

Development and Validation of a Nomogram for the Failed Conversion of Labor Analgesia to Cesarean Section Anesthesia

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Purpose: The conversion of epidural labor analgesia (ELA) to epidural surgical anesthesia (ESA) for intrapartum cesarean section (CS) often encounters failures. This study aimed to develop a nomogram for predicting the failure rate of this conversion.

Patients and Methods: A retrospective analysis was conducted on data from the Fujian Maternity and Child Health Hospital. Pregnant women (n=214) who underwent cesarean section after receiving labor analgesia. We performed correlation heat map and Lasso regression in terms of exclusion confounding factors and screening independent variables. A nomogram was developed to predict the occurrence.

Results: The developed nomogram incorporated variables such as pregnant history, weight, premature rupture of membranes (PROM), dural puncture epidural (DPE), anesthesiologist level of cesarean section (ALOCs), and Anesthesiologist level of labor analgesia (ALOLA). The model demonstrated good predictive performance, providing a practical tool for assessing the risk of failure in converting labor analgesia to cesarean section anesthesia.

Conclusion: The nomogram can aid anesthesiologists in making informed decisions and optimizing patient care. By utilizing the nomogram, clinicians can estimate the probability of conversion failure based on individual patient characteristics and clinical factors.

Keywords: labor analgesia, cesarean section anesthesia, conversion failure, nomogram, predictive model

Introduction

Labor analgesia, predominantly administered via epidural anesthesia, is instrumental in alleviating pain during childbirth.¹ Nevertheless, there are instances where a cesarean section (CS) becomes imperative, requiring a seamless transition from labor analgesia to CS anesthesia. Regrettably, this conversion is not always successful, posing challenges for anesthesiologists and potentially affecting the quality of patient care.^{2,3} A study by Yoon et al highlighted that the conversion of epidural labor analgesia (ELA) to epidural surgical anesthesia (ESA) for intrapartum CS often encounters failures, emphasizing the need for alternative approaches to ensure pain-free surgery during CS.⁴

To effectively address the challenges associated with the conversion from labor analgesia to CS anesthesia, it's imperative to comprehend the factors that contribute to its failure rate. Recognizing and quantifying these determinants enable healthcare professionals to devise strategies that enhance outcomes and elevate the standard of patient care. This article endeavors to introduce the formulation of a nomogram tailored to forecast the failure rate associated with the transition from labor analgesia to CS anesthesia. A study by Yoon et al underscores the complexities involved in such conversions,⁴ emphasizing the importance of understanding the underlying factors to ensure pain-free surgery during intrapartum CS.

Several studies have explored the challenges and risk factors associated with failed conversion, providing valuable insights into this complex clinical scenario. In a national survey conducted by Desai et al, the authors highlighted the

absence of best practice guidelines for the optimal management of failed epidural top-ups during CS anesthesia conversion.⁵ Another systematic review and meta-analysis conducted by Bauer et al identified seven risk factors associated with failed conversion, providing evidence-based insights into this issue.⁶

Furthermore, studies have investigated the association between specific conditions and failed conversion. For instance, a retrospective cohort study by Katakura et al examined the association between clinically diagnosed chorioamnionitis and failed conversion from labor analgesia to CS anesthesia.⁷ Elghamry et al proven that adding magnesium sulfate (MgSO_4) with levobupivacaine to speed up the conversion of labor epidural analgesia into enough anesthesia for emergency CS.⁸ Their findings shed light on the potential impact of factors on the success of the conversion process.

Nomogram has gained popularity in cancer prognosis due to their effectiveness in simplifying complex statistical models into a single numerical value.⁹ This value represents the likelihood of a specific event, like death or recurrence, and is customized to each patient's unique profile.¹⁰ In this work, we used nomogram to predict the incidence of transition from labor analgesia to cesarean section (CS) anesthesia failing. The aim of this study is to expand upon the current body of knowledge by introducing a nomogram that amalgamates various risk determinants and conditions to forecast the failure rate associated with the transition from labor analgesia to CS anesthesia. This predictive tool holds significant potential for healthcare practitioners, furnishing them with the capability to evaluate the probability of a successful conversion and thereby facilitating informed decision-making in patient management. Grizhimalsky et al's (2021) research is cited to illustrate the complexity of these conversions, underscoring the need to consider the numerous elements that can impact the outcomes.¹¹

By addressing the challenges associated with failed conversion and providing a predictive tool like the nomogram, healthcare providers can potentially reduce the incidence of failed conversions, improve patient outcomes, and enhance the overall quality of obstetric anesthesia care. Ultimately, the development and implementation of this nomogram will contribute to evidence-based decision-making and personalized care for parturient requiring labor analgesia and subsequent CS anesthesia.

Materials and Methods

Study Design and Data Collection

The present study employed a retrospective cohort design conducted in the Fujian Maternity and Child Health Hospital. The study population consisted of women who underwent delivery between July 1, 2022, and March 31, 2023, resulting in a total dataset of 3409 cases. After inclusion and exclusion criteria, the final sample size included 214 patients.

