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Sepsis mortality prediction based on predisposition, infection and response

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Abstract *Objective:* To empirically test, based on a large multicenter, multinational database, whether a modified PIRO (predisposition, insult, response, and organ dysfunction) concept could be applied to predict mortality in patients with infection and sepsis. *Design:* Substudy of a multicenter multinational cohort study (SAPS 3). *Patients:* A total of 2,628 patients with signs of infection or sepsis who stayed in the ICU for > 48 h. Three boxes of variables were defined, according to the PIRO concept. Box 1 (Predisposition) contained information about the patient's condition before ICU admission. Box 2 (Injury) contained information about the infection at ICU admission. Box 3 (Response) was defined as the response to the infection, expressed as a Sequential Organ Failure Assessment score after 48 h. *Interventions:* None. *Main measurements and results:* Most of the infections were community acquired (59.6%); 32.5% were hospital acquired. The median age of the patients was 65 (50–75) years, and 41.1% were female. About 22% ($n = 576$) of the patients presented with infection only, 36.3% ($n = 953$) with signs of sepsis, 23.6% ($n = 619$) with severe sepsis, and 18.3% ($n = 480$) with septic shock. Hospital mortality was 40.6% overall, greater in those with septic shock (52.5%) than in those with infection (34.7%). Several factors related to predisposition, infection and response were associated with hospital mortality. *Conclusion:* The proposed three-level system, by using objectively defined criteria for risk of mortality in sepsis, could be used by physicians to stratify patients at ICU admission or shortly thereafter, contributing to a better selection of management according to the risk of death.

Keywords Intensive care unit · Severity of illness · Infection · Sepsis · PIRO · Risk adjustment

Introduction

In 1991, the American College of Chest Physicians and the Society of Critical Care Medicine held a consensus conference to define the systemic inflammatory response to infection (or sepsis), including sepsis-associated organ dysfunction, hypoperfusion or hypotension (severe sepsis) and sepsis-induced cardiovascular failure despite adequate fluid resuscitation (septic shock) [1]. Criticized by some [2], these definitions nevertheless became heavily used by clinicians and researchers over the following years.

In 2001, several European and American critical care societies organized a second consensus conference to address the weaknesses of these definitions and to improve the early identification and stratification of patients with sepsis [3]. The result of this conference was the adoption of systemic inflammatory response syndrome as a broader definition of inflammation. Furthermore, minor changes were added to the definition of severe sepsis and septic

shock. A new system for risk stratification that had emerged from the Fifth Toronto Sepsis Roundtable in Toronto, Canada in October 2000 [4] was also adopted: the IRO system (insult, response, and organ dysfunction), that later became the PIRO (with the addition of predisposition) [5–8]. Although interesting and promising, this approach remained virtually conceptual.

The objective of this study was to empirically test – with the use of a large multicenter, multinational database – whether a modified definition of PIRO (using the concept of predisposition, infection, response, organ dysfunction/failure) could be useful for predicting mortality in patients with infection and sepsis.

Materials and methods

Details about project organization, data collection and cohort building were already presented in detail elsewhere [9]. Data were collected at intensive care unit (ICU) admission and on days 1, 2 and 3 and on the last day of the ICU stay. Data from the day of admission were collected within an hour before or after ICU admission, as recently described. Severity of illness was assessed using the SAPS 3 Admission Score [10]. On the following days of the ICU stay, further information was collected: number and severity of organ dysfunction, as measured by the Sequential Organ Failure Assessment (SOFA) [11]; length of ICU and hospital stay; and outcome data, including vital status at ICU and hospital discharge.

From the SAPS 3 Hospital Outcome Cohort (comprising 16,784 patients from 303 ICUs), 3,505 patients presented with an infection already at ICU admission (20.9% of the SAPS 3 cohort). From these, patients with a length of stay (LOS) in the ICU less than 48 h were excluded ($n = 877$), resulting in a study cohort of 2,628 patients (Fig. 1). Infection, sepsis, severe sepsis and septic shock were defined according to the published consensus criteria by using the worst state at the time of ICU admission [1]. Details about the formation of the SAPS 3 Hospital Outcome Cohort can be found elsewhere [9].

