

Cerebrospinal Fluid Leakage Combined with Blood Biomarkers Predicts Poor Wound Healing After Posterior Lumbar Spinal Fusion: A Machine Learning Analysis

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Objective: The objective of this study aimed to investigate the risk factors for poor wound healing (PWH) after posterior lumbar spinal fusion. Currently, there is limited research on the application of machine learning in analyzing PWH after spinal surgery. Thus, our primary aim is to using machine learning identify these risk factors and construct a clinical risk prediction model.

Methods: We retrospectively reviewed 2516 patients who underwent posterior lumbar spinal fusion at Guangxi Medical University's Second Affiliated Hospital between August 2021 and August 2023. The data was divided into test and validation groups in a 7:3 ratio. In the test group, logistic regression analysis, support vector machine (SVM), random forest (RF), decision tree (DT), XGboost, Naïve Bayes (NB), k-Nearest Neighbor (KNN), and Multi-Layer Perceptron (MLP) were used to identify specific variables. The top six models from the eight machine learning models with the highest area under curve (AUC) values were selected and used to construct a dynamic nomograms model. Model performance was evaluated using receiver operating characteristic (ROC) and calibration curves. The model's internal performance was then verified in the validation group using ROC and calibration curves.

Results: Data from 2516 patients were collected, with 411 eligible cases selected. By combining logistic regression analysis with six machine learning algorithms, this study identified six predictors associated with PWH: subcutaneous lumbar spine index(SLSI), albumin, postoperative glucose, cerebrospinal fluid leakage(CSFL), neutrophil (NEU), and C-reactive protein(CRP). These predictors were used to develop a prediction model, visually represented through a nomogram. The AUC value in the test group was 0.981, and the C-index of the model was 0.986 (95% CI 0.966–0.995), indicating excellent predictive capability. Calibration curve analysis showed good consistency between nomogram-predicted values and actual measurements.

Conclusion: SLSI, albumin, postoperative glucose, CSFL, NEU and CRP were identified as significant risk factors for PWH after posterior lumbar spinal fusion. The developed prediction model exhibited excellent predictive accuracy and usefulness.

Keywords: poor wound healing, posterior lumbar spinal fusion, machine learning, dynamic prediction model

Introduction

Posterior lumbar spinal fusion stands as a primary surgical intervention for managing lumbar degenerative disease (LDD), exhibiting a stable therapeutic outcome and a low recurrence rate. Nonetheless, the occurrence of poor wound healing (PWH) emerges as a prevalent complication following posterior lumbar spinal fusion, attributed to factors such as extensive trauma and prolonged surgical durations.¹ Studies have indicated that the incidence of PWH subsequent to posterior lumbar spinal fusion approximates 12%, leading to heightened postoperative discomfort, extended bed rest and recovery periods for patients, prolonged hospitalization, and increased treatment expenses.² Various factors contribute to

PWH, encompassing advanced age, diabetes, hypoproteinemia, cerebrospinal fluid leakage (CSFL), and dysregulation of inflammatory markers.^{3–5} Consequently, the evaluation of perioperative risk factors associated with PWH holds significant clinical relevance for spinal surgeons.

In the 21st century, artificial intelligence (AI) has gained extensive utilization in medical research, with the predictive capabilities of machine learning widely acknowledged within the medical domain.⁶ Serving as a powerful data processing and computational tool, machine learning demonstrates significant reliability in variable selection.⁷ Machine learning algorithms detect patterns and trends in data by automatically screening and identifying key features with predictive power in target variables. Through the analysis of extensive data, relevant clinical variables are identified, aiding medical researchers in pinpointing important factors that influence disease outcomes.^{6,8} Commonly employed techniques for model validation in classification and regression tasks involving nonlinear data include SVM, DT, KNN, and MLP. For validating multi-class predictions in high-dimensional datasets with large cardinality, methods such as RF, XGboost, and NB are frequently utilized.⁹

The primary objective of this study was to employ diverse machine learning algorithms for predicting PWH in patients undergoing posterior lumbar spinal fusion. By identifying optimal clinical variables through the convergence of these algorithms, a final predictive model was constructed for internal validation.

Materials and Methods

Study Design

The study retrospectively analyzed patients with lumbar degenerative disease (LDD) who underwent posterior lumbar spinal fusion at the Second Affiliated Hospital of Guangxi Medical University between August 2021 and August 2023. Inclusion criteria encompassed: (1) clinical diagnosis of LDD, including lumbar disc herniation, lumbar spinal stenosis, and lumbar spondylolisthesis based on medical history, symptoms, signs, and imaging findings; and (2) patients meeting clear indications for posterior lumbar interbody fusion (PLIF) and transforaminal lumbar interbody fusion (TLIF) surgeries. Exclusion criteria comprised: (1) preoperative diagnosis of participants with ankylosing spondylitis, spinal tumors, infections, tuberculosis, or pathological fractures; (2) patients with uncontrolled infections elsewhere in the body prior to surgery; (3) patients with a history of previous posterior lumbar spinal fusion surgery; and (4) individuals with incomplete medical records, lost to follow-up, or missing data.

Out of 2516 patients initially screened, 2105 were excluded for not meeting the specified inclusion or exclusion criteria. Consequently, our study comprised 411 patients, consisting of 198 males and 213 females. All surgical procedures were conducted by the same attending physician. The patient flowchart is illustrated in [Figure 1](#). The data were randomly partitioned into test and verification groups for analysis.

Diagnostic Criteria for PWH

The criteria for PWH assessment included: (1) presence of redness, swelling, heat, pain on the incision surface; (2) occurrence of purulent discharge, fever $>38^{\circ}\text{C}$; (3) identification of purulent effusion or other signs of poor healing at the wound site via surgical exploration, histopathology, or imaging studies; (4) diagnosis of incisional or deep infections by clinicians based on positive bacterial cultures from secretion samples following pathogen testing; and¹⁰ (5) manifestations such as surgical wound exudation, dehiscence, scar hypertrophy, sinus tract formation, or skin/flap necrosis.¹

Data Collection

The medical records of all hospitalized patients who met the inclusion criteria were thoroughly examined. Following the diagnostic criteria for PWH, the patients were categorized into two groups: the PWH group and the non-PWH group. [Table 1](#) illustrates the types of data gathered and facilitates a univariate logistic regression analysis.