Statistical Analysis and Clinical Characters

To establish the clinical characteristics, the study population was divided into two distinct groups: Failed conversion group and success conversion group. The "CBCgrps" package in the R programming environment was utilized to compare the clinical characteristics between these two groups.¹² This package facilitated the analysis and comparison of relevant variables, enabling a comprehensive understanding of the differences and similarities in clinical characteristics exhibited by the failed conversion group and success conversion group.

Univariate Analysis

In this study, the pROC package in R was utilized to conduct the ROC curve analysis and calculate the AUC.¹³ Receiver operating characteristic (ROC) curve analysis was performed to assess the discriminative ability and predictive performance of each factor under investigation. The pROC package provides a set of functions specifically designed for ROC analysis, including the ability to plot ROC curves, calculate AUC values, and compare the performance of multiple factors or models. This allowed for a comprehensive evaluation of the predictive ability of each factor in relation to the outcome of interest.

Collinearity Analysis

The correlation heat map was generated using the “corrplot” package in R. This package provides a range of functions and visualization tools specifically designed for correlation analysis. The correlation coefficients between variables were calculated, and the resulting matrix was represented graphically as a heat map. Collinearity among variables was assessed through a correlation heat map to identify any potential high correlations.

Machine Learning and Variable Selection

Machine learning techniques, specifically Lasso regression, were employed using the “glmnet” package in the R programming environment to select relevant candidate factors and identify potential risk factors associated with the outcome of interest.¹⁴ The application of Lasso regression facilitated the identification of potential risk factors by simultaneously estimating the coefficients of the predictors and promoting sparsity in the model.

Multivariate Analysis and Development of Nomogram

The dataset was randomly divided into a training cohort (85%, n=182) and a validation cohort (15%, n=32). Multivariate logistic regression analysis was then performed on the training cohort to determine the independent risk factors associated with the outcome. Using the risk factors identified from the analysis, a nomogram was constructed using the “rms” package in the R programming environment. The nomogram serves as a visual predictive tool, offering a graphical representation of the predictive model based on the identified risk factors.

Model Verification

To verify the accuracy of the nomogram, both internal and external validation methods were employed. This involved evaluating the performance of the nomogram using metrics such as the ROC curve and calibration curve.

Selection Criteria

The exclusion criteria were as follows: multiple pregnancy, gestational age less than 37 weeks, vaginal delivery after ELA, and unintended dural puncture.

Sample Size

The sample size of the study met the recommended criteria stipulated by the Events Per Variable (EPV) criterion, ensuring an adequate number of events in relation to the number of variables ($EPV \geq 10$).¹⁵ The failure rate of epidural labor analgesia was 35%, and seven variables were included in the model. Therefore, the estimated sample size was 200.

Ethical Approval

Prior to commencing the study, ethical approval was obtained from the Fujian Maternity and Child Health Hospital Institutional Review Board (IRB, July 2022, No. 2022YJ039). As per the guidelines of the IRB, patient consent for reviewing medical records was not required for this study. However, all patient data were handled and maintained with strict confidentiality in compliance with the Declaration of Helsinki. Measures taken to ensure confidentiality include de-identification of patient data and restricted access to data. We have registered the study on www.medicalresearch.org.cn.

Results

Clinical Characters

The baseline characteristics of the study population are presented in Table 1. The table includes demographic and clinical variables, stratified by the dependent variable, failed conversion. During the study period, total numbers of deliveries performed in our hospital were 3409, with a conversion rate of 6.3% (214/3409). According to the criteria for failed conversion of labor analgesia to cesarean section anesthesia, 214 pregnant women was divided into two group: success conversion group (n=127), and failed conversion group (n=87).

Table 1 Baseline Characteristics

Characteristics	Levels	Success (N=127)	Failed (N=87)	P
Age	Mean $\pm$ SD	30.05 $\pm$ 3.87	30.60 $\pm$ 3.41	0.285
Pregnancy history	No	92 (72.4%)	54 (62.1%)	0.147
	Yes	35 (27.6%)	33 (37.9%)	
Delivery history	No	116 (91.3%)	76 (87.4%)	0.476
	Yes	11 (8.7%)	11 (12.6%)	
Gestational age	Median (IQR)	39.00 (39.00 to 40.00)	39.00 (39.00 to 40.00)	0.508
Height	Mean $\pm$ SD	158.39 $\pm$ 5.20	159.11 $\pm$ 4.88	0.308
Weight	Median (IQR)	66.00 (60.00 to 71.90)	69.20 (64.00 to 73.00)	0.011*
BMI	Median (IQR)	26.31 (24.65 to 28.86)	27.01 (25.68 to 28.84)	0.044*
Cervical dilation (cm)	0.5	3 (2.4%)	2 (2.3%)	0.985
	1	39 (30.7%)	30 (34.5%)	
	1.5	1 (0.8%)	1 (1.1%)	
	2	74 (58.3%)	49 (56.3%)	
	3	9 (7.1%)	5 (5.7%)	
	4	1 (0.8%)	0 (0%)	
PROM	No	74 (58.3%)	64 (73.6%)	0.031*
	Yes	53 (41.7%)	23 (26.4%)	
Loading dose	Median (IQR)	8.00 (8.00 to 10.00)	8.00 (8.00 to 10.00)	0.976
Time interval	Median (IQR)	50.00 (45.00 to 50.00)	50.00 (45.00 to 50.00)	0.447
DPE	No	60 (47.2%)	58 (66.7%)	0.008*
	Yes	67 (52.8%)	29 (33.3%)	
ALOCS	Resident	61 (48%)	28 (32.2%)	0.002*
	Attending	31 (24.4%)	14 (16.1%)	
	Senior	35 (27.6%)	45 (51.7%)	
ALOLA	Resident	43 (33.9%)	48 (55.2%)	0.006*
	Attending	58 (45.7%)	30 (34.5%)	
	Senior	26 (20.5%)	9 (10.3%)	
ELA duration	Median (IQR)	12.00 (5.50 to 21.00)	14.00 (10.00 to 25.00)	0.016*

