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A nomogram utilizing LASSO-conditional logistic regression for predicting delayed post-polypectomy bleeding

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Abstract

Aim: Colorectal Cancer (CRC) is the third most common malignancy globally, with its development closely tied to the transition from adenoma to cancer. Resection of colorectal tumors plays a crucial role in effectively decreasing the incidence and overall burden of CRC. However, postoperative bleeding, particularly Delayed Post-Polypectomy Bleeding (DPPB), emerges as the primary complication following colorectal tumor resection. Despite its prevalence, the risk factors associated with delayed bleeding remain a subject of debate. Hence, the primary objective of this study was to develop a predictive model utilizing Lasso-conditional logistic regression to identify and analyze the risk factors linked to delayed bleeding.

Method: The medical records of inpatients who attended the Department of Gastroenterology for endoscopic colorectal tumour removal between January 2021 and October 2023 were retrospectively analysed in this study. Patients with DPPB were screened based on the inclusion and exclusion criteria, and final inclusion was determined using 1:4 propensity matching. LASSO regression was used to screen for risk factors associated with delayed bleeding. Subsequently, we developed a conditional logistic regression model. The results were visualised using a nomogram.

Results: The study initially included 4239 patients, with an overall bleeding rate of 1.65%. Univariate analysis and LASSO regression revealed several statistically significant risk factors, including hypertension, anticoagulant drug use, open diet time, treatment modality, polyp size, polyp multiplicity, and so on. The results of the conditional logistic regression analysis showed that hypertension, anticoagulant medication, and polyp prevalence were independent risk factors for the development of DPPB. A nomogram was created to visually represent the higher risk of DPPB in patients with combined hypertension, anticoagulant medication, and multiple polyps.

Conclusion: This study investigated independent risk factors for the development of DPPB, including hypertension, taking anticoagulants, and multiple polyps. Appropriate interventions should be implemented based on these risk factors.

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Introduction

Preventing Colorectal Cancer (CRC) is of great importance, as it is the third most common malignant tumor globally, accounting for approximately 10% of all new cancer cases annually [1,2]. The progression pattern from adenoma to carcinoma is widely accepted to play a crucial role in the development of colorectal cancer [3]. Removal of colonic tumors is effective in reducing the incidence and overall burden of CRC [4,5]. While colonoscopic tumor resection is a safe and effective procedure [6,7], it can still lead to serious complications, including bleeding, perforation, and electrocoagulation syndrome [8]. Postoperative bleeding is the most common complication after colorectoscopic tumor resection, with two main categories: bleeding in the immediate intraoperative period and Delayed Post-Polypectomy Bleeding (DPPB) [9,10]. The incidence of DPPB is low, with occurrences typically within 30 days after surgery [11]. Severe bleeding conditions that entail re-colonoscopic intervention, blood transfusion, or even colectomy may arise unpredictably and after hospital discharge [12]. Such complications increase the healthcare burden [13]. Therefore, identifying risk factors associated with DPPB and high-risk groups is significant in clinical practice to mitigate serious complications effectively.

Further studies are urgently required to clarify the risk factors associated with DPPB. The risk factors can be classified into three categories: patient-related, polyp-related, and operator-related. These factors include the surgical approach, immediate intraoperative bleeding, polyp size, number, morphology, pathological type, location, use of prophylactic titanium clips, and the use of antithrombotic medications [14,15]. Although many factors linked to DPPB have been identified, some still lack clarity, leading to controversy regarding the impact of prophylactic use of titanium clips, polyp location, and antithrombotic medication. Clinicians struggle to perform a comprehensive assessment due to the low accuracy of prediction schemes [16]. Therefore, it is essential to conduct further studies in order to achieve valid risk prediction and enhance understanding of the risk factors associated with DPPB.

LASSO regression, also known as least absolute shrinkage and selection operator regression, originally proposed by British scholar Robert Tibshirani [17], is a method specifically designed to address the challenge of handling a large number of potential predictors. Unlike traditional regression techniques, LASSO regression is effective at identifying the most relevant variables for the disease being studied. When faced with model fitting challenges characterized by small sample sizes and an abundance of variables, prioritizing LASSO regression for variable selection is recommended. Our study focused on exploring the use of LASSO regression to investigate risk factors associated with DPPB. We utilized total descent LASSO regression as a crucial method for selecting risk factors. Furthermore, we employed conditional logistic analysis to identify independent risk factors for DPPB.

