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Preoperative Risk Factors for Predicting Postoperative Human Serum Albumin Infusion after Hip Fracture Surgery: Development and Validation of a Nomogram

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Background: As one of the adverse events after hip fracture surgery, hypoalbuminemia is usually treated using human serum albumin infusion. However, the application of human serum albumin may cause complications such as postsurgical infection and increased mortality.

Aims: To examine the preoperative risk factors of human serum albumin infusion after hip fracture surgery, establish a nomogram prediction model, and verify its accuracy.

Study Design: A retrospective cross-sectional study.

Methods: Eligible patients who underwent hip fracture surgery were divided into the infusion and non-infusion groups according to whether human serum albumin was infused or not. All patients were divided randomly into a training set and a testing set in line with the ratio of 7:3. In the training set, independent risk factors of postoperative human serum albumin infusion were determined by univariate logistic regression analysis, LASSO regression, and multivariate logistic regression analysis. Then, a nomogram model was established. Furthermore, the receiver operating characteristic curve and calibration curve were plotted, and decision curve analysis was performed for the training and testing sets to assess the predictability, discriminative ability, and clinical usefulness of the model.

Results: This study included a total of 1,339 eligible patients, 141 of whom were injected with human serum albumin postoperatively. Altogether, the training set incorporated 939 patients, and the testing set included 400 patients. Multivariate logistic analysis indicated five independent risk factors, including chronic lung disease (odds ratio, 95% confidence interval, 2.618, 1.413-4.849, $p = 0.002$), (albumin; odds ratio, 95% confidence interval, 0.842, 0.787-0.900, $p < 0.001$), prothrombin time (odds ratio, 95% confidence interval, 1.252, 1.071-1.463, $p = 0.005$), red blood cells (odds ratio, 95% confidence interval, 0.370, 0.228-0.602, $p < 0.001$), and type of anesthesia (odds ratio, 95% confidence interval, 0.553, 0.327-0.937, $p = 0.028$). Fracture type, a clinically significant factor, was also considered. Finally, the nomogram model was built based on these seven predictors. The areas under the curve of the nomogram were 0.854 (95% confidence interval, 0.811-0.898) and 0.767 (95% confidence interval, 0.686-0.847) in the training and testing sets separately. As shown in the calibration curve, the predicted result was consistent with the observed one. The decision curve analysis indicated that the nomogram has good clinical value.

Conclusion: Low preoperative serum albumin levels, low preoperative red blood cell counts, prolonged preoperative prothrombin time, history of chronic lung disease, and general anesthesia were independent risk factors for postoperative human serum albumin infusion. Besides, the fracture type, clinically significant factor, was also included. The nomogram that combined these six predictors could accurately predict the risk of postoperative human serum albumin infusion.

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INTRODUCTION

With the increasing life expectancy and aging population worldwide, hip fractures have become a major public health problem,[1] which have a high disability rate, with 30-50% of the patients losing their basic life skills. Surgical treatment is the best option for hip fractures, which aims to relieve pain, avoid complications resulting from long-term sickbeds, and help patients recover as much as possible.[2,3] Despite the positive surgical outcomes, multiple postoperative complications such as postoperative anemia and hypoalbuminemia are inevitable.[4]

Hypoalbuminemia further increases the incidence of complications such as nonunion, non-septicemia, blood transfusion, and non-planning cannula in patients with hip fractures.[5] In addition, Uriz-Otano et al.[6] found that hypoalbuminemia was a strong predictor of postoperative mortality in hip fractures. Therefore, how to avoid hypoalbuminemia in the postoperative period of hip fractures has become an important clinical topic.

Albumin (ALB) is synthesized by the liver and is the most abundant protein in blood plasma, accounting for 50-60% of the total plasma protein.[7] ALB has various biological roles in the human body, including maintaining plasma colloid osmotic pressure, conveying several ions, lipids, and metabolites in the body, and exerting anti-inflammatory effects and antioxidant capacity.[8,9] When patients present with symptoms of hypoalbuminemia and liver function suggests ALB ≤30 g/l, clinicians usually administer human serum albumin (HSA) empirically to raise the level of plasma ALB in a short period.[10] Therefore, preoperative identification and correction of risk factors for postoperative HSA infusion in patients with hip fractures can reduce the incidence of postoperative HSA infusion and decrease the complications of hypoalbuminemia.

Nomogram can predict and visualize the risk of a particular event and is widely applied in the diagnosis and prognosis of diseases. Recently, Liu et al.[10] built a relevant model by studying the risk factors of HSA infusion after posterior lumbar interbody fusion; however, studies on hip fracture surgery are still lacking. Therefore, this study aimed to explore the incidence and preoperative risk factors of HSA infusion after hip fracture surgery and establish a nomogram model. The incidence of postoperative HSA infusion was systematically evaluated through the nomogram to more accurately guide surgeons in early intervention and treatment of patients and ultimately reduce the application of postoperative HSA infusion.

MATERIAL AND METHODS

This study was conducted based on the Declaration of Helsinki. This study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University (approval no. QYFY-WZLL-27124).

