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Are Blood Transfusions Associated with Greater Mortality Rates?

Results of the Sepsis Occurrence in Acutely Ill Patients Study

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Background: **Studies have suggested worse outcomes in transfused patients and improved outcomes in patients managed with restricted blood transfusion strategies. The authors investigated the relation of blood transfusion to mortality in European intensive care units (ICUs).**

Methods: **The Sepsis Occurrence in Acutely Ill Patients study was a multicenter, observational study that included all adult patients admitted to 198 European ICUs between May 1 and May 15, 2002 and followed them until death, until hospital discharge, or for 60 days. Patients were classified depending on whether they had received a blood transfusion at any time during their ICU stay.**

Results: **Of 3,147 patients, 1,040 (33.0%) received a blood transfusion. These patients were older (mean age, 62 *vs.* 60 yr; $P = 0.035$) and were more likely to have liver cirrhosis or hematologic cancer, to be a surgical admission, and to have sepsis. They had a longer duration of ICU stay (5.9 *vs.* 2.5 days; $P < 0.001$) and a higher ICU mortality rate (23.0 *vs.* 16.3%; $P < 0.001$) but were also more severely ill on admission (Simplified Acute Physiology Score II, 40.2 *vs.* 34.7; $P < 0.001$; Sequential Organ Failure Assessment score, 6.5 *vs.* 4.5; $P < 0.001$). There was a direct relation between the number of blood transfusions and the mortality rate, but in multivariate analysis, blood transfusion was not significantly associated with a worse mortality rate. Moreover, in 821 pairs matched according to a propensity score, there was a higher 30-day survival rate in the transfusion group than in the other patients ($P = 0.004$).**

Conclusion: **This observational study does not support the view that blood transfusions are associated with increased mortality rates in acutely ill patients.**

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ALTHOUGH blood transfusion can be life-saving in extreme circumstances, in the absence of life-threatening hemorrhage, the topic of transfusion is somewhat controversial. Blood transfusions have well-recognized problems, including the need to type and cross-match, and the potential transmission of diseases, such as hepatitis B and C, human immunodeficiency virus, and prions.[1] Transfusion-induced immunosuppression is also a potentially important factor.[2] However, anemia too has its own problems and is associated with increased morbidity and mortality.[3,4] Determining who and when to transfuse is thus a challenge for intensivists, and recent years have seen continuing debate and discussion regarding the optimal transfusion "trigger."

In an important Canadian trial, Hebert *et al.*[5] randomly assigned 838 critically ill patients to either a liberal protocol where transfusions were administered to maintain hemoglobin levels between 10 and 12 g/dl or a restricted strategy where hemoglobin levels were kept between 7 and 9 g/dl. Overall, the 30-day mortality rates were 19% in the restricted group and 23% in the liberal transfusion group (P = not significant), and these differences were significant in younger (age <55 yr, 5.7 *vs.* 13%; $P = 0.02$) and less sick (Acute Physiology and Chronic Health Evaluation II score ≤ 20, 8.7 *vs.* 16.1%; $P = 0.03$) patients. The overall hospital mortality was significantly less in the restricted transfusion group (22 *vs.* 28%; $P = 0.05$). These results had a definite influence on intensive care unit (ICU) practice, raising serious questions about the hitherto widely used 10 g/dl transfusion trigger, and encouraging intensivists to limit somewhat the use of transfusions. More recently, the Anemia and Blood Transfusion in Critical Care (ABC) study,[6] an epidemiologic survey of 3,534 patients in 146 western European ICUs, confirmed increased mortality rates (ICU and hospital) in transfused patients. The increased mortality rates were maintained in a propensity analysis with patients matched for age, sex, disease severity, admitting hemoglobin level, recent history of hemorrhage or anemia, and hospital duration of stay. Here, the 28-day mortality rate was 22.7% in transfused patients and 17.1% in those who did not receive a transfusion ($P = 0.02$). In a multivariate analysis, receipt of a blood transfusion increased the risk of dying by a factor of 1.4.[6] Similar results were reported in a multicenter observational study of 4,892 patients in 284 ICUs across the United States, with the number of erythrocyte transfu-

sions a patient received during the study being independently associated with longer ICU and hospital durations of stay and an increase in mortality.[7] Studies in trauma patients,[8] in patients with burns,[9] in patients undergoing cardiac surgery,[10] and in patients with acute coronary syndromes[11] have also suggested increased mortality rates associated with transfusions in these groups of patients. Finally, in a recent study in pediatric critically ill patients, Lacroix *et al.*[12] reported that restricting transfusions to patients with a hemoglobin threshold of 7 g/dl was associated with decreased transfusion requirements and no increase in adverse events compared with patients transfused according to a trigger of 9.5 g/dl.

