Risk Factors and Predictive Models for Early Cerebrospinal Fluid Leak after Anterior Surgery for Degenerative Cervical Myelopathy

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Abstract

OBJECTIVE To investigate the incidence of and risk factors for early cerebrospinal fluid (CSF) leak after anterior surgery for degenerative cervical myelopathy (DCM) and construct risk predictive models.

METHODS Patients diagnosed with DCM and treated with anterior surgery from January 2007 to August 2018 were retrospectively selected. The basic data of preoperative and intraoperative records were extracted. Subsequently, we analyzed the relationship between early postoperative CSF leak and variables by performing restrictive cubic splines (RCS) for continuous variables and univariate and multivariate logistic regression for possible variables. The selected independent variables and covariates were modeled based on the Akaike information criterion (AIC). We generated receiver operating characteristic (ROC) curves and calibration curves to evaluate the nomogram.

RESULTS Seventeen patients had CSF leak, with an incidence of 3.66%. There was a linear relationship between CSF leak and age ($P=0.003$) as well as bleeding loss ($P<0.001$). Variables were selected by logistic regression analysis, including age (per SD) ($OR=2.04$, $P=0.004$), revision surgery ($OR=1.13$, $P=0.032$), ossification of the posterior longitudinal ligament (OPLL) ($OR=4.07$, $P=0.027$), and blood loss (per SD) ($OR=1.75$, $P=0.002$). The predictive model included age (per SD), sex, revision surgery, OPLL, and blood loss (per SD), with c-statistic=0.821.

CONCLUSIONS Older age, revision surgery, OPLL and more intraoperative blood loss were independent risk factors for early postoperative CSF leak. The predictive model can be used to guide the prevention of CSF leak in DCM patients.

Introduction

Degenerative cervical myelopathy (DCM) is a chronic compressive disease of the spinal cord due to degeneration of the cervical spine. It is a collective term for pathological changes such as cervical spondylotic myelopathy, cervical disc herniation, and ligament hypertrophy or ossification[1]. According to statistics, DCM is the most common disease leading to chronic spinal cord injury, and its incidence is increases with age, thus it has become an important cause of spinal cord dysfunction in the middle-aged and elderly population[2].

Anterior cervical surgery is currently one of the main treatments for DCM[3,4]. Common anterior cervical procedures include anterior cervical discectomy and fusion (ACDF), anterior cervical corpectomy and fusion (ACCF), and artificial disc replacement (ADR). However, due to the complex anatomical structures such as vessels, nerves, trachea and esophagus in the anterior cervical spine, anterior surgery has many potential complications, including adjacent segment degeneration, dysphagia, C5 nerve root palsy, pseudoarthrosis, implant-related complications, and cerebrospinal fluid (CSF) leak[5–7]. Among them, CSF leak is one of the early serious complications after surgery, and its incidence has been reported to be between 0.03 and 7.7%[5]. Hence, it is essential for the prognosis of DCM patients to prevent the occurrence of CSF leak after surgery.

Materials And Methods

Study population

The records of cases admitted to our department from January 2007 to August 2018 that met the diagnosis of DCM and were treated with anterior surgery were searched. A total of 465 cases that met the inclusion and exclusion criteria were included. The patient and operation data were entered. The outcome we cared about was the occurrence of CSF leak within the period of postoperative discharge to discharge based on International Classification of Diseases, Tenth Revision (ICD-10) codes (G96.005). This study was approved by the Institutional Review Board of Airforce Military Medical University Tangdu Hospital (TDLL-No. 202111-06). Patient consent was waived as the study data were from the medical records which was approved by the Institutional Review Board of Airforce Military Medical University Tangdu Hospital. All methods were performed in accordance with the relevant guidelines and regulations.

Inclusion and exclusion criteria

Patients were included when they met the following inclusion criteria: (a) diagnosis of DCM[8,9]; (b) underwent anterior cervical decompression and fusion surgery, including ACDF, ACCF, or ACDF + ACCF (Hybrid); and (c) not younger than 18 years at the time of surgery. The exclusion criteria were as follows: (a) cases had not clinically presented myelopathy symptoms; (b)cases who had undergone posterior surgery or other sites (such as thoracic and lumbar decompression surgery, etc.); (c) the approach was microendoscopic or microscope-assisted surgery.

Data Analysis

The differences between the CSF leak and no CSF leak groups were compared with the t test and the chi-square test. Restricted cubic spline (RCS) curves were used to reflect the relationships between continuous variables and outcome measures (dependent variables). If the two meet the linear relationship, binary logistic regression analysis can be performed. If the two are nonlinear, it is necessary to transform independent variables into categorical variables before the regression analysis. Univariate and multivariate binary logistic regression were used to determine the independent risk factors of which effects were represented by odds ratios (ORs) and 95% confidence intervals (95% CIs). Covariates were screened by the method of one-by-one inclusion or exclusion according to accepted criteria: (a) a change in effect estimate of more than 10%; (b) associations with the outcomes of interest[10]. For the selection of the predictive model, we used the Akaike information criterion (AIC) stepwise method and selected the combination with the smallest AIC score as the optimal model[11]. The discrimination of the model was evaluated using the area under the curve (AUC) of the receiver operating characteristic (ROC) curve or Harrell's concordance statistics (C-statistics). To avoid overfitting, internal validation was performed using the bookstrap repeated sampling method with 500 samples. A calibration curve was formed to evaluate the calibration of the model. Statistical significance was considered at $P < 0.05$. Data were analyzed with the use of SPSS, version 26 (IBM, USA), statistical packages R (The R Foundation; http://www.r-project.org; version 3.6.3) and Empower (R). Graphpad Prism, version 9 performed the forest plots.

