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Scoring system for nosocomial pneumonia in ICUs

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Abstract *Objective*: To develop a scoring system for stratifying patients in intensive care units (ICUs) by risk of developing nosocomial pneumonia (NP), based on variables generally available in an ICU, and to determine the probability of a patient developing NP in the ICU.
Design and setting: A 2-year prospective cohort study conducted in a medical and surgical ICU.
Patients: 756 patients admitted to the ICU for 48 h or more were followed up until the development of NP or death or discharge from the ICU.
Measurements and results: 129 (17.1%) patients developed NP, 106 (14%) in the first 2 weeks. The following independent risk factors were identified by multivariate analysis: no infection on admission [relative risk (RR) = 3.1, 95% confidence intervals (CI) = 2.0 to 4.8]; thorax drainage (RR = 2.1, 95% CI = 1.2 to 3.5); administration of antacids (RR = 2.1, 95% CI = 1.4 to 3.1); partial pressure of oxygen (PO_2) >110 mmHg (RR = 1.6, 95% CI = 1.0 to 2.6); administration of coagulation factors (RR = 1.8, 95% CI = 1.0 to 3.2); male gender (RR = 2.7, 95% CI = 1.2 to 6.3); urgent surgery (RR = 2.4, 95% CI = 0.9 to 6.4); and neurological diseases (RR = 4.2, 95% CI = 1.9 to 9.4). To obtain a predictive risk index for NP, a scoring system was developed using a multivariate model. The probability of developing NP varied between 11.0% in the lowest risk group and 42.3% in the highest risk group. The patients' risk of acquiring NP was seven times higher in the highest score category (IV) than in the lowest one (I).
Conclusions: ICU patients can be stratified into high- and low-risk groups for NP. No infection on admission, thorax drainage, administration of antacids, and PO_2>110 mmHg were associated with a higher risk of NP during the entire 2-week period.

Key words Nosocomial pneumonia · Scoring system · Risk factors · Intensive care units

Introduction

Nosocomial infections represent a major health problem because of the excess morbidity, mortality, personal distress, and cost [1]. Pneumonia is the most common nosocomial infection in intensive care units (ICUs). As much as 50% of all nosocomial pneumonias (NPs) occurring among patients on the medical service and 70% of NP among patients on the surgical service occur in ICUs [2]. Case fatality rates of 20 to 50% in some studies of NP, despite the availability of potent antibiotics, emphasize the need for research directed at its prevention [3, 4]. Recently, a number of preventive measures aimed at re-

ducing the occurrence of NP have been investigated. These include the prophylactic administration of immune globulin, elevated head positioning to prevent aspiration, effective hand-washing, the use of sucralfate for gastric bleeding prophylaxis, and use of jejunal versus gastric enteral feeding.

One potential approach to preventing NP is to stratify patients early in their ICU stay into high- and low-risk groups for the development of NP. Interventions can then be directed specifically at the high-risk patients. To design effective strategies to prevent NP, it is important to identify not only the patients at highest risk for NP, but also the length of stay in the ICU associated with such a risk.

In the assessment of risk factors and the development of a scoring system, the fact that the patient acquired the infection in the ICU and when it was acquired are relevant. One patient develops NP at some time during a stay in the ICU, while other patients may have been discharged or may have died due to their severe illness by that time. Death and discharge, therefore, have to be regarded as so-called "competing risks" for the risk of developing NP. Therefore the occurrence of pneumonia has to be modelled by using methods appropriate for time-to-event data [5, 6].

The current study was designed to develop a simple, easy-to-use predictive model to stratify patients in the ICU into risk groups for NP.

Materials and methods

Patient population

The University Hospital of Freiburg, Germany, is a 1980-bed tertiary-care hospital with a 9-bed surgical ICU and 7-bed medical ICU. Of the patients admitted to these ICUs during the 2 years between July 1991 and July 1993, all patients 18 years of age or older who stayed in the ICUs for 48 h or more were entered into the study. Three investigators followed up the cohort of 756 patients daily until one of the following events occurred: discharge from the ICU or death.

