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A Novel Nomogram Developed Based on Preoperative Immune Inflammation-Related Indicators for the Prediction of Postoperative Delirium Risk in Elderly Hip Fracture Cases: A Single-Center Retrospective Cohort Study

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Objective: Postoperative delirium (POD) commonly occurs in elderly individuals following hip fracture surgery, with unclear pathophysiological mechanism. Inflammation is a known factor affecting the onset of delirium. The current work aimed to examine the associations of preoperative immune inflammation-related indicators with POD occurrence in elderly cases following hip fracture surgery.

Methods: The current retrospective cohort study included 437 elderly cases administered hip fracture surgery from January 2018 to December 2023. The clinicodemographic data and laboratory findings of all cases were retrospectively analyzed. Immune inflammation-related indicators were assessed, eg, MLR, NLR and PLR, as well as SII and SIRI. The bootstrap method was employed to assign cases at 7:3 to the training (48 and 258 cases in the POD and no-POD groups, respectively) and internal validation (13 and 118 cases in the POD and no-POD groups, respectively) cohorts. Next, LASSO, univariable and multivariable logistic regression analyses were applied to determine risk factors in the training cohort, based on which a nomogram model was built. The obtained nomogram was examined for accuracy by calibration plot analysis. Finally, the nomogram's clinical value was assessed by decision curve analysis (DCA), followed by internal validation based on the training cohort.

Results: Of all 437 cases, 61 developed POD, indicating a POD incidence of 13.96%. LASSO regression and multivariable analyses revealed preoperative SIRI independently predicted POD in the training cohort. The developed nomogram had an area under the curve (AUC) of 0.991 (95% CI 0.983~0.998) in the training cohort versus 0.986 (95% CI 0.966~1.000) in the validation cohort. Calibration curve analysis revealed nomogram-predicted and actual probabilities were in line. DCA demonstrated the novel nomogram could confer net benefits for POD prediction in elderly cases administered hip fracture surgery.

Conclusion: The immune inflammation-related indicators SIRI could predict POD in elderly cases following hip fracture surgery.

Keywords: postoperative delirium, hip fracture, elderly, immune inflammation related indicators, nomogram

Introduction

Because of steadily increasing population aging globally, hip fracture cases are expected to increase to about 6.1 million by 2050, indicating a yearly escalation of 1–3%,[1,2] which represents an important public health challenge in elderly individuals.[3] Hip fractures impose a significant economic burden on the society and are responsible for disability and multiple human ailments.[4] They are mainly treated by surgical operations, which unfortunately can induce many complications affecting distinct organs.[5,6] Delirium is a serious complication occurring in elderly individuals administered hip fracture surgery, with an incidence of 10–62%.[7,8]

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Postoperative delirium (POD) refers to acute changes in the fluctuating mental state of patients within 7 days after anesthesia or before discharge, primarily manifested as unclear consciousness, inattention, psychomotility disorders and sleep-wake cycle disorders, with rapid onset and short disease course, as well as potential missed diagnosis and misdiagnosis.[9,10] POD is considered a major complication in geriatric individuals administered surgery.[11] Despite the transient and reversible nature of POD in the vast majority of patients, it may result in neuropsychiatric conditions, prolonged hospitalization, elevated treatment cost and reduced ability to perform daily living activities, particularly in elderly individuals. Additionally, POD has potential associations with long-term cognitive impairment, dementia and even elevated mortality.[12–16] Although delirium has a high incidence, most cases are not detected in clinic.[17,18] Consequently, identifying molecular markers applicable for early detection of delirium is highly important both for patients and healthcare professionals.

The pathogenetic mechanism of delirium is not fully defined, but inflammation is thought to play a role in delirium onset.[19–21] Increasing evidence suggests elevated neutrophils and decreased lymphocytes in elderly delirium cases.[22] New non-specific inflammatory indicators have been developed, eg, monocyte-to-lymphocyte (MLR), neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte (PLR) ratios and systemic immune-inflammatory (SII) and systemic inflammatory response (SIRI) indexes.[23,24] The latter parameters better mirror systemic inflammatory response, with high availability and low cost. They play crucial roles in multiple cancers, autoimmune disorders, and cardiovascular diseases.[25–28] For example, SIRI, a ratio considering neutrophil, monocyte, and lymphocyte counts, is a critical biomarker of cancer development and progression. Recently, Lu et al[11] also demonstrated the SIRI reflects the degree of chronic inflammation in elderly patients after hip arthroplasty. Additionally, hypoalbuminemia independently predicts POD in surgically treated patients, suggesting malnutrition is associated with POD.[29,30] Albumin (Alb), an important player in acute inflammation, can be utilized to examine the nutritional status of individuals administered surgery. Hu and collaborators[31] reported that Alb-derived indexes based on inflammation and nutrition may be employed for POD prediction in geriatric individuals administered THA. Such albumin-related inflammatory and nutritional parameters include neutrophil-to-albumin (NAR) and CRP-to-albumin (CAR) ratios and prognostic nutritional index (PNI).

However, few studies have examined whether SII, SIRI, NLR, MLR, PLR, NAR, CAR and PNI are involved in POD in geriatric individuals with hip fractures. The nomogram model is a commonly employed prognostic tool in medicine to generate a single numerical probability of a given clinical event through integration of different prognostic variates, meeting the need for integrated biological and clinical models and promoting personalized medicine to assist clinical decision making. The present work aimed to determine potential risk factors for POD in geriatric hip fracture cases, with the goal of developing a nomogram to predict the risk of POD with high accuracy in geriatric individuals with hip fractures.

Materials and Methods

Patient Data

This observational, analytical, retrospective cohort case-control study collected the clinical data of geriatric hip fracture cases administered surgical procedures, including internal fixation surgery, total hip arthroplasty or artificial femoral head replacement, in the First People's Hospital of Neijiang, between January 2018 and December 2023. Data collection was performed in an independent manner by the first and second authors, with any discrepancy resolved by consensual discussion. The present study followed the 1964 helsinki Declaration and was approved by the Ethics Committee of the First People's Hospital of Neijiang, who required no informed consent because of the retrospective nature of the current analysis.