Patients

A total of 1,339 patients who underwent surgery for hip fractures between January 2014 and December 2021 were enrolled in this study. This study was also approved by the Ethical Committee of the Affiliated Hospital of Qingdao University. The criteria of human serum ALB infusion for patients in our paper were as following: 1. When patients had ALB less than 30 g/l and more than 25 g/l, accompanied by obvious clinical symptoms, such as edema, loss of appetite, abdominal pain, and so on, ALB was usually infused; 2. ALB was usually infused when it was below 25 g/l. As this study is based on retrospective analysis, informed consent from every participant was not required according to the committee. The selection criteria for this study were as follows: (1) fractures caused by low-energy injuries (e.g., osteoporotic fractures), (2) unilateral fractures, (3) patients who underwent hip arthroplasty or closed reduction and internal fixation, and (4) patients who received blood routine, immune function, coagulation function, liver and kidney function tests before surgery, which findings were normal. The exclusion criteria were as follows: (1) pathological fractures, (2) multiple fractures or multiple traumas, (3) patients without surgical treatment, and (4) patients with incomplete clinical data.

Table 1 shows the variables collected in this study, which included demographic characteristics, past medical history, accompanying diseases, laboratory examinations, types of fracture, and types of anesthesia. All information was acquired separately by two orthopedic surgeons from the medical data recording system of the Affiliated Hospital of Qingdao University. Any disputed information was agreed upon by these two orthopedic surgeons who extracted the information and a third independent orthopedic surgeon.

Data Analysis

All statistical analyses and figures were accomplished using SPSS 24.0 (SPSS Inc.; Chicago, IL, USA) and R software 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) (https://www.r-project.org). First, the risk factors that affect postoperative HSA infusion were categorized. To identify the normality of all continuous variables, Shapiro-Wilk test was performed using SPSS 24.0. Continuous variables that conformed to a normal distribution were represented as mean value ± standard deviation, whereas those with non-normal distribution were represented as median (interquartile range). Independent samples t-test or Wilcoxon signed-rank test was used for comparing continuous variables between the infusion group and the non-infusion group, and a chi-square test was utilized for the comparison of categorical variables. In this study, two-sided p of < 0.05 indicated statistical significance.

All patients were grouped into a training set and a testing set in a ratio of 7:3 at random using R software. Data from the training group were used to develop the nomogram model, whereas those from the testing group were used to validate the model. First, a univariate logistic regression analysis was performed on the training group to find factors related to HSA infusion after hip fracture surgery. Then, LASSO regression was conducted for predictors with $p < 0.05$ to avoid over-fitting. Finally, the variables identified by the LASSO analysis were included in the multivariate logistic analysis using "Forward LR" in SPSS 24.0 to determine independent risk factors of HSA infusion after hip fracture surgery.

TABLE 1. Demographic Characteristics of Infused and Non-infused Human Albumin

	Infused human albumin			
	Total (n = 1,339)	No (n = 1,198)	Yes (n = 141)	P
Age, years				<0.001
<55	134	129	5	
55-75	687	641	46	
>75	518	428	90	
Sex				0.119
Female	920	815	105	
Male	419	383	36	
Previous history				
Surgery	701	611	90	0.004
Blood transfusion	105	84	21	0.001
Allergies	31	27	4	0.560
Smoking	222	203	19	0.295
Drinking	196	182	14	0.094
Comorbidities				
Hypertension	424	366	58	0.011
T2DM	235	208	27	0.598
Coronary heart disease	147	121	26	0.003
Chronic lung diseases	138	96	42	<0.001
Digestive system disease	116	89	27	<0.001
Cerebral thrombosis	171	140	31	0.001
Laboratory tests				
PA, mg/l [mean (SD)]	180.90 (79.40)	183.00 (78.93)	148.00 (88.50)	<0.001
ALB, g/l [mean (SD)]	37.30 (5.30)	37.70 (4.93)	32.90 (7.50)	<0.001
GLO, g/l [mean (SD)]	27.40 (6.00)	27.50 (6.03)	27.00 (6.05)	0.844
TP, g/l [mean (SD)]	64.70 (8.00)	65.20 (7.60)	60.40 (10.35)	<0.001
ALB/GLO [mean (SD)]	1.36 (0.35)	1.37 (0.34)	1.17 (0.38)	<0.001
TBIL, μmol/l [mean (SD)]	17.70 (10.91)	17.86 (10.93)	16.40 (10.92)	0.009
DBIL, μmol/l [mean (SD)]	5.25 (3.66)	5.25 (3.67)	5.49 (3.86)	0.677
IBIL, μmol/l [mean (SD)]	12.40 (7.72)	12.50 (7.75)	11.20 (6.97)	<0.001
ALT, U/l [mean (SD)]	14.40 (8.10)	14.55 (8.43)	13.00 (8.00)	0.008
AST, U/l [mean (SD)]	16.80 (6.90)	16.85 (6.73)	16.00 (8.25)	0.794
ALT/AST [mean (SD)]	0.87 (0.37)	0.88 (0.38)	0.81 (0.31)	0.001
PT, s [mean (SD)]	11.60 (1.90)	11.50 (1.80)	12.10 (1.80)	<0.001
APTT, s [mean (SD)]	30.70 (6.20)	30.60 (6.03)	30.90 (7.25)	0.099
FBG, g/l [mean (SD)]	3.60 (1.24)	3.59 (1.18)	3.80 (1.46)	0.031
HB, g/l [mean (SD)]	124.00 (22.00)	126.00 (20.00)	105.00 (26.50)	<0.001
RBC, 10^13 [mean (SD)]	4.13 (0.74)	4.19 (0.71)	3.55 (0.92)	<0.001
MCHC, g/l [mean (SD)]	336.00 (15.00)	336.00 (15.25)	332.00 (20.00)	0.007
RDW.CV, [mean (SD)]	12.80 (1.20)	12.70 (1.10)	13.20 (1.70)	<0.001
MCV, fL [mean (SD)]	90.10 (5.70)	90.00 (5.72)	90.60 (6.75)	0.211
WBC, 10^9 [mean (SD)]	7.60 (3.03)	7.59 (3.01)	7.93 (3.28)	0.380
PLT, 10^9 [mean (SD)]	205.00 (87.00)	204.00 (83.00)	208.00 (107.50)	0.812
NEUT, 10^9 [mean (SD)]	5.34 (2.79)	5.30 (2.78)	5.45 (2.79)	0.380

