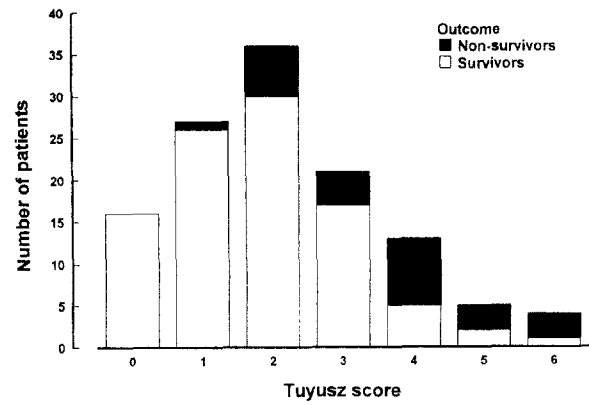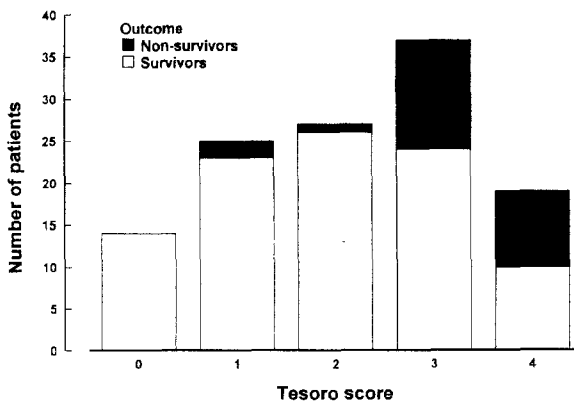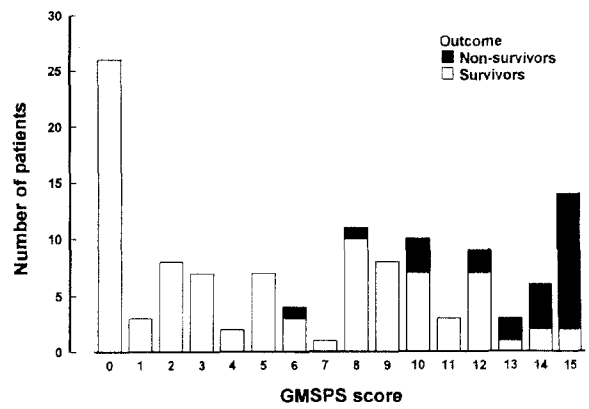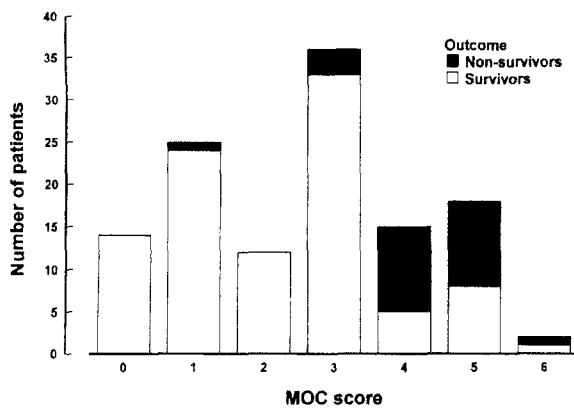
Stiehm score