Materials and methods

To ensure the validity and accuracy of the study findings, this research targeted individuals over 18 years old who underwent endoscopic colorectal tumor removal procedures as inpatients at the Department of Gastroenterology between January 2021 and October 2023. Exclusions were made for patients with confounding factors, such as intraoperative perforation, suspected intrinsic muscular layer injury, or the potential for bleeding unrelated to colorectal tumor removal. Moreover, individuals with specific medical histories, including haemorrhoids, small intestinal bleeding, gastric ulcer, inflammatory bowel disease, familial polyposis, intestinal malignancy, previous colorectal resection, comorbid malignant tumors in other locations, or hematological system diseases, were also excluded from the study. Delayed bleeding, on the other hand, refers to the presence of blood in the stool in any form within 30 days after polypectomy without initial bleeding or after successful hemostasis during surgery. It can be further categorized into two degrees [10]: mild and severe, based on the patient's clinical presentation and laboratory findings. Mild delayed bleeding is marked by self-limiting blood in the stool. In contrast, severe delayed bleeding is indicated by specific criteria such as the necessity for another colonoscopy, hemodynamic instability (defined as a systolic blood pressure decrease of greater than 10 mmHg or a systolic blood pressure below 100 mmHg, an increase in heart rate of at least 20 beats/min or a heart rate exceeding 100 beats/min), a decrease in hemoglobin of ≥20 g/L, or the need for a blood transfusion. This stands in contrast to immediate bleeding, which is characterized by intestinal bleeding lasting for more than one minute during the procedure or requiring immediate attention. This stringent selection process was implemented to focus on a specific patient population undergoing endoscopic colorectal tumor removal, thereby minimizing the impact of confounding variables and enhancing the robustness of the research findings.

A total of 4,239 cases were enrolled in the study, with 2,692 being male and 1,547 female, meeting the specified inclusion and exclusion criteria. These cases were categorized into two groups according to the presence or absence of DPPB. The non-bleeding group comprised 4,169 patients, while DPPB was identified in 70 patients, of which 54 were male and 16 were female. Specifically, 70 cases of patients with DPPB were included in the case group. To establish a comparison, a control group of 280 cases was selected from the non-bleeding group by matching propensity scores, maintaining a 1:4 ratio of gender to age. Approval for the study protocol was obtained from the Ethics Committee of the Fourth Affiliated Hospital of Zhejiang University School of Medicine (approval number K2023158).

Laboratory data, including haemoglobin, platelets, Prothrombin Time (PT), International Normalized Ratio (INR), Activated Partial Thromboplastin Time (APTT), D-dimer, Total Cholesterol (TC), triglycerides, High-Density Lipoprotein Cholesterol (HDL-C), and Low-Density Lipoprotein Cholesterol (LDL-C), was collected from the patients prior to endoscopic treatment. Further clinical details were gathered, encompassing patients' gender, age, Body Mass Index (BMI), history of alcohol consumption, history of smoking, underlying diseases, use of anticoagulant/antiplatelet drugs, and select psychotropic drugs (selective serotonin reuptake inhibitors). Also, additional clinical parameters were measured, such as total bilirubin, estimated Glomerular Filtration rate (eGFR), ultrasensitive C-reactive protein, Carcinoembryonic Antigen (CEA), Alpha-Fetoprotein (AFP), Carbohydrate Antigen 199 (CA199), and blood group. Postoperative records contained information on the time required to resume a regular diet and the onset of bleeding post-endoscopic treatment. Concurrently, endoscopic data was meticulously recorded, encompassing the Boston Scale score (BOSTON score), timing of endoscopic treatment (morning/afternoon), treatment modality, site, size, number, and morphology of polyps, prophylactic use of hemostatic clips, whether hemostatic clips were fully clamped or not, and attending physician.

Statistical analyses were performed with two software tools:

R software (version 4.3.1) and SPSSPRO (version 1.1.21). The case-control 1:4 propensity score matching was carried out using the 'MatchIt' package in R-Studio. Conventional one-way analyses were conducted using the SPSSPRO software. For measures that followed a normal distribution, the mean ± standard deviation (X±SD) was reported; for those that did not follow a normal distribution, the median and interquartile range [M, (P25, P75)] were reported. Between-group comparisons were performed using independent samples t-tests in case of homogeneous variance, while Welch's t-tests were applied in instances of non-homogeneous variance. Comparative analysis for non-normally distributed measures employed the Mann-Whitney U test. Count data were represented as percentages (%) and compared between groups using various chi-square tests such as Pearson's chi-square test, Yates' corrected chi-square test, and Fisher's exact test. The LASSO method was implemented through the 'glmnet' package in the R language, while conditional logistic regression was conducted using the SPSSPRO software. The significance level chosen for this study was set at P<0.05.