Note: * $P < 0.05$, statistical significance.

Abbreviations: PROM, premature rupture of membranes; DPE, dural puncture epidural; ALOCS, anesthesiologist level of cesarean section; and ALOLA, anesthesiologist level of labor analgesia; ELA, epidural labor analgesia.

Notably, the median weight and BMI were significantly higher in the failed conversion group ($P=0.011$ and $P=0.044$, respectively), and premature rupture of membranes (PROM) was more common in the failed conversion group ($P=0.031$). Additionally, the proportion of patients with DPE and Anesthesiologist level of cesarean section (ALOCS) score of seniors were significantly higher in the failed conversion group ($P=0.008$ and $P=0.002$, respectively), while Anesthesiologist level of labor analgesia (ALOLA) score of residents was more common in the non-failed conversion group ($P=0.006$). The ELA duration was also longer in the failed conversion group ($P=0.016$). These findings suggest that certain demographic and clinical factors may be associated with failed conversion and should be considered in clinical decision-making and patient management.

Univariate Analysis

The univariate analysis was conducted to assess the association between individual demographic and clinical variables and the incidence of failed conversion (Figure 1A). The AUC curve histogram shows the ranking of these variables (Figure 1B). In summary, the univariate analysis revealed that variables anemia ($P < 0.001$), labor analgesia ($P < 0.001$), the use of antihypertensive therapy during pregnancy ($P=0.004$), higher white blood cell ($P=0.003$), Mode of delivery ($P=0.045$), Postpartum DBP ($P=0.002$) and the incidence of prolonged third stage of labor ($P < 0.001$) demonstrated borderline or significant associations with preeclampsia, indicating the need for further multivariate analysis to determine their independent effects.

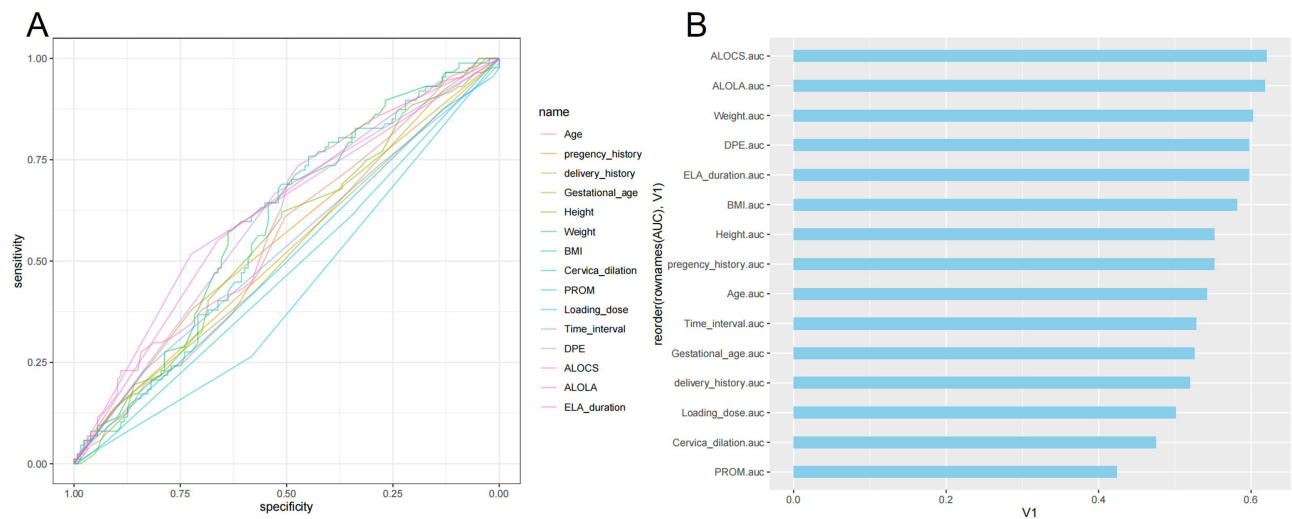


Figure 1 Assessment of demographic and clinical variables in relation to the incidence of failed conversion. **(A)** Univariate analysis displaying the association between individual variables and incidence of failed conversion. **(B)** AUC curve histogram illustrating the ranking of the evaluated variables.

Collinearity Analysis

The collinearity analysis revealed the presence of significant multicollinearity among the independent variables, indicating that caution should be exercised when including these variables in subsequent machine learning analyses to avoid potential biases associated with collinearity (Figure 2).

