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Individual Probability of Allogeneic Erythrocyte Transfusion in Elective Spine Surgery

The Predictive Model of Transfusion in Spine Surgery

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Background: **The aim of this study was to generate a score based on preoperative characteristics and predictive of the individual probability of allogeneic erythrocyte transfusion in patients undergoing elective thoracolumbar spine surgery.**

Methods: **Two hundred thirty consecutive patients were retrospectively included over a 15-month period (derivation set). Preoperative independent predictors of erythrocyte transfusion from the day of surgery until postoperative day 5 were determined by multivariable analysis, from which a model of individual probability of transfusion was derived and prospectively validated in 125 additional patients (validation set).**

Results: **Four preoperative independent predictors were associated with transfusion: age older than 50 yr (adjusted odds ratio = 4.9 [2–13.5]), preoperative hemoglobin level less than 12 g/dl (adjusted odds ratio = 6.9 [3.1–17.2]), fusion of more than two levels (adjusted odds ratio = 6.7 [3.1–15.2]), and transpedicular osteotomy (adjusted odds ratio = 19.9 [5.6–98.2]). A 0–4 score (0 = no risk, 4 = maximum risk) predictive of allogeneic transfusion was derived by weighting estimate parameters for each variable in a multivariable logistic regression model. Discriminating capacity of the score was 0.86 [0.81–0.92] in the receiver operating characteristics in the derivation sample and 0.83 [0.75–0.91] in the validation sample. The observed transfusion rates in the validation set and the individual probabilities of erythrocyte transfusion from the score were well correlated ($y = 0.98x + 0.04$; $P < 0.0001$), and the observed differences were not statistically different (goodness-of-fit chi-square, $P = 0.125$). The score was also correlated with the number of erythrocyte units transfused (Spearman $\rho = 0.61$; $P < 0.0001$).**

Conclusion: **The Predictive Model of Transfusion in Spine Surgery may be useful in clinical practice to identify patients undergoing spine surgery at risk of massive bleeding and encourage erythrocyte-saving strategies in these patients.**

SPINE surgery is considered at risk of significant intraoperative bleeding in adult patients.[1–3] Important variability in intraoperative bleeding and erythrocyte requirements has been reported in adult patients undergoing major spine surgery.[4] Therefore, predicting the need for allogeneic erythrocyte transfusion based on patient preoperative characteristics would be helpful (1) to identify the patient subpopulations undergoing spine surgery at risk of massive perioperative transfusion and encourage erythrocyte-saving strategies in these patients, (2) to improve patient information on their perioperative erythrocyte requirements, and (3) to properly allocate blood and mobilize donors. In adult patients, several lines of evidence support that blood loss is particularly frequent and important during surgery of spine tumors and arthrodesis with posterior incision.[5–8] Age, anemia, osteotomy, and fusion have been identified as risk factors for bleeding in the context of spine surgery.[5–7] In most of these studies, however, measurement of blood loss was restricted to the intraoperative period, which is likely to have underestimated total perioperative blood loss. The goal of the current study was to derive a model based on transfusion up to 5 days after surgery. For this purpose, the Predictive Model of Transfusion in Spine Surgery (PMTSS), based on preoperative characteristics, was generated to determine the individual probability of erythrocyte transfusion in adult patients undergoing spine surgery.

Materials and Methods

The protocol was approved by the institutional review board of the Groupe Hospitalo-Universitaire de Paris Nord, Bichat University Hospital, Paris, France, and informed consent was obtained from patients.

Patients

Patients scheduled to undergo elective spine surgery were included. More than 50% of the patients had an American Society of Anesthesiologists physical status of II or III. Exclusion criteria were exclusive cervical spine surgery, one-level laminectomy, and polytrauma. Clinical management was at the discretion of the attending anesthesiologists and surgeons. In the operating room, patients were continuously monitored with electrocardioscopy, blood pressure monitoring, pulse oximetry, capnography, and esophageal temperature monitoring. A Bair Hugger device (Arizant, Eden Prairie, MN) was used, and fluids were warmed. Anesthesia was induced with propofol (1.5–2.5 mg/kg), sufentanil (15 μg), and atracurium (0.7 mg/kg) and was maintained by a continuous infusion of sufentanil and atracurium, with desflurane in a 50%–50% vol/vol O_2–N_2O gas mixture. The rate of the sufentanil infusion and the inspired concentration

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of desflurane were adjusted to maintain mean blood pressure between 50 and 70 mm Hg without decreasing lower than 20% of the preanesthetic value measured immediately before induction of anesthesia. Patients were carefully placed in the decubitus, procubitus, or knee–chest position, and great attention was paid to protect the eyes from mechanical injury and to preserve thorax movements and inferior vena cava venous return. Tranexamic acid (1-g bolus before incision followed by a 10-mg $\cdot$ kg^{-1} $\cdot$ h^{-1} continuous infusion until skin closure) was used at the discretion of the attending anesthesiologist. Hemoglobin blood levels were repeatedly checked by a Hemocue device (Hemocue France, Meaux, France) (at least before surgical incision and before erythrocyte administration). A cell saver for intraoperative blood salvage was available in the operating room. Transfusion criteria were those established on the basis of the recommendations made by the Agence Française de Sécurité Sanitaire des Produits de Santé and the American Society of Anesthesiologists Task Force on perioperative blood transfusion and adjuvant therapies.[9,10] Briefly, erythrocyte transfusion was initiated intraoperatively or postoperatively in all cases when the hemoglobin level was lower than 7 g/dl. It was considered for hemoglobin levels between 7 and 10 g/dl depending on the cardiopulmonary reserve of the patients. After completion of surgery, patients were discharged to the postanesthesia care unit. Postoperative thromboprophylaxis with low-molecular-weight heparin molecules were started as soon as the hemorrhagic risk seemed minimal.

