Association between intraoperative fluid overload and postoperative debridement in major sacrum tumor resection: A propensity score matching study

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Abstract
Intra-aortic balloon occlusion (IABO) is used to reduce intraoperative bleeding and facilitate successful sacrum tumor resection. Up to 20% of patients experience postoperative wound healing problems, but the risk factors related to this complication have not been clearly defined. The anesthetic database of Peking University People’s Hospital, Beijing, China, was searched for all patients (aged 14-70 years old) who underwent sacrum tumor surgery with the application of IABO from 2014 to 2017. Data from 278 patients with an aortic occlusion duration of 72 ± 33 minutes were collected. Fifty-six patients required postoperative debridement because of wound infection. The independent risk factor identified by logistic regression was fluid excess (calculated as volume infused minus blood loss and urine output divided by body weight [kg]), and decision tree analysis revealed that the cutoff point for fluid excess was 38.5 mL/kg. Then patients were then divided into high fluid excess group (fluid excess > 38.5 mL/kg) and low fluid excess group (fluid excess ≤ 38.5 mL/kg) and 91 pairs of patients were generated through propensity score matching (PSM). Fluid excess was significantly higher in the high fluid excess group (46 vs 30 mL/kg, P < .001), and more patients required postoperative debridement than in the low fluid excess group (24 (26.3%) vs 12 (13.1%), P < .001). In this retrospective PSM study on sacrum tumor resection, fluid overload was related to postoperative debridement and further studies are needed to improve the clinical prognosis.

Abbreviations: ASA = American Society of Anesthesiologists, BIS = bispectral index, CRC = concentrate red cells, CSF = cerebrospinal fluid, FFP = frozen fresh plasma, IABO = intra-aortic balloon occlusion, ICU = Intensive Care Unit, PSM = propensity score matching.

Keywords: clinical outcomes, fluid therapy, intra-aortic balloon occlusion, sacrum tumor

1. Introduction
Sacrum tumor resection is characterized by massive bleeding due to complex anatomy and abundant blood supply to the tumor. Surgical removal with adequate margins remains the most definite treatment strategy, but perioperative management is complicated due to sacral nerves involvement, excessive bleeding and tumor malignancy. In recent years, some technological improvements have revolutionized surgical resection of sacrum tumor, including extremity saving strategy, one-stage sacrum reconstruction and blood loss control measures (intra-aortic balloon occlusion).[1,4] Blood loss control measures are crucial in modern surgical removal of sacrum tumor. Other than aortic clamping, intra-aortic balloon occlusion (IABO) has been applied to reduce distal arterial blood flow, substantially decrease intraoperative blood loss, and shorten the duration of surgery.[6] It is therefore applied in patients with identified risk factors, including tumor volume more than 200 cm³, tumor invading cephalad to the S2-S3 disc space, or tumor with an abundant blood supply.[7,8]

In case of massive bleeding, fluid repletion and blood product transfusion are often adopted to stabilize macrocirculation and microcirculation. Even though goal-directed fluid therapy with preload optimization improved clinical outcomes, the optimal fluid infusion strategy for major surgery has currently not established.[9] A moderate liberal approach, that is achieving a positive balance of 1 to 2 L at the end of major surgery is recommended to avoid acute kidney injury related with restrictive fluid management.[9] And infusing too much could

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The datasets generated during and/or analyzed during the current study are publicly available. Mendeley Data, V2, doi: 10.17632/6rrtmbsxtt.2

The study protocol (2020PHB107) was approved by the Ethics Committee of Peking University People’s Hospital, Beijing, China (Chairperson Prof S. Mu), which waived the requirement for informed consent because of the retrospective design.

Part of the study was presented as a poster in 2018 International Anesthesia Research Societies annual meeting, Chicago, USA. Abstract ID 1497.