Results

Patient Characteristics

CSFL occurred in 17 of 465 DCM patients after surgery, with an incidence of 3.66%. The patients were divided into the CSF leak group and the no CSF leak group. and the differences in the parameters were compared between the two groups. The results showed that age ($P < 0.001$), sex ($P = 0.070$), revision surgery ($P < 0.001$), OPLL ($P < 0.001$), and blood loss ($P < 0.001$) were statistically significant (Table 1).

Linear relationship between the risk of CSF leak and continuous variables.

The RCS showed that age ($P = 0.003$) and blood loss ($P < 0.001$) had a linear relationship with CSF leak, but BMI, course of disease, operation duration, and baseline mJOAS had no significant linear or nonlinear relationship with CSF leak ($P > 0.05$) (Fig. 1). The risk of CSF leak increases with age as well as with the amount of bleeding. Before the age of 53 years, the risk of CSF leak is less than 1, and when the age exceeds 53, the incident risk of CSF leak is more than 1; similarly, when the amount of bleeding exceeds 154 ml, there is a risk of CSF leak.

Independent the risk factors for CSF leak.

Univariate regression analysis showed that age per year increase (OR = 1.02, $P < 0.001$), age per SD increase (10.93 years, OR = 2.59, $P < 0.001$), revision surgery (OR = 7.70, $P < 0.001$), history of hypertension (OR = 2.86, $P = 0.038$), OPLL (OR = 8.12, $P < 0.001$), blood loss per 1 ml (OR = 1.003, $P < 0.001$), and blood loss per SD increase (178 ml, OR = 1.84, $P < 0.001$) were statistically significant (Supplementary table 1).

The results of stepwise forward multivariate regression showed that age per SD increase (OR = 2.40, $P = 0.004$), revision surgery (OR = 4.24, $P = 0.032$), OPLL (OR = 4.07, $P = 0.027$), and blood loss per SD (OR = 1.75, $P = 0.002$) were statistically significant (Table 2). To verify the independence of each included variable, 5 covariates were screened, including sex, operative levels, history of hypertension, course of disease, and operation duration (Supplementary table 2-3). The OR and 95% CI were calculated after adjusting for confounding factors, and a forest plot was presented to visualize the differences before and after adjustment (Fig. 2).

Formulation of predictive models and nomograms of risk score

Independent risk factors and covariates were included as prognostic variables to formulate the predictive model: age per SD, sex, revision, OPLL, blood loss per SD, surgery levels, history of hypertension, course of disease, and operation duration. Stepwise screening was performed based on the AIC of each permutation of AIC, and the optimal model was selected: age per SD, revision, OPLL, blood loss per SD, and sex (Supplementary table 4). In addition, because blood loss can only be measured intraoperatively, we constructed a preoperative model with intraoperative factor removed in order to evaluate the risk score of CSF leak before the operation (Supplementary table 5). A nomogram was presented to simply calculate the risk score (Fig. 3).

Validation of the predictive models

The ROC curves and internal validation results of the two models were shown to evaluate discrimination (Fig. 4). As seen from the AUC of ROC curves, the C-statistics of the optimal model was 0.836 (0.725, 0.946) and, with bookstrap 500, was 0.821 (0.688, 0.930); the C-statistics of the preoperative model was 0.799 (0.684, 0.914) and, with bookstrap 500, was 0.792 (0.669, 0.900). Additionally, the changes in C-statistics were plotted. With the introduction of factors step by step, the C-statistics approached 1 (Fig. 5). The calibration diagram of the models is shown in Fig. 6.

Discussion

Etiology of CSF leak after anterior cervical surgery

Except for spontaneous factors, the occurrence of CSF leak is generally due to intraoperative incidental durotomy (ID) or incidental dural tear (IDT) when cutting off the ossified posterior longitudinal ligament and osteophytes on the posterior surface of the vertebral body and removing the adherent nucleus pulposus. Although most ID/IDTs can be found during surgery, small tears with intact arachnoid membranes may be overlooked, and because of the complex anatomy of the anterior cervical vertebra and the narrow approach, it is difficult to repair, which also increases the possibility of postoperative CSF leak[12]. Therefore, any factor that can increase tissue adhesiveness, reduce toughness and thickness, or make the operation duration longer and more difficult may be a risk factor for CSF leak.

Incidence of CSF leak after anterior cervical surgery

Previous reports on the incidence of CSF leak after anterior cervical surgery vary greatly. The results of the systematic review showed that the incidence of CSF leak ranged from 0.03 to 7.7% in previous retrospective studies and 0.2 to 1% in prospective studies[5]. Another meta-analysis showed that the comprehensive incidence of dural tears in spinal surgery was 5.8% (95% CI = 4.4, 7.3). The reason for the difference was related to the location and type of spinal surgery[13]. The incidence of CSF leak in this retrospective study was 3.66%, which is within the range of reports in the literature. The higher incidence in this study may be because the patients included in this study had cervical myelopathy, all of whom presented with symptoms of spinal cord compression, and their dura mater was naturally involved. Previous clinical investigations have also shown that patients diagnosed with cervical myelopathy have a higher incidence of postoperative CSF leak than other types, in accord with our results[14,15]. In addition, due to the popularity of techniques and referral limitations, most patients who visited our hospital for cervical surgery were in severe condition, which is probably another reason.

Risk factors for early postoperative CSF leak after anterior cervical surgery

It has been previously reported that the risk factors for CSFL after anterior cervical surgery include age, sex, BMI, revision surgery, history of hypertension, OPLL, spinal stenosis, surgery levels, and intraoperative blood loss[15–21]. However, the conclusions are also very different in different studies, which may be related to the discrepancy between the included samples. The conclusion of this study was that age, revision history, surgical OPLL, and blood loss were independent risk factors for CSF leak.