TABLE 1. Continued

	Infused human albumin			
	Total (n = 1,339)	No (n = 1,198)	Yes (n = 141)	P
Type of fracture				<0.001
FNF	1004	936	68	
ITF	335	262	73	
Type of anesthesia				0.001
General	752	654	98	
Non-general	587	544	43	
Type of surgery				<0.001
Internal fixation	407	338	69	
Arthroplasty	932	860	72	

ALB/GLO, albumin/globulin; ALB, albumin; ALT/AST, alanine aminotransferase/aspartate aminotransferase; ALT, alanine aminotransferase; APTT, activated partial thrombin time; AST, aspartate aminotransferase; DBIL: direct bilirubin; FBG, fibrinogen; FNF, femoral neck fracture; GLO, globulin; HB, hemoglobin; IBIL, indirect bilirubin; ITF, intertrochanteric fracture; MCHC, mean corpuscular-hemoglobin concentration; MCV, mean corpuscular volume; Neut, neutrophils; PA, prealbumin; PLT, platelet; PT, prothrombin time; RBC, red blood cells; RDW.CV, red blood cell distribution width; T2DM, diabetes mellitus type 2; TBIL, total bilirubin; TP, total protein; WBC, white blood cells

Based on independent risk factors analyzed by multivariate logistic regression, the nomogram model was made with the "rms" package of R software. The area under the receiver operating characteristic curve (AUC) was employed to assess the discriminative ability of the nomogram. The AUC value ranged from 0.5 to 1.0. Generally, a well-performing model has an AUC value between 0.5 and 0.75, and AUC value exceeding 0.75 means that the model has excellent discriminating ability. Thus, the calibration curve was applied to estimate the calibration effect of the nomogram, whereas decision curve analysis (DCA) was utilized to assess the clinical value of the nomogram.

RESULTS

Baseline Characteristics

The flow chart of the study is shown in Figure 1. A total of 1339 patients were included. Among them, 1,198 patients did not receive HSA infusion, and the remaining patients had HSA infusion. Basic information of all enrolled patients is shown in Table 1, which suggested significant statistical differences in variables such as age, surgery, blood transfusion, hypertension, coronary heart disease, chronic lung diseases, digestive system disease, cerebral thrombosis, prealbumin, ALB, total protein, ALB/globulin (GLO), total bilirubin, indirect

