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Research Paper

Risk factors of major intraoperative blood loss at primary debulking surgery for ovarian cancer

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ABSTRACT

Objective: The goal of this study was to find the risk factors for major intraoperative blood loss (MBL) of primary debulking surgery (PDS) for ovarian cancer.
Methods: Patients with ovarian cancer who underwent PDS in our hospital, from 2010 to 2017, were enrolled. The association between risk factors and MBL was modeled with the use of logistic regression. Receiver operating characteristic (ROC) curve analysis was used to determine the predictive value of the logistic regression model.
Results: A total of 346 patients met the inclusion criteria. There were 150 patients with MBL. Tumor stage 3/4 ($P < 0.001$), American Society of Anesthesiologists (ASA) score ≥3 ($P = 0.044$), ascites volume ≥500 ml ($P = 0.002$), radical or ultra-radical surgery ($P = 0.002$), and diabetes ($P = 0.035$) were independent risk factors for MBL in patients with ovarian cancer. The logistic regression combined model of these five factors is more reliable in the prediction of MBL with an area under the ROC curve of 0.729 than the tumor stage (ROC curve = 0.645) and surgical complexity (ROC curve = 0.568).
Conclusion: In patients with ovarian cancer, five risk factors for major intraoperative bleeding were identified. Planned surgical procedures and preoperative risk factors can be used to predict perioperative blood requirements.

1. Introduction

Anemia is a prognostic factor for survival in patients with ovarian cancer.[1] Patients experience a high rate of anemia that ranges from 19% to 95%.[2] Both primary cytoreductive surgery (PDS) and interval cytoreduction are the main causes of anemia. A previous report indicated that major intraoperative blood loss (MBL) was more common in PDS than in repeat surgery.[3] Intraoperative blood loss is associated with postoperative hematologic complications.[4] Severe blood loss can lead to a mortality rate of up to 20%, and increase ICU admission, hospital stay, and economic costs. Moreover, besides the risk of infection, blood transfusions will also reduce the survival time of patients with ovarian cancer. American Society of Hematology opposed transfusing more red blood cells (RBCs) than were necessary to relieve symptoms of anemia or return a patient to a safe level of hemoglobin5. Thus, it is important to assess the volume of intraoperative blood loss ahead of time. The identification of risk factors for MBL affects the management of bleeding, and bleeding can be reduced by preventive treatment according to the identified risk factors. Our objective was to identify risk factors that are associated with intraoperative blood loss of at least 1000 ml among patients with ovarian cancer and to propose a reasonable perioperative blood management strategy according to the risk factors.

2. Methods

The retrospective study was approved by the Institutional Review Board of the Peking University People's Hospital. Informed consent was waived because of the retrospective nature of this study. All patients with

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epithelial ovarian cancer (EOC) undergoing PDS at the Department of Gynecology Oncology, Peking University People's Hospital, from January 1, 2010 to December 31, 2017, were evaluated for the study.

Patients were required to have a diagnosis of EOC, having undergone PDS at our hospital, and having complete clinical data to be eligible for inclusion. Patients who had a hematologic disease or experienced hysterectomy before PDS, or had any other concomitant cancers or serious disease (eg, systemic lupus erythematosus, tuberculosis, organ failure) that may have affected our study were excluded.

The MBL is defined as ≥1000 ml during surgery.[6,7] Health profile, preoperative comorbidities, and perioperative data were all evaluated. Variables included ovarian cancer stage, American Society of Anesthesiologists (ASA) score, age, body mass index (BMI), comorbidities (comorbidities with high incidence: preoperative hypertension and diabetes), ascites, preoperative hematocrit level, hemoglobin, albumin, white blood cell and platelet count, surgical complexity, and the methods of operation (laparoscopic surgery or laparotomy operation). Standard surgery including unilateral/bilateral salpingo-oophorectomy, hysterectomy, omentectomy, appendectomy, pelvic lymph node dissection, para-aortic lymph node dissection, and appendicectomy; radical or ultra-radical surgery (surgical complex group) including any surgical procedures that exceed the elements mentioned above, such as intestinal resection, hepatectomy, and splenectomy. All of these factors were categorized into two types.