Diagnosis was confirmed by X-ray and computed tomography (CT) with 3D reconstruction. Figure 1 presents the study flowchart. Inclusion criteria were: (1) diagnosis of hip fractures such as femoral neck, intertrochanteric and subtrochanteric fractures and first treatment by internal fixation surgery, total hip arthroplasty or artificial femoral head replacement; (2) Han nationality; (3) age ≥60 years; (4) traumatic factors including fall, body twisting, weight lifting fail, car accident, etc.; (5) availability of clinicodemographic data and laboratory findings. Exclusion criteria were: (1) multiple or pathological hip fractures; (2) neurological and psychiatric diseases; (3) postoperative infections; (4) treatment with antipsychotic medications in the last 3 months; (5) incomplete data.

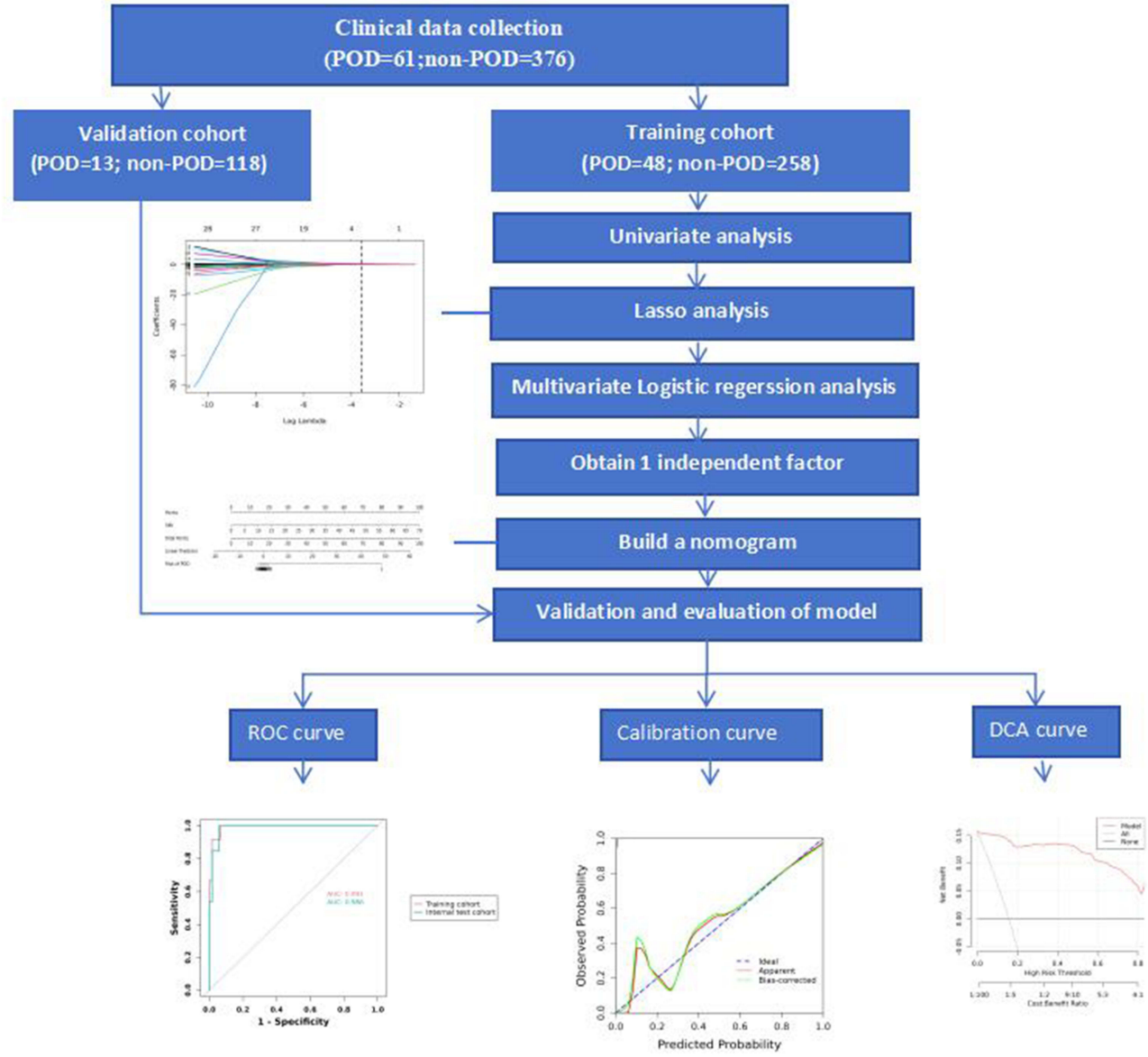

Figure 1 The enrollment flowchart.

POD Diagnosis

POD was diagnosed per the Confusion Assessment Method (CAM) criteria.[32–34] the CAM scale was assessed twice a day at the same period (10:00 am and 5:00 pm) every-day. POD incidence was recorded only within 7 postoperative days. The CAM questionnaire was administered by an experienced physician (the first author) based on the following criteria: (1) inattention; (2) acute onset and fluctuating course; (3) altered consciousness; and (4) disorganized thinking. Delirium was reflected by criteria (1) and (2), combined with either criterion (3) or (4). Firstly, individuals with typical words of delirium recorded postoperatively were retained. Then, cases administered drugs for POD were added. Thirdly, individuals uttering words of delirium or administered drugs for delirium preoperatively were excluded. Finally, preliminary diagnoses were confirmed by neurologists per the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria.[35]

Data Collection

Clinicodemographic variables included gender, age, body mass index (BMI), smoking, drinking, hypertension, heart disease, cerebrovascular diseases, diabetes, abnormal renal function, fracture type, surgical method, surgery time, intraoperative blood

loss, anesthesia method, ASA class (I/II/III/IV/V), red blood cell (RBC), hemoglobin (HGB), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), total protein (TP), albumin (ALB), NLR, PLR, MLR, SII, SIRI, aggregate index of systemic inflammation (AISI), NAR, lymphocyte-to-monocyte ratio (LMR), CAR, and PNI.

