

Prevalence, risk factors, and pain trajectories for persistent pain after repeated cesarean delivery: a prospective observational study

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Research Article

Keywords: Repeated cesarean delivery, Pain prevalence, Persistent pain, Pain trajectory, Parturient

Posted Date: October 7th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10981987/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background

Persistent maternal pain following cesarean delivery (CD) is common and can have deleterious consequences. Data about persistent pain characteristics, including distribution, predictors and trajectories following CD, especially in women undergoing repeated CD, are still limited.

Methods

This prospective observational study was performed at the Women's Hospital of Nanjing Medical University from May 2022 to November 2023 to identify factors associated with persistent pain in this cohort by LASSO and multivariable logistic regression analysis. Pain scores and anatomical locations were recorded through 90 days post-CD to delineate temporal patterns. And we also performed an exploratory analysis of postoperative pain trajectory distributions among the parturient by LCMM analysis.

Results

Of the 360 parturient women enrolled, 357 completed the final analysis of prevalence, risk factors, and pain trajectory. Pain prevalence after repeated CD fell sharply over time, from 99.7% on postoperative day (POD) 1 to 25.9% by POD 90. Multivariable logistic regression identified two independent risk factors for persistent pain at POD 90 using LASSO-selected variables across 20 imputed datasets: anxiety (adjusted OR 2.933; 95% CI 1.55 to 5.549; $P = 0.001$) and higher uterine contraction pain score on POD 1 (adjusted OR 1.174; 95% CI 1.015 to 1.361; $P = 0.031$). The logistic model showed modest discrimination (AUC 0.638; 95% CI 0.571 to 0.706). At the optimal cutoff of 0.259, sensitivity was 50.0% and specificity was 74.0%. An exploratory LCMM analysis identified three 90-day pain trajectories after repeated CD: Slow recovery from severe pain (Class 1, 37 (10.4%)), Persistent moderate pain (Class 2, 30 (8.4%)), and Consistent low pain (Class 3, 290 (81.2%)).

Conclusions

Approximately one in four women experience all-caused postoperative pain at day 90 following repeated CD. Prenatal anxiety and greater visceral pain at POD 1 are associated with higher likelihood of reporting persistent pain, with only modest discriminatory power. Further multi-center studies are needed to explore better interventions, such as emotional reassurance or multimodal analgesia, in anxious parturient when undergoing repeated CD. Exploratory trajectory analysis indicates a subset at higher risk either follow a slow-recovery trajectory or remain in a persistent pain state, who will also require increased attention in the future.

Trial registration

This study was registered in the Chinese Clinical Trial Registry (ChiCTR2200059487) on 02/05/2022.

Background

Persistent maternal pain after childbirth is not merely a physical symptom; it also undermines mental health, social functioning, and mother–infant bonding [1]. Definitions of chronic postsurgical pain (CPSP) or persistent pain following cesarean delivery (CD) vary markedly across studies, resulting in substantial heterogeneity in pain reporting. Two recent meta-analysis examining CPSP in parturients revealed an occurrence of scar-specific CPSP at different time intervals: 15.2% – 16.7% at 3 months, 9.5–11.4% at 6 months, and 5.05–8.8% at 12 months [2, 3]. This heterogeneity in pain incidence also underscores the complexity of the factors influencing persistent pain and the mechanisms underlying its development following CD. In addition, after cesarean delivery, ongoing postpartum pain compromises maternal self-care and the ability to care for the infant, and unmanaged pain can impair the quality of mother–infant interactions [4]. Approximately 10% of patients develop CPSP following CD, impacting their daily activities, employment, social interactions, and self-care, which with a very low quality of evidence according to Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) [2]. Together, these studies highlight major gaps in our understanding of the distribution and characteristics of persistent pain following CD and its downstream effects.

Women undergoing repeated CD also have a higher incidence of moderate to severe acute postoperative pain than those having a primary cesarean delivery [5, 6]. Previous cesarean delivery was considered as a significant risk factor (adjusted OR: 3.571, 95% CI 1.536–8.300) for moderate to severe postoperative pain after cesarean delivery [7]. Adhesion prevalence rose with increasing cesarean delivery history: 2.8% with no CD, 51% with one CD, and 62% with more than one CD [8]. Adhesions notably extended operation time, infant delivery time and blood loss in severe cases, possible contributors to increased postoperative pain scores following repeated CD. However, few studies specifically address postoperative pain in women undergoing repeated CD, and existing work includes only small samples of such parturients and provides little information on persistent postoperative pain. In China, the number of parturient women received repeated CD has risen markedly over the past decade, heightening the need to optimize post-cesarean pain management for this group. Therefore, characterizing the pain profile after repeated Therefore, characterizing the pain profile after repeat cesarean delivery in this population, mapping the trajectory of pain progression, and determining whether persistent pain has distinct predictors could provide evidence to guide clinical decision-making cesarean delivery in this population, mapping the trajectory of pain progression, and determining whether persistent pain has distinct predictors could provide evidence to guide clinical decision-making.

We therefore designed an observational study of persistent postoperative pain in women undergoing repeated cesarean delivery. By assessing potential physiological and psychological confounders before surgery and prospectively recording all pain-related complaints at multiple time points during the first

three months after surgery, the study has three goals: 1) identify perioperative risk factors for persistent pain at 90 days after repeated CD; 2) characterize the prevalence, location, and intensity of pain following repeated CD; and 3) define the temporal evolution of maternal pain using pain-trajectory analysis.

Methods

Study design

This single-center prospective observational study was conducted at the Women's Hospital of Nanjing Medical University. Parturients scheduled for repeat cesarean delivery were enrolled consecutively from May 18, 2022, to August 10, 2023, with final follow-up on November 10, 2023. Preoperative data collection included demographics, psychological assessment questionnaires, and pain-related measures. Maternal acute and persistent pain—including severity and anatomical location—were assessed up to three months postoperatively. The study was approved by the Ethics Committee of the Women's Hospital of Nanjing Medical University (2022KY-015-01) and registered at www.chictr.org.cn (ChiCTR2200059487; 02/05/2022). Informed consent was obtained from all participants, and the study followed clinical practice protocols and the Declaration of Helsinki.

Participants and data collection procedures

We enrolled parturient aged 20–45 years with gestational age ≥ 37 weeks, a singleton pregnancy, BMI ≤ 35 kg/m², and a planned elective repeat cesarean section. We excluded women with uterine fibroids or ovarian tumors requiring surgical intervention, those with severe preeclampsia, individuals who had used opioids or other sedative–analgesics within one week, and patients with severe cardiac, pulmonary, hepatic, or renal dysfunction. Eligible participants were identified one day before surgery based on these inclusion and exclusion criteria. After enrollment, investigators explained the trial protocol and obtained written informed consent.

On the day before surgery, we recorded demographic data (educational level, number of prior CDs, type of incision in the prior CD, and time since the prior CD), psychological measures (Fear of Pain Questionnaire-III, FPQ-III; Pain Catastrophizing Scale, PCS; and Generalized Anxiety Disorder-7, GAD-7), and pain-related information (history of pain during pregnancy, pain score for the prior CD, and expected pain score for the current CD) as the trial's pre-specified candidate factors. Details of the ten pre-specified candidate factors were provided in *Supp. A. of Additional Files*. Participants who underwent repeated cesarean delivery under combined spinal-epidural anesthesia (CSEA) proceeded to the postoperative follow-up phase. A single designated researcher collected all follow-up data at predefined postoperative time points, the method of accessing pain were provided in *Supp. B of Additional Files*. At 24 hours after surgery, pain (Visual analog scale, VAS) scores were recorded in the ward, including resting pain, movement pain, uterine contraction pain, and the average pain over 24 hours. At 7, 42, 60,

and 90 days after surgery, pain location and intensity (Numeric rating scale, NRS) were assessed by telephone to determine the prevalence and proportion of postoperative pain.

Anesthesia procedures

All subjects underwent repeat cesarean section with CSEA at the L3–4 level. Intraoperative monitoring included blood pressure, heart rate, and oxygen saturation (SpO₂). The attending anesthesiologist administered the CSEA and titrated 0.05% ropivacaine as needed to maintain a sensory block between T6 and T4. Vasoactive agents were permitted prophylactically or therapeutically to treat hypotension following spinal anesthesia. After delivery, all patients received 10 units of oxytocin intravenously; additional carbetocin or hemabate was given as required by the obstetrician to promote uterine contraction. Before peritoneal closure, patients received 50 mg flurbiprofen axetil for adjunctive postoperative analgesia and 3 mg granisetron to prevent postoperative vomiting. Postoperative analgesia was provided via patient-controlled intravenous analgesia (PCIA) with a total volume of 114 ml containing 12 mg butorphanol, 200 mg tramadol, and 6 mg granisetron. The infusion was set at 2 ml/hour with a 1.5 ml bolus and a 30-minute lockout interval.