Niklasson score

Leclerc score

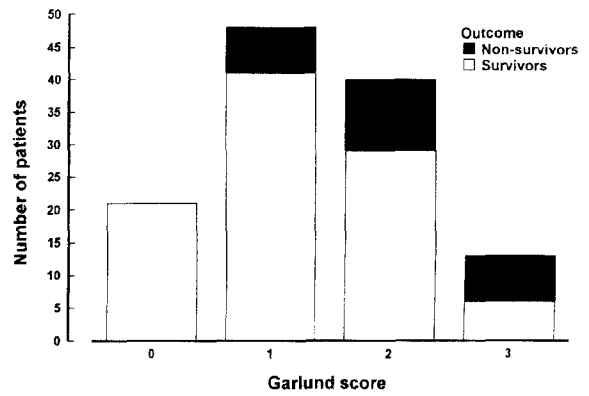Garlund score

MOC score

GMSPS score
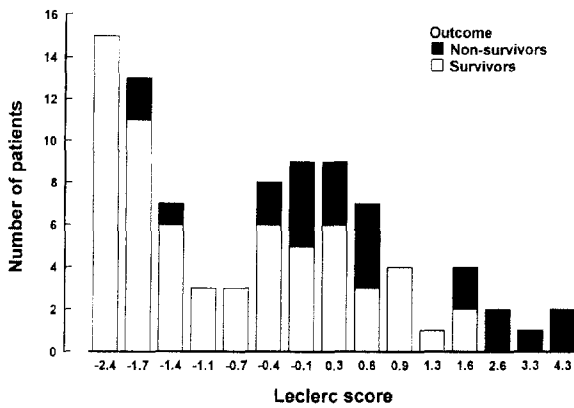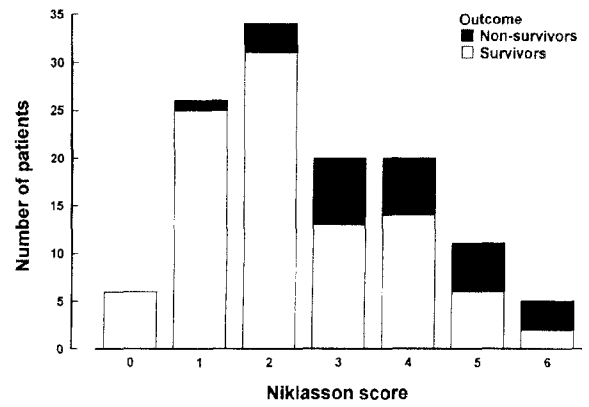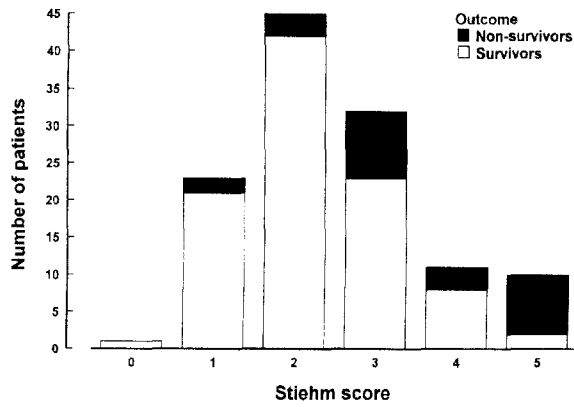

Tesoro score

Tuyusz score

Table 2 Univariate results and ROC results of eight prognostic scoring systems (s.e. standard error)

Scoring System	Univariate results			ROC results	
	Minimum	Median	Maximum	Area	s.e.
Stiehm	0	2	5	0.778	0.047
Niklasson	0	2	6	0.784	0.054
Leclerc	− 2.4	− 0.4	4.3	0.795	0.051
Garlund	0	1	3	0.743	0.056
MOC	0	3	6	0.866	0.048
GMSPS	0	8	15	0.925*	0.031
Tesoro	0	2	4	0.792	0.054
Tüysüz	0	2	6	0.825	0.046

*without base deficit: 0.918 (s.e. 0.033) – without base deficit and coma scale 0.867 (s.e. 0.04)

Fig. 3 Calibration of the Glasgow Meningococcal Septicaemia Prognostic Score in patients with meningococcal disease: average predicted probability of mortality and observed mortality rate in 5 groups of 25 patients each
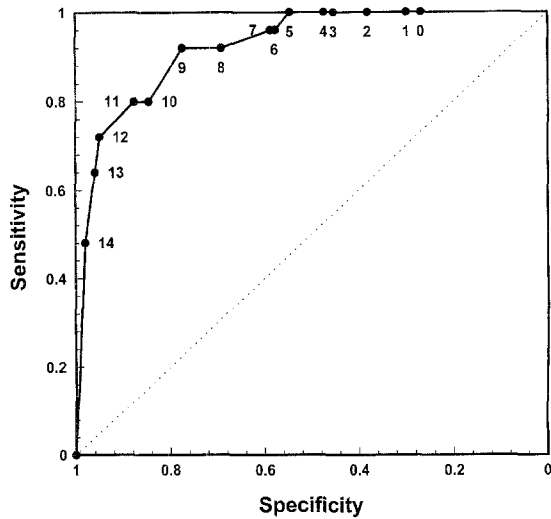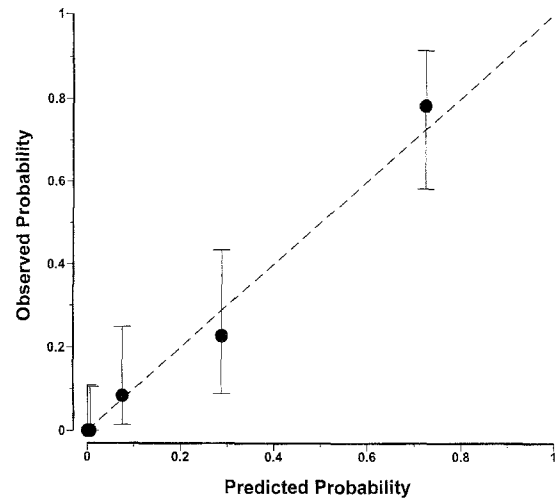

Fig. 2 Receiver Operating Characteristic curve for the Glasgow Meningococcal Septicaemia Prognostic Scores (GMSPS) in 125 patients with meningococcal disease

developed and evaluated in separate – and usually smaller – patient groups. No differences were observed in the predictive value of the different scores when they were evaluated over different time periods. Thus it may be assumed that small changes in treatment over time are relatively unimportant in respect to severity assessment.