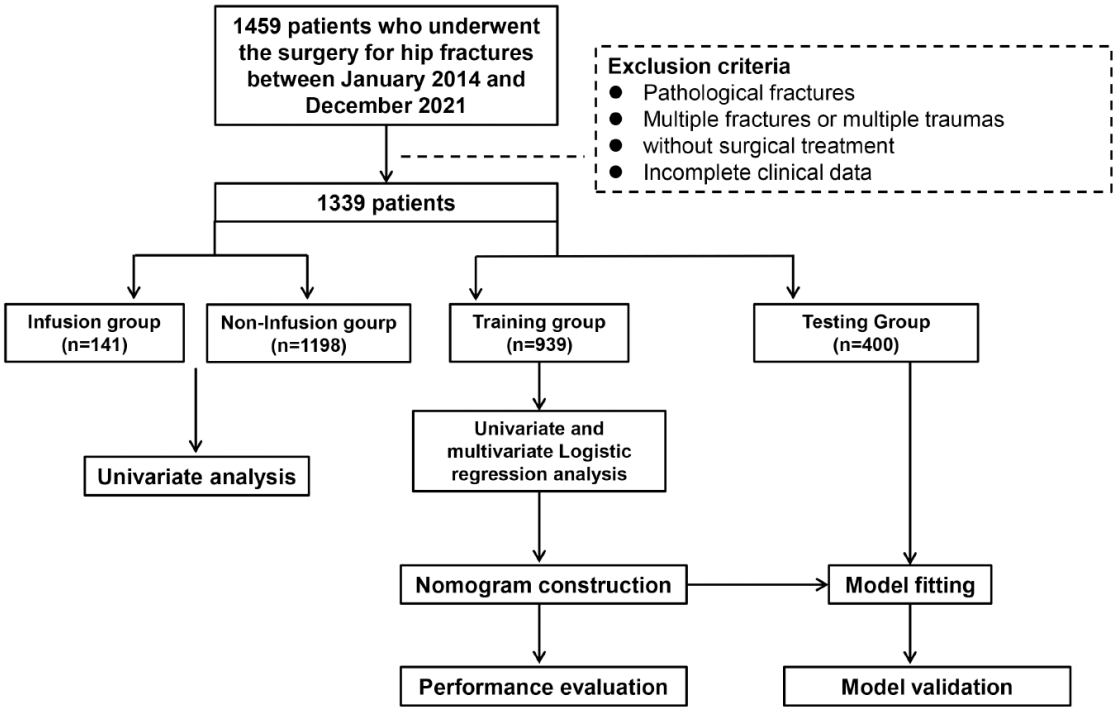

FIG. 1. Workflow of this study.

bilirubin, alanine aminotransferase, alanine aminotransferase/aspartate aminotransferase, prothrombin time (PT), fibrinogen, hemoglobin, red blood cells (RBC), mean corpuscular-hemoglobin concentration, RBC distribution width (RDW). CV, fracture type, anesthesia, type, and surgery type between patients with and without HSA infusion ($p < 0.05$).

Characteristics of Variables in two Clinical Sets

According to the aims of this study, 1,339 patients were divided into the training (n = 939) and testing (n = 400) sets randomly with a ratio of 7:3. Chi-square and Wilcoxon signed-rank tests of the clinical variables were conducted in both sets. As shown in Table 2, the training and testing groups were randomly assigned.

Independent Risk Factors for HSA Infusion after Hip Fracture Surgery in the Training Group

The univariate analysis suggested 23 variables with a p value of < 0.05 (Table 3). These 23 variables were enrolled in the LASSO regression analysis, which identified 13 variables as significant predictors, including age, blood transfusion, chronic lung disease, cerebral thrombosis, digestive system disease, fracture type, anesthesia type, ALB, ALB/GLO, PT, APTT, RBC, and RDW. CV (Figure 2). Subsequently, these 13 significant predictors were used for the multivariate analysis. Multivariate logistic regression analysis with "Forward LR" obtained the model with the smallest AIC value, showing five independent risk factors, including chronic lung disease (odds ratio [OR], 95% confidence interval [CI] 2.618, 1.413-4.849, $p = 0.002$), ALB (OR, 95% CI 0.842, 0.787-0.900, $p < 0.001$), PT (OR, 95% CI 1.252, 1.071-1.463, $p = 0.005$), RBC (OR, 95% CI 0.370, 0.228-0.602, $p < 0.001$), and anesthesia type (OR, 95% CI 0.553, 0.327-0.937, $p = 0.028$). Moreover, the fracture type, a clinically significant factor, was also incorporated. Finally, the nomogram model was built based on these six predictors. Among all influencing factors, the preoperative ALB score was the highest, indicating that this factor had the greatest influence on the model. The results are shown in Table 3.

Establishment and Validation of a Nomogram to Forecast the Risks of HSA Transfusion after Hip Fracture Surgery

The nomogram was established based on six predictive factors (Figure 3). The training set showed that the AUC of the nomogram was 0.854 (95% CI 0.811-0.898) (Figure 4a), demonstrating great accuracy in forecasting the risk of HSA infusion after hip fracture surgery. Besides, the calibration curve showed an excellent agreement of the prediction between the nomogram and the observation (Figure 4b). The DCA revealed that the use of this nomogram to predict risks of HSA infusion after hip fracture surgery had a higher net benefit (Figure 4c).

The AUC of the nomogram for forecasting the chance of HSA infusion reached 0.767 (95% CI 0.686-0.847) (Figure 5a) in the testing set. When it comes to the possibility of HSA transfusion after an operation, the calibration curve highly correlated with prediction and observation (Figure 5b). Moreover, the DCA curve testified that the nomogram had a high net benefit (Figure 5c).

DISCUSSION

HSA can enhance plasma colloid osmotic pressure and boost hypoalbuminemia. Therefore, HSA is applied for nutritional interventions or treatment of hypoalbuminemia, which was not proved by sufficient clinical evidence.[11] However, according to previous studies, HSA did not ameliorate the prognosis of patients with hypovolemia or hypoproteinemia and even result in mortality.[12] Another study showed that HSA used after the operation did not reduce the incidence of incision complications and even increased the risk of postoperative infection.[13] After the infusion of exogenous ALB, most of the ALB would leak outside blood vessels within 2 days, which may result in edema around the incision, offering conditions for bacterial colonization and aggrandizing the risk of infection.[14-16] In addition, although exogenous ALB contained different amino acids, it excluded tryptophan and isoleucine, so it has low nutritional value.[17] As a result, the European Forum of Medical Associations did not recommend applying ALB to correct postoperative hypoalbuminemia.[18]

