Predisposition, insult/infection, response, and organ dysfunction: A new model for staging severe sepsis

Francesca Rubulotta, MD; John C. Marshall, MD; Graham Ramsay, MD; David Nelson, MS; Mitchell Levy, MD; Mark Williams, MD, FCCM

Objective: **To generate and validate an initial version of the predisposition, insult/infection, response, and organ dysfunction (PIRO) staging model for risk stratification in severe sepsis. The goal was to create distinct levels of mortality risk within each of the four categories (P, I, R, and O), and that these risk levels would be meaningful in terms of prediction independent of the other categories.**

Design: **Retrospective analysis using a statistical model utilizing two large, global databases of patients with severe sepsis.**

Setting and Patients: **Database #1: Placebo-treated patients from a phase III clinical trial of patients with severe sepsis (PROtein C Worldwide Evaluation in Severe Sepsis [PROWESS], 840 patients). Database #2: Global severe sepsis registry performed in 276 intensive care units in 37 countries (PROmoting Global Research Excellence in Severe Sepsis [PROGRESS], 10,610 patients).**

Interventions: **None.**

Methods: **Classification and regression trees were used to classify patients and derive a scoring system from the PROWESS and PROGRESS databases with internal validation. Regression tree parameters included Chi-square tests and a minimum of five patients per node. The risk levels were done in a stepwise manner, adjusting for the previous categories. Initially, the predisposition scoring was developed, and subsequently, the infection scoring was then developed after adjusting for the predisposition levels, and so on. Logistic regression analyses, odds ratios, and area under the receiver operator characteristic curve were used to evaluate the scoring systems.**

Measurements and Main Results: **Each of the four PIRO components had similar odds ratios in multivariable logistic regressions. In PROWESS, the correlation of the PIRO total score and in-hospital mortality rates was 0.974 ($p < 0.0001$), and in PROGRESS, the correlation of the PIRO total score and hospital mortality rates was 0.998 ($p < 0.0001$).**

Conclusions: **PIRO can develop into an effective model for staging severe sepsis, seems to be predictive of mortality, and may be useful in future sepsis research. (Crit Care Med 2009; 37: 1329–1335)**

KEY WORDS: sepsis; staging; mortality; intensive care; outcomes

Severe sepsis remains a common and deadly condition despite recent advances in awareness and treatment. Recently, Martin et al (1, 2) demonstrated that the number of deaths from severe sepsis is increasing, in part due to the aging of the population. The heterogeneity of patients with sepsis makes risk stratification difficult, both for bedside prognostication and clinical trials. In 1991, a consensus panel of the American College of Chest Physicians and the Society of Critical Care Medicine developed operational definitions for sepsis to facilitate standardized enrolment into clinical trials (3). In addition, numerous tools are available to assess prognosis in critically ill patients (Acute Physiology and Chronic Health Evaluation [APACHE] II and III, Sequential Organ Failure Assessment, multiple organ dysfunction score, Simplified Acute Physiology Score [SAPS] II, etc); yet, these scoring systems have limitations in that they primarily focus only on the physiologic abnormalities (4–8). In 2001, a diverse group of sepsis experts at the International Sepsis Definitions Conference modified the definition of sepsis and severe sepsis (9). Members of this consensus conference expressed the need for a new, more sophisticated model for staging the severity of sepsis and the acronym PIRO was introduced: P, predisposition; I, insult/infection; R, response; and O, organ dysfunction. Theoretically, similar to the TNM system for oncology, the PIRO staging system for sepsis might be used in the following manner: to assess risk and predict outcome in septic patients, to assist with enrolment of patients into clinical studies, and to assess the likely patient response to specific therapeutic interventions. This proposed staging system is unique in that it considers multiple different known independent predictors of outcome. The authors of this proposed staging system cautioned that the PIRO concept was preliminary, intended to be hypothesis generating, and required extensive testing and refinement. In this article, for the first time, the PIRO model is developed from a large, controlled clinical trial and then tested in a large severe sepsis registry database. We used the placebo patients from the PROtein C Worldwide Evaluation in Severe Sepsis (PROWESS) clinical

From the Policlinico University Hospital Catania (FR), Italy; Saint Michaels Hospital (JCM), Toronto, Canada; West Hertforshire NHS Trust (GR), London, United Kingdom; Eli Lilly and Company (DN, MW), Indianapolis, IN; Brown University/Rhode Island Hospital (ML), Providence, RI.

Supported by Eli Lilly and Company.