Procedures

Data Collection. The following parameters were recorded from the patients' intraoperative and postoperative charts: demographic data (age, sex, weight, body mass index, American Society of Anesthesiologists physical status), duration of the surgery, number of levels,

Table 1. PMTSS Derivation Set: Variable Selection, Bivariate and Multivariable Analysis

	T(H)−	T(H)+	*P**	*P*†
n (% total)	156 (68)	74 (32)	—	
Patient variables				
Age, mean (SD), yr	56.0 (17.0)	61.5 (13.6)	0.015	0.0001
Sex, M/F, n	72/84	21/53	0.014	0.406
Weight, mean (SD), kg	74.9 (17.5)	66.5 (19.2)	0.001	0.216
Height, mean (SD), cm	168.8 (9.7)	163.1 (9.3)	< 0.0001	0.0547
BMI, mean (SD), k/m^2	26.1 (5.0)	24.9 (7.1)	0.148	—
Preoperative [Hb], mean (SD), g/dl	13.5 (1.3)	12.1 (1.6)	< 0.0001	< 0.0001
Underlying disease, all categories, n (%)	—	—	(< 0.0001)	—
Degenerative	100 (64)	24 (32)	< 0.0001	
Deformity	5 (3)	31 (42)	< 0.0001	
Tumor or infection	17 (11)	11 (15)	0.39	
Fracture	15 (10)	4 (5)	0.32	
Miscellaneous	19 (12)	4 (5)	0.16	
Surgery variables				
Redux, n (%)	25 (16)	24 (32)	0.006	0.573
Laminectomy levels, median [IQR], n	2 [1–3]	2 [1–3]	0.076	0.322
Fusion levels, median [IQR], n	1 [1–2]	3.5 [2–8]	< 0.0001	< 0.0001
Osteotomy, n (%)	3 (1.9)	26 (35)	< 0.0001	< 0.0001
Outcome variables				
Estimated blood loss, Ht = 30%, mean (SD), ml	1,280 (810)	3,300 (2,100)	< 0.0001	
Blood loss, mean (SD), % blood volume	27.9 (16.4)	82.1 (54.8)	< 0.0001	
Cell salvage, n (%)	9 (5)	25 (33)	< 0.0001	
Total erythrocytes, median [IQR], units	0 [0–0]	4 [2–8]	< 0.0001	
Day 5 postoperative [Hb], mean (SD), g/dl	10.7 (1.5)	10.1 (1.3)	0.0041	
PMTSS score, median [IQR]	2 [1–2]	3 [2–4]	< 0.0001	

1. Bivariate statistics (Fisher exact or chi-square test for frequencies, analysis of variance–Student *t* test or nonparametric Wilcoxon W for quantitative variables). Outcome variable perioperative homologous erythrocytes transfusion [T(H)±] is presented as "x" variable in table (see *P**).

2. Selection procedure of variables to include in the predictive multivariable model (see "Materials and Methods," "Procedures," "Derivation Set"): (a) Despite a significant association of underlying disease with transfusion, we chose to exclude this variable from multivariable analysis because of classification (as collected)–induced problems (fuzzy limits and difficulties to classify complex situations, and missing data; table 3). Moreover, further analysis revealed that strong association ("same information") could exist between disease and surgery (*e.g.*, deformity and osteotomy). (b) On the other hand, surgery-related variables (*e.g.*, blood loss, duration of surgery) were considered "intervening variables" (*i.e.*, on the pathway between a factor or "predictor," *e.g.*, surgery, and outcome transfusion) and were excluded from the multivariable analysis.

3. First multivariable statistical results (backward stepwise selection) with a reduced number of selected factors from bivariate analysis (see *P*†; outcome: transfusion defined as dependent "y" variable). By definition, these predictors related to the patient and planned surgery are always available preoperatively and objectively. Interactions between factors (not shown) were tested and considered nonsignificant. Factors were selected for the predictive model when $P < 0.05$ for adjusted variables.

BMI = body mass index; [Hb] = hemoglobin concentration; Ht = hematocrit; IQR = 25–75 interquartile range; PMTSS = Predictive Model of Transfusion in Spine Surgery; T(H)+ = homologous transfusion (erythrocytes); T(H)− = no homologous transfusion (erythrocytes).

type of operation (laminectomy, fusion, transpedicular osteotomy, osteosynthesis), underlying disease (posttraumatic, tumoral, septic, degenerative), intraoperative heart rate and blood pressure recorded every 10 min, necessity of reoperation, hemoglobin levels measured the day before surgery and on postoperative day 5, use of antifibrinolytics and epoetin, number of patients undergoing allogeneic (autologous, respectively) blood transfusion and number of allogeneic (autologous, respectively) erythrocyte units transfused, hemoglobin value immediately before transfusion, number of patients undergoing blood salvage, and volume of blood transfused. In the operating room, blood loss was estimated by hourly measurement of the volume of fluids aspirated by the surgeon and the hemoglobin level. Total erythrocyte loss (including both compensated and uncompensated loss) from the day of operation until postoperative day 5 was calculated by the appropriate formulas[11–13] as follows:

$$\text{Total erythrocyte loss} = \text{compensated} + \text{uncompensated erythrocyte loss}$$

$$\text{Uncompensated blood loss} = \text{total blood volume} \times (\text{hematocrit D0} - \text{hematocrit D5}),$$

where total blood volume = 70 ml/kg (65 ml/kg) in males (females),[18] hematocrit at day 0 (D0) corresponds to the preanesthetic hematocrit, and hematocrit D5 is the hematocrit on postoperative day 5.

$$\text{Compensated blood loss} = \text{sum of all erythrocyte received from all sources of transfusion (allogeneic, autologous, cell saver, } \textit{etc}.)\text{.}$$

A 250-ml erythrocyte unit with a hematocrit = 60% corresponds to 150 ml of pure erythrocytes (100% hematocrit). The mean hemoglobin level of blood obtained *via* the cell saver was 20 g/dl.

Therefore,

$$\text{Compensated erythrocyte loss} = (\text{number of erythrocyte units transfused} \times 150) + (\text{volume salvaged} \times 0.3).$$

Derivation Set. Between January 2006 and March 2007, all consecutive adult patients having undergone major elective thoracolumbar spine surgery were retrospectively included. We hypothesized that the population of inference would be future comparable patients in our center or possibly in other spine surgical centers. Because the transfusion rate in our spine surgical population was approximately 25%, and taking into consideration that we planned to derive a four- or five-variable logistic regression model, at least 50 patients receiving erythrocyte transfusion would need to be present in the sample, $50 \times 4 = 200$ patients at least to be enrolled.[14] Univariate descriptive statistics were performed to describe the patient demographics, characteristics of surgery, intraoperative and postoperative bleeding and erythrocyte transfusion (incidence and number of erythrocyte units). Bivariate statistics were used to examine the relation between the outcome variables (transfusion of erythrocytes) and other variables related to patients and/or surgery. Multivariable analysis was performed by backward stepwise selection of a restricted number of independent variables selected from the bivariate analysis.[15] Only independent preoperative variables related either to the patients (age, sex, body mass index, weight, size, preoperative hemoglobin level) or to surgery (reoperation, number of levels for laminectomy, number of levels for fusion, osteotomy) were entered into the multivariable analysis after intervening variables (intraoper-

