



Hidden blood loss and its risk factors in patients undergoing laparoscopy and laparotomy for cervical cancer management

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Abstract

Purpose Laparoscopy and laparotomy are the two most common surgical options used to treat women with early-stage cervical cancer. This study aimed to examine the volume of hidden blood loss (HBL) between laparoscopy and laparotomy for cervical cancer and to identify its risk factors.

Methods Sixty-one patients treated with laparotomy and 50 patients treated with laparoscopy were enrolled in this study. Their medical data were collected to calculate the HBL according to the Nadler and Gross formula, and its risk factors were identified by multiple linear regression analysis.

Results The visible blood loss was 574.9 ± 271.6 mL in the laparotomy surgery; however, the HBL was 345.2 ± 258.6 mL, accounting for $38.3 \pm 21.4\%$ of true TBL. The visible blood loss in the laparoscopy group was 168.9 ± 121.9 mL, and the HBL was 185.1 ± 130.5 mL ($52.3 \pm 28.1\%$ of true TBL). The HBL blood loss in laparotomy was more than laparoscopy ($p < 0.01$). Multiple linear regression analysis suggested that patient age ($p = 0.012$), surgical time ($p = 0.037$) and pathological tumour type ($p = 0.014$) were independent risk factors contributing to HBL in laparotomy. Meanwhile, the following risk factors were positively correlated with HBL in laparoscopy: pre-operative value of Hb ($p = 0.002$), pre-operative value of Hct ($p = 0.003$), surgical time ($p = 0.035$), pathological tumour type ($p = 0.036$) and diabetes mellitus ($p = 0.022$). Ten and eight patients had pre-operative anaemia in the laparotomy group and the laparoscopy group, respectively, and 54 and 29 post-operatively.

Conclusions HBL is seriously underestimated, and accounts for a large percentage of total blood loss both in laparotomy and laparoscopy for cervical cancer. Additionally, age, pathological tumour type, pre-operative value of Hb and Hct, surgical time and diabetes mellitus have the potential to increase HBL. A correct understanding of HBL can ensure patient safety and improve post-operative rehabilitation.

Keywords Cervical cancer · Hidden blood loss · Risk factor · Laparoscopy · Laparotomy

Abbreviations

HBL Hidden blood loss

ARH Abdominal radical hysterectomy

IBL Intra-operative blood loss

BMI Body mass index

Hct Hematocrit

Hb Haemoglobin

VBL Visible blood loss

EBV Estimated blood volume

TBL Total blood loss

PBL Post-operative blood loss

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Introduction

Cervical cancer is the third most common cancer and the fourth contributor-leading cause of malignant cancer-related death among women across the globe [1]. Surgery, radiation and chemotherapy are all effective methods and are usually

combined in the treatment of cervical cancer. Although abdominal radical hysterectomy (ARH) with pelvic lymphadenectomy is the current gold standard for the early-stage cervical cancer therapy, a growing number of gynaecologic oncologists choose laparoscopy as an alternative of laparotomy to treat cervical cancer [2]. When compared with abdominal radical hysterectomy, laparoscopic techniques are related with less intra-operative blood loss (IBL), shorter post-operative hospitalisation, faster recovery and better prognosis [3–5].

A large major of previous studies measured intra-operative blood loss (IBL) and post-operative drainage to evaluate peri-operative blood loss. However, blood lost due to haemolysis, extravasation into tissues and blood that remains in the third space (hidden blood loss; HBL), which are substantial, were neglected. Although a growing number of research studies have demonstrated that laparoscopic surgery is associated with less blood loss [6, 7], no study has yet evaluated HBL either in laparoscopy or laparotomy for cervical cancer management.

The concept of HBL was first raised by Sehat in 2000 [8]. Afterwards, more and more studies have investigated into and provided evidence for HBL in recent years. Wu et al. [9] indicated that the volume of HBL was 282 ± 162 mL after percutaneous kyphoplasty surgery. What was more, Chao Zhang et al. [10] suggested that the proportion of HBL averaged $64.3\% \pm 14.1\%$ of total blood loss in laparoscopy-assisted gastrectomy. The volume of HBL is much higher than most surgeons expect, and they should, therefore, devote more attention to HBL since it could affect patients' safety by causing hemodynamic instability during the whole peri-operative period.