Mr. Nelson and Dr. Williams have been employed with Eli Lilly. Dr. Williams holds stock ownership and options in Eli Lilly. Dr. Marshall has received honoraria from Eli Lilly, Eisai Inc, Leo-Pharma, Artisan Therapeutics, and Spectral Diagnostics. Dr. Levy has received honoraria from Eli Lilly and Edwards Life Sciences. Dr. Levy has received grant support from Eli Lilly, Philips Medical Systems, Novartis, and Biosite, Inc. The remaining authors have not disclosed any potential conflicts of interest.

For information regarding this article, E-mail: frubulotta@hotmail.com

DOI: 10.1097/CCM.0b013e31819d5db1

Table 1. Variables considered for inclusion in the predisposition, insult/infection, response, and organ dysfunction model based on information available in PROWESS

Age
Gender
Ethnicity
Tachycardia
Tachypnea
Leukocytosis of leukopenia
Thermodysregulation
No. of systemic inflammatory response syndrome criteria
Proven infection
Source of infection
Primary site of infection
Infection type
Mean Acute Physiology and Chronic Health Evaluation II
Mean number of baseline organ dysfunctions
Vasopressor requirement
Congestive heart failure
Chronic renal insufficiency
Chronic liver disease
Diabetes
Mechanical ventilation
Chronic lung disease
Altered consciousness
Active cancer
Recent surgery

database and the PROmoting Global Research Excellence in Severe Sepsis (PROGRESS) database, a large global registry for sepsis, to create a system to categorize patients according to the PIRO concept (10, 11).

METHODS

We analyzed variables available from the placebo-treated patients from the PROWESS (see Table 1) database to develop a classification system from PIRO (10). PROWESS was chosen to develop the model because it is a controlled clinical trial with a relatively homogeneous population. Study sites obtained Institutional Review Board approval and written, informed consent from all patients or their legal representatives. This database includes a total of 1690 patients; however, only 840 patients who received placebo were included in this analysis. We used the large database from a global registry of sepsis, PROGRESS (11), to further test the classification system. Entry into PROGRESS was strictly anonymous, and patients were tracked using a study-specific identifier code. Patients were required to have a diagnosis of severe sepsis, defined as evidence of infection with at least one sepsis-induced organ dysfunction. For consistency with the PROWESS placebo database, patients younger than 18 years and those treated with Drotrecogin alfa (activated) were excluded from these analyses. We used classification and regression tree methodology and logistic regression per standard methodology (12). Classification trees were designed to extract patient subgroups that were homogeneous with respect to both outcome and predictor variables. This was accomplished by "recursively" partitioning the data such that at each stage the variable (and its associated cutpoint) that best subdivided the data (in terms of optimizing homogeneity) was determined. Cross validation, or an independent test sample within the database, was then used to assess how many such divisions to adopt. Regression tree parameters included a Chi-square test <0.05 and a minimum of five patients per node. We derived variables associated with "P" by first scanning patients from PROWESS. Subsequently, we incorporated the results from each previous factor; so, all the PIRO variables were functionally independent. This approach started with a logistic regression in which "P" was used to predict survival, and then the "residuals" (the remaining variation not explained by "P") were used rather than survival status alone. This approach was designed to create trees independent of "P." Likewise, the tree for "R" was based on residuals from a logistic model based on P and I, and the tree for "O" was based on residuals from a logistic model based on P, I, and R. Logistic regression and their resulting odds ratios and area under the receiver operating curve, and Hosmer-Lemeshow goodness of fit tests were used to evaluate the components of the models. A final composite score was created, and this score's correlation to mortality rates was assessed with Pearson product-moment correlation coefficients. All computations were performed using SAS/STAT and SAS/Enterprise Miner software (SAS Institute Inc., Cary, NC).

Definitions. We defined chronic liver disease (CLD) as follows: clinical manifestations of esophageal varices, chronic jaundice, cirrhosis, or chronic ascites. We defined congestive cardiomyopathy (CC), New York Heart Association class IV, as patients with cardiac disease resulting in the inability to carry out physical activity without discomfort.