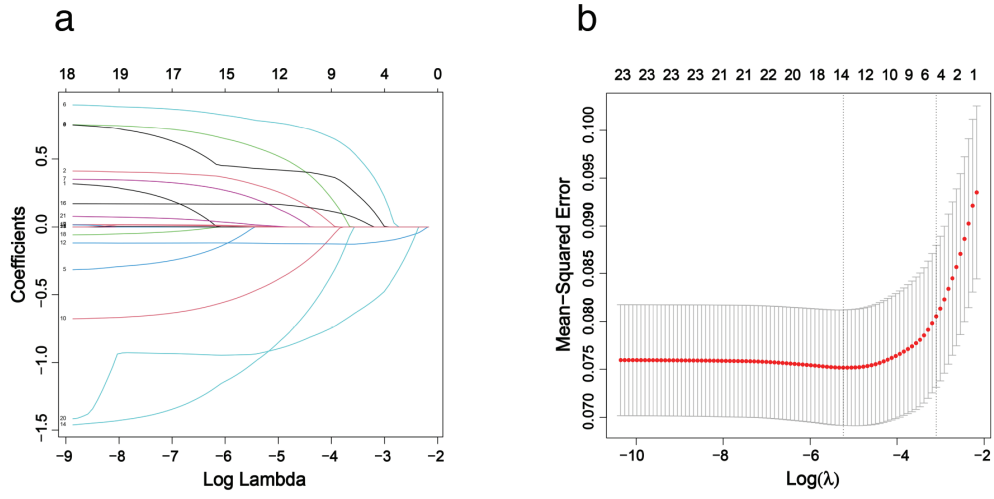

FIG. 2. LASSO analysis of 23 significant variables in the univariate analysis. (a) LASSO coefficient profiles. (b) LASSO deviance profiles.

TABLE 2. Demographic Characteristics of Patients with Hip Fracture in Training and Validation Populations

	Training group (n = 939)	Testing group (n = 400)	P
Age, years			0.615
<55	94	40	
55-75	474	213	
>75	371	147	
Sex			0.683
Female	642	278	
Male	297	122	
Previous history			
Surgery	480	221	0.166
Blood transfusion	73	32	0.888
Allergies	23	8	0.617
Smoking	155	67	0.913
Drinking	139	57	0.793
Comorbidities			
Hypertension	297	127	0.965
T2DM	151	84	0.030
Coronary heart disease	98	49	0.331
Chronic lung disease	91	47	0.257
Digestive system disease	83	33	0.726
Cerebral thrombosis	114	57	0.290
Laboratory tests			
PA, mg/l	180.10 (81.30)	181.00 (72.50)	0.924
ALB, g/l	37.30 (5.30)	37.10 (5.39)	0.725
GLO, g/l	27.30 (6.10)	27.72 (5.98)	0.236
TP, g/l	64.60 (8.20)	65.10 (7.78)	0.434
ALB/GLO	1.36 (0.34)	1.35 (0.39)	0.209
TBIL, μmol/l	17.90 (10.90)	16.67 (10.38)	0.023
DBIL, μmol/l	5.34 (3.78)	5.07 (3.48)	0.233
IBIL, μmol/l	12.60 (7.60)	11.64 (8.45)	0.012
ALT, U/l	14.20 (8.00)	14.90 (8.38)	0.502
AST, U/l	16.80 (7.00)	16.80 (6.88)	0.330
ALT/AST	0.87 (0.38)	0.88 (0.36)	0.090
PT, s	11.60 (1.90)	11.60 (1.80)	0.501
APTT, s	30.70 (6.20)	30.65 (6.20)	0.951
FBG, g/l	3.60 (1.18)	3.59 (1.30)	0.870
HB, g/l	124.00 (22.00)	124.00 (21.00)	0.761
RBC, 10^13	4.12 (0.74)	4.16 (0.78)	0.365
MCHC, g/l	336.00 (16.00)	335.00 (16.00)	0.256
RDW.CV	12.80 (12.20)	12.80 (1.20)	0.433
MCV, fL	90.10 (5.90)	89.90 (5.35)	0.295
WBC, 10^9	7.58 (2.92)	7.75 (3.05)	0.201
PLT, 10^9	202.00 (89.00)	215.00 (78.75)	0.004
NEUT, 10^9	5.27 (2.68)	5.45 (3.06)	0.265

TABLE 2. Continued

	Training group (n = 939)	Testing group (n = 400)	P
Type of fracture			0.329
FNF	697	307	
ITF	242	93	
Type of anesthesia			0.576
General	532	220	
Non-general	407	180	
Type of surgery			0.265
Internal fixation	294	113	
Arthroplasty	645	287	

ALB/GLO, albumin/globulin; ALB, albumin; ALT/AST, alanine aminotransferase/aspartate aminotransferase; ALT, alanine aminotransferase; APTT, activated partial thrombin time; AST, aspartate aminotransferase; DBIL, direct bilirubin; FBG, fibrinogen; FNF, femoral neck fracture; GLO, globulin; HB, hemoglobin; IBIL, indirect bilirubin; ITF, intertrochanteric fracture; MCHC, mean corpuscular-hemoglobin concentration; MCV, mean corpuscular volume; Neut, neutrophils; PA, prealbumin; PLT, platelet; PT, prothrombin time; RBC, red blood cells; RDW.CV, red blood cell distribution width; T2DM, diabetes mellitus type 2; TBIL, total bilirubin; TP, total protein; WBC, white blood cells

