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A Multicenter Validation of a Novel Prediction Model for Elbow Flexion Recovery after Nerve Transfer Surgery in Brachial Plexus Injuries

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Background: Nerve transfer surgery for brachial plexus injuries exhibits variable success rates, potentially resulting in prolonged limb dysfunction for more than 2 years. A proposed prediction model has been developed to predict the unsuccessful recovery of elbow flexion after the surgery. The model consisted of six variables, namely body mass index 23 kg/m^2 or more, smoking, total arm type, donor nerve, ipsilateral upper extremity fracture, and ipsilateral vascular injury. This study aimed to assess the external validity of the model for wider applicability.

Methods: This retrospective analysis examined the medical records of 213 eligible patients with traumatic brachial plexus injuries who underwent surgery at two referral centers between July 2008 and June 2022. The prediction model was applied to estimate recovery failure probability, which was compared with the observed outcomes for each patient. Both the original and simplified models were validated for discrimination and calibration using metrics including c-statistic, Hosmer–Lemeshow goodness-of-fit test, calibration plot, calibration slope, and intercept.

Results: Thirty-two percent of patients experienced unsuccessful elbow flexion recovery. Both the original and simplified models demonstrated good discrimination (c-statistics: 0.748 and 0.759, respectively). The Hosmer–Lemeshow test revealed strong agreement between predicted and observed probabilities for both models ($P = 0.66$ and $P = 0.92$, respectively). The calibration plot exhibited good agreement, with a calibration slope of 0.928 and an intercept of 0.377.

Conclusions: The prediction model showed strong external validation, confirming its clinical value. High-risk patients should be educated on the risks and benefits of nerve transfer surgery and consider alternative treatments such as primary free functioning muscle transfer. *(Plast Reconstr Surg Glob Open 2024; 12:e6118; doi: 10.1097/GOX.0000000000006118; Published online 3 September 2024.)*

INTRODUCTION

Brachial plexus injuries often result in permanent limb dysfunction, especially in severe cases. Surgical intervention is necessary for preganglionic and severe postganglionic injuries, aiming to restore elbow flexion—a key functional goal.[1]

Nerve transfer surgery is typically the primary choice due to its widespread applicability, promising outcomes, and minimal donor nerve morbidity.[2–4] However, the reported failure rates vary widely, between 6% and 34%.[5–10] Assessment usually occurs at the 2-year follow-up, where the limb may remain nonfunctional.[4,11,12] If initial surgery fails, salvage methods such as free functional muscle transfer can be considered, though achieving functional elbow flexion may necessitate an additional 2-year recovery period.[13–15] Given that most patients fall within the young adult to middle-age demographic, the burden of a delayed return to work cannot be overstated.[16–18]

Free functional muscle transfer can serve as a primary surgery, offering simultaneous restoration of elbow and finger flexion—a capability not achievable with nerve transfer for total arm–type patients.[14,15,19,20] However, being more invasive than nerve transfer surgery, it is typically reserved for cases with a high likelihood of nerve

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reconstruction failure, including delayed cases exceeding 1 year after injury.[14,15] Nonetheless, risks of failure persist even within the first year, prompting extensive studies to identify prognostic factors.[4,12,21–31] Overcoming limitations faced by other studies, such as the diversity of operations, limited study power, unaccounted confounding factors, and the descriptive nature of the research, a novel prediction model has finally been successfully developed. This model identifies six strong independent risk factors, including body mass index (BMI) 23 kg/m^2 or more, smoking, total arm–type injury, donor nerve selection, associated ipsilateral upper extremity fracture, and associated ipsilateral vascular injury.[32] Despite its strong internal validity, external validation is crucial to ensure model reliability across medical centers.[33]

The objective of this study is to conduct a multicenter external validation of a previously established prediction model designed to predict the unsuccessful recovery of functional elbow flexion 2 years after nerve transfer surgery in patients with brachial plexus injury.[32]

Takeaways

Question: Nerve transfer surgery for brachial plexus injuries has variable success rates, potentially leading to prolonged limb dysfunction lasting more than 2 years. Although a proposed prediction model has been developed, its generalizability remains uncertain and requires further investigation.

Findings: The model underwent validation in a different setting demonstrating favorable discrimination and calibration.

Meaning: The newly developed prediction model underwent effective external validation, affirming its clinical applicability. For patients at notably high risk of failure, primary free functioning muscle transfer should be considered.

