**Distribution of the Probability of Survival Is a Strategic Issue for Randomized Trials in Critically Ill Patients**

Bruno Riou, M.D., Ph.D.,* Paul Landais, M.D., Ph.D.,† Benoît Vivien, M.D.,‡ Philippe Stell, M.D.,§ Ilhe Labbene, M.D.,§ Pierre Carli, M.D.,||

**Background:** Many randomized clinical trials in trauma have failed to demonstrate a significant improvement in survival rate. Using a trauma patient database, we simulated what could happen in a trial designed to improve survival rate in this setting.

**Methods:** The predicted probability of survival was assessed using the TRISS methodology in 350 severely injured trauma patients. Using this probability of survival, the authors simulated the effects of a drug that may increase the probability of survival by 10–50% and calculated the number of patients to be included in a triad, assuming $\alpha = 0.05$ and $\beta = 0.10$ by using the percentage of survivors or the individual probability of survival. Other distributions (Gaussian, J shape, uniform) of the probability of survival were also simulated and tested.

**Results:** The distribution of the probability of survival was bimodal with two peaks ($< 0.10$ and $> 0.90$). There were major discrepancies between the number of patients to be included when considering the percentage of survivors or the individual value of the probability of survival: 63,202 versus 2,848 if the drug increases the probability of survival by 20%. This discrepancy also occurred in other types of distribution (uniform, J shape) but to a lesser degree, whereas it was very limited in a Gaussian distribution.

**Conclusions:** The bimodal distribution of the probability of survival in trauma patients has major consequences on hypothesis testing, leading to overestimation of the power. This statistical pitfall may also occur in other critically ill patients.

TRAUMA is the leading cause of death in young people and the leading cause of lost years of life in industrialized countries. Annual cost secondary to trauma (acute medical care, deaths, disability, lost wages, and taxes) in the United States has been estimated to exceed $150 billion. In the past, considerable improvement in the care of trauma patients has been accomplished by organization of prehospital care, development of regionalized trauma systems, and improvement in the assessment of trauma patients by modern imaging techniques. More recently, randomized trials in trauma patients testing the hypothesis that a pharmacologic intervention could improve survival have appeared, indicating that traumatology now deals with the same methodologic problems as other specialties.

Many of the large prospective randomized studies recently published provided negative and disappointing results. For example, although tirilazad has been demonstrated to decrease the deleterious consequences of brain trauma, it failed to decrease mortality in head trauma patients. More recently, two large trials on the use of a hemoglobin solution (Diaspirin Cross-Linked Hemoglobin; Baxter Hemoglobin Therapeutics, Boulder, CO) in the early phase of trauma resuscitation, one in the United States and the other in Europe, were prematurely terminated. The US trial was discontinued early because of an unfavorable imbalance in between-group mortality. The European trial was discontinued as a consequence of a failure to demonstrate evidence of benefit. The underlying reasons for early termination of these two trials have been caused, at least partially, by inappropriate study design leading to bias, inclusion of wrong patients (early deaths), and/or the impossibility of demonstrating any beneficial effect of the drug on mortality. These observations raised several issues: (1) it may not be ethically acceptable to include patients in trials that are not able to conclude anything; (2) it is possible that the development of interesting drugs in trauma patients could be prematurely stopped; (3) a very large amount of money has been spent in these negative or aborted trials, whereas resources allocated to trauma research are limited as compared with cancer or cardiovascular diseases; (4) it seems obvious that most of the progress that could be now expected in trauma care will come from large randomized trials testing pharmacologic interventions, and, thus, methodologic pitfalls could prevent significant progress in the future.

Because two of the authors (B.R. and P.C.) were involved in the analysis of pitfalls that led to the termination of the randomized trials with the hemoglobin solution in trauma, we realized that several important methodologic problems (inclusion and exclusion criteria, the determination of the number of patients to be included, and the assumptions used for this calculation) had not been appropriately considered because the main characteristics of trauma as a disease were not completely understood. In the current study, we used a
The SAMU system has been described elsewhere. The patients for this study were selected by the SAMU system to warrant direct admission of these patients to the emergency department of a level 1 trauma center. The severity of trauma was considered as high enough by the prehospital team to warrant direct entry into the hospital. The following scores were determined: Abbreviated Injury Scale, Injury Severity Score, and Revised Trauma Score (RTS). The Ps was then calculated using the TRISS methodology. Thus, in the following text, Ps is the TRISS score when applied to trauma patients.

