

Analysis of risk factors for recurrence of Budd–Chiari syndrome based on zero–inflated model

Shengli Li^{1,2#}[0000-0002-2612-0655], Xiangting Liu^{3#}[0000-0002-2334-5189], Muyao Zhou^{4#}[0009-0009-9396-1217], Hui Wang^{5#}[0000-0002-2729-6011], Na Yang⁶[0009-0007-8149-969X], Cuocuo Wang³[0009-0008-8640-6242], Qingqiao Zhang⁷[0000-0001-6177-7081], Maoheng Zu⁷[0000-0003-3093-3226], Lei Wang¹[0000-0002-2334-5189] *

¹ School of Computer Science and Technology, China University of Mining and Technology, Xuzhou, Jiangsu 221116, China

² Clinical Research Institute, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, Jiangsu 221006, China

³ Department of General Practice, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, Jiangsu 221006, China

⁴ Jiangsu Normal University, 101# Shanghai Road, Xuzhou, Jiangsu 221116, China

⁵ Department of Hepatobiliary Surgery, Xuzhou Central Hospital, Xuzhou, Jiangsu 221009, China

⁶ Artificial Intelligence Unit, Department of medical Equipment Management, Affiliated Hospital of Xuzhou Medical University, Xuzhou 221004, China

⁷ Department of Interventional Radiology, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, Jiangsu 221006, China

*Corresponding author: Lei Wang, leiwang@cumt.edu.cn.

Abstract

Objective: To identify the optimal model for assessing the recurrence frequency of BCS, and further analyze the factors contributing to BCS recurrence. **Methods:** The study included a total of 754 patients who were admitted to the Affiliated Hospital of Xuzhou Medical University between January 2015 and July 2022. We constructed four different count outcome models: the Poisson model, the negative binomial (NB) model, the zero-inflated Poisson (ZIP) model, and the zero-inflated negative binomial (ZINB) model. We selected the model with the best fitting performance for exploring factors associated with BCS recurrence. **Results:** Of all 754 respondents, 511 patients reported no recurrences. The LR tests indicated that the NB model performed better than the Poisson regression model ($\chi^2 = 124.91$, $p < 0.001$), and the ZINB model outperformed the ZIP model ($\chi^2 = 34.29$, $p < 0.001$). In the ZINB model, the analysis of the counting process revealed that the variables significantly associated with recurrence frequency included age (odds ratio [OR] = 0.69; 95% confidence interval [CI]: 0.57–0.84), sex (female: OR = 1.77; 95% CI: 1.24–2.55), anticoagulant use (warfarin vs. new oral anticoagulants [NOACs]: OR = 2.11, 95% CI: 1.34–3.31; not using anticoagulants vs. NOACs: OR = 1.98, 95% CI: 1.20–3.28), absence of cirrhosis (OR = 0.57, 95% CI: 0.40–0.82), and neutrophil count (OR = 1.22, 95% CI: 1.04–1.42). **Conclusions:** The zero-inflated model proves robust in identifying factors influencing BCS recurrence compared to other models, elucidating

the influence of gender, surgery, anticoagulation, cirrhosis, hospital duration, APOA, and neutrophil count on recurrence risk and frequency of BCS patients.

Keywords: ZINB regression; Dispersion; Budd-Chiari syndrome; Recurrence.

1 Introduction

Budd–Chiari syndrome (BCS) is a rare yet fatal vascular disorder characterized by hepatic venous outflow tract obstruction. This obstruction is independent of its level or underlying mechanism, provided that it is not attributed to pericardial disease, cardiac conditions, or veno-occlusive disease[1]. China may have the highest reported cases of BCS worldwide. With an estimated annual incidence of 0.88 per million and a prevalence of 7.69 per million, China hosts a significant population of over 20,000 documented patients with BCS, primarily concentrated in the Huanghuai region[2]. In contrast to Europe and India, where over 80% of BCS cases are associated with hypercoagulable states, the pathogenesis of BCS in China predominantly follows a dynamic pathological process characterized by “vascular endothelial damage - inflammatory reaction - endothelial recovery and intimal hyperplasia - thrombus formation and organization - membrane formation.”[3] The European Association for the Study of the Liver recommends a step-wise therapeutic approach for BCS treatment[4-6], which includes: (a) medical therapy; (b) percutaneous recanalization of hepatic veins and/or the inferior vena cava (IVC); (c) placement of a transjugular intrahepatic portosystemic shunt (TIPS); and (d) orthotopic liver transplantation. In cases where acute BCS with an identifiable clot is diagnosed, thrombolytic therapy is recommended.

