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ORIGINAL RESEARCH

Clinical Risk Factors for Thoracic Ossification of the Ligamentum Flavum: A Cross-Sectional Study Based on Spinal Thoracic Three-Dimensional Computerized Tomography

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Background: Inconsistent results of the clinical risk factors associated with thoracic ossification of the ligamentum flavum (TOLF) have been reported in limited previous studies.

Purpose: This retrospective study aimed to investigate the potential risk factors for TOLF by a retrospective cross-sectional study, which may provide valuable experience for further clinical and pathophysiological research.

Methods: A total of 2247 asymptomatic participants, who underwent spinal thoracic three-dimensional computerized tomography (3D-CT) scans at our institution from January 2016 to December 2019, were enrolled in this study according to the screening criteria. Demographic information such as age, sex, height, weight, body mass index (BMI), smoking and drinking history, diastolic blood pressure (DBP), systolic blood pressure (SBP), and pulse pressure (PP) were recorded. Laboratory results included serum low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglyceride (TG), uric acid (UA), creatinine (Cr), calcium, and phosphorus. Participants were divided into TOLF group and non-TOLF group in accordance with the thoracic 3D-CT manifestation.

Results: TOLF was observed in 153 (6.81%) asymptomatic participants. Comparison of demographic data and laboratory examinations between the two groups showed that participants in the TOLF group were older, had a higher BMI, as well as higher levels of DBP. In addition, there was no significant difference in sex, drinking, tobacco use, SBP, TC, TG, PP, and levels of LDL-C, HDL-C, sUA, sCr, calcium, and phosphorus between the two groups. Furthermore, dichotomous logistic regression analyses revealed that age (OR = 1.018, p = 0.041) and BMI (OR = 1.090, p < 0.001) were risk factors for TOLF.

Conclusion: Our study reveals that age and BMI are clinical risk factors for the development of TOLF, while age cannot be identified as an independent risk factor for female in subgroup analysis.

Keywords: ossification of the ligamentum flavum, risk factor, body mass index, uric acid, triglyceride

Introduction

Ossification of the ligamentum flavum (OLF) is a disease mainly affecting the thoracic spine, which is characterized by progressive ectopic ossification of the ligamentum flavum.[1] Thoracic OLF (TOLF) often leads to a progressive compression of the spinal cord, the nerve root, or the conus medullaris based on the location of the lesion. In 1920, Polgar first reported that TOLF was closely associated with thoracic myelopathy.[2] After that, many reports revealed that TOLF was an important pathogenesis to thoracic spinal canal stenosis and radiculomyelopathy, especially at the lower thoracic

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spine.[3] When progressive and severe symptom with evidence of spinal cord compression is observed, surgical intervention is always required.[4]

Worldwide, spinal ligament ossification diseases, such as TOLF and ossification of the posterior longitudinal ligament (OPLL), have a higher prevalence in China, Japan, and other eastern Asian countries.[5,6] This phenomenon suggests that genetic background is a significant influence factor even though the specific mechanisms beneath are still unclear.[7] So far, no consensus has been reached about the etiology and underlying mechanism of TOLF.[8] Kaneyama[9] and Maigne[10] proposed that local mechanical stress, especially rotation strain to the lower thoracic spine, is associated with the development of TOLF. Basic metabolic elements in the microenvironment seemed to play a key role in the development of TOLF.[11] Similarly, inflammatory cytokines, such as IL-6 and TNF-α, were also proved to be crucial to OLF through local milieu of the spinal canal.[12] Several clinical risk factors are considered associated with OLF, such as age, sex, ethnicity, obesity, ankylosing spondylitis, history of hypertension and diabetes, diffuse skeletal hyperostosis, uric acid, and abnormal metabolism of trace elements.[8,13,14] Furthermore, metabolic syndrome and leptin resistance are regarded as risk factors closely related to the process of TOLF.[15] Therefore, identifying the risk factors for TOLF is essential for the management of the disease.