Systemic Inflammatory, Albumin-Related Inflammatory and Nutritional Biomarkers

Systemic inflammatory, albumin-related inflammatory and nutritional biomarkers were calculated using the equations in Table 1.

Statistical Analysis

The included cases were randomized into the training and validation sets at 7:3. Data with non-normal distribution were reported as median and interquartile range. In univariable analysis, categorical variates were assessed by the chi-square or Fisher's exact test, while continuous variates were compared by the Student's *t*-test or rank-sum test. In the training set, the least absolute shrinkage and selection operator (LASSO) was applied in multivariable analysis to determine independent risk factors for developing a nomogram for POD prediction. The nomogram's performance was assessed by generating receiver operating characteristic (ROC) and calibration curves, with areas under the ROC curve (AUCs) ranging between 0.5 (no discriminant) and 1 (perfect discriminant). The net clinical benefit of the nomogram was examined by decision curve analysis (DCA). $P<0.05$ suggested statistical significance. R 4.2.2 was employed for data analysis.

Results

Baseline Features of the Patients

Totally 437 geriatric patients underwent surgery for hip fractures and met the eligibility criteria. The incidence of delirium was 13.96% (61/437). Then, the cases were assigned to the training and validation cohorts at 7:3 by computer-based randomization. The baseline clinicodemographic features of patients in both cohorts are summarized in Table 2.

Table 1 The Definitions of Systemic Inflammatory Markers, Albumin-Associated Inflammatory and Nutritional Markers

Variables	Definitions
SII	(Neutrophil*platelet)/lymphocyte ratio
SIRI	(Neutrophil* monocyte)/lymphocyte ratio
AISI	(Neutrophil*platelet* monocyte)/lymphocyte ratio
NLR	Neutrophil/lymphocyte ratio
PLR	Platelet/lymphocyte ratio
MLR	Monocyte/lymphocyte ratio
LMR	Lymphocyte/monocyte ratio
NAR	Neutrophil/albumin ratio
CAR	CRP/albumin ratio
SIS=0	LMR ≥ 2.17 and albumin ≥ 39.8 g/L
SIS=1	LMR < 2.17 or albumin < 39.8 g/L
SIS=2	LMR < 2.17 and albumin < 39.8 g/L

Abbreviations: SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index; AISI, aggregate index of systemic inflammation; CRP, C-reactive protein; SIS, systemic inflammation score.

Table 2 Patient Demographics and Baseline Characteristics

Characteristic	Cohort		p-value
	Training Cohort, N = 306	Internal Test Cohort, N = 131	
Gender, n(%)			0.125
Male	85 (27.8%)	46 (35.1%)	
Female	221 (72.2%)	85 (64.9%)	
Age (years)			0.419
Mean ± SD	80 ± 8	80 ± 9	
BMI			0.670
Mean ± SD	22.34 ± 2.73	22.49 ± 3.63	
Smoking, n(%)			0.682
Yes	22 (7.2%)	8 (6.1%)	
No	284 (92.8%)	123 (93.9%)	
Drinking, n(%)			0.360
Yes	11 (3.6%)	2 (1.5%)	
No	295 (96.4%)	129 (98.5%)	
Hypertension, n(%)			0.650
Yes	126 (41.2%)	57 (43.5%)	
No	180 (58.8%)	74 (56.5%)	
Heart disease, n(%)			0.241
Yes	51 (16.7%)	28 (21.4%)	
No	255 (83.3%)	103 (78.6%)	
History of Cerebrovascular diseases, n(%)			0.071
Yes	48 (15.7%)	30 (22.9%)	
No	258 (84.3%)	101 (77.1%)	
Diabetes, n(%)			0.858
Yes	70 (22.9%)	31 (23.7%)	
No	236 (77.1%)	100 (76.3%)	
Abnormal renal function, n(%)			0.876
Yes	13 (4.2%)	6 (4.6%)	
No	293 (95.8%)	125 (95.4%)	
Classification of fracture, n(%)			0.892
Intertrochanteric fracture	152 (49.7%)	66 (50.4%)	
Femoral neck fracture	154 (50.3%)	65 (49.6%)	
Surgical method, n(%)			0.714
Internal fixation	80 (26.1%)	31 (23.7%)	
HA	107 (35.0%)	51 (38.9%)	
THA	119 (38.9%)	49 (37.4%)	
Surgery time (minutes)			0.903
Mean ± SD	73 ± 28	73 ± 29	
Intraoperative blood loss (mL)			0.298
Mean ± SD	139 ± 74	148 ± 88	
Anesthesia method, n(%)			0.264
General anesthesia	18 (5.9%)	4 (3.1%)	
Combined spinal and epidural anesthesia	54 (17.6%)	24 (18.3%)	
Spinal anesthesia	126 (41.2%)	51 (38.9%)	
Intraspinal anesthesia	88 (28.8%)	36 (27.5%)	
Nerve block	20 (6.5%)	16 (12.2%)	
Anesthesia duration			0.678
Mean ± SD	132±35	130±37	

(*Continued*)

Table 2 (Continued).

