

Original Article

Gender of patients and level of osteotomy are predictive factors for blood loss in ankylosing spondylitis patients undergoing pedicle subtraction osteotomy

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Abstract: This study is to investigate the predictive factors of blood loss in ankylosing spondylitis (AS) patients. Retrospective analysis was performed in patients with thoracolumbar kyphotic deformity secondary to ankylosing spondylitis who underwent PSO from 2008 through 2013. Patient's demographics, preoperative and postsurgical global kyphosis (GK) angle, preoperative hematologic tests and other factors related to PSO were analyzed. Multiple regression analysis was used to determine the predictive factors of intraoperative blood loss. A total of 67 AS patients including 61 males and 6 females were included in the study. These had an average age of 33.97 years (17-55 years) and an average preoperative height of 167.77 cm (124-182 cm). There were 55 patients undergoing one-level osteotomy and 12 patients undergoing two-level osteotomy. Preoperative and postoperative GK angles were $79.08^\circ \pm 24.11^\circ$ and $35.68^\circ \pm 21.48^\circ$, respectively. The mean surgical correction rate was $56.62\% \pm 21.45\%$. The mean length of surgery was 404.25 ± 82.57 minutes, and the estimated intraoperative blood loss was 2899.25 ± 1444.54 ml. The average percentage of estimated blood loss (EBL)/estimated blood volume (EBV) was $69.98\% \pm 41.44\%$ (range, 23.57%-248.52%). Multiple stepwise analysis identified male sex ($P = 0.000$), and two-level osteotomy ($P = 0.016$) to be predictive factors of increased EBL/EBV percentage in AS patients undergoing PSO for thoracolumbar kyphosis. Male and two-level osteotomy are the two most significant factors predicting increased EBL/EBV percentage in AS patients undergoing PSO for thoracolumbar kyphosis. These predictors can provide more adequate preoperative preparations.

Keywords: Predictive factors, blood loss, ankylosing spondylitis, pedicle subtraction osteotomy, thoracolumbar kyphosis

Introduction

Massive hemorrhage is one of the most common complications of major corrective spinal surgeries in patients with ankylosing spondylitis (AS) undergoing pedicle subtraction osteotomy (PSO) for thoracolumbar kyphosis [1]. The corresponding requirement for fluid challenge and blood transfusion for potential hemorrhage is critical to successful anesthesia for major spine surgery [2]. AS patients undergoing PSO can present significant challenges to anesthesiologists due to massive hemorrhage. Some patients undergoing osteotomy can lose as much as 4,700 ml blood [3]. These patients often need blood transfusion to maintain perioperative hemodynamic equilibrium. Although the technique of blood screening has consider-

ably improved safety over the past decades, allogeneic blood is still with risks such as infective and immunological complications. Infective complications include transmission of viruses (e.g. hepatitis, human immunodeficiency viruses), parasitic diseases, and transfusion-associated bacterial sepsis. Immunological adverse events, such as allergic reactions, acute and delayed hemolytic reactions, graft-versus-host disease and alloimmunization, are rare but fatal. Moreover, allogeneic blood products are expensive.

Nowadays, several blood conservation alternatives have been developed to decrease the transfusion rate in major spine surgery, including preoperative autologous blood donation and erythropoietin administration, as well as

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Table 1. Demographic and preoperative data of AS patients undergoing PSO (N = 67)

	Males (N = 61)	Females (N = 6)
Demographics		
Age (year)	33.29 ± 9.27	40.83 ± 8.23
Height (cm)	169.18 ± 6.05	153.50 ± 15.24
Weight (kg)	61.28 ± 14.15	57.00 ± 13.16
BMI (kg/m ²)	21.47 ± 5.21	24.60 ± 6.54
EBV (ml)	4360.22 ± 508.08	3330.16 ± 693.16
ASA		
I	28	2
II	33	4
Cardiovascular disease		
Yes	31	4
No	30	2
Respiratory disease		
Yes	50	6
No	11	0
Curve parameters		
Preoperative GK angle (°)	79.29 ± 23.52	77.00 ± 32.13
Laboratory values		
Hemoglobin (g/L)	135.36 ± 19.55	125.33 ± 7.44
Hematocrit (%)	41.09 ± 4.74	38.60 ± 1.59
Platelet count (× 10 ⁹ /L)	263.22 ± 57.76	250.66 ± 70.39
PT (s)	11.94 ± 0.95	11.28 ± 0.71
APTT (s)	31.64 ± 5.21	26.20 ± 4.21
INR	1.04 ± 0.08	0.98 ± 0.06