To the best of our knowledge, there are few small sample size studies to assess the association between TOLF and clinical risk factors. In the current study, we aimed to investigate significant independent risk factors for TOLF, which mainly included clinical indicators and laboratory examinations.

Materials and Methods

Participant Selection

We conducted a retrospective cross-sectional study based on data from 3399 asymptomatic participants (no neurological symptoms but may be with back pain) who executed thoracic three-dimensional (3D) CT scans as a part of routine health examinations in the Affiliated Hospital of Qingdao University from January 2016 to December 2019. The study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University. Exclusion criteria were participants with missing clinical indicators (n = 275), missing laboratory examinations (n = 384), participants younger than 50 years old (n = 196), and participants with cancer or infection (n = 297). A total of 2247 asymptomatic participants were included in our analysis. Based on the imaging findings, all participants enrolled in the study were divided into two groups: the TOLF group and the non-TOLF group (Figure 1).

Demographic Data

All participants' age, sex, blood pressure, height, weight, body mass index (BMI), tobacco use, and history of drinking were recorded and collected. Blood pressure examinations included diastolic blood pressure (DBP), systolic blood pressure (SBP), and pulse pressure (PP). PP is defined as the difference between SBP and DBP.[16] The participants' degree of obesity and body fat were described by BMI. BMI was calculated as follows: BMI = weight/height^2 (kg/m^2). All participants were asked to take off their shoes and socks and wear light and thin clothes when their height (cm) and weight (kg) were measured.

Laboratory Examinations

Venous blood samples were collected from participants who had been fasting for at least 8 hours. Laboratory measurements included low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglyceride (TG), serum uric acid (sUA), serum creatinine (sCr), serum calcium, and serum phosphorus.

CT Examination

All thoracic CT scans were performed in the supine position with a 128-row MDCT scanner (GE Healthcare, Waukesha, USA). The gantry rotation time is 0.5 s, and tube voltage is 120 kV. Axial images obtained during CT examination were 1mm thick and were reconstructed into sagittal images, coronal images, and 3D images by this system.

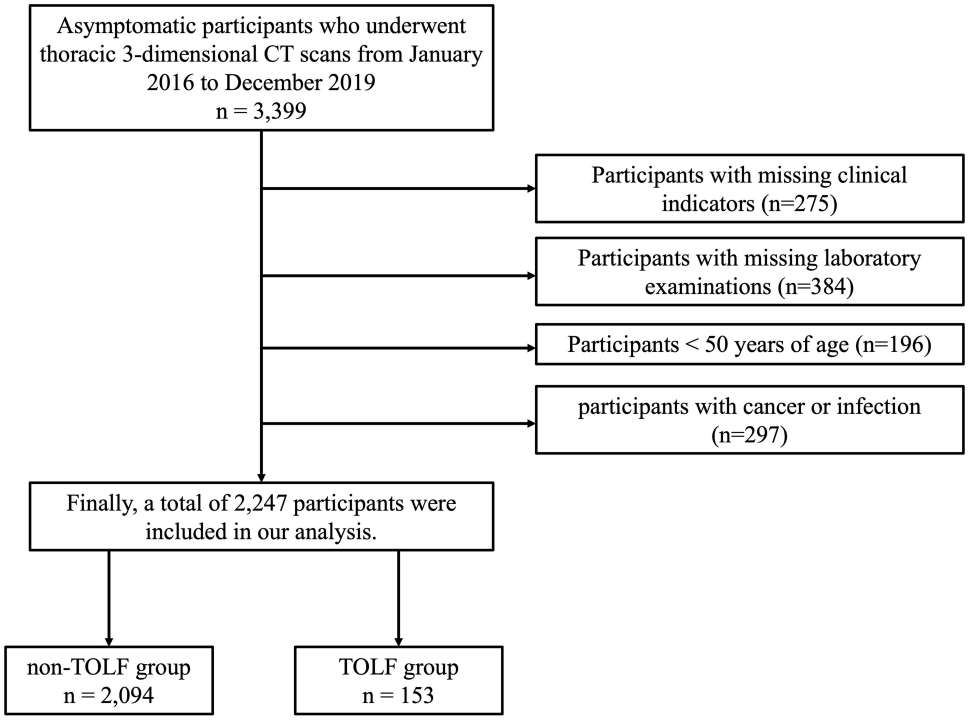

Figure 1 Flowchart of the study participants.