Results

In this study, a total of 4239 inpatients meeting the specified inclusion and exclusion criteria underwent endoscopic treatment for colorectal polyps. The mean age of the patients was 54.93±13.53 years, with ages ranging from 18 to 86 years. Among the participants, 70 individuals developed delayed hemorrhage, resulting in an overall hemorrhage rate of 1%. Specifically, out of the 2692 male cases, 54 cases (63.5%) experienced bleeding, leading to a hemorrhage rate of 3.01%. On the other hand, among the 1547 female cases, 16 cases (36.5%) encountered bleeding, resulting in a hemorrhage rate of 1.03%. Additional information regarding the demographic characteristics and medical history of all cases can be found in Supplementary Table 1.

To compare the two groups of patients, univariate analysis, including t-tests and chi-square tests, was conducted. Significant differences were observed in various risk factors, such as a history of hypertension, use of anticoagulant medication, duration of postoperative open diet, mode of treatment, size of the polyp, polyp singularity/multiplicity, morphology of the polyp, prophylactic use of hemostatic clips, pathological diagnosis, and pathological anomalousness grading (Supplementary Table 1).

Using the glmnet package in R software, the study conducted LASSO analysis (Figure 1). The selected variables for the model included hypertension, use of anticoagulant drugs, polyp size, single/multiple polyps, number of polyps excised, prophylactic use of haemostatic clips, duration of open diet, and blood type. λ's minimum mean square error was 0.034, while the minimum distance's standard error of λ was 0.065. Notably, the corresponding model variables comprised whether to take anticoagulation, polyp size, whether to use hemostatic clips prophylactically, and open diet time.

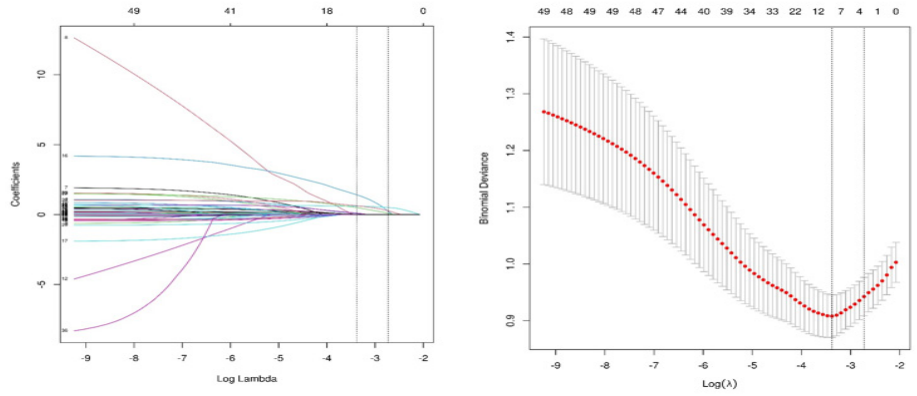

Figure 1: LASSO regression. Path diagram of regression coefficients for inclusion of 49 risk factors and cross validation curve.

Table 1: Conditional logistic regressionof factors associated with DPPB.

Influence factor	Regression coefficient β	Standard error S	Wald value	*P*	OR	95% CI
Multiple polyps	1.466	0.513	8.152	<0.01	4.33	1.583-11.844
Anticoagulant drugs	4.303	1.527	7.938	<0.01	73.893	3.704-1474.04
Hypertension	1.044	0.475	4.825	0.028	2.84	1.119-7.207
P<0.05 indicates a statistically significant difference						

During data collection, propensity matching analysis was utilized. The study employed traditional statistical methods including the t-test and chi-square test, as well as LASSO regression analysis, to identify factors with statistically significant differences. These factors were subsequently incorporated into the conditional logistic regression analysis, which is more suitable for multifactor analysis of paired or stratified data. The analysis confirmed that polyp multiplicity (P<0.01), the use of anticoagulant drugs (P<0.01), and hypertension (P=0.028) were independent risk factors for DPPB (Table 1).

