Risk Prediction and Treatment of Hemorrhagic Chronic Radiation Intestinal Injury Patients With LE-DVT

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Research

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Abstract

Background: After pelvic malignancy radiation, chronic radiation intestinal injury (CRII) is an unavoidable complication, and bleeding is one of the most common symptoms of CRII. Lower extremity deep venous thrombosis (LE-DVT) is another severe complication.Once hemorrhagic CRII patients suffer from LE-DVT, hemostasis and anticoagulation therapy will be adopted simultaneously, which is a therapeutic paradox, extremely intractable and serious. This study was aimed to investigate prevalence and risk factors for LE-DVT in CRII patients, and explore treatment for hemorrhagic CRII patients with LE-DVT

Methods: This is a retrospective study,a total of 608 CRII hospitalized patients from November 2011 to October 2018 after pelvic malignancy radiation in our hospital were included.Univariate and multivariate analysis were conducted to investigate the associated risk factors for LE-DVT in CRII patients. Receiver operating characteristic (ROC) curve analysis was performed to investigate the independent risk factors and determine their clinically valid cut-off points. Furthermore, treatment of hemorrhagic CRII patients with LE-DVT was explored.

Results: Of the 608 included CRE patients, there were 94 (15.5%) CRII patients with suspicious symptoms of LE-DVT in the lower limbs, and 32 (5.3%) patients were diagnosed with LE-DVT. Among the CRII patients with LE-DVT, 65.6% (21/32) patients were with bleeding simultaneously, 29 (90.6%) patients were anemic, with 17 (53.1%) patients having moderate anemia and 7 (21.9%) having severe anemia. Multivariate analysis showed recent surgical history (≤6 Months) (OR=0.480, 95% CI: 1.430~9.377, p=0.007) and hemoglobin (Hb) (OR=0.965, 95% CI: 0.945~0.986, p=0.001) significantly associated with development of LE-DVT. ROC curve analysis showed optimal cut-off values of Hb were 82.5 g/L (AUC=0.756, 95% CI: 0.688~0.824, sensitivity=71.9%, specificity=75.5%). After colostomy, obvious bleeding remission was found in 84.6% of hemorrhagic CRII patients with LE-DVT rapidly. And LE-DVT of the patients was obvious improved or disappeared following anticoagulation therapy or with vena cava filter or stent placement.

Conclusions: Prevalence of LE-DVT in hospitalized CRII patients was 5.3%. Recent surgical history and lower Hb were independently associated with LE-DVT developing in CRII patients. And colostomy could be a good choice for intractable hemorrhagic CRII patients with LE-DVT.

Introduction

Radiotherapy is among the most effective treatments for pelvic malignancy, with annually more than 1 million patients worldwide estimated to require curative radiotherapy for pelvic cancer[1]. It was reported by Chen et al. that there were 0.5 million new cases of pelvic malignancy in China in 2015 alone, and 35% to 61% patients require pelvic radiotherapy [2, 3]. However,radiation-induced intestinal injury (RII) is an unavoidable side effect and the most common complication of pelvic malignancy radiation, damaging the small and/or large intestine[4]. According to the end time of radiotherapy, RE has been divided into acute (less than 3 months after radiotherapy, ARII) and chronic (more than 3 months after radiotherapy, CRII) types. Ninety percent of patients present with ARE, and subsequently5% to 55% develop CRII post-

pelvic radiotherapy[5-7]. Most of the symptoms of ARE are transient and self-healing, and relieved within 3 months. While CRII often emerges in 12~24 months after the end of radiotherapy, and it is progressive and difficult to reverse[8, 9]. The main clinical presentation of CRII are intestinal obstruction, diarrhea, bleeding, abdominal cramping, anal pain, perforation, necrosis, abscess, fistulas, strictures, severe anemia, chronic malabsorption, and even death, seriously impairing quality of life[3, 10]. Chronic radiation proctitis (CRP) is another different term used to describe the involvement of the rectum and sigmoid colon, with the most prominent characteristic of bleeding, accounting for > 80% of CRP patients[11, 12].