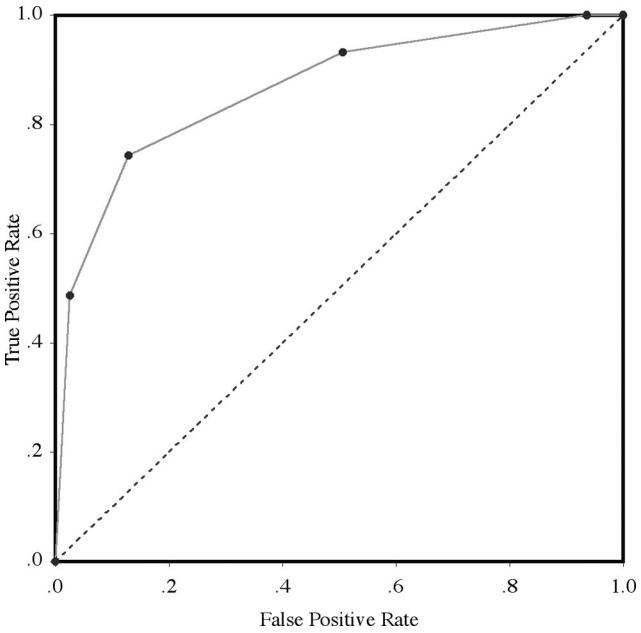


Fig. 1. Derivation set, score receiver operating characteristic curve to predict an allogeneic transfusion (95% confidence interval, 0.81–0.92; table 5).

Table 2. PMTSS Score Calculation

Parameter (Allogeneic Transfusion Predictor)	Assigned Points According to Item
Age > 50 yr	1
Preoperative Hb	
Hb < 12 g/dl	2
12 ≤ Hb ≤ 14 g/dl	1
Spine fusion levels (n) > 2	1
Transpedicular osteotomy	4

Predictive Model of Transfusion in Spine Surgery (PMTSS) is calculated as the arithmetic sum of points assigned to each item, except in case of osteotomy, where the maximum number of points (4) is allocated in any case. When age ≤ 50 yr, fusion level ≤ 2, hemoglobin (Hb) > 14, or no osteotomy is planned, 0 points are respectively allocated for each item. The score is then comprised between 0 and 4, and defined five distinct levels of allogeneic transfusion risk.

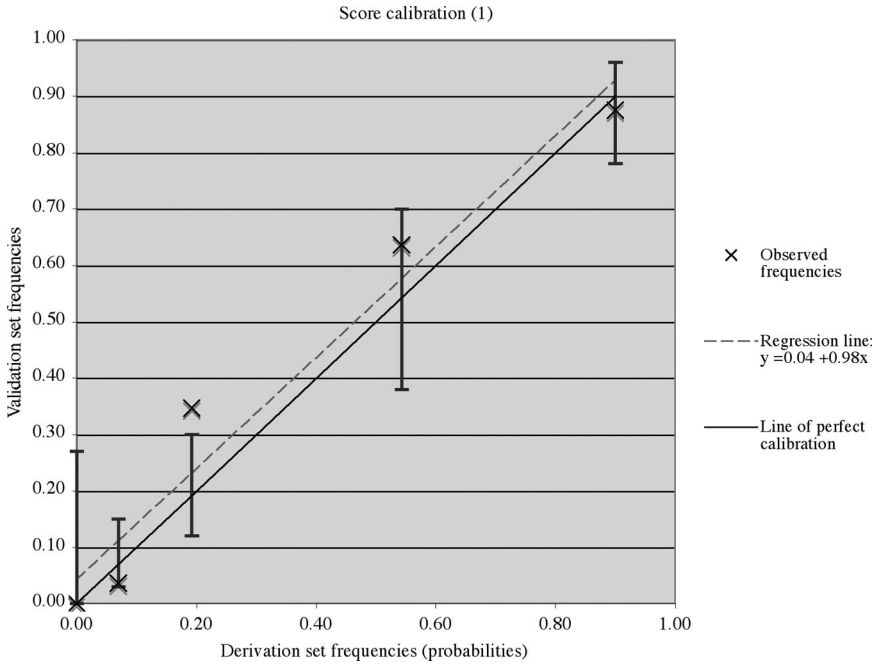


Fig. 2. Score calibration diagram. Comparison of the probability of predicted transfusion rates (probabilities are based on the score generated by the derivation set) to the observed frequency of transfusion rate in the validation set, $\chi^2 = 4.16$, $df = 2$, $P = 0.125$. The *bars* show the confidence intervals for the predicted values (confidence intervals were estimated according to the Wilson method). *Regression line*: y, validation frequency; x, derivation frequency.

ative blood loss, duration of surgery) and underlying disease had been excluded. Interaction between these factors (data not shown) were tested and considered nonsignificant. Only predictors significantly associated with homologous erythrocyte transfusion ($P < 0.05$) in the multivariable analysis were factors to be included in the PMTSS. The detailed process of PMTSS generation is reported in the appendix. The discriminating capacity of the PMTSS to predict the probability of erythrocyte transfusion was estimated by use of a receiver operating characteristic (table and curve) analysis.[16,17] Correlation of the PMTSS with the number of homologous erythrocyte units transfused was analyzed by the Spearman ρ correlation coefficient.

Validation Set. The PMTSS was then tested in a prospective validation cohort. There was a theoretical risk (called *contamination bias*) that practice may have been influenced by the score value collected during the validation period, because both predictors of erythrocyte transfusion and outcome (erythrocyte transfusion) were not assessed in a blinded fashion. Therefore, the duration of the validation study had to be minimized.[18] Because the transfusion rate in the derivation sample was 32%, dealing with a four-variable model (10 events