Age is usually a risk factor for a variety of diseases due to the aging of cells and degeneration of tissues. With increasing of age, dural degeneration makes its thickness thinner, and traction resistance decreases, so dural tears are more likely to occur [22]. The regression model of Kapadia et al.[15] showed that the risk of CSF leak was 1.25 times higher in the age group of 55–69 years age group than in the 40–54 years age group ($P = 0.038$, 95% CI: 1.01, 1.55), while the risk increased to 1.64 in the age group above 70 years age group ($P = 0.001$, 95% CI: 1.22, 2.20). Ehresman et al.[16] showed that the risk of ID/IDT increased by an average of 0.03 ($P < 0.001$, 95% CI: 1.012, 1.048) for per year of age. We found through the RCS curve that age and CSF leak had a linear relationship ($P = 0.003$), and that the risk of CSF leak rose continuously with increasing age. Moreover, the risk of CSF leak had a 1.09-fold change for every 11-years increase. When the age is over 53 years, the risk value is greater than 1, suggesting a higher risk of CSF leak after surgery for patients over 53 years.

In some patients, spinal symptoms are not relieved or recur after surgery, so revision surgery, a second operation in the same site, is necessary. Hannallah et al.[20] showed that patients who underwent revision surgery had a 2.75-fold higher incidence of CSF leak than those who underwent primary anterior surgery ($P = 0.05$, 95% CI: 0.85, 8.93). In this study, 17.9% (5/28) of revision surgery cases developed CSF leak, with a risk of 6.41 times that of primary surgery. The scar occurred after repetitive surgeries at the same level and adhered to the spine dura mater, predisposing patients to ID/IDT when separated[16]. Cunningham et al.[23] found in a rabbit laminectomy model that a second operation resulted in elevated TGF-β expression, which caused epidural fibrosis and aggravated adhesions, further increasing the risk of ID/IDT.

Studies have shown that the incidence of OPLL in the Asian population is high (2.4%), and the most common site is the cervical spine[24]. OPLL can lead to cervical spinal stenosis, causing spinal cord compression. Therefore, the incidence of OPLL is also higher in patients with DCM. The incidence of OPLL in this study was 7.5% (31/383), which may also be one of the reasons for the higher incidence of CSF leak in this sample. According to the literature, OPLL has been recognized as a risk factor for the occurrence of CSF leak in spinal surgery. Cervical OPLL usually presents with dura ossification (DO), and it is a great technical challenge to separate the ligament from the posterior longitudinal ligament once the ossified dura mater is fused with the posterior longitudinal ligament[25]. Hannallah et al.[20] reported that the incidence of CSF leak in patients with OPLL after cervical spine surgery was 12.5%, which was 13.7 times higher than that in the group without OPLL, and the data in our survey turned out to be 4.45. Considering the high risk of CSF leak for patients with OPLL, the ossified posterior longitudinal ligament may not be forcibly removed during the operation instead of being floated using a burr or ultrasonic osteotome. Otherwise, posterior surgery, such as open-door laminoplasty, may be performed[26].

A study of Desai et al.[19] argued that there was a significant correlation between intraoperative blood loss and ID/IDT (534.4/288.9 ml, $P < 0.001$). In anterior cervical surgery, bleeding likely contributes to the complex course and rich blood supply in the cervical epidural venous plexus. Due to more blood loss, the visual field of the operation area is unclear, which more easily causes ID/IDT. This study found that there was a linear relationship between the amount of bleeding and CSF leak ($P < 0.001$). Each additional bleeding of 178 ml increased the risk of CSF leak by 54%. Notably, 154 ml is a cutoff of interest. Once the amount of bleeding exceeds this volume, the risk effect of CSF leak will be greater than 1.

Previous studies have been highly controversial regarding gender differences in CSF leak. Takahashi et al.[27] reported in a study of risk factors for IDT in lumbar surgery that the incidence of IDT was significantly higher in women (5.6%) than in men (3%) ($P < 0.05$). A multicenter observational study by Ishikura et al.[17] also yielded similar conclusions (OR = 1.47, $P < 0.001$), but neither study proposed a reasonable explanation for the gender difference. The data obtained by Fam et al.[28] after analyzing skull base dural thickness in 20 cadavers indicated that dural thickness was thinner in women than in men ($P = 0.06$), which may be evidence to explain the former conclusion. However, disappointingly, Kwon et al.[22] showed that there was no significant difference in cervical capsule thickness between women and men ($P = 0.347$). In summary, there is no direct evidence that gender is one of the risk factors for CSF leak.

Evaluation and significance of predictive models

The evaluation indicators of the predictive model included discrimination and calibration[11]. Discrimination is the ability of the model to identify an event that occurs or does not, while calibration reflects the degree of consistency between the prediction and the actuality. The ROC curves can provide more sensitive measurements of discrimination, that is, C-statistics[29]. Our optimal model and preoperative model both had good discrimination (C-statistics > 0.5), and the forest plot of C-statistics further illustrated that with the introduction of variables, the discrimination of the model became increasingly better. Although the Hosmer-Lemeshow test is a relatively succinct method in calibration evaluation, it is blunted to test due to the dependency on sample size. The use of calibration curves, however, can take full advantage of the graph to respond to the calibration level of models[11,30].