However, a multicenter European study involving 157 patients with BCS managed through this step-by-step strategy (SSS) reported discouraging 5-year intervention-free survival rates[7]. In India, 5-year cumulative patency rates for recanalization and TIPS groups stood at 74% and 68%, respectively, among 510 patients receiving endovascular interventions[8]. In China, the reported rates of restenosis or occlusion range from 20%–40%[9-12], posing a significant threat to public health. In recent years, the incidence of BCS has been steadily rising in Shandong and the northern region of Jiangsu[13, 14]. With an anticipated increase in life expectancy, the number of recurrent cases is expected to rise, thereby worsening the societal and medical burdens. Therefore, it is imperative to identify the underlying risk factors for BCS recurrence to enhance surveillance and facilitate early intervention. Traditional statistical methods, such as logistic regression and Cox proportional hazard models, have been employed to evaluate prognosis. Recently, a nomogram model based on Cox regression has been established to predict the first recurrence of BCS following endovascular treatment[15]. However, conventional regression models are ill-suited for handling data with a substantial proportion of zeroes.

To address these limitations, alternative modeling approaches, such as zero-inflated models or hurdle models, are frequently used. Zero-inflated models explicitly account for excess zeros by incorporating two components: the first group generates an all-zero subset, whereas the second group follows a Poisson or negative binomial (NB) distribution for “non-zero” outcomes[16]. These extended models have found widespread application in areas such as microbiome research, infectious diseases, epidemics, and chronic diseases[17, 18]. Therefore, we aimed to identify

relevant risk factors associated with BCS recurrence based on the best-fitting model. This analysis will provide a valuable reference for formulating early personalized intervention plans for patients with BCS, marking a significant step toward the realization of precision medicine.

2 Methods

2.1 Patients

This retrospective investigation included 754 patients with BCS admitted to the Affiliated Hospital of Xuzhou Medical University between January 2015 and July 2022. BCS diagnoses were established using color Doppler ultrasonography, multimodal computed tomography, magnetic resonance imaging, and/or angiography[19]. Exclusion criteria included: 1. secondary BCS; 2. hepatic outflow obstruction attributed to congestive heart disease, sinusoidal obstruction syndrome, or other causes; 3. substantial dysfunction of vital organs such as the liver, kidney, brain, or malignancies, including liver cancer; 4. non-standardized anticoagulation; 5. patients lost to follow-up or who passed away prior to experiencing recurrence.

2.2 Data collection

Collected data included recurrence frequency, age, gender, occupation (whether farmers and workers), BCS classification, type of operation, anticoagulant use, presence of liver cirrhosis, thrombosis status, hospital duration, neutrophil count, platelet count (PLT), prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, thrombin time, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin (ALB), glucose (GLU), total bilirubin (TBIL), cholesterol (CHOL), triglyceride (TG), apolipoprotein A (ApoA), apolipoprotein B (ApoB), lipoprotein(a) [Lp(a)], high-density lipoprotein (HDL), low-density lipoprotein (LDL), cystatin C, lactate dehydrogenase (LDH) and alpha-fetoprotein. BCS was classified into three main types[20]: hepatic vein (HV) type, IVC type, and mixed type (HV + IVC). Operations were categorized into five main forms: simple balloon dilation, stent implantation, catheter-directed thrombolysis, TIPS, and conservative treatment. Anticoagulant options included warfarin, new oral anticoagulants (NOACs), or no anticoagulants.

2.3 Follow-up

Recurrence was defined as the presence of a newly thrombosed vessel or partial/complete occlusion in the IVC, HV, or collateral veins, with reversed or nonexistent flow. Additionally, new symptoms such as recurrent ascites, abdominal wall varicosity, lower limb swelling or upper gastrointestinal bleeding were considered indicative of recurrence after the patient's condition had initially stabilized[9, 15, 21]. Patients were subjected to regular 6-month follow-ups from July 2021 until the completion of the study in July 2023. To establish contact with patients or their family members, telephone communication and outpatient records were used. Respondents were divided into two groups: those with recurrence and those without.