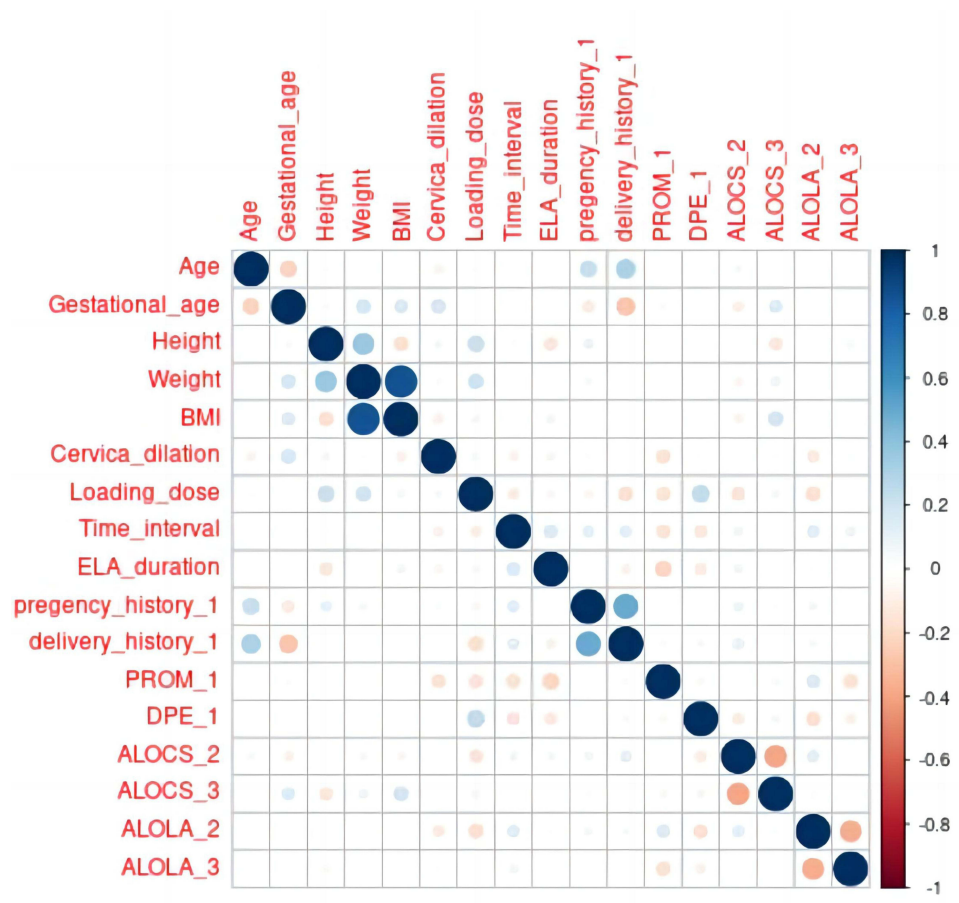


Figure 2 Collinearity analysis of the independent variables. The results highlight the presence of significant multicollinearity, suggesting the need for careful consideration when incorporating these variables into subsequent machine learning analyses to mitigate potential biases arising from collinearity.

Machine Learning and Variable Selection

The Lasso regression technique was utilized to conduct variable selection and identify factors associated with the outcome of interest (Figure 3A). Through Lasso regression, a subset of variables was chosen based on their coefficients being shrunk to zero, indicating their lack of significance in predicting the outcome. The selected variables, characterized by non-zero coefficients, were considered potential risk factors, and subjected to further analysis in the subsequent multivariate analysis. Ultimately, six variables (pregnancy history, weight, PROM, DPE, ALOCS and ALOLA) emerged as candidate signatures that demonstrated potential relevance to the outcome (Figure 3B).

Multivariate Analysis and Development of Nomogram

The multivariate analysis was conducted to investigate the association between various factors and the outcome of interest. After controlling for confounding variables, six candidate signatures were identified as significant predictors (Table 2): pregnancy history (OR: 2.19, 95% CI: 1.10–4.46), Weight (OR: 1.04, 95% CI: 1.182–1.616), Premature rupture of membranes (OR: 0.45, 95% CI: 0.22–0.91), Dural puncture epidural (OR: 0.22, 95% CI: 0.10–0.45), Anesthesiologist level of cesarean section (Attending) (OR: 1.04, 95% CI: 0.42–2.51), Anesthesiologist level of cesarean section (Senior) (OR: 3.74, 95% CI: 1.82–7.99), Anesthesiologist level of labor analgesia (Attending) (OR: 0.27, 95% CI: 0.12–0.56), and Anesthesiologist level of labor analgesia (Senior) (OR: 0.15, 95% CI: 0.05–0.39).

Based on these findings, a nomogram was developed as a visual predictive tool to estimate the probability of the outcome (Figure 4). The nomogram incorporated the six selected variables, allowing for individualized risk assessment and aiding in clinical decision-making. The nomogram provides a user-friendly interface for healthcare professionals to assess the likelihood of the outcome based on the values of these six predictors.

