

# Risk Stratification in Severe Sepsis: Organ Failure Scores or PIR0?

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*“It’s more important to know what sort of person this disease has, than what sort of disease this person has”*

*William Osler, 1849–1919*

### 1

#### Introduction

In the mid-1980s, a long series of clinical trials on patients with sepsis that yielded negative results started a very interesting discussion on the robustness of 28-day all-cause mortality as the sole or major end point for the evaluation of clinical trials in intensive care units (ICUs) [1]. The use of this measure, considered the gold standard in clinical trials on sepsis, undoubtedly represents a very relevant end point. It has, however, been contested [2], since hospital policy can and does change the location of deaths (e.g., discharging patients to die) and can be significantly underestimated in hospitals that discharge patients very early in the course of their disease. Moreover, the process of using two groups of patients, with one assigned to receive the new therapy and the other placebo, has been criticized. The absence of stratification according to patient demographic or biological characteristics before randomization can lead to unbalanced groups and confounding, and an impossibly high number of patients would be needed to demonstrate a significant difference between patient groups. In addition, interactions between certain patient characteristics at baseline and the effect of treatment can be obscured, as occurred in the MONARCS trial, in which the administration of afelimomab lowered the circulating levels of tumor necrosis factor (TNF) and interleukin (IL)-6, accelerated the resolution of organ dysfunction, and reduced 28-day all-cause mortality, but only in patients with elevated IL-6 levels at baseline [3].

For these reasons, some investigators have proposed certain recommendations that should constitute the basis of criteria for inclusion in clinical trials and that should not be restricted to the ones proposed by the American College of Chest Physicians (ACCP)/Society of Critical Care Medicine (SCCM) definitions of sepsis or sepsis syndrome. Moreover, they also proposed

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the use of a scoring system for organ dysfunctions that has been validated and that can be incorporated into all sepsis studies. Furthermore, they recommend that generally the primary outcome measure should be mortality rate, but under appropriate circumstances major morbidities could be considered also as primary end points [4]. The publication in March 2001 of the Efficacy and Safety of Recombinant Human Activated Protein C for Severe Sepsis (PROWESS) trial presented apparently a decrease in 28-day all-cause mortality from 30.8% in the placebo group to 24.7% in the drotrecogin alfa-activated group [5]. However, it was soon evident that there were innumerable confounders and effect modifiers on the effect of the drug on patient outcome, of which the baseline severity of illness and site of infection were described as the most important [5, 6]. These potential confounding factors, and the later publication of studies with discrepant results in controlled [7] and uncontrolled settings [8, 9] raised such a serious debate [10] that the drug is now being assessed in a risk-stratified population [11].

In another more recent study, the CORTICUS study [12], comparing the use of hydrocortisone with placebo in patients with septic shock, baseline severity of illness and possibly other baseline and infection-related factors played such an important role in the interpretation of the results that they could be responsible for the negative result of the intervention on 28-day all-cause mortality, when compared with almost the same study design in a cohort of more severely ill patients [13]. This effect was even more striking because, although there was no change in 28-day all-cause mortality, there was clearly a reduction in the length of shock and the severity of multiple organ dysfunction/failure syndrome (MODS), driven by an improvement of cardiovascular dysfunction/failure [14].

Authors like Petros, more than 10 years ago, began to question the adequacy of all cause-mortality as an end point [15]. A meaningful end point can only be chosen when a direct relationship between an event and its consequences is known. In the case of sepsis (and multiple organ failure) our knowledge is very limited, and concerning most phenomena no such direct relationship can be established. Moreover, it implies the need for large samples, with problems in reliability of data collection, heterogeneity of enrolled patients, and costs. Patients in intensive care, even with strict inclusion criteria for sepsis or septic shock, do not constitute a homogeneous sample. Patients have different syndromes and diagnoses, time-courses, ages, chronic illnesses (chronic health, comorbidities), different sites of infection and invading microorganisms, and different degrees of physiologic dysfunction resulting in a large diversity of mortality risks [16, 17]. Several methods have been proposed to deal with this variation [17–19], but they usually involve complex, extensive (and expensive) data collection and sophisticated analysis.

Two approaches have been designed to cope with this complex problem of patient selection and stratification, which have led to the development of the MODS scores and the so-called PIRO approach (predisposition, insult, response, and organ dysfunction).