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2.4 Related basic principles

2.4.1 Overdispersion test

O-test is a method based on mean and variance testing to determine whether there is over dispersion. For excessively discrete count data, Poisson regression often underestimates the standard error of parameter estimates, leading to larger statistical quantities, thereby increasing Type I errors and exaggerating the effect of explanatory variables. The calculation formula is:

$$O = \sqrt{\frac{n-1}{2}}(s^2 - \bar{x})/\bar{x}$$

Among them, n represents the total number of patients, and s^2 and \bar{x} are the variance and mean of the number of relapses. When the absolute value of the O statistic is greater than 1.96 and the mean is much smaller than the variance, it indicates that the data has over discreteness. Continuing to use the Poisson distribution will result in a decrease in standard error and estimation efficiency, while using the NB distribution is more reasonable. When $|O| < 1.96$, it cannot be considered that the variance is significantly greater than the mean, and there is no dispersion phenomenon in the data.

2.4.2 Vuong test

The Vuong test is suitable for comparing the goodness of fit of two non-nested models. The calculation formula is:

$$V = \frac{\sqrt{n}[(1/n)\sum_{i=1}^n m_i]}{\sqrt{(1/n)\sum_{i=1}^n (m_i - \bar{m})^2}} = \frac{\sqrt{Nm}}{S_m}$$

When $V < -1.96$, it is recommended to choose Poisson or NB; When $V > 1.96$, it indicates zero inflation in the data, and it is recommended to choose a zero inflation model; When $|V| < 1.96$, it is impossible to determine which model is better and other means are needed. The Vuong package in R can be loaded for calculation.

2.4.3 LR test

Assuming Model 1 is nested within Model 2, LR test can be used for model selection. The corresponding statistics are:

$$LR = -2(\ln L_2 - \ln L_1)$$

Among them, LR follows a chi square distribution with a degree of freedom of v , which is the number of restricted parameters. If the LR value is less than 0.05 under the chi square distribution, it can indicate that Model 1 is superior to Model 2. Use the `lrtest()` function of the `lmtest` package in R language to complete it.

2.5 Statistical analyses

All statistical analyses were conducted using R version 4.0.3 (<https://www.rproject.org/>) with the following packages: `mice`, `nnet`, `glmnet`, `glm`, `glmmTMB`, `MASS`, `pscl`, `lmtest`, and `ggplot2`. Significance was considered at $p < 0.05$. The predictive mean matching method was employed to

address missing data, with imputation performed across five imputation matrices, iterated over 50 cycles. Categorical variables were presented as counts, whereas continuous variables were expressed as means and standard deviations. The t-test was used for continuous variables, and the Chi-squared test was applied for categorical variables. Variance inflation factor (VIF) analysis was used to assess collinearity between variables, with variables selected based on elastic net techniques[22, 23]. To standardize laboratory indicator data and eliminate dimensional differences, Z-Score transformation was employed.

The entire dataset was randomly divided into training ($n = 603$) and validation ($n = 151$) sets, with a 7:3 ratio. Over-dispersion was detected using the O statistic. Poisson, NB, and zero-inflated regression models with identical variables were fitted to the data. Vuong statistics were used to compare the goodness of fit between the zero-inflation model and corresponding traditional models. Similarly, the log-likelihood ratio (LR) test allowed for comparisons of nested models (Poisson vs. NB, ZIP vs. ZINB). The selection of the optimal model relied on the minimum values of Akaike information criteria (AIC), corrected AIC (AICc), and -2LogLikelihood ($-2LL$). Additionally, the root mean squared error (RMSE), mean absolute error (MAE), accuracy, precision, and predictive curve were employed to evaluate forecasting performance.

3 Results

3.1 Patient characteristics

Of the initial 1300 patients, 454 cases were excluded for various reasons, including malignancies ($n = 202$), liver and kidney failure ($n = 85$), hepatic encephalopathy ($n = 25$), secondary BCS ($n = 30$), and irregular anticoagulant therapy ($n = 112$). Additionally, 92 patients were lost to follow-up before experiencing recurrence. Consequently, 754 patients were retained for modeling. A histogram (Figure 1) depicting the recurrence frequency of these patients revealed that 511 patients reported no recurrence, 157 patients experienced recurrence once, 49 patients experienced two recurrences, and 28 patients experienced three recurrences during the follow-up period. The variance (2.46) exceeded the mean (0.64), and the O statistic was 55.08 with a p-value less than 0.001, indicating data over-dispersion. Notably, high-risk areas were primarily concentrated in the Huanghuai region, particularly in Jiangsu ($n=295$), Shandong ($n = 140$), Anhui ($n = 131$), and Henan ($n = 55$) provinces. The top three recurrent symptoms included abdominal distension and pain, lower limb swelling, and abdominal wall varicose veins.