Statistical Analysis

The data were analyzed using IBM SPSS (version 23.0) and R software (version 4.3.2×64). Various machine learning algorithms, including logistic regression, support vector machine (SVM), random forest (RF), decision tree (DT),

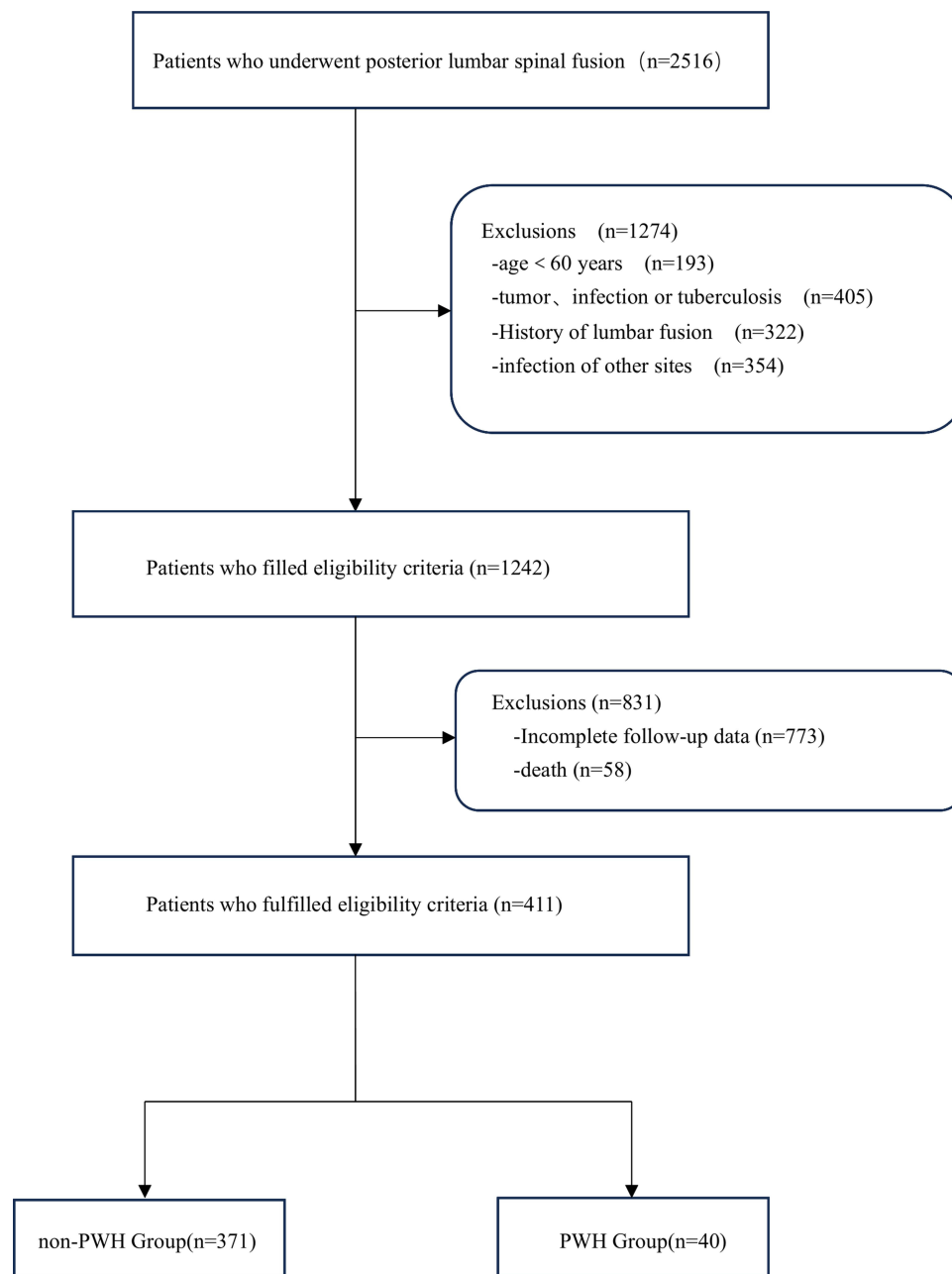


Figure 1 Patient flowchart.

XGBoost, Naïve Bayes (NB), k-Nearest Neighbor (KNN), and Multi-Layer Perceptron (MLP), were employed to identify potential risk factors for PWH following posterior lumbar spinal fusion. To refine the models, the dataset was scaled to the appropriate range, irrelevant or redundant variables were eliminated, and missing data was either interpolated or removed.

Specific variables identified through these seven methods were combined, and a comprehensive model was developed. Receiver Operating Characteristic (ROC) curves were utilized to evaluate sensitivity and specificity by calculating the area under the curve (AUC). Calibration plots were used to assess the performance characteristics of the predicted model. Furthermore, Decision Curve Analysis (DCA) was conducted to determine whether the model enhanced predictive ability. The model's performance was internally validated using ROC and calibration curves with a separate validation group.

Table I Comparisons of Baseline Between Patients Between Non-PWH and PWH Group

Variables	Non-PWH (n=371)	PWH (n=40)	t/ χ^2	P -value
Gender				
Male	171	27	6.628	0.010
Female	200	13		
Age	62.04±10.33	62.98±9.87	-0.549	0.583
Hypertension				
No	268	28	0.090	0.765
Yes	103	12		
Diabetes				
No	314	9	82.840	<0.001***
Yes	57	31		
Osteoporosis				
No	59	5	0.318	0.573
Yes	312	35		
Rheumatism				
No	353	35	3.998	0.046
Yes	18	5		
Smoking				
No	294	28	1.819	0.177
Yes	77	12		
Alcohol				
No	302	31	0.357	0.550
Yes	69	9		
Posterior fascia oedema				
No	194	17	1.386	0.239
Yes	177	23		
AAC				
No	192	20	0.044	0.833
Yes	179	20		
Paraspinal muscle degeneration				
I-II	253	17	10.577	0.001
III-IV	118	23		
BMI	23.59±3.08	27.13±3.38	-6.812	<0.001***
SLSI	0.434±0.257	1.019±0.449	-12.483	<0.001***
Level				
1	152	6	47.118	<0.01**
2	165	13		
3	52	17		
4	2	4		
Blood loss	288.57±239.89	707.75±526.9	-4.976	<0.001***
Operation time	101.19±27.50	143.53±58.53	-4.521	<0.001***
Length of incision	13.05±6.89	20.35±8.14	-6.246	0.001
CSFL				
No	352	19	19.251	<0.001***
Yes	12	28		
Medical intern				
No	238	27	0.177	0.674
Yes	133	13		

(Continued)

Table 1 (Continued).