This is an important issue, and large, randomized controlled trials are necessary to determine what the current rules of play should be; in the meanwhile, epidemiologic studies can provide useful information on the current status of transfusion practice and on associated outcomes, provided they include multivariate analyses. The Sepsis Occurrence in Acutely Ill Patients (SOAP) study[13] was designed to determine current ICU practice and the effects of that practice on outcomes for various topics, including blood transfusion.

Materials and Methods

Study Design

The SOAP study was a prospective, multicenter, observational study designed to evaluate the epidemiology of sepsis and other characteristics of ICU patients in European countries and was initiated by a working group of the European Society of Intensive Care Medicine (Brussels, Belgium). Institutional recruitment for participation was by open invitation from the study steering committee. Because this epidemiologic observational study did not require any deviation from routine medical practice, institutional review board approval was either waived or expedited in participating institutions, and informed consent was not required. We included all adult patients (older than 15 yr) admitted to the participating centers (see the appendix for a list of participating countries and centers) between May 1 and May 15, 2002. Patients were followed up until death, until hospital discharge, or for 60 days. Those who stayed in the ICU for less than 24 h for routine postoperative observation were excluded.

Data Management

Data were collected prospectively using preprinted case report forms. Detailed instructions, explaining the aim of the study, instructions for data collection, and definitions for various important items were available for all participants on a dedicated Web site before starting data collection and throughout the study period. The steering committee processed all queries during data collection.

Data were entered centrally by medical personnel using the Statistical Package for Social Sciences (SPSS) version 11.0 for Windows (SPSS Inc., Chicago, IL). A random sample of 5% of the data were reentered by a different encoder and revised by a third one; a consistency of more than 99.5% per variable and 98.5% per patient was observed during the whole process of data entry. In case of inconsistency, data were verified and corrected. Daily frequency tables were revised for all variables, and the investigators were queried when data values were either questionable or missing for required fields. Data collection on admission included demographic data and comorbid diseases. Clinical and laboratory data for the Simplified Acute Physiology Score II[14] were reported as the worst value within 24 h after admission. A daily evaluation of organ function that was based on a set of laboratory and clinical parameters according to the Sequential Organ Failure Assessment score[15] was performed, with the most abnormal value for each of the six organ systems (respiratory, renal, cardiovascular, hepatic, coagulation, and neurologic) being collected on admission and every 24 h thereafter. For a single missing value, a replacement was calculated using the mean value of the results on either side of the absent result. When first or last values were missing, the nearest value was carried backward or forward, respectively. When more than one consecutive result was missing, it was considered to be a missing value in the analysis. Circulatory shock was defined as a cardiovascular Sequential Organ Failure Assessment score greater than 2, *i.e.*, the use of dopamine at a dose greater than 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and/or epinephrine or norepinephrine at any dose. Sepsis, severe sepsis, and septic shock were defined according to the American College of Chest Physicians–Society of Critical Care Medicine consensus conference definitions.[16]

Statistical Methods

Data were analyzed using SPSS version 11.0 for Windows and SAS version 9.1.3 software (SAS Institute Inc., Cary, NC). Descriptive statistics were computed for all study variables. The Kolmogorov–Smirnov test was used, and stratified distribution plots were examined to verify the normality of distribution of continuous variables. Nonparametric tests of comparison were used for variables evaluated as not normally distributed. Difference testing between groups was performed using the two-tailed *t* test, Mann–Whitney U test, chi-square test, and Fisher exact test as appropriate. A Bonferroni correction was performed for multiple comparisons.