Outcomes

Descriptive Outcomes

Pain prevalence was reported descriptively at each follow-up (postoperative days 1, 7, 42, 60, and 90). The following pain characteristics were summarized: (1) pain intensity, expressed as the proportion of patients with mild (NRS 1–3), moderate (NRS 4–6), or severe (NRS 7–10) pain; and (2) pain type, classified as medical pain (incisional or abdominal pain) or other pain (labor-related low back pain and pubic symphysis pain). Categorical variables are presented as frequencies and percentages; nonnormally distributed continuous variables are reported as medians with interquartile ranges.

Primary Outcome

The primary outcome was the incidence of persistent pain at 90 days, defined as pain lasting at least 3 months after surgery, consistent with the chronic post-surgery pain (CPSP) definition recently proposed by the International Association for the Study of Pain (IASP) [9]. We prospectively included all-cause persistent pain related to repeat surgery or delivery, encompassing surgical incision pain, abdominal pain, pelvic or perineal pain, and low back pain. To identify factors associated with persistent pain at 90 days, we performed multivariable logistic regression, iteratively adjusting covariates selected by LASSO. Discrimination was evaluated by the area under (AUC) the receiver operating characteristic (ROC) curve, with 95% confidence intervals (CIs) computed by the DeLong method. Sensitivity and specificity at the optimal cutoff are reported for both the LASSO-derived penalized model and the final parsimonious logistic regression model.

Exploratory Outcome

Pain trajectories were examined as an exploratory, hypothesis-generating outcome. Using all repeated NRS measurements collected over the 90-day follow-up period, we fitted latent class mixed models (LCMM) to identify distinct subgroups of patients with similar pain evolution over time. The optimal number of trajectory classes was selected based on the Bayesian Information Criterion (BIC) and clinical interpretability. This exploratory analysis aimed to generate hypotheses about the heterogeneity of postoperative pain recovery.

Sample size

According to previous data, the incidence of persistent pain following repeat cesarean delivery was 32.6%[10]. In this study, we identified ten candidate meaningful factors based on previous research on persistent pain or CPSP, using ten events per variable (EPV) to ensure accurate estimation of regression coefficients and associated quantities for logistic analysis [11]. Ultimately, a total of 306 parturient women were required for the multivariable logistic analysis. To account for a potential 15% follow-up loss, we aimed to recruit a total of 360 parturient women.

Statistical analysis

All data were analyzed using R (version 4.4.3, R Foundation for Statistical Computing, Vienna, Austria). Missing data were handled using multiple imputation by chained equations (MICE) with the ‘mice’ (version 3.19.0) package under the missing at random assumption. A total of 20 imputed datasets were created.

Descriptive analysis

Descriptive statistics summarized the study population’s baseline characteristics. The Shapiro–Wilk test assessed normality for all continuous variables. Normally distributed continuous data are reported as mean $\pm$ SD; non-normally distributed variables are reported as interquartile range (IQR). Categorical variables are presented as frequencies and percentages. Data processing and analyses used the following R packages: dplyr (version 1.2.0) for data manipulation, tidyr (version 1.3.2) for data reshaping, and binom (version 1.1–1.1) for confidence interval estimation.

Primary analysis: LASSO and multivariable logistic regression analysis

For the primary analysis, we first performed variable selection with least absolute shrinkage and selection operator (LASSO) regression in the first imputed dataset because the final number of observed positive events in our cohort was insufficient to support the ten prespecified independent variables. After data cleaning, 20 candidate predictors—including the ten prespecified variables—were entered into the LASSO pool based on clinical relevance and literature review. To address multicollinearity, we computed

the Pearson correlation matrix for all candidate predictors. The average pain score at day 1, which had an absolute correlation coefficient ($|r|$) = 0.879, was excluded. We then calculated variance inflation factors (VIFs) for the remaining variables; all VIFs were below the threshold of 5, indicating no substantial multicollinearity among the predictors (Table S1 in the Additional Files).

LASSO was used to select the most relevant predictors by imposing an L1 penalty on regression coefficients, which shrinks coefficients of unimportant variables to zero and thus performs variable selection. The optimal regularization parameter λ was chosen by 10-fold cross-validation, seven variables with nonzero coefficients at $\lambda_{\min}$ were retained and then entered a multivariable logistic regression model for all imputed datasets. The regression coefficients and their standard errors were then combined across the 20 imputations using Rubin's rules to generate the final point estimates, 95% confidence intervals, and p-values. The discriminative ability of the final multivariable logistic regression model was evaluated using ROC curve analysis. The AUC was calculated with 95% CIs using the DeLong method. The optimal probability cutoff was determined by maximizing the Youden index (sensitivity + specificity - 1). To correct for potential overfitting due to model development and internal validation, we performed 500 bootstrap resamples to estimate the optimism-corrected AUC, as recommended for prediction model studies. All statistical analyses were conducted in R, using the 'glmnet' (version 4.1–10) package for LASSO. All ROC analyses were conducted using the 'pROC' package (version 1.18.0). A two-sided P-value < 0.05 was considered statistically significant.

Exploratory analysis: LCMM for pain trajectory analysis

Latent class mixed models (LCMM) were fitted using the 'hlme' function from the 'lcmm' package (version 2.2.2) to exploratorily identify the optimal number of latent trajectory classes. The model included a fixed linear effect of time and a random intercept, allowing individual variability around the class-specific trajectories. Latent class mixed models with 1–5 classes were estimated. Model fit was compared using the BIC and Akaike Information Criterion (AIC), with lower values indicating superior fit, and class separation was judged by entropy, with values nearer 1 denoting better classification. Final model choice prioritized lower BIC and AIC, higher entropy, parsimony, a minimum class size of 5% of the sample for clinical interpretability, and graphical confirmation of the clinical plausibility of the trajectories. Finally, the optimal trajectory model we selected comprised three groups.

Because Classes 1 ($n = 37$) and 2 ($n = 30$) were small, we avoided formal multivariable regression to prevent model overfitting and unstable estimates. Baseline demographic and clinical characteristics are summarized descriptively by the three trajectory classes. Given the limited sizes of Class 1 and Class 2, we did not perform hypothesis tests with P values to avoid overinterpreting unstable estimates. Instead, between-class differences were quantified with effect sizes: standardized mean differences (SMD, Cohen's d) for continuous variables and risk differences (RD) for categorical variables, using Class 3 (the largest class, $n = 290$) as the reference. $SMD \geq 0.20$ or $RD \geq 0.10$ were considered potentially clinically meaningful. Because of the small class sizes, multivariable regression was not attempted, and all comparisons should be interpreted as descriptive and exploratory. All data visualizations were implemented using the 'ggplot' package.

Sensitivity analysis

To assess the robustness of our primary analysis findings, we performed several sensitivity analyses. First, we repeated the multivariable logistic regression using complete case analysis (CCA) to evaluate the impact of missing data. Second, we adjusted for additional clinically relevant covariates (pain history during pregnancy and expected pain score) beyond the two significant variables included in the Logistic regression analysis. Third, we used alternative definitions of pain catastrophizing ($PCS \geq 30$) and three domains of FPQ-III as independent variables for the selection by LASSO analysis. All sensitivity analyses yielded results consistent with the primary analysis, supporting the robustness of our conclusions

Results

From May 2022 to November 2023, a total of 412 parturient were screened and 360 completed the collection of predefined risk factors one day before surgery and were included. Thirty-four parturient declined participation, 15 could not understand or complete the questionnaires, and 3 underwent emergency surgery before enrollment. Three additional participants dropped out for converting to general anesthesia due to failed CSEA. Ultimately, 357 participants were included in the final analysis (Fig. 1).

Baseline characteristics

Table 1 shows that the cohort ($N = 357$) had a mean age of 33.6 ± 3.5 years and a mean BMI of 27.5 ± 3.0 kg/m². Most participants held a bachelor's degree (46%) and had a horizontal prior incision (80%). Median gravidity was 3.0 (IQR, 2.0–4.0) and median parity was 1.0 (1.0–1.0). Preoperative psychological scores were low overall: median PCS 8.0 (3.0–15.0) and GAD-7 2.0 (0.0–3.0), with 16% screening positive for anxiety and 6.2% for pain catastrophizing. A history of moderate-to-severe pain during pregnancy was reported by 18% of participants.