Although it is a rare complication in anterior cervical surgery, CSF leak after cervical surgery becomes a challenge for surgeons due to its insidious occurrence and serious sequelae. Once CSF leak occurs, continuous lumbar drainage or permanent cerebrospinal fluid shunting are required, which reduces the quality of life and increases the economic burden for patients. Some may even die of severe meningitis or pneumocephalus[31]. Our predictive model includes an optimal model of five variables as well as a preoperative model with removal of intraoperative blood loss, which can be used for risk assessment at different stages. For example, the preoperative model can be used to guide the preoperative level of care and management. For patients with CSF leak, repair devices and materials should be prepared in advance to cope with unavoidable durotomy and tears. Microsurgery can be another selection if possible[32]. In another example, the removal of ossified ligaments during surgery has become a controversial topic. Some researchers believe that there may be herniated intervertebral disc substances in the ossified posterior longitudinal ligament, which should be removed together. The other view is that the posterior longitudinal ligament should be removed only when there is significant evidence[20]. The risk score calculated by the model can replace the subjective judgment of the surgeons and make them comprehensively consider whether to remove the posterior longitudinal ligament based on the risk and benefit.

Limitations

Our study has several limitations. First, this study was not a multicenter study, and the sample size was small. There were only 17 cases of cerebrospinal fluid leakage, which could not well reduce the sampling error. Second, the data were obtained from the medical records during hospitalization, so the patient's condition after discharge was unknown which caused the incompleteness of the data in time. Furthermore, all of the patients included in this study underwent open surgery, so the timeliness of the study may be reduced as microscope-assisted surgery develops further. Finally, our model included only five variables, which may limit the prediction ability. Therefore, we need to collect more case data to expand the sample size and conduct prospective studies to improve the level of evidence. Cases undergoing microscopic surgery should also be included. Last but not least, more scientific analytical methods should be used for further data mining, and more variables that can be included in the model should be found to improve its predictive power.

Conclusions

Older age, revision surgery, OPLL and more intraoperative blood loss were independent risk factors for early postoperative CSF leak. The predictive model had a good discrimination and calibration so that could be used to guide the prevention of CSF leak in DCM patients.

Declarations

Data availability

The datasets generated and/or analysed during the current study are not publicly available due further study but are available from the corresponding author on reasonable request.

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Author contributions

J.Q. and C.Z. designed the study. W.H., M.W. and F.W. collected the data and drafted the manuscript. W.H. and M.D. statistically analyzed the data. K.Z., H.G., J.Q. and C.Z. commented on and critically revised the manuscript.

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Competing interests

The authors declare no competing interests.

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Tables

TABLE 1. Characteristics of postoperative cerebrospinal fluid leak after anterior cervical spine surgery

Parameters	Total (%)	No CSF leak (%)	CSF leak (%)	*P* Value
Total	465 (100)	448 (96.3)	17 (3.7)	
Mean age ± SD, yrs	52.9 ± 10.9	52.6 ± 10.8	62.7 ± 10.8	**<0.001**
Sex				0.070
Male	313 (67.3)	305 (97.4)	8 (2.6)	
Female	152 (32.7)	143 (94.1)	9 (5.9)	
Mean BMI ± SD, kg/m^2	23.6 ± 2.5	23.6 ± 2.6	24.0 ± 1.7	0.529
Smoke	152 (32.7)	150 (98.7)	2 (1.3)	0.061
Drink	33 (7.1)	33 (100)	0 (0)	0.497
Revision	28 (6.0)	23 (82.1)	5 (17.9)	**<0.001**
Hypertension	95 (20.4)	88 (92.6)	7 (7.4)	0.064
Diabetes	43 (9.2)	40 (93.0)	3 (7.0)	0.429
Osteoporosis	11 (2.4)	11 (100)	0 (0)	0.513
Mean course of disease± SD, mths	26.0 ± 47.6	25.2 ± 46.6	47.1 ± 68.0	0.063
Mean baseline mJOAS ± SD	13.1 ± 0.8	13.1 ± 0.8	12.9 ± 0.7	0.644
OPLL	31 (7.5)	25 (80.6)	6 (19.4)	**<0.001**
Spinal stenosis	106 (22.8)	101 (95.3)	5 (4.7)	0.713
Spinal procedure				0.467
ACDF	285 (61.3)	277 (97.2)	8 (2.8)	
ACCF	158 (34.0)	150 (94.9)	8 (5.1)	
Hybrid	22 (4.7)	21 (95.5)	1 (4.5)	
Surgery levels				0.125
1 level	350 (75.3)	339 (96.9)	11 (3.1)	
2 levels	99 (21.3)	95(96.0)	4 (4.0)	
≥3 levels	16 (3.4)	14 (87.5)	2 (12.5)	
Mean operation duration ± SD, min	146.6 ± 63.9	145.5 ± 63.5	175.6 ± 69.0	0.057
Mean blood loss ± SD, ml	196.3 ± 178.1	188.6 ± 167.2	397.1 ± 306.4	**<0.001**

Abbreviations：CSF, cerebrospinal fluid; BMI, body mass index; mJOAS, modified Japanese orthopaedic association score; OPLL, ossification of the posterior longitudinal ligament; ACDF, anterior cervical discectomy and fusion; ACCF, anterior cervical corpectomy and fusion. Boldface type indicates statistical significance.

TABLE 2. Mutivariable analysis for risk of postoperative cerebrospinal fluid leak after anterior cervical spine surgery

Parameters	OR (95% CI)	*P* Value
Age per SD	2.40 (1.33, 4.34)	0.004
Revision	4.24 (1.13, 15.86)	0.032
OPLL	4.07 (1.17, 14.13)	0.027
Blood loss per SD	1.75 (1.24, 2.47)	0.002

Abbreviations: OR, odds ratio; CI, confidence interval; OPLL, ossification of the posterior longitudinal ligament.