Variables	Non-PWH (n=371)	PWH (n=40)	t/ χ^2	P-value
Season				
Spring	112	13	1.760	0.624
Summer	84	8		
Autumn	103	14		
Winter	72	5		
Mean air index	44.57±16.84	40.78±18.42	1.340	0.181
Atmospheric condition				
Sunny	103	6	3.249	0.197
Cloudy	187	25		
Rainy	81	9		
Sensible temperature	28.54±9.62	28.43±9.59	0.075	0.941
Atmospheric pressure	1013.33±7.53	1013.03±8.02	0.245	0.807
Air humidity	64.10±14.73	68.25±15.99	-1.679	0.094
Postoperative glucose	7.22±2.30	11.53±4.39	-10.052	<0.001***
ESR	11.26±5.29	16.25±6.24	-5.554	<0.001***
CRP	3.27±3.16	7.40±4.43	-5.741	<0.001***
Albumin	40.13±4.64	30.46±4.92	12.437	<0.001***
WBC	7.49±2.02	8.90±2.77	-3.111	0.003
RBC	4.96±7.26	4.55±6.91	0.357	0.722
HGB	128.89±18.10	115.21±25.95	3.248	0.002
NEU	4.73±1.78	7.18±3.43	-4.445	<0.001***
TBiL	13.95±3.73	17.45±8.11	-2.669	0.010
PT	11.86±7.32	11.35±6.97	0.440	0.660
APTT	29.70±3.77	29.60±3.06	0.165	0.869
FIB	3.62±1.03	3.40±0.64	1.344	0.180
TT	14.85±21.95	13.93±0.84	0.264	0.792
Potassium	3.79±0.46	3.81±0.31	-0.280	0.781
Sodium	139.76±3.59	139.72±4.49	0.068	0.946
Calcium	2.22±0.14	2.21±0.11	0.667	0.499
Magnesium	0.85±0.08	0.87±0.07	-1.263	0.207

Notes: "P<0.05": The representation was statistically significant; "***": P<0.01, indicates higher statistical significance. "****": P<0.001, indicates very high statistical significance.

Abbreviations: BMI, body mass index; AAC, aortic atherosclerotic calcification; SLSI, subcutaneous lumbar spine index; CSFL, cerebrospinal fluid leakage; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; WBC, white blood cell; RBC, red blood cell; HGB, hemoglobin; NEU, neutrophil; TBiL, total bilirubin; PT, prothrombin time; APTT, activated partial thromboplastin time; FIB, fibrinogen; TT, thrombin time.

Results

This study included 411 patients, with 288 patients in the test group and 123 patients in the validation group. Consistent with previous research, a significant association was observed between PWH and comorbid diabetes ($P < 0.001$), with postoperative glucose ($P < 0.001$) showing a close correlation with surgical recovery outcomes.

Initially, single-factor logistic regression was employed to evaluate the patients. Factors such as rheumatism ($P = 0.046$), paraspinal muscle degeneration ($P = 0.001$), BMI ($P < 0.001$), SLSI ($P < 0.001$), CSFL ($P < 0.001$), ESR ($P < 0.001$), CRP ($P < 0.001$), albumin ($P < 0.001$), WBC ($P < 0.001$), HGB ($P = 0.002$), and NEU ($P < 0.001$) were identified as significant risk factors for PWH (Table 1).

Multi- Machine Learning Models Comparison

In this study, a range of machine learning algorithms, including logistic regression, SVM, RF, DT, XGBoost, NB, KNN, and MLP, were utilized for data classification. The dataset was divided into a 7:3 ratio for test and validation, respectively, and validated through 5-fold cross-validation while scaling the model variables to a range of [0,1]. To

ensure consistency in test samples across various algorithms and facilitate a robust comparison of AUC values, the model was finally assessed on a 30% validation group.

The top ten risk factors for each model were identified and documented. Among the models tested, Random Forest exhibited the highest performance in both the test groups, achieving an AUC value of 0.982, and the validation group with an AUC value of 0.978. The performance evaluation of all machine learning models is presented in Figures 2 and 3. Performance metrics for the models in the validation group: RF: 0.982, SVM: 0.977, XGBoost: 0.974, DT: 0.862, Logistic Regression: 0.851, KNN: 0.822, MLP: 0.563.

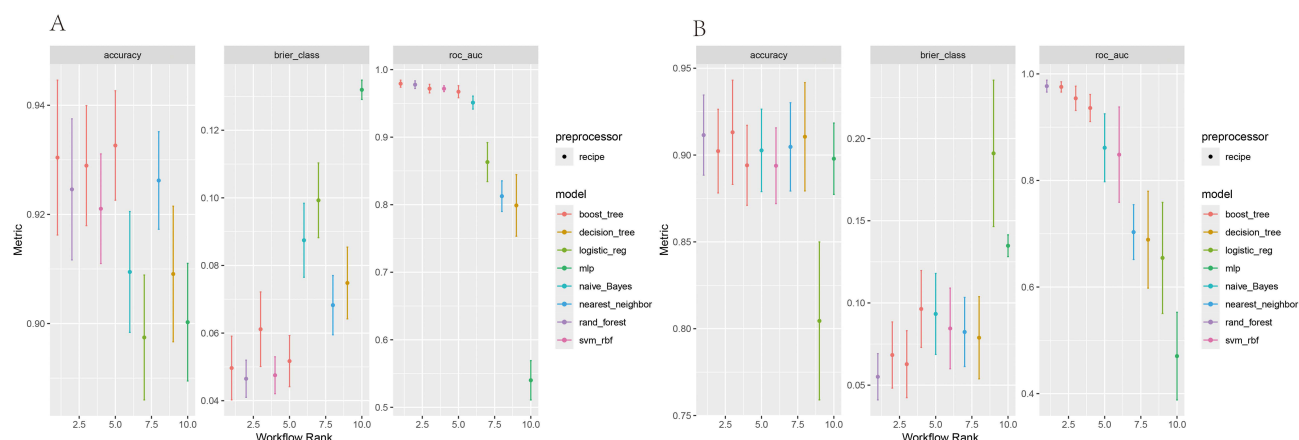


Figure 2 The AUC values of 8 models in the (A) test group (B) validation group.