To test the PIRO concept in the SAPS 3 database, three different logical boxes were defined:

Predisposition: The variables of the SAPS 3 Admission Score Boxes 1 and 2, which are not related to infection, were used. These include age, co-morbidities, use of vasoactive drugs before ICU admission, intrahospital location before ICU admission, length of stay in the hospital before ICU admission, reason(s) for ICU admission, planned/unplanned ICU admission, surgical status at ICU admission and, if applicable, the anatomic site of surgery.

Injury: For this box, all variables related to infection at ICU admission were used. These include acquisition of the infection, extension and site of infection, the presence of bacteremia and the microbial agents identified.

Response: To identify the response to infection, we used the development of organ dysfunction and failure, measured through the highest SOFA score values for each organ system between 24 and 48 h after ICU admission.

The definitions of these variables can be found in Appendix C of the electronic supplementary material (ESM). Because this was an observational study and no additional interventions were performed, the need for informed consent was waived by the institutional review board. Each ICU coordinator, however, was responsible for obtaining local permissions as necessary.

Data quality

Recorded data were evaluated for completeness of the documentation and reliability. Inter-rater quality control was performed through rescoring of the data and calculation of kappa coefficients and intra-class correlation coefficients, as appropriate [12]. Data quality was excellent; results were presented in detail in the ESM file of the SAPS 3 primary report [9].

Statistical analysis

Statistical analysis was performed using the SAS system, version 8e (SAS Institute, Cary, NC, USA). A p-value of < 0.05 was considered significant. Unless otherwise specified, results are expressed as median and interquartile ranges (quartile). Observed-to-expected (O/E) mortality ratios were calculated by dividing the number of observed deaths per group by the number of expected deaths per group (as predicted by the SAPS II). To test for statistical significance, we calculated 95% confidence intervals (CI) according to the method described by Hosmer and Lemeshow [13]. The Hosmer–Lemeshow goodness-of-fit $\hat{H}$- and $\hat{C}$-statistics [14] were used to evaluate the calibration of the developed prognostic model. Discrimination was tested by measuring the area under the receiver operating characteristic curve (aROC), as described by Hanley and McNeil [15].

Model development

Variables were selected according to their association with hospital mortality. To select significant predictors, we randomly extracted five roughly equal-sized parts based on ICUs from the database, as previously described in detail [9]. It was thus possible to run the model-building procedure five times, each time taking four parts of the sample as a development set and the fifth as the validation set. This allowed us to estimate the variability, and thus the stability, of the prediction.

Table 1 Basic descriptive statistics according to the presence and severity of infection, sepsis, severe sepsis and septic shock

	Cohort		Infection		Sepsis		Severe sepsis		Septic shock		*p*-value
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	
Number of patients	2628	100.0	576	100.0	953	100.0	619	100.0	480	100.0	
Female gender	1081	41.1	228	39.6	414	43.4	237	38.3	202	42.1	0.168
Age, years (median, Q1–Q3)	65 (50–75)		67 (54–76)		65 (48–75)		63 (49–73)		65 (53–75)		0.001
ICU LOS, days (median, Q1–Q3)	7.6 (4.0–14.7)		6.5 (3.9–13.7)		6.8 (3.8–13.9)		8.7 (4.8–15.5)		9.2 (4.4–16.8)		< 0.001
Admission status											0.001
Planned	311	11.8	91	15.8	98	10.3	80	12.9	42	8.8	
Unplanned	2267	86.3	473	82.1	838	87.9	528	85.3	428	89.2	
Missing	50	1.9	12	2.1	17	1.8	11	1.8	10	2.1	
Surgical status											0.007
No surgical procedure	1578	60.0	319	55.4	565	59.3	379	61.2	315	65.6	
Scheduled surgery	286	10.9	82	14.2	97	10.2	70	11.3	37	7.7	
Emergency surgery	637	24.2	144	25.0	244	25.6	142	22.9	107	22.3	
Missing	127	4.8	31	5.4	47	4.9	28	4.5	21	4.4	
Risk adjustment											
SOFA score (median, Q1–Q3)	5 (3–7)		5 (3–7)		3 (2–5)		6 (4–8)		8 (6–11)		< 0.001
SAPS 3 score (median, Q1–Q3)	62 (53–72)		59 (50.50–68.5)		57 (49–65)		65 (57–73)		74 (65–82)		< 0.001
Outcome											
ICU mortality (%)	29.7		23.3		24.4		33.8		42.7		
Hospital mortality (%)	40.6		34.7		35.4		44.9		52.5		
O/E ratios (95% CI)	0.97 (0.93–1.01)		0.96 (0.86–1.05)		1.10 (1.02–1.18)		0.96 (0.89–1.04)		0.87 (0.80–0.93)		
Comorbidities											
Chronic heart failure, NYHA IV	33	1.3	9	1.6	13	1.4	4	0.6	7	1.5	0.468
Chronic pulmonary failure	206	7.8	51	8.9	74	7.8	44	7.1	37	7.7	0.730
Liver cirrhosis	112	4.3	21	3.6	31	3.3	37	6.0	23	4.8	0.052
COPD	473	18.0	134	23.3	164	17.2	107	17.3	68	14.2	0.001
Diabetes, insulin-dependent	102	3.9	23	4.0	38	4.0	21	3.4	20	4.2	0.908
Diabetes, non-insulin-dependent	202	7.7	51	8.9	73	7.7	42	6.8	36	7.5	0.606
Metastatic cancer	65	2.5	14	2.4	28	2.9	15	2.4	8	1.7	0.540
Non-metastatic cancer	119	4.5	31	5.4	37	3.9	19	3.1	32	6.7	0.018
Chronic renal failure	200	7.6	47	8.2	37	3.9	65	10.5	51	10.6	< 0.001