Model Verification

The predictive performance of the developed model was assessed through model verification techniques. The receiver operating characteristic (ROC) curves were plotted to evaluate the discriminative ability of the model (Figure 5). The ROC curves demonstrated favorable predictive performance, as evidenced by the area under the curve (AUC) values of 0.794 for the training dataset and 0.688 for the testing dataset.

Additionally, the calibration curve was constructed to assess the calibration or agreement between the predicted probabilities and the observed outcomes (Figure 6). The calibration curve analysis yielded a C-index of 0.794, indicating

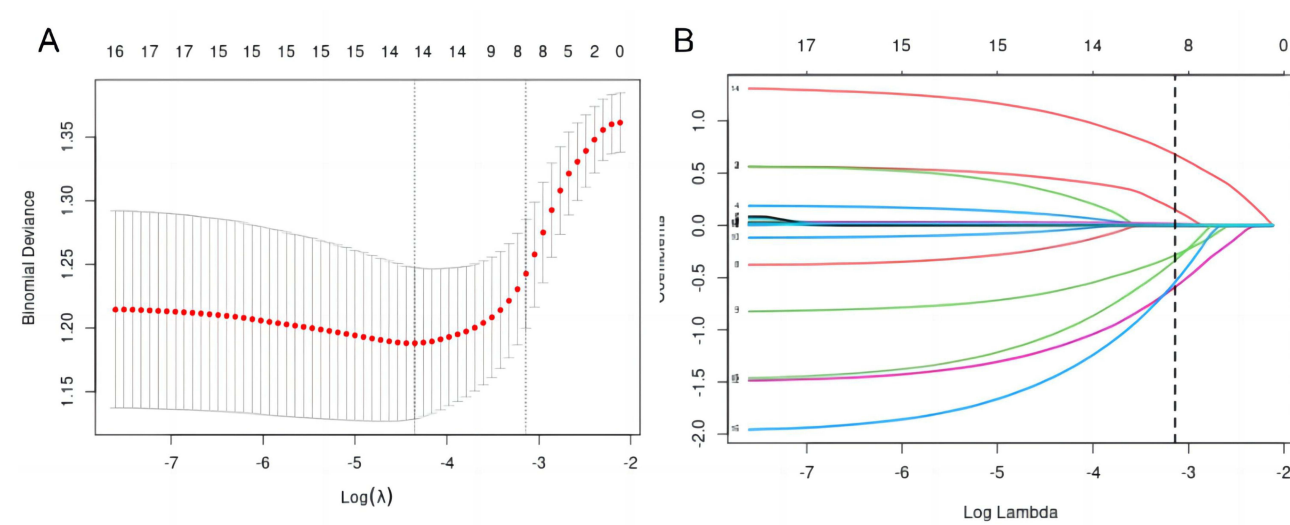


Figure 3 Application of Lasso regression for variable selection in relation to the outcome of interest. **(A)** Lasso regression results highlighting the variables with coefficients shrunk to zero, signifying their insignificance in predicting the outcome. **(B)** The identified subset of seven variables (pregnancy history, weight, PROM, DPE, ALOCS, and ALOLA) with non-zero coefficients, denoting them as potential risk factors that demonstrate relevance to the outcome. These were further evaluated in subsequent multivariate analysis.

Table 2 Logistic Regression with Variable Reduction (Variables Selected by Regularized Regression)

Dependent: Failed Conversion		OR (Univariable)	OR (Multivariable)
Age	Mean (SD)	1.04 (0.97–1.12, $P=0.284$)	–
Pregnancy history	No	–	–
	Yes	1.61 (0.90–2.88, $P=0.111$)	2.19 (1.10–4.46, $P=0.027$)
Delivery history	No	–	–
	Yes	1.53 (0.62–3.74, $P=0.349$)	–
Gestational age	Mean (SD)	1.15 (0.96–1.41, $P=0.155$)	–
Height	Mean (SD)	1.03 (0.97–1.09, $P=0.307$)	–
Weight	Mean (SD)	1.04 (1.01–1.08, $P=0.019$)	1.04 (1.00–1.09, $P=0.041$)
BMI	Mean (SD)	1.10 (1.00–1.21, $P=0.053$)	–
Cervical dilation	Mean (SD)	0.84 (0.53–1.30, $P=0.430$)	–
PROM	No	–	–
	Yes	0.50 (0.27–0.90, $P=0.023$)	0.45 (0.22–0.91, $P=0.028$)
Loading dose	Mean (SD)	0.95 (0.76–1.18, $P=0.629$)	–
Time interval	Mean (SD)	1.02 (0.97–1.07, $P=0.489$)	–
DPE	No	–	–
	Yes	0.45 (0.25–0.78, $P=0.005$)	0.22 (0.10–0.45, $P<0.001$)
ALOCS	Resident	–	–
	Attending	0.98 (0.45–2.11, $P=0.967$)	1.04 (0.42–2.51, $P=0.938$)
	Senior	2.80 (1.50–5.30, $P=0.001$)	3.74 (1.82–7.99, $P<0.001$)
ALOLA	Resident	–	–
	Attending	0.46 (0.25–0.84, $P=0.012$)	0.27 (0.12–0.56, $P=0.001$)
	Senior	0.31 (0.13–0.71, $P=0.008$)	0.15 (0.05–0.39, $P<0.001$)
ELA duration	Mean (SD)	1.03 (1.00–1.05, $P=0.029$)	1.01 (0.99–1.04, $P=0.293$)

Notes: Performance of multivariate model: Number in data frame = 214, Number in model = 214, Missing = 0, AIC = 249.3, C-statistic = 0.788, H&L = Chi-sq (8) 9.48 ($P=0.303$).