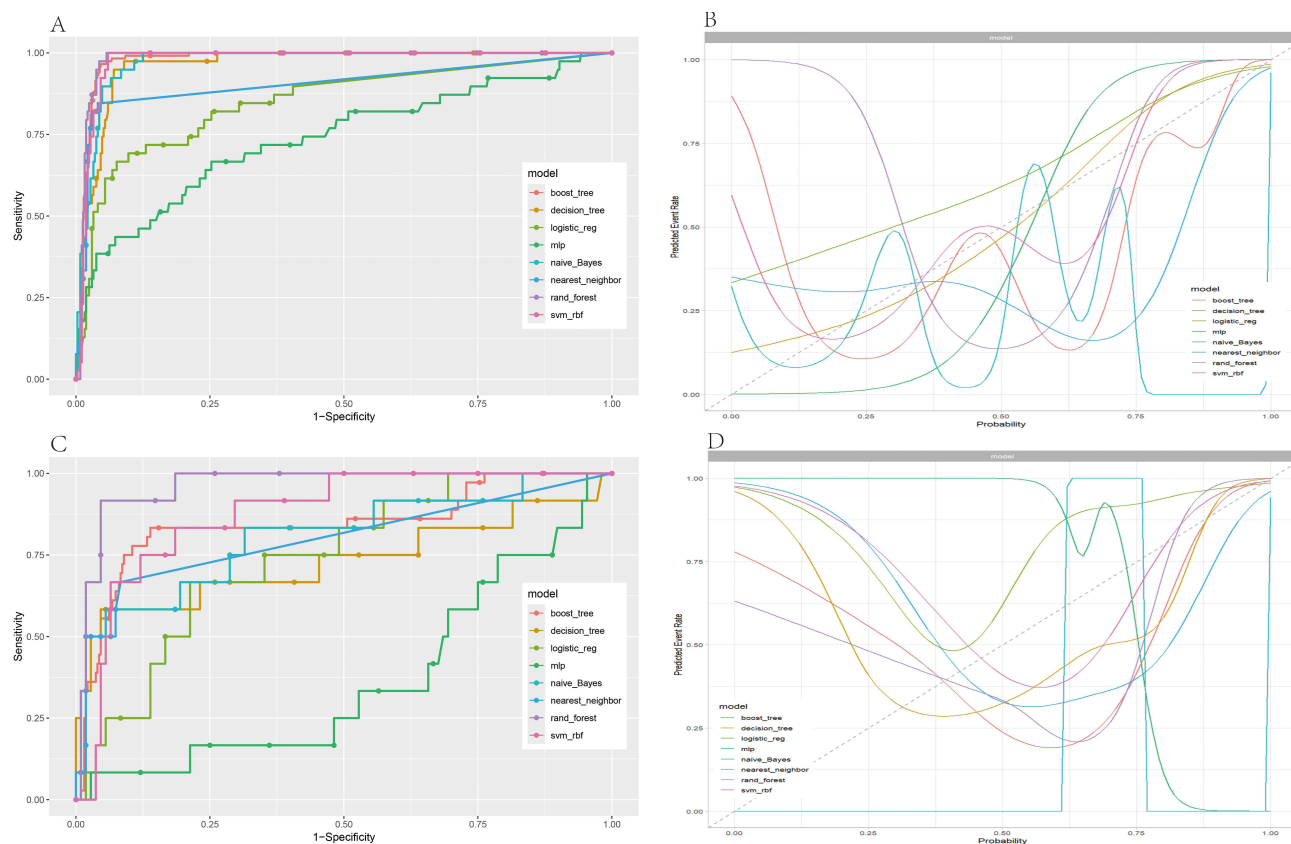


Figure 3 (A) Comparison of the AUC values of the 8 models in the test group; (B) Fitting degree of the 8 models in the test group; (C) Comparison of the AUC values of the 8 models in the validation group; (D) Fitting degree of the 8 models in the validation group.

Best Algorithm Model

Each machine learning algorithm has its optimal application scenario.^{11,12} Random Forest (RF) is known for its high classification accuracy but requires significant computational resources to ensure enhanced reliability.¹³ Considering the diverse data content of this study, which includes various laboratory blood tests and environmental factors, and after multiple fold calculations, RF demonstrates the most robust performance. The metric “%IncMSE” denotes the mean square error and serves as a random value assigned to each variable to assess its importance as a predictor. A higher value indicates a greater importance of the variable in the model. On the other hand, “IncNodePurity” represents node purity, indicating how variables influence the heterogeneity of observed values within each node of the classification tree. A higher value suggests a higher importance of the variable. Figure 4 illustrates the risk factor variables associated with RF.

Model Development

A Venn diagram was used to illustrate the shared predictors among the key variables identified by SVM, RF, DT, XGBoost, NB, and KNN models (Figure 5). Subsequently, six predictors—SLSI, albumin, post glucose, CSFL, NEU, and CRP—were selected. A predictive model was then developed based on these six variables (Figure 6).

Model Performance

ROC and calibration curves were generated using the test group to assess the model’s performance. The AUC value obtained was 0.981, indicating a high level of performance. Analysis of the calibration curve revealed a strong agreement between the predicted values from the nomogram and the actual measurements. Furthermore, the model’s C-index was calculated to be 0.986 (95% CI 0.966–0.995). For internal validation, the validation group was utilized, and ROC and calibration curves were depicted in Figures 7 and 8, respectively. The AUC value in this validation group was 0.955, with a corresponding C-index of 0.958 (95% CI 0.890–0.999), thus affirming the reliability of the model.