In our study, we performed a retrospective review to investigate HBL during laparoscopy and laparotomy for the surgical treatment of stage IA–IIA cervical cancer. The results may help us to clarify the actual blood loss during laparoscopy and laparotomy for cervical cancer, which can improve clinical assessment and ensure patient safety during the peri-operative period.

Patients and methods

Patients

The study protocol was reviewed and approved by the Ethics Committee of Second Affiliated Hospital of Wenzhou Medical University. In all, 111 patients with stage IA–IIA cervical cancer were treated with abdominal radical hysterectomy and pelvic lymphadenectomy (50 patients were treated with laparoscopy and 61 patients were treated with laparotomy) by the same experienced surgeon in our hospital from August 2016 to August 2018. Cervical cancer was confirmed

by histology for all patients, who underwent surgery prior to any chemotherapy or radiation therapy. All patient medical data were retrospectively reviewed. The data included age, weight, height, body mass index (BMI), pre-operative and post-operative red blood cell (RBC), haematocrit (Hct) and haemoglobin (Hb), the stage of cervical cancer, number of lymph nodes, surgical time, surgical bleeding, interval between biopsy and operation, use of anticoagulant, hypertension, and diabetes mellitus. Moreover, IBL volume, post-operative drainage, and volume of reinfused blood were also collected. Patients with bleeding disorders were excluded from the study. Abdominal drainage was used in all patients after surgery.

Management of blood loss

The visible blood loss (VBL) in the operating room was recorded in the anaesthesia records by anaesthetists and included the amount of blood in suction bottles (after subtracting the lavage fluid used during the surgery) and in weighed sponges that were used during the procedure. Hb and Hct levels were measured in all patients prior to surgery and on the third post-operative day, as the patient's haemodynamics tend to stabilise during this time. Pelvic drainage tubes were used on all the patients, and the blood remaining in the drainage bag was recorded.

Calculation of the PBL and the HBL

We used gender, weight and height to calculate the estimated blood volume (EBV) according to the method of Nadler [11], as follows:

$$\text{EBV (L)} = 0.3561 \times \text{height(m)}^3 + 0.03308 \times \text{weight (kg)} + 0.1833 \text{ (females)}.$$

Total red blood cell volume was estimated by multiplying the EBV by the patient's Hct. Therefore, the red blood cell volume was reflected through the change in Hct. Total blood loss (TBL) was calculated according to the formula described by Gross [12], as follows:

$$\text{TBL (mL)} = \text{EBV (L)} \times \frac{(\text{Hct}_{\text{pre}} - \text{Hct}_{\text{post}})}{\text{Hct}_{\text{ave}}} \times 1000.$$

In this equation, Hct_{pre} is the pre-operative Hct, Hct_{post} is Hct on the third post-operative day, and Hct_{ave} is the average of Hct_{pre} and Hct_{post} .

If a transfusion was required during surgery, the true TBL calculated from the Hct was smaller than what would be expected since a transfusion gives the patient a higher Hct than they actually would have had. Thus, the true TBL is

equal to the blood loss calculated from the change in Hct plus the transfusion volume.

True TBL (mL) = TBL (mL) + blood infused (mL).

TBL plus the volume transfused was the sum of the IBL, post-operative drainage volume, and HBL. VBL in patients was equal to the IBL plus the post-operative drainage volume. Post-operative blood loss (PBL) in patients was equal to the HBL plus the post-operative drainage volume. Finally, the HBL, VBL and PBL in the patients were calculated as follows:

$$\text{HBL (mL)} = \text{TBL (mL)} + \text{blood infused (mL)} \\ - \text{IBL (mL)} - \text{blood drained (mL)},$$

$$\text{VBL (mL)} = \text{IBL (mL)} + \text{blood drained (mL)},$$

$$\text{PBL (mL)} = \text{HBL (mL)} + \text{blood drained (mL)} \\ = \text{TBL (mL)} + \text{blood infused (mL)} - \text{IBL (mL)}.$$

We assumed that the blood volume would be the same on admission as on the third post-operative day, and thus the pre-operative and post-operative Hb were used to calculate the Hb loss during the peri-operative period, as follows:

$$\text{Hb}_{\text{loss}} (\text{g/L}) = \text{Hb}_{\text{pre}} - \text{Hb}_{\text{post}},$$

where Hb_{pre} is the initial pre-operative Hb, Hb_{post} is the Hb on the third post-operative day, and Hb_{loss} is the loss of Hb.