METHODS

Ethical Considerations

This study was approved by the institutional review boards of all participating institutions and registered at ClinicalTrials.gov, NCT06237270 (https://clinicaltrials.gov/study/NCT06237270).

Data Collection

Participants were recruited from two distinct tertiary medical centers. The medical records of patients who underwent brachial plexus surgery were retrieved from one of the tertiary medical centers, responsible for the development of the prediction model. However, the recruited patients were sourced from a different timeframe, spanning from August 2018 to July 2020, than that of the original study. Additional data were collected from patients who underwent brachial plexus surgery at another tertiary hospital specializing in hand and microsurgery, covering a period from July 2008 to June 2022. Initially, 58 patients from one hospital and 197 patients from another hospital, totaling 255 brachial plexus surgical patients, were enrolled. Within this cohort, 225 patients underwent nerve transfer surgery to restore elbow flexion. Strictly adhering to the inclusion and exclusion criteria outlined in the previous study, we excluded 12 patients who did not exhibit recovery of elbow flexion within 18 months after nerve transfer surgery and were lost to follow-up. No patients younger than the age of 10 years were included. The study did not identify any patients suitable for the last observation carried forward method. Consequently, the final analysis focused on the remaining 213 patients (Fig. 1).

Outcome Assessments

In accordance with the previous study, an unsuccessful restoration of functional elbow flexion was defined as the inability to achieve elbow flexor muscle power exceeding the Medical Research Council (MRC) grade 3 within a 24-month timeframe after nerve transfer surgery for restoring elbow flexion. However, the reporting

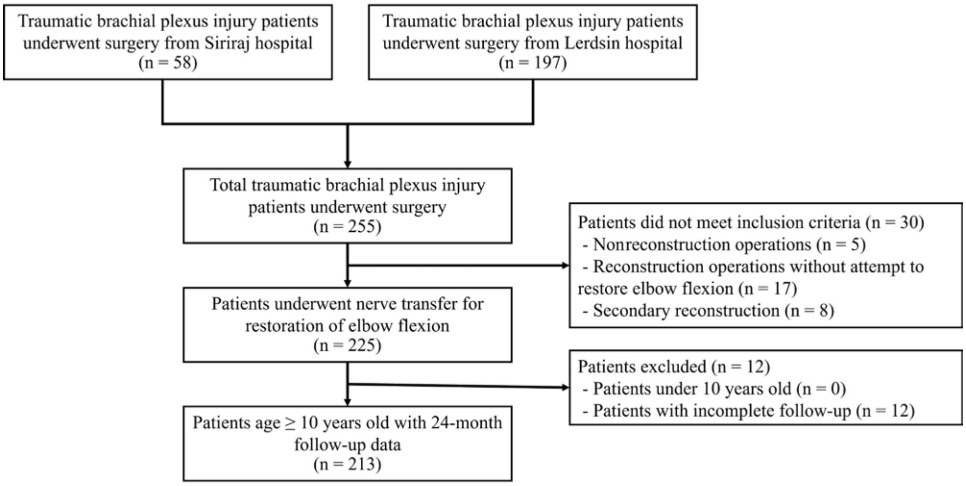

Fig. 1. The study flowchart for prediction model validation.

of outcomes was carried out by the surgeon responsible for performing the procedure, and no measures were implemented to blind the assessment. The ability to fully flex the elbow against gravity was regarded as an objective finding, potentially eliminating the need for blinding. Considering the restricted potential for additional functional recovery beyond the 24-month period, as evidenced across both centers, motor power assessment at 24 months after nerve transfer surgery was designated as the terminal point of the study. All patients in the cohorts had preoperative elbow flexion strength of MRC grade 0.

In this external validity study, the authors did not encounter any instances of motor grades 0 and 1 at the 18-month follow-up visit. Therefore, the last observation carried forward method was not applied.

Explanatory Variables

In reference to the previous study, six robust factors were recorded as a dataset for model validation. These factors consisted of BMI, smoking history within the past month, type of injury, donor nerve selection, associated ipsilateral upper extremity fracture, and associated ipsilateral vascular injury. Other preoperative factors such as age, sex, affected and dominant hand side, concomitant injuries, duration from the injury (in days), as well as the cause, mechanism, severity of the injury, type of injury according to ganglionic lesion (based on clinical, radiographic, electrodiagnostic, or intraoperative observations), nerve graft type and length, recipient nerve for nerve transfer surgery, and any complications were also recorded.