Definition of TOLF

TOLF presented as an ossified bridge or mass in the ligamentum flavum between two adjacent laminae on sagittal CT scan. The method of differential diagnosis of TOLF was in accordance with the recommendations of Kim et al.[17] The diagnosis of TOLF was based on radiological imaging manifestations, especially 3D CT scans, simultaneously analyzed and confirmed by two experienced spinal surgeons. Any disagreements were settled by discussion with another senior spinal surgeon. We calculated the intraclass correlation coefficient (ICC) to assess the inter-observer and intra-observer reliability by a two-way random effects model, and ICC values for radiographic parameters >0.85.

Statistical Analysis

All analyses were performed using SPSS Statistics software, version 22.0. (SPSS Inc., Chicago, IL, USA). The normality of the distribution of the measurement data was evaluated using the Kolmogorov–Smirnov test. Continuous normally distributed variables are shown as mean ± standard deviation and categorical variables are shown as percentages (%). Student's *t*-test was used to compare the clinical continuous variables between the cohorts. The clinical categorical variables were assessed using the chi-square test. The factors with P-values <0.2 selected in Student's *t*-test and chi-square test analysis were further incorporated into the dichotomous logistic regression analyses.[18] Dichotomous logistic regression analysis (stepwise regression analysis method) was also performed to compute odds ratios and 95% confidence intervals to determine the significant and independent risk factors associated with TOLF. A P-value <0.05 was considered statistically significant.

Results

Demographic Data

A total of 2247 participants (mean age, 67.87 ± 9.71 years; 918 male and 1329 female) were enrolled in the study, including 918 men and 1329 women. A total of 361 (16.07%) participants had a history of tobacco use, 360 (13.80%) participants had a history of drinking. The mean BMI was 24.54 ± 4.01 kg/m^2 (range, 13.06–45.72 kg/m^2), the mean sUA was 291.09 ± 92.56 μmol/L (range, 54.2–1034.9 μmol/L). The mean TC was 4.87 ± 1.18 mmol/l (range, 1.38–16.04

mmol/l). The mean TG was 1.41 ± 1.16 mmol/l (range, 0.2–28.87 mmol/l). The demographic data and clinical findings of the included participants are presented in Table 1.

Comparison Between the TOLF and Non-TOLF Groups

Asymptomatic TOLF was observed in 153 (6.81%) participants, and 2094 participants were enrolled in the non-TOLF group. In the TOLF group, 21 (13.73%) participants had a history of tobacco use, and 20 (13.07%) had a history of drinking. Comparison between the two groups showed that participants in the TOLF group were older (69.31 ± 8.82 vs 67.77 ± 9.77 years, $p = 0.040$), had a higher BMI (26.00 ± 3.46 vs 24.43 ± 4.03 kg/m^2, $p < 0.001$), as well as a higher level of DBP (83.23 ± 11.92 vs 79.31 ± 11.92 mmHg, $p < 0.001$). In addition, there was no significant difference in sex, drinking, tobacco use, SBP, TC, TG, PP, and levels of LDL-C, HDL-C, sUA, sCr, calcium, and phosphorus between the two groups (Table 2).

Risk Factors

The results of dichotomous logistic regression analyses revealed that age (odds ratio [OR] = 1.018, $p = 0.041$), and BMI (OR = 1.090, $p < 0.001$), were independent risk factors associated with TOLF. The results of the dichotomous logistic regression analyses are shown in Table 3.