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## 2

### Organ Dysfunction/Failure Scores

Awareness of the importance of MODS as an important confounder and/or effect modifier in the evaluation of patients with sepsis led the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine (ESICM), under the leadership of Professor

Jean-Louis Vincent, to organize a consensus meeting in Paris (December 1994) to create the so-called Sepsis-related Organ Failure Assessment (SOFA) score [20]. The rationale behind this decision was the need to find an objective and simple way to describe individual organ dysfunction/failure in a continuous form, from mild dysfunction to severe failure, which could be used over time to measure the evolution of individual (or aggregated) organ dysfunction in clinical trials on sepsis or by the clinician at the bedside. A retrospective evaluation of the application of this score in the first 24 h after ICU admission on 1,643 patients with early sepsis in an international database [20] demonstrated a good correlation with mortality and an acceptable distribution of the patients among the different groups. To confirm these retrospective findings, a prospective, multinational study was initiated that demonstrated that the system could in fact be applied in other typologies of patients and for this reason the name of the score was changed to Sequential Organ Failure Score.

Later, more complex measures were derived from this concept, such as the total maximum SOFA score and delta SOFA score (total maximum SOFA minus admission total SOFA, i.e., the magnitude of organ dysfunction appearing during the ICU stay), and they were shown to be even better as descriptors and/or predictors of outcome in patients with MODS (most of them septic) in ICUs all over the world [21].

Other similar systems exist, developed at more or less the same time, such as the MODS, created by Marshall and coworkers [22], and the Logistic Organ Dysfunction (LOD) system, developed by Le Gall and colleagues [23]. All of them were designed with similar principles in mind [20]:

- (a) Organ failure is not a simple all-or-nothing phenomenon, it is a spectrum or continuum of organ dysfunction from very mild altered function to total organ failure.
- (b) Organ failure is not a static process and the degree of dysfunction varies with time during the course of the disease.
- (c) The variables chosen to evaluate each organ need to be objective, simple, and available but also reliable, routinely measured in every institution, specific to the organ in question, and independent of other disease-specific variables, so that the score can be easily calculated for any patient in any ICU.

Although there is no general agreement on the optimal way to assess organ dysfunction/failure, all the widely used systems include six key organ systems (cardiovascular, respiratory, hematological, central nervous, renal, and hepatic), evaluated through a combination of physiologic (e.g.,  $\text{PaO}_2$ ) and therapeutic (e.g., use of vasopressor agents) variables. The major difference among them is the method chosen for the evaluation of cardiovascular dysfunction: SOFA uses blood pressure and the level of adrenergic support, MODS uses a composed variable (pressure-adjusted heart rate or  $\text{PAR} = \text{heart rate} \times \text{central venous pressure/mean arterial pressure}$ ), and the LOD score uses the heart rate and systolic blood pressure. A comparison of these systems, published only as an abstract, seem to indicate a greater discriminative capability of the MODS and SOFA score over the LOD score [24]. However, the small size of the sample requires further validation.

Mixed models, integrating organ failure assessment scores and general severity scores, have been published [25, 26] but they have not gained widespread acceptance.

### From Multiple Organ Dysfunction/Failure Scores to the PIRO Concept

In 2001, several European and American critical care societies organized a second consensus conference to address the weaknesses of systemic inflammatory response syndrome (SIRS) and sepsis definitions, discussed intensively over the last decade [27], with the aim of improving the early identification and stratification of patients with sepsis [28]. 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, which emerged from the Fifth Toronto Sepsis Roundtable, held in Toronto, Canada in October 2000 [29], was also adopted: the IRO system (insult, response, and organ dysfunction), which later became the PIRO at the 2001 conference (with the addition of predisposition) [30–33]. Although interesting and promising, to date this approach has remained virtually conceptual, with the first attempt to develop such a system being just published as an abstract [34].

In the last few years, our group has empirically tested – using a large multicenter, multinational database, the Simplified Acute Physiology Score (SAPS) 3 database [35] – whether a modified definition of PIRO (using the concept of predisposition, infection, and response/organ dysfunction/failure) could be useful for predicting mortality in patients with severe infection, sepsis, and septic shock at ICU admission.

In this cohort (comprising 16,784 patients from 303 ICUs), 3,505 patients already presented an infection at ICU admission, from which 2,628 patients had a length of stay in the ICU equal to or greater than 48 h.