Table 1
Baseline characteristics of parturient in the cohort population

Characteristics	Total (N = 357)
Demographic information	
Age (years)	33.6 ± 3.5
BMI (kg/m ²)	27.5 ± 3.0
Education level	
High school or below	149 (42%)
Bachelor's degree	165 (46%)
Graduate or above	43 (12%)
Gestational week (weeks)	38.7 ± 0.7
Gravidity	3.0 (2.0, 4.0)
Parity	1.0 (1.0–1.0)
Number of prior CD	1.0 (1.0–1.0)
The type of prior incision scar, n (%)	
Horizontal incision	286 (80%)
Longitudinal incision	71 (20%)
Psychological information	
FPQ-III	79.0 (67.0, 93.8)
Severe Pain	29.0 (25.0, 35.0)
Minor Pain	23.0 (19.0, 28.0)
Medical Pain	26.0 (22.0, 32.0)
PCS	8.0 (3.0, 15.0)
Pain catastrophizing, n (%)	22 (6.2%)
GAD-7	2.0 (0.0, 3.0)
Anxiety, n (%)	56 (16%)
Preoperative pain information	
Data are presented as mean ± SD, median (IQR), or number (percentage)	
<i>BMI</i> body mass index, <i>CD</i> Cesarean deliveries, <i>FPQ-III</i> Fear of Pain Questionnaire-III, <i>PCS</i> Pain Catastrophizing Scale, <i>GAD-7</i> Generalized Anxiety Disorder Scale-7	

Characteristics	Total (N = 357)
Demographic information	
History of pain	
Without pain	167 (47%)
Minor pain	125 (35%)
Moderate to severe pain	65 (18%)
Pain score of prior CD	4.4(2.5-5)
Expected pain score	4.5 (4.0-4.8)
Data are presented as mean $\pm$ SD, median (IQR), or number (percentage)	
<i>BMI</i> body mass index, <i>CD</i> Cesarean deliveries, <i>FPQ-III</i> Fear of Pain Questionnaire-III, <i>PCS</i> Pain Catastrophizing Scale, <i>GAD-7</i> Generalized Anxiety Disorder Scale-7	

Table 1 Baseline characteristics of parturient in the cohort population (at the end of the manuscript)

Data are presented as mean $\pm$ SD, median (IQR), or number (percentage)

BMI body mass index, *CD* Cesarean deliveries, *FPQ-III* Fear of Pain Questionnaire-III, *PCS* Pain Catastrophizing Scale, *GAD-7* Generalized Anxiety Disorder Scale-7

Prevalence and distribution characteristics of pain after repeated CD

The pain prevalence declined markedly over time following repeated CD (Table 2, Fig. 2a). Pain was reported by 99.7% (356 out of 357) of the participants on day 1 following repeated CD. By day 7, the prevalence decreased to 69.0%, further declining to 40.9% by day 42, 32.8% by day 60, and 25.9% by day 90. And median pain scores decreased from 4.0 (IQR 3.0–5.0) on day 1 to 2.0 (0.0–2.0) on day 7 and remained 0.0 thereafter. In addition, the proportion of moderate-to-severe pain fell from 51.8% on day 1 to 5.9% at day 90, while the proportion reporting minor pain fell from 52.1% on day 7 to 18.5% at day 90. By pain type, medical pain, including incision-related rest pain, movement-evoked pain, and uterine contraction pain, comprised 62.2% at day 7 but declined to 15.4% at day 90; conversely, other pain types (e.g., low back pain) appeared later, accounting for 23.8% at day 42 and 9.0% at day 90. Together, these findings show that although most women recovered rapidly, a substantial minority experienced persistent pain beyond the early postoperative period (Table 3, Fig. 2b, Fig. 2c).

Table 2
Pain prevalence at different time points after repeated
cesarean delivery in the cohort population

Time	N	Missing	Prevalence	95% CI
Day 1	357	0	356(99.7%)	98.4% - 100.0%
Day7	355	2	245 (69.0%)	64.0% - 73.6%
Day42	340	17	139 (40.9%)	35.8% - 46.2%
Day60	338	19	111 (32.8%)	28.1% - 38.0%
Day90	336	21	87 (25.9%)	21.5% - 30.8%

Data are presented as number (percentage), 95% CI

CI Confidence Interval, obtained by the Wilson method

Table 3

Pain distribution characteristics at different time points after repeated cesarean delivery in the cohort population

Variables	Day 1	Day 7	Day 42	Day 60	Day 90
Pain score	4.0 (3.0, 5.0)	2.0 (0.0, 2.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)
Pain level proportion, n (%)					
Without pain	1 (0.3%)	110 (30.8%)	201 (56.3%)	228 (63.9%)	249 (69.7%)
Minor pain	171 (47.9%)	186 (52.1%)	112 (31.4%)	83 (23.2%)	66 (18.5%)
Moderate to severe pain	185 (51.8%)	59 (16.5%)	27 (7.6%)	27 (7.6%)	21 (5.9%)
Pain type proportion, n (%)	NA [‡]				
Without pain	NA	109 (30.5%)	199 (55.7%)	227 (63.6%)	249 (69.7%)
Medical pain	NA	222 (62.2%)	56 (15.7%)	51 (14.3%)	55 (15.4%)
Other pain [†]	NA	24 (6.7%)	85 (23.8%)	60 (16.8%)	32 (9%)
N	357	355	340	338	336
Missing	0	2	17	19	21
Data are presented as number (percentage)					
NA Not Available					
[†] Other types of pain refer to pain not originating from surgical incisions, including labor-related low back pain and pubic symphysis pain					

[‡]It refers to the fact that postoperative pain follow-up on day 1 of the study recorded only incision-related pain associated with the surgery and did not capture other types of pain; therefore, data characterizing pain types are not available.

Risk factors for persistent pain at 90 days after repeated CD

To identify the most parsimonious set of risk factors from the candidate variables, we applied LASSO logistic regression using the 'glmnet' package in R. The optimal penalty parameter λ was chosen by ten-fold cross-validation at $\lambda_{\min}$ (0.02888) based on the coefficient paths and cross-validation plot of

LASSO (Fig. 3a, Fig. 3b). At λ .min, seven variables retained non-zero coefficients. These seven variables were entered together in a multivariable logistic regression model listed in Table 4 pooled from 20 imputed datasets using Rubin's rules. The adjusted odds ratios (aOR) were estimated with mutual adjustment for all other variables in the model (Table 4, Fig. 4), showed that perinatal anxiety (Adjusted OR = 2.933, 95% CI: 1.550–5.549, P = 0.001) and higher uterine contraction pain at POD1 (Adjusted OR = 1.176, 95% CI: 1.015–1.361, P = 0.03) remained statistically significant and were identified as independent predictors of persistent pain at day 90 following repeated CD.

Table 4
Multivariate logistic regression analysis for factors associated with persistent pain at 90 days following repeated CD (after multiple imputation)

Variables	aOR [†] (95% CI)	P - value
(Intercept)	0.002 (0–0.057)	0.000
Age (per 1 year)	1.047 (0.963–1.138)	0.283
Time since prior CD (per 1 year)	1.031 (0.948–1.122)	0.475
With pain during pregnancy (yes vs. no)	1.628 (0.963–2.751)	0.070
Blood loss (per mL)	1.002 (1–1.004)	0.110
Anxiety (yes vs. no)	2.933 (1.550–5.549)	0.001
Expected pain score (per 1 sore)	1.314 (0.989–1.745)	0.061
Uterine contraction pain at POD1 (per 1 score)	1.176 (1.015–1.361)	0.031

CD cesarean delivery, aOR adjusted odds ratio, CI confidence interval, POD postoperative day

[†]Adjusted for all variables in the multivariable model (selected by LASSO regression).

Results were pooled from 20 imputed datasets using Rubin's rules.

To assess the predictive discrimination if the model, we exploratorily constructed ROC curves for the LASSO-derived penalized model and the final multivariable logistic model (Fig. 5). The LASSO model, which included the selected seven predictors, showed a cross-validated AUC of 0.666 (95% CI: 0.600–0.733). The parsimonious logistic model limited to the two independently significant predictors (anxiety and uterine contraction pain at POD1) had an apparent AUC of 0.638 (95% CI: 0.571–0.706). To address potential overfitting, we performed internal validation with 500 bootstrap resamples. After optimism correction, the corrected AUC for the two-predictor model remained 0.638, closely matching the apparent estimate and the LASSO model's performance. These results indicate that the two-factor model captures the primary predictive signal with minimal overfitting, striking a reasonable balance between parsimony and discrimination, albeit with modest overall performance. In addition, for the LASSO-derived model, the optimal cutoff was 0.270 (Youden index), yielding a sensitivity of 46.7% and a

specificity of 80.4%. For the final parsimonious logistic model, the optimal cutoff was 0.259, with a sensitivity of 50% and a specificity of 74%.

Pain trajectories following repeated CD by LCMMs

Based on repeated postoperative pain scores collected from women undergoing repeat cesarean delivery, we conducted an exploratory pain-trajectory classification using the LCMM method. Table 5 reports model fit indices for LCMMs with 1–5 classes. The 3-class solution was chosen as optimal: it had the lowest BIC (6397.1) and AIC (6358.3), high entropy (0.956), and average posterior probabilities (AvePP) of 0.839–0.955, indicating excellent class separation. The LCMM identified three distinct postoperative pain trajectories (Fig. 6). The largest class (Class 3, Consistent low pain, $n = 290$, 81.2%) was characterized by consistently low pain scores throughout the 90-day follow-up period, with mean NRS scores remaining below 2.5 at all time points. Class 1 (Slow recovery from severe pain, $n = 37$, 10.4%) exhibited a moderate-to-severe pain level at baseline (NRS approximately 5.0), followed by a gradual linear decline toward mild pain by day 90. Class 2 (Persistent moderate pain, $n = 30$, 8.4%) showed a persistently moderate pain trajectory, with mean NRS scores fluctuating around 3.5 without significant improvement over time. The three trajectories were well separated, with minimal overlap in their confidence bands, supporting the clinical distinctiveness of each class.