The criterion for a predictor to enter the model was homogeneity across the five model-building processes: in principle, predictors should enter the model in all five development sets, but depending on the frequency of the predictor in the samples, the magnitude of the effect, and medical reasoning, some predictors were included if they appeared in the model in at least three subsamples. The quality of predictions in the validation sets was assessed by looking at the goodness-of-fit and the discriminative capability of the models. Variable selection was further confirmed by bootstrapping – drawing random data sets with replacement from our training set ($n = 2{,}628$ observations), where each sample had the same size as our original training set. This was done 100 times, producing 100 bootstrap data sets.

Using the parameter estimates from the logistic regression as starting values, a multilevel model (logistic regression with random effects) was applied in the next step, using patient characteristics as fixed effects and ICUs as a random effect.

Results

The patients in the cohort under analysis had a median age of 65 (50–75) years, and 41.1% were female. Approximately two thirds of the patients were admitted for medical reasons and one third after elective or acute surgery. Overall hospital mortality was 40.6% (Table 1).

Of the patients admitted, 21.9% ($n = 576$) presented with infection only, 36.3% ($n = 953$) with signs of sepsis, 23.6% ($n = 619$) with severe sepsis and 18.3% ($n = 480$) with septic shock. ICU and hospital mortality rates increased from those with infection to those with septic shock (Table 1). Most (59.6%) of the infections were community acquired, 32.5% hospital acquired (Table 2). Further demographic details can be seen in the ESM (Tables E1–E4).

The rate of disseminated versus localized infection changed over the groups: localized infection was seen in patients with infection without sepsis more often than in patients with septic shock. In contrast, the rate of disseminated infection increased with the progression of infection to sepsis and septic shock (Table 2). The lower respiratory tract was the most common site of infection (48.9%), and the digestive tract was the second most common site. Infection sites did not differ greatly among the various subgroups (Table 2).

Overall, gram-positive bacteria were the causative agents most often documented, followed by gram-negative bacteria ("other") (Table 3). However, for several agents, distribution was different in the different groups: gram-negative bacteria ("other") were present more often in patients with infection and showed decreasing incidence in those with sepsis and those with septic shock and severe sepsis. Details about the grouping of infective agents can