Consistent with the prior study, preoperative continuous predictors were stratified utilizing established thresholds from existing literature. The thresholds were defined at 40 years of age, a BMI of 23 kg/m^2, and a duration from injury onset of 120 days. The type of injury was classified as "total arm type" or "others." Smoking history, associated ipsilateral upper extremity fracture, and associated ipsilateral vascular injury were designated as either "yes" or "no." Donor nerve selection was categorized as "ulnar nerve," "spinal accessory nerve," "phrenic nerve," "median nerve," or "ulnar and median nerve." Candidates for donor nerve selection must exhibit preoperative MRC motor power of at least grade 4. This categorization was implemented for model validation and to enable data comparison with the previous study.

Efforts were made to maintain data consistency across both hospitals. Criteria for each predictor were thoroughly reviewed collectively before commencing the data retrieval process. Furthermore, the data from one hospital were secondarily reviewed by another hospital. Any potential misunderstandings or discrepancies were promptly addressed to ensure accuracy and reliability of the data.

Although surgical approaches to the brachial plexus may vary among institutions, nerve stimulation was consistently used in all cases at both centers. A reliable donor nerve must exhibit robust muscle contraction when stimulated intraoperatively. During the nerve transfer procedure, intraoperative nerve stimulation was also performed on the recipient nerve to validate its lack of function, as evidenced by the absence of muscle contraction after the nerve stimulation.

Sample Size

The primary objective of a validation study is to assess and measure the efficacy of an established model using distinct datasets. The determination of sample size requirements for validation studies lacks clear consensus and is often influenced by the available data. However, a commonly adopted rule of thumb, derived from empirical investigations, recommends a minimum of 10 outcome events per variable.[33–35] Given six variables in the prediction model, this implies a necessity for 60 outcome events for logistic regression analysis. In the previous study, the reported incidence of the unsuccessful elbow flexion events was 30.4%.[32] Consequently, a calculated sample size of at least 198 patients with brachial plexus injury was deemed preferable for the analysis. In this study, a cohort of 213 available records meeting the inclusion and exclusion criteria was analyzed, resulting in 68 outcome events of interest.

Analysis

The Shapiro–Wilk test was used to assess normality for continuous variables within the groups. As a nonnormal distribution was identified, quantitative variables were presented using the median and interquartile range, whereas categorical data were presented as the counted numbers and corresponding percentages. In this study, the occurrence of missing values in all six predictors was so minimal that multiple imputations were deemed unnecessary.

The beta-coefficients and intercept from the original model were utilized to calculate the probability of an unsuccessful nerve transfer surgery for each case within the current cohort (Table 1). Similarly, the simplified score from the previous study was assigned to each explanatory variable, and subsequently, a total score was computed for each case. Logistic regression analysis was used to evaluate the association between either the probability or total score and the observed outcome.

We evaluated the predictive performance of both the original and simplified prediction models on the current cohort by examining measures of calibration and discrimination. Calibration evaluates the degree of alignment between the predicted risk of unsuccessful nerve transfer surgery from the model and the observed occurrences of unsuccessful surgery within the cohort. Because unsuccessful surgery is a binary outcome, a smoothing technique was applied for improved visualization. The observed outcomes were plotted by decile of predictions, ensuring 10 equally sized groups.[36] This method allowed us to plot the calibration of the original prediction model on the current cohort outcome. Apart from visualization, agreement of the predicted and observed value was further demonstrated with calibration slope and intercept. Moreover, the Hosmer–Lemeshow goodness-of-fit test was used. For the simplified model, assessment of the correlation between the total score and the observed failure rate in the cohort were plotted for each group of patients with the same score.

Table 1. Details of How to Calculate a Predicted Probability and Simplified Total Score for Prediction of Unsuccessful Recovery of Elbow Flexion after Nerve Transfer Surgery in Patients with Brachial Plexus Injuries

Prognostic Factors	Beta-coefficient*	Standard Error	Simplified Score†
BMI ≥ 23 kg/m^2	0.58	0.24	1
Smoking	0.5	0.25	1
Total arm type	1.15	0.54	2.5
Donor nerve			
Ulnar nerve			0
Spinal accessory nerve	2.18	0.58	4.5
Phrenic nerve	1.51	0.63	3
Median nerve	0.98	0.62	2
Ulnar and median nerves	1.09	0.85	2
Ipsilateral upper extremity fracture	0.6	0.24	1
Ipsilateral vascular injury	0.75	0.45	1.5
Intercept	–4.27	0.69	

All predictors have a value of 1 if present, and 0 otherwise.

