Clinical Interventions in Aging

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ORIGINAL RESEARCH

Postoperative Serum NLRP1 as a Biochemical Predictor of Delirium and Cognitive Decline After Hip Fracture Surgery in Elderly Patients: A Single Center Observational Study

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Objective: Postoperative delirium (POD) and cognitive decline (POCD) are linked to inflammatory brain injury, and nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 1 (NLRP1) participates in neuroinflammation. Here, we investigated influential factors of serum NLRP1 levels and its predictive significance on POD and POCD of elderly patients with hip fracture.

Materials and Methods: In this observational analytical study, serum NLRP1 levels were quantified in 100 controls, and preoperatively and postoperatively in 271 elderly patients undergoing hip fracture surgery. Primary outcome was postoperative three-month POCD [Montreal cognitive assessment (MoCA) scores below 26], and secondary outcomes included in-hospital POD and serum NLRP1 levels. The associations with them were analyzed using multivariate methods.

Results: Compared to controls, patients had markedly heightened postoperative, but not preoperative, serum NLRP1 levels. Postoperative serum NLRP1 levels were independently associated with postoperative C-reactive protein levels and FRAIL scores. Postoperative serum NLRP1 and FRAIL scale scores were independently associated with POD, and together with POD, were also independently related to the MoCA scores and effectively predicted POCD. The results of the regression analyses were comparatively robust based on collinearity evaluation, sensitivity analysis, subgroup analysis, interactivity investigation, and restricted cubic spline analysis. The independent predictors of POD and POCD were integrated separately to form the respective models. The models were graphically delineated via nomograms and were efficaciously used to distinguish the risk of POD or POCD based on the calibration, decision, and receiver operating characteristic curves. By applying mediation analysis, POD may partially mediate the association between the postoperative serum NLRP1 levels and POCD.

Conclusion: Serum NLRP1 may be a potential predictor of POD and POCD in elderly patients undergoing hip fracture surgery and the combined use of FRAIL and NLRP1 may optimize the efficiency of screening in high-risk populations.

Keywords: NLRP1, inflammation, delirium, cognitive decline, postoperative, elderly, hip fractures

Introduction

Postoperative delirium (POD) and cognitive decline (POCD) are common in elderly patients, especially in those requiring hip fracture surgery.[1] POD is an accredited determinant of POCD occurrence, and POCD emerges as a causal factor for poor prognosis and mortality in elderly patients.[2] Multiple parameters result in POD and POCD, among which the FRAIL scale, a pivotal metric with a health sense in older subjects, is frequently corroborated to anticipate POD and POCD.[3] The pathophysiological processes of the two adverse events are multifaceted, and inflammatory damage, especially inflammatory brain injury, is believed to be a crucial facilitator of POD and POCD pathogeneses.[4] In addition to therapeutics, it is imperative to predict POD and POCD early and accurately during clinical management.[5] Until now, numerous biomarkers, such as C-reactive protein (CRP), tumor necrosis factor alpha, and

Received: 25 July 2025
Accepted: 25 October 2025
Published: 13 November 2025

interleukin-6, have been investigated among patients with POD or POCD, the use of any particular biomarker is not favored on account of insufficiently high discrimination efficiency in clinical practice.[6] As such, biomarkers have been always paid close attentions as regards their predictive ability on POD or POCD during recent years.[7]

Inflammasomes are vital complexes for evoking an early innate inflammatory response in numerous pathological scenarios.[8] Nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 1 (NLRP1) is a critical and early-identified inflammasome that triggers caspase-1, boosts maturation of interleukin-1β and −18, and subsequently hastens inflammatory reactions.[9] In the milieu of experimental brain injuries, NLRP1 expression in the cerebral cortex is strongly upregulated, and its supplementation augments neuroinflammation, disrupts the blood–brain barrier, promotes brain edema, and aggravates neuronal apoptosis.[10] Moreover, higher cerebrospinal fluid or blood NLRP1 levels were substantially related to poor clinical outcomes of acute brain injury diseases.[11–14] Thus, NLRP1 may act as a deleterious inflammatory factor to be a potential biomarker of brain injury.

Hip fracture surgery in the elderly may cause brain injury through various mechanisms, eg, microthrombus formation, intraoperative hypoperfusion, and blood loss.[15–17] Consequently, NLRP1 expressions after hip fracture surgery may be increased, either directly due to neuronal damage or indirectly through systemic inflammation that could also enhance NLRP1 synthesis in the brain. Overall, serum NLRP1 may be a predictor of POD and POCD. In order to validate such a hypothesis, we enrolled a cohort of elderly patients requiring hip fracture surgery to quantify their preoperative and postoperative NLRP1 levels and further to assess the role of serum NLRP1 in predicting POD and POCD.

Materials and Methods

Study Design, Setting, and Participant Enrollments

An observational analytical study was conducted at an academic institution, that is Wenzhou Central Hospital (Wenzhou, China), from January 2021 to July 2024. As shown in Figure 1, a cohort of elderly patients needing hip fracture surgery along with a group of controls were enrolled following the recruitment criteria, and two sub-studies, namely, the cross-sectional and prospective cohort studies, were performed. The former was designed to reveal variations of serum NLRP1 levels in elderly individuals undergoing hip fracture surgery as compared to controls, and the latter was adopted to determine predictive value of serum NLRP1 levels for in-hospital POD and POCD three months after surgery. Inclusion criteria of patients encompassed: (a) the elderly at age of at least 65 years; (b) undergoing hip fracture surgery; (c) preoperative Montreal Cognitive Assessment Scale (MoCA) score of 26 points or greater. Exclusion criteria of patients included: (a) past neuropsychiatric diseases, eg, dementia, psychosis, delirium, intracranial neoplasm, Parkinson's