The case histories of 350 consecutive blunt trauma patients were analyzed. All were cared for by a mobile intensive care unit (Paris SAMU system), and the severity of trauma was considered as high enough by the prehospital team to warrant direct admission of these patients to the emergency department of a level 1 trauma center. The SAMU system has been described elsewhere. The on-scene triage was based on the clinical assessment of the trauma patient. For each patient, the following data were recorded during the prehospital phase: age, sex, initial systolic arterial pressure (SAP), heart rate, respiratory rate, Glasgow Coma Score, occurrence of prehospital cardiac arrest, and SAP and heart rate at the arrival in the hospital. The following scores were determined: Abbreviated Injury Scale, Injury Severity Score, and Revised Trauma Score (RTS). The Ps was then calculated using the TRISS methodology. Thus, in the following text, Ps is the TRISS score when applied to trauma patients.

The observed survival (i.e., survival until hospital discharge) was compared with the expected survival. The expected percentage of survivors was calculated as follows:

\[ S\% = \sum Ps \cdot 100 \cdot n^{-1} \]

where \( n \) is the number of patients. As previously described, to compare our population with that of the Major Trauma Outcome Study (MTOS), we calculated the M, W, and Z scores. An M value less than 0.88 indicates a disparity in the severity match between the study group and the MTOS group. The W score is the number of survivors more or less than would be expected from the MTOS prediction for 100 patients. A Z score between −1.96 and +1.96 indicates no significant difference \( (P > 0.05) \) between the actual number of survivors and that expected. Because our population was selected by the SAMU system and was expected to include more severe trauma patients with a low Ps, we also calculated the standardized W score, which represents the W score that would have been observed if the case mix of severity was identical to that of the MTOS group. Accordingly, a standardized Z score was calculated. A Z score between −1.96 and +1.96 indicates no significant difference \( (P > 0.05) \) between the number of survivors and that expected, if the case mix severity was identical to that of the MTOS.

### Simulation of a Therapeutic Trial

In the second part of the study, we used our trauma population with the individual values of a priori Ps and its characteristic bimodal distribution of Ps to simulate a trial. This simulation does not take into account the fact that the number of survivors may differ from the expected number of survivors.

We tested the effects of a theoretical treatment that could be able to increase Ps by 10, 20, 30, or 50%. Because Ps must be between 0 and 1, we applied the following rule: for example, if a drug is thought to increase Ps by 10%, when Ps was below 0.50, it was increased by 10% of Ps, and when Ps was greater or equal to 0.50, it was increased by 10% of 1 − Ps.

To calculate the number of patients to include in a randomized trial comparing survival in two groups (control vs. treated groups), four numbers are required: the percentage of survivor in the control group, the expected percentage of survivor in the treated group, and the values of type I error (\( \alpha \)) and type II error (\( \beta \)). We calculated this number of patients to include in a trial, assuming \( \alpha = 0.05 \) and \( \beta = 0.10 \). We first calculated this number using the global percentage of survivors in our population, as usually performed in trials. For example, if a drug is thought to increase Ps by 10% and if the percentage of survivors was 75.0% in the control group, we expected that the percentage of survivors should be 77.5% in the treated group. Second, we calculated the number of patients to include in a trial by using the individual Ps. For this purpose, we applied the rule explained above to all individual Ps values, then we summarized all of these modified Ps values to obtain the percentage of survivors in the treated group, as described above. Nevertheless, a moderate discrepancy between the number of patients to be included using the global percentage of survivors or the individual Ps was
very high Ps (Ps 
considered three groups of trauma patients: those with a 
neity by selecting an appropriate subpopulation. We 
marked heterogeneity, we tried to reduce this heteroge-
distribution of the Ps in trauma patients (fig. 1) implies a 
1,000 theoretical patients whose distribution of the Ps 
was Gaussian and whose mean percentage of survivors 
Therefore, we also randomly generated a population of 
the case where all patients have exactly the same Ps). 
percent is not equivalent to taking the mean of the 
expected (mathematically, multiplying the mean Ps by x 
percent, except in the case where all patients have exactly the same Ps). Therefore, we also randomly generated a population of 1,000 theoretical patients whose distribution of the Ps was Gaussian and whose mean percentage of survivors was 75.0%, as observed in our trauma population.