Lower extremity deep venous thrombosis (LE-DVT) refers to the coagulation of venous blood in the deep venous blood vessels of the lower limbs, with the most common clinical manifestations of sudden swelling of one limb, local pain and aggravation during walking[13]. It was reported that the annual incidence of DVT was between 0.5 and 1.4 per 1000 in the general population[14, 15]. Although the incidence of DVT is relatively low, DVT can detach and embolize into the heart or lung to cause cardiopulmonary embolism, or even death. Previously, Numerous studies demonstrated that DVT is a complex multifactorial disease influenced by several risk factors, including surgery and trauma, prolonged immobilization myeloproliferative disorders, pregnancy and postpartum status, weight, age, smoking status and hormonal treatment[16-18]. Moreover, radiotherapy and cancer increase the risk of forming DVT [19-21]. It was reported that after radiotherapy, changes of the structure of the pelvic tissue, the blood composition and the vessel wall were more rapid than that of fibrosis [22, 23], and radio-necrosis and granulation of the small lymphatic vessels, lymph nodes, and soft tissue around vessels following radiotherapy, leading to accumulation of protein-rich fluid in the soft tissues secondary to inadequate lymphatic drainage [23-25]. Given the serious potentially consequence of LE-DVT, knowing its prevalence in CRII patients better is extraordinary important. In addition, bleeding is a quite common symptom of CRII. If LE-DVT and bleeding simultaneously occur in one CRII patient, hemostasis and anticoagulationtherapy will be conducted [26], which is a therapeutic contradiction, will greatly increase the difficulty of treatment.

To the best of our knowledge, studies regarding occurrence of LE-DVT and risk factors for developing LE-DVT in CRII patients are still scarce. Thus, to better prevent and treat CRII complicated with LE-DVT, the incidence and risk factors of LE-DVT in CRII patients were retrospectively analyzed in this study, and an appropriate treatment strategy was explored as well.

Materials And Methods

Patients

Three months later after pelvic malignancy radiation, patients presented with intestinal obstruction, diarrhea, bleeding, abdominal cramping, anal pain, perforation, necrosis, abscess, fistulas, strictures, severe anemia, etc., and confirmed by magnetic resonance imaging (MRI), computerized tomography (CT), endoscopy, etc. were diagnosed by CRII. The hospitalized CRII patients in Sun Yat-sen University Sixth Affiliated Hospital from November 2011 to October 2018 were retrospectively included. And the CRII

patients hospitalized needs to satisfy at least one of the following conditions: patients with moderate to severe bleeding, and severe complications with intestinal obstruction, perforation, necrosis, abscess, fistulas, strictures, severe anemia, chronic malabsorption etc..The clinical data of each included patient were carefully collected. In this study, the inclusion criteria were: patients diagnosed with CRII; patients hospitalized mainly for treating CRII or with symptom of DVT in lower limbs. The exclusion criteriawere:patients with acute radiation-induced enteritis (less than 3 months after radiotherapy, ARE); patients with previous blood related diseases or severe coagulation disorders; and patients with incomplete clinical data.

This study was approved by the Ethical Committee of Sun Yat-sen University Sixth Affiliated Hospital and was conducted in according with the provisions of the World Medical Association's Declaration of Helsinki of 1995 (revised in Tokyo, 2004). Informed consent was waived, because this was a retrospective study.

Data collection

CRII patients with suspicious symptoms of LE-DVT were routinely examined by bilateral lower extremity venous doppler ultrasonography. Clinical data were compared between patients with LE-DVT (observation group) and patients without LE-DVT (control group). The following data were compared: age, sex, body mass index (BMI), cardiovascular and cerebrovascular diseases, diabetes mellitus, blood transfusion history, smoking status, surgical history, recent surgical history, hemostasis drug use, tumor recurrence or metastasis, time to the end of radiotherapy, hormonal treatment, radiotherapy dose, hemoglobin (Hb), blood platelet count (BPC), mean platelet volume (MPV), white blood cells (WBC), albumin (ALB). The clinical data and laboratory values of the patients were collected initial after admission. Then, the risk factors for developing LE-DVT in CRII patients were retrospectively investigated. In addition, CRII patients with bleeding were graded at three levels according to the modified Subjective Objective Management Analysis (SOMA) [27, 28] to assess the severity of bleeding.