Table 5
Selection of LCMM ($ng = 1-5$)

Classes	Converged	BIC	AIC	Entropy	AvePP
1	TRUE	6568.8	6553.2	1	Class 1: 1
2	TRUE	6449.8	6422.6	0.984	Class 1: 0.96; Class 2: 0.989
3	TRUE	6397.1	6358.3	0.956	Class 1: 0.839; Class 2: 0.951; Class 3: 0.955
4	TRUE	6414.7	6364.3	0.892	NA
5	TRUE	6432.4	6370.3	0.803	NA

BIC Bayesian Information Criterion, *AIC* Akaike Information Criterion, *AvePP* Average Posterior Probabilities, *NA* Not Available

Baseline characteristics of the three trajectory classes are presented in Table 6. Compared with the predominant Class 3 (Consistent low pain, $n = 290$, 81.2%), both smaller classes exhibited distinct clinical profiles. Class 1 (Slow recovery from severe pain, $n = 37$, 10.4%) was characterized by substantially higher scores on psychological measures, including the PCS (SMD = 0.88 vs Class 3), the FPQ-III (SMD = 0.52), and the GAD-7 (SMD = 0.92). Patients in Class 1 also reported higher pain intensity from previous cesarean deliveries (pain VAS of prior CD, SMD = 0.76 vs Class 3) and a higher prevalence of anxiety (GAD-7 ≥ 5 : 37.8% vs 11.0%, RD = 0.27) and pain during pregnancy (64.9% vs 49.3%, RD = 0.16). Class 2 (Persistent moderate pain, $n = 30$, 8.4%) showed a similar pattern, with elevated FPQ scores

(SMD = 0.53 vs Class 3), GAD-7 scores (SMD = 0.78), and anxiety prevalence (33.3% vs 11.0%, RD = 0.22) compared with Class 3. Notably, Class 2 had the highest proportion of pain during pregnancy (76.7% vs 49.3%, RD = 0.27 vs Class 1) and greater intraoperative blood loss (SMD = 0.34), but lower PCS scores (SMD = 0.29) than Class 1. Other variables, including age, BMI, gestational weeks, and operation duration, showed negligible differences across classes (all SMD < 0.20).

Table 6

Baseline demographic and clinical characteristics of the overall cohort and by pain trajectory class

Variables	Class 1	Class 2	Class 3	Effect size	Effect size
	n = 37 (10.4%)	n = 30 (8.4%)	n = 290 (81.2%)	Class 1 vs 3	Class 2 vs 3
Age, years	33 (31–35)	33 (32–35)	33 (31–36)	SMD=-0.07	SMD=-0.01
BMI, kg/m ²	27.4 (26–29.7)	27.6 (25.9–30.6)	27.1 (25.3–29.3)	SMD = 0.16	SMD = 0.27
Gestational week, weeks	39 (38.6–39)	39 (38.4–39.1)	39 (38.5–39.1)	SMD = 0.11	SMD = 0.03
Number of prior CD	1 (1–1)	1 (1–1)	1 (1–1)	SMD = 0.1	SMD = 0.1
FPQ Score	89 (76–103)	91 (79.8–102.5)	76 (65–90)	SMD = 0.52	SMD = 0.53
PCS Score	16 (11–26)	10 (4–18)	6.5 (2–13)	SMD = 0.88	SMD = 0.29
GAD-7 Score	3 (2–6)	2 (1–5.8)	1 (0–3)	SMD = 0.92	SMD = 0.78
Blood, mL	450 (400–500)	500 (400–545)	450 (400–500)	SMD=-0.07	SMD = 0.34
Operation duration, min	35 (30–45)	36.5 (30–42.8)	37 (33–42)	SMD = 0.04	SMD=-0.13
Pain VAS of prior CD	4.9 (4.2–6.9)	4.4 (2.8–5)	4.3 (2.4–4.9)	SMD = 0.76	SMD = 0.1
Expected Pain VAS of the current CD	4.4 (3.3–4.9)	4.5 (4.2–4.8)	4.5 (4–4.8)	SMD=-0.12	SMD = 0.07
Education (Higher)	5 (13.5%)	3 (10%)	35 (12.1%)	RD = 0.01	RD=-0.02
Incision type (Longitudinal incision)	10 (27%)	8 (26.7%)	57 (19.7%)	RD = 0.07	RD = 0.07
Anxiety (GAD-7 ≥ 5)	14 (37.8%)	10 (33.3%)	32 (11%)	RD = 0.27	RD = 0.22
Pain history (With pain during pregnancy)	24 (64.9%)	23 (76.7%)	143 (49.3%)	RD = 0.16	RD = 0.27

Data are presented as median (IQR) for continuous variables and n (%) for categorical variables. Effect sizes comparing Class 1 vs Class 3 and Class 2 vs Class 3 are expressed as standardized mean differences (SMD) for continuous variables (Cohen's d, pooled SD) and risk differences (RD) for categorical variables (proportion in smaller class minus proportion in Class 3). SMD ≥ 0.20 or RD ≥ 0.10 were considered potentially clinically meaningful. Given the small sample sizes in Class 1 (n = 37) and Class 2 (n = 30), formal P values are not reported. *IQR* interquartile range, *SMD* standardized mean difference, *RD* risk difference, *FPQ* Fear of Pain Questionnaire-III, *PCS* Pain Catastrophizing Scale, *GAD-7* Generalized Anxiety Disorder Scale-7, *VAS* Visual Analogue Scale, *CD* cesarean delivery

Sensitivity outcome

To assess the robustness of our findings to missing data assumptions, we performed a sensitivity analysis using complete-case analysis, which yielded similar significance variables and predictive capability of predicted the model (AUC 0.654, 95% CI: 0.587–0.722), supporting the validity of the primary multiple imputation results (Table 7, Fig. 7). In addition, in the multivariable logistic regression fitted to the imputed dataset, forcing indices at the threshold of statistical significance (pain history and expected pain score) into the model produced predictive performance (AUC 0.647, 95% CI: 0.581–0.714), and closely matched that of the model containing only the two statistically significant predictors, indicating that the primary analysis model based on significant predictors is robust (Fig. S1 in Additional Files). Finally, PCS was defined as pain catastrophizing (diagnosed by PCS $\geq$ 30), and FPQ-III was represented by its three subdimensions, which were entered as independent variables into the LASSO selection pool. The result showed in Table S2 (Additional Files), finding the similar two significant predictors (Anxiety, adjusted OR 2.043, 95% CI 1.05–3.974, $P = 0.036$) and (Average pain score at POD 1, adjusted OR 1.566, 95% CI 1.092–2.248, $P = 0.015$).

Table 7
Multivariate logistic regression analysis for factors associated with persistent pain at 90 days following repeated CD (CCA, N = 333)

Variables	aOR [†] (95% CI)	P - value
Blood loss (per mL)	1.002 (1–1.004)	0.0527
Anxiety (yes vs. no)	2.532 (1.306–4.909)	0.0059
Expected pain score (per 1 sore)	1.293 (0.972–1.721)	0.0776
Uterine contraction pain at POD1 (per 1 score)	1.183 (1.02–1.372)	0.0263

CD cesarean delivery, CCA complete case analysis, aOR adjusted odds ratio, CI confidence interval, POD postoperative day

[†]Adjusted for all variables in the multivariable model (selected by LASSO regression).

Discussion

The cohort showed that on postoperative day 1 after repeated cesarean delivery, the median pain score was 4, with moderate-to-severe pain in 51.8% of parturients. Pain then declined over time; by postoperative day 90 the overall persistent pain rate was 25.9%, including 5.9% with moderate-to-severe pain and 15.4% with incision-specific pain. This is essentially consistent with the incidence of persistent pain at 3 months after cesarean delivery reported in the meta-analysis [2, 3]. During follow-up, we recorded pain not only at the incision but also in the lower back and pelvis. Chronic pelvic pain is one of the predominant forms of persistent pain following cesarean delivery and low back pain is partly

associated with the recovery process [12]. Thus, persistent pain following cesarean section manifests in a wider array of clinical presentations and may arise from more complex mechanisms.

Because the final dataset included only 87 patients experiencing pain at 90 days postoperatively, fewer than the threshold required to support regression analysis with 10 predictors, we developed and internally validated a predictive model for persistent pain at 90 days follow repeated CD using a combined LASSO-logistic regression approach. The LASSO regression was employed for its ability to handle potential multicollinearity among the 19 candidate predictors and to prevent model overfitting [13]. Using 10-fold cross-validation, the optimal penalty parameter was selected as $\lambda_{\min}$ (0.02888), yielding a parsimonious model. From the original 19 variables, 7 with nonzero coefficients were retained. Through multivariable logistic regression analysis, the final model included two significant predictors (anxiety and uterine contraction pain at POD 1), showing a moderate discrimination (AUC = 0.638). The optimal probability threshold for classifying patients as high-risk was determined by maximizing the Youden index. The calculated cut-off was 0.231, which yielded a sensitivity of 77.2% and a specificity of only 40%. These findings suggested that while the model may serve as a useful screening tool in clinical practice, its utility for individual risk prediction is limited. Future studies incorporating additional biomarkers or patient-reported outcomes are warranted to enhance the model's sensitivity.

