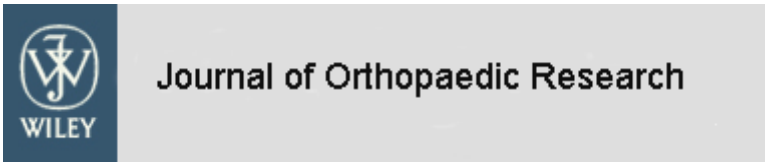

Preoperative paraspinal neck muscle characteristics predict early-onset adjacent segment degeneration in anterior cervical fusion patients: a machine-learning modelling analysis

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Preoperative paraspinal neck muscle characteristics predict early-onset adjacent segment degeneration in anterior cervical fusion patients: *a machine-learning modelling analysis*

Running Title: Cervical Muscles and ACDF Outcomes

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ABSTRACT

Early-onset adjacent segment degeneration (ASD) can be found within six months after anterior cervical discectomy and fusion (ACDF). Deficits in deep paraspinal neck muscles may be related to early-onset ASD. This study aimed to determine whether the morphometry of preoperative deep neck muscles (multifidus and semispinalis cervicis) predicted early-onset ASD in ACDF patients. Thirty-two cases of early-onset ASD after a two-level ACDF and 30 matched non-ASD cases were identified from a large-scale cohort. The preoperative total cross-sectional area (CSA) of bilateral deep neck muscles and the lean muscle CSAs from C3 to C7 levels were measured manually on T2-weighted MRI. Paraspinal muscle CSA asymmetry at each level was calculated. A support vector machine (SVM) algorithm was used to identify demographic, radiographic, and/or muscle parameters that predicted proximal/distal ASD development. No significant between-group differences in demographic or preoperative radiographic data were noted (mean age: 52.4±10.9 years). ACDFs comprised C3-C5 (n=9), C4-C6 (n=20), and C5-C7 (n=32) cases. Eighteen, eight, and six patients had proximal, distal, or both ASD, respectively. The SVM model achieved high accuracy (96.7%) and an area-under-the-curve (AUC=0.97) for predicting early-onset ASD. Asymmetry of fat at C5 (Coefficient: 0.06), and standardized measures of C7 lean (Coefficient: 0.05) and total CSA measures (Coefficient: 0.05) were the strongest predictors of early-onset ASD. This is the first study to show that preoperative deep neck muscle CSA, composition, and asymmetry at C5-C7 independently predicted postoperative early-onset ASD in ACDF patients. Paraspinal muscle assessments are recommended to identify high-risk patients for personalized intervention.

Keywords: cervical; spine; paraspinal; muscles; adjacent segment; degeneration; disc; disease

INTRODUCTION

Anterior cervical discectomy and fusion (ACDF) is one of the most commonly performed cervical spine surgeries.[1] While outcomes from ACDF are largely favorable, postoperative alterations in biomechanics may accelerate the onset of adjacent segment degeneration (ASD) and disease, with prevalence rates as high as 2.9% per postoperative year, respectively.[2,3] The incidence of ASD has drawn significant concern among investigators/clinicians as these changes largely portend greater neck pain, disability, and increased need for reoperations.[4,5] Theoretically, since the presence of radiographic ASD may lead to symptomatic adjacent segment disease, patients with early-onset ASD may have a higher risk of developing symptoms that require treatments.[6] Although several elements (e.g., older age, accumulation of degenerative disorders, and various operative characteristics) have been identified as risk factors for ASD following ACDF,[4,7] no studies have explored the role of paraspinal muscles on the development of ASD.

The *semispinalis cervicis*, *rotatores*, and *multifidus* muscles constitute the deepest cervical muscle layer that provides segmental stability through their small moment arms, and high proportion of slow twitch fibers.[8,9] However, studies have suggested that these muscles may largely be sensitive to changes in neck function and pain. Yun *et al* [10] revealed that patients with chronic unilateral cervical radiculopathy were characterized by asymmetric atrophy of cervical multifidus muscles at C5-6 level on the symptomatic side. Patients with whiplash related neck pain or chronic non-traumatic neck pain also display significantly smaller cross-sectional area (CSA) of *multifidus* than asymptomatic individuals although controversial findings have been reported.[11,12] Similarly, patients with whiplash-induced neck pain show increased fatty infiltration in *multifidus* and *semispinalis cervicis*, whereas patients with insidious-onset neck

pain may not consistently show increased fatty infiltration in neck muscles.[13,14] However, it remains unclear how deep cervical muscles may relate to symptoms of postoperative neck pain or disability, and how associated morphological changes may ultimately contribute to differences in postoperative outcomes.