Statistical analysis

The data analysis in this study was performed using SPSS software, version 19.0 (Chicago, IL, USA). Continuous variables were expressed as the means ± SDs or medians (interquartile range, IQR) and were compared using the t tests or the Mann-Whitney U tests as appropriate; Categorical variables were expressed as numbers and percentages and were compared using Fisher's test or the χ^2 test as appropriate. Stepwise, variables that were significantly different between groups in univariate analysis were included in the multivariate logistic regression model to assess the associations between potential risk factors and LE-DVT. For the independent risk factors, the best cut-off values distinguishing between CRII patients with and without LE-DVT were assessed by receiver operating characteristic (ROC) curve analyses. A two-sided p 0.05 was considered statistically significant.

Results

Demographics and characteristics

From November 2011 to October 2018, 737 hospitalized RE patients were screened, and a total of 608 CRII patients were included in this study and then allocated to the two groups (Figure 1). Table 1 shows the primary cancer of the CRII patients, and table 2 shows the bleeding-related data of the enrolled patients. As shown in table 1, the primary cancer of these CRII patients included cervical cancer (n=460), endometrial cancer (n=29), ovarian cancer (n=7), vaginal cancer (n=4), prostatic cancer (n=24), testicular cancer (n=1), rectal cancer (n=77), anal cancer (n=3), and colon cancer (n=1). Of the 608 included patients, there were 528 (86.8%) CRP patients including 439 (83.1%) patients with bleeding, and 387 (63.7%) CRII patients were presenting with anemia (shown in table 2).

Among the 608 patients eligible for this study, there were 94 (15.5%) CRIIpatients with suspicious symptoms of LE-DVT. After confirmed by bilateral lower extremity venous doppler ultrasonography, 32 patients were identified with LE-DVT. Thus, prevalence of LE-DVT in all of the hospitalized CRII patients after pelvic malignancy radiation was 5.3% (32/608). For these CRII patients with LE-DVT, 8 cases were located in the left lower limb, 13 in the right, and 11 in both lower limbs; the age of these patients was 57±11 years old; the median time to presentation of LE-DVT was 15 months after radiotherapy; the gender were 3 in male, and 29 in female. Primary cancers of the CRII patients with LE-DVT were 27 cases of cervical cancer, 1 of endometrial cancer, 1 of testicular cancer, and 3 of rectal cancer. The incidence of LE-DVT in CRII patients who had ever suffered from cervical cancer was 5.9% (27/460). In addition, 65.6% (21/32) of patients had rectal bleeding. After grading the hemorrhagic patients with LE-DVT according to SOMA, we found that there were 12.5% (4/32) of patients with Grade 1, 46.9% (15/32) with Grade 2, and 6.3% (2/32) with Grade 3. Further, there were 29 (90.6%) anemic patients with LE-DVT, with 53.1% having moderate anemia and 21.9% having severe anemia (listed in table 3).

Comparisons of the CRII patients with or without LE-DVT

Associations of the clinical data of the patients with or without LE-DVT are listed in Table 4. In the univariate analysis, a significantly larger proportion of the patients with recent surgical history (≤6 months) (31.4% vs. 8.7%, p<0.001), hemostasis drug use histories (53.1% vs. 31.3%, p=0.010), tumor recurrence or metastasis (34.3% vs. 17.0%, p =0.013), hormonal treatment (56.3% vs. 26.7%, p<0.001) and albumin (ALB) ≤35 g/L (56.3% vs. 24.8%, p<0.001), higher levels of white blood cells (WBC) [(5.8 (4.8-10.6) vs. 5.0 (4.0-6.5), p=0.003)], and lower levels of hemoglobin (Hb) (80.2±16.1 vs. 100.4±23.2, p< 0.001)] were found in patients of the observation group, compared to that of the control group. In contrast, there was also no significant difference in age, BMI, cardiovascular and cerebrovascular disease, diabetes mellitus, surgical history,smoking history, time to the end of radiotherapy, the platelet count (BPC), and mean platelet volume (MPV) between the two groups.

