Predictive Risk Factors of Poor Preliminary Postoperative Outcome for Thoracic Ossification of the Ligamentum Flavum

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Objective: The aim of the present study was to ascertain the independent risk factors of poor preliminary outcome and to reveal the value of these factors in predicting the postoperative prognosis.

Methods: A total of 165 patients diagnosed with thoracic myelopathy because of thoracic ossification of the ligamentum flavum (TOLF) were enrolled in this retrospective study. All of them underwent posterior decompressive laminectomy surgery in our hospital from May 2016 to June 2019. The postoperative improvement of symptoms was evaluated using the modified Japanese Orthopaedic Association (mJOA) scoring system. Clinical data, such as age, sex, body mass index (BMI), duration of symptoms, history of hypertension and diabetes, tobacco use, history of drinking, symptoms of incontinence, number of compressed segments, and preoperative mJOA score, were respectively recorded. Radiologic features data included sagittal maximum spinal cord compression (MSCC), axial spinal canal occupation ratio (SCOR), grades and extension of increased signal on sagittal T2-weighted images (ISST2I), types of increased signal on axial T2-weighted images (ISAT2I), and the classification of ossification on axial CT scan and sagittal MRI. The t-test, the χ2-test, Fisher’s exact test, binary logistic regression analyses, receiver operating characteristic (ROC) curves, and subgroup analyses were used to evaluate the effects of individual risk predictors on surgical outcomes.

Results: A total of 76 men and 89 women were enrolled in this study. The mean age of all patients was 58.53 years. After comparison between two groups, we found some risk factors that may be associated with postoperative outcomes, such as age, preoperative mJOA score, BMI, history of hypertension, MSCC, SCOR, grade and extension of ISST2I, type of ISAT2I, axial type of ossification, and sagittal type of ossification (P < 0.05, respectively). Binary logistic regression analysis revealed that older age (odds ratio [OR] = 1.062, 95% confidence interval [CI] = 1.006–1.121, P = 0.030), number of compressed segments (OR = 1.916, 95% CI = 1.250–2.937, P = 0.003), bilateral and bridged types of ossification (OR = 4.314, 95% CI = 1.454–8.657, P = 0.019; OR = 6.630, 95% CI = 2.580–17.530, P = 0.004), and grade 1 and 2 ISST2I (OR = 8.986, 95% CI = 3.056–20.294, P < 0.001; OR = 7.552, 95% CI = 3.529–16.004, P < 0.001) were independent risk factors for a poor preliminary postoperative outcome. ROC curve analysis showed that the grade of ISST2I had an excellent discriminative power (area under the curve [AUC] = 0.817). In addition, risk factors have different values for predicting the clinical outcome in each subgroup.

Conclusion: Age, duration of symptoms, number of compressed segments, SCOR, grade, and extension of ISST2I and classification of ossification were associated with the preliminary prognosis, and the intramedullary increased signal on sagittal T2-weighted MRI was highly predictive of poor postoperative outcome.

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Grant source: This work was supported by grants from the National Natural Science Foundation of China (81672200 and 81871804) and the National Key Research and Development Project (CN) (2019YFC0121400).

Disclosure: The authors confirm that they have no conflict of interest with respect to the manuscript content or funding.

Received 19 August 2020; accepted 26 October 2020
**Key words:** Clinical outcome; Ossification of the ligamentum flavum; Predictive factors; T2-weighted high signal change

**Introduction**

Thoracic ossification of the ligamentum flavum (TOLF) is a rare disease that is recognized as a major cause of thoracic spinal canal stenosis and thoracic myelopathy. TOLF is one of the presentations of degenerative changes of the spinal column and a systematic ossification trait of the vertebral ligaments due to aging. It is characterized by chronic ossification of the ligamentum flavum. In 1920, Polgar first reported that TOLF may be the cause of thoracic myelopathy. Enlarged ossification of the ligamentum flavum reduces the space of the thoracic spinal canal and leads to severe compression of the spinal cord and nerve roots, resulting in numerous slowly progressive clinical symptoms, including numbness, pain, motor weakness, gait disturbance, sensory abnormality of the trunk or lower extremities, and urinary dysfunction. Thoracic myelopathy caused by TOLF also has a high incidence in eastern Asian countries, such as Japan and China. It is most often diagnosed in the lower thoracic spine (T9–12).