Additional measurements

We used the Hb concentration to define anaemia, with threshold values for women, as established by the World Health Organization [$< 120 \text{ g/L}$ for women] [13]. The number of patients who experienced anaemia during the pre-operative and post-operative periods is shown in Fig. 1.

Statistical analysis

Statistical analyses were performed using SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Data are presented as the mean \pm standard deviation. Student's *t* test was used to compare continuous variables (age, height, weight, BMI, EBV, TBL, Hb_{loss} , VBL, IBL, post-operative drainage, PBL, and HBL). The chi-square test was used to compare dichotomous values (the pre-operative diagnosis). Multiple linear regression analysis was performed to identify risk factors involved in the HBL including four qualitative variables (hypertension, diabetes mellitus, diagnosis according to the FIGO staging system and the pathological tumour type) and ten quantitative variables (age, BMI, the number of lymph nodes, surgical time, surgical bleeding, interval between biopsy and operation, the use of anticoagulant, pre-operative value of Hb, pre-operative value of RBC and pre-operative

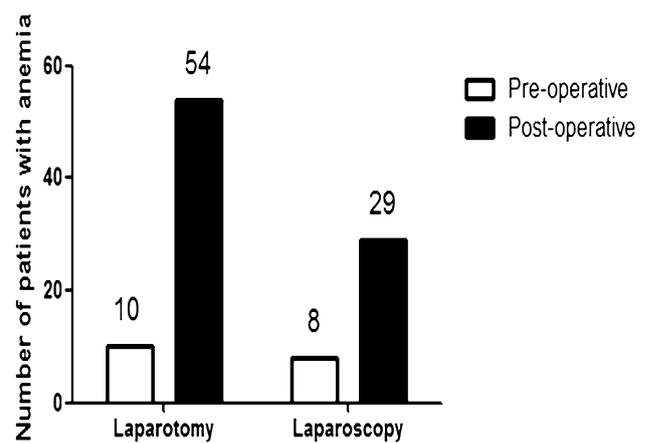


Fig. 1 The numbers of anaemic patients occurring during the pre-operative and post-operative periods

Table 1 Patient's demographic information

Parameters	Laparotomy	Laparoscopy	<i>p</i>
Number of patients	61	50	
Age (years)	49.5 \pm 10.2	48.4 \pm 10.7	0.556
Height (cm)	158.3 \pm 5.9	158.6 \pm 4.7	0.727
Weight (kg)	59.4 \pm 11.5	58.6 \pm 7.3	0.690
BMI (kg/m ²)	23.7 \pm 4.0	23.3 \pm 2.6	0.548
Pre-operative diagnosis			0.475
IA1–IA2	14	10	
IB1–IB2	36	28	
IIA1	11	12	

Data are mean \pm SD

BMI body mass index

value of Hct). Statistical significance was set prior to data collection at $p < 0.05$.

Results

A total of 111 patients underwent upfront management of cervical cancer from August 2016 to August 2018. All demographic data are summarised in Table 1. No significant differences were observed between groups in age ($p = 0.556$), height ($p = 0.727$), weight ($p = 0.690$), BMI ($p = 0.548$) or pre-operative diagnoses ($p = 0.475$).

The results of peri-operative blood changes between the two groups are shown in Table 2. The two groups showed similar EBV values. The mean TBL was $720.2 \pm 286.6 \text{ mL}$ in the laparotomy group, which was more than that in the laparoscopy group ($301.2 \pm 185.4 \text{ mL}$). Hb loss was $21.7 \pm 11.4 \text{ g/L}$ in the laparotomy group and $10.8 \pm 5.9 \text{ g/L}$ in the laparoscopy group. Significant differences were observed

Table 2 Peri-operative blood changed in the patients

Parameters	Laparotomy	Laparoscopy	<i>p</i>
Estimated blood volume (L)	3.6±0.5	3.5±0.3	0.828
Total blood loss (ml)	720.2±286.6	301.2±185.4	0.000*
Hemoglobin loss (g/L)	21.7±11.4	10.8±5.9	0.000*
Intra-operative blood loss (ml)	506.6±268.9	137.2±107.0	0.000*
Visible blood loss (ml)	574.9±271.6	168.9±121.9	0.000*
Post-operative drains (ml)	46.3±70.9	21.5±64.9	0.090
Post-operative blood loss (ml)	372.7±260.7	192.3±136.2	0.000*
Hidden blood loss (ml)	345.2±258.6	185.1±130.5	0.000*
HBL as a % of true TBL	38.3±21.4	52.3±28.1	0.003*