Note: Normally distributed continuous variables are expressed as means ± SD, and N is categorical variable. SD, standard deviation; BMI, body mass index; EBV, estimated blood volume; ASA, American Society of Anesthesiologists; GK, global kyphosis; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ration. EBV was calculated according to the formula described by Nadler. For males: $EBV = (0.3669 \times \text{height}^3/10^6 + 0.03219 \times \text{weight} + 0.6041) \times 1000$; for females: $EBV = (0.3561 \times \text{height}^3/10^6 + 0.03308 \times \text{weight} + 0.1833) \times 1000$.

intraoperative alternatives such as acute normovolemic hemodilution, deliberated hypotensive anesthesia, antifibrinolytic medications and autologous transfusion. The aforementioned blood conservation strategies are reported to be effective in diminishing the demand of allogeneic blood, but they are expensive and not risk-free.

Preoperative variables known to affect intraoperative surgical bleeding during spinal surgery were sex [4, 5] and osteotomy [3, 6]. Understanding the factors that contribute to increased blood loss could aid anesthesiologists in preoperative anesthetic preparations. If blood loss could be better predicted, more

appropriate blood salvage strategy could be used in this high-risk patient group. If the factors associated with blood loss are known, transfusion for patients who do not in real need of it can be avoided. Therefore, understanding these factors can help make better use of the limited blood bank resources, minimize wastage and maximize cost-effectiveness. This study was designed to determine the potential factors that were predictive of increased blood loss in AS patients undergoing PSO for the correction of thoracolumbar kyphotic deformity.

Materials and methods

Patients

Clinical and operative records of AS patients who underwent PSO for the correction of thoracolumbar kyphosis between April 2008 and November 2013 were retrospectively reviewed. Patients were excluded if they had any one of the following: i) prior history of spinal surgery; ii) revision surgery; iii) a procedure that involved an anterior approach or anterior instrumentation; iv) fusion that extended into the cervical spine; v) diagnosis of pseudarthrosis; vi) "growing" rod extending; vii) use of intraoperative antifibrinolytic drugs; viii) abnormalities in prothrombin time (PT)/activated partial thromboplastin time (APTT)/international

normalized ratio (INR); ix) uncompleted medical data. Finally, 67 AS patients met the predetermined inclusion criteria. Prior written and informed consent were obtained from every patient. Institutional review board approval was obtained from the Affiliated Drum Tower Hospital, Medical College of Nanjing University.

Demographic variables collected included gender, age, weight, height, body mass index, American Society of Anesthesiologists (ASA) grade, and preoperative medical comorbidities. Preoperative full spine radiographs were obtained and global kyphosis (GK) angles were measured by operative surgeons. Information pertaining to preoperative hematologic tests

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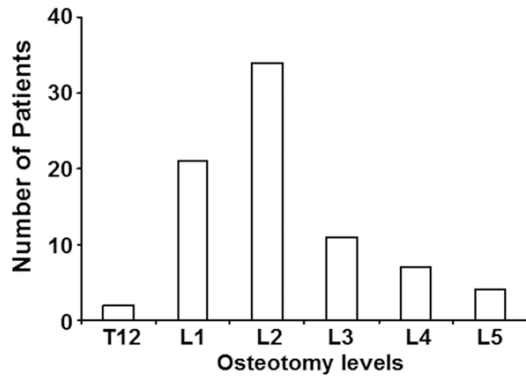


Figure 1. Distribution of osteotomy level in 79 osteotomy procedures. Seventy-nine pedicle subtraction osteotomy procedures were performed in 67 patients. T12, L1, L2, L3, L4 and L5 represent vertebral bodies. Of the 79 osteotomies, 2 were done over T12 vertebral body, 21 were done over L1 vertebral body, 34 were done over L2 vertebral body, 11 were done over L3 vertebral body, 7 were done over L4 vertebral body, and 4 were done over L5 vertebral body. Twelve patients underwent two-level vertebral osteotomy procedure due to severe deformity. Two-level osteotomy was performed at these segments as follows: T12 and L1 vertebral bodies in one patient, T12 and L3 vertebral bodies in one patient, L1 and L4 vertebral bodies in six patients, L2 and L5 vertebral bodies in four patients.