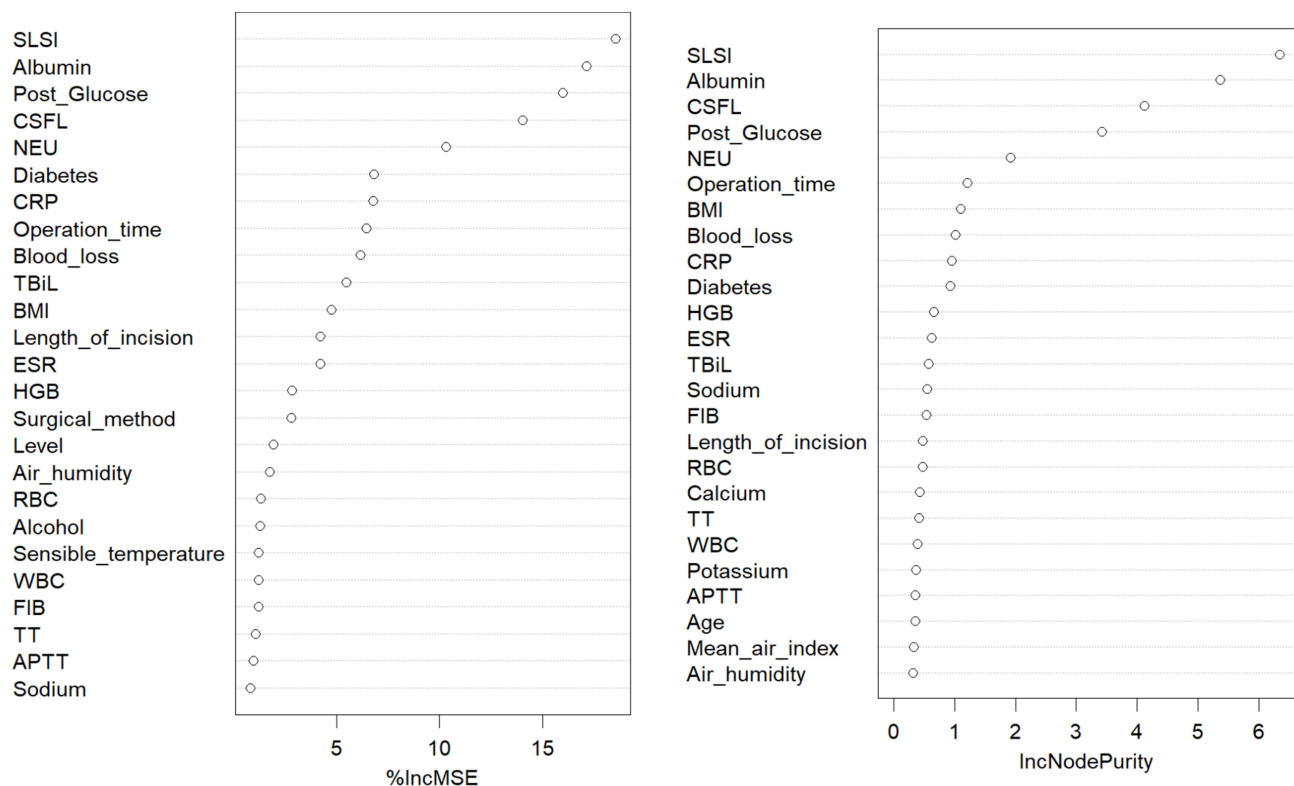


Figure 4 The RF model predicted PWH risk factor variables.

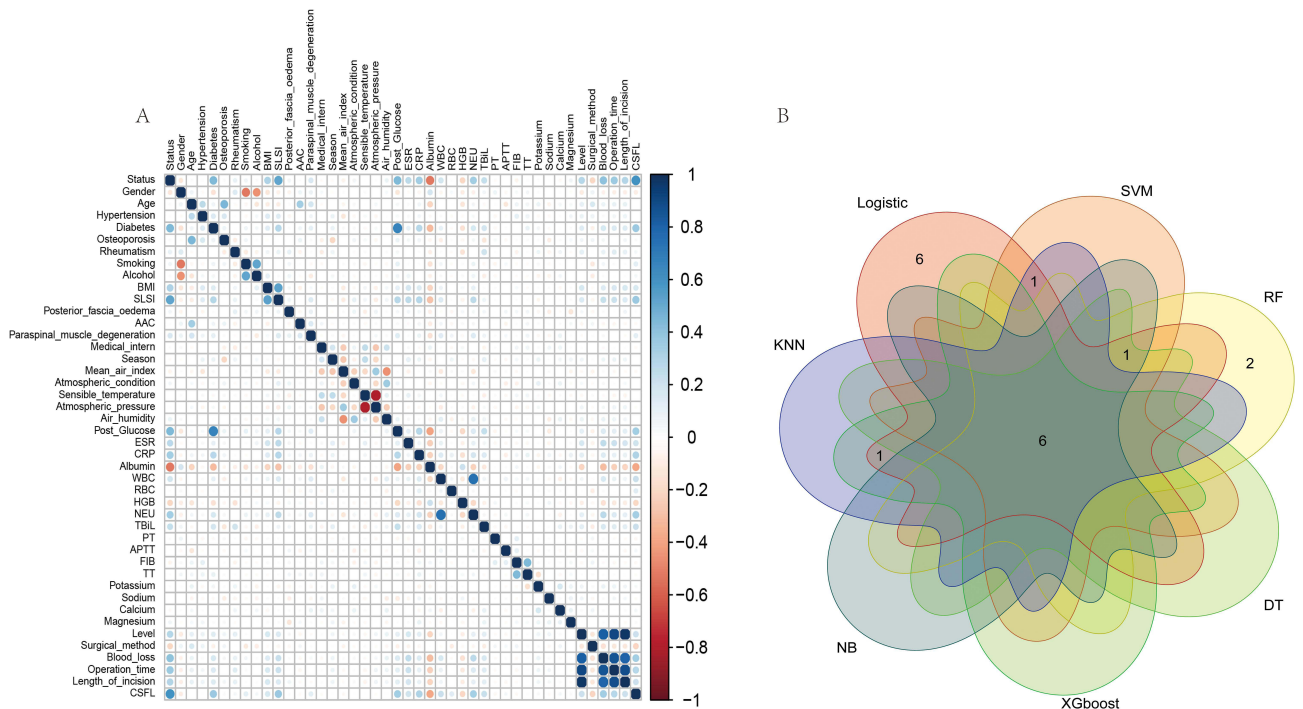


Figure 5 A:Heat map of the correlations between all the variables are shown; (B) The intersection of variables screened using seven machine learning methods.