Data collection

The investigators made all of the observations and chose relevant data daily by reviewing the patients' medical records, bedside flow sheets, and X-rays. At the time of entry into the study, the following data were recorded by chart review: age, sex, admitting service, body weight, smoking history, admission diagnosis, surgical interventions, hospital stay before ICU admission, and type and number of concomitant diseases. Concomitant diseases were: diabetes mellitus, cirrhosis of the liver, neurological diseases, endocrinological diseases, chronic abdominal diseases, chronic pulmonary diseases, cancer and/or immunosuppression. Each of the concomitant diseases was entered into the univariate analysis. In addition, the presence or absence of each of the following potential risk factors was recorded daily: intubation (nasal, oral, tracheostomy), disseminated intravascular coagulation, surgery, administration of catecholamines >250 mg/day, urinary catheters (transurethral, suprapubic), pulmonary artery, and central venous catheters, thorax drainage, administration of antibiotics, administration of histamine type 2 receptor (H_2) blockers and antacids, administration of coagulation factors (fresh frozen plasma or antithrombin 3), enteral and parenteral nutrition, Glasgow Coma Scale, aspiration, partial pressure of oxygen (PO_2), sodium, potassium, leukocyte count, and presence of ileus.

A diagnosis of NP required the presence of all of the following criteria: fever, leukocytosis, new or progressive lung infiltrate not attributable to another etiology (e.g., adult respiratory distress syndrome, congestive heart failure, or pulmonary embolism), and purulent respiratory secretion yielding growth of relevant microorganisms. A positive culture of blood, pleural fluid, bronchoalveolar lavage, or protected brush sample via bronchoscopy was regarded as additional proof of NP and as definitive for the etiology but was not required as a diagnostic criterion. Patients with pneumonia diagnosed on admission to the ICU were not excluded from the study. A diagnosis of NP in this group of patients required, in addition to the above criteria, a worsening of the clinical symptoms and a change in the causative microoganism in the tracheal secretion or bronchoalveolar lavage. Patient status was determined daily.

Statistical analysis

Univariate analysis of each factor was performed by fitting a Cox proportional hazard model to the pneumonia-specific hazard [7, 8]. For each factor the proportionality assumption was checked by an additional deterministic time-dependent covariate. Several potential risk factors did not meet the proportionality assumption over the whole study period. Therefore, the development of the scoring system was restricted to a model for the short-term prognosis in 2 weeks, i.e., the first 2 weeks in the ICU (phase 1: days 1–6 and phase 2: days 7–14). If the effect of a covariate did not differ significantly ($p > 0.1$) in the two phases, a common effect was estimated. In the model for the pneumonia-specific hazard deaths, sepsis and discharges were treated as censored observations as were patients still in the ICU at day 14 without signs of NP. The relative risk was estimated with corresponding asymptotic 95% confidence intervals. Significance tests were performed by the Wald test [5]. To select the variables for multivariate analysis, factors associated with an increased risk for pneumonia at the 5% significance level in the univariate analysis were entered into a stepwise procedure for the proportional hazard model; the significance level for entry was set at $p = 0.25$ and for stay at $p = 0.15$. All multivariate analyses were stratified for type of ICU. The results of the multivariate analysis were used to construct the scoring system.

For each patient in the study population an individual score was determined. Cut-off points to delineate categories for low- and high-risk patients were based on the observed distribution of scores. The 50, 75 and 90% quantiles of the distribution were used to delineate four score categories. To be able to judge the discriminative ability of the score, these categories have been entered into a Cox regression as "dummy" variables to determine the relative risk associated with each category.

In estimating the predictive probability of pneumonia, the probability of other "competing risks", such as death and discharge, have to be incorporated in the calculations. The (unadjusted) probability of NP in the strata defined by the score categories was estimated by the nonparametric Aalen-Johansen estimator for the transition probabilities in multistate models, taking into account the occurrence of death and discharge [9]. The adjusted probability of pneumonia based on the results of the Cox regression for the event-specific hazards of pneumonia, death, and discharge can conveniently be estimated by the methods described in Klein et al. [10]. The estimate of the adjusted probability of pneumonia, e.g., in the

highest pneumonia score category, is calculated as the average of the individually estimated probabilities of all patients in that category; this procedure is described for the estimation of adjusted probabilities in the survival model by Thomsen et al. and Makuch [11, 12].