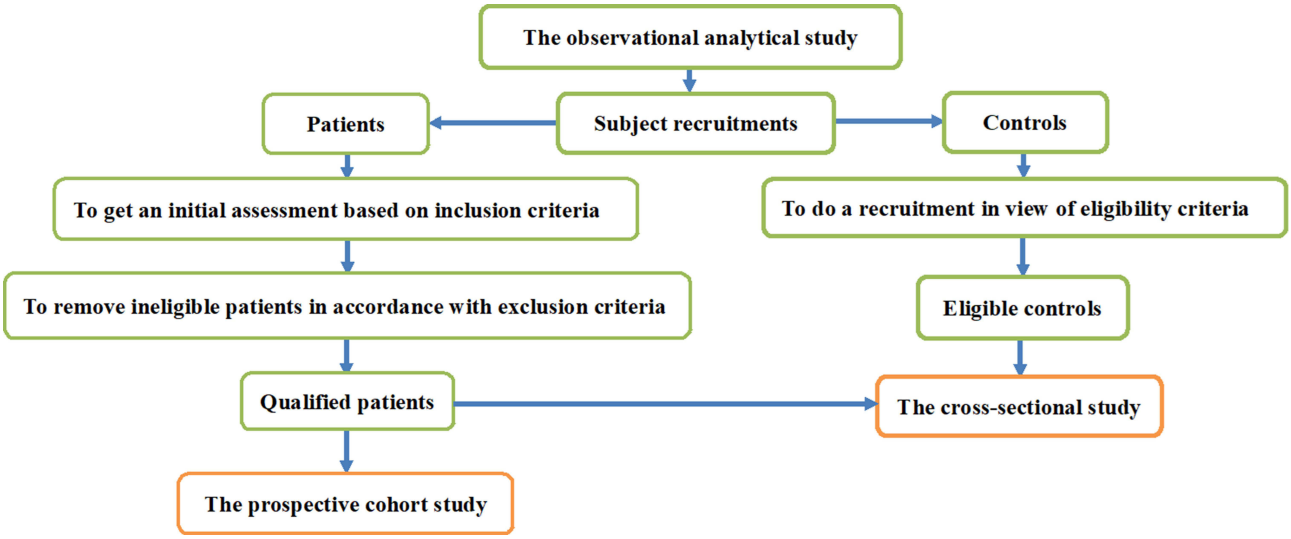

Figure 1 Flowchart of study design. This observational analytical study was divided into the cross-sectional analysis and prospective cohort analysis, in order to investigate change of serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 1 levels and its predictive significance on delirium and cognitive decline after Hip fracture surgery in elderly patients.

disease, intracranial infection, stroke, traumatic brain injury, multiple sclerosis, and more; (b) systemic diseases or severe diseases in other organs, such as malignancies, heart failure, liver cirrhosis, uremia, ascites, and so on; (c) other certain conditions, for instance, death within postoperative three months, surgery or infection within recent one month, declining participation, missed visits, inadequate materials, ineligible specimens, and so forth; (d) other specific situations influencing the scale assessment, for example, medications (ie, benzodiazepine, antidepressants, etc), aphasia, dysarthria, inability to communicate with Chinese language, visual or auditory damage, and others. Controls were enrolled according to eligibility criteria as follows: (a) the elderly at age of at least 65 years; (b) absence of some severe diseases, such as malignancies, heart failure, liver cirrhosis, uremia, ascites, and so on; but not including some conventional chronic diseases, eg, dyslipidemia, hypertension, diabetes mellitus, and more; (c) no apparent abnormal results in some conventional tests, such as electrocardiogram, chest radiograph, blood cell counts, and so forth. This study complied with the Terms of Ethics of the World Medical Association (Declaration of Helsinki), and consent for the protocol was obtained from the Institutional Ethics Committee of Wenzhou Central Hospital (approval number: No. L-03-020). All participants were acquainted with the study details and signed an informed consent form.

Data Gatherings and Outcome Assessments

Demographic data (sex, age, and body mass index), lifestyle habits (smoking tobacco and alcohol consumption), and chronic diseases (hypertension, diabetes mellitus, and dyslipidemia) were documented. Charlson Comorbidity Index (CCI) was calculated. The FRAIL scale, a judgement-based frailty tool ranging from 0 to 5, was adopted to mirror the health status of older adults.[18] Hip fractures were categorized as femoral neck and trochanteric types. Surgical risk was estimated via the American Society of Anesthesiologists rating scale (ASA scale).[19] The patients underwent hip arthroplasty or internal fixation under spinal or general anesthesia. The surgical duration, perioperative blood transfusion, and surgical delay after trauma were recorded. Based on the Confusion Assessment Method,[20] patients were assessed to identify POD twice daily until the seventh postoperative day or discharge. Cognitive function was evaluated by applying the MoCA at postoperative three months; and MoCA score of <26 was termed as POCD.[21] If the schooling educational duration did not exceed 12 years, the MoCA score plus 1 point was used to modify the bias of schooling years.[22] Here, the primary outcome was POCD, as well as secondary outcomes were POD and serum NLRP1 levels.

Biochemical Biomarkers Measurements

Controls provided blood samples upon enrolment. Patients offered specimens on the first preoperative and postoperative day. Blood glucose and CRP levels were measured using the conventional methods. To measure serum NLRP1 levels, samples were centrifuged at 3000 ×g for 10 min, and the separated supernatants were transferred into Eppendorf tubes for preserving at – 80 ◦C freezer to await next quantification. To avoid protein decomposition, all samples were gauged within three months following drawing. The enzyme-linked immunosorbent assay was performed to detect serum NLRP1 levels using a professional kit purchased from MyBioSource (Item Number: MBS924094). This kit has a detection range of 18.75 pg/mL to 1200 pg/mL, with a minimum detectable concentration of 4.67 pg/mL. Both intra- and inter-assay coefficients of variation were 10%. As per the specifications, all measurements were performed in duplicate by the identical proficient technician who were unclear about clinical details.

Statistical Methods

The SPSS 23.0 (SPSS Inc., Chicago, IL, USA), R 3.5.1 (www.r-project.org), GraphPad Prism 7.01 (GraphPad Software, Inc., San Diego, California, USA) and MedCalc 20 (MedCalc Software, Ltd., Ostend, Belgium) were applied for statistical analyses. Continuous variables were presented as medians (percentiles 25th-75th) or means (standard deviations) following normality examination by the Kolmogorov–Smirnov test or Shapiro–Wilk test as appropriate, while categorical variables were shown as frequencies (proportions). As applicable, the Mann–Whitney *U*-test, *t* test, chi-square test, or Fisher exact test was employed to compare data between two groups. The Kruskal–Wallis *H*-test was used for comparing data among several groups. Bivariate correlations were assessed by using the Spearman correlation coefficients. The multivariable linear regression approach was adopted for discerning factors, which were independently correlated with serum NLRP1 levels and three-month MoCA scores. The binary logistic stepwise regression analysis was

conducted to identify independent predictors of POD and POCD, in which there were variance inflation factor (VIF) for multicollinearity analysis,[23] E value for sensitivity analysis,[24] subgroup analysis for interactivity assessment,[25] and restricted cubic spline for linearity appraisal.[26] Independent predictors were incorporated to establish prediction models of POD and POCD. The models were pictorially described using the nomogram, and their effectiveness was assessed under the calibration curve, decision curve, and receiver operating characteristic (ROC) curve. Mediating effect of POD on association of postoperative serum NLRP1 levels with POCD was analyzed. The type 1 error (alpha) of 0.05, test power (1-beta) of 0.95, and effect size of 0.8 were specified to estimate sample size for comparing serum NLRP1 levels, analyzing correlations, and comparing area under the ROC curve (AUC). Demonstrably, 271 and 100 individuals were enough for clinical analysis. Sample size estimation was assessed for its accuracy by performing the priori power analysis within G*Power 3.1.9.4 (Heinrich-Heine Universität Düsseldorf, Germany).[27] Statistical differences in all analyses were set at two-sided P-value of <0.05.