Selection of a Subpopulation of Trauma Patients
In the third part of the study, because the bimodal 
distribution of the Ps in trauma patients (fig. 1) implies a 
marked heterogeneity, we tried to reduce this heteroge-
d by selecting an appropriate subpopulation. We 
considered three groups of trauma patients: those with a 
very high Ps (Ps ≥ 0.90), those with a very low Ps (Ps ≤ 0.10), and those with an intermediate Ps (0.10 < Ps < 0.90). We used all prehospital variables available (age, sex, SAP, heart rate, respiratory rate, RTS, Glasgow Coma Score, occurrence of cardiac arrest) to define the best criteria enabling to select trauma patients with a low Ps, a high Ps, and an intermediate Ps. In these three sub-
groups, we calculated the number of patients to be 
cluded in a trial assuming a type I error of 0.05 and a 
type II error of 0.10, as described above.

Simulation of Other Distributions
In the fourth part of the study, to assess the effects of 
other possible distributions of the Ps that could be en-
countered in nontraumatized critically ill patients, we 
randomly generated two other populations of 1,000 the-
etical patients whose distribution of the Ps were (1) 
uniform and (2) J shape. Indeed, a J-shape distribution 
has been observed in other critically ill patients such as 
patients with septic shock.16 Because a uniform distri-
bution implies a survival rate of 50%, we chose a J-shape 
distribution with a survival rate close to 50%.

Statistical Analysis
Data are presented as mean ± SD. All P values were 
two-sided. The NCSS statistical program (Release 6.0, 
Statistical Solution Ltd, Cork, Ireland) was used for all 
statistical analyses.

To calculate the number of patients to be included, we 
applied the Casagrande and Pike17 method assuming α = 
0.05 and β = 0.10 and using the percentage of survivors 
in control conditions and the percentage of survivors 
expected because of the drug effect (percentages were 
rounded to one decimal) and based on a two-sided 
analysis.

Identification of trauma patients in the high- and 
low-Ps groups were performed separately. For each 
procedure, the following steps were followed: first, all cri-
tera were analyzed using an univariate analysis (un-
paired Student t test or Fisher exact method). Second, 
for noncategoric variables that indicated a significant 
difference between groups, a cutoff value was deter-
dined using the receiver operating characteristics curve. 
The cutoff value was chosen as the value associated with 
the maximum value of sensitivity plus specificity. Then a 
stepwise logistic regression (P value at entry = 0.05) was 
applied to determine the appropriate criteria, using only 
categoric variables. The odds ratio and its 95% confi-
dence interval were calculated.

We used the random function of Excel 5.0 software 
(Microsoft Corporation, Seattle, WA) to randomly gener-
ate populations of 1,000 theoretical patients. By taking 
random numbers (RN) between 0 and 1, we generated a 
uniform distribution (mean Ps, 0.50). By taking RN1.8, 
we generated a J-shape distribution (mean Ps, 0.41). 
Lastly, by taking the mean of 10 random numbers + 
0.25, we generated a Gaussian distribution (mean Ps, 
0.75). Indeed, according to the central limit theorem, 
the sampling distribution tends toward a Gaussian distri-
bution, whatever the initial distribution.18

Results
In this population (N = 350), mean age was 36 ± 16 
(yr (range, 15–89 yr), and 253 (72%) patients were male. 
The mean Injury Severity Score was 28 ± 16 (median, 
29), mean RTS was 6.16 ± 2.27 (median, 7.11), and the 
mean TRISS was 0.750 ± 0.341 (median, 0.940). Figure 
1 depicts the distribution of Ps values in this population 
and reveals a bimodal distribution. The number of 
survivors (n = 277, 79%) was higher than that expected 
(n = 262, 75%). The W score was +5.1% (Z = 12.25, 
P < 0.001). As expected, the value of M = 0.64 indicated 
a disparity in the severity match between the study group 
and the MTO5 group.15 This disparity was mainly caused 
by a lower proportion of patients with a very high Ps 
(TRISS > 0.95, 46.9 vs. 82.8%) and a higher proportion 
of patients with a low Ps (TRISS < 0.25, 16.9 vs. 3.6%).