Figures

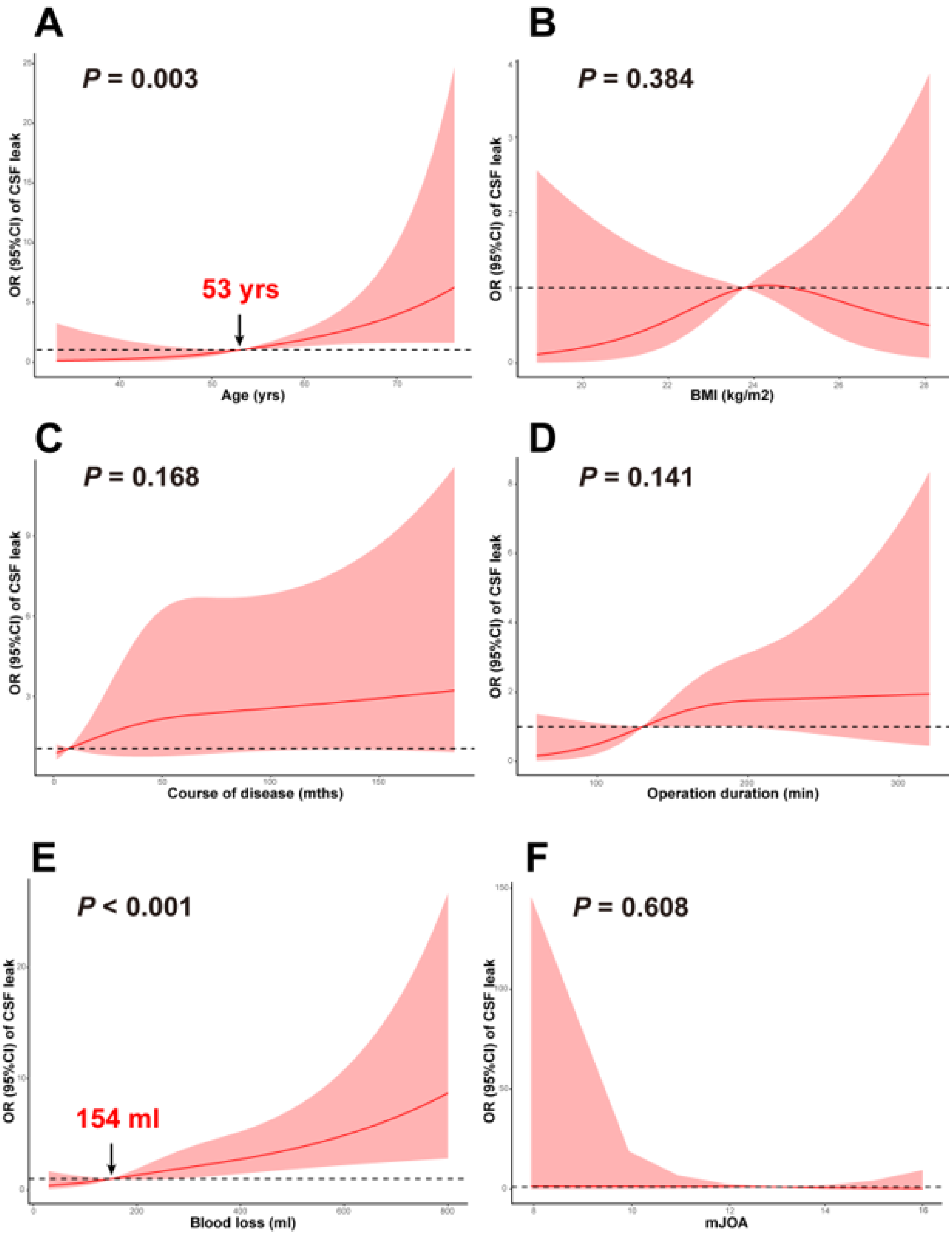

Figure 1

The relationships between continuous variables and risk of CSF leak. The threshold, nonlinear associations between age (A), BMI (B), course of disease (C), operation duration (D), blood loss (E), and baseline mJOA (F) were found in a generalized additive model (GAM) demonstrated by restrictive cubic splines (RCS) curves flexibly modeled with 3 knots at the 10th, 50th, and 90th percentiles. The solid red line represents the smooth curve fit between variables. Red bands represent the 95% CI from the fit.

Reference lines for no association are indicated by the dotted lines at an odds ratio of 1.0. CSF, cerebrospinal fluid; BMI, body mass index; mJOAS: modified Japanese orthopedic association score.