Table 2 Infection at ICU admission

	Cohort		Infection		Sepsis		Severe sepsis		Septic shock		*p*-value
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	
Documentation											0.138
Infection clinically probable/documented	1765	67.2	364	63.2	655	68.7	418	67.5	328	68.3	
Infection microbiologically documented	863	32.8	212	36.8	298	31.3	201	32.5	152	31.7	
Acquisition											0.433
Community-acquired	1567	59.6	335	58.2	584	61.3	355	57.4	293	61.0	
Hospital-acquired	855	32.5	189	32.8	293	30.8	220	35.5	153	31.9	
Missing	206	7.8	52	9.0	76	8.0	44	7.1	34	7.1	
Extension											< 0.001
Localized infection	1055	40.1	253	43.9	422	44.3	207	33.4	173	36.0	
Localized infection with regional involvement	500	19.0	115	20.0	213	22.4	115	18.6	57	11.9	
Disseminated infection	661	25.2	106	18.4	187	19.6	195	31.5	173	36.0	
Missing	412	15.7	102	17.7	131	13.8	102	16.5	77	16.0	
Site											
Neurologic	83	3.2	16	2.8	41	4.3	16	2.6	10	2.1	0.078
ORL (upper respiratory tract)	51	1.9	17	3.0	16	1.7	8	1.3	10	2.1	0.183
Lower respiratory tract	1286	48.9	281	48.8	448	47.0	321	51.9	236	49.2	0.315
Thoracic	77	2.9	11	1.9	23	2.4	24	3.9	19	4.0	0.081
Cardiac	51	1.9	16	2.8	14	1.5	12	1.9	9	1.9	0.355
Digestive	516	19.6	120	20.8	200	21.0	103	16.6	93	19.4	0.160
Urinary	227	8.6	41	7.1	96	10.1	45	7.3	45	9.4	0.113
Skin and Soft Tissue	155	5.9	36	6.3	63	6.6	34	5.5	22	4.6	0.444
Systemic infection	191	7.3	37	6.4	57	6.0	48	7.8	49	10.2	0.025
Catheter-related	51	1.9	8	1.4	15	1.6	17	2.7	11	2.3	0.260
Genital, bone and joint, unknown, other	100	3.8	20	3.5	53	5.6	17	2.7	10	2.1	< 0.01

Table 3 Groups of infective agents

	Cohort		Infection		Sepsis		Severe sepsis		Septic shock		*p*-value
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	
Anaerobier	52	1.98	18	3.13	21	2.2	5	0.81	8	1.67	0.033
Fungi	156	5.94	27	4.69	52	5.46	47	7.59	30	6.25	0.163
Enterobacter	213	8.11	41	7.12	60	6.3	61	9.85	51	10.63	0.009
Escherichia	232	8.83	64	11.11	73	7.66	46	7.43	49	10.21	0.046
Gram-negative, other	280	10.65	75	13.02	98	10.28	60	9.69	47	9.79	0.212
Gram-positive, other	330	12.56	59	10.24	131	13.75	80	12.92	60	12.5	0.249
Intracellular	56	2.13	6	1.04	23	2.41	17	2.75	10	2.08	0.189
Staphylococci	238	9.06	57	9.9	75	7.87	59	9.53	47	9.79	0.456
Viruses	65	2.47	12	2.08	24	2.52	18	2.91	11	2.29	0.820

be found in the ESM (Table E5). Further demographic details and mortality data for the patients excluded due to a LOS $\leq$ 48 h can be found in the ESM (Table E6).

Overall hospital mortality in our study cohort was 40.6% (varying from 18.7% in patients with no infection to 52.5% in patients with septic shock). The acquisition of nosocomial infection versus community-acquired infection was found to be associated with higher mortality (35.5% in non-infected patients, 49.8% in patients with hospital-acquired infections) at the time of ICU admission.

In the multivariate analysis, the following variables turned out to be significant. Predisposition (Box 1): age; location from which the patient was admitted to the ICU; co-morbidities; length of stay before ICU admission (days); and some reasons for ICU admission. Injury (Box 2): acquisition of infection; extension of infection; site of infection; and infective agent. Response (Box 3): dysfunction of the renal and coagulation systems; failure of the cardiovascular, respiratory, renal, coagulation and central nervous systems (Table 4, scoresheet).