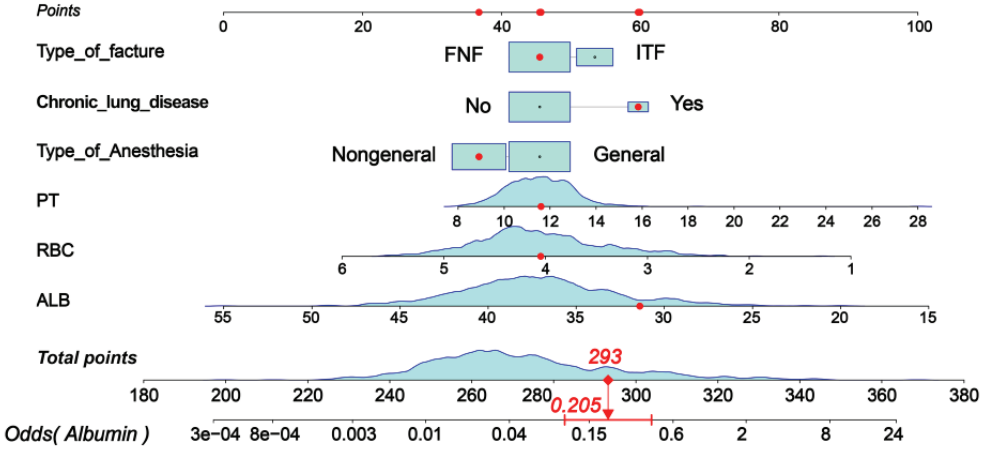

FIG. 3. Nomogram for predicting postoperative HSA infusion in patients who underwent hip fracture surgery.

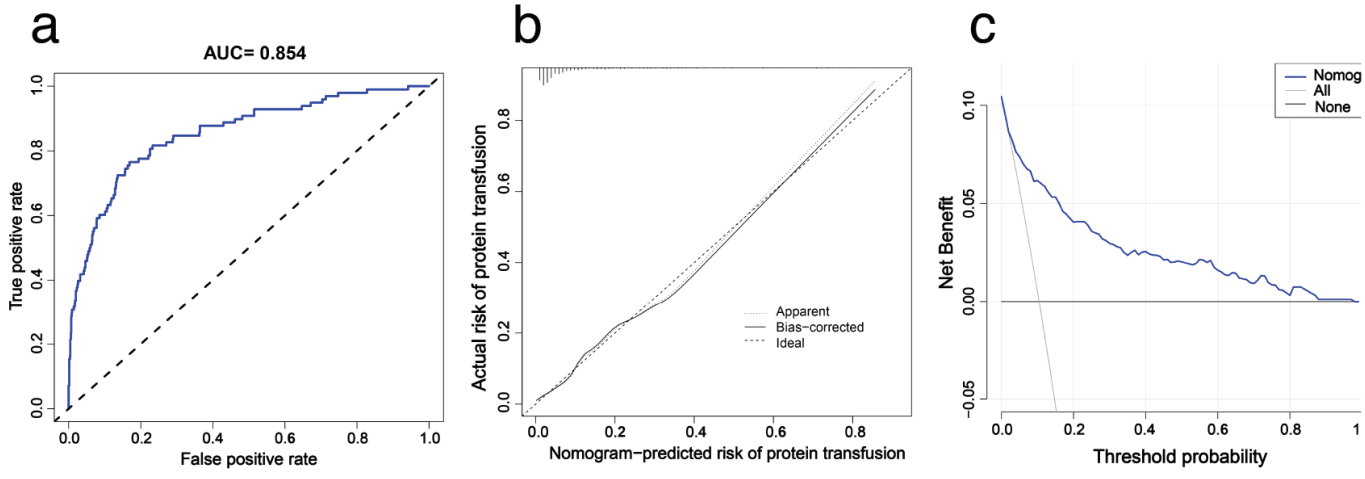

FIG. 4. Evaluating the performance of the nomogram in the training set. The receiver operating characteristic curve (a), calibration curve (b), and decision curve analysis (c) of the training set.

TABLE 3. Univariate and Multivariate Analysis of Human Albumin Infusion in the Perioperative Period in Patients with Patients Hip Fractures