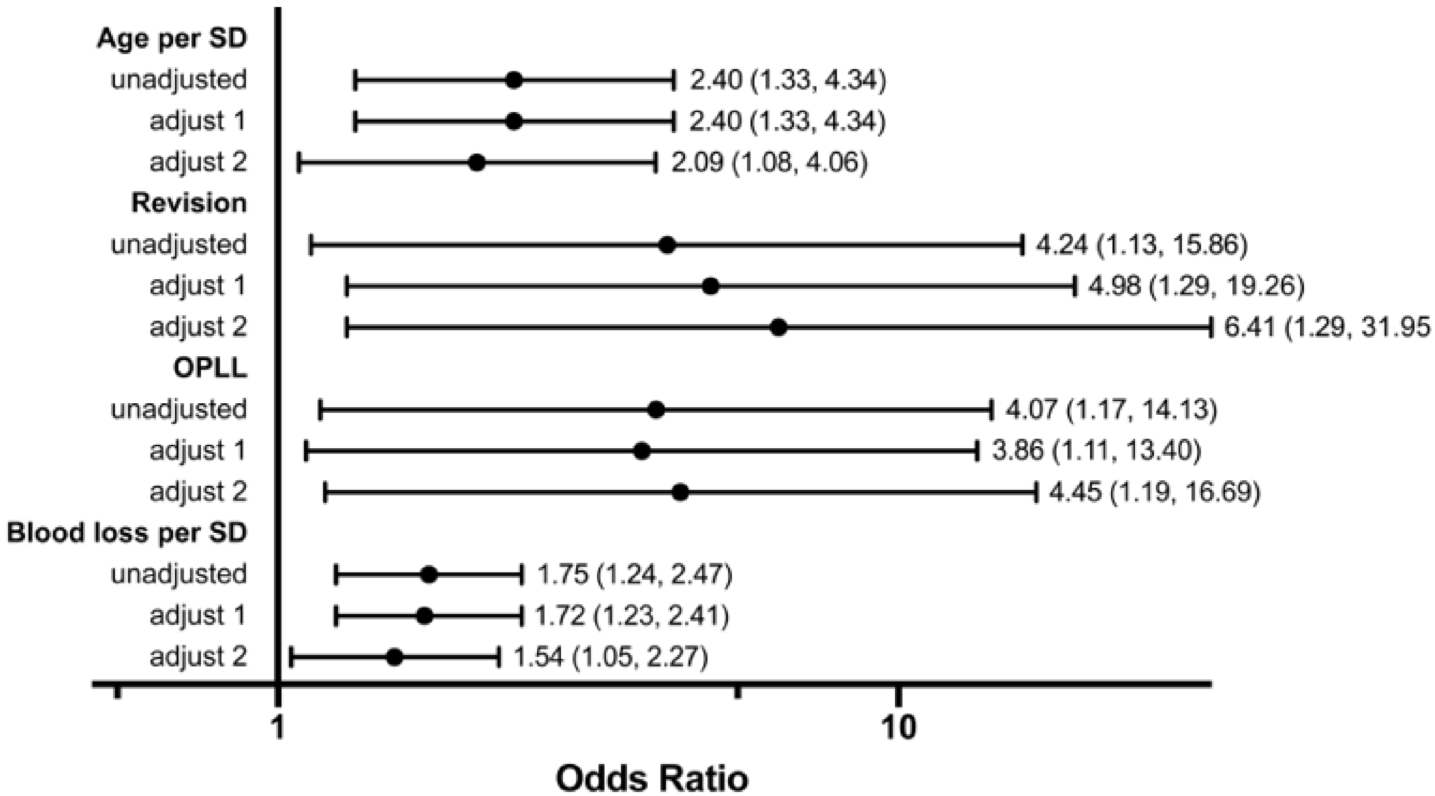

Figure 2

Odds ratio plot for adjusted risk of the postoperative CSF leak. The odds ratio (OR) and 95% confidence interval (95% CI) are demonstrated following the bars. Adjust 1: adjust for sex. Adjust 2: adjust for sex, surgery levels, course of disease, operation duration, hypertension. OPLL, Ossification of the posterior longitudinal ligament.

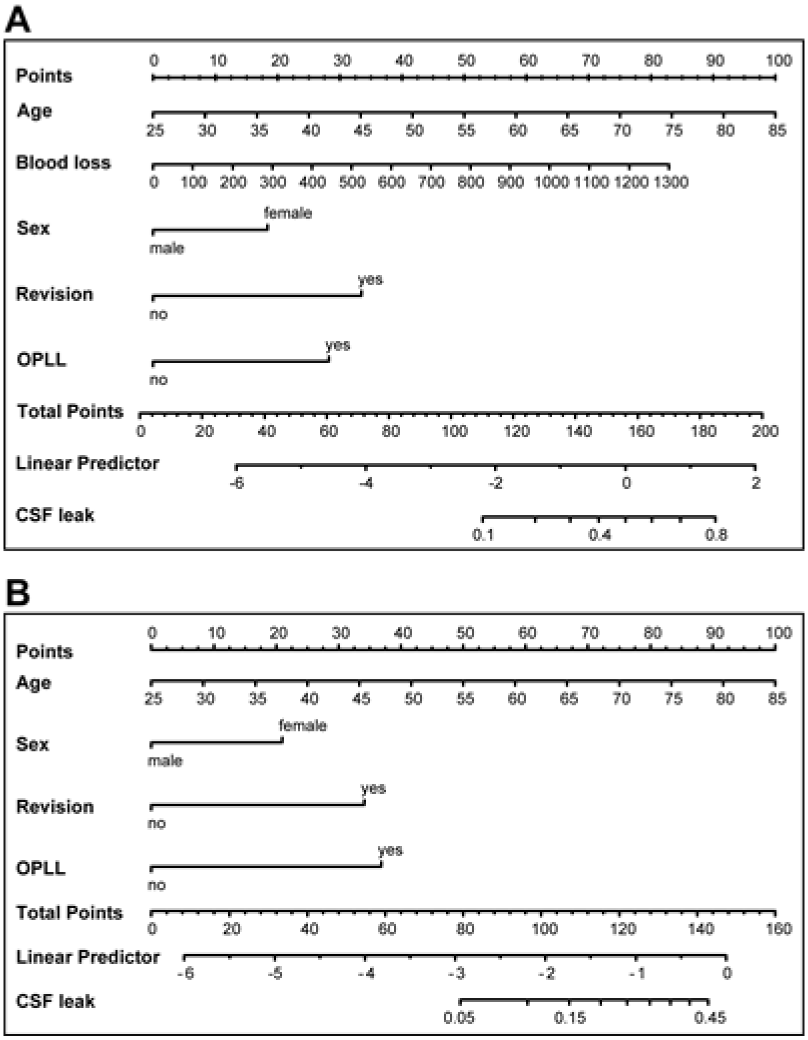

Figure 3

Nomogram for risk score of CSF leak. **A**, Optimal model; **B**, Preoperative model. CSF: cerebrospinal fluid; OPLL, Ossification of the posterior longitudinal ligament.