Results

Study Population Features

A total of 367 elderly patients got an initial assessment, we next excluded 30 patients with past neuropsychiatric diseases, 32 with systemic or severe diseases in other organs, 18 with other specific situations influencing the scale assessment, and 16 with other conditions, and 271 patients were finally retained for clinical analysis. Table 1 presents the baseline characteristics of 271 patients and 100 controls. As shown in Table 1, the following basic parameters did not differ

Table 1 Baseline Characteristics Between Elderly Patients Undergoing Hip Fracture Surgery and Elderly Controls

Variables	Patients	Controls	*P* value
Age (years)	72.3±6.1	71.1±6.0	0.138
Gender (male/female)	102/169	42/58	0.444
Body mass index (kg/m^2)	23.3±3.0	24.0±3.6	0.111
Tobacco smoking	52 (19.2%)	24 (24.0%)	0.308
Alcohol drinking	48 (17.7%)	22 (22.0%)	0.349
Hypertension	77 (28.4%)	26 (26.0%)	0.645
Diabetes mellitus	42 (15.5%)	12 (12.0%)	0.397
Dyslipidemia	78 (28.8%)	23 (23.0%)	0.330
Charlson's Comorbidity Index	1 (1–2)	1 (1–2)	0.144
FRAIL scale scores	2 (1–3)	2 (1–3)	0.097
Preoperative Montreal Cognitive Assessment scores	29 (27–29)	29 (28–29)	0.112
Preoperative systolic blood pressure (mmHg)	137.5±24.0		
Preoperative diastolic blood pressure (mmHg)	85.7±11.9		
Type of fracture (femoral neck fracture/ trochanteric fracture)	162/109		
American Society of Anesthesiologists scale (I/II/III)	19/147/105		
Type of anesthesia (spinal/general)	57/214		
Type of surgery (internal fixation/arthroplasty)	65/206		
Duration of surgery (minutes)	104 (95–112)		
Delay of surgery (hours)	39 (33–46)		
Perioperative blood transfusion	75 (27.7%)		
Postoperative blood glucose levels (mmol/l)	6.7 (4.7–8.8)		
Postoperative serum C-reactive protein levels (mg/l)	9.3 (7–13.6)		
Postoperative Montreal Cognitive Assessment scores	28 (26–29)		
Postoperative delirium	88 (32.5%)		
Postoperative cognitive decline	61 (22.5%)		

Notes: Data were presented as means (standard deviations), medians (percentiles 25th-75th) or counts (percentages) as suitable, and were compared by adopting the chi-square test, Fisher exact test, Mann–Whitney *U*-test or independent-sample *t* test as applicable.

significantly between patients and controls (all P>0.05): age, sex, BMI, cigarette smoking, alcohol consumption, hypertension, diabetes mellitus, dyslipidemia, CCI, FRAIL scale scores, and preoperative MoCA scores.

Serum NLRP1 Levels and Other Baseline Indices

As shown in Figure 2, postoperative, but not preoperative, serum NLRP1 levels of patients were markedly higher than those of controls (P<0.001). In Supplementary Figure 1, postoperative serum NLRP1 levels were gradually increased with heightened FRAIL scale scores (P<0.001). As listed in Table 2, postoperative serum NLRP1 levels were tightly correlated with age, CCI, FRAIL scale scores, preoperative MoCA scores, ASA scale scores, and blood glucose and CRP levels (all P<0.05). The aforementioned factors were all entered into the multivariate model, and then postoperative NLRP1 levels were independently related to FRAIL scale scores [beta, 8.568; 95% confidence interval (CI), 4.654–12.482; VIF, 1.315; P<0.001] and serum CRP levels (beta, 4.294; 95% CI, 3.472–5.116; VIF, 1.071; P<0.001) of patients.

Serum NLRP1 Levels and POD

Postoperative serum NLRP1 levels were linearly correlated with POD likelihood (P for nonlinear > 0.05; Supplementary Figure 2). As shown in Table 2, POD patients, as opposed to those not presenting with the event, were substantially older, had notably lower preoperative MoCA scores, and had significantly higher CCI, ASA scale scores, and FRAIL scale scores, postoperative serum CRP levels, blood glucose levels, and serum NLRP1 levels (all P<0.05). These significantly different variables were forced into the binary logistic regression model and then postoperative serum NLRP1 levels (odds ratio, 1.014; 95% CI, 1.004–1.024; VIF, 1.890; P=0.005) and FRAIL scale scores (odds ratio, 1.926; 95% CI, 1.381–2.686; VIF, 1.407; P=0.001) were the two independent predictors of POD. Alternatively, POD was effectively predicted by postoperative serum NLRP1 levels (Figure 3A). Moreover, serum NLRP1 was transformed into the binary variable based on cutoff value (97.6 pg/mL); and serum NLRP1 levels above 97.6 pg/mL independently predicted POD with odds ratio value of 8.746 (95% CI, 1.673–45.911; VIF, 2.392; P=0.010). No interactional effects were found between serum NLRP1 levels and other factors (all