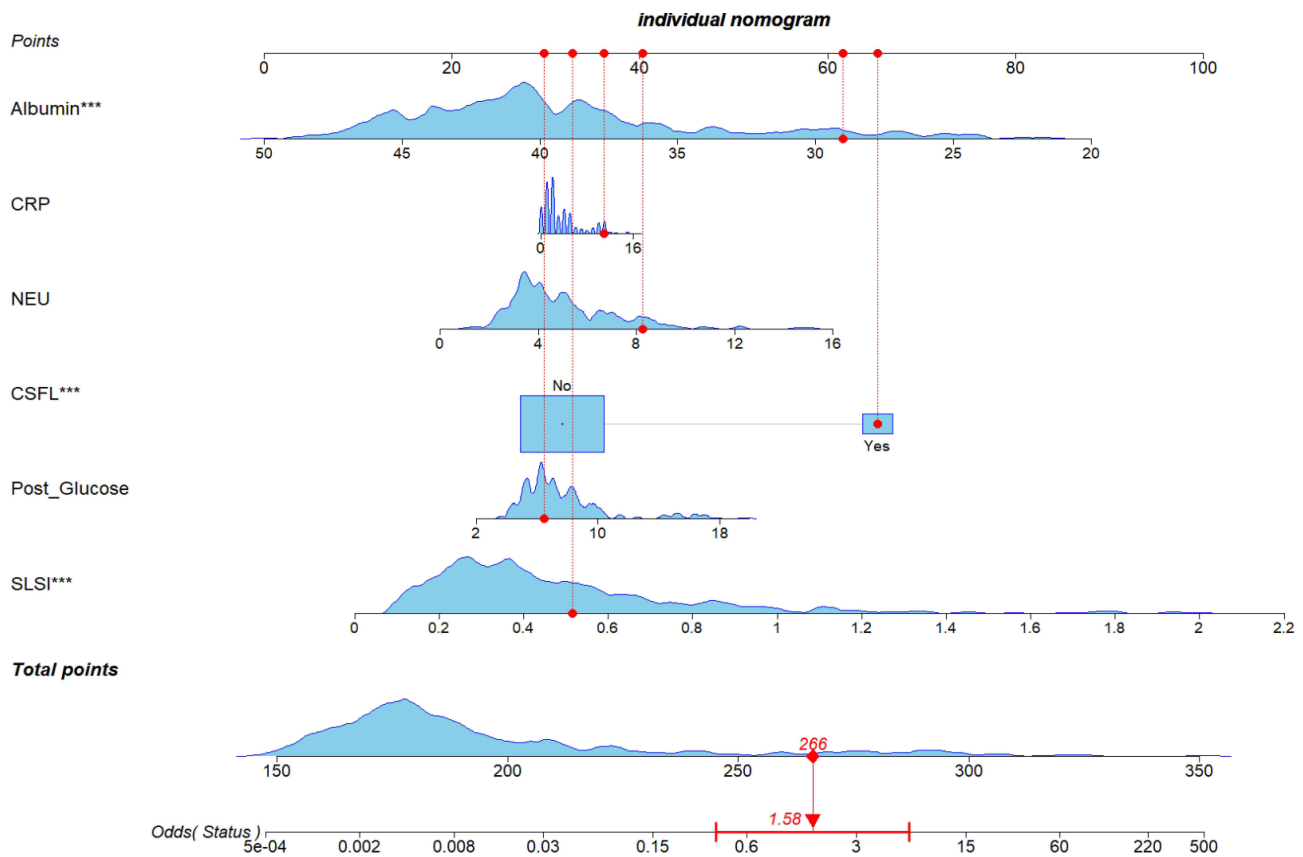


Figure 6 Visualisation nomogram model for PWH after posterior lumbar spinal fusion.
Notes: ***: indicates very high statistical significance.
Abbreviations: CRP, C-reactive protein; NEU, neutrophil; CSFL, cerebrospinal fluid leakage; Post_Glucose, postoperative glucose; SLSI, subcutaneous lumbar spine index.