Fig. 1. Histograms showing the distribution of the probability of 
survival in the studied group of trauma patients (N = 350).
The standardized W score was +0.4% (Z score = 0.15, nonsignificant), indicating that it was not significantly different from that of the MTOS. In fact, we observed that only trauma patients with a low Ps (i.e., TRISS < 0.25) experienced a higher number of survivors than that expected by MTOS (W = 25.7%, Z = 57.1, P < 0.001).

**Simulation of a Therapeutic Trial**

As shown in table 1, there were major discrepancies between the number of patients to be included in a trial when considering the global percentage of survivors or the individual value of Ps. As shown in table 2, this phenomenon was very limited in the theoretical population with a Gaussian distribution of Ps (fig. 2), demonstrating that it was mainly related to the marked heterogeneity of the trauma population and not to the mode of calculation (global percentage of survivors versus individual probability or survival).

**Subpopulations of Trauma Patients**

We compared trauma patients with a low Ps (Ps ≤ 0.10) and the other trauma patients. The univariate analyses showed that initial SAP (43 ± 47 vs. 114 ± 32 mmHg), heart rate (67 ± 60 vs. 98 ± 23 beats/min), Glasgow Coma Score (4 ± 2 vs. 12 ± 4), and respiratory rate (10 ± 11 vs. 20 ± 5), occurrence of prehospital cardiac arrest (51 vs. 2%) and RTS (1.22 ± 1.50 vs. 6.74 ± 1.51) were significantly different between groups. The area under the receiver operating characteristics curve was 0.98 ± 0.16 for the RTS, with a cutoff value of 4.5 (sensitivity = 97%, specificity = 90%). The logistic regression indicated that an RTS less than 4.5 was the only independent predictor of a low Ps (table 3). We also compared trauma patients with a high Ps (Ps ≥ 0.90) and the other trauma patients. The univariate analysis showed that initial SAP (120 ± 25 vs. 88 ± 49 mmHg), Glasgow Coma Score (14 ± 2 vs. 7 ± 4), and respiratory rate (20 ± 5 vs. 17 ± 9), occurrence of prehospital cardiac arrest (0 vs. 16%) and RTS (7.54 ± 0.62 vs. 4.23 ± 2.34) were significantly different between groups. The area under the receiver operating characteristics curve was 0.93 ± 0.07 for the RTS, with a cutoff value of 6.3 (sensitivity = 94%, specificity = 82%) and 0.91 ± 0.07 for the Glasgow Coma Score, with a cutoff value of 12 (sensitivity = 88%; specificity = 85%). The logistic regression indicated that an RTS greater than 6.30 and a...
Glasgow Coma Score greater than 13 were independent predictors of a high Ps (table 3).

Figure 3 shows the distribution of Ps in the low-Ps, high-Ps, and intermediate-Ps groups. Sixty-seven patients (19%) were included in the low-Ps group, 62 (18%) in the intermediate-Ps group, and 221 (63%) in the high-Ps group. Using these selected populations, the number of patients to be included in a trial when considering the global percentage of survivors or the individual value of Ps are shown in table 4.

### Table 4. Selected Trauma Populations: Discrepancies between the Number of Patients (N) To Include in a Trial (α = 0.05, β = 0.10) When Considering the Global Percentage of Survivors (Global) or the Individual Value (Individual) of the Probability of Survival (Ps)

<table>
<thead>
<tr>
<th>Expected Drug Effect</th>
<th>Control</th>
<th>+10%</th>
<th>+20%</th>
<th>+30%</th>
<th>+50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Ps</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global</td>
<td>% of survivors</td>
<td>15.5</td>
<td>17.0</td>
<td>18.6</td>
<td>20.1</td>
</tr>
<tr>
<td>N</td>
<td>—</td>
<td>25,158</td>
<td>6,054</td>
<td>2,816</td>
<td>1,050</td>
</tr>
<tr>
<td>Individual</td>
<td>% of survivors</td>
<td>15.5</td>
<td>16.2</td>
<td>17.0</td>
<td>19.5</td>
</tr>
<tr>
<td>N</td>
<td>—</td>
<td>113,862</td>
<td>20,528</td>
<td>2,998</td>
<td>1,418</td>
</tr>
<tr>
<td>Intermediate Ps</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global</td>
<td>% of survivors</td>
<td>67.3</td>
<td>70.6</td>
<td>73.8</td>
<td>77.1</td>
</tr>
<tr>
<td>N</td>
<td>—</td>
<td>8,140</td>
<td>2,002</td>
<td>834</td>
<td>264</td>
</tr>
<tr>
<td>Individual</td>
<td>% of survivors</td>
<td>67.3</td>
<td>68.6</td>
<td>69.9</td>
<td>74.4</td>
</tr>
<tr>
<td>N</td>
<td>—</td>
<td>53,864</td>
<td>10,798</td>
<td>1,348</td>
<td>564</td>
</tr>
<tr>
<td>High Ps</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global</td>
<td>% of survivors</td>
<td>94.8</td>
<td>95.3</td>
<td>95.8</td>
<td>96.4</td>
</tr>
<tr>
<td>N</td>
<td>—</td>
<td>78,316</td>
<td>18,424</td>
<td>6,652</td>
<td>2,170</td>
</tr>
<tr>
<td>Individual</td>
<td>% of survivors</td>
<td>94.8</td>
<td>94.9</td>
<td>95.2</td>
<td>96.1</td>
</tr>
<tr>
<td>N</td>
<td>—</td>
<td>2,049,664</td>
<td>101,078</td>
<td>8,522</td>
<td>3,018</td>
</tr>
</tbody>
</table>