Table 2. Baseline characteristics for PROWESS and PROGRESS

Characteristic	PROWESS (n = 840)	PROGRESS (n = 10,610)
Mean age (yr)[a]	60.6 ± 16.5	60.5 ± 17.6
Male gender (%)	58.0	59.4
White (%)	82.0	43.8
Mean Acute Physiology and Chronic Health Evaluation II[a]	25.0 ± 7.8	23.3 ± 8.3
Vasopressor requirement (%)	64.4	78.2
Mechanical ventilation (%)	77.6	84.9
Single-organ dysfunction (%)	24.2	18.4
Multiple organ dysfunction (%)	75.8	81.6
Mean number of baseline organ dysfunctions[a]	2.4 ± 1.1	2.7 ± 1.2
Recent surgery (%)	30.6	37.5
In-hospital mortality (%)	34.9	49.6

[a]Mean ± standard deviation.

RESULTS

Baseline characteristics for PROWESS and PROGRESS are described in Table 2. The mean age and percentage of males enrolled in the studies were similar. There were significantly fewer White enrolled in PROGRESS given the very diverse geographic nature of this global sepsis registry. With respect to baseline disease severity, the mean APACHE II score at baseline was similar between the two groups but the patients enrolled in PROGRESS had greater baseline vasopressor and mechanical ventilation requirements. The PROGRESS population also had a higher mean number of organ dysfunctions compared with the PROWESS group. The patients in PROGRESS had higher observed mortality compared with those in PROWESS.

Predisposition. The classification and regression tree for the P component of PIRO incorporated age, CLD, and CC, and resulted in the following classification, from least to greatest risk of mortality: P0, patients younger than 46 years; P1, patients aged from 46 to 64 years, with no CLD; P2, patients aged from 64 to 85 years, with no CLD and no CC; P3, patients aged from 46 to 64 years, with CLD, or patients aged from 64 to 85 years, with CC; and P4, patients aged from 64 to 85 years, with CLD, or patients older than 85 years. Increasing thresholds of "P" (P0, P1, P2, etc.) were associated with an increase in the odds of mortality (see Table 3). The P score defined in this study guarantees similar intervals in the increase of the mortality rate from P0 to P4. Using P alone, the area under the curve to predict the in-hospital mortality rate was 65.1% for the PROWESS placebo patients and 58.7% to predict hospital mortality for the PROGRESS registry.

Insult/Infection. For both PROWESS and PROGRESS, if a specific aspect (e.g.,

Table 3. Mortality in PROWESS and PROGRESS per P "predisposition" classification

Data Set (n)	Mortality Rates					Odds Ratio and CI of Increased Odds of Death for One-Point Increase		
	P0	P1	P2	P3	P4	Odds Ratio	95% CI Lower	95% CI Upper
PROWESS placebo (total n = 840)	171	249	333	53	34			
In-hospital mortality (%)	15.4	29.5	44.0	48.1	61.8	1.76	1.51	2.05
Overall PROGRESS (total n = 10,610)	2293	2688	3709	1245	675			
In-hospital mortality (%)	37.6	46.7	53.3	59.0	64.2	1.32	1.28	1.37

CI, confidence interval.

Table 4. Mortality for I "insult/infection" with stratification within levels of P within the PROGRESS registry

Data Set (n)	Mortality Rates					Odds Ratio and CI of Increased Odds of Death for One-Point Increase		
	I0	I1	I2	I3	I4	Odds Ratio[a]	95% CI Lower	95% CI Upper
PROWESS placebo (total n = 840)	50	16	552	212	10			
In-hospital mortality (%)	20.0	33.3	32.5	44.0	50.0	1.47	1.19	1.82
Overall PROGRESS (total n = 10,610)	381	165	6399	3521	144			
In-hospital mortality (%)	28.9	44.2	47.5	55.0	69.4	1.44	1.36	1.53
P0	23.3	44.4	34.9	43.0	50.0	1.36	1.18	1.57
P1	24.0	51.3	43.8	53.1	62.5	1.44	1.28	1.62
P2	26.2	41.4	52.4	58.1	74.1	1.46	1.33	1.61
P3	40.0	39.1	57.0	64.2	93.8	1.47	1.24	1.74
P4	38.9	46.7	65.1	70.1	71.4	1.50	1.24	1.82

CI, confidence interval.
[a]Odds ratio based on logistic regression for an increase of one I level after adjusting for P.