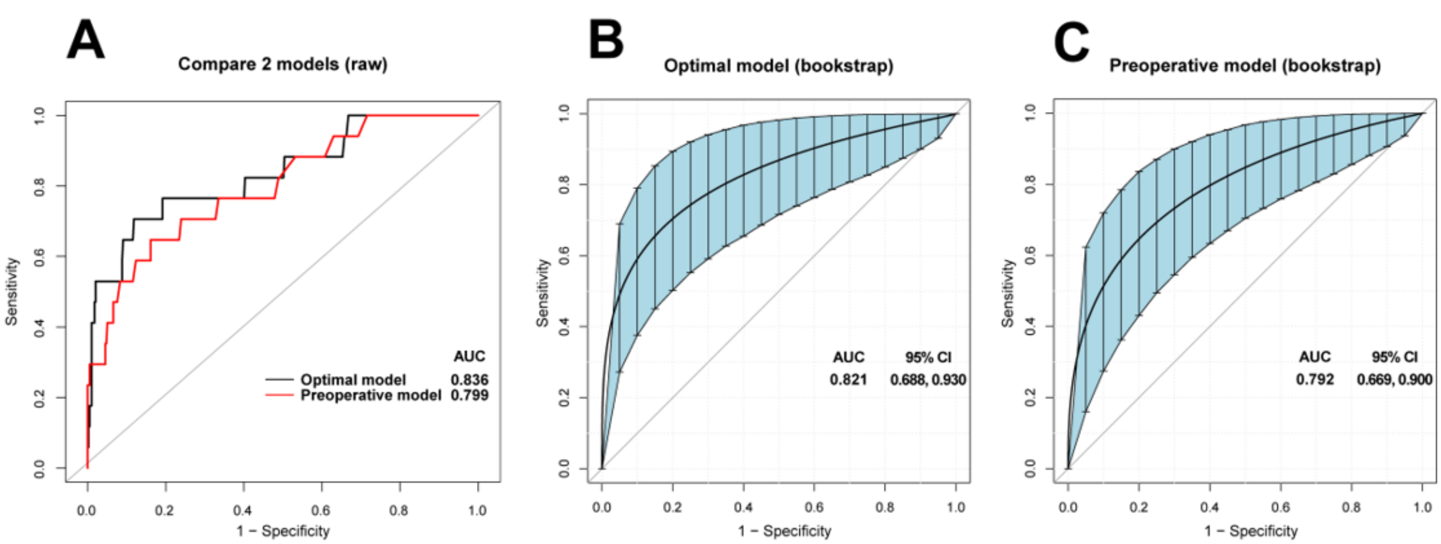

Figure 4

ROC curves of the two predictive models. ROC showing results for selected predictive models of CSF leak. Sensitivity versus one minus specificity plotted for every observed threshold. **A** The curves compare two models in different colors. **B** and **C**, ROC of the optimal model and the preoperative model. Blue shading shows the bookstrap estimated 95% CI with the AUC. AUC, Area under the curve.