The final model identified two independent predictors for persistent pain at day 90 following repeated CD, including anxiety (Adjusted OR = 2.933, 95% CI: 1.550–5.549, $P = 0.001$) and higher uterine contraction pain at POD1 (Adjusted OR = 1.176, 95% CI: 1.015–1.361, $P = 0.03$). Anxiety is the strongest independent risk factor, indicating parturient with prenatal anxiety have almost a threefold increased risk of experiencing persistent pain at 90 days compared with those without anxiety. These findings are consistent with majority of other studies, which indicated that preoperative anxiety not only exacerbated acute postoperative pain but may also promote the chronification of postoperative pain via its effect on acute pain [7]. Preoperative anxiety was reported as an independent risk factor for moderate-to-severe pain within the first 24 postoperative hours (Adjusted OR: 2.849, 95% CI: 1.276–6.359), even after adjusting for confounders [14]. A brief screening tool that includes anxiety assessment could also predict postoperative opioid consumption [15]. The high-anxiety group required significantly more morphine-equivalent doses than the low-anxiety group ($P = 0.001$), suggesting that anxiety impacts both subjective pain levels and objective analgesic needs. Postoperative acute pain, a strong predictor of chronic pain, was confirmed in our analysis: each 1-point increase in the day-1 pain score corresponded to a 17.6% higher risk of persistent pain at 90 days. We divided day-1 pain into resting pain, movement-evoked pain, and contraction pain, and entered these variables into LASSO and multivariable logistic regression models. Only higher contraction pain remained independently associated with increased risk of persistent pain, a finding that contrasts with reports identifying movement-evoked pain as the key predictor ($P = 0.023$) [16]. This relationship supports the hypothesis that intense acute nociceptive input in the immediate postoperative period triggers central sensitization, contributing to the transition from acute to chronic pain. Consequently, aggressive multimodal analgesic strategies should be prioritized during the first 24 hours after surgery.

Interestingly, two variables approached but did not meet the conventional significance threshold of 0.05: pain history during pregnancy (Adjusted OR 1.63, $P = 0.07$) and expected pain score (Adjusted OR 1.31, $P = 0.06$). These associations should be interpreted cautiously, as the limited sample size likely reduced power, but the odds ratios indicate potentially meaningful clinical effects. The presence of chronic pain in other body regions preoperatively (e.g., low back pain, pelvic girdle pain) reflected a preexisting state of central sensitization and constitutes a risk factor for persistent postoperative pain [3]. While high expected pain scores were significantly positively correlated with acute postoperative pain intensity, representing an amplification of perception driven by psychological expectation [17]. In contrast, age and time since prior CD were not retained as significant predictors. In the sensitivity analysis, we forced pain history and expected pain score into the multivariable logistic regression model. The four-variable model showed similar predictive performance to the two-variable model (AUC 0.647 versus 0.638). These findings collectively indicate that anxiety and uterine pain on day 1 are independent and significant predictors in the cohort undergoing repeat cesarean delivery.

Notably, variables such as fear of pain (FOP) and pain catastrophizing, which have been previously reported as significant risk factors for post-surgery pain [14, 18, 19], were not selected in our model. Fear of pain is especially common among surgical patients, which can lead to pain catastrophizing, avoidance behavior, and functional disability [20]. The FPQ-III has been widely used to assess pain-related fear and anxiety in both healthy and clinical populations with acute or persistent pain [21, 22]. It includes three domains of fear and anxiety associated with pain: fear of severe pain, fear of minor pain, and fear of medical pain. Findings indicate that greater fear of severe pain and lower fear of medical pain are associated with longer pain duration and more frequent pain episodes. This likely reflects our use of only total questionnaire scores for FPQ-III and pain catastrophizing, despite these instruments having distinct subdimensions or clinically meaningful cutoffs. As a result, our approach probably underestimates their predictive value in groups with high pain-related fear or pronounced catastrophizing. In addition, the relatively low prevalence of these factors (such as prevalence of pain catastrophizing, PCS 30 or higher, $n = 22$ (6.2%)) in our study population or their strong correlation with other selected variables. Further sensitive analysis, we decomposed the FPQ-III into three dimensions and defined PCS as pain catastrophizing using a cutoff value, then reintroduced into LASSO regression for variable selection. Although the set of variables selected by LASSO changed, the subsequent multivariable regression identified a largely similar group of significant predictors (anxiety and high pain score at day 1). Therefore, these findings indicate that in our repeat cesarean delivery cohort, prenatal anxiety and acute pain at day 1 exhibited more prominent and independent roles in predicting persistent postoperative pain, whereas pain-related fear and pain catastrophizing did not demonstrate significant predictive value.

We then performed an exploratory analysis using latent class mixed models (LCMM) to identify subgroups of patients with distinct pain trajectories [23, 24]. This approach allowed us to characterize individual heterogeneity in postoperative pain recovery after repeated cesarean delivery and to detect patient groups with persistently adverse pain recovery patterns. Three distinct pain trajectories were identified in our cohort by LCMM provide important insights into the heterogeneous recovery patterns

following repeat cesarean delivery. Most women (81.2%) belonged to the low-pain class, indicating that most patients experience minimal postoperative discomfort and recover uneventfully. This finding is reassuring and may help clinicians identify low-risk patients who require less intensive follow-up. However, nearly one in five women (18.8%) followed a less favorable course—either experiencing a delayed decline from severe pain (Class 1, 10.4%) or exhibiting persistent moderate pain without improvement (Class 2, 8.4%). These subgroups may benefit from targeted interventions, such as enhanced pain management protocols or psychosocial support, particularly given that Class 2's flat trajectory suggests a potential risk of chronic pain development.

The baseline characteristics of the three trajectory classes revealed several clinically meaningful patterns. Notably, the two subgroups with unfavorable pain courses—Class 1 (gradual decline) and Class 2 (persistent moderate pain)—consistently exhibited higher scores on psychological measures, particularly anxiety (GAD-7) and pain catastrophizing (PCS), compared with the low-pain Class 3. The effect sizes for these psychological variables were among the largest observed (SMD up to 0.92 for GAD-7 and 0.88 for PCS in Class 1), suggesting that preoperative psychological distress may play a substantial role in shaping postoperative pain trajectories. This finding aligns with a growing body of evidence linking anxiety and pain catastrophizing to poorer surgical outcomes and supports the integration of psychological screening into preoperative risk assessment. The distinct profiles between Class 1 and Class 2 also warrant attention. Class 1, characterized by a gradual decline from moderate-to-severe pain, had higher PCS scores (SMD = 0.88) and higher prior cesarean pain (SMD = 0.76), suggesting that this subgroup may be particularly sensitive to pain-related fear and prior painful experiences. In contrast, Class 2, which showed a persistently moderate pain trajectory without improvement, was distinguished by the highest proportion of pain during pregnancy (76.7%) and greater intraoperative blood loss (SMD = 0.34), while its PCS scores were notably lower than Class 1. This suggests that the mechanisms underlying persistent moderate pain may be more closely tied to ongoing nociceptive input (e.g., pre-existing pain, surgical trauma) rather than psychological amplification. However, given the small sizes of these subgroups ($n = 37$ and $n = 30$), these observations are hypothesis-generating and require confirmation in larger cohorts.

Limitations

There are some limitations in this study should be acknowledged. First, multiple imputation was used to handle missing data, which is a strength as it reduces bias compared to complete-case analysis. However, our findings are contingent on the assumption that data are missing at random. If missingness was related to unobserved factors (MNAR), our estimates could be biased. While we included key predictors in the imputation model to make the MAR assumption more plausible, this limitation should be considered when interpreting the results. Second, the modest AUC of 0.638 suggests that while our two-variable model outperforms random chance, its discriminative ability is insufficient for standalone clinical decision-making. This is likely attributable to the complexity of postoperative pain, which involves multifactorial biological and psychosocial pathways not fully captured by our selected variables. Third, the relatively small class sizes ($n = 37$ and $n = 30$) limited our ability to compute stable confidence bands

around the trajectory estimates. Consequently, our trajectory findings should be interpreted as descriptive and exploratory, and external validation in larger cohorts is warranted to confirm the stability of these subclasses.

Conclusions

In this study, roughly 25% of women experienced postoperative pain of various causes within 90 days following repeated CD. Prenatal anxiety and greater visceral pain on postoperative day 1 are linked to a higher probability of experiencing persistent pain at the 90-day, albeit with limited predictive accuracy. Through exploratory trajectory analysis, a subgroup with elevated risk either exhibit a slow recovery pattern or continue to endure persistent pain. Due to parturient with prenatal anxiety are more susceptible to experiencing slower postoperative pain recovery and developing persistent postoperative pain, may warrant more attention. Further multi-center studies are needed to explore better interventions, such as emotional reassurance or multimodal analgesia, in anxious parturient when undergoing repeated CD.