Characteristic	Cohort		p-value
	Training Cohort, N = 306	Internal Test Cohort, N = 131	
ASA(I/II/III/IV/V), n(%)			0.948
I	1 (0.3%)	0 (0.0%)	
2	71 (23.2%)	33 (25.2%)	
3	226 (73.9%)	95 (72.5%)	
4	8 (2.6%)	3 (2.3%)	
RBC (10^{12}/L)			0.517
Mean ± SD	3.78 ± 0.75	3.74 ± 0.68	
HGB (g/L)			0.810
Mean ± SD	112 ± 19	112 ± 20	
ESR (mm/h)			0.861
Mean ± SD	33 ± 21	33 ± 22	
CRP (mg/L)			0.727
Mean ± SD	37 ± 37	38 ± 34	
TP (g/L)			0.629
Mean ± SD	66 ± 6	65 ± 6	
ALB (g/L)			0.337
Mean ± SD	37.7 ± 4.0	37.3 ± 4.2	
NLR			0.368
Mean ± SD	11 ± 8	11 ± 7	
PLR			0.814
Mean ± SD	241 ± 170	237 ± 128	
MLR			0.354
Mean ± SD	0.83 ± 0.59	0.79 ± 0.39	
SII			0.202
Mean ± SD	2127 ± 2189	1892 ± 1545	
SIRI			0.105
Mean ± SD	7.4 ± 7.1	6.4 ± 4.9	
AISI			0.114
Mean ± SD	1475 ± 2218	1210 ± 1250	
NAR			0.062
Mean ± SD	0.22 ± 0.09	0.20 ± 0.08	
LMR			0.479
Mean ± SD	1.59 ± 0.80	1.53 ± 0.71	
CAR			0.696
Mean ± SD	1.01 ± 1.04	1.05 ± 0.95	
SIS			0.365
Mean ± SD	1.49 ±0.60	1.54 ±0.57	

Abbreviations: BMI, body mass index; HA, hemiarthroplasty; THA, total hip arthroplasty; RBC, red blood cell; HGB, hemoglobin; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; TP, total protein; ALB, albumin; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index; AISI, aggregate index of systemic inflammation; NAR, neutrophil-to-albumin ratio; LMR, lymphocyte-to-monocyte ratio; CAR, CRP-to-albumin ratio; SIS, systemic inflammation score.

Similar gender distributions were found in the training (N=306) and internal validation (N=131) cohorts (p=0.125). Patient ages were also similar in both sets (p=0.419), ie, 80±8 and 80±9 years in the training and internal validation cohorts, respectively. Likewise, BMI, smoking status, drinking habits, fracture classifications, and the prevalence rates of hypertension, heart disease, cerebrovascular diseases, diabetes and abnormal renal function did not differ significantly between cohorts. Notably, various surgical methods and associated parameters such as surgery time, intraoperative blood loss, anesthesia method, and ASA classification also showed no significant differences. Laboratory indexes such as RBC,

HGB, ESR, CRP, TP, ALB, NLR, PLR, MLR, SII, SIRI, AISI, NAR, LMR, CAR, and PNI were comparable between the two cohorts, with no statistical significance (p>0.05). These findings suggest a high degree of similarity in baseline characteristics in the training and internal cohorts in our predictive study.

Various indexes were next compared by the Wilcoxon or chi-square test between the POD and No-POD groups. In the training set, gender (P=0.047), heart disease (P=0.035), fracture classification (P=0.010), surgical method (P=0.003), NLR (P<0.001), PLR (P<0.001), MLR (P<0.001), SII (P<0.001), SIRI (P<0.001), AISI (P<0.001), NAR (P<0.001) and LMR (P<0.001) showed significant differences (Table 3).

Table 3 Comparison of Variables Between POD Group and No-POD Group

Characteristics	Training Cohort			Internal Test Cohort		
	No-POD (n=258)	POD (n=48)	p-value	No-POD (n=118)	POD (n=13)	p-value
Gender, n(%)			0.047			0.378
Female	192 (74%)	29 (60%)		78 (66%)	7 (54%)	
Male	66 (26%)	19 (40%)		40 (34%)	6 (46%)	
Age (years)			0.072			0.218
Mean ± SD	79 ± 8	81 ± 7		80 ± 9	83 ± 9	
BMI			0.597			0.713
Mean ± SD	22.38 ± 2.68	22.13 ± 3.02		22.51 ± 3.82	22.36 ± 0.61	
Smoking, n(%)			0.760			0.577
No	240 (93%)	44 (92%)		111 (94%)	12 (92%)	
Yes	18 (7%)	4 (8%)		7 (6%)	1 (8%)	
Drinking, n(%)			>0.999			0.189
No	248 (96%)	47 (98%)		117 (99%)	12 (92%)	
Yes	10 (4%)	1 (2%)		1 (1%)	1 (8%)	
Hypertension, n(%)			0.807			0.049
No	151 (59%)	29 (60%)		70 (59%)	4 (31%)	
Yes	107 (41%)	19 (40%)		48 (41%)	9 (69%)	
Heart disease, n(%)			0.035			>0.999
No	38 (15%)	13 (27%)		25 (21%)	3 (23%)	
Yes	220 (85%)	35 (73%)		93 (79%)	10 (77%)	
History of Cerebrovascular diseases, n(%)			0.819			0.074
No	217 (84%)	41 (85%)		94 (80%)	7 (54%)	
Yes	41 (16%)	7 (15%)		24 (20%)	6 (46%)	
Diabetes, n(%)			0.714			0.505
No	198 (77%)	38 (79%)		91 (77%)	9 (69%)	
Yes	60 (23%)	10 (21%)		27 (23%)	4 (31%)	
Abnormal renal function, n(%)			>0.999			0.109
No	247 (96%)	46 (96%)		114 (97%)	11 (85%)	
Yes	11 (4%)	2 (4%)		4 (3%)	2 (15%)	
Classification of fracture, n(%)			0.010			0.365
Intertrochanteric fracture	120 (47%)	32 (67%)		61 (52%)	5 (38%)	
Femoral neck fracture	138 (53%)	16 (33%)		57 (48%)	8 (62%)	
Surgical method, n(%)			0.003			0.251
Internal fixation	59 (23%)	21 (44%)		29 (25%)	2 (15%)	
HA	90 (35%)	17 (35%)		43 (36%)	8 (62%)	
THA	109 (42%)	10 (21%)		46 (39%)	3 (23%)	
Surgery time (minutes)			0.244			0.861
Mean ± SD	72 ± 28	78 ± 32		73 ± 28	72 ± 36	
Intraoperative blood loss (mL)			0.847			0.348
Mean ± SD	139 ± 75	137 ± 72		149 ± 91	133 ± 55	

(*Continued*)

Table 3 (Continued).