Table 5. Mortality for R "response" with stratification within levels of P and I within the PROGRESS registry

Data Set (n)	Mortality Rates		Odds Ratio and CI of Increased Odds of Death for One-Point Increase		
	R0	R1	Odds Ratio[a]	95% CI Lower	95% CI Upper
PROWESS placebo (total n = 840)	31	809			
In-hospital mortality (%)	35.5	34.8	1.02	0.47	2.25
Overall PROGRESS (total n = 10,610)	2169	8441			
In-hospital mortality (%)	41.1	51.8	1.60	1.45	1.76
P0	26.7	39.8	1.82	1.42	2.32
P1	37.3	48.9	1.61	1.32	1.96
P2	44.8	55.8	1.56	1.34	1.82
P3	50.2	61.4	1.58	1.20	2.07
P4	54.1	66.9	1.72	1.18	2.49
I0	22.6	31.2	1.56	0.92	2.64
I1	37.5	46.4	1.44	0.70	3.00
I2	39.9	49.5	1.47	1.30	1.67
I3	45.3	57.4	1.63	1.38	1.92
I4	73.7	68.8	0.79	0.27	2.34

CI, confidence interval.
[a]Odds ratio based on logistic regression for an increase of the one R level after adjusting for P and I.

lung) of infection information was unknown or missing, they were classified as "No." We used a logistic regression in which "P" was used to predict survival, and then the "residuals" (the remaining variation not explained by "P") were used rather than survival status alone. This approach was designed to create trees independent of "P." The infection score based on an "I" adjusted for "P" resulted in the following classification: I0, community-acquired urinary tract infections, Gram-negative stain negative; I1, community-acquired urinary tract infections, not Gram-negative stain negative; I2, community-acquired (except all urinary tract) or nosocomial Gram-negative stain positive; I3, nosocomial acquired (except Gram-negative stain positive) or nosocomial fungal nonabdominal infections; and I4, nosocomial abdominal fungal infections. Table 4 demonstrates mortality rates by I staging in both PROWESS and PROGRESS. Given the very large population in PROGRESS, we were able to report mortality rates in groups according to both P and I stage, for example, P2, I3. Inclusion of I increased the area under the curve from 65.1% for P alone to 67.1% in the PROWESS trial population and from 58.7% for P alone to 61.1% in the PROGRESS registry population.

This infection score is based on existing databases. If the proposed score has to be used at the bedside, one would have to include "suspected site of infection."

Response. The systemic inflammatory response syndrome criteria were not highly significant risk factors compared with other variables in the PROWESS database, and no regression tree was generated. Based on the larger PROGRESS database, two levels of "R" were generated: R0, either no tachycardia or no tachypnea; R1, both tachycardia and tachy-

Table 6. Mortality for O "organ dysfunction" with stratification within levels of P, I, and R within the PROGRESS registry

Data Set (n)	Mortality Rates					Odds Ratio and CI of Increased Odds of Death for One-Point Increase		
	O0[a]	O1[a]	O2	O3	O4	Odds Ratio[b]	95% CI Lower	95% CI Upper
PROWESS placebo (total n = 840)	469	7	217	111	36			
In-hospital mortality (%)	28.0	28.6	37.7	50.0	61.1	1.35	1.20	1.51
Overall PROGRESS (total n = 10, 610)	4498	330	2255	1914	1613			
In-hospital mortality (%)	35.5	38.2	51.5	62.4	73.0	1.46	1.42	1.50
P0	23.6	30.3	40.6	52.2	65.0	1.55	1.46	1.64
P1	33.5	35.4	46.9	61.4	69.6	1.45	1.38	1.53
P2	41.1	43.8	56.5	63.5	73.7	1.39	1.33	1.45
P3	43.0	42.1	56.0	72.3	82.1	1.53	1.42	1.66
P4	47.1	66.7	65.4	68.8	83.0	1.46	1.32	1.62
I0	16.2	20.0	31.8	35.1	50.0	1.48	1.28	1.72
I1	21.7	0.0	71.4	45.0	63.0	1.54	1.24	1.91
I2	32.2	33.7	48.2	62.0	73.7	1.53	1.48	1.59
I3	43.6	44.4	58.0	67.3	74.2	1.39	1.32	1.45
I4	50.0	66.7	61.3	76.9	90.2	1.63	1.27	2.08
R0	31.3	29.7	44.0	56.8	68.9	1.44	1.35	1.53
R1	36.9	42.5	53.4	63.7	73.6	1.46	1.42	1.51

CI, confidence interval.

[a]Significance level between O0 and O1 for PROGRESS study is at $p = 0.151$; [b]Odds ratio based on logistic regression for an increase of one O level after adjusting for P, I, and R.