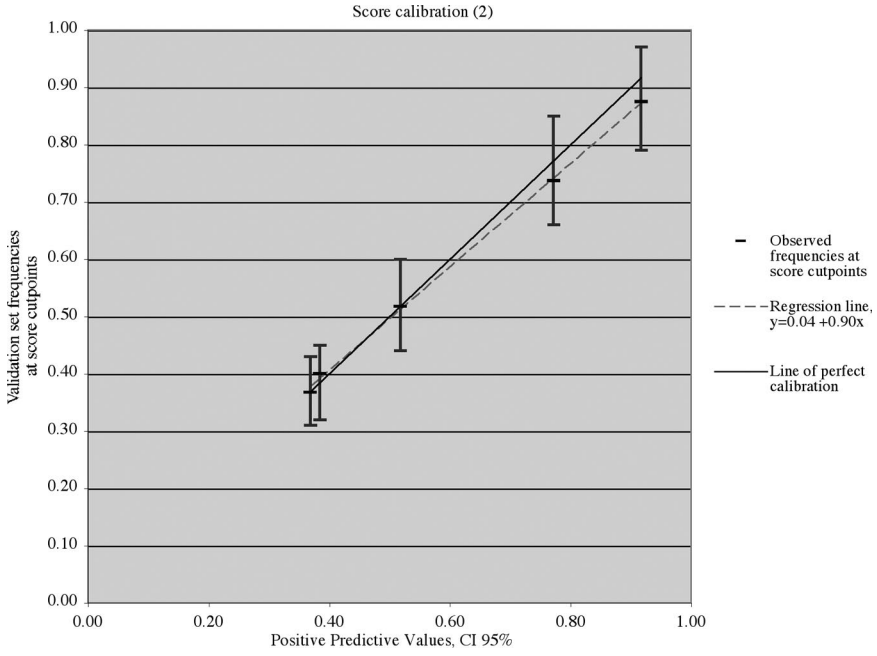


Fig. 3. Comparison of the positive predicted values of transfusion (probabilities are based on the score generated by the derivation set and likelihood ratios corresponding to cut points; pretest probability is the validation transfusion rate) to the observed frequency of transfusion rate in the validation set. The *bars* show the confidence intervals (CIs) (Wilson method) for the positive predictive values. *Regression line*: y, validation frequency; x, derivation frequency.

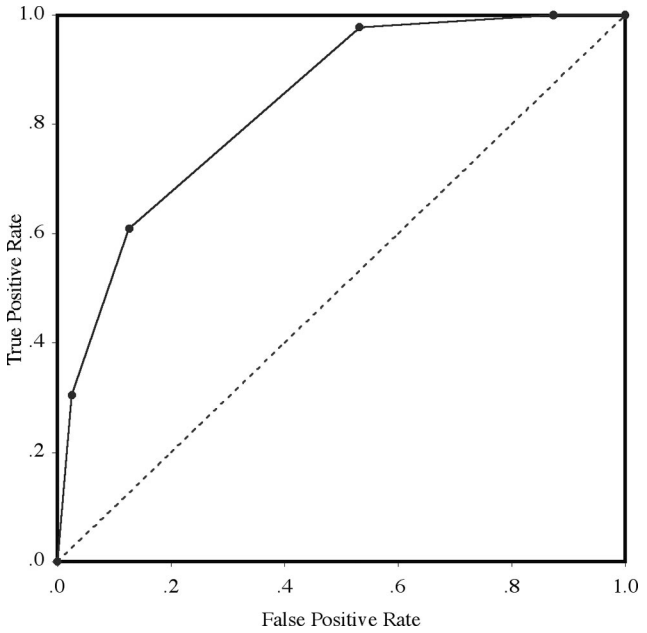


Fig. 4. Score discrimination, receiver operating characteristic curve to predict an allogeneic transfusion in the validation set (95% confidence interval, 0.75–0.91; table 8).

per variable, 1 event = 1 transfused patient), 125 patients were required in the validation sample.[14] The same descriptive analysis (univariate and bivariate statistics, multivariable model checking) as in the derivation cohort was performed to describe the validation sample. The calibration of the score in predicting the individual probability of erythrocyte transfusion was examined by fitting the data (*i.e.*, transfusion rates at each score level in the validation set) to expected transfusion frequencies (probabilities) obtained from the derivation set. Then, the observed frequencies of transfusion at each score cutoff value in the validation set were plotted against the corresponding predicted positive values of erythrocyte transfusion. The predictive positive values were calculated from the observed prevalence of transfusion and intrinsic diagnostic characteristics (sensitivity, specificity, likelihood ratios) derived from the derivation study.

Statistical Analysis

Statistical analysis was performed using Excel® version 11.3.5 (Microsoft Corporation, Redmond, WA; 2004) and JMP version 7 (SAS Institute Inc., Cary, NC; 1989–2007). Data are expressed as mean and SD for variables following normal distribution and as median [25–75 interquartile range] for others. Normality of distributions and equality of variances were checked by using the goodness-of-fit (normal distribution) Shapiro–Wilk W test before parametric statistics were undertaken. Bivariate analysis was performed by analysis of variance and the Student *t* test for continuous dependent variables (corrections for unequal variances were used when needed). Ordinal and nonnormally distributed dependent variables were analyzed by the nonparametric rank sum Wilcoxon/Kruskal–Wallis tests. The Fisher exact test (two-tailed) was used for both binary dependent and independent variables. Simple logistic regressions were performed when the outcome variable was binary (transfusion) and independent variables were continuous. Pearson–Yates chi-square tests were used for nominal variables. The Spearman rank correlation coefficient was calculated for studied correlations. Multivariable analyses were performed using linear regression and nominal logistic models according to the dependent variables selected. Estimate parameters were tested by Wald tests. Recursive partitioning was used after identifying predictors to help determine optimal cutoff points taking natural significance and size conditions into consideration. Confidence intervals (CIs) for areas under receiver operating characteristic curves were calculated according to the Hanley and Hill methods. Those corresponding to proportions were calculated by the Wilson method. $P < 0.05$ was considered the threshold for significance.

Results

Derivation Set

Two hundred thirty consecutive patients were included in the derivation population. The median [range] total erythrocyte loss was 1,437 [106–9,070] ml. Intraoperative blood salvage was used in 32 of 230 patients (13.9%). The allogeneic transfusion rate was 74 in 230 (32%), and the number of erythrocyte units administered in transfused patients was 3.5.[1,13] Of the 286 transfused erythrocyte units, 212 (74%) were administered intraoperatively. The remaining erythrocytes were administered postoperatively (14.3% after postoperative day 1). The preoperative hemoglobin level was 13.2 [7.4–16.6] g/dl. This value was less than 12 g/dl in 45 of 230 patients (19.5%) and less than 10 g/dl in 23 of 230 patients (10%). The incidence of the use of antifibrinolytics in this cohort was 17.4% (66.7% in the validation cohort).