To determine the relative hazard of death due to blood transfusions, we performed a multivariate Cox proportional hazard model in the overall population with time to in-hospital death right censored at 30 days as the dependent factor, to avoid a positive effect of early mortality on duration of stay. Variables considered for

Table 1. The Logistic Regression Model Used to Calculate the Propensity Score*

	Coefficient	SEM	Wald	Odds Ratio (95% CI)	*P* Value
Age, per year	0.001	0.003	0.128	1.01 (0.99–1.02)	0.720
Female sex	0.203	0.088	5.272	1.23 (1.03–1.46)	0.022
Medical admission	−1.026	0.094	118.151	0.36 (0.29–0.43)	<0.001
Trauma	0.863	0.163	27.956	2.37 (1.72–3.26)	<0.001
Solid cancer	−0.035	0.126	0.076	0.97 (0.76–1.24)	0.783
Hematologic cancer	0.573	0.282	4.115	1.77 (1.02–3.08)	0.043
COPD	0.148	0.138	1.153	1.16 (0.89–1.52)	0.283
Cirrhosis	0.649	0.221	8.610	1.91 (1.24–2.95)	0.003
Heart failure	−0.011	0.142	0.006	0.99 (0.75–1.31)	0.940
Diabetes	0.145	0.163	0.793	1.16 (0.84–1.59)	0.373
SAPS II, per point	0.017	0.004	15.490	1.02 (1.01–1.03	<0.001
Sepsis on admission	0.378	0.166	5.217	1.46 (1.06–2.02)	0.022
SOFA respiratory, per point	0.010	0.033	0.089	1.01 (0.95–1.08)	0.765
SOFA hepatic, per point	0.147	0.054	7.440	1.16 (1.04–1.38)	0.006
SOFA hematologic, per point	0.347	0.049	49.776	1.42 (1.29–1.56)	<0.001
SOFA renal, per point	0.055	0.037	2.170	1.06 (0.98–1.136)	0.141
SOFA CNS, per point	−0.195	0.039	24.840	0.82 (0.76–0.89)	<0.001
SOFA cardiovascular, per point	0.226	0.036	38.962	1.25 (1.67–1.35)	<0.001
Mechanical ventilation	0.309	0.110	7.918	1.36 (1.09–1.69)	0.005
Hemofiltration	0.118	0.273	0.187	1.13 (0.66–1.92)	0.666
Hemodialysis	0.343	0.341	1.010	1.41 (0.72–2.75)	0.315
Constant	−0.253	0.634	0.159	—	—

* Logistic regression analysis with the need for blood transfusion at any time during the intensive care unit stay as the dependent variable. All included variables represents those collected on the day of admission to the intensive care unit. Interaction terms, pairwise, between comorbidities and between comorbidities and type of admission were tested; none of them were significant, and they were not introduced in the final model. Hosmer and Lemeshow goodness-of-fit $\chi^2 = 13.2$ ($P = 0.21$). Nagelkerke $R^2 = 0.256$.

CI = confidence interval; CNS = central nervous system; COPD = chronic obstructive pulmonary disease; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment.

the Cox regression analysis included age, sex, comorbid diseases, Simplified Acute Physiology Score II and Sequential Organ Failure Assessment score on admission, the type of admission (medical or surgical), the presence of sepsis during the ICU stay, and the country of origin. All variables were introduced in the model after exclusion of the presence of colinearity, based on $R^2 > 0.7$. The time-dependent covariate method was used to check the proportional hazard assumption of the model; an extended Cox model was constructed, adding interaction terms that involve time, *i.e.*, time-dependent variables, computed as the by-product of time and individual covariates in the model (time × covariate). Individual time-dependent covariates were introduced one by one and in combinations in the extended model, none of which were found to be significant (Wald chi-square statistics). To reduce the number of countries in the final model, the country effect was tested in a separate Cox regression model as a categorical variable with hospital mortality right censored at 30 days as the dependent variable. All countries that were not significant at $P < 0.2$ were reduced to one category, and all of the countries were introduced in the final model. The need for blood transfusion was introduced in the model as a categorical variable.

Propensity scores[17] were obtained through logistic regression of patient characteristics on blood transfusion status, *i.e.*, need for blood transfusion as the dependent factor (table 1). The propensity score was calculated as the probability based on the final model. A greedy matching technique[18] was used to match individual patients who received a blood transfusion at any time with individual patients who did not, based on propensity scores. The best-matched propensity score was identical to five digits. Once a match was made, the control patient was removed from the pool. This process was then repeated using four-digit matching, then three-digit matching, and so on. The process proceeded sequentially to a single-digit match on propensity score. If a match was not obtained at this point, the patient who had received a blood transfusion was excluded.