Deep cervical extensor muscles, as discussed earlier, may be the main active tissues to maintain spinal alignment, stability and mobility at the early postoperative period.[15-17] Preliminary research has shown that preoperative morphometry of cervical muscles may affect the results of ACDF. Choi *et al* [16] found that smaller CSAs of deep paraspinal cervical extensors (i.e., *multifidus and semispinalis cervicis*) at C4-5, C5-6, C6-7 were significantly related to longer bone fusion time at the C5-6 segment following ACDF. They also found that CSA of deep paraspinal cervical muscles at C5-6, C6-7, and C7-T1 were negatively related to the bone fusion time at the C6-7 segment. Since patients with adjacent segment disease after lumbar fusion had significantly smaller preoperative CSA of paraspinal lean muscle than patient controls,[18] it is possible that preoperative constitutive quality and morphometry of deep cervical extensors are related to ASD development after ACDF.

Despite this, the inherent complexity of cervical muscle symmetry largely complicates its routine application in clinical practice. Namely, given the relatively large breadth of assessed measures, routine statistical analyses are limited in their capacity to identify the "strongest" predictors for various clinical outcomes. Combined with other issues that permeate clinical research (missing data, small sample sizes, etc.), study of such factors is perhaps best addressed with the variable regularization provisions routinely employed within machine learning.[19] Support vector machines (SVMs) are one potential solution to such issues, offer flexibility through application of various kernel functions, and may retain conceptual interpretability in

cases of binary classification. As a whole, medicine has been relatively slow to adopt such analytical techniques, though recent studies have begun to demonstrate the efficacy of SVMs and other machine learning analyses, leading to significant improvements in the accuracy of generated models and corresponding increases in predictive capacity.[20]

Against this background, this study aimed to explore the relationship between preoperative paraspinal cervical muscle morphometry and evidence of early-onset radiographic ASD within 6 months following ACDF, after adjusting for other confounders. The findings might help develop a risk-stratification tool to identify patients amenable to future development of early-onset adjacent-level degenerative pathology as well as assist in patient counselling and understanding expectations, and surgical planning implications.

METHODS

Study design and setting

After obtaining ethics approval from the Institutional Review Board, the medical records of 1,164 consecutive patients who underwent multi-level (i.e. 2 or more levels) ACDF for degenerative cervical spine pathology between 2008 and 2015 were reviewed. Patients were excluded if they were less than 18 years old, received an ACDF for traumatic, infectious or neoplastic lesions, or had less than 6 months of postoperative follow-up. A total of 546 patients underwent multi-level ACDFs for spinal degeneration were eligible for the current study. From this group, a random sample of 32 cases of early-onset radiographic ASD within 6 months after a two-level ACDF were identified. A patient was classified as having radiographic ASD if there was evidence of new/enlarged anterior osteophytes, new/increased anterior longitudinal ligament calcification, new/increased disc space narrowing by >30º, spondylolisthesis >2mm, and/or new

endplate sclerosis at the proximal/distal adjacent level(s) of the fused construct (**Figure 1**).[2,21] Following a case-control design and available imaging, 30 non-ASD two-level cases were identified based on matching for age, gender, body mass index (BMI), and follow up time (in months).

Extraction of demographics data

Data related to age, gender, BMI, smoking status, pain intensity, and neck pain-related disability of patients at the time of follow-up were documented. Pain intensity was measured by a visual analog scale. The neck pain-related disability was quantified by Neck Disability Index (NDI).[22] Higher scores indicate greater disability.

Preoperative radiographic assessments

To identify imaging biomarkers that might predict early-onset ASD following ACDF, various parameters of the passive (non-muscle soft tissues and bone) and active (muscle) structures on preoperative 1.5T magnetic resonance (MR) images and lateral radiographs of the cervical spine were measured. Preoperative cervical sagittal parameters (i.e. C2-7 sagittal vertical axis (SVA), C2-7 lordosis, T1 slope) were measured from neutral lateral radiographs. C2-7 and segmental lordosis were calculated using the Cobb angle measurement technique, while C2-7 SVA was measured as the horizontal distance between a vertical plumb line intersecting the center of the C2 vertebral body and the posterosuperior corner of the C7 vertebra.[23,24] The T1 slope was estimated from the angle between a line drawn tangent to the T1 upper endplate and a horizontal line.[25]

Additionally, the presence or absence of black discs (T2-hypointense), disc herniation, disc narrowing, high intensity zone in discs, endplate abnormalities, Modic changes cephalic and caudal to each intervertebral segment, osteophytes at each level, and overall spondylolisthesis on T1- and T2-weighted MR images were recorded. Similarly, the preoperative spinal canal and spinal cord CSAs at C2 and C7 levels were measured from axial T2-weighted images using Mimics v22.0 software (Materialise, NV, Belgium).