Characteristics	Training Cohort			Internal Test Cohort		
	No-POD (n=258)	POD (n=48)	p-value	No-POD (n=118)	POD (n=13)	p-value
Anesthesia method, n(%)			0.577			0.212
General anesthesia	14 (5%)	4 (8%)		4 (3%)	0 (0%)	
Combined spinal and epidural anesthesia	45 (17%)	9 (19%)		19 (16%)	5 (38%)	
Spinal anesthesia	109 (42%)	17 (35%)		45 (38%)	6 (46%)	
Intraspinal anesthesia	75 (29%)	13 (27%)		35 (30%)	1 (8%)	
Nerve block	15 (6%)	5 (10%)		15 (13%)	1 (8%)	
Anesthesia duration			0.386			0.949
	131 ± 35	136 ± 36		130 ± 37	130 ± 35	
ASA(I/II/III/IV/V), n(%)			0.446			0.220
1	1 (0%)	0 (0%)		0 (0%)	0 (0%)	
2	63 (24%)	8 (17%)		29 (25%)	4 (31%)	
3	188 (73%)	38 (79%)		87 (74%)	8 (62%)	
4	6 (2%)	2 (4%)		2 (2%)	1 (8%)	
RBC (10^{12}/L)			0.136			0.399
Mean ± SD	3.75 ± 0.69	3.97 ± 0.99		3.72 ± 0.66	3.93 ± 0.86	
HGB (g/L)			0.965			0.521
Mean ± SD	112 ± 18	112 ± 21		111 ± 20	115 ± 23	
ESR (mm/h)			0.431			0.903
Mean ± SD	33 ± 21	31 ± 20		33 ± 22	32 ± 22	
CRP (mg/L)			0.330			0.960
Mean ± SD	36 ± 37	42 ± 42		38 ± 34	39 ± 31	
TP (g/L)			0.152			0.220
Mean ± SD	65.6 ± 6.2	67.1 ± 6.6		65 ± 6	68 ± 8	
ALB (g/L)			0.211			0.042
Mean ± SD	37.6 ± 4.0	38.4 ± 4.2		37.0 ± 4.1	39.9 ± 4.4	
NLR			<0.001			<0.001
Mean ± SD	9 ± 5	22 ± 9		9.4 ± 5.4	20.9 ± 9.4	
PLR			<0.001			0.059
Mean ± SD	212 ± 126	397 ± 266		225 ± 110	349 ± 212	
MLR			<0.001			0.003
Mean ± SD	0.68 ± 0.29	1.65 ± 1.00		0.72 ± 0.26	1.44 ± 0.70	
SII			<0.001			0.010
Mean ± SD	1616 ± 1154	4879 ± 3827		1639 ± 1033	4186 ± 3021	
SIRI			<0.001			<0.001
Mean ± SD	5.2 ± 2.8	19.2 ± 10.8		5.3 ± 3.0	16.6 ± 7.0	
AISI			<0.001			0.004
Mean ± SD	945 ± 709	4324 ± 4400		964 ± 675	3440 ± 2553	
NAR			<0.001			<0.001
Mean ± SD	0.20 ± 0.07	0.32 ± 0.08		0.19 ± 0.07	0.30 ± 0.04	
LMR			<0.001			<0.001
Mean ± SD	1.74 ± 0.76	0.74 ± 0.28		1.61 ± 0.70	0.81 ± 0.29	
CAR			0.412			0.888
Mean ± SD	0.99 ± 1.02	1.14 ± 1.16		1.06 ± 0.95	1.02 ± 0.88	
SIS			0.090			0.980
Mean ± SD	1.47 ± 0.62	1.60 ± 0.49		1.54 ± 0.58	1.54 ± 0.52	

Abbreviations: POD, postoperative delirium; BMI, body mass index; HA, hemiarthroplasty; THA, total hip arthroplasty; RBC, red blood cell; HGB, hemoglobin; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; TP, total protein; ALB, albumin; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index; AISI, aggregate index of systemic inflammation; NAR, neutrophil-to-albumin ratio; LMR, lymphocyte-to-monocyte ratio; CAR, CRP-to-albumin ratio; SIS, systemic inflammation score.

Nomogram Developed Based on Logistic Regression Analysis

Candidate predictors, ie, gender, heart disease, classification of fracture, surgical method, NLR, PLR, MLR, SII, SIRI, AISI, NAR and LMR, were entered in the initial model, and 2 potential predictive factors were finally retained after LASSO regression analysis in the training set (Table 4 and Figure 2A). Figure 2B shows cross-validation errors, with the best model in cross-validation including 2 variables (NLR and SIRI).

ROC curve analysis of NLR and SIRI yielded AUCs of 0.919 and 0.991, respectively (>0.5) (Figure 3). Further multivariable analyses were carried out in the training cohort (Table 5). A simple-to-use nomogram incorporating one independent predictive factor, SIRI, was developed (Figure 4). The nomogram had outstanding predictive performance

Table 4 The Coefficients of Lasso Regression Analysis

Coefficient	Variable
−5.606896417	(Intercept)
0.000000000	Gender_level_
0.000000000	Age_level_
0.000000000	BMI_level_
0.000000000	Smoking_level_
0.000000000	Drinking_level_
0.000000000	Hypertension_level_
0.000000000	Heart.disease_level_
0.000000000	Cerebrovascular.diseases_level_
0.000000000	Diabetes_level_
0.000000000	Abnormal.renal.function_level_
0.000000000	Classification.of.fracture_level_
0.000000000	Surgical.method_level_
0.000000000	Surgery.time_level_
0.000000000	Intraoperative.blood.loss_level_
0.000000000	Anesthesia.method_level_
0.000000000	Anesthesia.duration_level_
0.000000000	ASA.I.II.III.IV.V._level_
0.000000000	RBC_level_
0.000000000	HGB_level_
0.000000000	ESR_level_
0.000000000	CRP_level_
0.000000000	TP_level_
0.000000000	ALB_level_
0.004440599	NLR_level_
0.000000000	PLR_level_
0.000000000	MLR_level_
0.000000000	SII_level_
0.411701721	SIRI_level_
0.000000000	AISI_level_
0.000000000	NAR_level_
0.000000000	LMR_level_
0.000000000	CAR_level_
0.000000000	SIS_level_

Abbreviations: RBC, red blood cell; ALB, albumin; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index; AISI, aggregate index of systemic inflammation; NAR, neutrophil-to-albumin ratio; LMR, lymphocyte-to-monocyte ratio; SIS, systemic inflammation score.