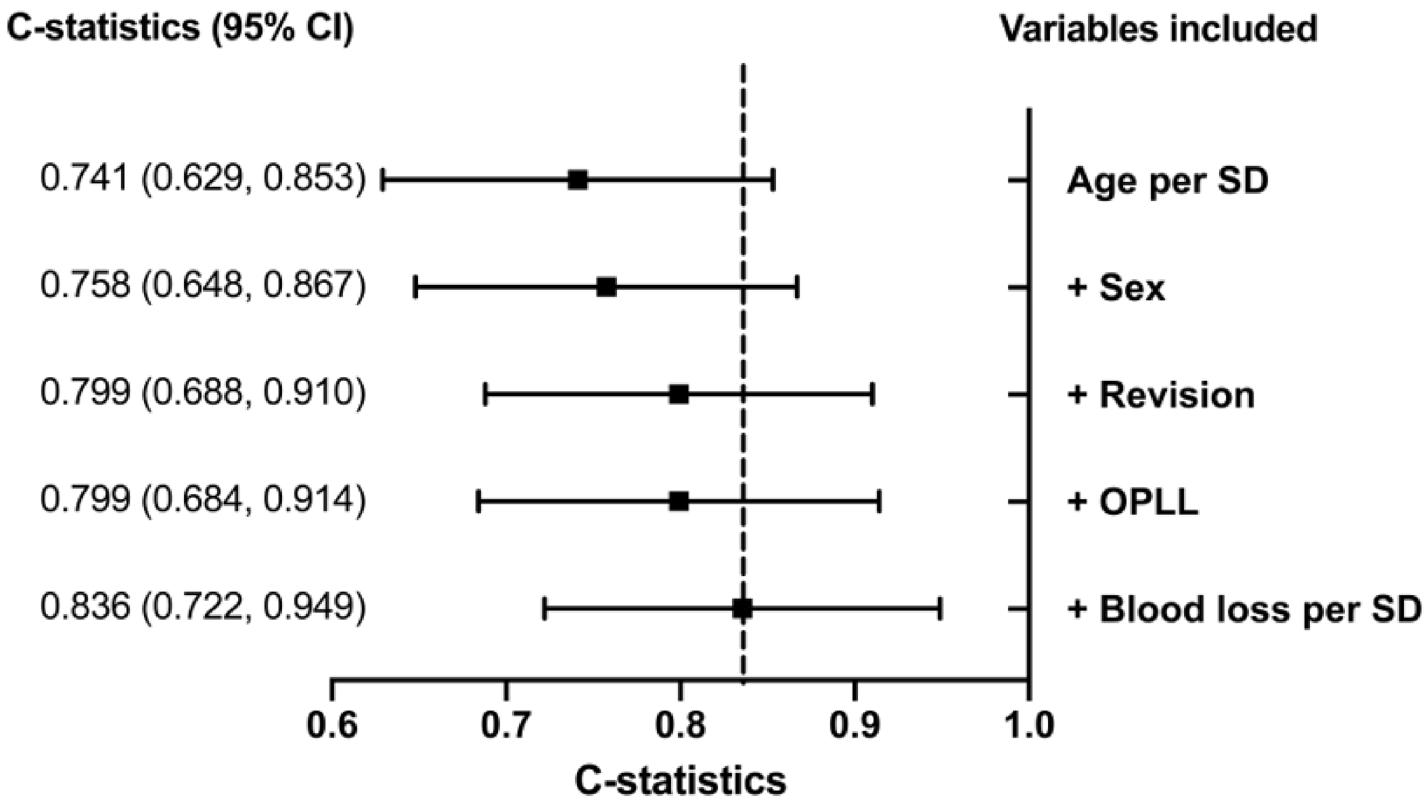

Figure 5

Forest plot showing C-statistics (95% CI) for prognostic factors in predictive models of CSF leak.

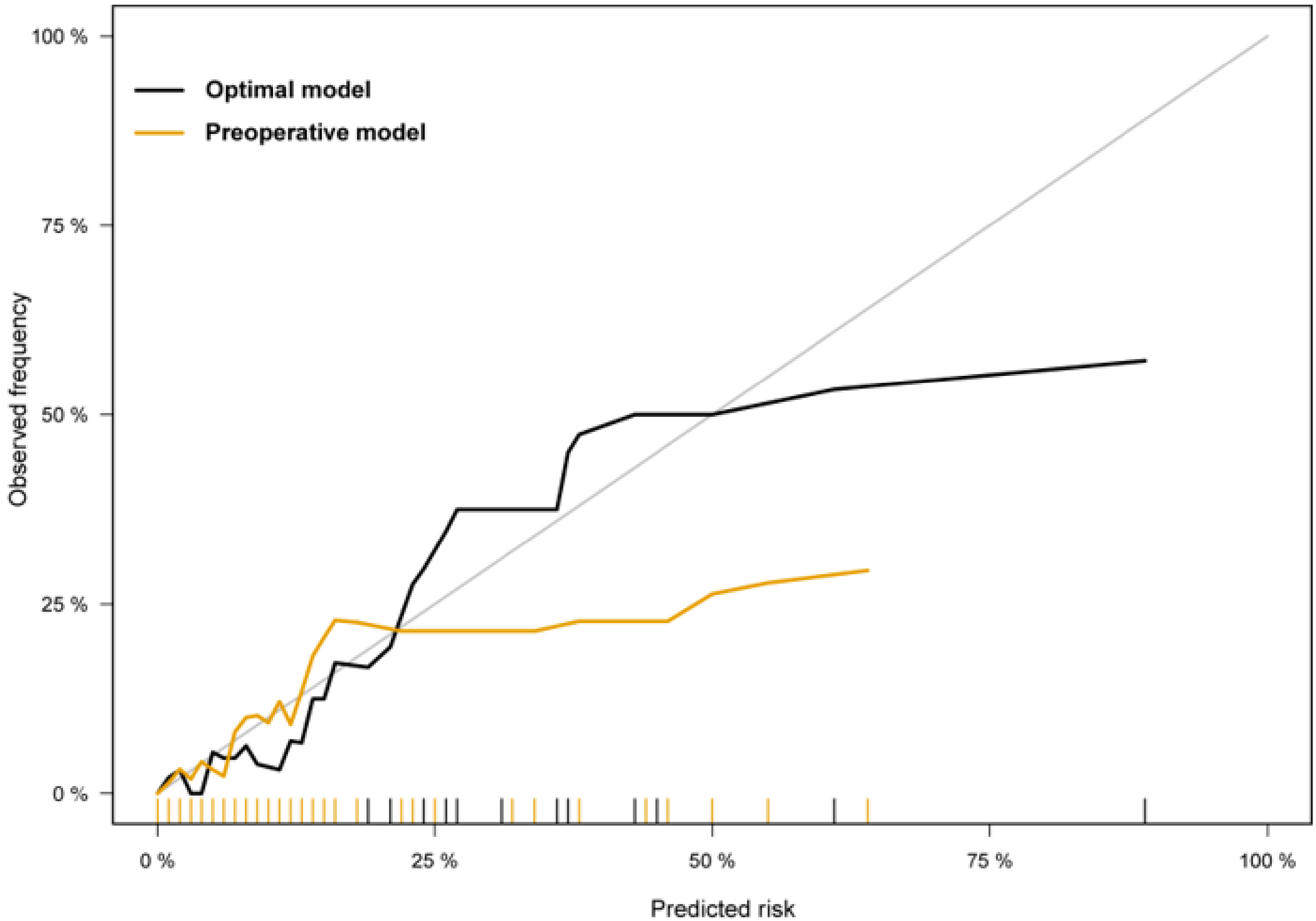

Figure 6

Calibration plot of the two predicting models showing the mean predicted risk versus the observed proportion of CSF leak, expressed in percentage terms.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarytable15.docx