Variables of potential risk factors that were significantly different between groups were included in the multivariate logistic regression analysis. Table 4 showed that Hb (OR=0.965, 95% CI: 0.945~0.986, p=0.001) and recent surgical history (≤6 months)(OR=0.480, 95% CI: 1.430~9.377, p=0.007) were

significantly associated with the occurrence of LE-DVT. The results suggested that lower levels of Hb and recent surgical history independently increased the risk of forming LE-DVT in CRII patients.

ROC curve of the independent factors

ROC curve analysis was used to evaluate the potency of the identified independent factor of Hb in predicting the occurrence of LE-DVT in CRII patients (Figure 2). The results showed that the AUC value of Hb was 0.756 (95% CI: 0.688~0.824). The cut-off of Hb was 82.5 g/L (sensitivity=71.9%, specificity=75.5%).

Treatment

In order to investigate the treatment strategies adopted for hemorrhagic patients with LE-DVT in this study, the hemorrhagic CRII patients with LE-DVT had been followed up for at least 1 year. We found that, because of uncontrollable bleeding, colostomy treatment was conducted by 61.9% (13/21) hemorrhagic CRII patients with LE-DVT, which was significantly higher than that conducted by hemorrhagic CRII patients without LE-DVT (17.5%, 73/418). In addition, as for the remaining 8 hemorrhagic CRII patients with LE-DVT, 3 patients operated with bowel resection because of unendurable pain or fistula, the other 5 received no surgery. Moreover, after colostomy, obvious bleeding remission was rapidly found in 11 (84.6%) hemorrhagic CRII patients with LE-DVT, and LE-DVT of all these patients disappeared or improved following anticoagulation therapy or with vena cava filter or stent placement (LE-DVT of 2 patients obviously improved and 1 disappeared with following anticoagulation therapy, and 1 patients remarkably relieved and 2 patients cured by following vena cava filter or stent placement with anticoagulation therapy). By contrast, the 5 hemorrhagicCRII patients with LE-DVT treated without colostomy, bleeding existed for at least one year. Unfortunately, the follow-up data of LE-DVT treatment from the remaining hemorrhagicCRII patients with LE-DVT patients were unacquirable because there were no ultrasonic examination after the patients being treated or we can’t contact with the patients.

Discussion

CRII is a commonly observed side effect of pelvic radiation therapy, with the characteristic pathologic changes are inflammatory disease, endarteritis of arterioles, epithelial atrophy, vascular thrombi, capillary compensatory hyperplasia, ischemia, necrosis, and excessive fibrosis[4]. Because of pelvic radiation therapy and cancer history, the incidence of LE-DVT in CRII patients may increase. Therefore, in the present study, prevalence of LE-DVT in CRII patients after pelvic malignancy radiation we evaluated was 5.3%, which was much higher than that in general population [14].Although the prevalence of LE-DVT was not very high, the issue of CRII patients with LE-DVT and bleeding at the same time was extremely intractable and serious. The result showed (460/608, 75.7%) most of the included patients had cervical cancer, it may be because the treatment strategy of high dose radiation for cervical cancer, correspondingly, the small and large intestines in the pelvic cavity also received relatively high radiation doses and thus damaged [29]. In further, incidence of LE-DVT in CRII patients with cervical cancer we then evaluated was 5.7%, which was in accordance with papers that documented 5.5%–16.7% of LE-DVT in

patients with cervical cancer [30-32]. However, in this study, only 94 CRII patients with suspicious symptoms of LE-DVT like edema, pain in the lower extremity etc. were tested to verify the presence of LE-DVT, while other patients may do have LE-DVT but showed no symptom. Therefore, the occurrence of LE-DVT in CRII patients after pelvic malignancy radiation might be underestimated.