Abbreviations

CD Cesarean delivery

LASSO Least Absolute Shrinkage and Selection Operator

LCMM Latent Class Mixed Models

POD Postoperative day

CPSP Chronic postsurgical pain

GRADE Grading of Recommendations, Assessment, Development, and Evaluations

FPQ-III Fear of pain questionnaire-III

PCS Pain catastrophizing scale

GAD-7 Generalized anxiety disorder-7

CSEA Combined spinal-epidural anesthesia

VAS Visual analog scale

NRS Numeric rating scale

PCIA Patient-controlled intravenous analgesia

IASP International Association for the Study of Pain

ROC Receiver operating characteristic

AUC Area under curve

BIC Bayesian information criterion

AIC Akaike information criterion

VIF Variance inflation factors

AvePP Average posterior probabilities

EPV Events per variable

MICE Multiple imputations by chained equations

SMD Standardized mean differences

RD Risk differences

CCA Complete case analysis

BMI body mass index

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Women's Hospital of Nanjing Medical University (2022KY-015-01) and registered at www.chictr.org.cn (ChiCTR2200059487; 02/05/2022). Informed consent was obtained from all participants.

Consent for publication

Not applicable.

Availability of data and materials

The original data of this study are not publicly available to date for some institutional policy. *But data are available from the corresponding authors on reasonable request.*

Funding

Not applicable.

Acknowledgements

We would like to thank all personnel who participated and supported this project, including all our staff, participants

Authors' contributions

Caijuan Li and Zhiqiang Zhou conceived the study; Caijuan Li wrote the manuscript; Caijuan Li and Minhui Wu analyzed the data; Minhui Wu and Mao Mao conducted the investigation; Fan Xia helped to collect the data; Shanwu Feng checked the data analysis; Shanwu Feng and Zhiqiang Zhou revised the manuscript. All authors reviewed the manuscript.

Declarations of interests

The authors report no conflicts of interest to this manuscript.

Disclosure

Sentence polishing was assisted by ChatGPT (OpenAI, GPT-5.5). After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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Figures

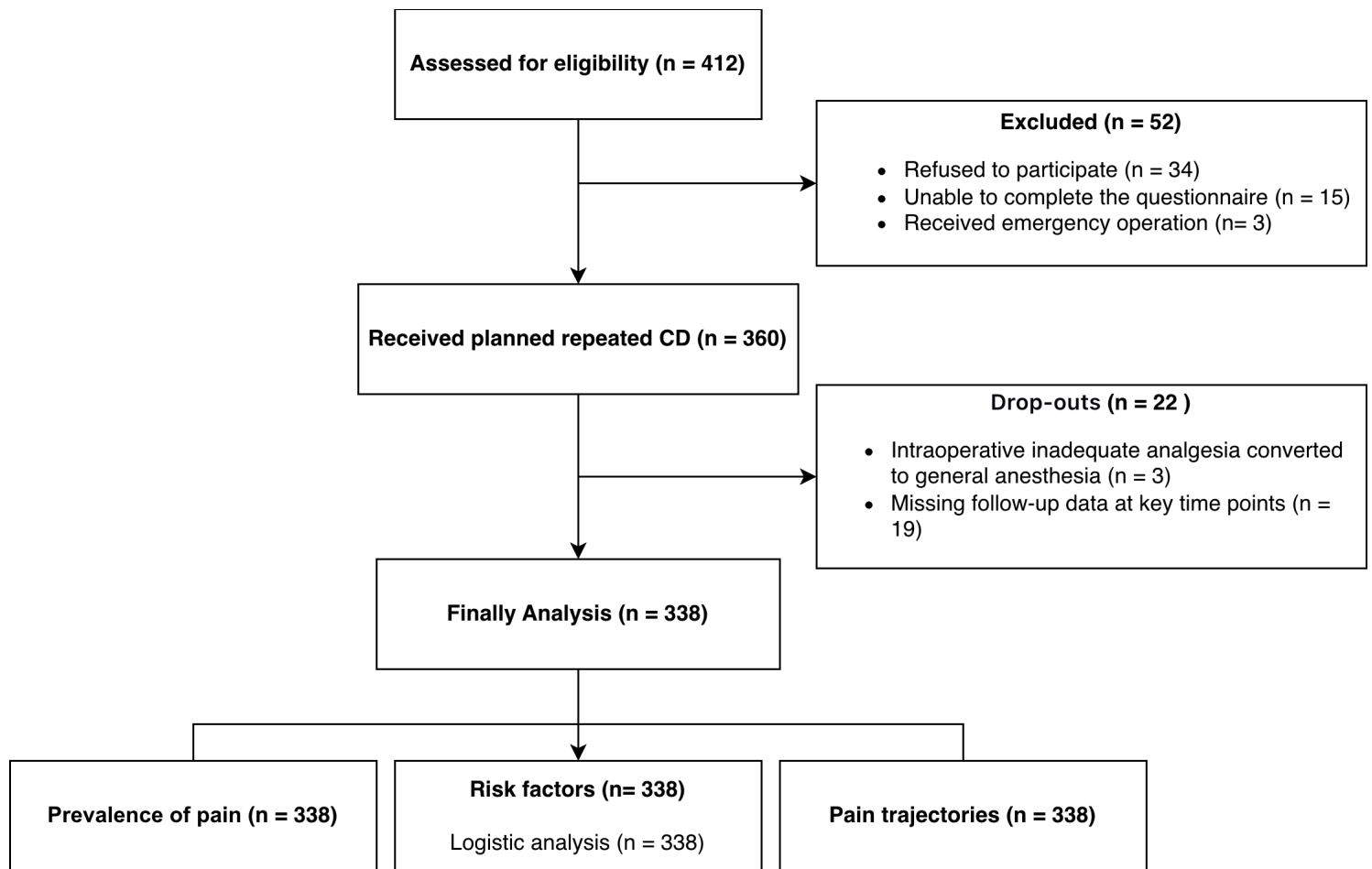


Figure 1

Flowchart of the study. CD cesarean delivery, LCMM Latent Class Mixed Model

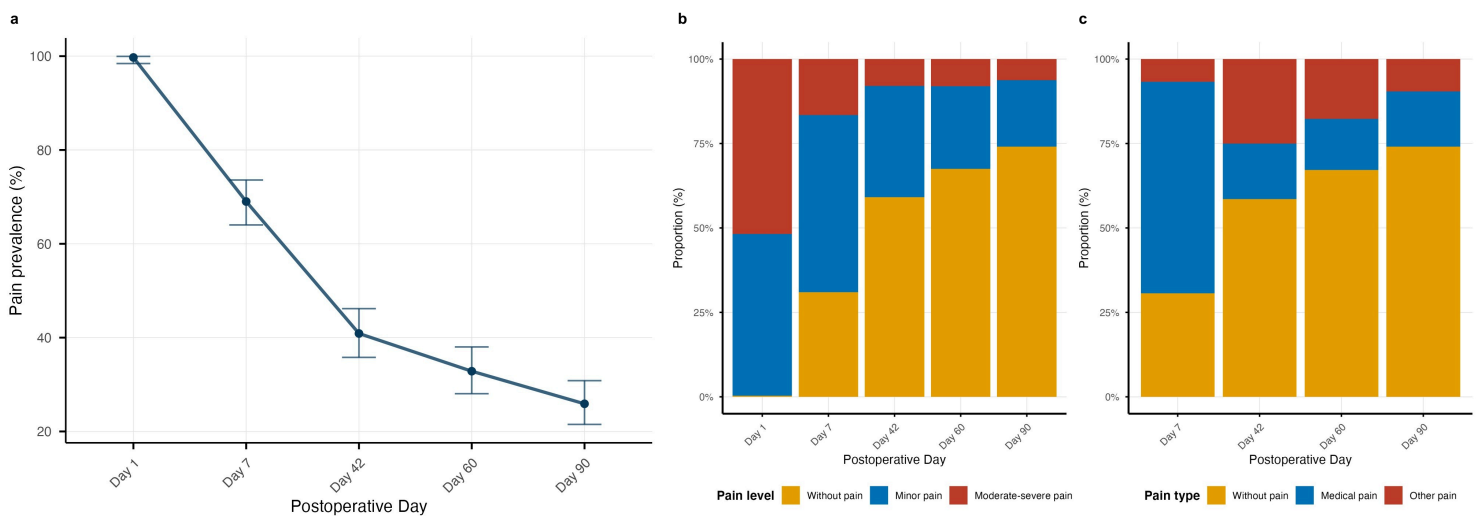


Figure 2

Prevalence and distribution of pain following repeated CD. a. Prevalence of all-cause pain within 90 days following repeated cesarean delivery. b. Distribution characteristics of pain severity at each follow-

up time point. c. Distribution characteristics of pain types at each follow-up time point. CD cesarean delivery