including hemoglobin, hematocrit, platelet count, PT, APTT, and INR were also noted. Intraoperative data collected included number of fused levels, number of placed pedicle screws, the length of surgery, estimated blood loss (EBL), the volume of cell salvaged blood, fluid management data, and transfusion-related complications. Postoperative data collected included postoperative GK angle, correction rate, total postoperative blood loss, and early complications.

Surgery

Sixty-seven patients underwent single-stage PSO for the correction of thoracolumbar kyphotic deformity. All operations were performed by a single spinal surgeon with 11 years of experience. During the surgery, the patient was placed in prone position on an adjustable arch-shaped frame, leaving the abdomen free to decrease inferior vena cava pressure. The patient's shoulder, chest, and pelvis were supported by soft bolsters. Comprised meticulous subperiosteal plane dissection, firm packing, expeditious instrumentations and electrocau-

tery were used to minimize intraoperative blood loss. Two drains were routinely placed under the muscles of the back at the end of surgery to allow continuous suction. The volume of drainage was recorded every day and the drainage was removed no later than postoperative day 3, when output volume diminished below 100 ml over 24 hours.

Anesthesiology

All patients underwent standard general anesthetic protocol. The patients were induced by intravenous midazolam (0.05 mg/kg), fentanyl (5 µg/kg), propofol (2-3 mg/kg), and vecuronium (0.1 mg/kg), or succinylcholine (100 mg). After anesthetic induction, the patients were intubated with an armored endotracheal tube. Anesthesia was maintained by continuous infusion of propofol, remifentanyl, dexmedetomidine and cisatracurium to sustain bispectral index within 40-60. Continuous electrocardiogram, bispectral index, anal temperature, heart rates, end-tidal carbon dioxide, invasive arterial blood pressure, central venous pressure, urine output and blood-gas analysis were routinely monitored during the intraoperative period. All patients underwent wake-up tests and neurophysiological monitoring (somatosensory and motor-evoked potentials) to determine whether spinal neurologic impairment occurred or not during surgery. Perdipine and nitroglycerin were used to achieve a target mean arterial pressure between 65 and 75 mmHg unless contraindicated. After the surgery, the patients were sent to postanesthesia care unit. The endotracheal tube was removed when the patients woke up and resumed spontaneous ventilation.

Transfusion

Decision of transfusion was made intraoperatively by the attending anesthesiologist and on the ward by the patient's surgical team after surgery. Transfusion decisions were informed in the following cases: i) symptomatic anemia such as hypotension that was inadequately responsive to fluid challenge; ii) hemoglobin concentration of less than 80 g/L; or iii) hemoglobin level less than 100 g/L with signs of hemodynamic instability (e.g. tachycardia, poor peripheral perfusion). Transfusion of fresh frozen plasma was recommended in the setting of massive transfusion to prevent dilutional coagulopathy. Transfusion-related complications

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Table 2. Surgical variables and fluid management of AS patients undergoing PSO (N = 67)

	One-level osteotomy (N = 55)	Two-level osteotomy (N = 12)
Surgical variables		
Duration of surgery (min)	381.45 ± 64.79	508.75 ± 76.13
Number of level fused	7.40 ± 0.99	8.25 ± 1.13
Number of screw placed	14.72 ± 1.97	16.16 ± 2.32
Postoperative GK angle (°)	31.80 ± 19.50	53.50 ± 21.93
Correction rate (%)	57.81 ± 21.48	51.16 ± 21.33
Fluid management		
Intraoperative EBL (ml)	2729.09 ± 1360.37	3679.16 ± 1620.81
EBL/EBV (%)	63.89 ± 35.83	97.92 ± 54.43
Postoperative blood loss (ml)	744.09 ± 354.75	766.91 ± 425.31
Crystalloids (ml)	2350.90 ± 798.40	2854.16 ± 808.88
Colloids (ml)	1990.90 ± 683.74	2416.66 ± 821.12
Allogeneic RBC (ml)	1887.27 ± 948.49	2591.66 ± 1169.66
Autologous RBC (ml)	0 (0, 695.00)	0 (0, 937.50)
FFP (ml)	400 (0, 625.00)	557.50 (85.7, 1081.25)