Abbreviations: PROM, premature rupture of membranes; DPE, dural puncture epidural; ALOCS, anesthesiologist level of cesarean section; and ALOLA, anesthesiologist level of labor analgesia; ELA, epidural labor analgesia.

a strong concordance between the predicted and observed outcomes. This suggests that the developed model accurately estimates the probabilities of the outcome of interest and provides reliable predictions.

Taken together, the results of the model verification indicate that the developed model performs well in terms of predictive accuracy and calibration, highlighting its potential utility in clinical settings.

Discussion

The current study aimed to develop a nomogram for predicting the failure rate of converting labor analgesia to cesarean section anesthesia. The developed nomogram integrated several key variables, including pregnant history, weight, premature rupture of membranes (PROM), dural puncture epidural (DPE), anesthesiologist level of cesarean section (ALOCS), duration of labor analgesia, and anesthesiologist level of labor analgesia (ALOLA). The results of our study demonstrated that this comprehensive model exhibited a strong predictive performance, offering a valuable tool to assess the risk of failure in the conversion process.

In our research, we identified several key factors influencing the inefficiency of transitioning labor analgesia to cesarean section anesthesia. The inclusion of antenatal history and maternal weight in the nomogram underscores their significance as potential predictors. These variables may represent inherent physiological variations and individual responses to anesthesia, which subsequently have a profound impact on the success of the anesthesia conversion process. A study by Grizhimalsky et al emphasized the importance of adequate epidural analgesia and highlighted patient height as a risk factor for conversion failure, further supporting the intricate relationship between these variables and the efficacy of anesthesia conversion.¹¹

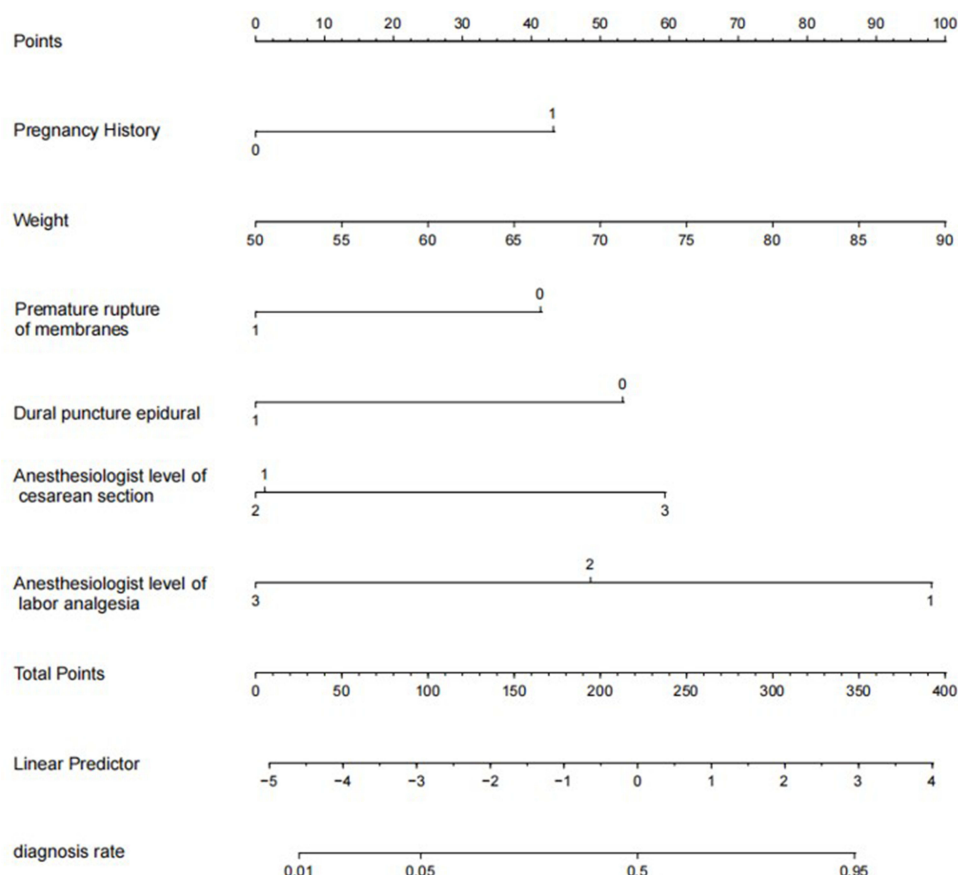


Figure 4 Nomogram representation for predicting the probability of the outcome. This visual tool incorporates the six selected variables, enabling individualized risk assessment to facilitate clinical decision-making. The nomogram offers a user-friendly interface, allowing healthcare professionals to gauge the likelihood of the outcome based on the specific values of the incorporated predictors.