Data are mean ± SD

**p* < 0.05

in TBL (*p* = 0.000) and Hb loss (*p* = 0.000) between the two groups. The IBL (*p* = 0.000), VBL (*p* = 0.000) and PBL (*p* = 0.000) in the laparoscopy group were less than those in the laparotomy group. The mean HBL was 345.2 ± 258.6 mL (38.3 ± 21.4% of the true TBL) in the laparotomy group and 185.1 ± 130.5 mL (52.3 ± 28.1% of the true TBL) in the laparoscopy group, and this difference was clinically significant (*p* = 0.000). However, the post-operative drainage volumes were not significantly different (*p* = 0.090) between the two techniques.

Multiple linear regression analysis was then performed to find out the connection between HBL and its potential

risk factors in laparotomy and laparoscopy, respectively. As was shown in Table 3, the age (*p* = 0.012), surgical time (*p* = 0.037) and pathological tumour types (*p* = 0.014) yielded a significant influence on HBL in laparotomy, as patients with squamous carcinoma were more likely to experience higher HBL compared with their counterparts with adenocarcinoma. However, BMI, the number of lymph nodes, surgical bleeding, interval between biopsy and operation, the use of anticoagulant, pre-operative Hb value, pre-operative RBC level, pre-operative Hct value, the FIGO type, hypertension and diabetes mellitus were not correlated with HBL significantly.

Meanwhile, the following risk factors were positively correlated with HBL in laparoscopy: pre-operative value of Hb (*p* = 0.002), pre-operative value of Hct (*p* = 0.003), surgical time (*p* = 0.035), pathological tumour type (*p* = 0.036) and diabetes mellitus (*p* = 0.008). However, as shown in Table 4, BMI, number of lymph nodes, surgical bleeding, pre-operative RBC level, the interval between biopsy and operation, the FIGO type, post-operative use of anticoagulant and hypertension demonstrated no significant association with HBL.

As shown in Fig. 1, 10 and 54 patients in the laparotomy group, and 8 and 29 patients in the laparoscopy group had pre-operative and post-operative anaemia, respectively.

Table 3 Multiple linear regression analysis on risk factors of HBL in laparotomy

	Unstandardized		Standardised β	<i>T</i>	<i>p</i>
	β	SE			
Age (years)	7.999	3.061	0.317	2.613	0.012*
BMI (kg/m ²)	-12.152	7.635	-0.187	-1.592	0.118
Number of lymph nodes (s)	2.235	3.723	0.068	0.600	0.551
Surgical time (min)	1.424	0.663	0.257	2.147	0.037*
Surgical bleeding (mL)	-0.038	0.120	-0.040	-0.320	0.750
Post-operative anticoagulant time (days)	0.149	6.070	-0.003	0.025	0.981
Interval between biopsy and operation (days)	2.824	3.630	0.096	0.778	0.441
Pre-operative value of Hb (g/L)	-5.540	6.221	-0.231	-0.891	0.378
Pre-operative value of RBC (10 ¹² /L)	229.087	156.952	0.231	1.460	0.151
Pre-operative value of Hct (l/L)	2133.828	2317.065	0.243	0.921	0.362
FIGO staging	-66.368	47.683	-0.165	-1.392	0.171
Pathological tumour types	203.576	79.479	0.294	2.561	0.014*
Hypertension	-19.301	66.217	-0.032	-0.291	0.772
Diabetes mellitus	-178.010	135.182	-0.150	-1.317	0.981

Dependent variable: HBL (mL)

BMI body mass index

**p* < 0.05

Table 4 Multiple linear regression analysis on risk factors of HBL in laparoscopy