Subgroup Analysis

Univariate regression analysis of subgroups showed that BMI of participants with TOLF was significantly higher in both male and female (Table 4). Multivariate regression analysis of subgroups showed that BMI was also significant (Table 5). In addition, the results of dichotomous logistic regression analyses revealed that age (OR = 1.031, $p = 0.02$) were also significant risk factors associated with TOLF in male.

Discussion

Both OLF and OPLL are in a cluster of systematic ossification of the spinal ligaments and have high rates of prevalence in Eastern Asia, particularly in Japan.[1] Mori et al[5] reported that the incidence of TOLF in Japanese population was as high as 36%. Therefore, OLF was once termed as "Japanese disease".[19] In our study, TOLF accounts for 6.81% of all asymptomatic participants, which is lower than most previous reports but higher than 3.8% in Southern Chinese

Table 1 Demographic Data of All Participants

Variable	All Participants (n=2247)
Age (yr)	67.87±9.71
Sex (n,%)	
Male	918 (40.85%)
Female	1329 (59.15%)
BMI (Kg/m^2)	24.54±4.01
Tobacco use (y/n)	361 (16.70%)
Drinking (y/n)	310 (13.80%)
DBP (mmHg)	79.46±11.95
SBP (mmHg)	135.96±37.85
PP (mmHg)	56.50±35.76
LDL-C (mmol/l)	2.85±0.89
HDL-C (mmol/l)	1.36±0.35
TC (mmol/l)	4.87±1.18
sUA (μmol/l)	291.09±92.56
sCr (μmol/l)	82.65±60.97
TG (mmol/l)	1.41±1.18
Ca (mmol/l)	2.23±0.17
P (mmol/l)	1.15±0.30

Table 2 Comparison Between Non-TOLF Group and TOLF Group

Variable	Non-TOLF Group (n=2094)	TOLF Group (n=153)	P-value
Age (yr)	67.77±9.77	69.31±8.82	0.040
Sex (n,%)			0.270
Male	849 (40.54%)	69 (45.10%)	
Female	1245 (59.45%)	84 (54.90%)	
BMI (Kg/m^2)	24.43±4.03	26.00±3.46	<0.001
Tobacco use (y/n)	340 (16.24%)	21 (13.73%)	0.494
Drinking (y/n)	290 (13.85%)	20 (13.07%)	0.903
DBP (mmHg)	79.31±11.92	81.58±12.06	0.023
SBP (mmHg)	135.80±38.86	138.15±18.93	0.459
PP (mmHg)	56.50±36.82	56.57±14.82	0.981
LDL-C (mmol/l)	2.86±0.90	2.85±0.79	0.898
HDL-C (mmol/l)	1.36±0.35	1.34±0.35	0.439
TC (mmol/l)	4.87±1.18	4.87±1.11	0.962
sUA (μmol/l)	290.41±92.66	300.42±90.69	0.197
sCr (μmol/l)	82.14±57.78	89.56±94.24	0.146
TG (mmol/l)	1.40±1.18	1.47±0.78	0.512
Ca (mmol/l)	2.23±0.17	2.24±0.16	0.479
P (mmol/l)	1.15±0.31	1.13±0.21	0.402

Table 3 Binary Logistic Regression Analysis Risk Factors for TOLF

Variable	OR	95% CI	P-value
Age (yr)	1.018	1.001–1.035	0.041
BMI (Kg/m^2)	1.090	1.051–1.130	<0.001

Table 4 Comparison of Biochemical and Clinical Parameters Between Participants with and without TOLF in Subgroups