Table 7. Multivariate logistic regression to assess risk associated with each of the PIRO components

Domain	Stratification Level				
	0	1	2	3	4
Predisposition	P0 Age <46 yrs	P1 Age 46–64 yrs, no CLD	P2 Age 64–85 yrs, no CLD and no congestive cardiomyopathy	P3 Age 46–64 yrs with CLD or 64–85 yrs with congestive cardiomyopathy	P4 Age 64–85 yrs with CLD or age >85 yrs
Insult/infection	I0 CA-UTI Gram-negative	I1 CA-UTI not Gram-negative	I2 CA infection except CA-UTI or nosocomial Gram-positive	I3 Nosocomial acquired infection except Gram-positive or nosocomial fungal nonabdominal infection	I4 Nosocomial abdominal fungal infection
Response	R0 No tachycardia and/or no tachypnea	R1 Both tachycardia and tachypnea			
Organ dysfunction	O0 2 OF	O1 3 OF, 1 hepatic	O2 3 OF, none hepatic	O3 4 OF	O4 5 OF

CLD, chronic liver disease; CA-UTI, community-acquired urinary tract infections; OF, organ failures.

pnea, as demonstrated in Table 7. R0 was a combination of two levels of the regression tree because analyses indicated that nontachypnea patients did not differ significantly from tachypnea patients without tachycardia ($p = 0.20$ after adjusting for P and I). Only patients with both tachypnea and tachycardia were at increased risk of death. Table 5 demonstrates the mortality rate by various P and I stages with R1 vs. R2. Although the PROWESS sample did not have significance associated with an increased risk of death based on R1 vs. RO, the observation that the odds ratio was 1.42 (95% CI: 0.60–3.37) was consistent with the larger PROGRESS database. The odds ratio and the width of the confidence interval indicate that PROWESS may not have sufficient sample size to assess R, but given the numerical consistency with PROGRESS and the validation within PROGRESS of the finding, the two R levels add value. Inclusion of R yielded an AUC of 67.1% in the PROWESS trial population (no change from P and I alone), whereas, the PROGRESS registry population increased from 61.1% for P and I alone to 62.2% with the inclusion of R.

Organ Dysfunction. We formulated an "O" based on using number of organ failures (0–6) and each individual organ failure (hepatic, cardiovascular, respiratory, hematologic, renal, and metabolic acidosis). The classification was based on the residual tree from PROGRESS using the residuals from a logistic regression using "P," "I," and "R." The organ failure score based on an "O" adjusted for "P," "I," and

Table 8. Multivariate logistic regression to assess risk associated with each of the PIRO components

	PROWESS		PROGRESS	
Component	Odds Ratio (95% CI)	*p*	Odds Ratio (95% CI)	*p*
P	1.72 (1.47–2.02)	<0.0001	1.33 (1.28–1.38)	<0.0001
I	1.53 (1.23–1.90)	0.0001	1.51 (1.42–1.60)	<0.0001
R	0.94 (0.42–2.09)	0.87	1.40 (1.27–1.55)	<0.0001
O	1.35 (1.20–1.51)	<0.0001	1.46 (1.42–1.50)	<0.0001