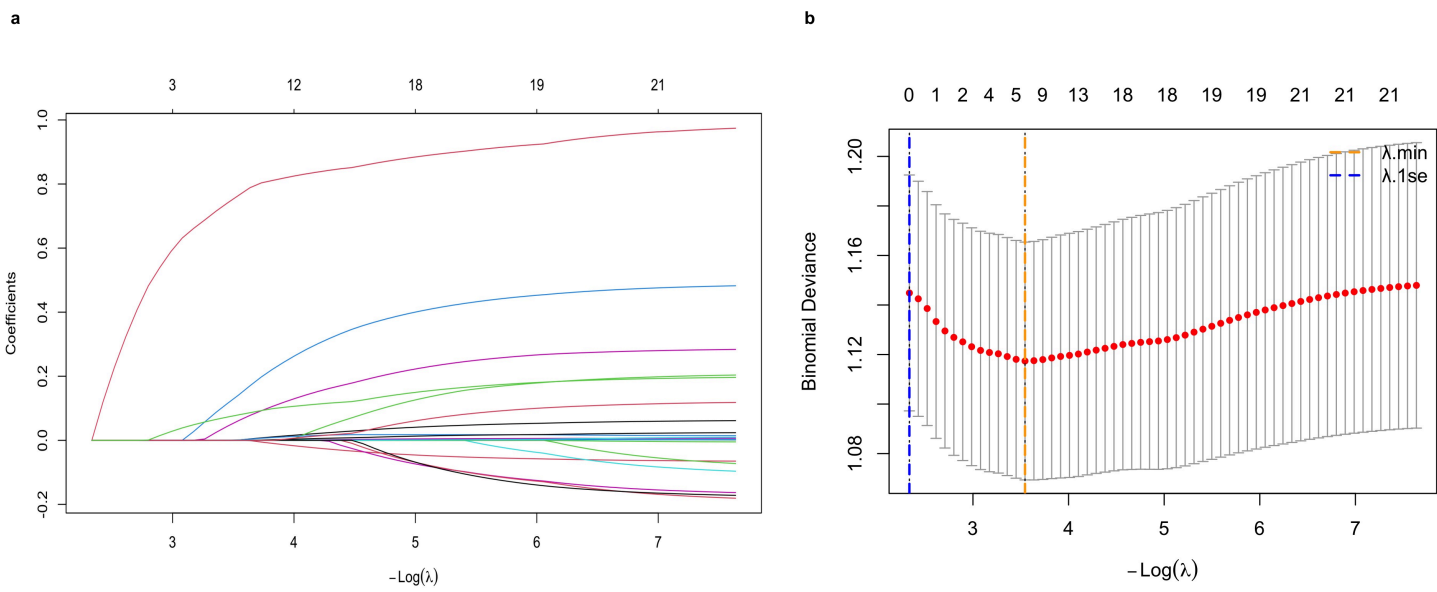


Figure 3
Coefficient path plot and cross-validation plot for LASSO regression. a. coefficient path plot. b. cross-validation plot. The orange dashed line denotes lambda.min (0.02888), and the blue dashed line denotes lambda.1se (0.09681).

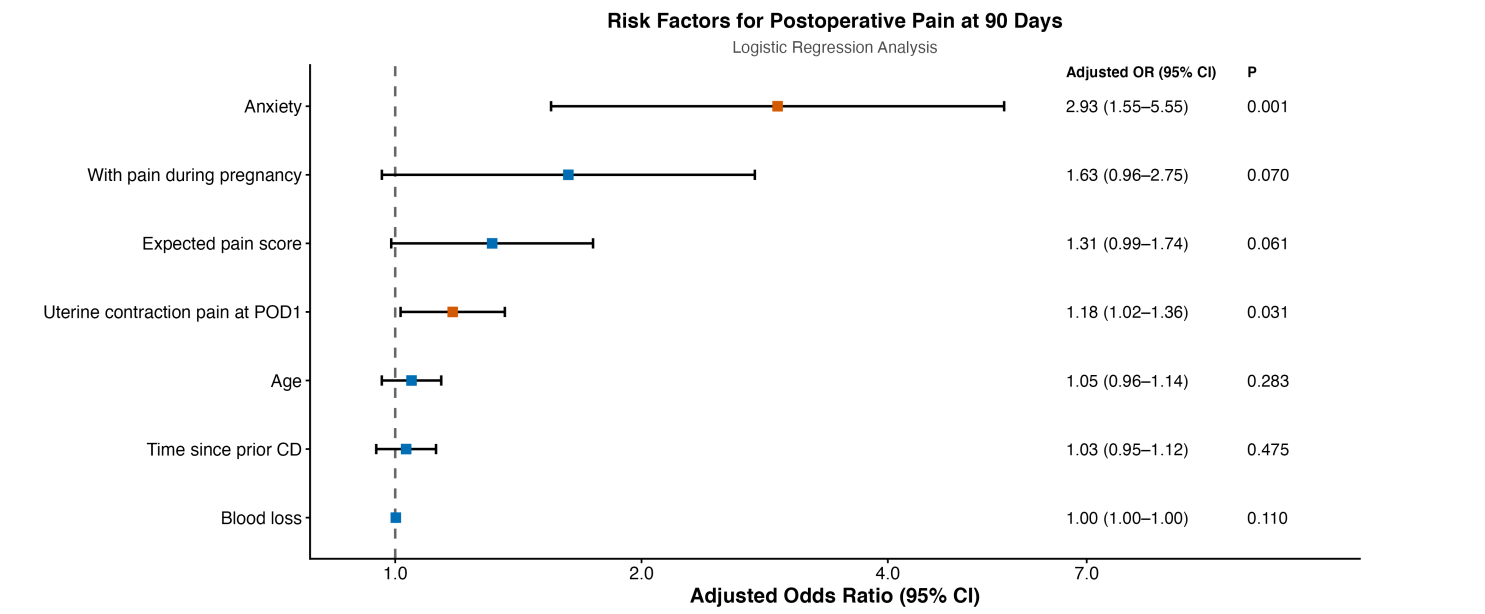


Figure 4
Forest plot of multivariable logistic regression analysis for factors associated with persistent pain at 90 days following repeated CD (after multiple imputation). Red dots represent adjusted ORs for factors

with statistical significance, while blue dots represent adjusted ORs for factors without statistical significance. *CD* cesarean delivery, *aOR* adjusted odds ratio, *CI* confidence interval, *POD* postoperative day

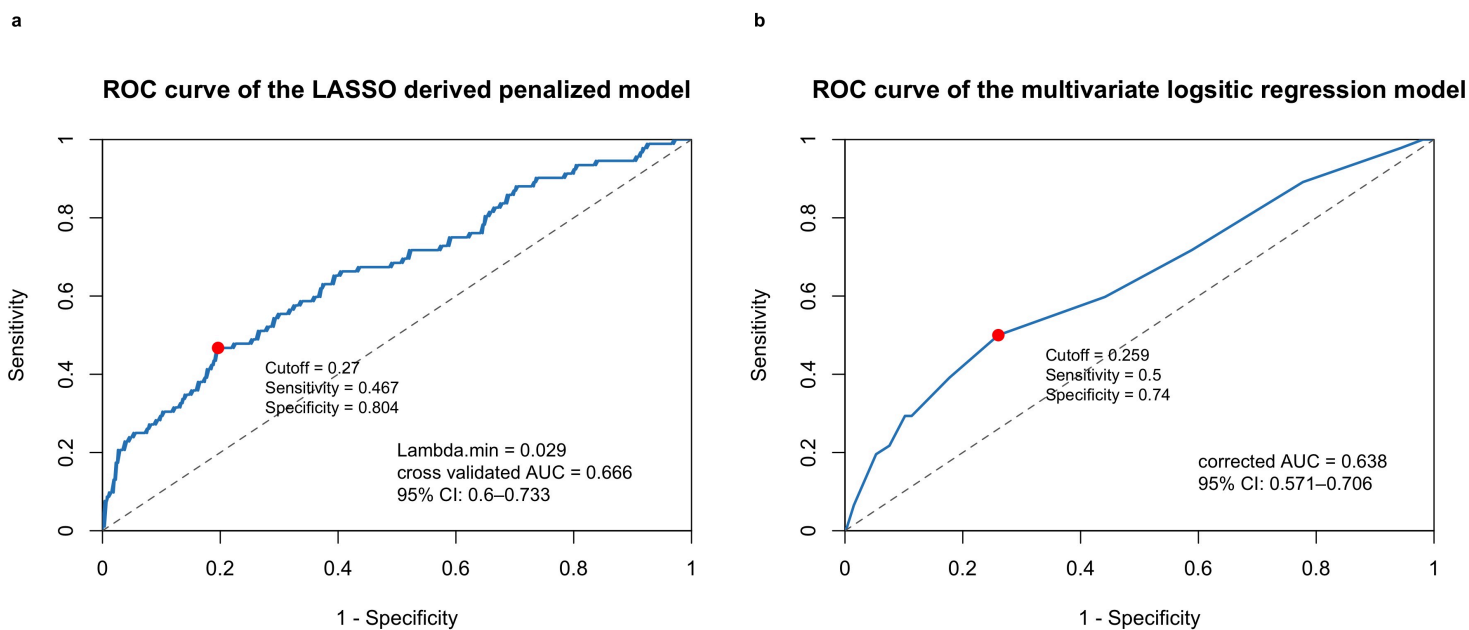


Figure 5

Receiver operating characteristic (ROC) curves for predictive models. a. ROC for the LASSO-derived model, b. ROC for the final parsimonious logistic model. AUCs were corrected for optimism using 500 bootstrap resamples. The red dot indicates the model's optimal cutoff value determined by the Youden index. *AUC* Area Under Curve, *CI* Confidence Interval