Observational Study

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result in tissue edema, which was associated with tissue-healing complications. As shown in our previous study involving 387 patients who received sacrectomy from 1997 to 2009, 113 (29.2%) patients suffered from wound infection or dehiscence, and the average blood loss was 3215 mL but the maximum infusion volume at the end of surgery was 10 L. The big gap between fluid gain and fluid loss during major sacrum tumor resection, and its relationship with postoperative complications should be investigated.

Hence, in this retrospective case-control study, we collected sacrum tumor surgery data, aiming to explore perioperative predictors of postoperative debridement with the focus on the effect of fluid overload.

### 2. Materials and Methods

The anesthetic database of Peking University People’s Hospital was searched for all patients (aged between 14 and 70 years of old) who received sacrum tumor surgery from May 1, 2014 to April 30, 2017. Anesthesia records and medical charts were reviewed to document anesthesia management details, blood loss, fluid therapy, pathological diagnosis and length of hospital stay. Emergent procedures, surgeries on the lumbar spine and sacrum simultaneously, on the pelvis or not using IABO were excluded. The study protocol (2020PHB107) was approved by the Ethics Committee of Peking University People’s Hospital, Beijing, China (Chairperson Prof S. Mu), which waived the requirement for informed consent because of the retrospective design. This article complied with the STROBE guidelines for a case-control study.

#### 2.1. Anesthesia management

All patients were induced with intravenous anesthetics, propofol 1.5 to 2.5 mg/kg, sufentanil 0.3 μg/kg and rocuronium 0.6 mg/kg. Anesthesia maintenance was accomplished by sevo-flurane inhalation, continuous propofol and remifentanil infusion to achieve bispectral index (BIS) range of 40 to 60. An arterial line through one radial artery and a central line through the right internal jugular vein were established after anesthesia induction.

#### 2.2. Balloon insertion and intraoperative use

All patients received temporary IABO during surgery because they were with risk factors of suffering from intraoperative extensive bleeding (blood loss > 2000 mL), including tumor volume more than 200 cm³, tumor invading cephalad to the S2-S3 disc space, or tumor with an abundant blood supply. Patients were assessed routinely through computed tomography and computed tomography angiography about their risks of intraoperative extensive bleeding.

Insertion of intra-aortic balloon was accomplished after anesthesia induction. Patients’ right femoral artery was punctured with an 11F percutaneous introducer sheath (CROSSOVER, Cordis), through which a double-lumen balloon catheter (MAXILD; Cordis, a Johnson & Johnson company, Bridgewater, New Jersey) was inserted into the abdominal aorta. Under the guidance of an X-ray C-arm, the balloon was positioned distal to the superior mesenteric artery and both renal arteries.

When the surgeons were ready to remove the tumor mass, the aortic balloon catheter was inflated to occlude the aorta completely. After the surgeons removed the tumor and positioned the pedicle screws, the aortic balloon was deflated. In order to conquer the pathologic alterations such as ischemic reperfusion brought by the IABO release, minimizing aortic occlusion duration, gradual release of the balloon and close monitoring of blood gas analysis after aortic balloon deflation were recommended.

#### 2.3. Intraoperative bleeding management and fluid therapy

The surgeons and anesthesiologists estimated the intraoperative blood loss as the exact volume of suction and the estimated volume absorbed by sponges and dressings. Concentrate red cells (CRC) were given when hemoglobin decreased to 80 g/L. Usually frozen fresh plasma (FFP) was prescribed in a 1:1 ratio with CRC. For intraoperative fluid therapy, Ringer’s lactate and hetastarch (Voluven® 130/0.4; maximum volume being 1000 mL) were used to maintain a central venous pressure above 4 mm Hg. Blood pressure less than 90/60 mm Hg would be treated with ephedrine 6 mg.

After the surgery most patients recovered and were extubated in the postoperative care unit.

#### 2.4. Outcome measurement

Postoperative surgical debridement during hospitalization undergone in the operating room was recorded, as well as prolonged length of stay (>28 days). Other complications such as cerebrospinal fluid (CSF) leak and thrombosis of femoral artery (due to aortic balloon insertion, indwelling or extraction) were also documented. Fluid excess was calculated as volume infused (crystalloid, colloid, CRC and FFP), minus volume lost (blood loss and urine output), divided by body weight (kg).