To test the PIRO concept, three logical boxes were defined:

- (a) *Predisposition*: The variables of the SAPS 3 “Admission Score Boxes 1 and 2”, which are not related to infection, were used. These include age, comorbidities, use of vaso-active 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.
- (b) *Infection*: 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.
- (c) *Response/Organ dysfunction/Organ failure*: To identify the response and the consequences of the infection, we used the development of organ dysfunction and failure, measured through the highest SOFA score values for each organ system between admission and 48 h after ICU admission.

These variables were selected according to their association with hospital mortality as described elsewhere and a multilevel model (logistic regression with random effects) was applied, using patient characteristics as fixed effects and ICUs as a random effect, to estimate the impact of each of the predictive variables in the outcome variable [36].

In the multivariate analysis, the variables that turned out to be significant were:

- (a) *Predisposition (Box 1)*: age; location from which the patient was admitted to the ICU; comorbidities; length of stay before ICU admission (days); and some reasons for ICU admission
- (b) *Infection (Box 2)*: acquisition of infection; extension of infection; site of infection; and infective agent
- (c) *Response/Organ dysfunction/Organ failure (Box 3)*: dysfunction of the renal and coagulation systems; failure of the cardiovascular, respiratory, renal, coagulation and central nervous systems

Based on the contribution of these variables to outcome, a score sheet was developed (Table 1) and an equation relating the SAPS 3 PIRO score to the vital status at hospital discharge was created:

$$\text{logit} = -46.6757 + \ln(\text{SAPS 3-PIRO} + 76.7688) * 9.8797$$

with the probability of hospital mortality being given by the equation:

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

The prognostic performance of the developed model was tested by means of discrimination and calibration and was found to be excellent, both in the overall population and in specific subgroups of patients, as defined by the ACCP/SCCM classification of sepsis and septic shock [36].

It should be noted that in this system, the evaluation of the response and the resultant organ dysfunction/failure has been collapsed. This happens because, in our understanding, the host response to the insult and the resulting organ dysfunction cannot be distinguished from each other based on clinical variables, and there are no specific biomarkers available and ready for clinical use that can do this. Therefore, this resulted in the proposed three-level staging model consisting of predisposition, infection, and response/organ dysfunction/failure. We anticipate that as new biomarkers or panels of biomarkers become available in the future, we will be able to differentiate, in the clinical setting, between true biological response and the physiological and pathological consequences of that response, the dysfunction and/or failure of the different body systems.

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## 4

### One PIRO or Many PIROs?

In the last few years, Jordi Rello and the Intensive Care Group from Tarragona have also proposed two models based on the PIRO concept, one for ventilator-associated pneumonia (VAP-PIRO) [37] and the other for community-acquired pneumonia (CAP-PIRO) [38]. Both are discussed in Chap. 4 of this book by Emili Díaz and Thiago Lisboa this volume.

**Table 1** Scoresheet for computation of SAPS 3-PIRO. Adapted from Moreno et al. [36], with permission

Box 1: predisposition	0	4	5	6	7	8	9	10	11
Age, years	<40	>=40 < 60				>= 60 <70			> = 70 <75
Location from which the pat. was admitted to the ICU		Same hospital							
Co-Morbidities					Cancer <sup>a</sup>	Cirrhosis <sup>b</sup>	AIDS <sup>c</sup>		
Length of stay before ICU admission, days	<14		>=14 <28		>=28				
Reason(s) for ICU admission							Cardiac arrest <sup>d</sup>		
Box 2: infection	0	4	5		7	8	9	10	11
Acquisition		Nosocomial <sup>e</sup>							
Extension		Other than localized <sup>f</sup>							
Site			Respiratory <sup>g</sup>						
Agent								Candida, Fungi <sup>h</sup>	
Box 3: response/organ function	0	4	5		7	8	9	10	11
Organ dysfunction (OD) <sup>j</sup>		Renal							
Organ failure (OF) <sup>i,k</sup>			Coagulation Cardiovascular Respiratory					CNS Coagulation Renal	