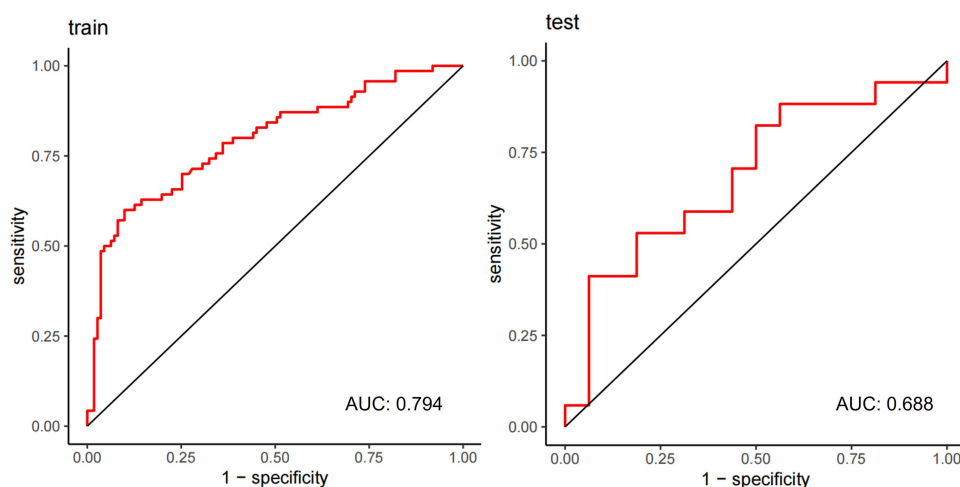


Figure 5 Receiver operating characteristic (ROC) curves evaluating the discriminative ability of the developed model. The ROC curves showcase the model's predictive performance, with AUC values of 0.794 for the training dataset and 0.688 for the testing dataset, indicating a favorable prediction capability of the model across both datasets.

The presence of premature rupture of membranes (PROM) is a pivotal factor in anesthesia management during medical procedures, particularly in obstetrics. This condition, characterized by the early breaking of the amniotic sac, leads to a decrease in amniotic fluid volume, significantly altering the pressure dynamics within the uterus.^{16,17} Such

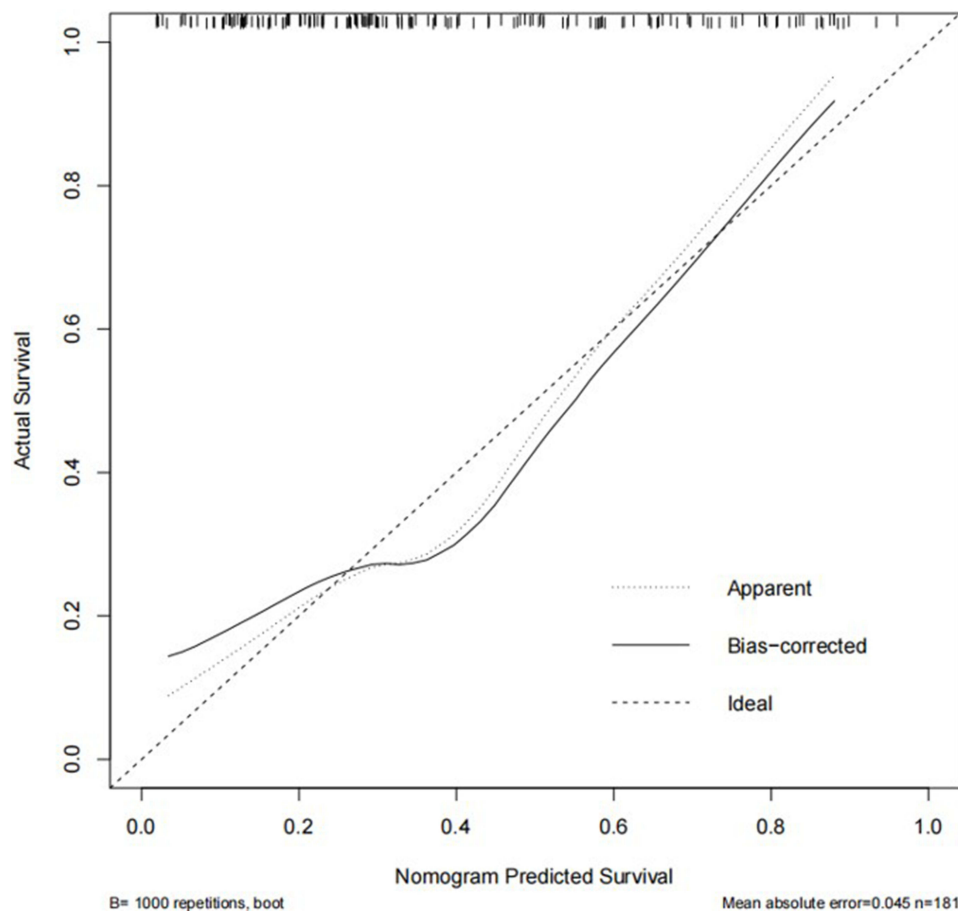


Figure 6 Calibration curve for evaluating the agreement between the model's predicted probabilities and the observed outcomes. The calibration analysis resulted in a C-index of 0.794, signifying a robust concordance between predicted and actual outcomes. This indicates the model's efficacy in accurately estimating the probabilities and ensuring reliable predictions for the outcome of interest.