Note: Normally distributed continuous variables are expressed as means ± SD. Variables without normal distribution are expressed as median (25th, 75th) percentiles. GK, global kyphosis; EBL, estimated blood loss; EBV, estimated blood volume; RBC, red blood cell; FFP, fresh frozen plasma; SD, standard deviation. EBV was calculated according to the formula described by Nadler. For males: $EBV = (0.3669 \times \text{height}^3/10^6 + 0.03219 \times \text{weight} + 0.6041) \times 1000$; for females: $EBV = (0.3561 \times \text{height}^3/10^6 + 0.03308 \times \text{weight} + 0.1833) \times 1000$.

were monitored and defined as any undesirable clinical occurrence in any study patient.

The intraoperative EBL was determined by the anesthetist as the sum of gauze weight and the difference between suction and irrigation volumes. The estimated blood volume (EBV) was calculated according to the formula described by Nadler et al. [7].

Statistical analysis

Qualitative variables were expressed as absolute count and percentage, while quantitative variables were expressed as means and standard deviation if normally distributed, or medians and 25th and 75th percentiles if not normally distributed. The information of blood loss was presented as percent EBL/EBV. Pearson's correlation tests were used to identify linear relations between EBL/EBV percentage and independent variables. Variables entered into the stepwise multiple regression analyses were those that showed significant relations ($P < 0.05$) with percent EBL/EBV. All P values were two-sided, and statistical significance was

assumed when $P < 0.05$. Statistical analysis was performed using SPSS 21.0 software (SPSS Inc, Chicago, IL, USA).

Results

Demographics and information of surgical procedures are not different between patients undergoing two-level osteotomy and patients undergoing one-level osteotomy

To determine the factors that were correlated with blood loss, retrospective analysis was performed in 67 AS patients who underwent PSO for the correction of thoracolumbar kyphosis. A total of 61 males (91%) and 6 females (9%), with an average age of 33.9 years, underwent the surgery. The average height of male patients was 169.18 ± 6.05

cm, and female patients had an average height of 153.50 ± 15.24 cm. The major comorbid conditions were cardiovascular disease ($n = 35$; 52.2%) and pulmonary disease ($n = 56$; 83.5%). There were 6 patients without comorbidity, and 28 patients with two comorbid conditions. The preoperative GK angle averaged $79.08^\circ \pm 24.11^\circ$ and ranged from 34° to 133° . Laboratory test results showed that male patients had a higher mean value of hemoglobin than that of female patients. However, according to the preoperative hemoglobin value, 13 male patients should be diagnosed with anemia symptom (**Table 1**). For the correction of thoracolumbar kyphosis in AS patients, 79 PSO procedures were performed in 67 patients, including 55 and 12 patients undergoing one-level and two-level vertebral osteotomy procedures, respectively. Most of the vertebral osteotomy procedures (55 of 79) were performed at L1 vertebral body and L2 vertebral body. Two-level vertebral osteotomy procedure was performed at the following segments: T12 and L1 vertebral bodies in one patient, T12 and L3 vertebral bodies in one patient, L1 and

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Table 3. Univariate correlations with EBL/EBV percentage (N = 67)

Variables	Pearson's correlation r	Significance P value (2-tailed)
Demographics		
Sex (1 = male, 2 = female)	0.469	0.000
Age (yr)	-0.084	0.501
Weight (kg)	0.043	0.727
Height (cm)	-0.351	0.004
BMI (kg/m ²)	0.043	0.727
ASA grade (1 = I, 2 = II)	-0.056	0.651
Cardiovascular disease (1 = yes, 2 = no)	-0.001	0.996
Respiratory disease (1 = yes, 2 = no)	-0.054	0.662
Preoperative hematologic tests		
Hemoglobin (g/L)	-0.131	0.292
Hematocrit (%)	-0.129	0.298
Platelet count ($\times 10^9/L$)	-0.050	0.690
PT (s)	-0.007	0.955
APTT (s)	-0.030	0.811
INR	-0.002	0.988
Surgical variables		
Preoperative GK angle (°)	0.097	0.433
Postoperative GK angle (°)	0.012	0.925
Correction rate (%)	0.029	0.815
Operation time (min)	0.384	0.001
Osteotomy (1 = one-level, 2 = two-level)	0.317	0.009
Number of fused levels	-0.059	0.635
Number of placed screws	-0.136	0.273