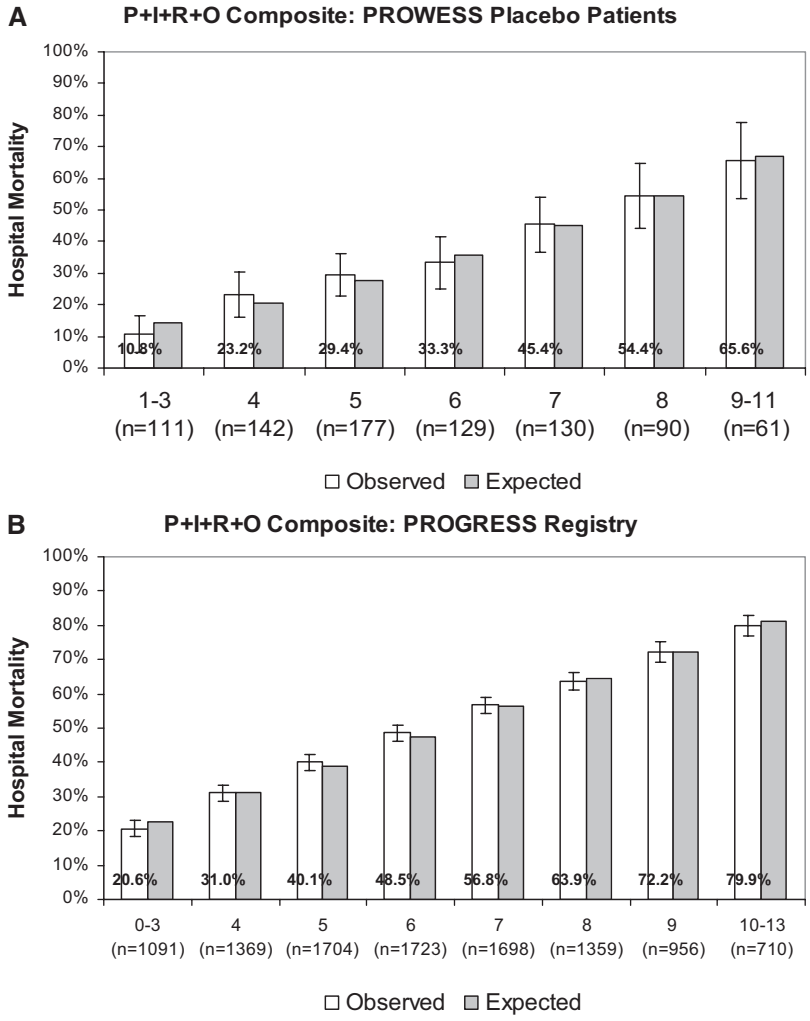

Figure 1. *A*, Hospital mortality and 95% confidence intervals by composite predisposition, insult/infection, response, and organ dysfunction (*PIRO*) stage in PROWESS placebo patients, and expected mortality rates based on the Hosmer-Lemeshow test. *B*, Hospital mortality and 95% confidence intervals by composite PIRO stage in PROGRESS patients, and expected mortality rates based on the Hosmer-Lemeshow test.

"O" was as follows: O0, two or fewer organ failures; O1, three organ failures, one of which is hepatic failure; O2, three organ failures, excluding hepatic failure; O3, four organ failures; and O4, five or more organ failures. The relationship with the O stage and mortality is demonstrated in Table 6. Among the PROGRESS population, these groups of two or fewer organ failures and three organ failures (one of which is hepatic) were only a trend of significance ($p = 0.15$), although the results were consistent within two randomly selected populations of PROGRESS. However, PROWESS mortality rates for O0 were numerically greater than O1, indicating a lack of consistency.

Inclusion of O increased the AUC from 67.1% for P, I, and R alone, to 70.0% in the PROWESS trial population. By comparison, APACHE II had an AUC of 68.6% within the PROWESS placebo group. When APACHE II is added to PIRO for PROWESS, only the AUC increased to 73.7%. The PROGRESS registry population increased from 62.2% for P, I, and R alone to 69.6% with the inclusion of O.

Composite. Table 7 summarizes the PIRO domains with each respective stratification level. The risk associated with each of the PIRO components was assessed in both of the datasets (Table 8). For the PROWESS placebo database, all individual components except R have a significant increase in odds ratio for mortality in logistic regression after adjustment for an earlier variable for PIRO, and as noted, because of the observed odds ratio and width of confidence interval, this may be due to underpowered sample sizes of PROWESS to detect "R" effects. The Hosmer-Lemeshow tests for PROWESS ($p = 0.33$) indicate that the model using P, I, R, and O has a good fit of the data across all patients, from high to low risk of death. In the PROGRESS dataset, all PIRO components were significant ($p < 0.0001$). Generally, all of the components were similar in their increase in risk of death for every one-point increase (odds ratios range from 1.3 to 1.5 for one level increases). A nonsignificant Hosmer-Lemeshow test ($p = 0.45$) indicated that the model had a good fit of the data across all patients, from high to low risk of death. Comparing odds ratios allows one to assess the relative contributions of changes in each component. Because, generally, all of the components were similar in their increase in risk of death for every one point increase, we performed an analysis of mortality by composite PIRO score with a minimum of 0 and a maximum of 13. Figure 1, *A* and *B* demonstrate the in-hospital mortality by composite PIRO score from PROWESS and PROGRESS, respectively. In PROWESS, the correlation of the PIRO total score and in-hospital mortality rates was 0.974 ($p < 0.0001$), and in PROGRESS, the correlation of the PIRO total score and hospital mortality rates was 0.998 ($p < 0.0001$).