Independent variables associated with allogeneic erythrocyte transfusion identified by bivariate analysis and the results from multivariable analysis with selected factors for allogeneic transfusion are shown in table 1. Four independent preoperative predictors of homologous erythrocyte transfusion were identified: age older than 50 yr (adjusted odds ratio [aOR] = 4.9; 95% CI, 2–13.5), preoperative hemoglobin level less than 12 g/dl (aOR = 6.9; CI, 3.1–17.2), fusion of more than two levels (aOR = 6.7; CI, 3.1–15.2), and transpedicular osteotomy (aOR = 19.9; CI, 5.6–98.2). The discriminant capacity of the PMTSS obtained from transformation of the four factors identified as independent predictors for allogeneic erythrocyte transfusion in the multivariable analysis was good (area under the curve = 0.86; 95% CI, 0.81–0.92; fig. 1). Of note, when the score was greater than 2, it had a sensitivity of 0.74, a specificity of 0.87, a positive likelihood ratio of 5.8, a negative likelihood ratio

Table 3. Patient Characteristics in Derivation Sample, Blood Losses, and Transfusion Rates

	Total	Degenerative Disease	Deformity	Tumor or Infection	Fracture	Miscellaneous
n	230	124	36	28	19	23
M/F, n	93/137	49/75	9/27	20/8	9/10	6/17
Age, mean (SD), yr	58 (16)	63 (15)	56 (14)	55 (15)	40 (14)	49 (12)
Height, mean (SD), cm	167 (10)	167 (9)	163 (10)	172 (10)	168 (10)	165 (9)
Body weight, mean (SD), kg	72 (19)	74 (16)	65 (17)	71 (20)	77 (25)	69 (23)
BMI, mean (SD), kg/m^2	25.7 (5.8)	26.4 (4.5)	24.6 (5.6)	23.9 (6.5)	27.4 (10.5)	24.8 (5.3)
Preoperative hemoglobin, median [IQR], g/dl	13.2 [12.3–14.2]	13.7 [12.8–14.3]	12.9 [12.1–14.0]	12.8 [11.5–14.4]	12.8 [12.5–13.9]	11 [10.5–13.6]
Duration of surgery, mean (SD), min	185 (76)	166 (57)	278 (88)	205 (61)	134 (45)	156 (60)
Estimated blood loss, median [IQR], ml	1,400 [800–2,400]	1,100 [750–1,700]	4,300 [2,300–5,600]	2,200 [1,300–3,000]	1,400 [1,100–1,850]	700 [450–1,200]
Estimated blood loss, % EBV	45	31	108	53	34	24
Cell salvage use, n (%)	32 (13.9)	7 (5.6)	23 (64)	0	1 (5.3)	0.7 (0.4)
Cell salvage volume when used, median, units	3	2	3	—	1	2
Allogeneic erythrocyte transfusion, patients, n (%)	74 (32)	24 (19)	31 (86)	11 (39)	4 (21)	4 (17)
Allogeneic cerythrocytes when transfused, median, units	4	2	5	4	3	2
Postoperative day 5 hemoglobin, median [IQR], g/dl	10.6 [9.6–11.5]	11.1 [10.1–12.0]	10.1 [9.1–10.9]	10 [9.3–10.9]	10.3 [8.9–10.7]	10.2 [9.6–11.1]

Deformity: scoliosis or kyphosis; degenerative disease: stenosis or posterior fusion. Miscellaneous included nonspecified underlying disease in database. Total calculated blood loss is expressed as volume of whole blood at hematocrit = 30%. Volume of cell salvage is expressed in equivalent of erythrocytes units (around 250 ml).

BMI = body mass index; EBV = estimated blood volume; IQR = interquartile range.

of 0.29, a positive predictive value of homologous erythrocyte transfusion of 0.73, and a predictive negative error of 0.12. The corresponding individual probabilities of perioperative erythrocyte transfusion were 0, 7, 19, 54, and 90% for PMTSS values of 0, 1, 2, 3, and 4, respectively.

Validation Set

Patient characteristics were similar compared with the derivation sample (narrow validation; table 2). No comparison was justified. The transfusion rate was slightly increased in the validation set (37% *vs.* 32% in the derivation set), and osteotomy was less frequently performed (6.4% *vs.* 12.6%). Bivariate and multivariate statistics revealed similar trends to identify preoperative independent predictors of erythrocyte transfusion. There was a good fit between the observed rates of transfusion and the probabilities of transfusion obtained from the model (regression line: $y = 0.98x + 0.04$, $P < 0.0001$; goodness of fit χ^2, $P = 0.125$). We found a good fit between the observed transfusion rates at different score thresholds and the corresponding positive predictive values generated by the score ($y = 0.90x + 0.04$, $P < 0.0001$; figs. 2 and 3). The score also correlated with the number of erythrocyte units transfused (Spearman = 0.61, $P < 0.0001$). The receiver operating characteristic curve analysis in the validation set showed a very good discriminating capacity of the PMTSS (area under the curve = 0.83 [0.75–0.91]; fig. 4). The corresponding individual probabilities of perioperative erythrocyte transfusion were 0, 4, 35, 64, and 88% for PMTSS values of 0, 1, 2, 3, and 4, respectively.

Data Presented in the Appendix

This section contains material for readers specifically interested in epidemiologic or methodologic aspects of

Table 4. Derivation Set: Nominal Logistic Fit for Allogeneic Transfusion (with Parameter Estimates)

Whole Model Test

Model	Log Likelihood	*df*	χ^2	Prob > χ^2
Difference	56.610	5	113.219	< 0.0001
Full	87.870			
Reduced	144.480			
Observations	230			

Lack of Fit

Source	Log Likelihood	*df*	χ^2	Prob > χ^2
Lack of fit	6.016	15	12.032	0.677
Saturated	81.854	20		
Fitted	87.870	5		

Hosmer and Lemeshow Goodness-of-Fit Test

	χ^2	*df*	Prob > χ^2
Goodness-of-fit test * Pooling categories.	2.692	4	0.611

Parameter Estimates

Term	Estimate	SE	95% CI		Wald χ^2	Prob > χ^2	Adjusted Odds Ratio	95% CI	
Age > 50 yr	1.638	0.490	0.731	2.669	11.180	0.0008	5.14	2.08	14.42
Hbi 12–14 *vs.* > 14	1.189	0.527	0.211	2.307	5.080	0.0241	3.28	1.23	10.05
Hbi < 12 *vs.* 12–14	1.599	0.460	0.712	2.526	12.080	0.0005	4.95	2.04	12.50
Fusion level > 2	1.835	0.413	1.041	2.669	19.760	< 0.0001	6.26	2.83	14.42
Osteotomy	3.196	0.740	1.867	4.834	18.640	< 0.0001	24.43	6.47	125.71

Table shows multivariable (nominal logistic) model derivation with selected predictors for allogeneic transfusion, goodness-of-fit, parameter estimates, and adjusted odds ratios. Interactions between factors were first tested and considered nonsignificant. *Cells have expected count less than 5. Cut points for interval variables (age, hemoglobin, and fusion levels) were defined after a first multivariable analysis using continuous independent factors—corresponding R^2 (U) = 0.45, area under receiver operating characteristic curve = 0.91—but influential observations were found. Cutoff points were chosen by using both discriminating (recursive partitioning) and "natural" cutoffs (age, hemoglobin) or equal-size groups (fusion levels).