Results

Table 1 summarizes the baseline characteristics and the interventions performed on the 756 patients who were entered in the study. The most frequent admission diagnosis was related to trauma/head trauma (25.4%) and to the cardiopulmonary system (24.8%). Patients were almost equally distributed between medical and surgical services, although there were discrepancies between the patient populations in the ICUs. In the medical ICU (MICU) the patients' mean age was 10 years older than in the surgical ICU (SICU), and the most frequent admission diagnosis was cardiopulmonary disease compared to trauma in the surgical service. Seventy-two percent of the patients were intubated, 86.5% of them orally. The mean (±SD) hospital stay in the SICU was 9.3 (9.7) days and in the MICU 9.9 (11) days. The median hospital stay in the SICU was 6 days (2–73 days), and in the MICU 7 days (2–81 days).

A total of 197 (26.1%) patients acquired one or more nosocomial infections; 129 patients (17.1%) met the study definition for NP (18.6 episodes per 1000 patient-days; 25.2 episodes per 1000 patient-days of intubation); 106 (14.0%) patients acquired NP in the first 2 weeks of their stay in the ICU. The incidence of NP varied with patient age. NP occurred in 16.0% of patients <45 years old, in 14.2% of patients 45 to 65 years old, and in 11.9% of patients older than 65 years. Risk factors for NP which were statistically significant on univariate analysis are shown in Table 2. Statistically significant risk factors in univariate analysis were entered into a proportional hazard model, and a multivariate analysis was performed. No infection on admission, thorax drainage, administration of antacids, and altered consciousness emerged as independent risk factors for NP (Table 3). In addition to the above factors, the administration of coagulation factors, urgent surgery, $PO_2 > 110$ mmHg, and male gender approached, but did not achieve, statistical significance. Administration of coagulation factors was identified as an

Table 1 Characteristics of the study cohort. Age (mean ± SD) = 53.5 ± 19.9 years for all patients, 49.03 ± 17.6 years for patients with pneumonia

	All patients		Patients with pneumonia	
	(n = 756)	%	(n = 106)	%
Female gender	297	39.3	37	34.9
Hospital stay before ICU admission	447	59.1	59	55.6
Obesity	194	25.7	24	22.6
Admission diagnosis:				
Cardiopulmonary	187	24.8	22	20.7
Trauma	192	25.4	42	39.6
Abdominal	102	13.5	12	11.3
Head trauma	36	4.8	1	0.9
Infections	128	16.9	17	16.4
Urogenital	11	1.5	1	0.9
Others	100	13.2	11	10.4
Admission service:				
Medicine	316	42	56	52.8
Surgery	440	58	50	47.2
Intubation:	541	71.7	77	72.6
Nasal	45	6.0	9	8.5
Oral	468	62.0	66	62.3
Tracheostomy	28	3.7	2	1.9
Operation:	349	46.2	50	47.2
Elective	116	5.2	11	10.4
Urgent	233	30.8	39	36.8
Antibiotics	469	62.1	66	62.3

Table 2 Risk factors for NP; univariate analysis. All variables were coded as 1 for "factor is present" and 0 for "factor is absent"

Factor	Relative risk	95% confidence intervals
No infection on admission	2.5, phase 1+2	1.65 to 3.66
Trauma[a]	1.9, phase 1+2	1.13 to 3.13
Urgent surgery	2.4, phase 2 only	0.97 to 5.68
Head trauma[b]	2.8, phase 1 only	0.96 to 8.48
Neurological diseases	2.4, phase 2 only	1.12 to 5.01
Administration of coagulation factors	1.9, phase 1 only	1.11 to 3.26
Pneumothorax	2.2, phase 1 only	1.00 to 4.80
Central venous catheter	2.3, phase 1 only	1.05 to 5.13
Thorax drainage	2.0, phase 1+2	1.18 to 3.26
Administration of antacids	1.8, phase 1+2	1.21 to 2.64
$PO_2 > 110$ mmHg	1.8, phase 1+2	1.18 to 2.87
Male gender	2.6, phase 2 only	1.16 to 6.04

[a] The variable "trauma" is an admission diagnosis and includes all patients with multiple injuries only, with head trauma only and with multiple injuries and head trauma
[b] The variable "head trauma" means all other head injuries

Table 3 Risk factors for NP; multivariate analysis

Risk factor	Number of patients (%)	Relative risk	95% confidence intervals	*p*-value
No infection on admission	344 (45.5)	3.1	2.0 to 4.8	0.0001
Thorax drainage	84 (11.1)	2.1	1.2 to 3.5	0.008
Antacids	272 (36.0)	2.1	1.4 to 3.1	0.001
$PO_2 > 110$ mmHg	153 (21.2)	1.6	1.0 to 2.6	0.045
Administration of coagulation factors (days 1 – 6)	144 (19.1)	1.8	1.0 to 3.2	0.044
Male gender (days 7 – 14)	459 (60.7)	2.7	1.2 to 6.3	0.021
Urgent surgery (days 7 – 14)	233 (30.8)	2.4	0.9 to 6.4	0.094
Neurological diseases (days 1 – 6)	101 (13.4)	4.2	1.9 to 9.4	0.001

independent risk factor for NP only in the first week of ICU stay, whereas male gender, urgent surgery, and neurological diseases were associated with an increased risk of developing NP only in the second week of ICU stay. All other risk factors predisposed for the acquisition of NP over the whole 2-week period.