Patient characteristics were analyzed using frequency analysis. Univariate and multivariate analyses were used to evaluate factors predicting MBL. Univariate analysis was performed with the chi-square test to analyze the correlation between perioperative factors and MBL. Logistic regression analysis was performed on all possible influencing factors and MBL. Multivariable analyses were performed for variables with a *P*-value of <0.10 based on univariate analysis. Odds ratio (OR) and the corresponding 95% confidence intervals (CIs) were considered as relative risks. Receiver operating characteristic (ROC) curve analysis was used to determine the predictive value of risk factors for intraoperative blood loss of at least 1000 ml. All calculated *P* values were 2-sided. $P < 0.05$ was considered statistically significant for all statistical analyses. SPSS 20.0 was used to perform all statistical analyses.

3. Results

From January 2010 to December 2017, 346 patients with EOC met the inclusion criteria. There were 150 patients with intraoperative blood loss of at least 1000 ml. The main characteristics of the patients are summarized in Table 1. The mean age was 55.0 ± 10.1 (22–80) years, and the mean BMI was 24.0 ± 3.3 kg/m^2 (range 16.2–35.5). At diagnosis, 117 out of 346 patients (33.8%) had stage 1/2 EOC and 229 patients (66.2%) had stage 3/4 EOC according to the International Federation of Gynecology and Obstetrics (FIGO) classification. The histologic types include serous carcinoma (69.1%), mucinous carcinoma (2.9%), clear-cell carcinoma (13.6%), endometrial carcinoma (11.8%), and others (2.6%). Among all the patients, 85 (24.6%) patients had hypertension and 40 (11.6%) patients had diabetes. All surgical procedures performed during PDS are listed in Table 2. In addition to hysterectomy, salpingo-oophorectomy, omentectomy, lymphadenectomy, and appendectomy, the most frequent radical surgical procedure was intestinal resection, which was conducted in 27 patients (7.8%).

Multivariable analysis was performed for variables with a *P*-value <0.10 based on univariate analysis. Finally, FIGO stage 3/4 ($P < 0.001$), laparotomy operation ($P = 0.027$), radical or ultra-radical surgery ($P < 0.001$), ascites volume ≥500 ml ($P < 0.001$), ASA score ≥3 ($P = 0.002$), diabetes ($P = 0.011$), preoperative albumin <35 g/L ($P = 0.006$) and platelet >400 × 10^9/L ($P = 0.068$) were included in multivariable analyses (Table 3).

Finally, in the multivariable analyses, by comparing the MBL group (n = 150) and non-MBL group (n = 196), we found that MBL was more likely to occur in patients with FIGO stage 3/4 (125, 83.3% vs 105, 53.6%), ASA score ≥3 (23, 15.3% vs 10, 5.1%), ascites volume ≥500 ml (62, 41.3% vs 37, 18.9%), radical or ultra-radical surgery (26, 17.3% vs 6, 3.1%) and diabetes (25, 16.7% vs 15, 7.7%). FIGO stage 3/4 (OR 2.712, 95% CI, 1.576–4.666, $P < 0.001$), ASA score ≥3 (OR 2.373; 95% CI, 1.550–7.318, $P = 0.044$), ascites volume ≥500 ml (OR 2.254; 95% CI, 1.867–4.909, $P = 0.002$), radical or ultra-radical surgery (OR 4.644; 95% CI, 2.526–15.879, $P = 0.002$), and diabetes (OR 2.240; 95% CI, 1.223–4.761, $P = 0.035$) were independent risk factors for MBL in patients with ovarian cancer (Table 4).

The ROC curves indicated that the logistic regression model with 5 independent risk factors of FIGO stage III/IV, ASA score ≥3, ascites volume ≥500 ml, radical or ultra-radical surgery, and diabetes is more reliable in the prediction of MBL with an area under the ROC curve of 0.729 (CI, 0.676–0.782) than the tumor stage (ROC curve = 0.645, CI, 0.588–0.703) and surgical complexity (ROC curve = 0.568, CI, 0.506–0.630; Fig. 1).

Table 1
Baseline characteristics of 346 women with epithelial ovarian cancer who underwent primary debulking surgery.