Conservative treatment and physical therapy are usually effective only in the early stages, and surgical treatment is necessary when conservative treatment is ineffective or in patients with severe symptoms. In addition, massage and stretch therapy may cause more stress to the lesion, leading to the prospect of severe compression, which may cause worse paralysis. Posterior decompressive laminectomy is the most commonly performed and the classic surgery for TOLF. The chief goals of surgical treatment are resection of ossification and the vertebral plate, neurologic decompression, and stabilization of the vertebral segments with instrumented fusion. Although posterior decompressive surgery is regarded as an effective treatment option for this disease, the surgical outcome of TOLF is not always satisfactory.

In previous studies, several clinical risk factors have been considered to affect the surgical prognosis of patients with thoracic myelopathy caused by TOLF, including age, sex, body mass index (BMI), gender, hypertension, preoperative modified Japanese Orthopaedic Association (mJOA) score, and signal intensity changes of the spinal cord on T2-weighted MRI. No consensus has been reached about the signiﬁcant independent risk factors associated with poor surgical outcome of TOLF. The encroachment ratio of ossification to the spinal canal. It shows the location, shape and volume of ossiﬁcation only can measure the maximum compression of the thoracic spinal cord in the axial position but not evaluate the overall compression of the spinal cord. Therefore, the combined evaluation of axial and sagittal maximum compression of the spinal cord can better reveal the degree of compression of the spinal cord. This helps surgeons to accurately predict the surgical outcome of TOLF based on a patient’s individual demographic data and radiologic characteristics. However, a standard for predicting the prognosis of TOLF has not been established.

The purpose of the current study was: (i) to identify the significant independent risk factors associated with poor surgical outcome in TOLF patients; (ii) to assess the sensitivity and speciﬁcity of risk factors and reveal prognostic values of the independent risk factors using receiver operating characteristic (ROC) curves; and (iii) to ascertain the independent risk factors related to poor preliminary postoperative outcome in each subgroup.

**Materials and Methods**

**Participants**

Based on the screening criteria, 165 patients were enrolled in this retrospective study between May 2016 and June 2019. The procedures were approved by the ethics committee of the Affiliated Hospital of Qingdao University.

The inclusion criteria were as follows: (i) patients with thoracic myelopathy caused by TOLF; (ii) patients who had neural symptoms, such as motor weakness, gait disturbance,
and urinary dysfunction; and (iii) patients who underwent posterior decompressive laminectomy in the Affiliated Hospital of Qingdao University. The exclusion criteria were as follows: (i) patients with serious systemic diseases or who had not undergone surgical treatment; (ii) patients with previous thoracic surgery or recurrent TOLF; (iii) patients with incomplete clinical indicators and imaging data; (iv) patients with mental incapacity; and (v) patients who had trauma, arachnoiditis, active infection (local or systemic) or spinal metastasis.

All diagnoses were based on clinical symptoms and neuroradiological imaging manifestations, especially three-dimensional CT scanning and MRI scans. All radiographic parameters were analyzed and confirmed by a spine surgeon and a radiologist. The postoperative improvement of symptoms was evaluated using the mJOA scoring system. All patients were followed up by telephone or outpatient review. The mJOA scores were obtained and used to evaluate the postoperative recovery rate at 12 months after the operation. Patients with a recovery rate ≥50% were included in the good prognosis group and those with a recovery rate ≤50% were included in the poor prognosis group.

Clinical Data and Radiologic Features
The collected demographic and clinical data included age, sex, BMI, duration of symptoms, history of hypertension and diabetes, tobacco use, history of drinking, symptoms of incontinence, number of compressed segments, and preoperative mJOA score.

Maximum Spinal Cord Compression
The MSCC degree was described based on diameters of three levels (diameter of the most compressed spinal cord diameter [di] and diameters of the nearest normal level above [da] and below [db] the level of sagittal most compressed) on the sagittal midsagittal of MRI. The MSCC was calculated according to the method reported by Nouri et al., as follows: MSCC = [1 – di/((da + db)/2)] × 100%.

Spinal Canal Occupation Ratio
According to a previous study, the axial maximum compression degree of the thoracic spinal cord was described by SCOR at the level of maximum encroachment. The SCOR was calculated as follows: SCOR = (axial ossified mass area/spinal canal area) × 100%.