#### 2.5. Statistical analysis

Statistical analysis was performed using the SPSS 20.0 statistical software package (SPSS Inc., Chicago, IL). Continuous variables are expressed as mean ± SD or medians (Q1, Q3) and categorical variables as numbers and percentages. Chi square or Fisher’s exact test was used for univariate analysis. Multivariate logistic regression was adopted to identify risk factors for postoperative debridement and prolonged length of stay (>28 days).

The cutoff point for different risk variables would be identified through decision tree analysis, that is, classification and regression trees.

Patients would be divided into two groups, that is high fluid excess group (whose fluid excess was beyond the cutoff point) and low fluid excess group (whose fluid excess was lower than or equal to the cutoff point). Propensity score matching (PSM) was carried out between two groups in order to reduce the effect of potential confounding factors and the collinearity of blood loss and fluid excess. PSM groups would be generated with similar demographic, surgical and anesthetic profiles and the incidence of postoperative debridement would be compared between matched groups.

### 3. Results

A total of 410 patients were identified as patients received sacrectomy for the study. Then 132 patients were excluded after chart review as their actual surgeries were on the lumbar spine.
and sacrum simultaneously (n = 40), on the pelvis (n = 15) or not using IABO (n = 77). In the end, data of 278 patients who received temporary IABO were analyzed (Table 1, Fig. 1).

Of all the patients, 270 received posterior sacrum tumor resection and reconstruction, and 8 patients received En bloc resection with reconstruction through posterior approach only. The average duration of IABO was 72 ± 33 minutes, and 4 out of 278 patients required two episodes of occlusion (occlusion duration 85 & 50, 65 & 25, 80 & 120, 150 and 130 minute) due to surgical complexity or high tumor malignancy.

Fifty-six patients required surgical debridement due to wound infection during hospitalization and 49 patients suffered from prolonged hospital stay (>28 days) (Table 1).

3.1. Risk assessment of postoperative debridement
In multivariate logistic regression model, 2 factors including duration of anesthesia (OR 1.005, 95% CI (1.001, 1.009), P = .039), and fluid excess (OR 1.025, 95% CI (1.007, 1.044), P = .008) constructed the model (Fig. 2A). Fluid excess was