The rate of NP also varied by admission diagnosis. While 11.8% of patients with underlying diseases of the cardiopulmonary system developed NP, 11.7% of patients with diagnoses involving the gastrointestinal tract, 9.0% of patients with urogenital disorders, 18.9% of patients with trauma, and 13.3% of patients who already had an infection on admission to the ICU developed NP. None were entered into the scoring system.

The case-fatality rate for patients with NP was 21.7% compared with a crude mortality of 25.3% among all patients. The mortality in patients without nosocomial infection was 14.8%, in patients with "other" nosocomial infections 7.4%, and in patients with nosocomial infections of the blood 62.3%. These figures might explain the "protective" effect of NP due to the very high mortality from infections of the blood. The incidence of NP per hospital day from admission is shown in Fig. 1.

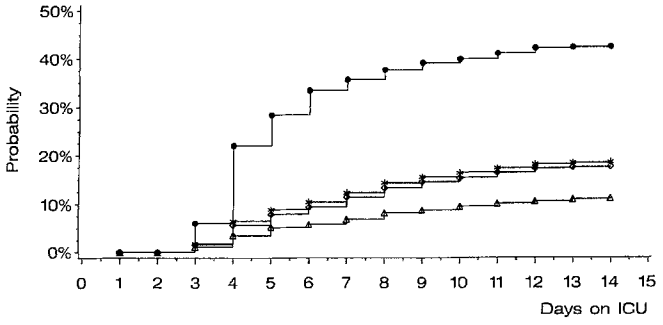

Fig. 1 Incidence of nosocomial pneumonia per hospital day after admission (number of cases occurring each day divided by the number of patients at risk at each day). See Table 5 for category and score; pneumonia score: △-△-△ = I; ◇-◇-◇ = II; ✳-✳-✳ = III; ●-●-● = IV

The scoring system and its use in the study cohort

Table 4 presents the scoring system that was derived from the selected proportional hazards model. The score assigned to each risk factor represents the rounded regression coefficient multiplied by 10 for each risk factor of the Cox model. According to the phase-wise models, two score values have to be computed per patient: score 1 for the risk of pneumonia occurring in the first week in the ICU, score 2 for the risk of pneumonia occurring in the second week in the ICU.

The numbers of patients who developed NP in the first and second week of their ICU stay are presented in Table 5. In category IV, 26.5% of patients developed NP in the first week, whereas 28.1% of the 327 patients still in the ICU at day 7 acquired NP in the second week of their stay. The patients' risk of acquiring NP in various score categories relative to category I is shown in Table 6. A patient with a score in the highest category has a seven-times higher risk of NP compared with a patient with a score in the lowest category. The estimated probability for pneumonia in the first week of ICU stay in category IV is 33.4% and in the second week of ICU stay, 42.3%.

Table 4 Scoring system to stratify patients by risk of developing nosocomial pneumonia

Risk factor	Score if risk factor is present	
	Score 1 (days 1 – 6)	Score 2 (days 7 – 14)
No infection on admission	11	11
Thorax drainage	7	7
Antacids	7	7
$PO_2 > 110$ mmHg	5	5
Administration of coagulation factors[a]	6	–
Male gender	–	10
Urgent surgery	–	9
Neurological diseases	–	14

[a] Fresh frozen plasma or antithrombin 3

Table 5 Pneumonia rates for score categories

Category		Number of patients	Number of patients with pneumonia (%)
	Score 1	*Admission*	*Days 1–6*
I	0–<11	456	27 (5.9)
II	11–<16	129	12 (9.3)
III	16–<22	102	11 (10.8)
IV	>22	69	18 (26.5)
		756	68 (9.0)
	Score 2	*Day 7*	*Days 7–14*
I	0–<18	166	10 (6.0)
II	18–<25	83	7 (8.4)
III	25–<31	46	12 (26.1)
IV	>31	32	9 (28.1)
		327	38 (11.6)