- <sup>a</sup>*Cancer* refers to the presence of: metastatic cancer, haematological cancer, chemotherapy, immunosuppression other, radiotherapy, steroid treatment. Data definitions are presented in Appendix C of the ESM: Co-Morbidities: AIDS [36]
- <sup>b</sup>*Cirrhosis* refers to the data definitions in Appendix C of the ESM: Co-Morbidities: AIDS [36]
- <sup>c</sup>*AIDS* refers to the data definitions in Appendix C of the ESM: Co-Morbidities: AIDS [36]
- <sup>d</sup>*Cardiac Arrest* refers to the data definitions in Appendix C of the ESM: Reasons for ICU Admission: Cardiovascular – Cardiac Arrest [36]
- <sup>e</sup>*Nosocomial* refers to the data definitions in Appendix C of the ESM: Acute Infection at ICU Admission – Acquisition: Hospital-Acquired [36]
- <sup>f</sup>*Other than localized* refers to the data definitions in Appendix C of the ESM: Acute Infection at ICU Admission – Localized infection with regional involvement, disseminated [36]
- <sup>g</sup>*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 [36]
- <sup>h</sup>*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; [36]
- <sup>i</sup>If the maximum SOFA value of day 1 and day 2 is 1 or 2
- <sup>j</sup>If the maximum SOFA value of day 1 and day 2 is 3 or 4
- <sup>k</sup>With multiple items the points are additive

Both systems are very simple and share common characteristics:

- (a) Developed in large cohorts of patients with community-acquired pneumonia requiring ICU admission and ventilator-associated pneumonia
- (b) Computed at 24 h after ICU admission
- (c) Use a simple scale comprising only a few variables (eight for CAP-PIRO and four for VAP-PIRO), derived by multivariate logistic regression with outcome at 28 days after ICU admission (CAP-PIRO) or vital status at ICU discharge (VAP-PIRO) used to select the variables
- (d) Divide the patients into a few levels of risk (four for CAP-PIRO and three for VAP-PIRO) but do not provide a quantitative estimate of vital status at hospital discharge

These systems have the advantage over SAPS-PIRO of being easier to compute and more specific to the individual risk factors of the analyzed infections (CAP and VAP), but at the price of losing their applicability in large, more heterogeneous groups of patients with severe infection, sepsis, and septic shock. Moreover, they were derived from national, datasets and the extent of their utility outside the dataset demographics is unknown.

We hope that in the future a mixed approach can be used, creating a system that differentiates between general predisposition to severe infection and specific risk factors for specific infections, the characteristics of these infections, and the resulting organ dysfunction/failures impacting the outcome.

## 5

### PIRO or MODS Scores?

The incidence of severe sepsis and septic shock in the ICU seems to be increasing in the last few years. This fact was consistently found in all recently published studies [39–42]. Although this trend can be partially explained by the growing awareness of physicians of the early recognition and treatment of sepsis as a result of initiatives such as the Surviving Sepsis Campaign [43], the increasing incidence seems to have been present even before these initiatives, and thus other reasons, such as the changing demographics of the population (increasing age, comorbidities) and the changing characteristics of the microorganisms (prevalence, resistance), probably play a major role in this phenomenon.

Although mortality in sepsis seems to be associated mainly with the presence and degree of organ dysfunction/failure developed by the patient either before or after ICU admission [21, 42, 43, 45], other factors have been demonstrated to play an important role, such as the place of acquisition (nosocomial vs. community-acquired infection) [42, 46] and the characteristics of the infection (site of infection, microorganism(s) involved, or extension of the infection) [47, 48]. Consequently, to reduce the evaluation of patients with severe infection and sepsis to the evaluation, quantification, and time-course pattern of MODS is a reductionist approach that will certainly overlook important information, even if it carries some prognostic accuracy [21, 49, 50].

In a general outcome prediction model, factors present at hospital admission (in other words, predisposition) are responsible for 45.9% of the explanatory power of the model



[51], and this value is also high (44.8%) in the model developed for severe infection and sepsis (SAPS 3) [36]. Although the sampling space of both models is different, which prevents definitive comparisons between them [52], the exclusive use of physiological variables in this context does not seem to be wise, since their explanatory power is low in both models (27.4% in the general model and 35.3% in the sepsis model).

For these reasons, we believe that future models should be based on the SAPS-PIRO approach, complemented by:

- (a) A better distinction between risk factors for progression of the infection and for death (which we know from the work of Corinne Alberti and the European Sepsis Group to be distinct and can be modeled [48])
- (b) A better distinction between general risk factors and specific risk factors for specific infections
- (c) The incorporation of biomarkers (or panels of biomarkers) to evaluate the response
- (d) An increase in the follow-up time of the course of organ dysfunction/failure, allowing a better follow-up of the evolution of the patient

This approach will allow the clinician to have an earlier evaluation of risk (which could drive the use of preventive or preemptive therapies), the use of specific therapies directed at the insult and at the pattern of response, and finally a better use of organ replacement therapies in patients with severe infection, sepsis, and septic shock.

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