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Age, years			0.000			
<55			Reference			
55-75	2.123	0.635-7.092	0.221			
>75	6.324	1.941-20.604	0.002			
Gender						
Female			Reference			
Male	0.804	0.505-1.282	0.360			
Previous history						
Surgery	1.583	1.031-2.429	0.036			
Blood transfusion	2.942	1.633-5.302	0.000			
Allergies	1.296	0.378-4.444	0.680			
Smoking	0.753	0.409-1.387	0.362			
Drinking	0.482	0.228-1.017	0.055			
Comorbidities						
Hypertension	1.423	0.924-2.192	0.109			
T2DM	0.937	0.525-1.673	0.825			
Coronary heart disease	1.969	1.113-3.485	0.020			
Chronic lung disease	6.023	3.652-9.932	0.000	2.618	1.413-4.849	0.002
Digestive system disease	2.920	1.665-5.122	0.000			
Cerebral thrombosis	2.038	1.192-3.483	0.009			
Laboratory tests						
PA, mg/l	0.988	0.984-0.992	0.000			
ALB, g/l	0.748	0.707-0.792	0.000	0.842	0.787-0.900	0.000
GLO, g/l	1.014	0.969-1.062	0.542			
TP, g/l	0.880	0.848-0.912	0.000			
ALB/GLO	0.037	0.014-0.095	0.000			
TBIL, μmol/l	0.976	0.952-1.001	0.062			
DBIL, μmol/l	1.014	0.955-1.078	0.646			
IBIL, μmol/l	0.945	0.909-0.983	0.004			
ALT, U/l	1.002	0.986-1.019	0.797			
AST, U/l	1.015	0.997-1.033	0.114			
ALT/AST	0.510	0.254-1.025	0.059			
PT, s	1.446	1.240-1.686	0.000	1.252	1.071-1.463	0.005
APTT, s	1.063	1.018-1.109	0.006			
FBG, g/l	1.249	1.026-1.520	0.027			
HB, g/l	0.943	0.931-0.955	0.000			
RBC, 10^13	0.160	0.109-0.234	0.000	0.370	0.228-0.602	0.000
RDW.CV	1.309	1.162-1.475	0.000			
MCHC, g/l	0.985	0.970-1.000	0.046			
MCV, fL	1.043	1.002-1.085	0.038			
WBC, 10^9	1.024	0.941-1.114	0.583			
PLT, 10^9	1.000	0.997-1.002	0.839			
NEUT, 10^9	1.045	0.956-1.142	0.333			

TABLE 3. Continued

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Type of fracture						
FNF		Reference			Reference	
ITF	4.930	3.196-7.603	0.000	1.715	0.999-2.944	0.050
Type of anesthesia						
General			Reference			
Non-general	0.515	0.327-0.811	0.004	0.553	0.327-0.937	0.028
Type of surgery						
Internal fixation			Reference			
Arthroplasty	0.341	0.223-0.521	0.000			

ALB/GLO, albumin/globulin; ALB, albumin; ALT/AST, alanine aminotransferase/aspartate aminotransferase; ALT, alanine aminotransferase; APTT, activated partial thrombin time; AST, aspartate aminotransferase; DBIL, direct bilirubin; FBG, fibrinogen; FNF, femoral neck fracture; GLO, globulin; HB, hemoglobin; IBIL, indirect bilirubin; ITF, intertrochanteric fracture; MCHC, mean corpuscular-hemoglobin concentration; MCV, mean corpuscular volume; Neut, neutrophils; PA, prealbumin; PLT, platelet; PT, prothrombin time; RBC, red blood cells; RDW.CV, red blood cell distribution width; T2DM, diabetes mellitus type 2; TBIL, total bilirubin; TP, total protein; WBC, white blood cells

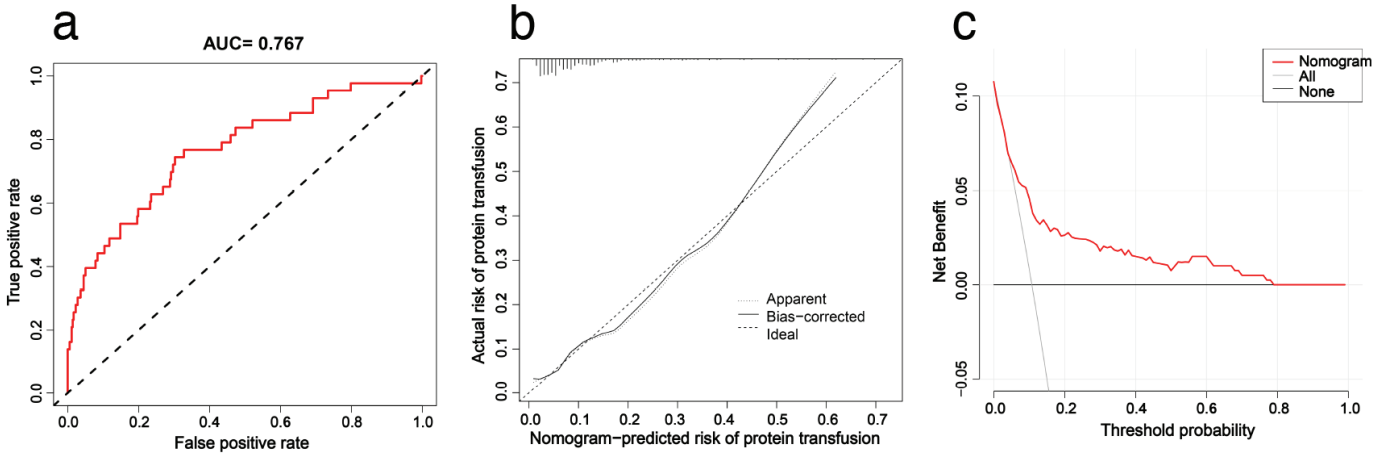

FIG. 5. Validating the predictive ability of the nomogram in the testing set. The receiver operating characteristic curve (a), calibration curve (b), and decision curve analysis (c) of the testing set.