Table 1 shows the demographic and clinical characteristics of the patients. The male-to-female ratio was 1.32:1, with a mean age of 48.80 ± 13.22 years (range: 12–82 years). Farmers and workers represented the majority, accounting for 46.15% of patients. Percutaneous angioplasty with or without stent placement was the predominant therapeutic modality for BCS in our country. In particular, 502 patients underwent balloon dilation, 78 patients received stent implantation, 45 patients were treated with thrombolytic therapy, 27 patients received stent placement, and the remaining 102 patients underwent conservative treatment. A total of 555 patients regularly used oral anticoagulants, including warfarin, rivaroxaban, apixaban and dabigatran. More than half of the patients had comorbid liver cirrhosis, and 141 patients presented with thrombosis. Significant differences in age, occupation, BCS type, operation type, anticoagulant use, hospital duration,

neutrophil count, PLT, PT, APTT, ALB, TBIL and HDL were observed between the relapse and non-relapse groups.

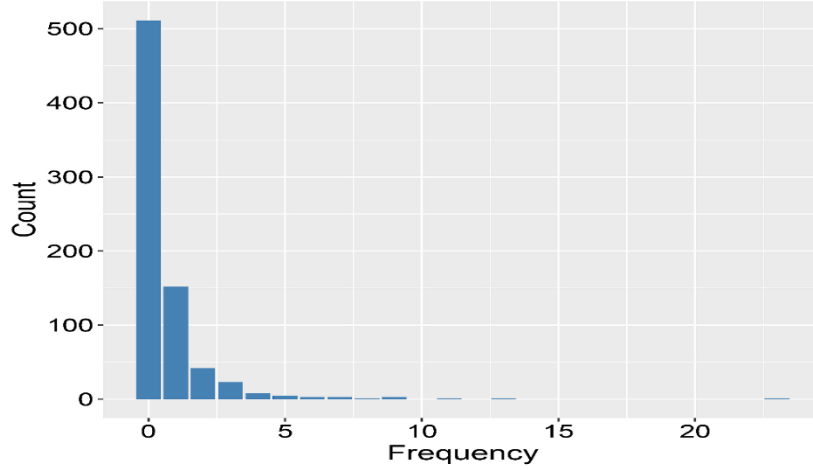


Fig. 1. Recurrence frequency histogram

Table 1. Baseline characteristics in the study cohort

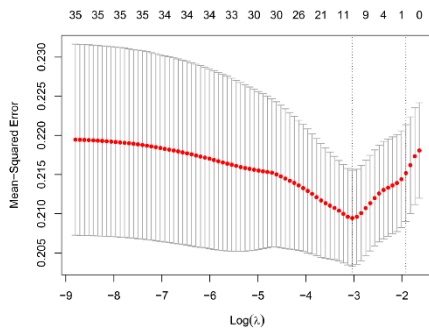
Variables	Total n=754	Not-recurrent n=511	Recurrent n=243	<i>p</i> value
Age (years old)	48.80 ± 13.22	50.91 ± 12.36	44.34 ± 13.89	<0.001
Gender (male/female)	429/325	278/233	151/92	0.054
Laborer (yes/no)	348/406	260/251	88/155	<0.001
Type (HV/IVC/MIX)	463/173/118	342/101/68	121/72/50	<0.001
Cirrhosis (yes/no)	441/313	309/202	132/111	0.128
Thrombus (yes/no)	141/613	86/425	55/188	0.070
Operation (PTA/stent/thrombolysis/TIPS/none)	502/78/45/27/102	337/61/24/14/75	165/17/21/13/27	0.011
Anticoagulants (warfarin/NOACs/none)	389/166/199	266/99/146	123/67/53	0.019
Hospital duration (days)	11.22 ± 6.25	10.71 ± 5.52	12.30 ± 7.47	0.001
NEU (10 ⁹ /L)	2.81 ± 1.88	2.69 ± 1.81	3.06 ± 2.00	0.013
PLT (10 ⁹ /L)	120.59 ± 68.69	117.18 ± 63.13	127.76 ± 78.77	0.048
PT (sec)	14.47 ± 5.46	14.13 ± 5.36	15.20 ± 5.59	0.012
APTT (sec)	34.26 ± 9.61	33.55 ± 8.73	35.75 ± 11.12	0.003
FIB (g/L)	2.37 ± 0.81	2.34 ± 0.74	2.44 ± 0.92	0.104
TT (sec)	17.60 ± 5.18	17.38 ± 1.58	18.07 ± 8.83	0.085
AST (U/L)	33.29 ± 60.34	32.85 ± 70.59	34.20 ± 28.76	0.774
ALT (U/L)	25.99 ± 33.52	25.03 ± 37.10	28.00 ± 24.26	0.256
ALB (g/L)	40.75 ± 6.40	41.22 ± 6.30	39.77 ± 6.53	0.004
TBIL (umol/L)	33.16 ± 35.96	31.17 ± 31.19	37.34 ± 44.14	0.028