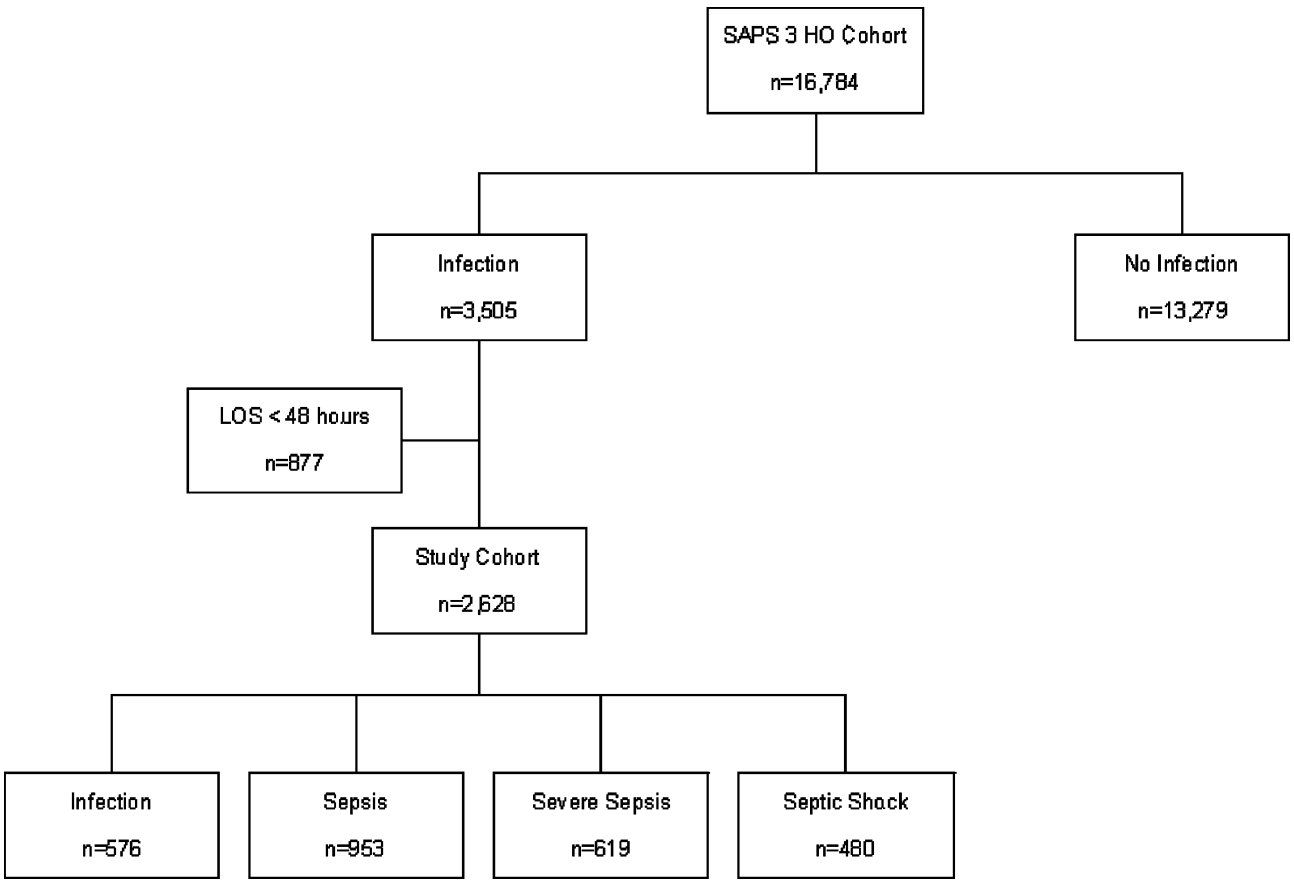

Fig. 1 Cohort development. *HO*, hospital outcome; *LOS*, length of stay

Table 4 Scoresheet: results of the multivariate analysis

Box 1: Predisposition	0	4	5	6	7	8	9	10	11	14	16
Age, years	< 40	≥ 40 < 60				≥ 60 < 70			≥ 70 < 75	≥ 75 < 80	≥ 80
Location from which the patient was admitted to ICU		Same hospital									
Comorbidities				Cancer [a]		Cirrhosis [b]	AIDS [c]				
Length of stay before ICU admission, days	< 14		≥14 < 28		≥28						
Reason(s) for ICU admission							Cardiac arrest [d]				

Box 2: Infection	0	4	5	7	8	9	10	11	14	16
Acquisition		Nosocomial [e]								
Extension		Other than localized [f]								
Site			Respiratory [g]							
Agent							Candida, fungi [h]			

Box 3: Response	0	4	5	7	8	9	10	11	14	16
Organ dysfunction (OD) [i]		Renal	Coagulation							
Organ failure (OF) [j,k]			Cardiovasular respiratory			CNS, coagulation renal				