Table 6 Risk of NP (positive predictive value) and relative risk with 95% confidence intervals in various score categories

Category: score	Up to day 6	Up to day 14	Relative risk (95% CI)	Relative risk (after shrinkage)
I: 0–<11	5.9%	11.0%		1
II: 11–<16	9.4%	17.5%	1.6 (0.9 to 2.8)	1.5
III: 16–<22	10.4%	18.4%	3.2 (1.9 to 5.5)	2.7
IV: >22	33.4%	42.3%	7.3 (4.2 to 12.7)	5.4

Cross-validation

To estimate how the predictive value of the scoring system will be in the validation sample, the "shrinkage effect" was estimated by cross-validation [13, 14]. For each patient, the scoring coefficients were estimated based on all the other patients in the sample (leave-one-out principle). With these coefficients, the score of the patients left out was computed. The idea was to treat the left-out patient as if (s)he was a new patient for whom prognosis should be evaluated. This was repeated for all patients in the sample. By fitting a Cox regression model to the resulting individual score values, the regression coefficient of this model can be interpreted as expected "shrinkage factor" in a validation data set.

With a shrinkage factor close to 1, the prediction in the validation sample is expected to be not much worse than in the development sample. We performed cross-validation of the scoring system on the study cohort. The resulting "shrinkage factor" was 0.85. Therefore, we expect a slight decrease in the ability of the scoring system to predict NP in an independent group of patients. We used the "shrinkage factor" to adjust the relative risk estimates shown in Table 7. The relative risk in category IV is expected to be estimated around 5 in a validation sample compared with the value of 7 in the development sample.

Discussion

We have developed a predictive model that may be used to stratify adult patients admitted to the ICU into high- and low-risk groups for NP. Patients identified as being at high risk are potentially the most likely to benefit from preventive interventions. This model is simple to use at the bedside and has a good predictive ability in the cohort from which it was derived, maintaining its predictive ability after cross-validation on the same cohort. The ability of this model to identify certain ICU patients as being at high risk has an additional advantage. In the high-risk patients, infection control precautions should be rigorously followed, and the need for invasive interventions should be carefully assessed. In a previous study, the overall risk of nosocomial infection was significantly reduced when high-risk patients were identified soon after admission [15].

In the present study, the nosocomial infection rate was 26.1%, with an almost equal distribution between the medical and surgical ICUs (26.3% and 25.9%, respectively). NP was the most common infection (17.1%), followed by nosocomial infections of the blood (8.9%). The results are in agreement with findings in other studies [16, 17].

Four independent risk factors for NP were identified using multivariate analysis: no infection on admission, thorax drainage, administration of antacids, and neurological diseases. In addition, urgent surgery, male gender, administration of coagulation factors, and $PO_2 > 110$ mmHg approached statistical significance. Although several of these risk factors have previously been recognized, thorax drainage is a preventable risk factor not emphasized in earlier studies. The association between the use of thorax drainage and the development of NP must be viewed with caution. It is possible that the common indications for which thorax drainage was performed, i.e., after thoracic surgery or for pneumothorax or pleural effusion, placed this group of patients at a high risk of NP independently of the procedure itself. The absence of infection on admission had not previously been identified as a risk factor for NP. However, in this study, patients admitted to the ICUs without any infection had a significantly higher risk for developing NP. A possible explanation may be that patients without infection have not been treated with antibiotics, which is a well known risk factor for ventilator-associated pneumonia [18]. Administration of antacids and altered consciousness have been described as risk factors for NP in other studies also [19–21]. Joshi et al. [21] described recent bronchoscopy and intubation as risk factors for NP. However, intubation did not achieve statistical significance on multivariate analysis. One reason for our finding that neither intubation nor mechanical ventilation was a risk factor for NP may be the difference in the patient population in our ICU units as compared with, for example, ICUs in the United States,

as well as the method used to predict NP, which did not take duration of intubation into account. In both ICU units there were mainly mechanically ventilated patients. As soon as the patients' conditions stabilized they were transferred to other units. This may contribute to the absence of the risk of developing NP for intubation and/or mechanical ventilation. In this study population, bronchoscopy was performed in only 13 patients for diagnostic but not therapeutic purposes. Because of the limited number of procedures carried out, we did not include this factor in the statistical analysis. One explanation for the somewhat surprising result that patients with $PO_2 > 110$ mmHg had a higher risk for NP may be that these patients had a lower mortality compared to the patient group with $PO_2 < 70$ mmHg. This would result in a longer ICU stay and therefore in an increased risk for developing a nosocomial infection.