CysC (mg/L)	0.92 ± 0.30	0.93 ± 0.33	0.90 ± 0.22	0.370
GLU (mmol/L)	5.22 ± 1.82	5.21 ± 1.67	5.24 ± 2.10	0.871
CHOL (mmol/L)	3.53 ± 0.93	3.57 ± 0.94	3.44 ± 0.93	0.072
TG \pm mmol/L)	0.85 ± 0.41	0.85 ± 0.40	0.86 ± 0.42	0.684
ApoA (g/L)	1.03 ± 0.29	1.04 ± 0.28	1.00 ± 0.31	0.101
ApoB (g/L)	0.64 ± 0.21	0.64 ± 0.22	0.64 ± 0.21	0.727
LPa (mg/L)	168.54 ± 152.71	162.16 ± 141.79	181.95 ± 173.01	0.096
HDL (mmol/L)	1.20 ± 0.43	1.22 ± 0.43	1.14 ± 0.43	0.01
LDL (mmol/L)	1.95 ± 0.76	1.96 ± 0.80	1.91 ± 0.66	0.390
LDH (U/L)	212.47 ± 105.15	208.72 ± 99.22	220.34 ± 116.47	0.156
AFP (ng/mL)	5.85 ± 28.86	5.26 ± 17.18	7.10 ± 44.34	0.413

3.2 Screen for relapse-related risk factors

VIFs corresponding to operation type, anticoagulant use, APTT, AST, ALT, CHOL, TG, HDL, LDL, ApoA, and ApoB exceeded 2, indicating multicollinearity. The elastic net method was employed to compress regression coefficients of unnecessary variables to zero and subsequently eliminate them from the model for variable screening. Figure 2 indicates the selection of potential predictors through the least absolute shrinkage and selection operator regression. Nine variables with non-zero coefficients were selected based on the minimum lambda, including age, sex, occupation, operation type, anticoagulant use, neutrophil count, ALB, GLU, and LDH. In addition, the influence of liver cirrhosis, BCS type, and elevated TBIL levels on patient prognosis had been previously confirmed[11, 15, 24-29]. Furthermore, Simone Talen had suggested that decreased levels of APOA may play a role in the etiology of thrombosis in patients with BCS and potentially in other patients with venous thrombosis[30]. Thus, the variables of age, sex, occupation, operation type, anticoagulant use, neutrophil count, ALB, GLU, LDH, liver cirrhosis, BCS type, and TBIL were used to build models in the training set.