The hazard of death was compared using an analysis of paired failure times[19] with SAS Proc PHREG (SAS Institute Inc.) in the propensity score–matched pairs. To avoid survivor bias, an extended Cox proportional hazard model was constructed using the aforementioned covariates and adjusting for erythrocyte transfusion as a time-dependent covariate in the whole population and in the propensity-matched groups. All statistics were two-tailed, and $P < 0.05$ was considered to be significant.

Results

Of 3,147 patients, 1,040 (33.0%) received a blood transfusion and 2,107 (67.0%) did not. Table 2 presents the principal clinical data of the patients according to the transfusion status. Patients who received blood transfusions were somewhat older (mean age, 62 *vs.* 60 yr;

Table 2. Characteristics of the Study Group

	All Patients (n = 3,147)	Stratified According to Transfusion Status		
		No Transfusion (n = 2,107)	Transfusion (n = 1,040)	*P* Value
Age,* mean ± SD, yr	61 ± 17	60 ± 18	62 ± 17	0.035
Male sex,† n (%)	1,920 (61.7)	1,293 (62.0)	627 (61.0)	0.570
Chronic diseases, n (%)				
COPD	340 (10.8)	228 (10.8)	112 (10.8)	0.965
Cancer	415 (13.2)	267 (12.7)	148 (14.2)	0.224
Heart failure	307 (9.8)	190 (9.0)	117 (11.3)	0.047
Diabetes	226 (7.2)	146 (6.9)	80 (7.7)	0.435
Liver cirrhosis	121 (3.8)	54 (2.6)	67 (6.4)	<0.001
Hematologic cancer	69 (2.2)	30 (1.4)	39 (3.8)	<0.001
HIV/AIDS	26 (0.9)	14 (0.7)	12 (1.2)	0.225
Medical admissions, n (%)	1,759 (55.9)	1,352 (64.2)	407 (39.1)	<0.001
SAPS II, mean ± SD	36.5 ± 17.1	34.7 ± 17.1	40.2 ± 16.5	<0.001
SOFA score, mean ± SD				
Initial SOFA score	5.1 ± 3.8	4.5 ± 3.6	6.5 ± 3.9	<0.001
Mean SOFA score	4.5 ± 3.5	3.9 ± 3.3	5.8 ± 3.5	<0.001
Maximum SOFA score	6.6 ± 4.4	5.5 ± 4.0	8.7 ± 4.5	<0.001
ICU stay, median [IQR]	3.0 [1.7–6.9]	2.5 [1.4–4.9]	5.9 [2.6–14.3]	<0.001
Hospital stay,‡ median [IQR]	15 [7–32]	13.0 [6.0–25.0]	23.0 [12.0–46.0]	<0.001
Infection, n (%)	1,177 (37.4)	622 (29.5)	555 (53.4)	<0.001
On admission	777 (24.7)	446 (21.2)	331 (31.8)	<0.001
ICU acquired	279 (8.9)	113 (5.4)	166 (16.0)	<0.001
Severe sepsis, n (%)	930 (29.6)	447 (21.2)	483 (46.4)	<0.001
On admission	552 (17.5)	291 (13.8)	261 (25.1)	<0.001
Septic shock, n (%)	462 (16.5)	179 (8.5)	283 (27.2)	<0.001
On admission	243 (7.7)	106 (5.0)	137 (13.2)	<0.001
ICU mortality,§ n (%)	583 (18.5)	344 (16.3)	239 (23.0)	<0.001
Hospital mortality,‡ n (%)	747 (23.7)	436 (21.0)	311 (30.2)	<0.001

Missing data: * 9 missing age (6 with no transfusion and 3 with transfusion). † 35 missing sex (23 with no transfusion and 12 with transfusion). ‡ 45 missing (35 with no transfusion and 10 with transfusion). § 1 missing (with transfusion).

AIDS = acquired immunodeficiency syndrome; COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus; ICU = intensive care unit; IQR = interquartile range; SAPS = Simplified Acute Physiology Score; SOFA = sequential organ failure assessment.