### Table 1

| Fluid excess > 38.5 mL/kg (n = 111) | Fluid excess ≤38.5 mL/kg (n = 167) | Statistical value | P Value | Fluid excess > 38.5 mL/kg (n = 91) | Fluid excess ≤38.5 mL/kg (n = 91) | Statistical value | P Value |
|-----------------------------------|-----------------------------------|-------------------|--------|-----------------------------------|-----------------------------------|-------------------|--------|
| Male gender                       | 56 (50.4%)                        | 92 (55.0%)        | 0.576  | 46 (50.5%)                       | 45 (49.4%)                       | 0.002             | 1.000  |
| Age (years)                       | 45 ± 15                           | 53 ± 16           | 4.081  | .001*                            | 45 ± 13                          | 44 ± 15            | .0123  | .903   |
| Height (cm)                       | 164 ± 6.2                         | 166 ± 6.2         | 0.63   | .26                              | 164 ± 5.3                        | 164 ± 5.3          | .356   | .722   |
| Weight (kg)                       | 63.2 ± 6.9                        | 67.6 ± 9.8        | 0.166  | .434                             | 64.6 ± 5.8                       | 64.3 ± 6.6         | .298   | .766   |
| ASA classification (n)            | 0.927                             | .609              |        |                                  |                                   | 0.444             | .801   |
| Diagnosis (n %)                   | 0.29                              | .865              |        |                                  |                                   | 0.207             | .901   |
| Benign                             | 42 (37.8%)                        | 58 (34.7%)        |        |                                  | 33 (36.3%)                       | 34 (37.4%)         |        |        |
| Malignant                          | 54 (46.6%)                        | 86 (51.4%)        |        |                                  | 46 (50.5%)                       | 47 (51.6%)         |        |        |
| Metastatic                         | 15 (13.5%)                        | 23 (13.7%)        |        |                                  | 12 (12.3%)                       | 10 (10.9%)         |        |        |
| Recurrent tumor (n)               | 33 (29.7%)                        | 59 (35.3%)        | 0.354  | .200                             | 28 (28.5%)                       | 34 (37.4%)         | 1.591  | .270   |
| Total En bloc (n)                 | 8                                 | 0                 | 2.267  | .132                             | 222.2%                          | 303.3%             |        |        |
| Duration of surgery (min)         | 294 (76)                          | 190 (65)          | -2.801 | <.005*                           | 200 (70)                         | 190 (70)           | -1.456 | .145   |
| Duration of anesthesia (min)      | 303 ± 65                          | 265 (62)          | -4.028 | .000*                            | 290 (75)                         | 276 (76)           | -0.908 | .364   |
| Duration of aortic occlusion (min)| 70 (30)                           | 60 (30)           | -2.273 | .023*                            | 65 (40)                          | 65 (40)            | -0.207 | .836   |
| Hemoglobin before surgery (g/L)   | 102 ± 7.5                         | 102 ± 7.6         | -1.08  | .281                             | 101 ± 7.5                        | 103 ± 7.2          | -1.454 | .148   |
| Hemoglobin after surgery (g/L)    | 83.4 ± 5.0                        | 83.4 ± 5.1        | 0.0    | 1.0                              | 83.4 ± 5.0                       | 83.2 ± 5.1         | 0.190  | .850   |
| Patients required ephedrine (n %) | 10 (9.0%)                         | 16 (9.6%)         | 0.021  | .885                             | 10 (10.9%)                       | 14 (15.3%)         | 0.768  | .331   |
| Blood loss (mL)                   | 1200 (1200)                       | 1100 (700)        | -2.704 | .038*                            | 1100(1000)                       | 1100 (1150)        | -0.501 | .617   |
| CRC infused (mL)                  | 780 (520)                         | 520 (260)         | -4.719 | <.001*                           | 780 (520)                        | 520 (260)          | -3.069 | .002   |
| FFP infused (mL)                  | 600 (600)                         | 400 (400)         | -5.697 | <.001*                           | 600 (400)                        | 400 (400)          | -2.757 | .006   |
| Crystalloid/colloid (mL)          | 3820 (1160)                       | 2780 (800)        | -9.795 | <.001*                           | 3740 (1200)                      | 2820 (840)         | -7.393 | <.001* |
| Fluid excess (mL/kg)              | 47.5 (17)                         | 28.6 (12)         | -14.119| <.001*                           | 46 (15)                         | 30 (11)            | -11.625| <.001* |
| Complications                     | Extensive bleeding (n %)          | 32                 | 29     | 5.116                             | 21                               | 20                 | 0.031  | 1.000  |
| Debridement (n %)                 | 32 (28.8%)                        | 24 (14.3%)        | 8.664  | .004                             | 24 (26.3%)                       | 12 (13.1%)         | 4.986  | .04*   |
| ICU (n %)                         | 8 (7.2%)                          | 9 (5.3%)          | 0.384  | .612                             | 5 (5.4%)                         | 5 (5.4%)           | 0.000  | 1.000  |
| CSF leak (n %)                    | 8 (7.2%)                          | 5 (2.9%)          | 2.665  | .146                             | 2.2%                            | 2 (2.2%)           | 2.2%   | 1.000  |
| Thrombosis (n %)                  | 6 (2.2%)                          | 2 (2.0%)          | 0.028  | .818                             | 2.2%                            | 2 (2.2%)           | 0.000  | 1.000  |
| Length of stay (days)             | 21 (15)                           | 18 (10)           | -3.987 | <.001*                           | 21 (14)                         | 20 (13)            | -0.432 | .666   |
| Prolonged hospital stay (n %)     | 49 (17.6%)                        | 5 (6.4%)          | 5.794  | .016*                            | 21 (23.1%)                       | 15 (16.2%)         | 1.247  | .352   |

Data shown in mean ± SD, median (IQR), n (%). ASA = American Society of Anesthesiologist, CRC = concentrate red cell, CSF = cerebrospinal fluid, FFP = frozen fresh plasma, ICU = intensive care unit, IQR = interquartile range, PSM = propensity score matching, SD = standard deviation; .