	Unstandardized		Standardised β	<i>T</i>	<i>p</i>
	β	SE			
Age (years)	−2.449	2.273	−0.194	−1.077	0.289
BMI (kg/m ²)	22.517	9.853	0.428	2.285	0.058
Number of lymph nodes (s)	0.189	0.189	0.013	0.094	0.926
Surgical time (min)	0.928	0.422	0.346	2.200	0.035*
Surgical bleeding (mL)	0.233	0.259	0.183	0.899	0.375
Post-operative anticoagulant time (days)	4.947	3.388	0.211	1.460	0.153
Interval between biopsy and operation (days)	0.391	1.240	0.046	0.315	0.754
Pre-operative value of Hb (g/L)	24.623	7.532	2.653	3.269	0.002*
Pre-operative value of RBC (10 ¹² /L)	−220.028	131.654	−0.598	−1.671	0.104
Pre-operative value of Hct (l/L)	1175.830	365.968	2.884	3.134	0.003*
FIGO staging	72.676	40.834	0.342	1.780	0.084
Pathological tumour types	152.679	70.086	0.394	2.178	0.036*
Hypertension	−86.702	55.276	−0.258	−1.569	0.126
Diabetes mellitus	390.124	162.453	0.406	2.401	0.022*

Dependent variable: HBL (mL)

BMI body mass index

**p* < 0.05

Discussion

The first laparoscopic radical hysterectomy with pelvic and para-aortic lymphadenectomy was performed by Nezhat et al. in 1989 and was recorded in the literature in the 1990s [14]. Laparoscopy takes the advantage of a minimally invasive incision and reduced tissue dissection. Meanwhile, the surgical techniques used for abdominal radical hysterectomy (ARH) and pelvic lymphadenectomy during laparoscopy are the same as those used for laparotomy.

A large body of evidence showed that the average blood loss was significantly lower in patients who underwent laparoscopy compared with those who underwent laparotomy for early-stage (IA–IIA) cervical cancer [3]. However, these studies only determined the peri-operative total blood loss by measuring the intra-operative blood loss and the post-operative drainage. The change in peri-operative haematocrit did not correspond to the visible blood loss. A comprehension of the HBL can help us to evaluate the patients' peri-operative haemodynamic stability more accurately and objectively. However, to the best of our knowledge, no research before has examined the issue of HBL in gynaecological surgery.

In this study, the mean IBL was 506.6 ± 268.9 mL in the laparotomy group. Surprisingly, our statistical analysis showed that the TBL was 720.2 ± 286.6 mL (879.2 ± 360.9 mL for true TBL), which was much greater than which could be attributed to visible loss. HBL is comprised up to 38.3% of TBL in the laparotomy group. These results are similar to those observed in the laparoscopy group. Although the IBL was 137.2 ± 107.0 mL for the laparoscopy group, TBL reached 301.2 ± 185.4 mL

(329.2 ± 186.7 mL for true TBL). In addition, when we compared the results between the two groups, we found no significant difference in post-operative drainage.

Other studies [5, 15] suggested that blood loss and transfusion rates were lower in laparoscopic surgery compared with laparotomy. Our results showed that TBL in the laparotomy group (720.2 ± 286.6 mL) was significantly higher than that in the laparoscopy group (301.2 ± 185.4 mL), which was similar to what was reported in previous studies. In addition, the HBL of patients who underwent laparotomy (345.2 ± 258.6 mL) was significantly higher than that of those who underwent laparoscopic surgery (185.1 ± 130.5 mL). This is expected because the patients who underwent laparoscopy were subjected to less muscular dissection and less rigorous peritoneal haemostasis. Furthermore, all patients had post-operative wound drainage. The drainage fluid in the drainage tube, which contained lymph fluid, was calculated as part of the post-operative blood loss. This will lead to further underestimation of hidden blood loss.

HBL is seriously underestimated. However, it accounts for a large proportion of TBL in patients who undergo abdominal radical hysterectomy (ARH) and pelvic lymphadenectomy. It is generally accepted that HBL is caused by extravasation of blood into tissue as well as to haemolysis [9, 16]. However, the details of HBL remain obscure. Applying labelled red blood cells, McManus et al. found that HBL was developed by peri-operative bleeding into tissue compartments [17].

Due to the fact that the HBL in laparotomy group was different from that in laparoscopy group, we conducted

multiple linear regression analysis, respectively, to figure out risk factors affecting HBL. The result indicated that the age ($p=0.012$), surgical time ($p=0.037$) and pathological tumour type ($p=0.014$) were risk factors in laparotomy group. And the peri-operative level of Hb ($p=0.002$) and Hct ($p=0.003$), surgical time ($p=0.035$), pathological tumour type ($p=0.036$) and diabetes mellitus ($p=0.008$) had potential to increase the HBL in group laparoscopy.