*Probability can be calculated as follows: $P_{\text{failure}} = \frac{e^z}{1+e^z}$, where P_{failure} denotes the probability for a patient to have an unsuccessful surgery, and Z = –4.27 + 0.58 × BMI ≥ 23 kg/m^2 + 0.5 × smoking + 1.15 × total arm type + 2.18 × spinal accessory nerve + 1.51 × phrenic nerve + 0.98 × median nerve + 1.09 × ulnar and median nerves + 0.6 × ipsilateral upper extremity fracture + 0.75 × ipsilateral vascular injury.

†Total score = 1 × BMI ≥ 23 kg/m^2 + 1 × smoking + 2.5 × total arm type + 4.5 × spinal accessory nerve + 3 × phrenic nerve + 2 × median nerve + 2 × ulnar and median nerves + 1 × ipsilateral upper extremity fracture + 1.5 × ipsilateral vascular injury.

Adapted from J Neurosurg. 2022;139:212–221.[32]

Discrimination assesses the capability of the prediction model to differentiate between patients who do and do not experience an outcome event during the study period. This measure is quantified by calculating the area under the receiver operating characteristic curve (ROC curve) (c-statistics), where a value of 0.5 represents the chance, and 1 represents the perfect discrimination.[37] ROC curves were plotted, and c-statistics were calculated for both the original and simplified prediction models. All statistical analyses, along with calibration plots and ROC curves, were conducted using Stata software (version 16.1; Stata Corp LLC).[38]

RESULTS

Patient Characteristics

Table 2 presents the patient characteristics of the validation dataset, which are relatively comparable to those of the development dataset. Among the 213 patients, 90% were male, with a median BMI of 23.5 kg/m^2 and a median age of 25 years. The smoking history was observed in 26% of the patients, which is similar to the rate in the development dataset (30%). Most brachial plexus injuries resulted from motorcycle accidents (98%) and traction injuries (99%). In comparison to the development dataset, a lower rate of total arm–type injuries was observed (64% in the validation set versus 78% in the development dataset). Upper arm–type injuries were found in 36% of this cohort. Similar to the development dataset, no lower arm–type injuries were identified in this study. The two most notable differences were the proportion of patients exhibiting signs of a preganglionic lesion and those with associated injuries. The development dataset reported 74% of patients with signs of preganglionic lesions and 71% with concomitant injuries, whereas only 21% and 28%, respectively, were found in the validation dataset.

Surgical Factors and Outcomes

The median duration from injury to surgical intervention exhibited a notable disparity between the validation dataset (223 days) and the development dataset (169 days). Most patients (73%) underwent surgery more than 180 days after the injury. The donor nerves used in this study included the spinal accessory nerve (31%), a combination of both ulnar and median nerves (29%), the phrenic nerve (15.5%), the median nerve (11%), the intercostal nerve (8.5%), and the ulnar nerve (6%). In this study, 46.5% of patients required an interposition nerve graft, as opposed to 60.5% in the previous study.

Eighteen patients utilized intercostal nerves as donors for nerve transfer surgery. In the development of the prediction model, intercostal nerves were omitted due to their low prevalence. If the inclusion of the intercostal nerve as an explanatory variable is considered, the model would require updating. Given that the primary aim of this study is solely to externally validate the model, patients involving the intercostal nerve were excluded from the validation analysis.

Some missing data were observed in the independent variables, including smoking (11 patients, 5%), graft type (one patient, 1%), and graft length (18 patients, 18%). Among these, smoking status was the only predictive variable with missing values, which were managed through complete case analysis.

Among the cohort of 213 patients, the recovery rates for patients were 2.4%, 11.2%, 35.2%, and 62.4% within 6, 9, 12, and 18 months, respectively. One hundred forty-five patients (68%) had biceps motor power of at least grade 3 within 24 months after nerve transfer surgery, whereas 68 patients (32%) had a grade 2 or less during the last follow-up visit. Therefore, the failure rate of this cohort at 24-month follow-up was 32%. This aligns closely with the failure rate of nerve transfer surgery observed in the development dataset, which is 30%, indicating a comparable outcome to our study.