Characteristics	N (%)
Age (years), mean (SD)	55.0 (10.1)
<65	291 (84.1)
≥65	55 (15.9)
BMI (kg/m^2), mean (SD)	24.0 (3.3)
<25	221 (63.9)
≥25	125 (36.1)
ASA score	
<3	313 (90.5)
≥3	33 (9.5)
Preoperative albumin (g/L)	
≥35	313 (90.5)
<35	33 (9.5)
FIGO stage	
I/II	117 (33.8)
III/IV	229 (66.2)
Histology	
Serous	239 (69.1)
Mucinous	10 (2.9)
Clear cell	47 (13.6)
Endometrioid	41 (11.8)
Other	9 (2.6)
Ascites volume (ml)	
≤500	247 (71.4)
>500	99 (28.6)
Intraoperative blood loss (ml)	
<1000	196 (56.6)
≥1000	150 (43.4)

ASA, American Society of Anesthesiologists; *BMI*, body mass index; *FIGO*, International Federation of Gynecology and Obstetrics; *SD,* standard deviation.

Table 2
Surgical procedures performed during primary debulking surgery.

Surgical procedures	No. of patients (%)
Unilateral/bilateral	344 (99.4)
Hysterectomy	346 (100.0)
Omentectomy	336 (97.1)
Appendectomy	261 (75.4)
Pelvic lymph node dissection	312 (90.2)
Para-aortic lymph node dissection	299 (86.4)
Intestinal resection	27 (7.8)
Hepatectomy	2 (0.6)
Splenectomy	2 (0.6)

4. Discussion

Due to the extensive nature of surgical procedures of ovarian cancer, cytoreductive surgery is often associated with massive blood loss.[8]

Table 3
Univariate analysis of risk factors for major intraoperative blood loss in ovarian cancer n (%).

Characteristics	MBL group (n = 150)	Non-MBL group (n = 196)	χ^2	*P* value
Age ≥65 years	26 (17.3)	29 (14.8)	0.375	0.556
BMI ≥25 kg/m^2	58 (38.7)	67 (34.2)	0.661	0.432
ASA score ≥3	23 (15.3)	10 (5.1)	10.309	**0.002**
FIGO stage 3/4	125 (83.3)	105 (53.6)	32.562	**< 0.001**
Preoperative chemotherapy	19 (12.7)	24 (12.2)	0.009	1.000
Ascites volume ≥500 ml	62 (41.3)	37 (18.9)	20.582	**< 0.001**
Laparotomy operation	150 (100)	186 (94.9)	5.477	**0.027**
Hypertension	38 (25.3)	48 (24.5)	0.021	0.901
Diabetes	25 (16.7)	15 (7.7)	6.629	**0.011**
Radical or ultra-radical surgery	26 (17.3)	6 (3.1)	20.420	**< 0.001**
Preoperative hemoglobin <110 g/ml	35 (23.3)	34 (17.3)	1.821	0.222
Preoperative albumin <35 g/L	22 (14.7)	11 (5.6)	7.952	**0.006**
White blood cell >10 × 10^9/L	13 (8.7)	9 (4.6)	2.318	0.181
Hematocrit <30%	10 (6.7)	12 (6.1)	0.036	1.000
Platelet >400 × 10^9/L	24 (16.0)	18 (9.2)	3.610	**0.068**

ASA, American Society of Anesthesiologists; BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; MBL, major intraoperative blood loss.

Table 4
Multivariate analysis for major intraoperative blood loss during primary debulking surgery n (%).

Characteristics	MBL group (n = 150)	Non-MBL group (n = 196)	Multivariable analysis adjusted OR (95% CI)	*P* value
FIGO stage III/IV	125 (83.3)	105 (53.6)	2.712 (1.576, 4.666)	**< 0.001**
ASA score ≥3	23 (15.3)	10 (5.1)	2.373 (1.026, 5.492)	**0.044**
Ascites volume ≥500 ml	62 (41.3)	37 (18.9)	2.254 (1.333, 3.813)	**0.002**
Radical or ultra-radical surgery	26 (17.3)	6 (3.1)	4.644 (1.787, 12.070)	**0.002**
Diabetes	25 (16.7)	15 (7.7)	2.240 (1.058, 4.744)	**0.035**

ASA, American Society of Anesthesiologists; FIGO, International Federation of Gynecology and Obstetrics; MBL, major intraoperative blood loss.