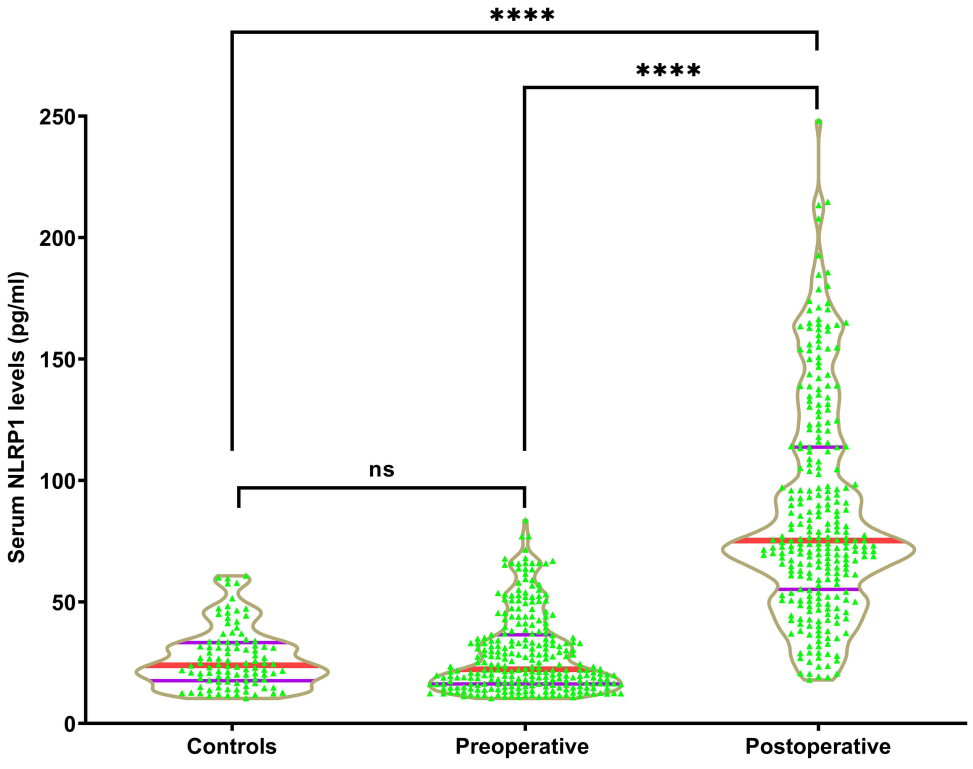

Figure 2 Serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 1 levels of elderly patients with Hip fractures. Compared with controls, elderly patients with hip fracture had notably increased postoperative, but not preoperative, serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 1 levels (****P<0.001). NLRP1 indicates nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 1; ns, non-significant.

https://doi.org/10.2147/CIA.S556318

Table 2 Factors Correlated with Serum NOD-Like Receptor Family Pyrin Domain-Containing 1 Levels and Delirium After Hip Fracture Surgery in Elderly Patients

Variables	Spearman Test		Two-Group Comparison		
	ρ	P value	POD	Non-POD	P value
Age (years)	0.186	0.002	75 (69–78)	70 (66–76)	0.001
Gender (male/female)	−0.049	0.426	28/60	74/109	0.170
Body mass index (kg/m^2)	−0.078	0.199	23.1 (21.4–25.2)	22.8 (21.1–25.1)	0.303
Tobacco smoking	0.080	0.191	19 (21.6%)	33 (18.0%)	0.486
Alcohol drinking	0.083	0.173	17 (19.3%)	31 (16.9%)	0.631
Hypertension	0.098	0.106	27 (30.7%)	50 (27.3%)	0.566
Diabetes mellitus	0.079	0.194	15 (17.0%)	27 (14.8%)	0.625
Dyslipidemia	0.103	0.092	27 (30.7%)	51 (27.9%)	0.632
Charlson's Comorbidity Index	0.151	0.013	1 (1–2)	1 (1–2)	0.015
FRAIL scale scores	0.423	<0.001	2 (2–3)	1 (1–2)	<0.001
Preoperative Montreal Cognitive Assessment scores	−0.345	<0.001	28 (26–29)	29 (28–29)	<0.001
Preoperative systolic blood pressure (mmHg)	0.037	0.543	130 (121–151)	131 (122–150)	0.887
Preoperative diastolic blood pressure (mmHg)	0.010	0.866	84 (76–95)	85 (76–95)	0.848
Type of fracture (femoral neck fracture/ trochanteric fracture)	−0.011	0.852	58/30	104/79	0.154
American Society of Anesthesiologists scale (I/II/III)	0.176	0.004	4/40/44	15/107/61	0.027
Type of anesthesia (spinal/general)	−0.104	0.087	15/73	42/141	0.264
Type of surgery (internal fixation/arthroplasty)	−0.065	0.287	19/69	46/137	0.522
Duration of surgery (minutes)	−0.037	0.542	105 (95–115)	104 (94–111)	0.301
Delay of surgery (hours)	−0.055	0.365	42 (32–45)	38 (33–47)	0.401
Perioperative blood transfusion	0.078	0.198	30 (34.1%)	45 (24.6%)	0.102
Postoperative blood glucose levels (mmol/l)	0.161	0.008	7.6 (4.7–11.3)	6.3 (4.8–8.5)	0.021
Postoperative serum C-reactive protein levels (mg/l)	0.552	<0.001	13.3 (6.0–14.4)	8.7 (7.2–11.5)	0.001
Postoperative serum NLRP1 levels (pg/mL)	-	-	113.9 (74.3–154.5)	70.1 (49.6–87.7)	<0.001

Notes: Correlation was reported as ρ via the Spearman test. For two-group comparison, data were summarized as medians (percentiles 25th-75th) or counts (percentages) as deemed suitable, and comparisons were done through the chi-square test, Fisher exact test, or Mann–Whitney *U*-test as appropriate. NLRP1 stands for NOD-like receptor family pyrin domain-containing 1.
Abbreviation: POD, postoperative delirium.

P interaction >0.05; Supplementary Figure 3), E value was 1.16 (Supplementary Figure 4), and AUC for POD prediction was similar between the two POD predictors, that is serum NLRP1 levels and FRAIL scale scores (P>0.05; Figure 3B). Blood CRP levels had AUC at 0.630 (95% CI, 0.554–0.706), which was significantly smaller than those of the two predictors (both P<0.001). The combined model containing the two predictors was visualized using the nomogram (Supplementary Figure 5). AUC of the model for POD prediction substantially surpassed those of the two predictors (both P<0.05; Figure 3B). Moreover, the model was rather steady under calibration curve (Supplementary Figure 6) and was clinically valid under decision curve (Supplementary Figure 7).

Serum NLRP1 Levels and POCD

In Supplementary Figure 8, the higher the patients' postoperative three-month MoCA scores were, the lower their postoperative serum NLRP1 levels were (P<0.001). Additionally, postoperative MoCA scores were highly related to age, CCI, FRAIL scale scores, preoperative MoCA scores, ASA scale scores, POD, postoperative serum CRP levels, blood glucose levels, and serum NLRP1 levels (all P<0.05; Table 3). Multivariate analysis encompassing the preceding substantially correlated factors showed that postoperative MoCA scores were independently linked to FRAIL scale scores (beta, −0.379; 95% CI, −0.555 to −0.203; VIF, 1.508; P<0.001), POD (beta, −1.120; 95% CI, −1.535 to −0.706; VIF, 1.428; P<0.001), and postoperative NLRP1 levels (beta, −0.016; 95% CI, −0.021 to −0.011; VIF, 1.973; P<0.001) of patients.