As for CRII patients, thromboembolic complications may develop but were overlooked. In order to diagnose possible LE-DVT existing in CRII patients, the associated risk factors of LE-DVT in CRII patients were then investigated. A previous study declared that cancer is a hypercoagulable state, and the risk of developing DVT is much higher in patients with active cancer[33]. Further, hemostasis drug use history willaggravate the hypercoagulable state and hypoalbuminemia significantly increases DVT formation[34]. In this study, significant differences were also observed between the observation and control groups in the proportion of patients who had hemostasis drug use histories, tumor recurrence or metastasis and whose ALB levels were less than 35 g/L. And growing evidence demonstrated that inflammatory triggers a variety of responses that lead to increased coagulation and thrombosis[35, 36]. Our result also showed that the inflammatory cells (WBC) were obviously associated with the development of LE-DVT in CRII patients. In addition, surgery and trauma increased the risk of developing DVT, and surgery operation will prolong immobilized time[17]. And recent surgical history (≤6 months) in our result is indeed independently related to developing LE-DVT in CRII patients. Additionally, this study showed hormone like hexadecadrol or budesonide treatment significantly increase the risk of developing LE-DVT, which was in accordance with the research of Lieber et al[37].

Strikingly, it was very gratifying to find that lower Hb was another independent risk factor for LE-DVT in CRII patients, and ROC curve analysis showed that the AUC of Hb was 0.756, and the cut-off of Hb was 82.5 g/L (sensitivity=71.9%, specificity =75.5%), indicating that Hb was an useful diagnostic indicator forpredicting the presence of LE-DVT.

In this study, of all the included patients, 86.8% were CRP patients. Among these CRP patients, 83.1% (439/528) were hemorrhagic CRP patients, and 63.6% (336/528) were anemic patients. As a previous study reported, bleeding is the most frequently occurring symptom of CRP patients, which account for more than 80% and will probably give rise to anemia[12]. As we all know, Hb is a key maker reflecting whether there exist anemia or not. A level of Hb lower than 82.5 g/mL indicates moderate to severeanemia according to the diagnostic criteria for anemia. Moreover, this study demonstrated that there were 90.6% anemic patients with LE-DVT, of whom 75% patients had moderate to severe anemia. Previously, it was proved that anemia increased DVT forming, because anemia is considered a hyperkinetic state which disturbs endothelial adhesion molecule genes that can lead to thrombus formation, and blood flow augmentation and turbulence can result in the migration of this thrombus, producing artery-to-artery embolism, which can have more severe consequences[38].

The present study showed that among the 32 CRII patients with LE-DVT, 21 (65.6%) were presenting with bleeding and 90.6% with anemia. Hemostasis and anticoagulation therapy were needed for CRII patients suffered from bleeding and LE-DVT simultaneously, which was a paradox and largely increased the

difficulty of treatment. Moreover, CRII patients receiving anticoagulation therapy were observed to have a significantly increased incidence of severe anemia compared to that with non-anticoagulation therapy (13.5% vs. 3.7%, p=0.016 <0.05) in this study. In further, according to the experience of our research team, theduration of bleeding was at least more than one or two years once the patients developed the symptom of bleeding. Therefore, how to detect LE-DVT in CRII patients earlier and to maintain the treatment balance is extremely important. Additionally, monitoring Hb also played a key role in the course of treatment of hemorrhagic CRII with LE-DVT.

However, until now nostandard treatment strategies or procedures are established for treating hemorrhagic CRP. According to the experience of our research team, an ascending ladder therapy was adopted as follows. For mild to moderate hemorrhagic CRP, a novel mixture enema (almagate combined with thrombin, epidermal growth factor,metronidazole and hexadecadrol or budesonide) was an effective strategy, with 90% and 69% short-term and long-term effective rates, respectively[39]. For moderate hemorrhagic CRP, argon plasma coagulation is a well-tolerated and effective treatment option[40, 41]. For moderate to severe hemorrhagic CRP without massive ulcers which is refractory to medical management, modified formalin irrigation is an effective and safe method, with an effectiveness rate of 79.1%[42]. Further, if CRP patients suffer from severe intractable bleeding refractory to the above conservative treatments or require blood transfusions because of bleeding, diverting colostomy is a simple, effective and safe procedure, which obtained a higher rate of bleeding remission (94% vs. 12%) and obviously elevated hemoglobin levels, compared to conservative treatment[28]. Moreover, if hemorrhagic CRP patients couldn't manage after undergoing colostomy and conservative treatment or have fistula or necrosis that with unbearable anal pain, resection of the severe damaged intestine and then colostomy could be a good choice. In addition, these hemorrhagic CRP patients without colostomy were suggested to adopt a low residue and high protein diet.