$P = 0.035$) and were more likely to have liver cirrhosis or hematologic cancer, to be a surgical admission, and to have an infection and sepsis. Transfused patients had a longer duration of ICU stay (5.9 *vs.* 2.5 days; $P < 0.001$) and a higher ICU mortality rate (23.0 *vs.* 16.3%; $P < 0.001$) but they were also more severely ill, as shown by a higher Simplified Acute Physiology Score II (40.2 *vs.* 34.7; $P < 0.001$) and a higher Sequential Organ Failure Assessment score (6.5 *vs.* 4.5; $P < 0.001$) on admission than the other patients (table 2). As anticipated, there was a direct relation between the number of blood transfusions and the mortality rate (table 3). Patients with longer ICU stays were more often transfused and received more units of blood (table 4). When asked whether they had been using leukodepleted blood at the time of the study, 76% of centers who replied stated that they had been routinely using leukodepleted blood, 19% stated that they had not been using leukodepleted blood, and 4% did not know.

In a multivariate Cox regression analysis including sex and age, type of admission, main medical history (including cancer or hematologic cancer, cirrhosis, chronic lung disease), fluid balance, Simplified Acute Physiology Score II, and severity of organ dysfunction on admission

Table 3. Simplified Acute Physiology Score II, ICU and Hospital Mortality According to the Number of Transfused Units during ICU Stay

Units Transfused	Frequency (%)	SAPS II	ICU Mortality (%)	Hospital Mortality (%)
1	144 (13.8)	37.4 ± 16.7	24 (16.7)	32 (22.2)
2	291 (28.0)	38.0 ± 15.9	54 (18.6)	77 (26.7)*
3	114 (11.0)	40.8 ± 15.5	21 (18.4)	32 (28.6)†
4	123 (11.8)	40.7 ± 18.1	33 (26.8)	42 (34.1)†
>4	368 (35.4)	42.8 ± 16.4	107 (29.2)‡	128 (34.8)*

Missing data: * 3 missing. † 2 missing. ‡ 1 missing.

ICU = intensive care unit; SAPS = Simplified Acute Physiology Score.

Table 4. Transfusion Rate and Mean Number of Units Transfused According to ICU Duration of Stay

ICU Duration of Stay, days	Number	Transfused (%)	Mean Units Transfused ± SD
All patients	3,147	1,040 (33.0)	5.0 ± 5.8
≤2	1,111	213 (19.2)	3.4 ± 3.7
>2	2,036	827 (40.6)	6.0 ± 6.2
>7	775	459 (59.2)	7.9 ± 7.5

ICU = intensive care unit.

as assessed by Sequential Organ Failure Assessment score, erythrocyte transfusion was not associated with an increased relative hazard of death at 30 days (relative hazard = 0.89; 95% confidence interval [CI] = 0.76–1.05; $P = 0.159$; table 5).

Eight hundred twenty-one pairs were matched according to the propensity score: 349 pairs (42.5%) at five digits, 342 pairs (41.7%) at four digits, and 130 pairs (15.8%) at three digits. ICU and hospital mortality rates were similar between transfused patients for whom matches could be identified and those who could not be matched (29 *vs.* 34.6%; $P = 0.134$ and 22.1 *vs.* 26.5%; $P = 0.176$, respectively). Baseline characteristics, severity scores, incidence of sepsis syndromes, and invasive procedures on the day of ICU admission were similar between the matched groups (table 6). There was a lower 30-day hazard of death in the transfused group compared with the other patients (hazard ratio = 0.73; 95% CI = 0.59–0.90; $P = 0.004$; fig. 1).

In an extended Cox proportional hazard analysis, adjusting for erythrocyte transfusion as a time-dependent variable, erythrocyte transfusion was associated with a decreased relative hazard of death at 30 days in the whole population (relative hazard = 0.69; 95% CI = 0.48–1.01; $P = 0.055$) and in the propensity score–matched groups (relative hazard = 0.57; 95% CI = 0.36–0.9; $P = 0.016$).

Discussion

In this observational study, patients who received blood transfusions had higher ICU and hospital mortality rates than those who did not. This may be expected because blood transfusions are an index of severity of illness. However, after adjusting for confounding factors using a Cox regression model or propensity score case matching, patients who were transfused did not have higher mortality rates than those who were not transfused. In fact, from the extended Cox proportional hazard analysis, transfused patients had a better survival.