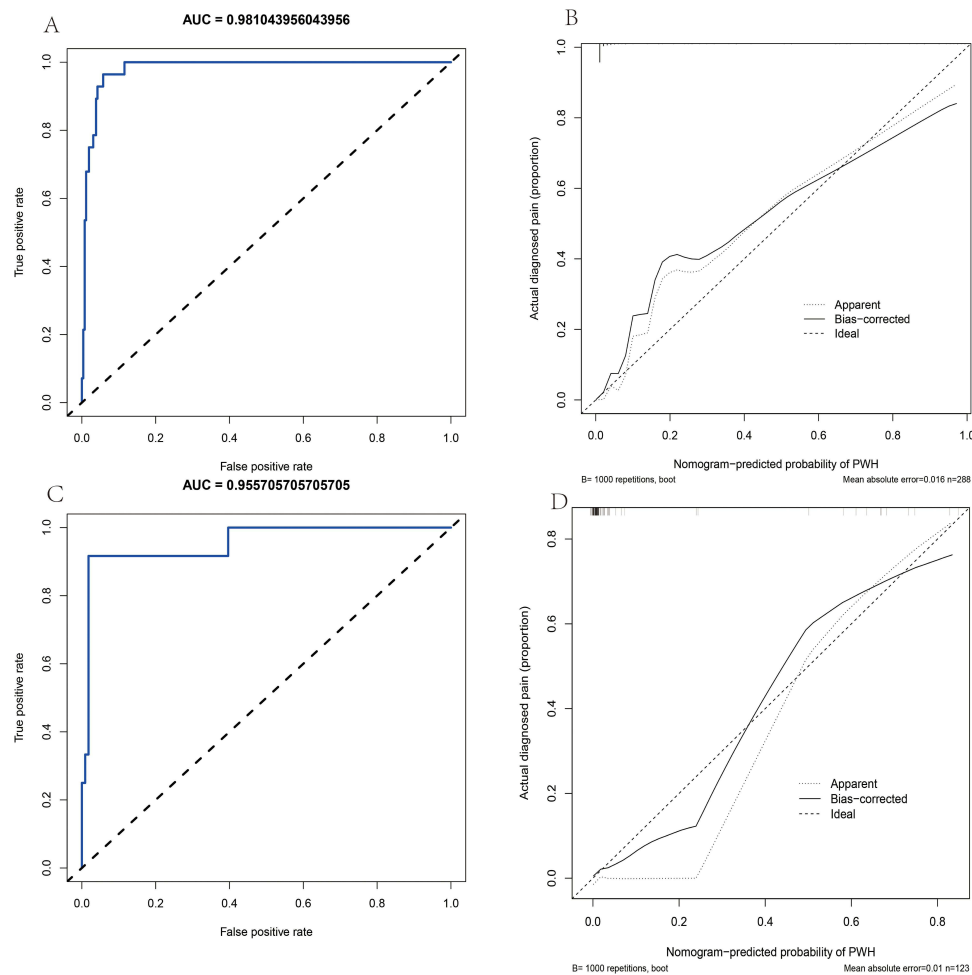


Figure 7 Validation and decision curve analysis of the model. (A) ROC curve for the prediction test model; (B) calibration curve for the prediction test model; (C) ROC curve of the external validation; (D) calibration curve of the external validation.

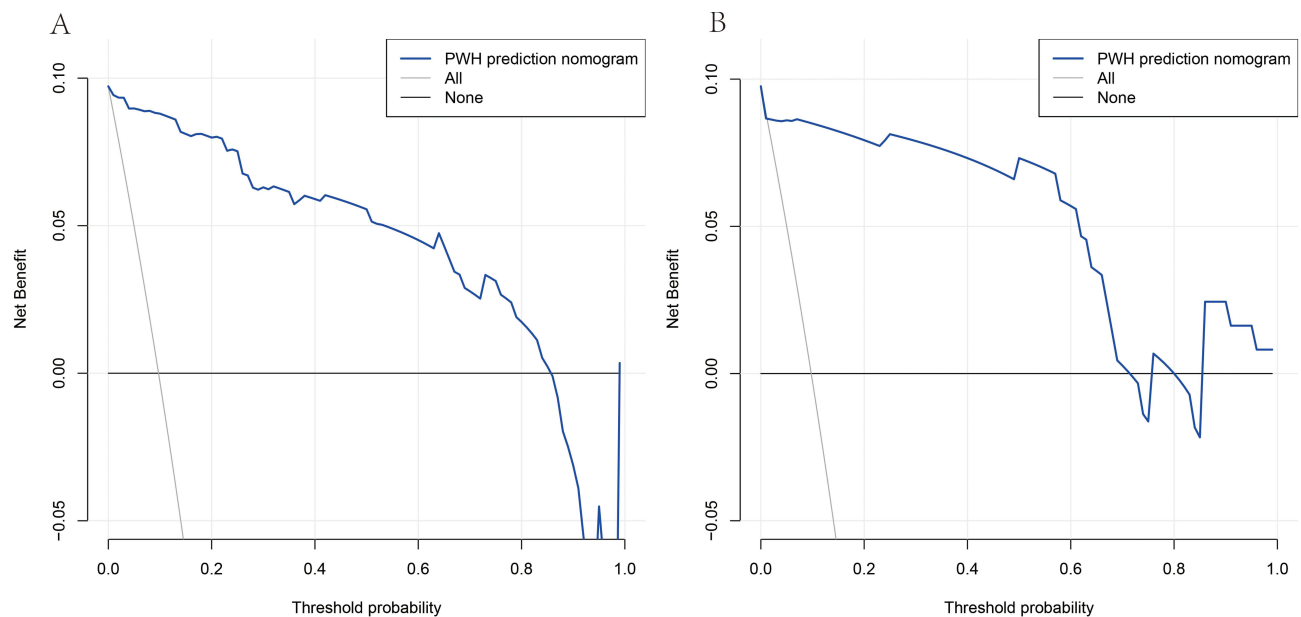


Figure 8 Decision curve analysis(DCA) of the predictive model. (A) DCA for the prediction test model; (B) DCA of the external validation.

Discussion

Numerous studies have investigated risk factors for PWH following posterior lumbar spinal fusion,^{14,15} but there is little literature on predicting PWH based on machine learning.^{16,17} Many studies have primarily focused on analyzing the pre-surgery nutritional status and general patient information, often overlooking environmental factors like the surgical season, air humidity, and mean air index etc. In recent years, there has been a lack of emphasis on exploring the association between blood parameters, routine laboratory indicators, and PWH.¹⁸ This study introduces environmental factors alongside blood parameters and routine laboratory indicators to comprehensively analyze the risk factors affecting PWH in the perioperative period. Six closely related risk factors for PWH were identified: SLSI, albumin, postoperative glucose, CSFL, NEU, and CRP. The prediction model, with strong predictive and visualization capabilities, simplifies PWH assessment and intervention.

Previous studies have often focused on using BMI for assessing PWH, but its accuracy is limited by variations in muscle mass and fat distribution.¹⁹ Some studies suggest that subcutaneous fat thickness (SFT) may be a more reliable indicator of waist fat mass compared to BMI. However, SFT only reflects the local fat status at the fusion segment and does not account for the impact of spinous process height on PWH after surgery. In posterior lumbar spinal fusion procedures, a higher SLSI indicates either thicker subcutaneous fat or a shorter spinous process, which can complicate surgical field exposure. Prolonged intraoperative muscle traction can reduce blood flow to the paravertebral muscles, increasing the risk of muscle injury and necrosis.^{20,21} Furthermore, a higher SLSI may require greater tissue exposure using electrocautery devices, potentially elevating the risk of postoperative fat necrosis. Deeper incisions in patients with a higher SLSI may lead to larger cavities at suture sites, impacting internal tissue healing.²² In clinical practice, it is crucial to formulate a personalized surgical plan for patients with high SLSI levels prior to surgery. One effective strategy involves the blunt dissection of muscle layers through the multifidus approach. This technique minimizes extensive soft tissue stripping, thereby preserving the integrity of the muscle-vertebrae connection. By maintaining muscle integrity, this approach helps to reduce muscle tone, which in turn mitigates the risk of tearing and protects the bony structures of the spine. Furthermore, this method minimizes tissue damage and decreases reliance on electro knives. Additionally, suturing the intermuscular fascia can effectively diminish deep dead space, thereby lowering the occurrence of PWH.