CI = confidence interval; Hbi = preoperative (initial) hemoglobin, expressed as g/dl; Prob = probability.

this study. Details of the generation of the score from the four selected independent predictors of erythrocyte transfusion are given in the appendix.

Discussion

The main original findings of the current study can be summarized as follows: A 0–4 score based on preoperative patient characteristics, the PMTSS, was derived from a large cohort of adult patients undergoing major elective thoracolumbar spine surgery and prospectively validated. The strategy used here was pragmatic, and differed from a classic explanative attitude when using a multivariable analysis insofar as a selection process of the variables was decided on specific criteria, and the study was powered to address this goal. The PMTSS was found a reliable predictive model of allogeneic transfusion requirements

Table 5. Score Derivation, Receiver Operating Characteristic Table

Cut Score	TPR	FPR	Youden Index	LR(+)	LR(−)	PPV	NPE
0	1.000	1.000	0.000	1.000	—	0.322	—
1	1.000	0.936	0.064	1.068	0.000	0.336	0.000
2	0.932	0.506	0.426	1.841	0.137	0.466	0.061
3	0.743	0.128	0.615	5.797	0.295	0.733	0.123
4	0.486	0.026	0.461	18.973	0.527	0.900	0.200

Score discrimination and diagnostic (prognostic) features. Youden index = (sensitivity + specificity) − 1. Cut score corresponds to a threshold value of the score (≥). When score > 2, sensitivity = 0.74, specificity = 0.87, likelihood ratio for a positive "test" result (actual score ≥ score cut point) [LR(+)] = 5.8, likelihood ratio for a negative "test" result [LR(−)] = 0.29, positive predictive value (PPV) of homologous transfusion (erythrocytes) = 0.73, predictive negative error (NPE) = 0.12. Area under the curve = 0.865; SE = 0.029; 95% confidence interval, 0.809–0.922 (fig. 1).

FPR = false-positive rate; TPR = true-positive rate.

Table 6. PMTSS Validation Set, Bivariate Statistics

	T(H)−	T(H)+	*P*
n (% total)	79 (63)	46 (37)	—
Patient variables			
Age, mean (SD), yr	55.5 (15.8)	58.5 (16.7)	0.31
Sex, M/F, n	42/37	23/23	0.71
Weight, mean (SD), kg	73.7 (16.1)	70.2 (12.8)	0.21
Height, mean (SD), cm	167.2 (9.8)	165.7 (12.0)	0.43
BMI, mean (SD), kg/m^2	26.2 (4.4)	25.7 (5.3)	0.55
Preoperative [Hb], mean (SD), g/dl	13.6 (1.4)	12.5 (1.5)	< 0.0001
Surgery variables			
Redux, n (%)	9 (11)	17 (37)	0.001
Laminectomy levels, median [IQR], n	2 [1–2]	3 [2–4.5]	0.0001
Fusion levels, median [IQR], n	1 [1–2]	4 [2.5–8]	< 0.0001
Osteotomy, n (%)	1 (1)	7 (15)	0.003
Outcomes variables			
Estimated blood loss, Ht = 30%, mean (SD), ml	1,200 (960)	3,400 (1,860)	< 0.0001
Blood loss, mean (SD), % blood volume	25 (20)	78 (45)	< 0.0001
Cell salvage, n (%)	10 (12)	17 (37)	0.003
Total erythrocytes, median [IQR], units	0 [0–0]	4 [2–6]	< 0.0001
Day 5 postoperative [Hb], mean (SD), g/dl	11.5 (3.7)	10.5 (1.6)	0.08
PMTSS score, median [IQR]	2 [1–2]	3 [2–4]	< 0.0001

BMI = body mass index; [Hb] = hemoglobin concentration; Ht = hematocrit; IQR = 25–75 interquartile range; PMTSS = Predictive Model of Transfusion in Spine Surgery; T(H)+ = homologous transfusion (erythrocytes); T(H)− = no homologous transfusion (erythrocytes).

in adult spine surgery. It may be useful in clinical practice to identify patients undergoing spine surgery at risk of particularly important transfusion, properly allocate blood, and encourage erythrocyte-saving strategies in these patients.

Four independent predictors for erythrocyte homologous transfusion were identified in patients undergoing major spine surgery and entered into the process of generating the PMTSS. Our study confirms and extends the prevalence of preoperative anemia (defined as a hemoglobin level less than 13 g/dl for males and 11.5 g/dl for females), which is very close to those reported by others for patients presenting for major orthopedic surgery, including spine surgery.[5,19] Measurements of blood loss were obtained from the day of operation until postoperative day 5. This represents an original finding because most of the studies had focused only on intraoperative blood loss.[5–8] The intraoperative median blood loss reported in our study was also consistent with the values previously reported for spine surgery.[5–7] Interestingly, the range of blood loss was broad, indicating that some patients have undergone massive perioperative hemorrhage. Of note, Murrey *et al.* [4] reported an average intraoperative blood loss of 2,342 ml for transpedicular osteotomy, with maximal bleeding of 9,000 ml in some cases. Intraoperative blood salvage was used in a minority of patients (13.6%). We used validated criteria recommended to initiate erythrocyte transfusion in both the derivation and the validation cohorts.[9] These criteria were fairly consistent with those published later by the American Society of Anesthesiologists Task Force.[10] The adequacy of this strategy is supported by the median hemoglobin levels found at postoperative day 5 (10.6 g/dl in the derivation cohort and 10.8 g/dl in the validation cohort). These moderate values support that erythrocyte transfusion was not overused in our study.

We found that fusion surgery involving more than two levels was an independent risk factor predictive of allogeneic transfusion. The number of levels fused has been previously shown to be a risk factor for intraoperative bleeding in spine surgery.[4–6,20] Our results confirm and extend these findings by showing that this risk factor also applies to postoperative bleeding. We also found that transpedicular osteotomy was a major independent risk factor of blood loss in this context. Transpedicular osteotomy represents major reconstructive surgery and is associated with a high rate of complications, including severe hemorrhage.[21,22] Indeed, because of the nature of the resection, bleeding originates from the vertebra itself. This explains that control of intraoperative bleeding is particularly difficult for the surgeon in this situation.