A: cross-validation curve



B: regression coefficient path plot

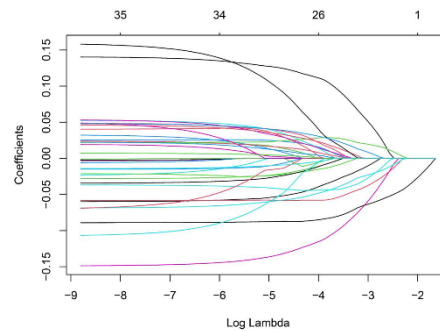


Fig. 2. Lasso regression cross-validation method for analyzing clinical features

3.3 Modeling and comparison

The non-nested models (i.e. Poisson vs. ZIP and NB vs. ZINB) were compared using the Vuong test. The results of the Vuong test provide evidence for the preference of the ZIP over the Poisson ($z = 4.11$, $p < 0.001$) and the ZINB over the NB ($z = 3.40$, $p < 0.001$) (Table 2). For nested models, the log-likelihood of the Poisson model ($LL = -635.40$) was greater than that of NB ($LL = -572.94$) with a statistic of 124.91 ($p < 0.001$), which revealed that the latter was better. Similarly, the ZIP ($LL = -567.27$) was inferior to ZINB ($LL = -550.13$) with a statistic of 34.29 ($p < 0.001$). ZINB exhibited the smallest $-2LL$ (1100.26), AIC (1182.26), AICc (1188.40), MAE (0.94), and RMSE (2.02), and the largest accuracy (58.94%) and precision (28.07%) (Table 3). As shown in Figure 3, the prediction effect of the zero-inflated model was consistent with actual values than traditional count models. Finally, the ZINB model was chosen as the optimum model for further analysis of recurrence-related indications.

Table 2. Vuong test and LR test results

relationship		Vuong test		Likelihood ratio test	
		z	p-value	χ^2	p-value
NB vs Poission	test	-	-	124.91	<0.001
ZINB vs ZIP	test	-	-	34.29	<0.001
ZIP vs Poission	non-test	4.11	<0.001	-	-
ZINB vs NB	non-test	3.40	<0.001	-	-

Table 3. Comparison of the fitness indicators and predictive indicators for four models

	Fitness Indicators				Predictive Indicators			
	AIC	AICc	BIC	-2LL	RMSE	MAE	Accuracy	Precision
Poission	1310.80	1312.24	1398.84	1270.80	2.23	1.01	56.29%	23.73%
NB	1187.89	1189.48	1280.33	1145.89	2.36	1.02	56.29%	24.14%
ZIP	1214.55	1220.38	1390.62	1134.55	2.08	0.96	55.63%	23.21%
ZINB	1182.26	1188.40	1362.74	1100.26	2.02	0.94	58.94%	28.07%