Variable	Female (n=1329)			Male (n=918)		
	Non-TOLF (n=1245)	TOLF (n=84)	P-value	Non-TOLF (n=849)	TOLF (n=69)	P-value
Age (yr)	68.28±9.74	69.40±8.33	0.240	67.02±9.77	69.19±9.43	0.075
BMI (Kg/m^2)	24.58±4.18	25.88±3.18	0.006	24.20±3.78	26.16±3.79	<0.001
Tobacco use (y/n)	21 (1.69%)	2 (2.38%)	0.637	319 (37.57%)	19 (27.54%)	0.960
Drinking (y/n)	84 (6.75%)	0 (0%)	0.312	275 (32.39%)	20 (28.99%)	0.560
DBP (mmHg)	136.78±47.99	137.94±18.57	0.826	134.37±18.66	138.41±19.48	0.085
SBP (mmHg)	78.51±11.80	80.55±11.14	0.109	80.48±12.02	82.82±13.07	0.119
PP (mmHg)	58.27±46.21	57.39±14.23	0.862	53.89±14.30	55.57±15.55	0.353
LDL-C (mmol/l)	2.95±0.89	3.01±0.77	0.566	2.71±0.88	2.64±0.76	0.547
HDL-C (mmol/l)	1.42±0.35	1.44±0.35	0.684	1.28±0.34	1.22±0.31	0.188
TC (mmol/l)	1.46±1.30	1.50±0.68	0.763	1.32±0.97	1.42±0.88	0.398
sUA (μmol/l)	269.81±79.69	282.61±75.47	0.153	320.63±101.71	322.09±102.79	0.909
sCr (μmol/l)	75.74±46.95	74.65±19.87	0.832	91.52±69.72	107.71±136.98	0.092
TG (mmol/l)	5.06±1.20	5.17±1.04	0.393	4.59±1.10	4.51±1.09	0.551
Ca (mmol/l)	2.24±0.15	2.25±0.15	0.435	2.22±0.18	2.23±0.16	0.700
P (mmol/l)	1.17±0.22	1.17±0.17	0.931	1.12±0.41	1.08±0.23	0.429

population using magnetic resonance imaging.[2,5,20,21] This may be a consequence of regional divergence and different modalities used in diagnosis. Limited studies attempted to reveal the clinical risk factors for TOLF. Kim et al[8] utilized chest CT as the screening method of TOLF for 4999 individuals in Korea and found that after logistic regression analysis,

Table 5 Binary Logistic Regression Analysis Risk Factors for TOLF in Subgroups

Variable	Female			Male		
	OR	95% CI	P-value	OR	95% CI	P-value
Age (yr)	-	-	-	1.031	1.005–1.058	0.02
BMI (Kg/m^2)	1.067	1.019–1.117	0.006	1.142	1.075–1.213	<0.001

gender and thoracic kyphosis were significantly related to TOLF. There are several distinctions between Kim's and our studies. Kim et al adopted a different age range (younger than 20 years old) from our study (younger than 50 years old) in exclusion criteria. Even though patients in both studies were free from neurological deficits, the individuals in the two studies seeking for different radiological examinations because of disparate symptoms (back versus pulmonary symptoms). The results of collected data obtained from distinctive population backgrounds may then vary. Therefore, the conclusions should be determined in a limited and specific condition.

Our dichotomous logistic regression analyses indicate that age is positively correlated with TOLF. OLF is regarded as a presentation of degenerative changes in the spinal column due to aging.[1] The incidence of OLF positively increases with age has also been reported in previous studies.[2,22] Park et al[23] reported that degeneration mainly affected the local milieu, and then induced ossification of human ligamentum flavum cells. Lang et al[20] reported that TOLF was more frequently observed in the lower thoracic regions and its prevalence increased with age. Thus, age and associated degenerative factors seemed to play important roles in the development of TOLF. Unlike Kim's conclusion that gender was correlated with TOLF, no statistical difference in gender was observed between the TOLF and non-TOLF groups in our study. A previous study utilizing gender-stratified risk factor analysis showed that aging had a negative impact on TOLF in female.[17] In the present study, age was identified as a risk factor of TOLF in all participants, but not as an independent risk factor in the subgroup of female. That means it is yet to reach a consensus in the correlation between age and TOLF in female. Therefore, further epidemiologic studies are warranted to demonstrate the potential correlation.