Table 2. Comparison of Patient Characteristics between Development and Validation Datasets

Baseline Characteristics	Development Cohort, n = 433	External Validation Cohort, n = 213
Patient factors		
Median age (IQR), y	25 (20–32)	25 (20-33)
Males, n (%)	394 (91)	192 (90)
Median BMI (IQR), kg/m^2*	22 (20–25)	23.5 (21.5-25)
Smoking, n (%)*	130 (30)	55 (26)
Injury factors		
Injury to nondominant hand, n (%)	240 (55)	110 (52)
Total arm type, n (%)*	337 (78)	137 (64)
Preganglionic lesion, n (%)	320 (74)	44 (21)
Mechanism of injury, n (%)		
Traction injury	426 (98)	212 (99.5)
Penetrating injury	6 (1)	1 (0.5)
Blast injury	1 (0.2)	0 (0)
Cause, n (%)		
Motorcycle accident	406 (94)	208 (98)
Car accident	12 (3)	1 (0.5)
Others	15 (3.5)	4 (2)
Associated injury, n (%)	308 (71)	59 (28)
Ipsilateral upper extremity fracture*	238 (55)	38 (18)
Lower extremity fracture	97 (22)	24 (11)
Maxillofacial injury	17 (4)	6 (3)
Abdominal organ injury	11 (2.5)	3 (1)
Chest injury	54 (12.5)	11 (5)
Head injury	45 (10)	13 (6)
Ipsilateral vascular injury*	26 (6)	4 (2)
Cervical spine injury	12 (3)	6 (3)
Thoracolumbar spine injury	7 (2)	1 (0.5)
Surgical factors		
Median days to surgery (IQR)	169 (132–203)	223 (177-301)
Days to surgery, n (%)		
>90	412 (95)	210 (99)
>120	362 (84)	203 (95)
>180	182 (42)	155 (73)
>270	13 (3)	74 (35)
Donor nerve, n (%)*		
Ulnar nerve	72 (17)	12 (6)
Spinal accessory nerve	208 (48)	65 (31)
Phrenic nerve	54 (12.5)	33 (15.5)
Median nerve	76 (18)	24 (11)
Ulnar and median nerves	23 (5)	61 (29)
Intercostal nerves	0 (0)	18 (8.5)
Recipient nerve, n (%)		
Musculocutaneous nerve	231 (53)	45 (21)
Nerve to biceps	171 (39.5)	96 (45)
Nerve to brachialis	5 (1)	7 (3)
Nerve to biceps and nerve to brachialis	26 (6)	65 (30.5)
Graft usage, n (%)	262 (60.5)	99 (46.5)
Graft type, n (%)		
Sural nerve	252 (96)	85 (86)
Medial antebrachial cutaneous nerve	9 (3)	7 (7)
Ulna nerve	1 (0.4)	1 (1)
Median graft length (IQR), cm	13 (12–16)	23 (22-23.5)
Unsuccessful surgery, n (%)†	132 (30.5)	68 (32)

IQR, interquartile range.
*Variables included in the prediction model.
†Outcome variable.

Discrimination and Calibration

Figures 2 and 3 display the performance of both the original prediction model and the simplified model through ROC curves. The area under the ROC curve, or c-statistics, was 0.748 (95% confidence interval, 0.674–0.823) for the original model and 0.759 (95% confidence interval, 0.686–0.831) for the simplified model. The performance in the validation dataset was slightly lower (0.017