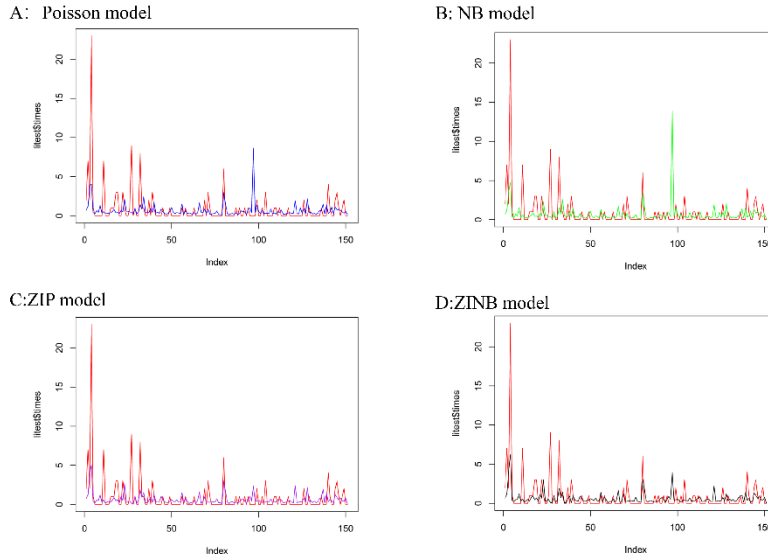


Fig. 3. Visualization line graph of predicted and actual value curves

3.4 Result of the ZINB model

The coefficients, corresponding standard errors, z-scores, and p-values of each of the variables in the ZINB model wereshown in Table 4. In the zero section of the right side, gender, surgery, anticoagulants, liver cirrhosis, hospital duration, and APOA were determinants of recurrence. The number of BCS recurrences was more likely to become zero among women patients (OR = 22.43, 95% CI: 2.41–208.46). Using warfarin (OR = 7.10, 95% CI: 1.12–45.15) or not using anticoagulants (OR = 14.51, 95% CI: 2.33–90.24) exhibited a higher risk of developing recurrence than NOACs. Furthermore, not having liver cirrhosis (OR = 0.15, 95% CI: 0.04–0.62), long hospital duration (OR = 0.4, 95% CI: 0.20–0.81), and higher levels of APOA (OR = 0.37, 95% CI: 0.18–0.74) were associated with increased odds of reporting zero recurrence with BCS. Patients with stent implantation (OR = 17.49, 95% CI: 1.32–231.99) were more sensitive to recurrence than those with simple balloon dilatation. Results from the count section revealed that age, gender, anticoagulation, presence or absence of cirrhosis, and neutrophil count exerted significant effects on the recurrence frequency of BCS. Older patients (OR = 0.69, 95% CI: 0.57–0.84) and patients without liver cirrhosis (OR = 0.57, 95% CI: 0.40–0.82) showed fewer relapse times. However, female patients (OR = 1.77, 95% CI: 1.24–2.55), patients using warfarin or no anticoagulants (OR = 2.11, 95% CI: 1.34–3.31), and patients with increased neutrophil count (OR = 1.98, 95% CI: 1.20–3.28) showed more relapse times.

Table 4. Zero-inflated negative binomial regression analysis

Variables	Count component					Zero component				
	Estimate	SE	z value	Pr (> z)	OR (95% CI)	Estimate	SE	z value	Pr(> z)	OR (95% CI)

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(Intercept)	-0.63	0.21	-3.09	<0.05	0.53(0.35-0.79)	-3.21	1.36	-2.37	<0.05	0.04(0.00-0.58)
Age	-0.37	0.1	-3.61	<0.001	0.69(0.57-0.84)	0.3	0.34	0.87	0.38	-
Gender										
female (vs. male)	0.57	0.19	3.1	<0.05	1.77(1.24-2.55)	3.11	1.14	2.74	<0.01	22.43(2.41-208.46)
Laborer										
YES (vs. NO)	-0.26	0.18	-1.45	0.15	-	-0.66	0.64	-1.03	0.3	-
Type										
HV (vs. IVC)	0.18	0.22	0.8	0.43	-	-0.95	0.73	-1.31	0.19	-
MIX (vs. IVC)	-0.11	0.25	-0.45	0.65	-	-0.77	0.9	-0.86	0.39	-
Operation										
stent (vs. PTA)	0	0.41	0.01	0.99	-	2.86	1.32	2.17	<0.05	17.49(1.32-231.99)
thrombolysis (vs. PTA)	0.3	0.28	1.07	0.29	-	-17.9	3849.21	-0.01	1	-
TIPS (vs. PTA)	-0.74	0.4	-1.82	0.07	-	-2.85	1.85	-1.54	0.12	-
none (vs. PTA)	0.17	0.35	0.49	0.62	-	0.58	0.99	0.59	0.56	-
Anticoagulants										
warfarin (vs. NO-ACs)	0.75	0.23	3.23	<0.05	2.11(1.34-3.31)	1.96	0.94	2.08	<0.05	7.10(1.12-45.15)
none (vs. NOACs)	0.69	0.26	2.68	<0.05	1.98(1.20-3.28)	2.68	0.93	2.87	<0.01	14.51(2.33-90.24)
Cirrhosis										
NO (vs. YES)	-0.56	0.18	-3.05	<0.05	0.57(0.40-0.82)	-1.87	0.71	-2.63	<0.01	0.15(0.04-0.62)
long	-0.08	0.08	-1.01	0.31	-	-0.92	0.36	-2.54	<0.05	0.40(0.20-0.81)
NEU	0.2	0.08	2.67	<0.05	1.22(1.06-1.42)	0.22	0.24	0.92	0.36	-
ALB	-0.16	0.1	-1.68	0.09	-	0.54	0.32	1.71	0.09	-
GLU	0.06	0.1	0.63	0.53	-	-0.49	0.33	-1.5	0.13	-
TBIL	0.07	0.07	1.08	0.28	-	-0.1	0.19	-0.56	0.58	-
APOA	-0.09	0.12	-0.7	0.48	-	-1	0.36	-2.79	<0.01	0.37(0.18-0.74)
LDH	0.09	0.09	1.02	0.31	-	0.18	0.16	1.18	0.24	-
Log (theta)	0.46	0.3	1.52	0.13	-	-	-	-	-	-