DISCUSSION

There is enormous heterogeneity in the patient population suffering from severe sepsis. Many risk stratification models have been developed for sepsis, yet a recent study demonstrated that in the first 24 hours of intensive care unit ad-

mission physicians predicted mortality more accurately than scoring systems (13). However, the authors also found that the accuracy of the physician's prognostication was only moderate, which underscores the need for better tools for risk assessment in both clinical practice and clinical trial stratification. Many studies have demonstrated that intensive care unit scoring systems are better at predicting outcome of populations than individual patients (14). There are several organ dysfunction scoring systems, but none of these scoring systems is exclusive for patients with sepsis syndrome.

We have demonstrated that each component of PIRO contributes to the overall risk of death in this model with an increase in odds of death of approximately 30% to 50% for each increase in one level per individual PIRO component, even after adjustment for other components. As demonstrated in Figure 1, *A* and *B*, the composite PIRO score accurately predicted mortality over a broad range of scores in both the PROWESS and PROGRESS databases. How could the PIRO score be used in both clinical trials and patient care? We envision potentially using this novel model in a way similar to how the TNM staging system is used in clinical oncology. The model also allows researchers and clinicians to speak a common language, which facilitates communication that allows us to put patients with similar prognosis and treatment in the same staging group. Given the heterogeneity of this patient population as well as the providers that care for them, we believe these types of efforts to improve our taxonomy are crucial. Additionally, treatment guidelines rely on proper staging of disease to optimize care for an individual patient. For example, a patient with a T1N0M0 lung cancer will have very different treatment options than a patient with a T3, N3, M1 tumor classification. The PIRO staging system potentially could be used for risk stratification in a severe sepsis clinical trial, which is aiming to enroll patients at a high risk of death who are not moribund. As an example, a patient with a composite PIRO score of 6 or greater could be part of a trial's inclusion criteria. In addition, as the PIRO score undergoes further refinement, we could envision that a patient with a P1, I2, R1, O2 vs. a patient staged at P4, I3, R1, O4 would be prescribed different treatments for severe sepsis. Clinicians are always searching for additional tools to help with risk stratification for clinical trials, with an appropriate use of intensive care unit resources, and to assist with family discussions.

How does PIRO compare with other commonly used tools to predict outcome from severe sepsis? In this study, the area under the curve analysis for PIRO in the validation cohort was 0.696. In the recent publication of the global sepsis registry PROGRESS, multiple severity scores (APACHE II, APACHE III, Sequential Organ Failure Assessment, SAPS II, and MODS) were assessed and demonstrated area under the curves ranging from 0.6 to 0.7 (11). In our opinion, the PIRO staging system is less laborious than the APACHE II score, which has been demonstrated to have significant problems with reproducibility when applied to individual patients (15). Thus, although PIRO does not seem superior to other scoring systems in predicting mortality, it performs in a comparable fashion despite the fact that this is the first version of this model. Historically, outcome models have been reviewed and revised over time resulting in improved discrimination (16).

To our knowledge, we are the first to generate a PIRO model from a large severe sepsis database and subsequently validate this model in a large global sepsis database. Moreno (17) describes an analysis of 2628 patients from the SAPS III multinational cohort database and reported a partial PIRO covering only P, I, and R developed from a subset of the SAPS III database. As it stands, their model is different from our's as it uses organ dysfunction/failure as "R" rather than providing distinct "R" and "O" scales. They categorized variables from the SAPS model into three of the four domains of the PIRO model—predisposition, injury, and response—and evaluated the impact of each of these on patient stratification. The article reports the results of these analyses, broken down by diagnostic category of sepsis (sepsis, severe sepsis, septic shock, and infection alone). This is a laudable effort to try to explore the utility of the PIRO model using the SAPS database, but our study has a much larger pool of patients diagnosed with severe sepsis (11,500 vs. 1,099). We have used classification trees to optimize the ability to place patients in distinct groups that maximize risk differences. For example, rather than determining age cut-offs heuristically before or after a logistic regression, classification and regression tree determines age cut-points that maximize differences of mortality risk. Also, we believe the sequential creation of components that account for the mortality risk not accounted by the preceding components to be a novel approach to independent risk factors that contain no significant pairwise interactions.