[a] Cancer refers to the data definitions in Appendix C of the ESM: Comorbidities: Metastatic cancer, Hematological cancer, Chemotherapy, Immunosuppression other, Radiotherapy, Steroid Treatment; [b] Cirrhosis refers to the data definitions in Appendix C of the ESM: Comorbidities: Cirrhosis; [c] AIDS refers to the data definitions in Appendix C of the ESM: Comorbidities: AIDS; [d] Cardiac arrest refers to the data definitions in Appendix C of the ESM: Reasons for ICU Admission: Cardiovascular-cardiac arrest; [e] Nosocomial refers to the data definitions in Appendix C of the ESM: Acute infection at ICU admission-acquisition: Hospital-acquired; [f] Other than localized refers to the data definitions in Appendix C of the ESM: Acute infection at ICU admission -Localized infection with regional involvement, Dissiminated; [g] Respiratory refers to the data definition in Appendix C of the ESM: Acute infection at ICU admission -Site: Lower respiratory tract: Pneumonia, Lung abscess, other; [h] Candida, fungi refer to the data definitions in Appendix C of the ESM: Acute infection at ICU admission -Agent and -Bacteremia: if any of the following was present in any of the fields: *Candida albicans*; *Candida* spp, other; *Fungi*, other; [i] If the maximum SOFA value of day 1 and day 2 is 1 or 2; [j] If the maximum SOFA value of day 1 and day 2 is 3 or 4; [k] With multiple items the points are additive

The mean SAPS 3 PIRO score was 31.2 points (median 31, quartiles 22–39). The relationship between the SAPS 3 PIRO score and vital status at hospital discharge is given by the equation:

$$\text{Logit} = -46.6757 + \ln(\text{SAPS 3 PIRO score} + 76.7688) \times 9.8797$$

and the probability of mortality by the equation:

$$\text{Probability of death} = \frac{e^{\text{logit}}}{1 + e^{\text{logit}}}$$

Mean predicted mortality was 40.7% (median 39%, quartiles 21–57%). Complete descriptive statistics for the SAPS 3 PIRO score, corresponding predicted hospital mortality and observed to expected mortality ratios in the global cohort and in subgroups are presented in the ESM (Tables E7 to E9).

Prognostic performance of the developed model was tested by means of discrimination and calibration. Calibration, as evaluated through the Hosmer–Lemeshow goodness-of-fit test, was found to be excellent in the overall cohort ($\hat{C}$-test: 3.51, $p = 0.97$; $\hat{H}$-test: 5.33, $p = 0.87$) as well as in the tested subgroups of infection, sepsis, severe sepsis and septic shock (ESM, Appendix B). Discrimination was also very good, with an aROC of 0.772, better than that of the SAPS 3 admission model in this cohort (aROC: 0.735). For further details, see Appendix B of the ESM.

Discussion

Sepsis, defined as the systemic reaction to infection [1], remains an important cause of morbidity and mortality in ICUS worldwide [16–18]. Despite the development of new therapies and integrated approaches for diagnosis and care of the patient with sepsis [19], mortality remains high [17].

Mortality seems, moreover, to be associated mainly with the presence and amount of organ dysfunction/failure [20, 21]. This fact prompted several researchers to propose a new method to classify sepsis, which includes not only criteria for infection, but also for predisposition of the patient and for the reaction of the organism to the injury – the PIRO concept [4]. Since that proposal, a number of researchers have tried to study the predisposition and progression from sepsis to severe sepsis and septic shock [22, 23], assuming that the organ dysfunction/failure is just the final stage of the path that leads to death.

We have modified the original concept. First, the development of the SAPS 3 Admission Score clearly showed the impact of predisposition on the outcome of patients. For this reason we decided to keep predisposition in the model. Second, in our understanding, the host response to the insult and the resulting organ dysfunction cannot be distinguished from each other. This is because – from a pragmatic point of view – definitions of organ failure incorporate a series of physiological and therapeutic variables so that the evaluation of the response and the evaluation of organ dysfunction/failure overlap. Perhaps in the future specific biomarkers that announce the response to infection may become available, allowing us to detect the response of the organism to infection prior to the development of organ dysfunction or failure. No such markers are yet clinically available, however. Also, some of these biomarkers may eventually be used to predict the response to specific treatments, similarly to but earlier than the baseline degree of organ dysfunction (as has been demonstrated for a number of interventions, including antibiotics, anti-TNF therapies and activated protein C [24]). Altogether, this resulted in a three-level staging model consisting of predisposition, injury and response.

The SAPS 3 database represents a large cohort, comprising critically ill patients from several countries worldwide, with a rate of infection or sepsis at ICU admission (20.9%) comparable to other recent cohort studies such as the European Sepsis Project [16]. Recently Vincent et al. found an even higher incidence of 37.4%, but with a broad variation between countries: from 18% in Switzerland to 73% in Portugal [25].