Miao et al. reported that the amount of HBL was positively related with age in total hip arthroplasty [18]. And Zhang et al. [10] suggested that patients older than 70 years were likely to develop higher HBL compared with their younger counterparts, and had longer post-operative hospital stay ($p<0.05$). Considering childbearing history and looser fibre tissues around womb caused by ageing, we conjecture that there may be greater possibilities that blood penetrates into these loose tissues in elderly patients. Meanwhile, it has been proved by previous studies that elderly patients are usually treated more conservatively compared with their younger counterparts, which increases the potential of more complex comorbidities [19]. Our data suggested patients with cervical adenocarcinoma were more likely to develop HBL compared with others with cervical squamous cell carcinoma. Currently, the therapeutic method of the two histological tumour types has no difference. However, more evidence suggested that cervical adenocarcinoma differs from cervical squamous cell carcinoma in cell viability, migration capacity and invasion potential [20]. The former is more likely to develop lymph node metastasis and higher reoccurrence [21]. Whether it is necessary to establish specific treatment of the two tumour types remains controversial. Combining our result with studies before, we consider that it is valuable to conduct further researches into the genesis and development of cervical adenocarcinoma and cervical squamous cell carcinoma.

Our study also showed that the pre-operative value of Hb and Hct were independently related to the amount of HBL. Liu et al. [22] suggested that post-operative hyperfibrinolysis may elevate the accumulation of HBL in the third space between tissues and higher level of pre-operative value of Hb and Hct can participate in the process. It strikes us that although sometimes patients have normal value of Hb and Hct, there is still great possibility of large amount of HBL and we should implement stricter monitor of post-operative blood change to ensure patients' safety. Prasad et al. [23] reported that higher BMI did not relate with higher amount of HBL and post-operative morbidity in total knee arthroplasty. In line with their research, the BMI is not a risk factor of HBL in our study. In other words, it supports the conclusion that obesity is not a risk factor of post-operative hemodynamic instability. However, we found out that the amount of HBL was strongly connected with

diabetes mellitus ($p<0.01$) which was usually associated with dehiscence of the incision, post-operative infectious complications, prolonged hospitalisation, and mortality. There are previous studies [24, 25] showing that diabetes mellitus is an independent unfavourable prognostic factor in Asian patients with early cervical cancer, even after curative treatments. Therefore, we consider that limiting the amount of HBL by controlling peri-operative level of blood glucose has a positive effect on patients' rehabilitation.

A previous study [25] reported that HBL may be associated with an increase in post-operative anaemia. There have been numerous researches on the consequences of post-operative anaemia, which demonstrated that it could lead to negative outcomes such as prolonged hospitalisation, increased mortality and higher likelihood of re-admission. Based on our results, HBL accounted for a large percentage of the TBL; at the same time, the frequency of post-operative anaemia in both groups increased significantly ($p<0.05$). This suggests that HBL may be a contributing factor of post-operative anaemia in patients who undergo ARH and pelvic lymphadenectomy, which could increase the incidence of post-operative complications. Bringing HBL into the limelight can help us to prevent side effects caused by post-operative anaemia [26].

Last, some limitations of this study should be mentioned. First, due to the fact that the number of patients enrolled in this retrospective study was small, more patients with cervical cancer in multi-institutions should be recruited in future prospective studies to verify our findings. Second, we collected the post-operative Hct within 2 or 3 days after the operation. However, there is evidence that the Hb level of many patients decreases and then increases on the seventh day after surgery. In other words, the estimated Hct loss would be deceptively lower which hence influenced the results.

Conclusions

In a word, a significant peri-operative HBL is ignored by most surgeons when laparoscopy and laparotomy are performed for the treatment of stage IA–IIA cervical cancer. And age, surgical time, pathological tumour type, pre-operative value of Hb and Hct, and diabetes mellitus are risk factors to increase HBL. This phenomenon seems important enough for surgeons to shed lights on the research of HBL. It is expected that more effective control of HBL will improve patient rehabilitation through a reduction in complications related to blood loss and anaemia, and improve our clinical post-operative work further.

Author contributions YZ and WL conceived the study and developed the protocol. JH, XZ and JX collected data. YH and RS analysed data. QZ and MZ wrote and edited the manuscript. All authors read and approved the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study protocol was reviewed and approved by the Ethics Committee of Second Affiliated Hospital of Wenzhou Medical University.

Informed consent Informed consent was obtained from all individual participants included in the study.

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