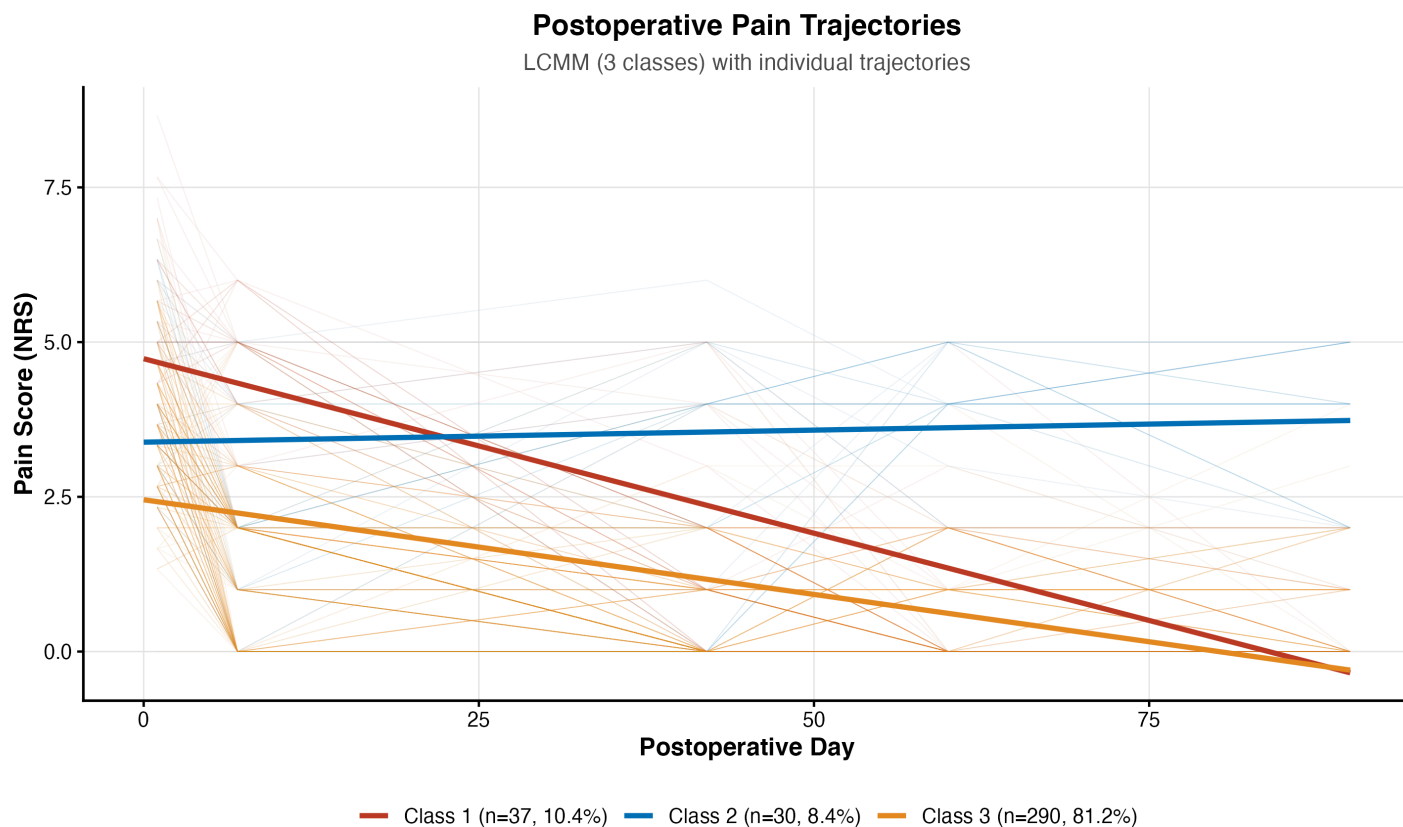


Figure 6

Postoperative pain trajectories during the 90-day follow-up period after repeated cesarean delivery

Individual patient trajectories are shown as thin colored lines; class-specific mean trajectories are shown as colored bold lines: Class 1 (n=37, 10.4%, blue, moderate-to-severe pain with gradual decline), Class 2 (n=30, 8.4%, red, persistently moderate pain), and Class 3 (n=290, 81.2%, orange, consistently low pain). Confidence intervals are omitted due to the small class sizes in the two non-dominant classes, which would yield imprecise interval estimates. *NRS* Numeric Rating Scale (NRS, 0–10).

ROC curve of multivariate logistic regression model (CCA)

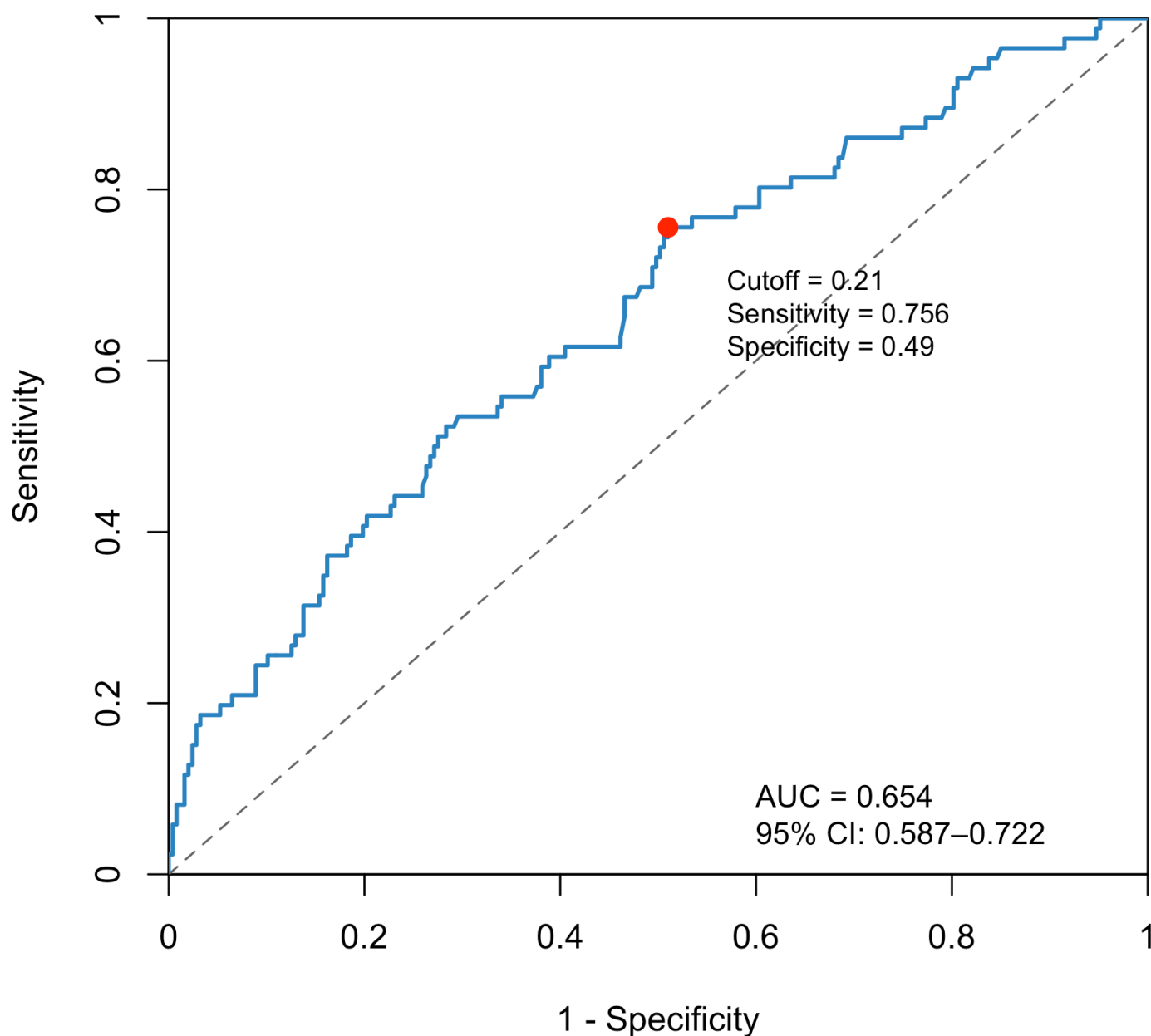


Figure 7

Receiver operating characteristic (ROC) curves for predictive models (CCA). AUCs were corrected for optimism using 500 bootstrap resamples. The red dot indicates the model's optimal cutoff value determined by the Youden index. CCA complete case analysis, *AUC* Area Under Curve, *CI* Confidence Interval

Supplementary Files

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