ROC curve analysis was conducted to evaluate the predictive value of factors identified with a significance level of P<0.05 in the conditional logistic regression analysis for DPPB. The Area Under the Curve (AUC) serves as an indicator of predictive capacity, with larger AUC values suggesting stronger predictive value. As depicted in Figure 2, the AUC values for polyps singular/multiple, use of anticoagulant drugs, and hypertension were determined to be 0.589, 0.527, and 0.580, respectively. These results imply that polyps singular/multiple, utilization of antico-

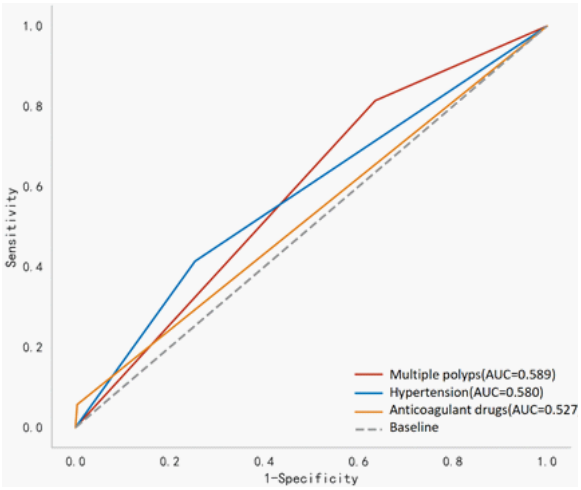

Figure 2: ROC curves for conditional logistic regression models.

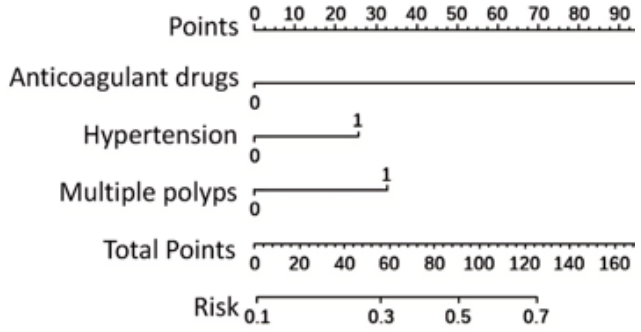

Figure 3: A nomogram model for predicting the risk of DPPB,

agulant drugs, and the presence of hypertension could potentially serve as valuable diagnostic markers for DPPB.

The risk value of patients for the occurrence of DPPB was calculated using a column chart model constructed with the nomogram function in the rms package of the R language. Each indicator corresponds to a vertical line on the horizontal axis and intersects with the scoring scale to obtain a score. The sum of all indicator values represents the patient's risk value. In the columnar model, the use of anticoagulants was found to increase weight by 100 points, while the presence of hypertension increased weight by 27.5 points, and the presence of polyps increased weight by 35 points. Figure 3 depicts the column chart that predicts the risk of DPPB.

Discussion

Endoscopic removal of colorectal neoplastic polyps significantly reduces the incidence of colorectal cancer and related deaths. Despite significant improvements in haemostatic equipment and techniques, bleeding remains a common complication following colorectal polypectomy, including both immediate and delayed bleeding. While most instances of bleeding after polypectomy are rare and long-term complications are uncommon, patients remain at risk of unpredictable hemorrhage that can lead to severe or life-threatening bleeding post-discharge. The overall incidence of DPPB currently ranges between 0.3% and 2.8%. The study observed a delayed bleeding incidence of 1.65%, aligning with findings from previous research. Analyzing the risk factors associated with delayed bleeding is crucial for predicting DPPB and can offer guidance for clinical practice.

Patients with comorbid underlying diseases were found to have a higher risk of DPPB when they also had hypertension, as shown in this study. The risk of DPPB was determined to be 2.84 times greater in hypertensive patients compared to non-hypertensive patients. This aligns with the findings of previous studies conducted by Choung et al. and Lu et al. [18,19], which similarly observed a significantly higher prevalence of hypertension among DPPB cases as opposed to the control group. It is theorized that the prolonged presence of hypertension could lead to atherosclerosis and dysfunction in vasoconstriction, resulting in diminished elasticity of vessel walls and compromised vascular function among patients compared to the general population. Hypertensive patients often exhibit impaired vascular endothelial cell function, impacting vascular constriction and relaxation. Moreover, hypertension can cause significant fluctuations in blood pressure, increasing the risk of postoperative bleeding [20]. Consequently, careful monitoring and management of blood pressure levels is crucial for hypertensive patients in clinical settings. Future studies should delve into factors such as the degree of blood pressure control and the duration of hypertension to provide further insights on this correlation with DPPB.