Postoperative serum NLRP1 levels were linearly related to the POCD probability of patients (P for nonlinear >0.05; Supplementary Figure 9). As displayed in Table 3, POCD patients, relative to those not experiencing this affair, were likely to be substantially older; were prone to harbor markedly lower preoperative MoCA scores; were likely to possess

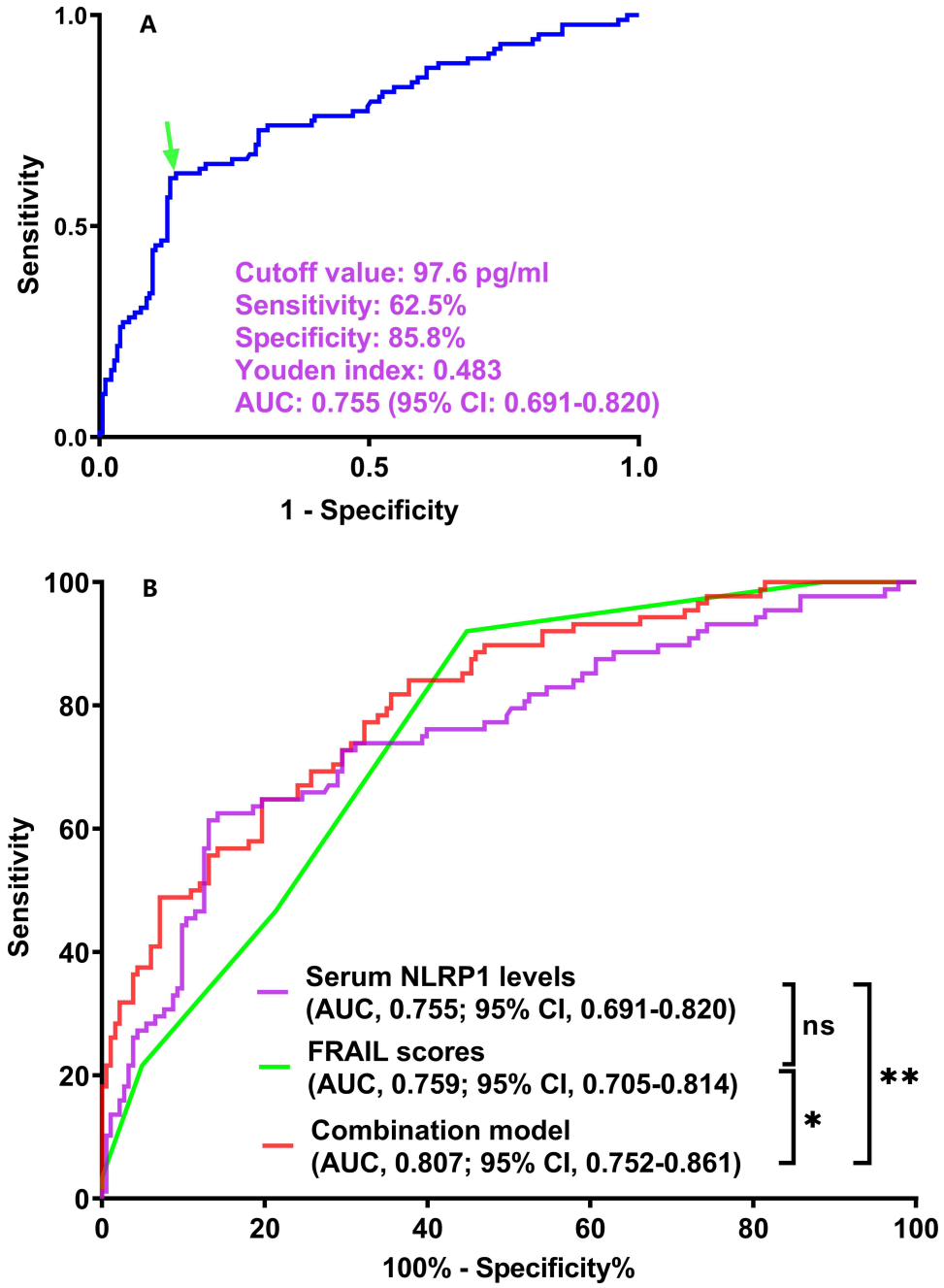

Figure 3 Receiver operating characteristic curve analysis for predicting delirium following Hip fracture surgery in elderly patients. Delirium after hip fracture surgery in elderly patients was efficiently predicted by postoperative serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 1 levels (**A**). Serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 1 levels had area under curve comparable to FRAIL scale scores (P>0.05; **B**). The two variables were merged to form combined model, and the model had area under curve significantly transcending serum protein levels (**P<0.01; **B**) and FRAIL scale scores (*P<0.05; **B**). NLRP1 denotes nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 1. Arrow indicates cutoff value.
Abbreviations: AUC, area under the curve; 95% CI, 95% confidence interval; ns, non-significant.

markedly higher CCI, ASA scale scores, FRAIL scale scores, postoperative serum CRP levels, blood glucose levels, and serum NLRP1 levels; and were inclined to occupy a notably higher proportion of POD (all P<0.05). After the inclusion of all these significant factors in the regression model, postoperative serum NLRP1 levels (odds ratio, 1.010; 95% CI, 1.001–1.018; VIF, 1.502; P=0.025), POD (odds ratio, 7.885; 95% CI, 3.643–17.065; VIF, 1.153; P=0.001), and FRAIL scale scores (odds ratio, 1.570; 95% CI, 1.090–2.259; VIF, 1.158; P=0.015) appeared to be independent predictors of POCD. In addition, POCD risk was efficiently discriminated by postoperative serum NLRP1 levels (Figure 4A).

https://doi.org/10.2147/CIA.S556318

Table 3 Factors Correlated with the Montreal Cognitive Assessment Scale Scores and Cognitive Decline at Three Months After Hip Fracture Surgery in Elderly Patients