Increased Signal on Sagittal T2-Weighted Images
The grade and extension of the ISST2I were also investigated. The ISST2I was classified into three grades: grade 0, none; grade 1, light (obscure); and grade 2, intense (bright). The extension of the ISST2I was estimated by the maximum sagittal diameter of hyperintense signal. If there was no high signal change, the extension value was 0 (Fig. 1).

Increased Signal on Axial T2-Weighted Images
The ISAT2I were classified into four types: normal, diffuse, fuzzy focal, and discrete focal (Fig. 2).

Type of Ossification
The classification of ossification was also regarded as a risk factor associated with the preliminary recovery outcomes for patients. According to Sung et al., the ossification was classified into three types (unilateral, bilateral, and bridged) on axial CT scan and two types (round and beak) on sagittal MRI (Fig. 3).

Modified Japanese Orthopaedic Association Score
The mJOA scoring system is one of the most frequently used clinical outcome measures to evaluate the improvement of thoracic function before and after treatment. A higher score indicates more complete neurological status. Compared with the JOA scoring system, the mJOA eliminates the motor and sensory scoring sections for upper extremity function and the total score is 11 points. The recovery rate (%) = (postoperative mJOA score – preoperative mJOA score)/(11 – preoperative mJOA score) × 100%. According to the score, the recovery rate was classified into four grades: excellent (75% to 100%), good (50% to 74%), fair (25% to 49%), and poor (0% to 24%).

Statistical Analysis
All collected data were analyzed by SPSS Statistics software, version 22.0. (SPSS, Chicago, IL, USA). The continuous data were assessed with t-tests or the Mann–Whitney U-test. The χ²-test was applied to compare the clinical categorical variables between the cohorts. Clinically relevant variables and the factors with P-values < 0.2 selected in univariable analysis were further incorporated into the binary logistic regression analyses. Binary logistic regression analysis was performed to determine the independent significant risk factors. ROC curves were used to assess the sensitivity and the specificity of the risk factors. The discriminative power of risk factors was described by the area under the ROC curve (AUC). Furthermore, the subgroup analyses of patients were also conducted according to gender, age, and SCOR. A P-value less than 0.05 was considered statistically significant.

Results
Demographic Data
The mean age of the 165 patients enrolled in the study was 58.53 ± 9.63 years. There were 76 men and 89 women included in the study. The good recovery rates in men and women were 49 (44.14%) and 62 (55.86%), respectively. The duration of preoperative symptoms ranged from 1 week to 10 years (5.85 ± 23.34 months). The mean recovery rate was 58.14% ± 18.35% according to the preoperative and postoperative mJOA score. The preoperative mJOA score ranged from 4 to 9 (6.19 ± 1.08). In the poor group, there were 23 (42.59%) patients with a history of hypertension,
12 (22.22%) patients with a history of diabetes, 7 (12.96%) patients with a history of tobacco use, 2 (3.70%) patients who had a history of drinking and 6 (11.11%) patients who had symptoms of incontinence. Compared with the good prognosis group, the poor prognosis group may have a lower preoperative mJOA score (12.78 ± 14.81 vs 15.09 ± 26.39,
$P = 0.011$), older age (62.76 ± 8.24 vs 57.73 ± 9.78, $P = 0.001$), and higher BMI (27.22 ± 4.80 vs 25.56 ± 2.97, $P = 0.007$). Meanwhile, the poor group had a significantly higher rate of hypertension than the good group (42.59% vs 24.32%, $P = 0.001$). Although there was no significant difference between poor and good groups for number of compressed segments (2.22 ± 1.40 vs 2.00 ± 0.86, $P = 0.197$), drinking (3.70% vs 11.71% $P = 0.093$), and history of diabetes (22.22% vs 12.61%, $P = 0.112$), they were further incorporated into the binary logistic regression analyses. No significant difference was observed between the poor and good groups in sex ($P = 0.479$), duration of symptoms ($P = 0.551$), tobacco use ($P = 0.949$), and symptoms of incontinence ($P = 0.782$). Further demographic data of the patients are listed in Table 1.

**Maximum Spinal Cord Compression and Spinal Canal Occupation Ratio**

In the poor group, the MSCC ranged from 13.60% to 86.20% and showed significantly more serious compression than the good group (69.94 ± 13.60 vs 62.04 ± 15.67, $P = 0.002$). The poor group had significantly higher SCOR than the good group (59.4 ± 16.29 vs 50.96 ± 15.37, $P = 0.002$).