Age older than 50 yr was the third independent predictive factor of allogeneic erythrocyte transfusion, as was suggested previously in one study.[6] This factor was still present after adjustment of blood loss to the type of surgical procedure. Several hypotheses can be proposed to account for this finding. This could be explained by an increased prevalence of comorbidities such as hypertension or situations for which medications interfering with coagulation or platelet function were required. Aspirin intake has been reported to increase the risk for bleeding and transfusion in the case of hip arthroplasty.[23] On the other hand, data on the effect of clopidogrel in patients scheduled to undergo noncardiac surgery are scarce, and their levels of proof are low.[24] Alternatively, patients older than 50 yr had more posterior fusions (46% *vs.*

Table 7. PMTSS Validation Set, Multivariable Analysis

Nominal Logistic Fit for Allogeneic Transfusion (Multivariable Model)

Whole Model Test

Model	−Log Likelihood	*df*	χ^2	Prob > χ^2
Difference	31.901	5	63.803	< 0.0001
Full	47.862			
Reduced	79.763			
R^2 (U)	0.40			
Observations (or sum weights)	125			

Lack of Fit

Source	*df*	−Log Likelihood	χ^2	
Lack of fit	12	3.476	6.951	
Saturated	17	44.386		Prob > χ^2
Fitted	5	47.862		0.861

Receiver Operating Characteristic

Area under curve	0.88

Effect Wald Tests

Source	No. of Parameters	*df*	Wald χ^2	Prob > χ^2
Age > 50 yr	1	1	4.376	0.037
Hbi level	2	2	14.217	0.001
Fusion level > 2	1	1	25.281	< 0.0001
Osteotomy	1	1	1.365	0.243

Derived multivariable model checking: Outcome variable was perioperative homologous erythrocyte transfusion [T(H)±]. Small sample size, a lower rate of osteotomy in the validation sample compared with derivation sample, and insufficient overlapping (24 possible patterns from the model) could explain the statistical nonsignificance of osteotomy when adjusted on the other cofactors of the model.

Hbi = preoperative (initial) hemoglobin; PMTSS = Predictive Model of Transfusion in Spine Surgery; Prob = probability.

22.4%), fewer anterior fusions (4.3% *vs.* 14.9%), and less posttraumatic disease (3.1% *vs.* 20.9%) than those aged 50 yr or younger, which may contribute to explain this result.

The generation of a simplified transfusion risk score, the PMTSS, represents a major original result of this study. A classification bias was unlikely to be present, because the variables collected were objective ones (age, hemoglobin level, fusion of more than two levels, transpedicular osteotomy). This supports reproducibility of our results. Similarly, it could be argued that an observation bias may have contributed to decrease the incidence of homologous erythrocyte transfusion in the validation population and subsequently to decrease the discriminant capacity of the score. This seems unlikely to be the case, because the discriminant capacity of the PMTSS was very good (area under the curve = 0.83) in the validation population. The cutoff points were defined *a posteriori* to comply with clinical coherence and sample size. This choice emphasizes the importance of the prospective validation of the PMTSS. The discriminant capacity of the PMTSS was remarkable (area under the curve > 0.80) in the derivation population. Small sample size and insufficient overlapping could

Table 8. PMTSS Score Validation, Receiver Operating Characteristic Table

Cut Score	TPR	FPR	Youden Index	LR(+)	LR(−)	PPV	NPE
0	1.000	1.000	0.000	1.000	—	0.368	—
1	1.000	0.873	0.127	1.145	0.000	0.400	0.000
2	0.978	0.532	0.447	1.840	0.046	0.517	0.026
3	0.609	0.127	0.482	4.809	0.448	0.737	0.207
4	0.304	0.025	0.279	12.022	0.714	0.875	0.294

When score > 2, sensitivity = 0.61 and specificity = 0.87 to predict a transfusion of homologous erythrocytes, likelihood ratio for a positive "test" result (actual score > 2) [LR(+)] = 4.8, positive predictive value (PPV) = 0.74 in the validation sample. Youden index = (sensitivity + specificity) − 1. Area under the curve = 0.836; SE = 0.040; 95% confidence interval, 0.757–0.915 (fig. 4).

FPR = false-positive rate; LR(−) = likelihood ratio for a negative "test" result; NPE = negative predictive error; PMTSS = Predictive Model of Transfusion in Spine Surgery; TPR = true-positive rate.

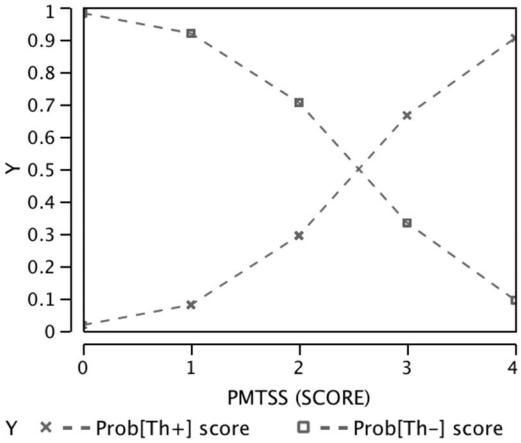
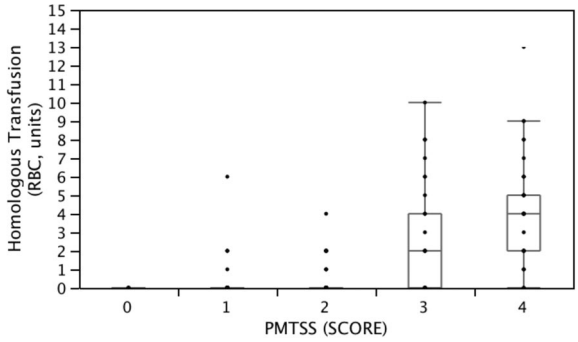


Fig. 5. Probabilities of transfusion according to the score level. PMTSS = Predictive Model of Transfusion in Spine Surgery; Prob(Th+) = probability to be transfused (homologous erythrocytes); Prob(Th−) = probability to be nontransfused.