Variables	Spearman Test		Two-Group Comparison		
	ρ	P value	POCD	Non-POCD	P value
Age (years)	−0.270	<0.001	75 (67–79)	71 (66–76)	0.036
Gender (male/female)	0.108	0.075	20/41	82/128	0.374
Body mass index (kg/m^2)	0.089	0.146	22.3 (21.1–24.5)	22.9 (21.2–25.3)	0.279
Tobacco smoking	−0.044	0.472	13 (21.3%)	39 (18.6%)	0.632
Alcohol drinking	−0.032	0.605	12 (19.7%)	36 (17.1%)	0.649
Hypertension	−0.067	0.272	15 (24.6%)	62 (29.5%)	0.452
Diabetes mellitus	−0.050	0.412	11 (18.0%)	31 (14.8%)	0.543
Dyslipidemia	−0.070	0.254	19 (31.1%)	59 (28.1%)	0.643
Charlson's Comorbidity Index	−0.224	<0.001	1 (1–2)	1 (1–2)	0.019
FRAIL scale scores	−0.614	<0.001	3 (2–3)	1 (1–2)	<0.001
Preoperative Montreal Cognitive Assessment scores	0.674	<0.001	28 (27–29)	29 (28–29)	<0.001
Preoperative systolic blood pressure (mmHg)	0.036	0.551	130 (121–143)	131 (122–151)	0.474
Preoperative diastolic blood pressure (mmHg)	0.110	0.071	83 (76–92)	85 (76–95)	0.280
Type of fracture (femoral neck fracture/ trochanteric fracture)	−0.018	0.767	39/22	123/87	0.452
American Society of Anesthesiologists Scale (I/II/III)	−0.174	0.004	3/25/33	16/122/72	0.022
Type of anesthesia (spinal/general)	0.010	0.866	8/53	49/161	0.085
Type of surgery (internal fixation/arthroplasty)	0.002	0.968	11/50	54/156	0.216
Duration of surgery (minutes)	−0.094	0.121	105 (95–118)	104 (94–112)	0.267
Delay of surgery (hours)	0.084	0.170	44 (32–45)	38 (33–46)	0.866
Perioperative blood transfusion	−0.074	0.225	19 (31.1%)	56 (26.7%)	0.491
Postoperative delirium	−0.511	<0.001	48 (78.7%)	40 (19.0%)	<0.001
Postoperative blood glucose levels (mmol/l)	−0.167	0.006	7.7 (5.0–13.3)	6.3 (4.7–8.6)	0.003
Postoperative serum C-reactive protein levels (mg/l)	−0.277	<0.001	13.5 (5.9–14.0)	8.7 (7.2–12.2)	0.032
Postoperative serum NLRP1 levels (pg/mL)	−0.587	<0.001	113.3 (81.2–154.3)	71.0 (50.6–95.8)	<0.001

Notes: Correlation was reported as ρ via the Spearman test. For two-group comparison, data were summarized as medians (percentiles 25th-75th) or counts (percentages) as deemed suitable, and data were compared via applying the chi-square test, Fisher exact test, or Mann–Whitney *U*-test as appropriate. NLRP1 stands for NOD-like receptor family pyrin domain-containing 1.
Abbreviation: POCD, postoperative cognitive decline.

Moreover, serum NLRP1 was converted into the binary variable according to cutoff value (77.0 pg/mL); and serum NLRP1 levels more than 77.0 pg/mL independently predicted POCD with odds ratio value of 3.411 (95% CI, 1.647–7.065; VIF, 2.187; P=0.001). There were no interactivities between serum NLRP1 levels and other variables (all P interaction > 0.05; Supplementary Figure 10), and E value was equivalent to 1.11 (Supplementary Figure 11). AUC was similar when serum NLRP1 levels were compared with POD and FRAIL scale scores (both P>0.05; Figure 4B). Blood CRP levels harbored AUC at 0.590 (95% CI, 0.501–0.680), which was substantially lower than those of the three POCD predictors, that is FRAIL scale scores, POD and postoperative serum NLRP1 levels (all P<0.001). The nomogram was configured to describe the combined model integrating the three predictors (Supplementary Figure 12). AUC of the combined model apparently exceeded those of the three predictors (all P<0.01; Figure 4B). According to calibration curve, the model had acceptable goodness of fit (Supplementary Figure 13). In accordance with decision curve, the model conferred satisfactory clinical benefit (Supplementary Figure 14). Alternatively, POD partially mediated association between postoperative serum NLRP1 levels and POCD of patients (Figure 5A) and this mediating effect was rather robust by sensitivity analysis (Figure 5B).

Discussion

To the best of our knowledge, blood NLRP1 has never been measured in elderly patients undergoing hip fracture surgery. Via this study, some results were found. First, patients possessed postoperative, but not preoperative, apparently raised serum NLRP1 levels as compared to elderly controls. Second, postoperative serum NLRP1 levels independently