In contrast to previously reported studies, the definitions applied for meningococcal meningitis and meningococcal septic shock in our study were strict, and only patients with a positive culture of *N. menin-*

Fig. 1 Distribution of the scores on eight scoring systems for survivors (shown in white) and non-survivors (shown in black) in 125 patients with meningococcal disease

gitidis and well defined symptoms of systemic meningococcal disease were included. One can criticize the fact that patients with a clinical suspicion of meningococcal disease but in whom no *N. meningitidis* was isolated, were not enrolled in this study. However, this was the case in only 11 patients, a number that could be further reduced to four if also those patients should have been included in whom the Gram-stain of the CSF or skin biopsy showed Gram-negative diplococci but who had a negative culture.

We did not study the more general scoring systems. Most of these severity scores have been developed for adults, are complex, time-consuming and require an evaluation over time, hence precluding the possibility of rapid scoring. In addition, the majority of severity scoring systems were not specifically designed for sepsis. Previously established sepsis scores include sepsis-related factors, such as patient's age, length of stay in the hospital and ICU, indication for ICU admittance and variables such as underlying disease and type of infection, and are therefore not appropriate for children who suddenly develop fulminant meningococcal disease. The PRISM score is a complex score that can be applied to children admitted to the ICU. This score has recently been validated [26]. The 14 parameters included in this mortality risk assessment consist of laboratory data and hourly vital signs on the day of admission [3]. A score is calculated by taking the worst results of each measurement into account. Therefore, this score apparently is not suited to include the rapid changes in physiological stability that are not uncommon in patients with meningococcal disease.

The GMSPS did accurately reflect the mortality experience of patients with meningococcal disease. Although the evaluation of calibration has to take into

account the amount of "over-optimism" that results from constructing and evaluating a score in one group of patients, only the two parameters of the logistic transformation were estimated in our cohort, not the actual scoring system itself. Moreover, the system was not explicitly designed to yield scores on an interval difference.

Ideally, a system for scoring severity of meningococcal disease should be easy to obtain at the bedside limited cost and soon after admission. To be useful for monitoring in time – a purpose not evaluated in this study – the scores should also be sensitive to relevant changes in the patient's condition over time. The GMSPS is a meningococcal disease outcome score that includes mainly clinical variables and one laboratory value. As most variables are easy to score, the score can be obtained quickly. Nonetheless, two shortcomings of the GMSPS need to be mentioned. Firstly, the GMSPS is not completely 'bedside', because the base deficit is included as one of the variables, which introduces a delay. Secondly, most patients who are artificially ventilated are also sedated, making the scoring of the modified coma scale impossible. The MOC score lacks these disadvantages and constitutes a very simple score that includes seven bedside variables [14]. However, in contrast to the GMSPS, this score is not dynamic and does not allow for rescoring if a patient deteriorates. Therefore, we recalculated the GMSPS excluding the base deficit to obtain a bedside score, and subsequently excluded both the base deficit and the modified coma scale. The performance of this minimized score was still acceptable. Hence, it seems that the GMSPS can also be used as a bedside score and allows for rescoring in patients for whom no coma scale can be obtained.

Severity scoring systems provide a useful method for performance evaluation, comparison of different treatment modalities and stratification according to severity of disease. On the other hand, it remains doubtful whether scoring systems will ever be a basis for decision-making in individual patients. Although withholding treatment in patients that are going to die anyway constitutes a case of averting futile medical action, none of the scoring systems was able to identify a group of patients with a (close to) 100% mortality. Even if they did, predictions based on such small samples are likely to be too imprecise for practical purposes. Nevertheless, a validated quantified risk assessment, even if associated with some degree of imprecision, may be helpful in discussing a patient's prognosis with family members, clinical colleagues or other medical personnel.

The utility of prognostic scoring systems, as evaluated in this study, is more likely to be found in performance evaluation, in the construction of aggregated comparisons of treatment outcome and for making appropriate balances of case-mix. At the low-risk side of the spectrum, one application deserves mentioning explicitly. Low values of the GMSPS score were associated with a zero mortality. It would be erroneous to conclude that these patients were treated too aggressively, as we do not know the consequences and outcome of alternative management strategies. Yet this observation offers opportunities for making safe and efficient decisions in excluding these patients from future clinical trials aimed at evaluating the effectiveness of new treatment alternatives for meningococcal disease. As patients in these score categories seem to survive anyway under current medical treatment, their outcome cannot be improved by new treatment alternatives. Randomizing these patients between current and new treatment will therefore only induce additional "noise" in statistical comparisons. We regret that we cannot set any cut-off points based on our patient series. To assess the external validity of these scores, and the feasibility of applying specific cut-off points for patient selection, interinstitutional comparative analyses of these scores, in larger groups of patients, are a prerequisite.

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