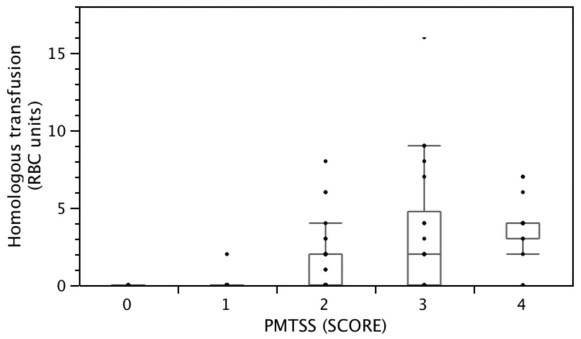
explain the nonsignificant statistical value of osteotomy when adjusted to the other cofactors of the model in the validation population. Indeed, the PMTSS is a four-variable model with three of them giving two possibilities for a patient (age $>$ or $\leq$ 50 yr, osteotomy or no osteotomy, fusion $>$ 2 levels or $\leq$ 2 levels) and one giving three possibilities for the last variable (preoperative hemoglobin $>$ 14 or between 12 and 14 or $\leq$ 12). Therefore, $3 \times 2 \times 2 \times 2 = 24$ possible patterns were identified. The rate of osteotomy in the validation sample was decreased in comparison with the derivation sample (15% *vs.* 35%) and was too low to cover all possible patterns (insufficient overlapping). The discriminant capacity of the PMTSS remained also excellent in the validation population despite that slightly different characteristics were present in this population compared with the derivation set. Cell salvage was more frequently used



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	6
2	0	0	0	0	0	2	4
3	0	0	0	2	4	8	10
4	0	0.1	2	4	5	8	13

Fig. 6. Derivation set: one-way analysis of allogeneic transfusion (erythrocyte units) by Predictive Model of Transfusion in Spine Surgery (PMTSS). Figure and linked quantiles table show transfused erythrocyte units (quantiles) according to the score level. Wilcoxon/Kruskal–Wallis (rank sum) test, $P < 0.0001$; Spearman $\rho = 0.64$, $P < 0.0001$. RBC = red blood cell.



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	2
2	0	0	0	0	2	3	8
3	0	0	0	2	4.75	9	16
4	0	0	3	4	4	7	7

Fig. 7. Validation set: one-way analysis of homologous transfusion (erythrocyte units) by Predictive Model of Transfusion in Spine Surgery (PMTSS). Figure and linked quantiles table show transfused erythrocyte units (quantiles) according to the score level. Wilcoxon/Kruskal–Wallis (rank sum) test, $P < 0.0001$; Spearman $\rho = 0.61$, $P < 0.0001$. RBC = red blood cell.

in the validation sample (22% *vs.* 14%). Also, the use of tranexamic acid was threefold in comparison with the derivation population. Therefore, it is unlikely that the use of either blood salvage or antifibrinolytics impaired the performance of the PMTSS. The calibration of the score for predicting the individual probability of transfusion, as well as the number of erythrocyte units to be transfused, was robust.

Our study has limitations. One of them is the retrospective nature of a major part of this work. Also, it can be argued that the external validity of this single-center study could be limited.[25] Nevertheless, our findings may be relevant to other surgical centers routinely practicing major spine surgery in adults, provided that their transfusion rate remains within a 30–40% range. Finally, the clinical impact of using the PMTSS in routine practice has not been examined as a primary endpoint and deserves further investigation in a prospective, multicenter trial. It can be suggested that preoperative calculation of the PMTSS could be helpful and cost-saving by identifying the patient subpopulations at risk of massive bleeding, therefore encouraging erythrocyte-saving strategies in these patients. Determination of the individual probability of erythrocyte transfusion may improve patient information on their perioperative erythrocyte requirements and give them the opportunity to start with a preoperative transfusion-sparing strategy (autotransfusion and/or epoetin). It can be speculated that patients with a PMTSS value greater than 2 could benefit from postponing surgery if sufficient blood amounts were not available (*e.g.*, for rare phenotypes). Finally, preoperative calculation of the PMTSS may help to identify those patients for whom antifibrinolytics and/or intraoperative blood salvage could be beneficial.

In conclusion, we have found four independent predictive factors of intraoperative and postoperative allogeneic erythrocyte transfusion in thoracolumbar spine surgery. A score of individual probability of allogeneic transfusion for spine surgery, the PMTSS, has been generated and prospectively validated. This strategy may contribute to improve proper allocation of blood in the perioperative context and mobilize donors.

Appendix: Generation of 0–4 the Score from the Four Selected Independent Predictors of Erythrocyte Transfusion

Guidelines for reporting observational studies were followed throughout.[26] Hosmer and Lemeshow goodness-of-fit of the model, parameter estimates, and adjusted odds ratios were first determined. Cutoff points for interval variables (age, hemoglobin levels, and number of fusion levels) were defined *a posteriori* after the variables were selected from a first multivariable analysis using continuous independent factors, because influential observations were found. Cutoff points were chosen by using both discriminating (recursive partitioning) and "natural" cutoff points (age, hemoglobin levels) or equal-size groups (fusion levels). The goal was then to generate a clinically relevant and easy-to-use four-variable model for predicting erythrocyte transfusion. Therefore, we started from ordering multivariable estimates (additive in a multiplicative scale) and assessment of the probability of distribution of allogeneic transfusion according to the logistic model which seemed multimodal. We also noticed a 90% transfusion rate in case of transpedicular osteotomy along with a relative risk of transfusion of 3.8 (adjusted odds ratio = 24, which is similar to the unadjusted odds ratio = 27). A 4-point score (0–4) was then proposed and defined as follows: 4 points (maximum value) were allocated to transpedicular osteotomy. Other estimates were close to each other (1.6, 1.6, and 1.8, which corresponds to an adjusted odds ratio for transfusion of 5). Because preoperative hemoglobin level has a major impact on perioperative transfusion rate and treatment decision, new cutoff points corresponding to maximal statistical gain were investigated for this variable. Therefore, three intervals defined by preoperative hemoglobin levels (hemoglobin $>$ 14 g/dl, 12 g/dl $<$ hemoglobin $<$ 14 g/dl, hemoglobin $<$ 12 g/dl) were considered. One point (zero, respectively) was attributed to age $>$ 50 yr ($\leq$ 50 yr, respectively), spine fusion levels $>$ 2 ($\leq$ 2, respectively), and preoperative hemoglobin $\leq$ 14 g/dl ($>$ 14 g/dl, respectively); two points were allocated when preoperative hemoglobin $<$ 12 g/dl. The score was calculated as the arithmetic sum of points corresponding to each item. The maximal total score was 4, which defined five classes of probability levels. Transpedicular osteotomy was allocated 4 points whatever the other items. The probability of transfusion (*P*) was estimated by considering the score as an internal variable as follows:

$$P(\text{transfusion}) = 1/1 + E^{(b * \text{score} + A)},$$

where B = 1.61, A = −4.56, or (delta + 1 point of the score = 5).

Correlations of probability distributions between the original model and the PMTSS demonstrated a good fit (Spearman correlation coefficient = 0.97). Patient characteristics, bleeding, and transfusion rates in the derivation and validation sets are reported in table 2. Details of the model and of the receiver operating characteristic analysis are given in tables 3–8. Plots of the model performance are displayed in figures 5–7.

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