Note: The relationships between all variables and dependent variables (percent EBL/EBV) were examined using Pearson's bivariate correlations. All P values less than 0.05 were considered significant. BMI, body mass index; EBV, estimated blood volume; ASA, American Society of Anesthesiologists; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ration; GK, global kyphosis; EBL, estimated blood loss; FFP, fresh frozen plasma.

L4 vertebral bodies in six patients, and L2 and L5 vertebral bodies in four patients (**Figure 1**). These data indicated that demographics and information of surgical procedures are not different between patients undergoing two-level osteotomy and patients undergoing one-level osteotomy.

Patients undergoing two-level osteotomy lose more blood and have higher EBL/EBV percentage than patients undergoing one-level osteotomy

To compare the differences with regard to operative parameters between one-level and two-level vertebral osteotomy procedures, surgical variables and fluid management of AS patients undergoing PSO were measured. The length of

operation for one-level and two-level PSO averaged 381.45 ± 64.79 minutes and 508.75 ± 76.13 minutes, respectively. The average EBL for one-level and two-level PSO was 2729.09 ± 1360.37 ml and 3679.16 ± 1620.81 ml, respectively. In addition, patients with two-level PSO were transfused with more volume of crystalloids, colloids, allogeneic red blood cells, and fresh frozen plasma (**Table 2**). No transfusion-related complications were found during surgery. In addition, the average EBL/EBV percentage of these patients was $69.98 \pm 41.44\%$, and the maximum value was 248.52%. The EBL/EBV percentage for one-level and two-level PSO averaged $63.89 \pm 35.83\%$ and $97.92 \pm 54.43\%$, respectively (**Table 2**). There were 3 female patients and 7 male patients who lost more than one volume of their own total blood in the operation. These data indicated that patients undergoing two-level osteotomy lost more blood and had higher EBL/EBV percentage than patients undergoing one-level osteotomy.

Male gender and two-level vertebral osteotomy are the

two significant predictive factors for increased EBL/EBV percentage

To test which factors were correlated with blood loss, the correlation of variables with EBL/EBV percentage was investigated. The EBL/EBV percentage had a significant correlation with sex ($r = 0.469$; $P = 0.000$), height ($r = -0.351$; $P = 0.004$), operative time ($r = 0.384$; $P = 0.001$), and type of osteotomy ($r = 0.317$; $P = 0.009$) (**Table 3**). Multiple stepwise regression model was used to identify independent predictors of increased EBL/EBV percentage. The model showed that two significant predictors for increased EBL/EBV percentage were male sex ($P = 0.000$) and two-level vertebral osteotomy ($P = 0.016$) (data not shown). Our model could account for 26.5% of the variability in EBL/EBV

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percentage ($R^2 = 0.265$). These data suggested that male gender and two-level vertebral osteotomy were the two significant predictive factors for increased EBL/EBV percentage.

Discussions

Hemorrhage is an ongoing research subject because of its importance in the performance of corrective spinal surgery. With the increase in the number and complexity of corrective spinal surgeries, the possibility of greater hemorrhage is increasing. AS, a chronic inflammatory rheumatic disease, can affect axial skeleton and cause inflammatory back pain [8]. AS patients usually take analgesic medications such as non-steroidal-anti-inflammatory (NSAIDs) to relieve pain and reduce inflammation [9]. However, this could decrease platelet function [3]. In addition, many AS patients are poorly nourished and relatively poor in general physical status, which may adversely influence coagulation and bleeding. Advanced AS patients should undergo surgical interventions for refractory pain and physical disability. However, prediction of blood loss in PSO for the correction of thoracolumbar kyphosis in AS patients was difficult for anesthesiologists.