Intraoperative blood loss will not only cause anemia but also lead to many other postoperative hematologic complications. Comorbidities and intraoperative bleeding are the most relevant findings related to surgical complications.[9] Perioperative blood transfusion was also linked to an increased risk of total mortality and a reduction in the 3-year overall survival.[10] The mortality rate will rise to 34.4% when the postoperative hemoglobin levels fall to 4.1–5.0 g/dL.[11] To prevent these consequences in advance, a timely blood transfusion is needed. However, previous studies have indicated that blood transfusions are associated with increased perioperative morbidity and mortality.[12–16] To improve prognosis, allogeneic blood transfusions should be avoided, if possible, especially during surgery.[17] Therefore, we need to assess the possible intraoperative blood loss to prepare adequate blood.

The most MBL in our study was in the advanced stage ovarian cancer group (66.2%). In multivariable analysis, the occurrence of intraoperative blood loss of 1000 ml or more was associated with tumor stage, surgical complexity, ascites, ASA score, and diabetes. A previous study found that postoperative blood transfusion was associated independently with ascites and additional surgical procedures in patients undergoing hysterectomy for ovarian cancer.[2] This is in accordance with our results. Patient-based management with an appropriate preoperative evaluation

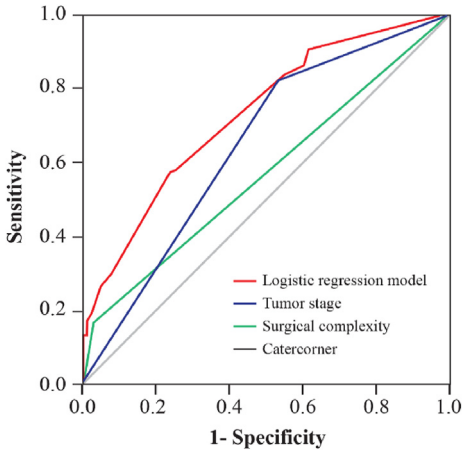

Fig. 1. Comparisons of ROC curves for logistic regression model of five independent risk factors, tumor stage, and surgical complexity for predicting MBL.

may also avoid morbidity of extended/extensive surgical approaches.[18,19] Vizzielli et al.[20] developed a simple adjusted laparoscopic score system. In their study, the degree of surgical complexity was related to the severity of postoperative complications and the degree of postoperative hemoglobin decline. Since surgical complexity is a crucial independent risk factor for MBL, in order to prepare an appropriate amount of blood, it is very important to assess the extent of resection before surgery, such as bowel resection, hepatectomy, splenectomy, and upper abdominal lymph node resection.[21,22] The most important prognostic factor at PDS is complete gross resection. But in a few cases, when blood resources are scarce, such as in the initial period of the pandemic of COVID-19 when people's social life was restricted, radical surgery for patients with advanced ovarian cancer may not be completed as planned due to lack of blood supply. In this particular situation, neoadjuvant chemotherapy (NACT) followed by interval debulking surgery is an alternative strategy. We also found that tumor stage and ASA score are independent risk factors for MBL. ASA class is also associated with transfusion of pelvic reconstructive surgery.[23] It indicates that the severity of the disease and the general conditions of patients are also important factors for intraoperative bleeding. Therefore, NACT is an alternative for advanced ovarian cancer patients with massive ascites and high ASA scores.

Our study showed that diabetes was an independent risk factor for MBL. The incidence rate of MBL was 62.5% for patients with diabetes and 40.8% for patients without diabetes. Diabetes is a common complication. Erik Stenberg et al.[24] also found that diabetes is a risk factor for intraoperative blood loss during laparoscopic gastric bypass surgery. Yu Zhao et al.[25] found that diabetes is positively correlated with hidden blood loss in laparoscopy for cervical cancer. Hidden blood loss cannot be ignored either. That means we also need to pay attention to patients with diabetes when assessing the volume of intraoperative blood loss. Previous report found that diabetes increased the risk for leakage.[26] Although diabetes is related to wound healing and infection, the micro- and macrovascular complications may increase the risk for postoperative bleeding.[24] Apoptosis, vascular inflammation, and endothelial permeability all affect the microangiopathy of diabetes. Vascular regression and loss of pericytes then cause hyperpermeability of the microangiopathy.[27] And all these may play a role in intraoperative blood loss. Hyperglycemia is considered one of the most common causes of Ang2 upregulation and Ang1 downregulation, both of which lead to vascular damage and destabilization of endothelial cells.[27] Therefore, preoperative blood glucose control is necessary for EOC patients with diabetes.