Fluid excess = fluid infused (including CRC and FFP) – (blood loss + urine output)/body weight. Extensive bleeding was defined as intraoperative blood loss > 2000 mL. Prolonged hospital stay was defined as hospital stay longer than 28 days.

* P < .05. PSM propensity score 0.02. The propensity score was calculated by logistic regression analysis using the following covariates: age, gender, height, body weight, ASA grade, duration of aortic occlusion, duration of surgery and duration of anesthesia, pathology and blood loss.
identified as a risk factor in multivariate logistic regression (OR 1.021, 95% CI (1.002, 1.041)), as each milliliter per body weight fluid excess infused resulted in 2.1% increase of debridement possibility. It was noticeable that extensive bleeding (intraoperative bleeding > 2000 mL) (OR 1.763, 95% CI (0.913, 3.406), \( P = .091 \)) was not selected for model construction. Decision tree analysis was applied to identify the cutoff value for excess fluid infusion, which showed that for those whose intraoperative fluid excess exceeded 38.5 mL/kg were more likely to suffer from wound infection, 32/111 (28.8%) versus 24/167 (14.4%), OR 2.302 (1.246, 4.251), \( P = .008 \) (Fig. 2C). Then patients were divided into high fluid excess group (fluid excess > 38.5 mL/kg) and low fluid excess group (fluid excess ≤ 38.5 mL/kg).

### 3.2. PSM for fluid excess analysis

In order to reduce the effect of potential confounding factors and the collinearity of blood loss and fluid excess (Fig. 3), PSM was carried out between two groups. The propensity score was calculated by logistic regression analysis using the following covariates: age, gender, height, body weight, ASA grade, duration of aortic occlusion, duration of surgery and duration of anesthesia, pathology and blood loss. After calculating the propensity scores, we used the nearest-available neighbor matching method with a caliper radius score of 0.02 to pair the participants from each group in a 1:1 ratio based on the propensity score similarities (Table 1).

Ninety-one matched pairs were generated using the PSM, which was effectively performed for both groups to counterpoise each preoperative variable. After matching, the duration of aortic occlusion, surgery and anesthesia, and blood loss were comparable between two groups, but fluid excess was significantly different (46 vs 30 mL/kg, \( P < .001 \)). More patients in high fluid excess group required postoperative debridement than patients in low fluid excess group (24 (26.3%) vs 12 (13.1%), \( P < .001 \)). More patients tended to have prolonged length of stay in High fluid excess group than patients in Low fluid excess group (21 (23.1%) vs 15 (16.2%), \( P = .352 \)).

### 3.3. Risk assessment of other adverse events

Forty-nine patients suffered from prolonged hospital stay, and the independent risk factor was postoperative debridement,

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**Figure 1.** Trial profile. The anesthetic database of Peking University People’s Hospital was searched for all patients (aged between 14 and 70 years of old) who received sacrum tumor surgery from 2014 to 2017. Data of 278 were analyzed.

**Figure 2.** Logistic regression and decision tree analysis for complications related with sacrum resection. (A) Multivariate regression for postoperative debridement. (B) Multivariate regression for prolonged hospital stay. (C) Decision tree analysis for fluid excess as a risk factor of postoperative debridement.
10 patients having a tumor-free survival in a 3-year follow-up. 

Reduced surgical burden and stress on the patients, with 7 out of bloc resection through posterior-only approach significantly sarcoma 0.2 per 100,000 patients per year. 