Study used the Selected Population of Trauma Patients with Low (LPs group), High (HPs group), or Intermediate (IPs group) Probability of Survival. Several hypotheses were tested regarding the expected effect of the drug on Ps (+10, +20, +30, and +50%). See text and figure 1 for explanation.

### Other Distributions

Figure 4 shows the distributions (uniform or J shape) of Ps generated by the computer in 1,000 theoretical patients. As shown in table 5, there were some discrepancies between the number of patients to be included in a trial when considering the global percentage of survivors or the individual value of Ps in both groups. For a drug expected to increase Ps by 20%, the increase in the number of patients to be included was 22-fold in the bimodal distribution (table 1), 3.2-fold in the uniform distribution, 2.5-fold in the J-shape distribution (table 5), and only 1.04-fold in the Gaussian distribution (table 2).

### Discussion

The current study demonstrated that the bimodal distribution of the Ps in trauma patients has major consequences on the main assumptions of hypotheses testing. Obviously, the power of randomized trials intended to demonstrate an improvement in survival was markedly overestimated. This problem also occurred in other...
types of distribution (uniform, J shape), although to a lesser degree, when compared with a bimodal distribution such as the one observed in trauma patients.

Our trauma population slightly differed from the MTOS population because we included more severe trauma patients. This discrepancy was expected, because only trauma patients who underwent severe trauma and/or were suspected to have severe trauma lesions were directly admitted in our unit. The senior physician in the SAMU system was responsible for this on-scene triage.8 The TRISS methodology has been widely used to assess Ps in trauma patients. The TRISS score has been criticized and other severity scores have been proposed, such as ASCOT or International Classification of Disease related scores.19,20 Three main limitations of the TRISS have been documented.21 First, there is a lack of homogeneity within the patient subcategory of penetrating injuries (i.e., gun shot vs. stab wounds). Second, there is an inability of the TRISS to predict the survival rate of patients suffering low falls. Third, the TRISS is unable to account for multiple severe injuries to a single part of the body. In our study, only blunt trauma patients were included. Patients suffering low falls were not included. Thus, the first two limitations did not seem to apply. However, patients with multiple injuries to a single part of the body did occur, so this limitation could have occurred in our study. This being said, the TRISS score has been widely used not only in the United States but also in Canada22 and in European countries23,24 and should be presently considered as the most reliable and validated method to predict survival rate in trauma patients.

By calculating the number of patients to include in a simulated randomized trial, we observed marked differences when the hypotheses were based on the percentage of survivors in the population or on the individual Ps (table 1). The bimodal distribution of Ps in our population obviously explains this discrepancy. In fact, when considering the percentage of survivors in the population, we imply that most patients had nearly the same prognosis, which is thought to be reflected by the observed percentage of survivors. Mathematically, multiplying the mean Ps (i.e., the percentage of survivors) by x percent (the expected drug effect) is not equivalent to taking the mean of the multiplication of individual Ps by x percent, except in the case where all patients have exactly the same Ps. As expected, when using a Gaussian distribution of Ps in a theoretical population (fig. 2), the discrepancy between the two modes of calculation of the number of patients was very moderate (table 2).
compared with that observed in the bimodal distribution (table 1). Indeed, in a bimodal distribution, the mean Ps (equivalent to the percentage of survivors) does not appropriately describe the distribution of Ps in this population: the mean Ps (0.75) was very different from the median Ps (0.94). Although the bimodal distribution of Ps in trauma patients has been previously described, we outline that the consequences on hypothesis testing were not, to date, appropriately drawn.