The study examined the correlation of risk factors for antiplatelet and anticoagulant drugs separately, with results in line with prior research. It found that the use of antiplatelet drugs did not significantly affect the occurrence of DPPB, consistent with previous findings. In contrast, a previous study indicated an increased risk of DPPB with warfarin use (OR: 13.4, 95% CI: 4.1-43.7) [21]. The study specifically focused on patients using rivaroxaban and warfarin as anticoagulants, revealing that anticoagulants are an independent risk factor for DPPB, as supported by existing literature. Consequently, individuals taking anticoagulants should be classified as a high-risk population for DPPB, necessitating meticulous caution during endoscopic operations and the implementation of effective postoperative prophylaxis. The study identified polyp size as a significant risk factor through univariate analysis and LASSO regression. However, no statistical difference was observed in conditional LR analysis. This discrepancy is potentially attributable to the inclusion of polyps with predominantly subtypical morphology and moderate blood supply.

The study categorized polyp location as right hemicolon, left hemicolon, and rectum, which are widely accepted risk factors for DPPB, although conflicting reports exist. Previous studies that examined the left hemicolon and rectum separately showed a significant correlation between polyp location and the risk of DPPB; however, the results of this study revealed no significant correlation. This lack of correlation may be attributed to the small proportion of rectal polyps among the included polyp locations. The role of histology and morphology of polyps in the development of DPPB has been hypothesized but has not been identified as a significant risk factor [22,23]. It has been reported that adenomatous and hyperplastic polyps have a higher incidence of DPPB in terms of histological type, while sessile polyps are associated with a higher incidence of DPPB compared to pedunculated polyps in terms of morphology [24].

In this study, the presence of a higher proportion of sessile polyps and adenomas in the DPPB group was observed, although the association between these factors and DPPB could not be definitively determined due to limited data from a large sample. Therefore, further investigations in subsequent large-sample studies are warranted to explore this potential association. Polyp multiplicity was identified in our study as an independent risk factor for DPPB. However, given the multifaceted nature of this risk, including the influence of factors such as

polyp size, location, pathology, morphology, and the expertise of the operating practitioner, additional well-designed prospective studies are needed to elucidate the precise impact of polyp multiplicity on the risk of bleeding in patients. Moreover, the ABO blood grouping system has been linked to various hemorrhagic disorders, particularly in individuals with blood types other than O. Such disorders include traumatic hemorrhage, upper gastrointestinal hemorrhage, cerebral hemorrhage, postpartum hemorrhage, and epistaxis [25,26]. The potential role of blood group O as a risk factor for DPPB remains unclear and warrants further investigation.

The study found that blood type may be a high-risk factor for DPPB based on LASSO regression analysis. However, conditional logistic regression results suggested that blood type O was not an independent risk factor. This discrepancy could be attributed to potential confounding factors like coagulation function and blood routine. Therefore, further research with a larger sample size is needed to elucidate the precise impact of blood type on DPPB. Prior literature has not definitively established the influence of Selective Serotonin Reuptake Inhibitors (SSRIs) on DPPB among psychotropic drugs [27,28]. Although this study did not identify a statistically significant difference, the limited number of relevant studies necessitates additional research in this area. Notably, the LR analysis revealed no significant differences between the two patient groups in terms of laboratory test results, smoking and alcohol history, use of anaesthetic medications, postoperative dietary restrictions, and operating physicians (P>0.05). These findings suggest that these factors may not be strongly linked to DPPB in the current dataset. Nevertheless, further investigation is warranted to rule out potential confounders or data overfitting, as certain variables were highlighted as significant in the model characteristics analysis.

Conclusion

Various risk factors have been identified as strongly associated with the development of DPPB. These risk factors include hypertension, anticoagulant use, duration of open diet, treatment modality, polyp size, polyp multiplicity, polyp morphology, prophylactic tourniquet use, polyp pathology, pathological heterogeneity grading, and blood group. Based on these identified risk factors, it is recommended that appropriate interventions be implemented to prevent or manage the development of DPPB.

Declarations

Funding statement: The study was not supported by a Foundation.

Conflict of interest: The authors declare no potential conflicts of interest.

Data access statement: The data supporting this study's findings are available from the corresponding author upon reasonable request.

Authorship contribution statements: The authors confirm responsibility for study conception and design, data collection, analysis and interpretation, and manuscript preparation.

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