Although a prospective, controlled randomized clinical trial is, of course, the optimal means of demonstrating cause and effect, epidemiologic studies with adequate multivariable analysis can provide valuable information. A similar approach has been taken to show that aspirin administration may reduce complications after coronary artery bypass grafting.[20] Our study is limited by its observational design. However, the multivariate regression analysis and

Table 5. Multivariate Cox Proportional Hazard Analysis with Time to In-hospital Mortality at 30 Days as the Dependent Variable

	Coefficient	SE	Relative Hazard (95% CI)	*P* Value
Age, per year	0.012	0.003	1.01 (1.01–1.02)	<0.001
Female	0.092	0.078	1.1 (0.94–1.28)	0.236
Medical admission	0.383	0.087	1.47 (1.24–1.74)	<0.001
Cancer	0.256	0.108	1.29 (1.05–1.6)	0.018
Hematologic cancer	0.412	0.173	1.51 (1.08–2.12)	0.017
COPD	0.148	0.113	1.16 (0.93–1.45)	0.191
HIV infection	0.130	0.389	1.14 (0.53–2.44)	0.739
Cirrhosis	0.792	0.149	2.21 (1.65–2.95)	<0.001
Heart failure	0.108	0.123	1.11 (0.88–1.42)	<0.380
Diabetes	−0.036	0.137	0.96 (0.74–1.26)	0.791
SAPS II, per point	0.041	0.003	1.04 (1.04–1.05)	<0.001
Sepsis on admission	−0.039	0.080	0.96 (0.82–1.13)	0.625
SOFA score on admission, per point	0.058	0.013	1.06 (1.03–1.09)	<0.001
Erythrocyte transfusion	−0.012	0.083	0.89 (0.76–1.05)	0.159
Country*				
1	0.432	0.287	1.54 (0.88–2.7)	0.132
2	−0.739	0.431	0.48 (0.21–1.11)	0.086
3	−0.410	0.183	0.66 (0.46–0.95)	0.025
4	1.141	0.586	3.13 (0.99–9.87)	0.051
5	0.358	0.183	1.43 (0.99–2.05)	0.051
6	0.826	0.220	2.28 (1.48–3.51)	<0.001
7	0.945	0.367	2.57 (1.25–5.28)	0.01
8	−0.362	0.266	0.69 (0.41–1.17)	0.173
All other countries	−0.076	0.180	0.93 (0.65–1.32)	0.675

* Each category is compared with all other categories.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment.

Table 6. Patient Characteristics by Transfusion Status for the Propensity-matched Patients

	No Transfusion (n = 821)	Transfusion (n = 821)	*P* Value
Age, mean ± SD, yr	62.2 ± 17.1	61.8 ± 16.9	0.511
Male sex, n (%)	482 (58.7)	499 (60.8)	0.392
Chronic diseases, n (%)			
COPD	108 (13.2)	92 (11.2)	0.227
Cancer	135 (16.4)	126 (15.3)	0.544
Heart failure	92 (11.2)	93 (11.3)	0.938
Diabetes	58 (7.1)	67 (8.2)	0.402
Liver cirrhosis	44 (5.4)	42 (5.1)	0.825
Hematologic cancer	21 (2.6)	28 (3.4)	0.310
HIV/AIDS	5 (0.6)	9 (1.1)	0.386
Medical admissions, n (%)	359 (43.7)	363 (44.2)	0.842
Trauma, n (%)	70 (8.5)	75 (9.1)	0.664
SAPS II, mean ± SD	38.5 ± 18.6	39.0 ± 16.4	0.308
Admission SOFA score, mean ± SD	5.8 ± 4.0	5.9 ± 3.8	0.455
Admission SOFA scores, median [IQR]			
Respiratory	0.0 [0.0–3.0]	0.0 [0.0–3.0]	0.970
Hepatic	0.0 [0.0–1.0]	0.0 [0.0–1.0]	0.943
Coagulation	0.0 [0.0–1.0]	0.0 [0.0–1.0]	0.623
Renal	0.0 [0.0–2.0]	0.0 [0.0–2.0]	0.386
CNS	0.0 [0.0–2.0]	0.0 [0.0–2.0]	0.369
Cardiovascular	1.0 [0.0–3.0]	1.0 [0.0–3.0]	0.775
Sepsis syndromes on admission			
Sepsis	246 (30.0)	244 (29.7)	0.914
Severe sepsis	174 (21.2)	180 (21.9)	0.719
Septic shock	80 (9.7)	78 (9.5)	0.867
Procedures on admission, n (%)			
Mechanical ventilation	565 (68.8)	559 (68.1)	0.727
Hemofiltration	26 (3.2)	26 (3.2)	1.000
Hemodialysis	11 (1.3)	17 (2.1)	0.253
ICU mortality, %	186 (22.7)	181 (22.1)*	0.777
Hospital mortality, n (%)	235 (29.1)†	236 (29.0)‡	0.655

Missing data: * 1 missing. † 13 missing. ‡ 8 missing.