Inflammatory and immune biomarkers such as C-reactive protein (CRP), neutrophils (NEU), white blood cells (WBC), and erythrocyte sedimentation rate (ESR) provide valuable insights into the body's inflammatory response.²³ However, there has been limited research exploring the relationship between preoperative serology and PWH following posterior lumbar spinal fusion. This study delves into multiple inflammatory and immune biomarkers, highlighting the significant impact of CRP and NEU on PWH. It plays a pivotal role in regulating the host's defense mechanisms against infection, tissue injury, and autoimmunity.²⁴ Elevated CRP levels before surgery indicate an immune environment imbalance in patients, while NEU levels signify the ongoing inflammatory and immune status. High preoperative levels of inflammatory factors, including CRP, NEU, WBC, and ESR, can trigger an inflammatory cascade that exacerbates oxidative stress injuries, ultimately accelerating PWH in postoperative patients.²⁵ By incorporating CRP and NEU, this study demonstrates the predictive capacity of preoperative inflammatory and immune biomarker concentrations in predicting PWH following posterior lumbar spinal fusion.²⁶ In this context, considering the dynamic interaction with other inflammatory markers such as IL-6, ESR, and WBC, preoperative prophylactic treatment with low-intensity broad-spectrum antibiotics proves beneficial in preventing postoperative PWH development. For spine surgeons who experience high levels of inflammatory markers in their clinical work, it is advisable to prolong the administration of low-intensity antibiotics to 48 hours post-surgery. Furthermore, postoperative dynamic monitoring of inflammatory markers, enhanced nutritional support, and optimized pain management strategies can effectively decrease the incidence of PWH.

Typically, preoperative albumin levels and postoperative blood glucose levels are more indicative of overall bodily function.²⁷ Albumin serves as a critical marker of patients' nutritional status.²⁸ Research indicates that surgical stress can disrupt albumin levels, compromising the body's defense mechanisms against pathogens.²⁹ Prolonged surgery and intraoperative blood loss can further reduce albumin levels. Low levels of albumin significantly heighten the risk of postoperative wound healing complications following posterior lumbar fusion and weaken the body's defense barriers. Persistent postoperative hyperglycemia leads to elevated levels of inflammatory cytokines, disrupting the balance

between pro-inflammatory and anti-inflammatory factors, increasing blood fragility, reducing collagen synthesis, creating a favorable environment for bacterial proliferation, inducing tissue ischemia and hypoxia at the incision site, ultimately impeding wound healing.^{30–32} In perioperative preparation, for patients exhibiting significantly lower serum albumin levels than the normal standard, it is recommended to administer human blood albumin or encourage consumption of high-protein foods before and after surgery to address the low-protein state. Additionally, surgeons managing such patients should focus on controlling blood loss and minimizing surgical duration during the procedure. When necessary, options such as autologous blood transfusion or intraoperative infusion of human blood albumin can be considered. For patients experiencing postoperative hyperglycemia or those with chronic diabetes exhibiting inadequate blood sugar control, implementing blood glucose management interventions during the perioperative period may be warranted. Continuous 24-hour glucose regulation through techniques like insulin pump installation can swiftly rectify or adjust the elevated glucose levels, thereby reducing tissue oxygen consumption at the surgical site. In conclusion, these clinical interventions hold significant clinical relevance in guiding efforts to minimize PWH occurrences post-surgery.

Cerebrospinal fluid leakage (CSFL) represents a potential complication following posterior lumbar spinal fusion. In our study, it is recognized as a risk factor for PWH, consistent with findings from other researchers.³³ Intraoperative tears in the dural membrane can lead to persistent leakage of cerebrospinal fluid after surgery, disrupting the Virchow-Robin space surrounding blood vessels and resulting in localized accumulation of cerebrospinal fluid.³⁴ This accumulated fluid contains various inflammatory factors that continuously irritate the adjacent tissues, ultimately hindering proper wound healing.³⁵ In cases of CSFL, preoperative imaging and physical assessments can assist in predicting the likelihood of intraoperative CSFL, underscoring the importance of careful dural protection during surgery. Therefore, during posterior lumbar fusion procedures, it is advisable to refrain from forcible decompression of the laminae in patients with severe spinal stenosis and significant dural adhesions to surrounding tissues. The use of specialized tools such as ultrasonic bone knives can facilitate safe laminar decompression. In the event of intraoperative CSFL, prompt repair of the dural membrane through suturing is recommended, accompanied by postoperative administration of antibiotics to reduce the risk of intracranial infections. These measures can contribute significantly to reducing the incidence of PWH.

Limitation

The study is subject to several limitations: (1) It was a single-center retrospective study lacking randomized control; (2) The study population may not be fully representative of the general population; (3) Despite comprehensive data collection, the retrospective design of the study could introduce recall bias. Consequently, future research efforts should prioritize prospective multi-center studies with larger sample sizes to validate the predictive model proposed in this study.

Conclusion

Our study identified SLSI, albumin, postoperative glucose, CSFL, NEU, and CRP as independent risk factors for PWH issues in patients undergoing posterior lumbar spinal fusion. Furthermore, our risk prediction model exhibited strong predictive ability and clinical utility.

Ethics Approval and Consent to Participate

Ethical approval was obtained from the Institutional Review Board of the Second Affiliated Hospital of Guangxi Medical University (Approval Number: 2024-KY(0514)) for this retrospective study, which adhered to the principles outlined in the Declaration of Helsinki. The Institutional Review Board of the Second Affiliated Hospital of Guangxi Medical University approved the informed consent process. All participants in this study provided written or verbal informed consent.

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Author Contributions

Zixiang Pang and Yangqin Ou contributed to the work equally and should be regarded as co-first authors. All authors have contributed significantly to the reported work, encompassing various aspects such as conception, study design, execution, data acquisition, analysis, and interpretation. They have collectively participated in drafting, revising, and critically reviewing the article, ultimately providing their final approval for publication. Furthermore, all authors have reached a consensus on the submission of the article to the chosen journal and have accepted responsibility for the integrity of the work.

Disclosure

All authors declare that there are no conflicts of interest in this article. This paper has been uploaded to Research Square as a preprint: <https://www.researchsquare.com/article/rs-4877978/v1>

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