4 Discussion

In this study, zero values were close to 70% and all tests for goodness of fit reported that the ZINB regression model better fitted the data of BCS recurrence than other models. Parameters, such as gender, surgery, anticoagulation, cirrhosis, hospital duration, and APOA considerably affected the risk of recurrence. Furthermore, age, gender, anticoagulation, cirrhosis, and Neutrophil count was considered as the risk factors for the number of BCS recurrences. This rare disease predominantly affects middle-aged individuals around the age of 45 and exhibits a higher rate of multiple relapses than in older patients. Zhang Jing et al.[31] reported that this may be because recurrent symptoms are easy to detect in young patients and they show a strong willingness to proactively seek medical attention. BCS affects women in the reproductive age group; therefore, it may be associated with the use of oral contraceptives, secondary hormonal abnormalities, and undiscovered genetic factors. However, Enpu Guo et al. and Shengli Li et al. found no gender-based difference in the pathogenesis of BCS[13, 32]. Approximately half of the patients were employed as farmers and workers, indicating that the disease is more likely to occur in relatively underdeveloped areas and low-income, heavy manual labor populations. Further studies are warranted to determine the relationship between the higher number of male patients and gender differences in labor intensity[33]. Increased neutrophil count and decreased AOPA were promoting factors of relapse. Neutrophil count produces oxygen radicals and inflammatory mediators infiltrating ischemic tissue, releases tissue factors, or induce other cells to cause tissue factors to promote thrombosis. HDL protects endothelial cells because it has anti-inflammatory, antioxidant, and antithrombotic properties. APOA is the main structural protein of HDL. Therefore, APOA was a protective factor for BCS sufferers.

NOACs, such as Rivaroxaban, Apixaban and Dabigatran, might be advantageous over low-molecular-weight heparin (LMWH) or VKA treatment because these drugs can be taken orally. They do not have to be monitored by international normalized ratio and can directly inhibit coagulation factors, such as Xa and IIa, reduce the rate of thromboembolic events in cardiovascular and stroke diseases, cause fewer anticoagulant–anticoagulant interactions, and do not interfere with the Model for End-Stage Liver Disease[34–37]. A study by the VALDIG[38] consortium in which 14% of the study patients had BCG showed that NOACs exhibited comparable safety and efficacy to vitamin K antagonists (VKA). Li Weizhi[39] et al. reported that compared with aspirin, rivaroxaban can improve stent patency in patients with BCS after percutaneous intravascular intervention and might not increase massive bleeding. According to Du Xiaofei et al.[40], low-dose rivaroxaban is safe for patients with decompensated liver cirrhosis, which causes no significant bleeding or liver injury. However, the high cost and lack of effective antagonists hinder the widespread application. NOACs are effective and safe in the long-term anticoagulation treatment of BCS, which warrants further prospective studies.

PTA combined with stent placement has always achieved excellent long-term patency and survival in most Chinese patients with BCS[12, 41]. Nevertheless, the recurrence risk of the stent group was higher than the simple balloon group in this study. This could be due to the following three reasons: (1) only 78 patients underwent stent implantation; however, the number of patients in the balloon group was six times more than that of the stent group. An unbalanced sample size

may lead to bias in statistical analysis. (2) Patients undergoing stent implantation are usually associated with more numbers of diseased vessels, more serious stenosis, more wide-ranging vessel disease, and longer vessel disease. (3) The damage in the vascular endothelium due to the balloon is usually transient and reversible. In contrast, the metal materials and design features on the surface of the stent can cause platelet activation, vascular endothelial inflammatory response, and proliferative response, which can increase the possibility of recurrence.

To the best of our knowledge, this is the first study to investigate the application of ZI models to BCS recurrence through a large sample size, single-center retrospective study. However, our study lacks external validation and requires a large sample and a multi-centered and randomized controlled approach to further validate its clinical significance. In the future, more factors should be considered, including stricture length, stent type, and preoperative and postoperative hepatic vein or portal vein pressure, to provide evidence-based support for screening risk factors of BCS. To summarize, the zero-inflated model is a robust tool to screen factors that affect BCS recurrence, facilitating the implementation of personalized precision intervention treatment.

Author contributions. SL participated in the design and interpretation of the data and revising the manuscript. XL and HW conceived of the study, and participated in its design and interpretation and helped to draft the manuscript. CW and QZ performed the statistical analysis and revised the manuscript critically. As the corresponding author, LW participated in its design and interpretation and helped to revise the manuscript critically. SL, XL, MZ and HW contributed equally to this work and should be regarded as co-first authors. All authors read and approved by the final manuscript.

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