changes necessitate careful adjustments in anesthesia techniques and dosages to ensure the safety of both mother and fetus.¹⁸ Anesthesiologists, in collaboration with obstetricians and neonatologists, must closely monitor these dynamics and the patient's response to anesthesia, adapting their approach in cases of early delivery or additional complications like infection.¹⁹ Moreover, the psychological impact of PROM on expectant mothers, including increased stress and anxiety, requires healthcare providers to offer reassurance and clear communication about the procedure.²⁰ Overall, managing anesthesia in the context of PROM demands a comprehensive, multidisciplinary approach, ensuring the well-being of both mother and baby during the delivery process.

Interestingly, the involvement of anesthesiologist expertise, as indicated by anesthesiologist level of cesarean section (ALOCs) and Anesthesiologist level of labor analgesia (ALOLA), emerged as influential variables. Similar results were also reported by M.E. Bauer et al, non-obstetric anesthesiologist was one of the risk factors for failed conversion of labor epidural analgesia to cesarean delivery anesthesia.⁶ This finding underscores the importance of the anesthesiologist's skills and experience in these procedures. It suggests that the outcome of such conversions is significantly influenced by the healthcare provider's expertise. Recognizing this, there is a clear need for further investigation into how anesthesiologist training and decision-making can be optimized, especially in complex cases. Enhancing provider education and skills could be a key strategy in improving the success rates of these critical medical procedures, ensuring better outcomes for both mothers and infants during cesarean deliveries.

The duration of labor analgesia and the incidence of dural puncture epidural (DPE) have been incorporated into the nomogram, highlighting the complex relationship between the length of analgesia and potential complications that might emerge during its administration. According to a study by Tan et al, the quality of labor analgesia may be influenced by

the DPE technique, especially in obese parturient, emphasizing the importance of this relationship.²¹ Our research indicates that vigilant observation of the labor analgesia process and timely intervention in instances of DPE can significantly improve the likelihood of successful conversion. In fact, inadequate labor pain relief can all be responsible for failed conversion of LE to surgical anesthesia for CS.²² In conclusion, the findings of our study and others underscore the critical need for careful management of labor analgesia, particularly in the context of DPE. By enhancing the understanding of these relationships and improving monitoring and intervention strategies, anesthesiologist can better navigate the complexities of labor analgesia, thereby increasing the success rate of converting labor epidural to surgical anesthesia for cesarean sections. This approach not only improves the quality of care for the parturient but also ensures safer and more effective anesthesia management during childbirth.²³

The predictive accuracy of the nomogram underscores its potential clinical relevance.^{24–26} By facilitating healthcare professionals to incorporate patient-specific data, the nomogram provides an efficient and objective tool for assessing the likelihood of conversion failure. A study by Wu et al demonstrated the utility of a nomogram in predicting patient outcomes, emphasizing the value of such tools in clinical decision-making.²⁷ This can empower anesthesiologists and medical teams in making evidence-based decisions and anticipating potential obstacles during the conversion phase.

While the constructed nomogram exhibits notable predictive potential, it's essential to acknowledge the limitations inherent in our study. The research was based on a specific cohort, emphasizing the need for external validation across broader and more varied populations to determine its wider applicability. Furthermore, although the model integrates key variables, there might be other factors not yet explored that could influence the failure rate, necessitating comprehensive research. A study by Cai et al highlighted the significance of external validation in assessing the generalizability of a nomogram, emphasizing the importance of such validation in diverse populations.²⁸

Conclusion

In conclusion, our study's results provide a valuable nomogram for predicting the risk of failure in converting labor analgesia to cesarean section anesthesia. This model, incorporating pregnant history, weight, PROM, DPE, ALOCS, and ALOLA, holds promise as a practical clinical tool. Its potential to enhance decision-making and patient safety underscores the importance of ongoing research and validation to refine its accuracy and applicability.

Acknowledgments

We would like to extend our deepest gratitude to the staff and management of the Fujian Maternity and Child Health Hospital for their unwavering support and for granting us access to the invaluable data that made this research possible. We are particularly thankful to the anesthesiologists and medical staff who provided insights and expertise that greatly assisted the research. Our appreciation also goes to the pregnant women who participated in this study, without whom this research would not have been feasible. We are indebted to our colleagues who provided constructive feedback during the various stages of this study, and to those who assisted in the statistical analysis, ensuring the robustness of our findings. Lastly, we would like to thank our families and friends for their continuous encouragement and understanding throughout the duration of this project. Their belief in the significance of our work has been a constant source of motivation.

Disclosure

The authors declare that there are no conflicts of interest regarding the publication of this paper. No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article. All data and materials used in this research are publicly available and are referenced accordingly. The research was conducted with the highest standards of integrity, and all findings and conclusions are drawn from the data without any external influence.

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