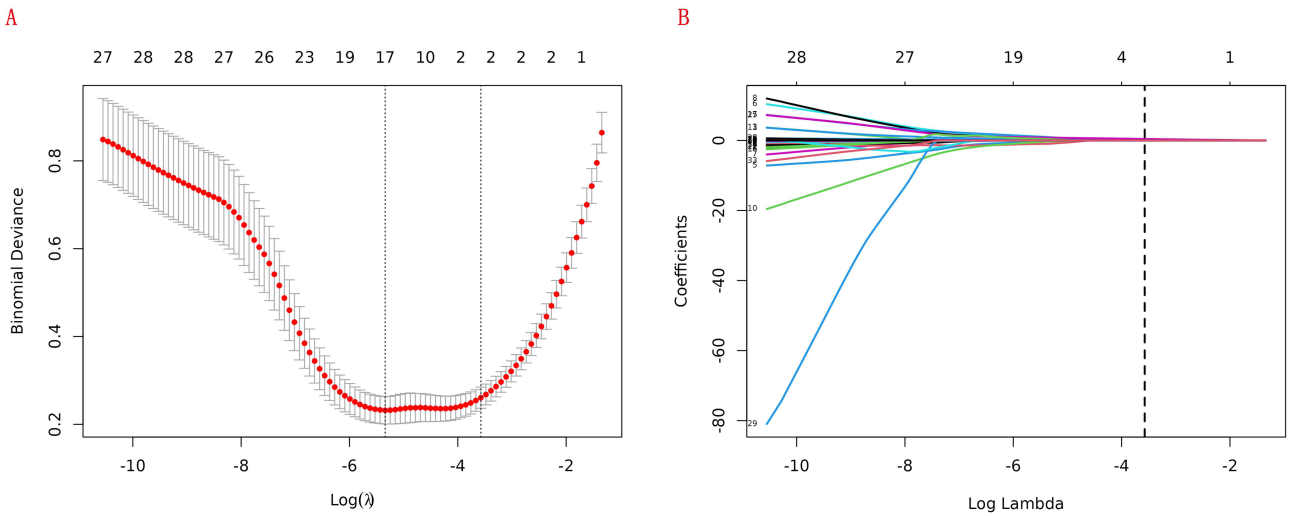

Figure 2 Lasso regression cross-validation plot (**A**) and lasso regression coefficient path plot (**B**).

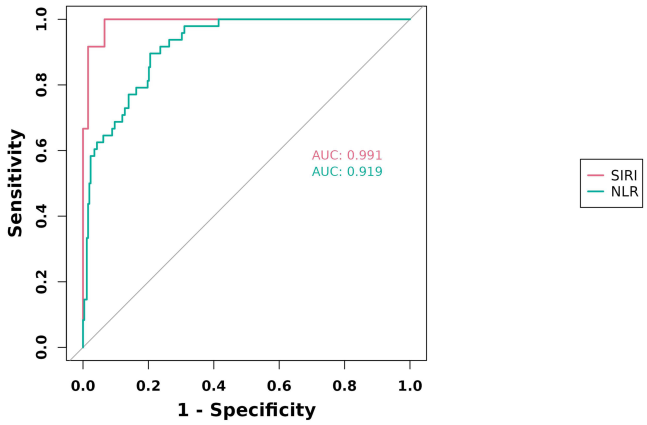

Figure 3 ROC curve analysis 2 candidate diagnostic indicators.

(Figure 5), with AUCs of 0.991 (95% CI 0.983~0.998) and 0.986 (95% CI 0.966~1.000) in the training and internal validation sets, respectively. Calibration analysis of the nomogram (Figure 6A and B) showed a high concordance between the actual and predicted probabilities of POD occurrence. These data indicate the novel nomogram can be accurately used to predict POD in these patients. DCA curve analysis of the nomogram is depicted in Figure 7A and B, revealing the nomogram provides overt net benefits for POD prediction in clinic.

Table 5 Results of Multivariate Logistic Regression for Training Cohort

Characteristic	N	Event N	OR	95% CI	p-value
NLR	306	48	0.98	0.89, 1.09	0.758
SIRI	306	48	3.08	1.96, 4.84	<0.001

Abbreviations: OR, odds ratio; CI, confidence interval; RBC, red blood cell; NLR, neutrophil-to-lymphocyte ratio; SIRI, systemic inflammatory response index.

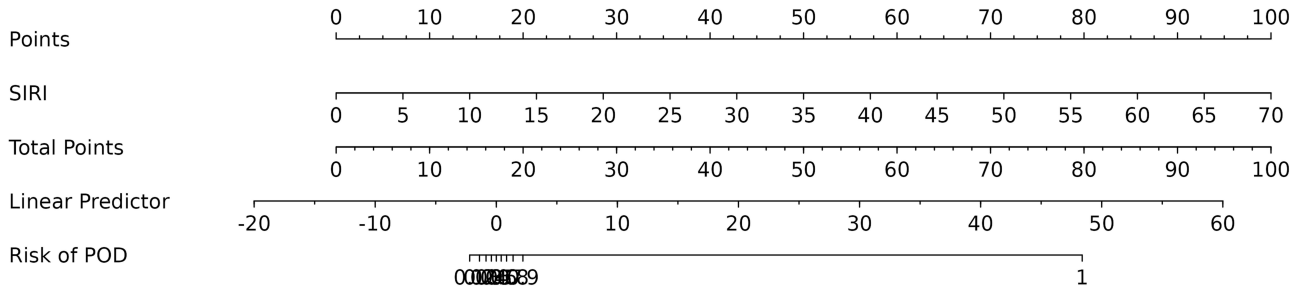

Figure 4 Nomogram of probability to develop postoperative delirium risk in elderly Hip fracture patients using preoperative immune inflammation-related indicators. To use the nomogram, draw an upward vertical line from each covariate to the points bar to calculate the number of points. Based on the sum of the covariate points, draw a downward vertical line from the total point's line to calculate the probability of developing postoperative delirium.