To test the concept of the response of the organism to the injury (infection), we included only those patients who stayed for > 48 h in the ICU. We did this to give patients a minimum amount of time for response to became evident. An evaluation at ICU admission or shortly thereafter may highlight the insult but underestimate the impact of the response. This inclusion criterion can, however, represent a limitation of the present study, since the SAPS 3 database registers and analyses only infections present at ICU admission (excluding therefore patients with ICU-acquired infection) and staying at least 48 h in the ICU (which can exclude some patients that die from sepsis very early after admission, particularly those with septic shock; see Table E6).

Our results seem to confirm the hypothesis that the incidence of severe sepsis and septic shock in the ICU is increasing. This tendency has been consistently noted in all recently published studies [17, 26, 27]. Physicians' increasing awareness of the early recognition and treatment of sepsis, as a result of initiatives such as the Surviving Sepsis Campaign [19], might in part explain this trend. On the other hand, the increasing incidence became apparent before these initiatives, so other factors, such as increasing age, co-morbidities, characteristics of the infection or the presence and amount of organ dysfunction and failure at ICU admission, might be responsible for the observed phenomenon.

Mortality for hospital-acquired infection in our cohort was slightly lower than that reported by Friedman et al.

(49.7%) [28], but higher than that reported in the Finnsepsis study (28.3%) [29]. The impact on mortality of nosocomial sepsis versus community-acquired sepsis was similar to the recently published results of Alberti et al. [16]. Some factors related to the infection characteristics (such as the site of infection, the microorganisms involved or the extension of the infection) have been demonstrated to be important in the past. For example, aerobic gram-negative bacteria [22] or infection with *Candida* spp. [30] were found to be associated with increased mortality. Our results add to this evidence: *Candida* and other fungi remained a significant predictor of mortality in the multivariate analysis (Table 4). The number of cases of sepsis caused by fungal organisms seems also to be increasing, with fungi being responsible in our cohort for as many as 6.3% of the cases of septic shock, as suggested previously [17].

Although several studies have addressed the question of which factors affect the outcome of patients with sepsis, we believe this is the first study in which the three levels of predisposition, injury and response have been addressed together. This approach allows for a better adjustment of different baseline characteristics of the populations being evaluated: researchers are now able to compare patients in three individual categories that have been found to be important for prognosis in addition to the aggregate score. The way these categories of prognostic factors interact to lead to death, mediated by the development of multiple organ dysfunction/failure, is complex and will certainly depend on various other factors, such as the genetic background and the type and timing of eventual therapeutic interventions. Since organ dysfunction/failure is currently defined in the SOFA score by a combination of physiological and therapeutic variables (e.g., blood pressure and/or use of vasoactive agents), it is at this time extremely difficult to dissociate consequences of the injury from the response to therapeutic interventions. It should be noted that in this system to model the risk of mortality from sepsis, different weights were attributed to specific organ failures (with more importance attributed to CNS, renal and coagulation failures than to cardiovascular or respiratory failures), contrary to the original SOFA, in which all organ failures had the same weight. The use of these three levels of prognostic factors, with physiology being accessed only by the presence and degree of organ dysfunction/failure, makes the system conceptually different from general outcome prediction models, such as the SAPS 3 admission model [10]. Although these systems, developed for application to heterogeneous populations of critically ill patients, share some prognostic variables with the PIRO model, they do not include information about the insult (namely the characteristics of the infection), and the degree of physiological derangement is accessed in those models through the use of a heterogeneous group of variables measured at ICU admission (a mixture of physiological and therapeutic variables rather than the presence and degree of organ dysfunction/failure as in PIRO).

Many more factors have been identified as having prognostic importance in patients with sepsis, such as polymorphisms in genes encoding key inflammatory molecules [31]. To date, however, these markers have not been incorporated in clinical practice or in the design of clinical trials. Possibly in the future, the Predisposition box could and should be expanded to include such factors, but it is too soon to know whether and when such markers will be available.

In conclusion, the results of our study – the SAPS 3 PIRO score (Table 4) – could be used by physicians to stratify patients at ICU admission or shortly thereafter, contributing to a better selection of management according to the risk of death. The proposed system should, however, be prospectively validated in an independent cohort in order to demonstrate its usefulness.

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