**Increased Signal on Sagittal T2-Weighted Images**

A total of 59 patients observed intramedullary high signal intensity changes on T2WI. The grade of ISST2I was related to the mJOA recovery rate ($P < 0.001$). The poor recovery rate group included 12 cases of grade 0 ISST2I (22.22%), 19 cases of grade 1 ISST2I (35.19%), and 23 cases of grade 2 of ISST2I (42.59%). In the good recovery rates group, there were 94 cases (84.68%) of grade 0 ISST2I, 9 cases of grade 1 of ISST2I (8.11%), and 8 cases of grade 2 of ISST2I (7.21%). The poor group had significantly longer extension of ISST2I than the good group (8.80 ± 6.90 vs 1.32 ± 3.52, $P < 0.001$).

**Type of Increased Signal on Axial T2-Weighted Images**

The types of ISAT2I were identified to be associated with postoperative outcome ($P < 0.001$). The poor group included 12 normal cases (22.22%), 25 diffuse cases...
(46.30%), 11 fuzzy focal cases (20.37%), and 6 discrete focal cases (11.11%).

Type of Ossification
The type of ossification (axial, $P = 0.001$; sagittal, $P = 0.004$) had significant differences between the two groups. In the poor group, the rates for unilateral type, bilateral, and bridged of ossification were 3.70% (2 cases), 61.11% (33 cases), and 35.19% (19 cases), respectively. The rates for round and beak types were 55.56% (30 cases) and 44.44% (24 cases) in the poor group, respectively.

Binary Logistic Regression Analyses
Furthermore, the results of binary logistic regression analyses showed that age (odds ratio [OR] = 1.062, 95% confidence interval [CI] = 1.006–1.121, $P = 0.030$), grade 1 ISST2I (OR = 8.986, 95% CI = 3.056–20.294, $P < 0.001$), grade 2 ISST2I (OR = 7.552, 95% CI = 3.529–16.004, $P < 0.001$), bilateral type of TOLF on axial CT scan (OR = 4.314, 95% CI = 1.454–8.657, $P = 0.019$), bridged type (OR = 6.630, 95% CI = 2.580–17.530, $P = 0.004$), and number of compressed segments (OR = 1.916, 95% CI = 1.250–2.937, $P = 0.003$) were the significant independent risk factors for predicting poor preliminary postoperative outcome for TOLF (Table 2).

Receiver Operating Characteristic Curve
The ROC curve analysis showed that age, types of ossification on axial CT scan, and number of compressed segments had low discrimination power (AUC < 0.7, respectively) in predicting the recovery rate, whereas the discrimination power of the grade of ISST2I (AUC = 0.817) was significantly higher than that of other risk factors (Fig. 4).

Subgroup Analyses
Traditionally, it was thought that gender, age, and SCOR had obvious effects on the postoperative outcome in daily clinical practice. Subgroup analyses were conducted according to gender, age, and SCOR, demonstrating that grades 1 and 2 of ISST2I were independent risk factors in both male and female patients ≥60 years old and patients with SCOR ≥50% ($P < 0.05$, respectively). Similar to the results of binary logistic regression analyses in the total study population, the poor preliminary postoperative outcome of TOLF was significantly associated with age and number of compressed segments in three subgroups. SCOR and extension of ISST2I were also significantly associated with the poor postoperative outcome in patients aged less than 60 years old ($P < 0.05$, respectively). After adjustment, the poor preliminary postoperative outcome of TOLF was only associated with the extension of ISST2I ($P < 0.001$) in patients with SCOR <50%. The results of subgroup analyses among the six groups are presented in Table 3.

Discussion
Thoracic ossification of the ligamentum flavum is probably the most common source of thoracic myelopathy around the world, which is the main indication for a thoracic spinal operation. Posterior decompressive laminectomy is often considered the best solution for TOLF.5, 6, 11, 13, 22, 23.