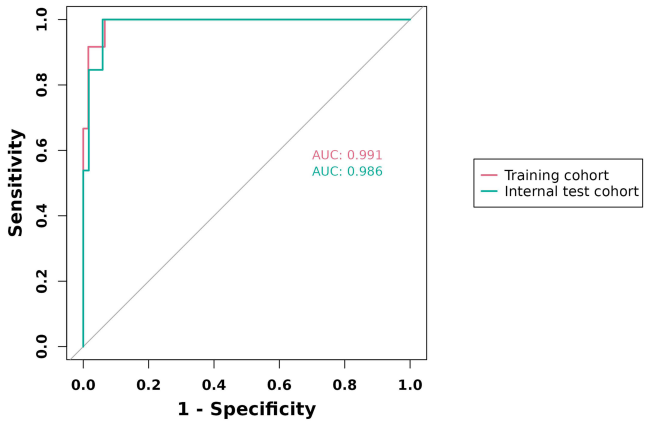

Figure 5 ROC curve for the nomogram based on the training cohort (The AUC is 0.991) and internal validation cohort (The AUC is 0.986).

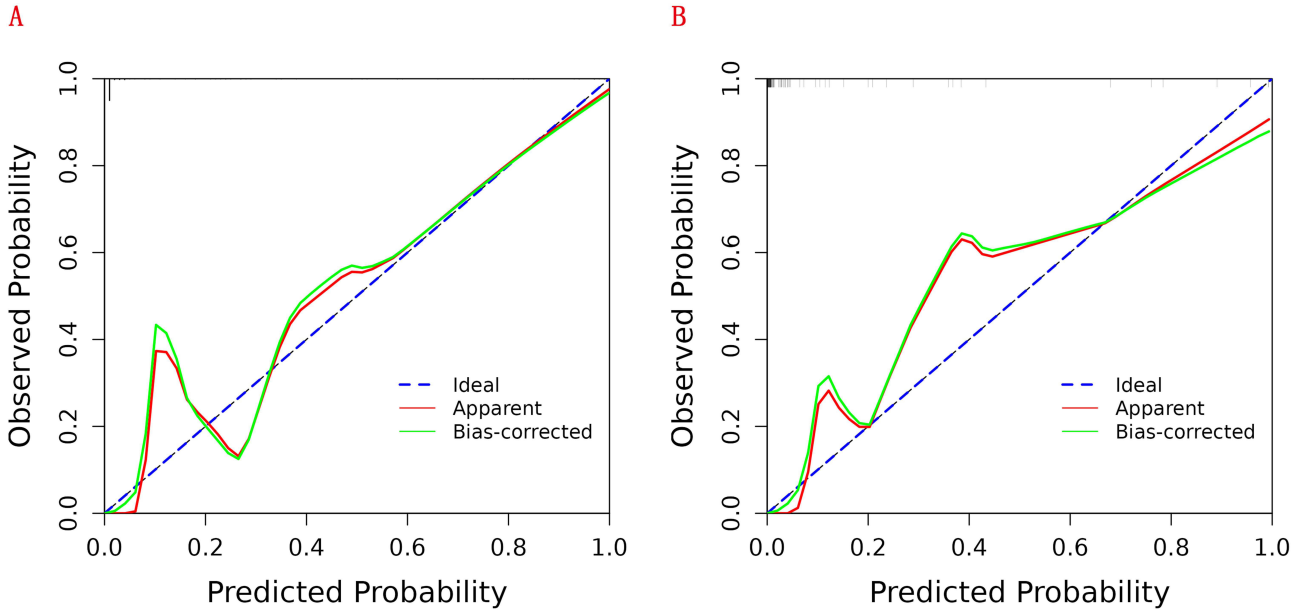

Figure 6 (**A**) Calibration curves of the nomogram for predicting postoperative delirium from the training cohort; (**B**) Calibration curves of the nomogram for predicting postoperative delirium from the internal validation cohort.