BMI was closely associated with TOLF in the total population or subgroup analyses. Fan et al[15] demonstrated that leptin was critically associated with obesity and the pathological development of TOLF. It is not clear that how obesity contributes to TOLF, but some researchers believe that hyperleptinemia and the STAT3 signaling pathway play important roles in the pathogenesis of TOLF.[15] Leptin was identified as an adipocyte-derived cytokine that can stimulate the osteogenic differentiation of ligament cells. In addition, hyperleptinemia is a common feature of obese people, and its synthesis and secretion are significantly increased in obese people.[24] In addition, leptin receptors were expressed but showed different osteogenic effects in both TOLF and non-TOLF cells. Therefore, they confirmed STAT3 as a critical molecule in mediating leptin-stimulated cell osteogenesis in TOLF.[15]

In the present study, TC and TG were not identified as risk factors in dichotomous logistic regression analysis. In addition, there was no significantly different in TC and TG of participants between the TOLF group and the non-TOLF group. However, the results were not all the same in previous researches, and there may be some differences upon pathological mechanisms between TOLF and OPLL. A retrospective study collecting 1789 asymptomatic subjects who underwent whole-body CT scans showed that subjects with OPLL had higher levels of TG than subjects without OPLL.[13] Banks et al[25] suggested that triglycerides could truly inhibit leptin transport across the blood–brain barrier, inducing receptor resistance to leptin and insulin. In addition, leptin and insulin resistance can promote further obesity and lead to a vicious cycle. But hypertriglyceridemia does not necessarily mean obesity. Thus, further studies are needed to confirm the possibility of interactions among TOLF, obesity, and TG.

Some metabolic markers were once reported or predicted to affect the process of TOLF.[26] Li et al used metabolomics and transcriptomics to identify the molecular mechanism and diagnostic biomarkers in TOLF, and the result shows that uric acid might be the potential biomarker for TOLF and play an important role in the detailed pathway.[27] However, there were only 25 patients with TOLF and 23 healthy volunteers included in the research. Thus, the relatively small sample size may cause bias of result. Different from the previous research, the result of the present study show that uric acid levels do not influence the incidence of TOLF. Matsui et al[28] reported that the increased content of calcium in the ligament flavum was associated

with overloaded stress on the spine and the development of ossification. Wang et al[11] reported that calcium and phosphorus content tended to increase in OLF specimens, and phosphorus content in serum was also significantly higher in participants with TOLF. However, as the study sample size is small, the conclusions are not convincing enough. Although previous studies documented that calcium was closely associated with elastin and could stimulate osteoblast-like cells with enhanced expression of c-jun and c-fos,[29] the calcium or phosphorus content in the tissue of OLF may not be correlated with that in the serum. Therefore, it is comprehensible that the serum calcium and serum phosphorus did not show significant differences between the TOLF and non-TOLF groups in the present study.

Limitations

There are some limitations of the study that must be noted. First, we did not have detailed information on some important metabolic indicators, such as glycosylated hemoglobin, thyroid hormone, 25-hydroxyvitamin D, and osteocalcin. Those metabolic indicators were not detected routinely for most individuals. Therefore, some potential risk factors may be neglected. Second, although the stringent excluding criteria was adopted, the participants with subtle clinical symptoms cannot be distinguished from asymptomatic participants. Finally, the number of participants enrolled in the present study was relatively small. Therefore, further large-sample epidemiological data and more comprehensive laboratory indicators are needed.

Conclusions

Our study shows that age and BMI are clinical risk factors associated with TOLF in older adults with or without back pain, while age cannot be identified as an independent risk factor for female in subgroup analysis.

Ethics and Consent

All procedures were performed in compliance with the Declaration of Helsinki and were approved by the Ethics Committee of the Affiliated Hospital of Qingdao University. All patients involved gave written informed consent to review their medical records. All personal details were erased before analysis to cover patient data confidentiality.

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Disclosure

The authors declare no relevant financial, personal, political, intellectual or religious conflicts of interests for this work.

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