As mentioned above, we found five prediction factors of MBL through multifactor analysis, among which the largest amount of bleeding is in stage III/IV (82.8%). To achieve optimal tumor reduction, radical surgery is necessary. Therefore, tumor stage and radical or ultra-radical surgery

are generally recognized as the most important bleeding factors, which should occupy a larger weight value among the five factors. In order to better determine the predictive value of risk factors, a logistic regression model was established with these five risk factors. ROC curve analysis was used. The ROC curves indicated that the logistic regression model is more reliable in predicting value with an area under the ROC curve of 0.729 than tumor stage (ROC curve = 0.645) and surgical complexity (ROC curve = 0.568). The results showed that the predictive value of our regression model is better than the tumor stage and surgical complexity. Our results could be more useful in clinical practice in assessing the intraoperative blood loss volume. Thus, we may need to prepare more blood for patients with these risk factors. Besides intraoperative blood loss, we also need to pay attention to other causes of perioperative blood transfusions. Women selected for NACT were more likely to be anemic at diagnosis and became progressively anemic during NACT. Despite less blood loss during debulking surgery, it is observed that patients undergoing NACT received more blood transfusions perioperatively than patients undergoing PDS.[28]

Perioperative blood management is important for ovarian cancer patients undergoing cytoreductive surgery. Preoperative iron reserve examination may also need to be performed to ensure surgical safety. For patients with advanced ovarian cancer undergoing PDS, acute normovolemic hemodilution appears to reduce allogenic RBCs transfusion rates versus historical controls without increasing perioperative complications.[8] Intraoperative autologous blood transfusion is not suitable for PDS. According to a previous report, patients receiving tranexamic acid and cryoprecipitate during cytoreductive surgery and hyperthermic intraperitoneal chemotherapy appear to have an overall reduction in blood loss.[29] Hemoglobin-based oxygen carrier (HBOC) is currently undergoing phase 1/2 clinical trials. For patients with no other choices, this product may be an alternative to provide support for oxygen delivery.[30] At present, the concept of blood management in China has been paid attention to and consensus on perioperative blood management of gynecological tumors has been developed by experts. It is believed that pre-management and control when combined with the high-risk factors that we have found lead to intraoperative massive hemorrhage, will definitely improve the current situation of intraoperative blood loss of PDS for ovarian cancer.

As a retrospective analysis, our study has the limitation of methodology, which implies possible bias of selection and data collection. Other potential factors, such as the patients' specific factors that may also affect the occurrence of intraoperative blood loss could not be excluded. However, our results are consistent because they originate from a single institution, which ensures standardization of preoperative and intraoperative routines, including an indication of surgery and routine operations.

5. Conclusions

Our study first demonstrated the risk factors for major intraoperative bleeding in EOC patients undergoing PDS. The occurrence of intraoperative blood loss of at least 1000 ml was associated with tumor stage, surgical complexity, ascites, ASA scores, and diabetes. The ROC curves indicated that by integrating these predictors into a single prediction system, logistic regression was more reliably predicted (area under the ROC curve = 0.729) than tumor stage and surgical complexity. This could better predict intraoperative blood loss and anticipated blood requirements. Precise prediction of blood requirements and perioperative blood management will not only prevent serious postoperative mortality and morbidity, but also avoid unnecessary waste of precious blood resources.

Ethics approval

The retrospective study was approved by the Institutional Review Board of the Peking University People's Hospital.

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Authors' contribution

DS: Data analysis, Manuscript writing; CJ: Data Collection, Manuscript writing; WY: Data Collection; ZC: Data Collection CH: Project development; LY: Project development, Manuscript editing.

Synopsis

The risk factors for major intraoperative bleeding in ovarian cancer patients undergoing primary debulking surgery were analyzed. Planned surgical procedures and preoperative risk factors can be used to predict perioperative blood requirements. Neoadjuvant chemotherapy (NACT) is an alternative for advanced ovarian cancer patients with massive ascites and high ASA scores. Glycemic control in diabetic patients is also critical.

Informed consent

Informed consent was waived because of the retrospective nature of this study, which was approved by the Institutional Review Board of the Peking University People's Hospital.

Data availability statement

The data used to support the findings of this study are included within the article.

Declaration of competing interest

The authors declare no conflict of interest.

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