Some investigators had already examined the effects of one or several factors on blood loss in spinal surgery. The factors that could put patients at increased risk for greater intraoperative blood loss were gender [4, 5], vertebral osteotomy [3, 6], preoperative Cobb angle [4, 10], the number of fused levels [6, 10, 11], operative time [4, 10], the patient's diagnosis [12, 13], the experience of surgeon and distension of the epidural veins [14]. Our patients underwent PSO for the correction of thoracolumbar kyphotic deformity by shortening the posterior column, which could restore their ability to see ahead, relieve compression of abdominal viscera by rib margin, and improve diaphragmatic respiration. There were 55 and 12 patients undergoing one-level and two-level vertebral osteotomy, respectively. The results of our study suggested that two important factors, male sex and two-level vertebral osteotomy, could predict the likelihood of EBL/EBV percentage in AS patients undergoing PSO for the correction of thoracolumbar kyphosis.

One of the two predictors, male gender, should be responsible for EBL/EBV percentage. As

reported by Ialenti *et al.* [4] and Zheng *et al.* [5], male sex was a risk factor for intraoperative hemorrhage during spinal surgery. The results were in accordance with a previous report in posterior lumbar spine fusion [15]. This may be related to the fact that male patients inherently have a higher value of hemoglobin and greater weight than female patients. Males with more muscle mass are likely to lose more blood because they probably require greater manipulation and longer operative time to achieve adequate correction. Similarly, our results also suggested that male sex was a predictor for increased EBL/EBV percentage in AS patients undergoing PSO for thoracolumbar kyphosis.

Another predictive factor identified in our study was two-level vertebral osteotomy that could contribute to blood loss. In order to achieve adequate correction for patients with rigid curves, multiple corrective osteotomies and greater surgical manipulation are often performed [16]. During surgery, the exposure of the spine and the stripping of muscles off bones could put patients at increased risk of greater blood loss. Under this circumstance, surgeons had no ideal methods to control bleeding [17]. Hu *et al.* [3] demonstrated that patients undergoing vertebral osteotomy could bleed as much as 4700 ml. Yu *et al.* [6] reported that patients undergoing vertebral osteotomy had risk of excessive blood loss 4.64 times higher than those who did not undergo vertebral osteotomy. Similarly, our study suggested that patients undergoing two-level vertebral osteotomy had higher EBL/EBV percentage than those who underwent one-level vertebral osteotomy.

Some other points of our study should be mentioned. Although our data analysis was retrospective, the patient data capture was complete, minimizing the likelihood of any referral bias. In addition, we chose the way that presented the information of blood loss by calculating blood loss as a percentage in relation to patients' EBV. Compared with absolute blood loss, representation of blood loss as EBL/EBV percentage would be more convincing because it takes patient size into account. The last but not the least, all patients underwent the same surgical intervention and these operations were performed by a single experienced spine surgeon. This could eliminate the effect of surgical intervention and the training level of sur-

geons on blood loss. Our study also showed that the operative time was correlated with EBL/EBV percentage ($r = 0.384$, $P = 0.001$). However, operative time was excluded from the multiple regression analysis because it was determined by the extent and complexity of the surgery and the surgeon's skills. Operative time could not be used to predict blood loss in spinal surgery because it could not be determined before surgery.

However, our study still has some limitations and shortcomings. First, the characteristics of retrospective study design meant that some important data were unavailable such as non-steroidal anti-inflammation related to blood loss, because patients were not likely to tell their physicians about their intakes of non-prescription drugs. Second, our multivariable analysis could account for only 26.5% of the variability due to the relatively small number of patients ($N = 67$). Further studies with larger number of patients are needed and multicenter trials would be more convincing. Third, we presented the information of intraoperative blood loss by visual estimation rather than direct measurement. This could possibly result in overestimation of intraoperative blood loss by 40% on average [18]. Fourth, our study may have included patients with subclinical coagulation or platelet abnormalities, which could possibly affect blood loss. However, they did not undergo rigorous preoperative laboratory testing in our hospital.

In summary, AS patients undergoing PSO for the correction of thoracolumbar kyphotic deformity can have substantial intraoperative hemorrhage, with some risk factors being predictable and some others not. Our results indicated that male sex and two-level vertebral osteotomy were the two important predictors. Knowledge of these predictors should help anesthesiologists make more adequate preoperative preparations, and guide the use of more appropriate blood conservation techniques.

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Disclosure of conflict of interest

None.

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