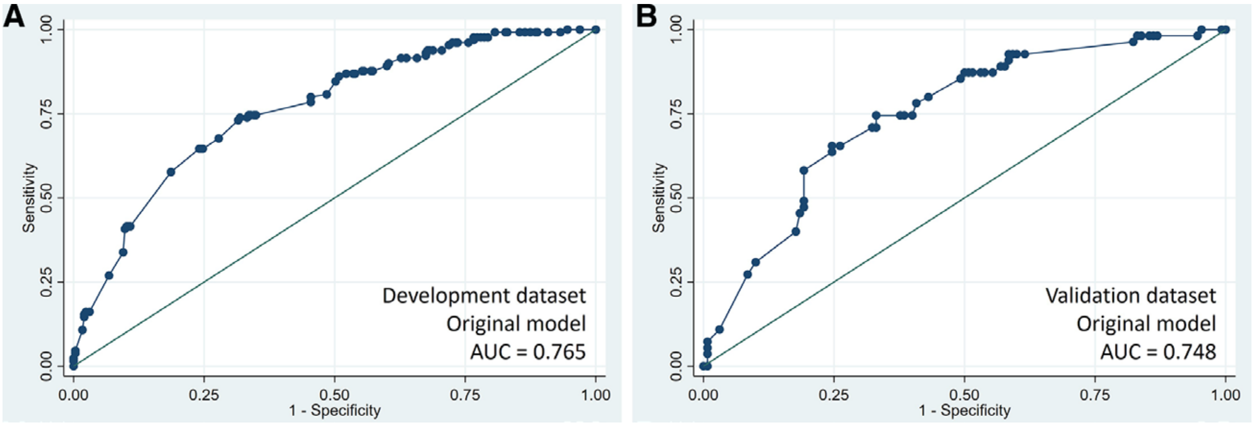

Fig. 2. Graphs representing the ROC curve of the original prediction model performance on the development dataset (A), compared with the validation dataset (B) of unsuccessful nerve transfer surgery for elbow flexion in patients with brachial plexus injuries. AUC, area under the ROC curve.

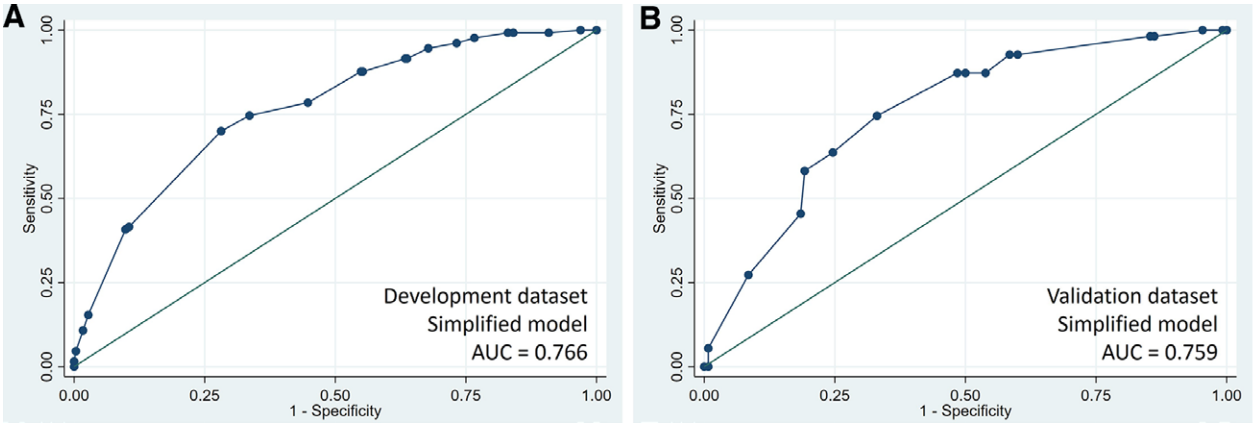

Fig. 3. Graphs representing the ROC curve of the simplified prediction model performance on the development dataset (A), compared with the validation dataset (B) of unsuccessful nerve transfer surgery for elbow flexion in patients with brachial plexus injuries. AUC, area under the ROC curve.

in the original model and 0.007 in the simplified model) than the performance in the development dataset.

Figure 4 illustrates the calibration plot of predicted probability using the original model on the validation dataset, showing good agreement with the observed unsuccessful nerve transfer surgery patients. With a calibration slope of 0.928, slightly less than 1, the estimated risk derived from the prediction model is considered to be increasing with a faster rate than the actual probabilities. This suggests that the estimation tends to be slightly elevated for patients at high risk and slightly underestimated for patients at low risk. The intercept or calibration-in-the-large value was determined to be 0.377, surpassing 0, indicating a slight overall underestimation of the model to predict the actual probabilities. A comparison of predicted probabilities generated by the simplified model against observed outcomes is illustrated in Figure 5.

Additionally, external validation reveals a good agreement between predicted and observed probabilities for both the original model ($P = 0.66$) and simplified model ($P = 0.92$), as demonstrated by the Hosmer–Lemeshow goodness-of-fit test.