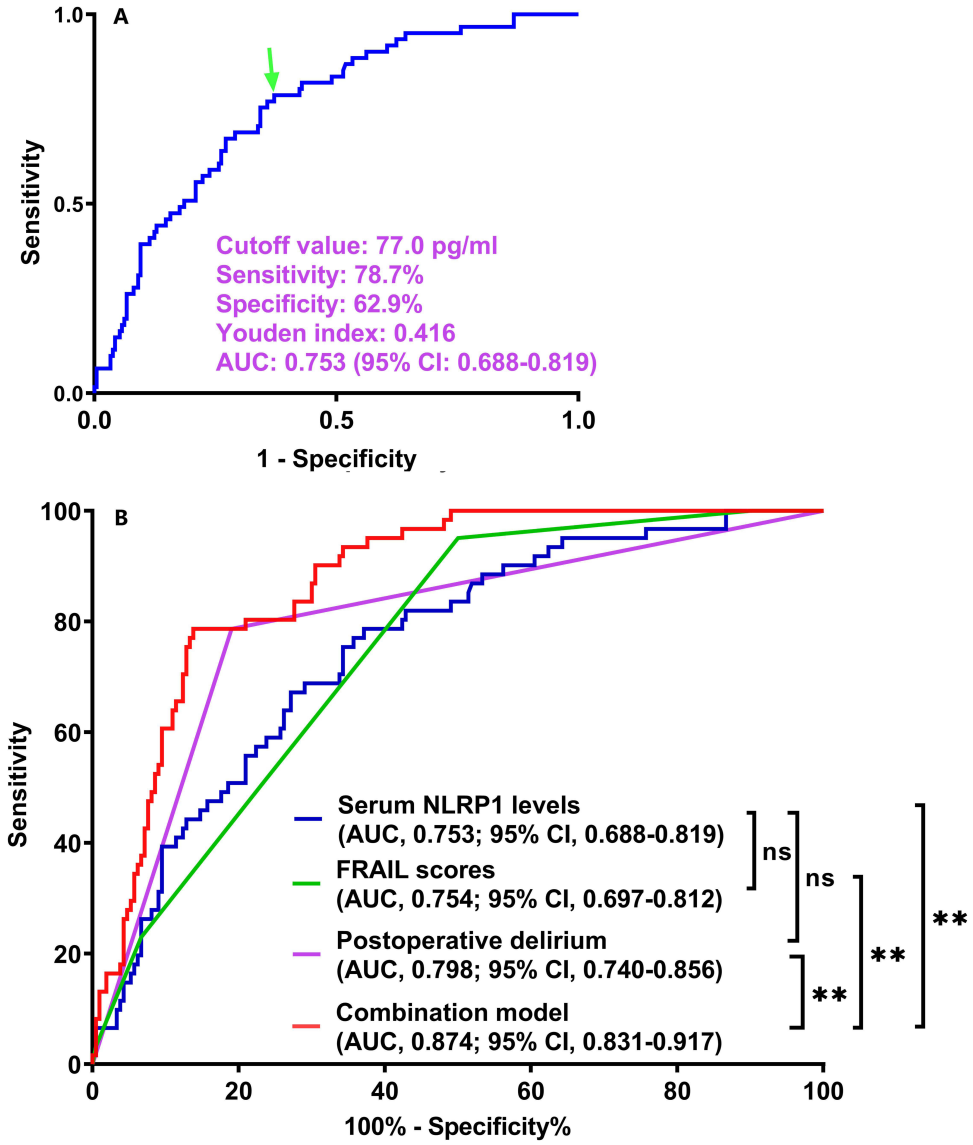

Figure 4 Receiver operating characteristic curve analysis for predicting postoperative cognitive decline following Hip fracture surgery in elderly patients. Postoperative cognitive decline of elderly subjects was effectively predicted through postoperative serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 1 levels (**A**). Serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 1 levels harbored area under curve analogous to postoperative delirium and FRAIL scale scores (both P>0.05; **B**); and they were incorporated to establish combination model, and the model's area under curve significantly surpassed those of serum protein levels, postoperative delirium and FRAIL scale scores (all **P<0.01; **B**). NLRP1 signifies nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 1. Arrow indicates cutoff value.

Abbreviations: AUC, area under the curve; 95% CI, 95% confidence interval; ns, non-significant.

correlated with postoperative serum CRP levels and FRAIL scale scores, and effectively predicted POD and POCD. Third, the combined models of POD and POCD performed efficiently. Finally, POD partially mediated association of postoperative serum NLRP1 levels with POCD. Collectively, postoperative serum NLRP1 may be a potential biomarker of POD and POCD in the elderly following hip fracture surgery.

Frailty can predispose patients to physiological insult[28] and preoperative frailty tends to increase the risk of POD and POCD in older subjects.[29] Demonstrably, frail elderly subjects are vulnerable to atherosclerosis and endothelial dysfunction, both of which easily disturb noradrenergic/cholinergic neurotransmission, and cause perioperative hypoxia, microembolisms, hypotension, and postoperative inflammatory and oxidative alterations, altogether provoking imperceptible brain injury and consequently eliciting POD and POCD.[29,30] Clinically, FRAIL scale is accredited as an indicator of frailty in older persons and