In an attempt to reduce the heterogeneity of our trauma population, we identified simple prehospital variables (Glasgow Coma Score and RTS), which were appropriately able to identify trauma patients with an intermediate Ps (table 3 and fig. 3B). The aim of this selection was to identify either patients with a high or low Ps. Using these selection criteria, the discrepancy between the two methods to calculate the number of patients to be included in a study was markedly reduced, especially in patients with an intermediate Ps (table 4).

Nevertheless, it should be pointed out that the number of patients to include remains very high because a pharmacologic intervention that could potentially increase Ps by 50% is not very realistic. Because patients from the intermediate-Ps group represented only 18% of trauma patients, it suggests that a multicenter design is probably relevant.

Trauma is unique as a disease. Indeed, most deaths occur early (80% within 24 h), and a precise measure of Ps requires a complete assessment of trauma lesions that usually cannot be obtained in the early phase. In contrast, it is usually thought that a pharmacologic intervention expected to improve survival rate should be administered as soon as possible, i.e., before accurate determination of Ps. These characteristics contrast dramatically with cancer, where a precise assessment of the prognosis can be performed before randomization, enabling us to compare groups with relatively homogeneous prognoses. A randomized trial testing a new chemotherapy that would have included patients with skin epithelial cancer as well as those with metastatic carcinoma of the pancreas would be considered as a nonsense. However, this situation is suspected to have occurred in some of the randomized trials performed in trauma. Heterogeneity is the cornerstone of the problem. It should be pointed out that even in cancer research where prognostic factors have been extensively used for stratification, heterogeneity is now recognized as a factor that leads to a substantial loss of power.

Our study may have equal consequences for clinical researchers, health authorities, or pharmaceutical companies. First, our study indicates that the number of patients should be carefully determined in a randomized trial in trauma and should consider the characteristics of the distribution of Ps. When the number of patients to be included is definitely nonrealistic, alternative approaches should probably be considered. Using a three-variable (predicted risk of mortality, drug treatment, and predicted risk of mortality-drug treatment interaction) log-normal regression model, Knaus et al. were able to demonstrate the efficacy of an anticytokine therapy in sepsis. Second, depending on the nature of the problem, information provided in table 4 may facilitate decision-making in different situations. Care providers or funders may be interested in conducting a trial in patients with a high Ps because most of trauma patients belong to this group, even if the size of the trial is large. Pharmaceutical companies may be rather interested in conducting a trial in patients with an intermediate Ps because the size of the trial should be the lower and because there are numerous arguments to suggest that this population should benefit most from a pharmaceutical intervention (resuscitation fluid, immunomodulation, etc.). Prehospital or emergency physicians may be rather interested in conducting a trial in patients with a low Ps because their survival is critically dependent on the efficiency of the organization of the emergency systems. Third, because of the bimodal distribution of Ps and its consequences on the power of a study, the mortality rate may be an unattainable end point in many situations. Regulatory agencies should include this information when discussing clinically relevant end points with pharmaceutical companies. In such situations, other end points should be explored to promote progress in drug therapy. For example, the possibility of using a composite end point (mortality, sepsis, renal failure, acute respiratory distress syndrome, and multiple organ failure) could be considered.

We suggest that the problem identified in the current study might not only occur in trauma trials but also in other disorders affecting critically ill patients, such as acute respiratory distress syndrome or sepsis. Indeed, numerous large randomized trials conducted in the critical care setting in the past decade failed to provide positive results. For example, randomized trials have failed to demonstrate any significant benefit of nitric oxide in acute respiratory distress syndrome, whereas it is known to markedly improve gas exchange. This topic should probably be reconsidered in the light of the current findings. Establishing accurate predictors of mortality for these diseases and verifying the nature of the distribution of Ps should be a high priority before undergoing randomized trials. Indeed, although the influence of the distribution of Ps is less important in other types of distribution (table 5) than in a bimodal distribution, it clearly remains clinically relevant. Thus, our study might have important consequences for the design of randomized trials in critical care in the future.

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