AIDS = acquired immunodeficiency syndrome; CNS = central nervous system; COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus; ICU = intensive care unit; IQR = interquartile range; SAPS = Simplified Acute Physiology Score; SOFA = sequential organ failure assessment.

the propensity score matching yielded similar results. Nevertheless, other confounders not reported in our study could have contributed to either more beneficial or more deleterious effects of erythrocyte transfusion. Although the SOAP study was primarily designed to study the incidence of sepsis, the current substudy was one of several analyses planned before the SOAP study was conducted.

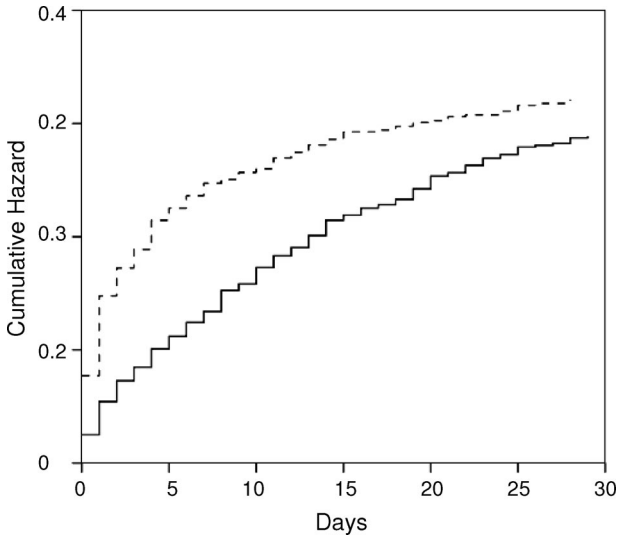

Fig. 1. Cumulative hazard of death in the propensity-matched groups (*solid line* = transfusion; *dashed line* = no transfusion). Hazard ratio = 0.73; 95% confidence interval = 0.59–0.90; *P* = 0.004.

Importantly, we used exactly the same approach in the ABC study[6] but found different results. The study protocols between these two studies (ABC and SOAP) were very similar, with the only possible difference being that Eastern European countries contributed a minority of patients in the current study and none in the ABC study; owing to the small numbers of patients involved, we do not believe this could have influenced the results substantially. Data analysis was also performed in exactly the same way.

Hence, differences are likely to be due to differences in the blood transfusions *per se*. Heightened awareness of the possible risks of blood transfusion have led to changes in blood preparation so that blood transfusions are perhaps safer today in terms of viral transmission than they were a decade ago. Leukodepletion, which may reduce some of the negative immunosuppressive effects of transfusions, has also been widely implemented. The leukocyte component of transfused blood has been implicated in some of the adverse effects associated with blood transfusion, including transfusion-re-

lated immunomodulation and transfusion-related acute lung injury. Leukoreduction is a process in which the leukocyte component is deliberately reduced by centrifugation or filtration, thus potentially limiting some of these effects. Leukoreduction is also effective in reducing the transmission of cell-associated viruses.[21]

In the ABC study, few data were collected regarding leukodepleted blood (46% of centers indicated that they used leukodepleted blood most of the time, 35% used it some of the time, and 19% never used it), showing simply that it was not widely used in Europe at that time. In the current SOAP study, 76% of centers who replied were routinely using leukodepleted blood, demonstrating that leukodepleted blood is now much more commonly used across Europe. It is interesting to speculate that this may account for the differences between the previous ABC study and the current SOAP study. Hebert *et al.*[22] performed a study comparing patient outcomes before and after introduction of routine blood leukodepletion and noted reduced in-hospital mortality rates after the introduction of leukodepletion compared with the control period (6.19 *vs.* 7.03%; $P = 0.04$). Other studies have also shown improved survival rates with transfusion of leukodepleted compared with standard blood,[23–25] although these findings have not been universal.[26]

In conclusion, this study suggests that blood transfusions may no longer be associated with increased mortality rates and may be associated with improved survival. A randomized controlled study similar to that conducted by Hebert *et al.* between 1994 and 1997 is urgently needed to confirm these findings.

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