DISCUSSION

We conducted a multicenter external validation of the prediction model to assess unsuccessful recovery of elbow flexion after nerve transfer surgery in patients with brachial plexus injury. This model aimed to identify patients at high risk of failure to restore elbow flexion after nerve transfer surgery. To aid in decision-making, four risk groups were established using a simplified model. Free functional muscle transfer should be considered for patients scoring 7 or higher, indicating a high or very high-risk group (>30% failure rate).[32] In this study, performance on an external validation dataset demonstrated that the model exhibits good discrimination and calibration.

Most patients in the validation dataset were enrolled from a tertiary hospital different from the one that contributed to the development dataset. Noteworthy disparities were observed in the patient characteristics. Patients

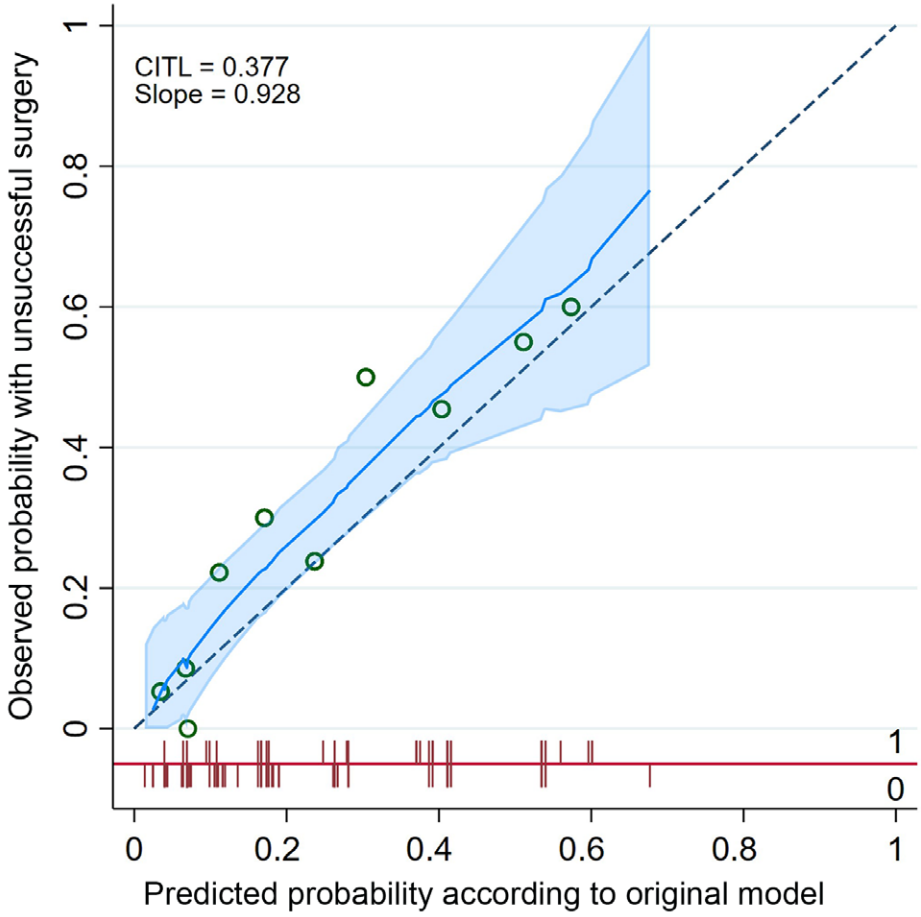

Fig. 4. The calibration plot of predicted probability using the original model on the validation dataset. CITL, calibration-in-the-large.

in the validation dataset displayed a reduced frequency of concomitant injuries and fewer preganglionic lesions, suggesting lower-energy insults. Additionally, surgery in the validation dataset tended to be performed later than in the development dataset. In the validation dataset, 35% of patients underwent surgery 270 days or more after the injury, whereas in the development dataset, this proportion was only 3%. The rate of graft usage was also lower in the validation dataset (46%) compared with the development dataset (60%). Despite these discrepancies, both the original and simplified models exhibited a strong capacity to differentiate between potential failure and successful patients in the validation dataset. This suggests that the six factors in the model are robust, leading to good generalizability, which was previously a point of concern.