In this research, among the 21 hemorrhagic CRII patients with LE-DVT, 13 patients had recurrent refractory rectal bleeding or even need blood transfusion, and anticoagulation therapies which will aggravate bleeding were cautious and often withdrawn for these patients. Then, these 13 patients underwent colostomy treatment, and obvious bleeding remission was rapidly found in 11 patients. Thus, subsequent anticoagulation therapy was much safer than either anticoagulation or hemostasis therapy after bleeding remission, and LE-DVTs in some patients were indeed alleviated or cured after colostomy and subsequently anticoagulation therapy, according to our follow-up data. However, further studies must be conducted to investigate effects of colostomy in hemorrhagic CRP patients with LE-DVT because of the small number of these patients until now.

However, our research had some weaknesses. A first limitation was that only CRII patients with symptoms of DVT in the lower limbs were examined. Secondly, the fact that only the hospitalized CRII patients were included which involved an inevitable patient selection bias. Thirdly, this study was limited by the small numbers of CRII patients with LE-DVT and hemorrhagic CRII patients with LE-DVT treated by colostomy. Fourthly, our study was also limited by a lack of access to complete and long-term follow-up data on

treatment of the CRII patients with LE-DVT. Further studies will be conducted to confirm our findings and further investigate the effect of colostomy for CRII patients with LE-DVT.

In conclusion, the incidence of LE-DVT was 5.3% in CRII patients after pelvic malignancy radiation, and recent surgical history, and reduced Hb levels were independent risk factors, which could potentially be diagnostic markers for predicting the presence of LE-DVT in CRII patients. When the Hb lower than 82.5 g/L in CRIIpatients or/and recent surgical history shorter than six months, it is necessary to note whether there is LE-DVT or noteven if no suspicious symptoms of LE-DVT occurred. In addition, colostomy treatment might be a good choice for intractable hemorrhagic CRII patients with LE-DVT, in whom it was much safer to adopt anticoagulant therapy after colostomy, followed by obvious bleeding remission.

Abbreviations

RII: Radiation intestinal injury; CRII: Chronic radiation intestinal injury; ARI: Acute radiation intestinal injury; CRP: Chronic radiation proctitis; DVT: deep venous thrombosis; LE-DVT: lower extremity deep venous thrombosis; ROC: Receiver operating characteristic; AUC: Area under the receiver-operating characteristic curve; BMI: body mass index; Hb: Hemoglobin; BPC: Platelet count; MPV: Mean platelet volume; WBC: White blood cells; ALB: Albumin.

Declarations

Acknowledgments

Not applicable

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Availability of data and materials

All datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contribution

TM and XH designed the study, and XH, YK wrote the manuscript. TM, HW and ZY critically reviewed the manuscript. XH, YK and MZ were involved in the data acquisitionand interpretation of the data. XH and ZY performed the statistical analyses. YH, HW, QG and QZ contributed to the analysis and interpretation of the data. All authors approved the final version of the manuscript.

Consent for publication

All authors declare that there is no conflict of interest.

Competing interests

The authors declare no conflicts of interest.

Ethics approval and consent to participate

The study protocol was approved by the Ethical Committee of Sun Yat-sen University Sixth Affiliated Hospital and was conducted in according with the provisions of the World Medical Association's Declaration of Helsinki of 1995 (revised in Tokyo, 2004).As this study was a retrospective study and did not include any potentially identifiable patient data, Informed consent was waived.

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Tables

Table 1

Modified subjective/objective management analysis system to assess the severity of bleeding

Grade	Bleeding	Severity	Anemia (Hb, g/L)
1	Mild bleeding	Occasional or occult	Mild anemia (Hb: ≥ 90 g/L)
2	Moderate bleeding	Persistent	Moderate anemia (Hb: 70-90 g/L)
3	Severe bleeding	Gross	Severe anemia, transfusion needed (Hb: < 70 g/L)