Several risk factors identified in previous studies did not emerge as statistically significant in this study. These include older age, smoking, chronic obstructive pulmonary disease (COPD), obesity, malnutrition, and tracheostomy. In our study, a trend toward an increased risk of NP was noted in patients younger than 45 years. Many of the patients admitted to the surgical ICU were young, otherwise healthy, persons with multiple injuries/head trauma as the admission diagnosis. These patients very often developed NP. Information on smoking, COPD, and malnutrition was not available for many patients, thus restricting our ability to draw meaningful conclusions from these data. There were too few patients with a tracheostomy to make statistical comparisons. Gastric pH was not routinely in our ICUs. Therefore, we did not have enough data to enter in the multivariate analysis. In this study the Acute Physiology and Chronic Health Evaluation (APACHE II) was used to score severity of illness. Although some authors have suggested that scores typically used to assess the severity of acute illness estimating mortality risk may also be an appropriate measure of underlying risk for nosocomial infection, data from our study could not confirm this [22]. Patients with up to 12 points had a relative risk of 1 of developing NP, patients with up to 16 points, 0.86, and in those with more than 21 points the relative risk was 0.45. The correlation of APACHE II with mortality was very good in this study population. In the second score category relative risk was 2.3, in the third 3.5, and in the fourth 4.7.

The majority of scores developed so far predict ICU outcome. Physicians' overly static approach to prognostication has been carried over to most actuarial predictors used in intensive care medicine. For example, the pediatric risk of mortality score, APACHE II, and the mortality prediction model rely on data available at the time of admission to grade severity of illness and estimate mortality risk [23–25]. Some authors intended to develop dynamic outcome predictors using linear time trends and combine the outcome probabilities estimated at admission with the probabilities observed after 24 and 48 h of ICU care [26, 27]. In modelling the risk of NP we applied statistical methods appropriate for time-to-event data. Thus, we used the information that also the time when NP occurred, as well as the time when a patient died or was discharged from the ICU. However, we used only information about potential risk factors available on admission or on day 1. Further studies are required to construct and evaluate risk scores which can be updated during the hospital stay. Then, factors like duration of ventilation until day of prediction could be incorporated. Because the importance of some risk factors diminished during follow-up while the importance of others increased, we divided the ICU stay into three periods (1–6 days, 7–14 days, and longer than 14 days), modelling only the first two periods because of small numbers of patients in the third period. Using this approach, it could be shown that the same score predicts a different infection risk in the second week of hospital stay in comparison to hospital admission. This is a first step of incorporation of risk factors changing over time of hospital stay.

The estimation of relative risks can be used to judge the discriminative ability of the score; to estimate its predictive value, the probability of pneumonia occurring at a certain point in time is required. In the absence of competing risks, standard methods for survival analysis, as, for example, the Kaplan-Meier estimate, can be applied to estimate the probability of pneumonia by time t [28]. However, several risks acting simultaneously would overestimate the probability of NP. We therefore adopted nonparametric methods for estimating the transition probabilities in multistate models. The risk of death and discharge were taken into account for estimating the probability of NP.

Two limitations of this study deserve to be mentioned: protected brush bronchoscopy specimens were not required for diagnosing NP. As a result, some cases with noninfectious etiologies for pulmonary infiltrates may have been misclassified as NP. Previous investigators have used similar definitions and have identified similar risk factors [29, 30]. The first 48 h of stay in the ICU were not studied. This "cut-off" was chosen based on the definition of NP and on previous data indicating that a large proportion of patients admitted to the ICU are discharged within this time period and that this group of patients is at a low risk of NP. This scoring model can therefore only be applied to patients staying in the ICU for at least 48 h.

In conclusion, we have developed a clinically useful method to identify those patients in the ICU who are at greatest risk for NP. The predictive value of the scoring system in the category with more than 22 points is 42.3%. Although not very high, one can realistically not expect better values. While our scoring system has good predictive ability in the cohort from which it was derived – maintaining this predictive ability after cross-validation

on the same cohort – it will need to be validated on a separate cohort of ICU patients in the same and other hospitals before its clinical utility is established.

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