A major strength of our study is that we were able to generate a PIRO model in one sepsis dataset and subsequently validate the model in a larger, more diverse dataset. The large PROWESS and PROGRESS databases had detailed data collection performed, which is ideal for generating such models. Another strength of this study is the nature of PROGRESS, a global sepsis registry involving 37 countries, which increases the spreading of the PIRO model in this study. We are pleased by the general consistency of the PIRO classes across both datasets, and the potential that the system can be applied to multiple mortality measures and patient populations. Although there are several variables that would be beneficial to include in the future, PROWESS and PROGRESS provided comprehensive information from more than 10,000 patients. The ability to compare PIRO to multiple other prognostic scores in PROGRESS is also a unique strength. There are important limitations in this study. First, we did not have sufficient genomic data to incorporate it into the model, which might have improved the prognostic ability of the P component. Second, the R variable only included the standard systemic inflammatory response syndrome criteria, whereas other signs or biomarkers could have significantly improved the R variable. Future sepsis studies should focus on collecting additional biomarkers to help expand the R variable. For a statistical analysis such as this, there are many approaches that could be used. The regression tree approach was our choice because it inherently gives rules to classify patients rather than merely stating which risk factors are significant. Of course, the score has been developed retrospectively and prospective use at the bedside, in real time, may be different (for instance, in assessing source and type of infection).

We believe our study has implications for future research in sepsis. First, the PIRO model could be used to stratify patients for inclusion into a severe sepsis trial. We believe this PIRO model represents a pilot stratification system, which requires additional testing and validation. Second, the composite PIRO score could

be used as a prospectively defined subgroup analysis outcome variable for future clinical trials. Third, as this model is reviewed and refined over time, we anticipate that this severe sepsis staging system could be used like the TNM system to determine prognosis and individual treatment recommendations for an individual patient suffering from severe sepsis. Finally, this score could even be used as a triage tool or as a tool to assist with end-of-life discussion.

In conclusion, our evaluation of the utility of the PIRO model for risk assessment in patient with severe sepsis shows that each variable contributes to outcome prediction with a 30% to 50% increase in odds of death. We repeat that this should be seen as a preliminary, hypothesis-generating version of the model. Subsequent studies will be needed to test the clinical efficacy and further refine the PIRO scoring system in the diagnosis and risk assessment of severe sepsis.

REFERENCES

1. Martin GS, Mannino DM, Eaton S, et al: The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003; 348:1546–1554
2. Martin GS, Mannino DM, Moss M: The effect of age on the development and outcome of adult sepsis. *Crit Care Med* 2006; 34:15–21
3. Bone RC, Balk RA, Cerra FB, et al: American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 1992; 101:1644–1655
4. Knaus WA, Draper EA, Wagner DP, et al: APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13: 818–829
5. Knaus W, Wagner D, Draper E: APACHE III study design: Analytic plan for evaluation of severity and outcome in intensive care unit patients. Implications. *Crit Care Med* 1989; 17(Suppl 2): S219–S221
6. Vincent JL, De Mendonca A, Cantraine F, et al: Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: Results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med* 1998; 26:1793–1800
7. Marshall JC, Cook DJ, Christou NV, et al: Multiple organ dysfunction score: A reliable descriptor of a complex clinical outcome.[see comment]. [Review] *Crit Care Med* 1995; 23: 1638–1652
8. Le Gall JR, Lemeshow S, Saulnier F: A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study.[erratum appears in *JAMA* 1994; 271:1321]. *JAMA* 1993; 270:2957–2963
9. Levy MM, Fink MP, Marshall JC, et al: 2001 SCCM/ESICM/ACCP/ATS/SIS International sepsis definitions conference. *Crit Care Med* 2003; 31:1250–1256
10. Bernard GR, Vincent JL, Laterre PF, et al: Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; 344:699–709
11. Beale R, Reinhart K, Brunkhorst F, et al: PROGRESS (Promoting Global Research Excellence in Severe Sepsis): Lessons from an International Sepsis Registry. *Infection* in press
12. Breiman L. Classification and Regression Trees. New York, Kluwer Academic Publishers, 1984.
13. Sinuff T, Adhikari NK, Cook DJ, et al: Mortality predictions in the intensive care unit: Comparing physicians with scoring systems. *Crit Care Med* 2006; 34:878–885
14. Skrobik Y, Kavanagh BP: Scoring systems for the critically ill: Use, misuse and abuse. *Can J Anesth* 2006; 53:432–436
15. Booth FV, Short M, Shorr AF, et al: Application of a population-based severity scoring system to individual patients results in frequent misclassification. *Crit Care* 2005; 9:R522–R529
16. Le Gall JR, Neumann A, Hemery F, et al: Mortality prediction using SAPS II: An update for French intensive care units. *Crit Care* 2005; 9:R645–R652
17. Moreno RP, Metnitz B, Adler L, et al: Sepsis mortality prediction based on predisposition, infection and response. *Intensive Care Med* 2008; 34:496–504