Therefore tumor oncological control. According to our previous study, En building the surgery databases and establishment of optimal centers with an annual caseload of 300 cases contributed to being 5500 mL during our study period. Sacrum tumor resection remains mainstay therapy for long-term oncologic control, 

Primary sacrum tumor is rare, as the incidence for chordoma was 0.08 per 100,000 patients, chondrosarcoma 0.5 per 100,000, and Ewing's sarcoma 0.2 per 100,000 patients per year. Therefore tumor centers with an annual caseload of 300 cases contributed to building the surgery databases and establishment of optimal oncological control. 

Even though surgical removal of sacrum tumor is difficult because of complex anatomy, sacral nerves involvement, massive bleeding and tumor malignancy. Primary sacrum tumor is rare, as the incidence for chordoma was 0.08 per 100,000 patients, chondrosarcoma 0.5 per 100,000, and Ewing's sarcoma 0.2 per 100,000 patients per year. Therefore tumor centers with an annual caseload of 300 cases contributed to building the surgery databases and establishment of optimal oncological control.

In our study, the fact that fluid overload was associated with postoperative debridement and sequential longer hospital stay, could be explained by the negative effect brought by large volume of infusion such as tissue edema. Fluid therapy is crucial, complicated and affects clinical outcomes in major surgeries. Actually the maximum fluid excess is 100 mL/kg during this three-hour surgery. In order to eliminate the collinearity between blood loss and infusion, propensity-matching score was applied. Ninety-one matched pairs of patients were generated with similar blood loss, similar duration of aortic occlusion, surgery and anesthesia. But fluid excess was significantly different and more patients in high fluid excess group suffered from surgical debridement than those in low fluid excess group. Given the fact that median blood loss of 1100 mL, repletion of blood loss with 780 mL CRC and 600 mL FFP, the infusion of 3740 mL crystalloid and colloid at the same time should be of concern.

Possible explanations for big fluid excess (median value 46 mL/kg in High fluid excess group) in this major bleeding procedure may include the following four. First, the optimal fluid management protocol for major surgery has not been established. Second, using CVP and blood pressure as the goal of resuscitation is not recommended in goal-directed therapy. Third, dynamic assessment of fluid responsiveness has not been adopted due to certain limitations. The prone position prohibited the use of esophageal cardiography, and the accuracy of fluid responsiveness assessment by Flotraq® in prone position and the aortic occlusion is not clear. Fourth, similarly, individualized hemodynamic monitoring and guidance was not used because of some restraints. Preload optimization could not be achieved as discussed above, goal cardiac index and indications of the vasopressors to balance the $V_{\text{stressed}}$ and $V_{\text{unstressed}}$ could not be applied appropriately as a result.

The red cell transfusion threshold of 80 g/L was adopted in this study to reduce homologous transfusion. The postoperative hemoglobin of 83 g/L showed the plausibility of our red cell transfusion protocol by not targeting at hemoglobin higher than 90 g/L. From the perspective of patient blood management, preoperative anemia should be corrected by using ferrum/erythropoietin and intraoperative cell salvage should be used to reduce homologous transfusion.

The institutional patient blood management program is determining detailed bundles to decrease blood product consumption and fluid therapy protocol in order to improve patients' outcomes. This study may be criticized for focusing on patients' in-hospital outcomes only and the nature of a retrospective design. We managed to present anesthesia management for this complicated surgery with large fluid shift, but follow-up information was not collected to investigate patients' walking ability, visceral function or pain intensity after discharge. Also Bonferroni correction should be considered in multiple multi-variable analysis. Since this was an exploratory study and the limited occurrence of complications, Bonferroni correction lacked feasibility in this study. Further studies are mandatory to investigate anesthesia refinement and patient blood management on long-term outcomes such as tumor recurrence and quality of life.

In conclusion, in this retrospective case-control study about sacrum tumor resection, fluid overload was related with high morbidity and further studies are needed to improve clinical prognosis.

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