Table 2

Primary cancer of included CRII patients

Primary cancer	Total in study (n = 608)	Total with LE-DVT (n = 32)	Proportion
Cervical cancer	460	27	5.9%
Endometrial cancer	29	1	3.4%
Ovarian cancer	7	0	0
Vaginal cancer	4	0	0
Prostatic cancer	24	0	0
Testicular cancer	1	1	100%
Rectal cancer	77	3	3.9%
Anal cancer	3	0	0
Colon cancer	1	0	0

Table 3
Bleeding-related data of the included CRII patients

n (%)	Total in study (n = 608)	Total with LE-DVT (n = 32)
CRP	528 (86.8%)	26 (81.3%)
Bleeding	439 (72.2%)	21 (65.6%)
Severity of bleeding		
Grade 1	272 (44.7%)	4 (12.5%)
Grade 2	105 (17.3%)	15 (46.9%)
Grade 3	62 (10.2%)	2 (6.3%)
Anemia	387 (63.7%)	29 (90.6%)
Mild anemia	173 (28.5%)	5 (15.6%)
Moderate anemia	135 (22.2%)	17 (53.1%)
Severe anemia	79(13.0%)	7 (21.9%)
Abbreviations: CRP, chronic radiation proctitis		

Table 4

Characteristics of the CRII patients with or without LE-DVT

Variables	Observation group (n = 32)	Control group (n = 576)	*p*
Age ≥ 50 y, n (%)	25 (78.1)	438 (76.0)	0.788
Male, n (%)	3 (9.4)	72 (12.5)	0.805
BMI ＜ 18.5 kg/m^2, n (%)	6 (18.8)	146 (25.3)	0.382
Cardiovascular and cerebrovascular diseases, n (%)	5 (15.6)	95 (16.5)	0.897
Diabetes mellitus, n (%)	2 (6.3)	70 (12.2)	0.469
Blood transfusion history, n (%)	7 (21.9)	171 (29.8)	0.344
Smoking status, yes, (n (%)	0 (0)	13 (2.3)	0.391
Surgical history, n (%)	23 (71.9)	345 (59.9)	0.177
Recent surgical history (≤6 months), n (%)	11 (34.4)	50 (8.7)	0.000
Hemostasis drug use history, n (%)	17 (53.1)	180 (31.3)	0.010
Tumor recurrence or metastasis, n (%)	13 (40.6)	98 (17.0)	0.001
Time to the end of radiotherapy≥24 months, n (%)	9 (28.1)	190 (33.0)	0.568
Hormonal treatment, n (%)	18 (56.3)	152(26.7)	0.000
Radiotherapy dose, Gy, median (IQR)	79.0 (69.5-88.5)	80.0 (56.0-86.0)	0.333
Hb, g/L mean ± SD	80.2±16.1	100.4±23.2	0.000
BPC, ×10^9/L, median (IQR)	241.8 (162.1-387.0)	235.0 (186.0-295.5)	0.668
MPV, fl, mean ± SD	8.6±1.4	9.1±1.3	0.054
WBC, ×10^9/L, median (IQR)	5.8 (4.8-10.6)	5.0 (4.0-6.5)	0.003
ALB ≤ 35 g/L, n (%)	18 (56.3)	143 (24.8)	0.000

Data were expressed as means ± SDs, medians (IQR) or n (%).

Abbreviations: BMI, body mass index; IQR, interquartile range; SD, standard deviation; Hb, Hemoglobin, BPC, Platelet count; MPV, Mean platelet volume; WBC, White blood cells; ALB, Albumin.

Table 5
Multivariate logistic regression analysis for developing LE-DVT in CRII patients after pelvic malignancy radiation

Variables	Coefficient	Standard error	OR	95% CI Lower limit~ Higher limit	*p*
Hemostasis drug use history	0.274	0.489	1.315	0.505~3.428	0.575
Tumor recurrence or metastasis	0.804	0.432	2.235	0.958~5.213	0.063
Hormonal treatment	0.479	0.512	1.614	0.592~4.403	0.350
Hb	-0.036	0.011	0.965	0.945~0.986	0.001
WBC	0.061	0.044	1.063	0.975~1.159	0.163
ALB ≤ 35 g/L	-0.247	0.457	0.781	0.319~1.913	0.589
Recent surgical history (≤6 months)	1.298	0.480	3.663	1.430~9.377	0.007

Abbreviations: OR, odds ratio; CI, confidence interval; Hb, Hemoglobin; WBC, White blood cells; ALB, Albumin.