Although several levels of calibration methods were proposed, our study used two of four methods, the calibration intercepts and slope, to demonstrate the effectiveness of the prediction model.[39,40] This specific level of calibration, when compared with more advanced calibration techniques, has been considered advantageous for external validation. The calibration intercepts and slope provide a comprehensive and concise assessment of potential discrepancies in risk calibration, particularly in the context of a relatively modest sample size.[39]

Although achieving a higher level of calibration would further confirm the model's applicability for another dataset, it necessitates a larger sample size. However, brachial plexus surgery is among the most technically demanding and time-consuming procedures. Along with its relatively low prevalence, recruiting a larger sample size poses significant challenges. Despite these challenges, additional external validation, particularly in different patient settings, is crucial before integrating the model fully into clinical practice. Above all the outlined limitations, our study demonstrated strong external validity of the prediction model for unsuccessful recovery of elbow flexion after nerve transfer surgery in patients with brachial plexus injuries.

Both the original and simplified prediction models presented in Table 1 serve as valuable tools for assessing the risk of failure after nerve transfer surgery aimed at restoring elbow flexion in patients with brachial plexus injury. However, the simplified model offers enhanced ease of use and practicality for quick calculations in outpatient clinics while maintaining comparable accuracy to the original model. Despite its utility, surgeons intending to utilize

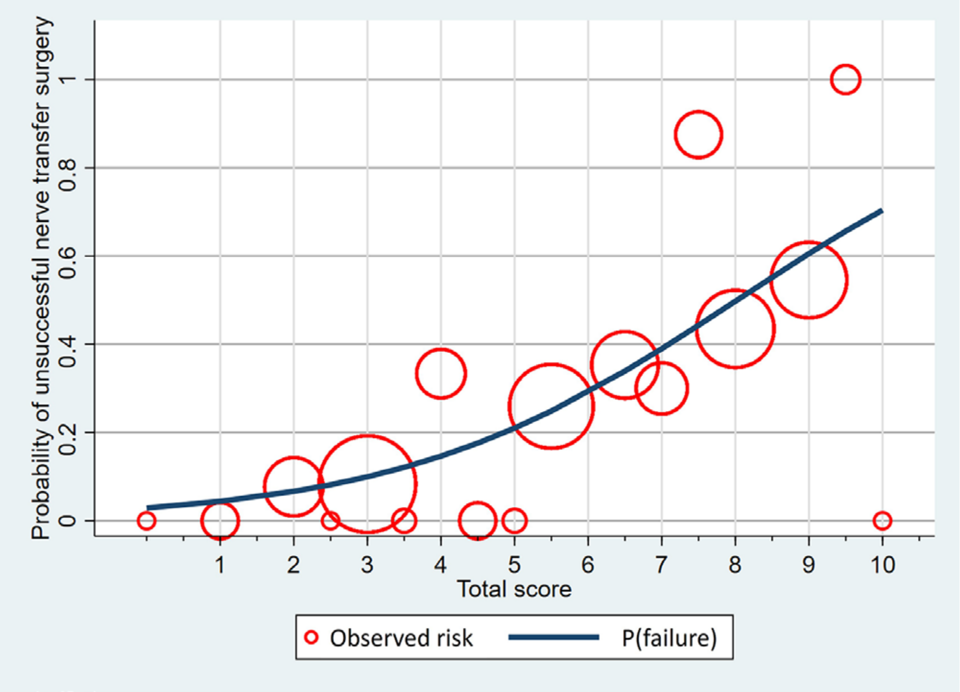

Fig. 5. The calibration plot, with the red circles representing an unsuccessful recovery of elbow flexion after nerve transfer surgery categorized by the patient score from 0 to 10. The size of the circle represents the total number of patients in each score. The blue line represents the probability of failure predicted by the simplified model. A higher score correlates with a higher failure rate of both observed and predicted values.

intercostal nerve as a donor for nerve transfer surgery cannot rely on the model to calculate risk. This limitation arises from the practice within our institution of reserving intercostal nerves for potential future free functional muscle transfer procedures in the event of failed nerve transfer surgery. Consequently, there is a lack of data regarding the beta-coefficients of intercostal nerves within the model.

CONCLUSIONS

This study provides a multicenter external validation for the prediction model concerning unsuccessful recovery of elbow flexion after nerve transfer surgery in patients with brachial plexus injuries. We have demonstrated good discrimination and calibration. With this latest evidence of generalizability, we advocate for its utilization in preoperative counseling and shared decision-making with patients regarding the option of surgery for traumatic brachial plexus injuries. Identifying high-risk candidates may enable them to benefit from a more reliable alternative procedure, that is, free functional muscle transfer surgery, thereby avoiding the costs associated with a failed operation and minimizing prolonged time off work.[13]

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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