Risk Factors
The duration of symptoms was regarded as the important predictor of recovery in previous studies. Zhang et al.5 reported that duration of symptoms is significantly associated with prognosis of TOLF because long-standing compression of the spinal cord may lead to irreversible damage. However, we found that duration of symptoms was only associated with the poor postoperative outcome in male patients. In the present study, gender has no effect on the preliminary postoperative outcome. The JOA scoring system is one of the most frequently used clinical outcome measures.

| Variable | Odds ratio (95% confidence interval) | $P$-value |
|----------|-------------------------------------|-----------|
| Age (year) | 1.062 (1.006–1.121) | 0.030 |
| Number of compressed segments | 1.916 (1.250–2.937) | 0.003 |
| Grade of ISST2I (n, %) | 1 | |
| Grade 0 | 8.986 (3.056–20.294) | < 0.001 |
| Grade 1 | 7.552 (3.529–16.004) | < 0.001 |
| Classification of ossification (axial, n, %) | 4.314 (1.454–8.657) | 0.019 |
| Unilateral | 6.630 (2.580–17.530) | 0.004 |

Figure 4 Receiver operating characteristic (ROC) curve of age (AUC = 0.613), grade of ISST2I (AUC = 0.817), types of ossification on axial CT scan (AUC = 0.648), and the number of compressed segments (AUC = 0.503).

TOLF, thoracic ossification of the ligamentum flavum.
### Table 3: Subgroup analyses

| Variable                  | Male (n = 76) | Female (n = 89) | Age <60 (n = 78) | Age ≥60 (n = 87) | SCOR <50% (n = 57) | SCOR ≥50% (n = 108) |
|---------------------------|---------------|-----------------|------------------|------------------|--------------------|--------------------|
| Age (years)               | 1.863         | 1.603           | 1.044            | 1.075            | 1.028              | 1.119              |
| Duration of symptoms (months) | 1.086         | 1.603           | 1.044            | 1.075            | 1.028              | 1.119              |
| Number of compressed segments | 1.001         | 1.048           | 1.044            | 1.075            | 1.028              | 1.119              |
| SCOR (%)                  | 1.044         | 1.048           | 1.044            | 1.075            | 1.028              | 1.119              |
| Grade ISST2I (n, %)       |                |                 |                  |                  |                    |                    |
| Grade 1 ISST2I            | 7.289         | 2.163           | 1.920            | 1.966            | 1.075              | 3.022              |
| Grade 2 ISST2I            | 9.473         | 3.029           | 1.986            | 1.966            | 1.075              | 3.022              |
| Extension of ISST2I (mm)  | 1.242         | 1.440           | 1.242            | 1.440            | 1.242              | 1.440              |

CI, confidence interval; OR, odds ratio.

According to previous studies and subgroup analyses, advanced age may be associated with more complications.
and poorer outcomes after surgery. Compared with grade 0 of ISTST2I, abnormally obscure and bright signal intensity represent serious spinal cord injury and advanced myelopathy. However, we found that grades 1 and 2 of ISTST2I were not identified as independent risk factors in patients aged less than 60 years old and in patients with SCOR <50%. We also observed the postoperative recovery of intramedullary abnormally high signal in some relatively young patients during follow up. We speculate that young age and lower SCOR are correlated with greater recuperative potential and milder neuropathological alteration in the spinal cord. In addition, the extension of ISTST2I was identified as an indicator of poor prognosis in the two subgroups. The grade of ISTST2I had the best predictive ability (AUC = 0.817), which was significantly higher than that of other MRI parameters. Consistent with the previous research, the results of our study showed that bilateral and bridged types of ossification on axial CT scans were the risk factors associated with poor surgical outcome in TOLF patients. We believe that the two types of ossification may represent larger ossification and more serious spinal cord compression. In addition, the predictive value of the number of compressed segments was the lowest (AUC = 0.503).

Limitations of the Study

Some limitations of the study must be noted. First, some inherent biases may be present in the retrospective study design and the data of patients. Second, the number of patients enrolled in the study was relatively small. Some potential risk factors may have been neglected in the study because of the limited number of TOLF patients and the different statistical analyses. Finally, the use of an independent large-scale database for external validation would improve the reliability of the study. In addition, each high-resolution CT and MRI system has different working parameters and characteristics.

Conclusion

The present study demonstrated that the intramedullary increased signal intensity on sagittal T2-weighted MRI was a great risk factor of poor preliminary postoperative outcome. Age, duration of symptoms, number of compressed segments, SCOR, extension of ISTST2I, and classification of ossification were also associated with the prognosis in the total study population or subgroup analyses but with lower predictive values. Complete evaluation of radiologic features, especially the intramedullary increased signal intensity, will be valuable in predicting the preliminary outcome of TOLF.

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