The use of a nomogram is important to identify risk factors preoperatively and take intervention measures to reduce HSA transfusion postoperatively. According to the multivariate regression analysis, independent risk factors for postoperative HSA transfusion included low preoperative ALB level, prolonged preoperative prothrombin time, low preoperative RBC count, general anesthesia, and history of chronic lung disease. In previous studies, preoperative hypoalbuminemia was proved to be related to unsatisfactory outcomes of surgeries for hip, shoulder, knee, and distal radius fractures, involving wound infection, readmission, transfusion, other complications, and mortality.[19] Surgery is a key factor that leads to postoperative hypoalbuminemia. Intraoperative bleeding would contribute to the ALB loss and then reduce the concentration of serum ALB.[20] The physiological stress state and inflammatory response induced by operations could damage the capillary endothelial cells, increasing the capillary permeability. Consequently, ALB in blood vessels would penetrate the tissue space and reduce the concentration of serum ALB.[21] Under stress, the liver lowered ALB synthesis and prioritized acute phase protein synthesis including C-reactive protein.[23,24] However, preoperative hypoalbuminemia would further aggravate the above situation.

Prothrombin time is the most commonly used coagulation test method worldwide. Based on clinical practice, prolonged PT usually means reduced coagulation function and increased bleeding risk.[22] For people with normal prothrombin time, their bleeding rate will increase as PT rises.[23] In this study, PT appears higher in the infusion group than in the non-infusion group, which may have caused more intraoperative blood loss and postoperative drainage, resulting in more ALB loss. Postoperative nausea and vomiting are the most common adverse reactions to general anesthesia, especially in older people.[24,25] As a result, this can lead to decreased appetite and reduced food intake in patients. Moreover, older people have poorer digestion and absorption

than younger people, further reducing postoperative ALB levels.[10] Researchers found that preoperative RBC count may be an independent risk factor of postoperative hypoalbuminemia. Consistent with serum ALB, the RBC count usually reflected the nutritional status of the body, whereas it also reflected the potential of protein synthesis and erythropoiesis for older patients. An appropriately high RBC count meant adequate protein nutrition and good metabolism and satisfying RBC function. Similarly, low RBC count usually indicated that patients had protein deficiency and poor metabolism.[26] Chronic bronchitis (including emphysema and chronic obstructive pulmonary disease), lung cancer, and pneumonia are common in clinical practice. Therefore, these three diseases are included in our study and are collectively referred to as chronic lung diseases. Chronic lung diseases are independent risk factors for HSA infusion postoperatively. Usually, older people with chronic lung diseases have symptoms such as chronic cough and expectoration, which can lead to increased consumption of protein including ALB.[27,28] Severe lung infections may prompt the body to synthesize inflammatory mediators such as interleukin-6 and tumor necrosis factor, which can boost protein catabolism.[29,30] Previous studies have also confirmed that patients with chronic lung disease were prone to hypoalbuminemia.[28]

The nomogram can significantly improve the prediction and diagnosis for HSA transfusion after hip fracture surgery, based on which the preoperative treatment strategies are developed to reduce the risk of postoperative hypoproteinemia in high-risk cases. For low-risk cases, we can reduce the corresponding intervention measures, thus lowering the chance of side effects and alleviating the economic burden on patients. However, the clinical prediction model cannot forecast the occurrence of postoperative hypoproteinemia with 100% accuracy, and the nomogram has limitations.

This study also has several limitations. First, this was a retrospective cross-sectional study. The information was collected from a single center rather than from various centers, and the predictive and discriminatory ability of the nomogram ought to be confirmed by more tests. Second, we did not include more possible factors to reduce selective bias. Meanwhile, the number of cases was inadequate; thus, we should collect more to optimize the performance of the nomogram. Third, this study focused mainly on preoperative risk factors that affect postoperative hypoproteinemia and ALB infusion and did not follow patients for a long period for complications. The relationship between ALB infusion and complications was not studied. Our team will conduct prospective studies to make up for these deficiencies. Fourth, the sample size was not enough. The age of the enrolled patients ranged vastly from 40 to 97 years, and patients aged <70 years take up almost half of all enrolled patients. To our knowledge, hip fractures in older people differ vastly to the younger population. Therefore, in future studies, we will enroll much more patients in a relevant small age range to further examine the factors that influence postoperative HSA infusion.

In conclusion, independent risk factors for HSA infusion after hip fracture surgery include low preoperative ALB level, prolonged preoperative prothrombin time, low preoperative RBC count, general anesthesia, and history of chronic lung diseases. Besides, fracture type, a clinically significant factor, was also included. These six predictors can help forecast the risk of HSA infusion after hip fracture surgery. We have formed and confirmed a predictive model for predicting the risk of postoperative HSA transfusion. The model has strong predictive power and could be used in clinical practice to decrease HSA transfusion after hip fracture surgery.

Ethics Committee Approval: This study was conducted based on the Declaration of Helsinki. This study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University (approval no. QYFY-WZLL-27124).

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Design- X.C., X.L., J.P., P.Y., S.R.; Data Collection or Processing- X.L., J.P.; Analysis or Interpretation- X.C., S.R.; - X.C., P.Y.

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