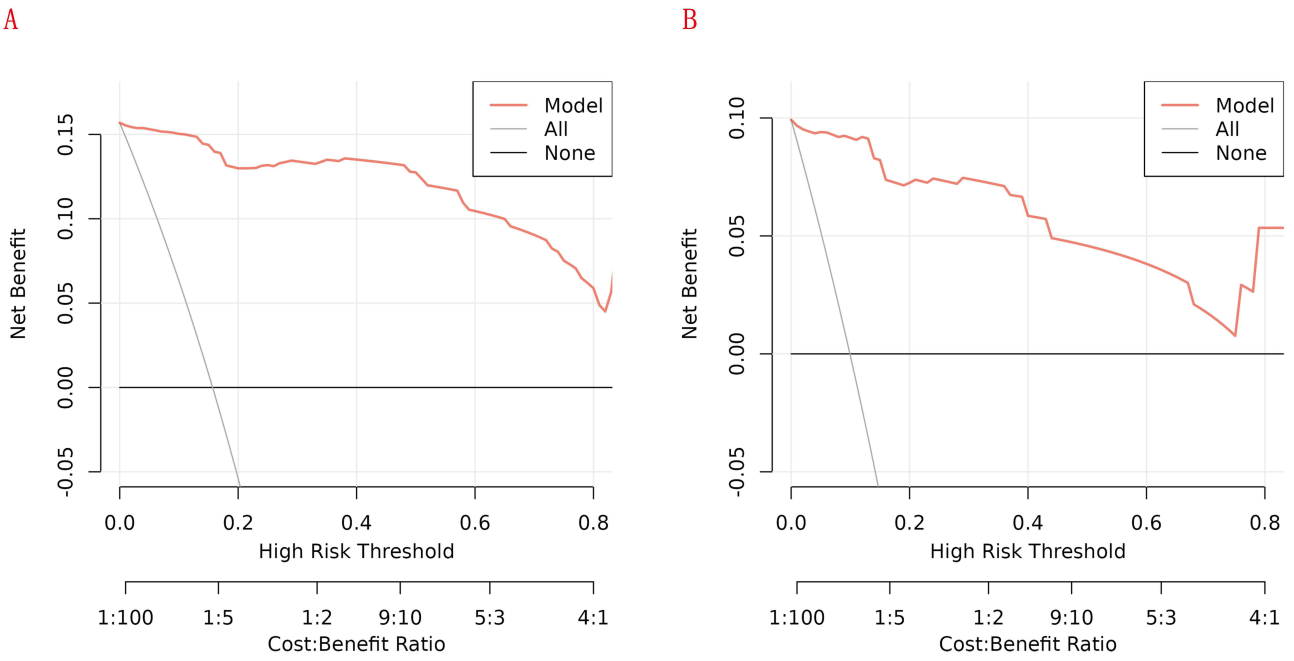

Figure 7 Decision curve analysis (DCA) of the nomogram: (**A**) The DCA curve of the training cohort; (**B**) The DCA curve of the internal validation cohort.

Discussion

Hip fractures threaten the health of geriatric individuals and decrease their quality of life, with multiple complications, including bedsores, lung infections.[36] Currently, geriatric hip fracture cases are mostly treated by surgical procedures such as arthroplasty and fracture internal fixation.[37] However, these surgical treatments may also result in multiple complications, of which POD is a major postoperative complication in geriatric hip fracture cases. POD pathogenesis is very complex and remains unclear so far. In recent years, many hypotheses have emerged,[38–40] including the central neurotransmitter theory, the theory of changes in brain metabolic level, the surgical stress theory, and the inflammation hypothesis. This study aimed to establish a novel inflammatory composite scoring system and to construct a nomogram model that could predict POD in hip fracture cases. The novel nomogram model may be utilized as an important strategic guide for perioperative management and targeted to screen patients for POD risk before surgery for early prevention and treatment.

Previous studies have demonstrated that NLR has significant associations with POD and cognitive decline.[41,42] Findings by Wen and colleagues revealed that preoperative SIRI and NLR levels are correlated with hip arthroplasty in elderly individuals, with SIRI independently predicting hip arthroplasty, corroborating our findings.[11,43] Additionally, stress response, associated with inflammation, trauma, and surgical and anesthetic procedures, activates the peripheral immune system, increases neutrophil and monocyte contents, and reduces lymphocyte amounts.[44] Upon activation, neutrophils and monocytes secrete anaerobic free radicals, chemokines, and inflammatory cytokines, as a potential mechanism for POD. Increasing evidence suggests preoperative inflammatory mediators, inflammation and immune responses induced by surgery or anesthesia contribute to the pathogenetic mechanism of POD.[45,46] Since neutrophils, lymphocytes, and monocytes represent crucial components of the peripheral immune system, cerebral immune-inflammatory responses are induced by proinflammatory cytokines produced by circulating immune cells, which might activate microglia and thus cause POD.[47,48] Therefore, NLR and SIRI as comprehensive inflammatory indicators might help predict immune and inflammatory disorders.

In this study, POD incidence in 437 elderly hip fractures was 13.96% (61/437). This finding suggests almost one-sixth of the patients experienced POD, and individuals with higher NLR and SIRI levels were prone to develop POD, corroborating previously reported data.[11,31] This study firstly explored the associations of 12 indicators, including gender, heart disease, fracture classification, surgical method, NLR, PLR, MLR, SII, SIRI, AISI, NAR and LMR, and POD. The results showed that these 12 indexes were closely related to POD occurrence in hip fracture cases. In this study, LASSO regression analysis optimized the 2 included indicators, ie, NLR and SIRI, which showed AUCs of 0.919 and 0.991 in ROC curve analysis,

respectively. These AUC values were greater than 0.5, indicating high predictive value and clinical significance. As demonstrated above, NLR and SIRI were both higher in POD patients before surgery, and SIRI had a greater AUC compared with NLR, indicating that preoperative SIRI is a better indicator to predict POD than NLR. Logistic regression analysis revealed SIRI as an independent risk factor for POD in hip fracture cases. The current findings suggest the preoperative inflammatory condition should be examined in elderly individuals scheduled for hip fracture surgery.

However, this study had limitations. By excluding patients with dementia, this study excluded one of the groups of patients at highest risk for delirium. Despite the relatively large sample size, the nomogram model was not verified by external data sets. Our analysis of gender, heart disease, fracture classification, surgical method, NLR, PLR, MLR, SII, SIRI, AISI, NAR and LMR at a single time point rather than studying their dynamic changes may hamper the understanding POD development. Besides, there are many potential influencing factors of POD, and the nomogram model may miss other important risk factors. Also, the study only screened POD within 7 days after surgery, which this might be a limitation of the study. Finally, this was a single-center study, and generalization of the proposed nomogram model may require further validation.

Conclusion

In summary, the novel nomogram constructed in the present study has a satisfactory accuracy in predicting POD. Therefore, assessing preoperative immune inflammation-related indicators in elderly hip fracture cases, combined with using the nomogram model constructed in the current study, may provide early detection of patients at high risk of POD and improve perioperative treatment strategies.

Data Sharing Statement

Datasets utilized and/or analyzed in this study are available from the corresponding author upon reasonable request.

Ethical Approval and Consent to Participate

The current study had approval from the ethics committee of the First People's Hospital of Neijiang (No. 2023-lunshenpi-39), who waived the requirement for informed consent in this retrospective analysis. All patient data was treated with confidentiality.

Author Contributions

Xiao Chen, Yuanhe Fan and Hongliang Tu are the co-first authors who contributed equally to this work. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest.

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