Figures

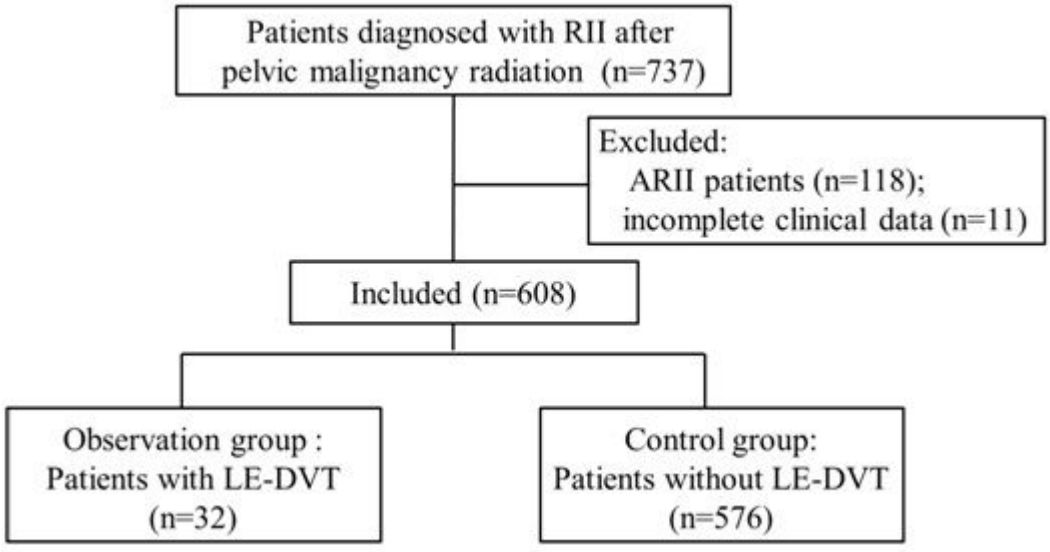

Figure 1

Flow chart of patient selection

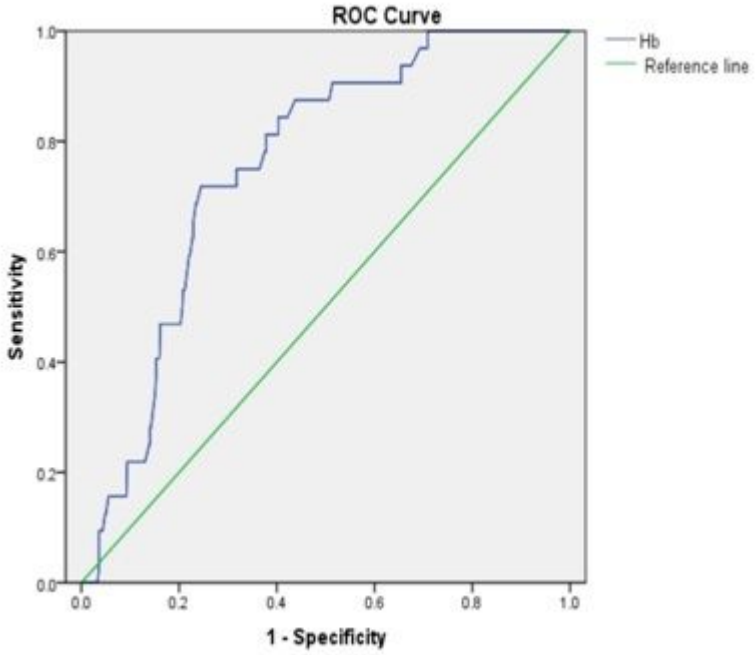

Figure 2

ROC curve of Hbfor predicting LE-DVT development in CRII patients after pelvic malignancy radiation The AUC value of Hb was 0.756 (95% CI: 0.688~0.824). Abbreviations: ROC: Receiver operating characteristic; AUC: area under the receiver-operating characteristic curve; Hb, Hemoglobin

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