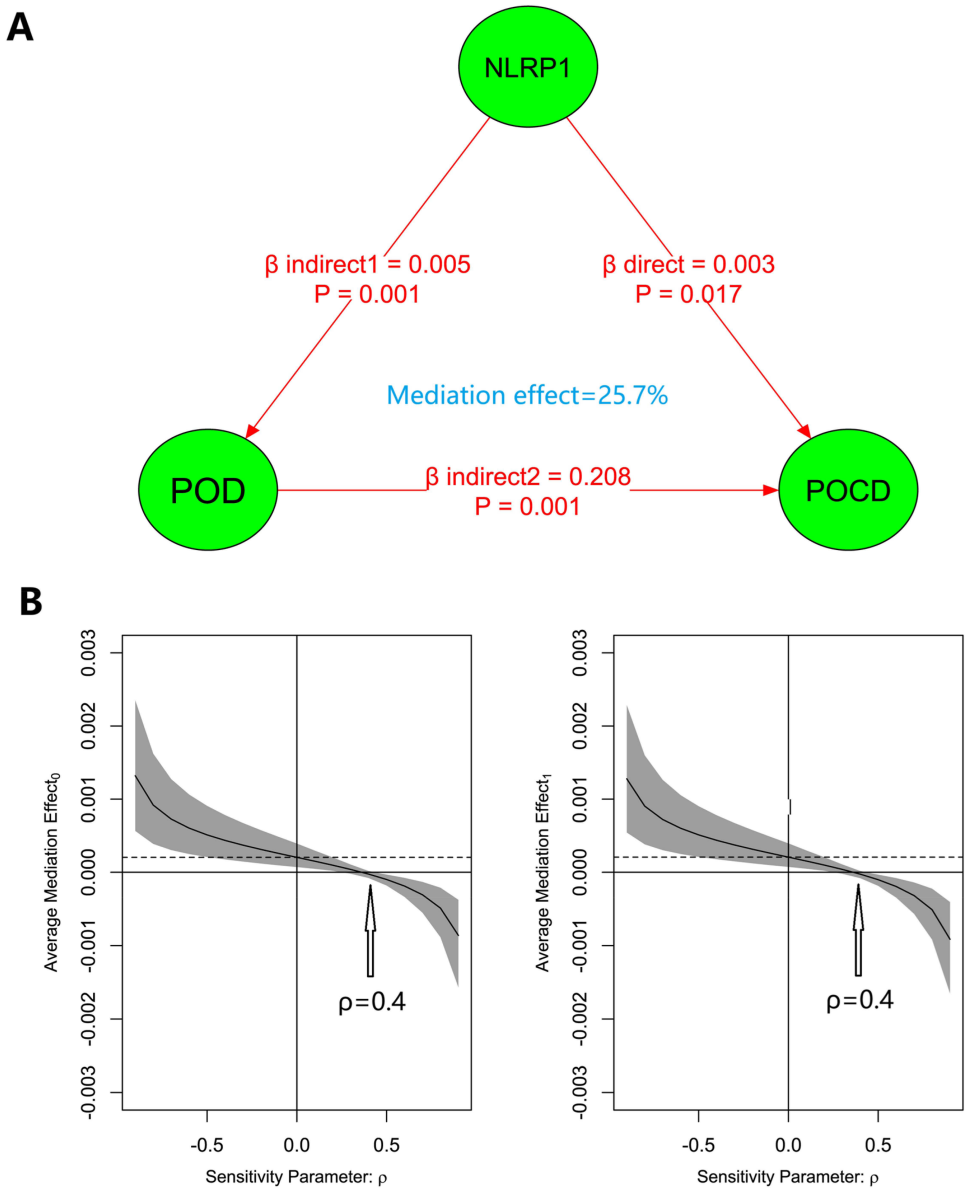

Figure 5 Mediating effect of postoperative delirium on association of serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 1 levels with cognitive decline following Hip fracture surgery in elderly patients. Postoperative delirium partially mediated relationship between postoperative serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 1 levels and postoperative cognitive decline in elderly patients (**A**). Moreover, this sort of mediating effect was robust using sensitivity analysis (**B**). NLRP1 stands for nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 1. Arrow indicates sensitivity parameter.

Abbreviations: POD, postoperative delirium; POCD, postoperative cognitive decline.

can effectually predict POD and POCD.[3] Similarly, our study demonstrated FRAIL scale as an independent predictor of POD and POCD in elderly patients in need of hip fracture surgery, further supporting its predictive significance.

NLRP1 can be secreted in the central nervous system, subsequently releasing to peripheral system, and induces a pro-inflammatory reaction by participating in inflammasome assembly, thereby triggering inflammatory injury.[10] Virtually, NLRP1 is implicated in pathophysiological processes of several degenerative diseases, including traumatic brain injury, ischemic stroke, and Alzheimer's disease, and could exert deleterious effects on brain tissues via provoking various inflammatory signaling pathways, damaging blood–brain barrier, increasing brain edema and causing neuronal demise.[31–36] Clinical studies of intracerebral hemorrhage, traumatic brain injury, and aneurysmal subarachnoid hemorrhage have fully confirmed serum NLRP1 as a potential biomarker of brain injury.[11–14] In this cohort of elderly patients undergoing hip fracture

surgery, postoperative, but not preoperative, serum NLRP1 levels were substantially elevated as compared to elderly controls, indicating that traumatic stresses or resultant fractures may not obviously impact NLRP1 levels in the blood of the elderly. In other words, systemic inflammation after hip fracture should insufficiently trigger NLRPl pathway, therefore, leading to nonsignificant change of serum NLRP1 levels after hip fracture. This condition has been observed in a group of patients with hip fracture, in whom blood CRP levels and systemic immune-inflammation index were significantly elevated, but blood red cell distribution width, neutrophil-to-lymphocyte ratio, and composite CRP-albumin-lymphocyte index not.[37] Taken together, surgical operation may be an initiator of NLRP1 production following hip fracture surgery in the elderly, alluding to the notion that postoperative serum NLRP1 may be a specific biomarker of brain injury following hip fracture surgery in the elderly.

Inflammatory mediators can activate glial cells, thereby eliciting inflammation and brain injury during POD and POCD.[38,39] There is an interrelationship between frailty and inflammation, indicating that frailty may predispose individuals to inflammation and vice versa.[40,41] Blood NLRP1 levels were strongly correlated with blood CRP levels in inflammation-related disease.[42] CRP can maintain relatively high levels in the peripheral blood of patients with POD risk.[43,44] Currently, postoperative serum CRP levels and PRAIL scale scores were independently associated with postoperative serum NLRP1 levels of elderly patients, leading to the extrapolation that NLRP1 may be involved in postoperative inflammatory processes of elderly patients requiring hip fracture and frailty may be a facilitator of postoperative NLRP1 production. Moreover, our study showed that postoperative NLRP1 levels were independently associated with POD and POCD, as well as POD partially mediated the relationship between postoperative NLRP1 levels and POCD. Given that inflammation is pertinent to NLRP1,[9] POD,[38] and POCD,[39] inflammatory response may be a mediator of their intricate interplay. Altogether, the preceding data are strongly supportive of the conception that serum NLRP1 may be a potential biomarker of POD and POCD.

Blood CRP levels were associated with POD of patients.[6] In this study, discrimination efficiency of blood CRP was inferior to those of serum NLRP1 and FRAIL scale whether in predicting POD or POCD. Here, both serum NLRP1 and FRAIL scale were independent predictors of POD and POCD in this group of elderly patients. Moreover, they held similar predictive ability for POD and POCD under the ROC curve. Afterwards, they were combined to construct the two prediction models, and the models owned apparent advantages in predicting both POD and POCD. Alternatively, the models had satisfactory goodness of fit and clinical benefit by aid of the calibration curve analysis and decision curve analysis. In a word, serum NLRP1 may be of clinical value in predicting POD and POCD, and its conjunction with FRAIL scale may be a better adjunctive tool for predicting delirium and cognitive decline following hip fracture surgery in elderly patients.

Several limitations need to be pointed out here. First, the current sample size generated from statistical analysis was sufficient for clinical analysis, but not adequate for subgroup analyses as for different fracture types; thus, the conclusions should be validated in a larger cohort study and even in a multicenter study. Second, based on mediation analysis, mediating role of POD was found on association of serum NLRP1 levels with POCD in elderly patients requiring hip fracture surgery. Nevertheless, detailed mechanisms underlying this link should be studied in the future. Finally, the predictive value of serum NLRP1 levels on POD and POCD was confirmed in elderly patients who underwent hip fracture surgery. It is unclear whether the conclusion can be generalized to other types of diseases or patients, such as stroke, patients needing cardiological surgery and acute pancreatitis, therefore necessitating further investigation.

Conclusions

In elderly patients undergoing hip fracture surgery, elevated postoperative serum NlRP1 levels are closely related to postoperative serum CRP levels and FRAIL scale scores, and may effectively predict POD and POCD as well; and POD may in part mediate the association of postoperative serum NLRP1 levels with POCD. Overall, postoperative serum NLRP1 may be a potential predictor of delirium, and cognitive decline after hip fracture surgery in elderly patients and the combined use of FRAIL and NLRP1 may optimize the efficiency of screening in high-risk populations.

Acknowledgments

The authors thank all staff in the Department of Anesthesiology and Department of Orthopedics for their technical support.

Funding

This study was financially supported by grants from the Medical Health Science and Technology Project of the Zhejiang Provincial Health Commission (No.2025KY1507).

Disclosure

The authors declare that they have no conflicts of interest in this work.

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