In addition, the morphometry of the deep neck paraspinal muscles (i.e., *multifidus* and *semispinalis cervicis*) were measured on axial T2-weighted images by an accessor with over 250 hours of experience in measuring morphometry of paraspinal muscles on MR images. Specifically, the preoperative total cross-sectional area (TCSA) of bilateral deep neck paraspinal muscles from C3 to C7 levels was measured by manually tracing along the fascial boundary of the target muscles on an MR image slice immediately above the inferior endplate at each vertebral level. (**Figure 2**). To account for variations due to body habitus, an adjusted CSA ratio (aCSA ratio) was calculated using the formula: CSA of the target muscle/CSA of the vertebral body on the same axial image.[26] Asymmetry of paraspinal musculature was calculated as the percentage difference in CSA measures at each vertebral level: [(larger-smaller)/smaller x 100%].[27] Since prior research reported the average percentage between-side difference in CSA of deep neck extensor muscles was 12.8% in healthy, any between-side difference in CSA that exceeded 12.8% was considered as aberrant asymmetry.[27] The lean muscle CSA (functional CSA, FCSA) of a given muscle on each slide was estimated manually using the thresholding and crop functions in the Mimics software program to define the lean muscles of the target muscle. Since the signal intensity of fat tissue varied between individuals and MR scan slides within individuals,[28] no single set of threshold values was used to quantify FCSA on all the slides

within each participant. The FCSA/TCSA ratio was calculated to estimate the relative amount of lean muscle within a target muscle. The intra-rater reliability of the accessor in measuring FCSA and TCSA of cervical paraspinal muscles was estimated from 10 additional cases randomly selected from the medical record. The cases were measured twice 7 days apart.

Machine Learning Methodology and Statistical analysis

Data was analyzed using SPSS v23 (IBM Corp, Armonk, NY, USA). The significance level was set at 0.05. All preoperative and follow-up phenotypes were compared between the two groups using independent t tests or Mann-Whitney U tests for continuous variables depending on normality, and chi-square/Fisher's exact tests for categorical data. Intra-rater reliability was calculated by intra-class correlation coefficients ($ICC_{3,1}$). Intra-rater reliability was classified excellent, good, moderate, and poor if the ICC values were 0.90 to 1.00, 0.75 to 0.90, 0.50 to 0.75, and < 0.50, respectively.[29]

To determine if cervical muscle measures could predict outcomes of early-onset ASD, the data was optimized for use in a support vector machine algorithm. All models were trained and assessed using the *sklearn* v. 0.21.3 package in Python v. 3.6. To address missing values, imputation was performed with the calculated mean of each respective variable. Following normalization of potential predictors (cervical muscle measures, patient demographics, sagittal radiographic parameters), determination of the relative strength in predictive power of each variable was performed by calculating the cumulative accuracy of all possible variable combinations. This was supplemented with model regularization to prevent model overfitting. Assessments of accuracy were then performed within the entire dataset (to determine sufficiency of learning capacity), and with six folds of cross-validation (to internally validate and determine

accuracy of the model on independent data sets given the relatively small sample size). Final model coefficients were calculated for each selected variable to determine magnitude and relationship with development of early-onset ASD. Accuracies were assessed by sequentially entering the strongest predictors into each fitted model to determine accuracy convergence with respective determination of the area under the receiver operating characteristic curve (AUC). Lastly, to further assess variables as potential predictors for early-onset ASD, all possible variable combinations were iteratively assessed as independent models, and testes for model accuracy. Model accuracies were then summed for each variable and plotted to empirically determine the relative strength of each as predictors for the present data set.

RESULTS

The average age of patients was 52.4 ± 10.9 years and 45.2% of them were males. Neck and arm pain were common prior to ACDF and 27.1% had signs of myelopathy (**Table 1**). Spinal fusions were conducted at C3-C5 (n = 9), C4-C6 (n = 20), and C5-C7 (n = 33) levels. Eighteen patients developed proximal ASD, eight developed distal ASD, and six developed both proximal and distal ASD (one at C2 and C6; three at C3 and C7; and two at C4 and T1). Four out of the 32 patients with ASD underwent reoperation after the 6-month follow up. No patients in this sample without ASD required repeated surgery. There was no significant between-group difference in the demographic and preoperative phenotypes of all passive structures (**Tables 1 & 2**). The intra-rater reliability for TCSA and FCSA measurements ranged from 0.90 to 0.95 (**Table 4**).

While the absolute values of TCSA and FCSA of deep neck muscles in ASD patients were generally smaller than those of non-ASD patients, only the mean left FCSA of deep neck

muscles at C7 level in ASD patients was significantly smaller than that of non-ASD patients (**Table 3**). Further, compared to non-ASD patients, ASD patients demonstrated significantly greater asymmetry in TCSA of deep neck muscles at C3, C5, C6, and C7 levels. When aberrant muscle asymmetry was considered, ASD patients demonstrated significantly higher frequency of aberrant asymmetry in TCSA and FCSA of deep neck muscles at C5-C7 levels and C6-C7 levels, respectively than non-ASD counterparts. Similarly, compared to non-ASD patients, ASD patients appeared to have smaller preoperative FCSA in deep neck extensors, and larger side-to-side asymmetry in FCSA of deep neck extensors across all cervical levels (**Table 3**).

Following training and validation of the SVM, the strongest predictors of early-onset ASD generally involved cervical extensor CSA measures at C5, C6, and C7. Specifically, percentage fat composition, standardized CSA measures, and asymmetry were identified as factors predictive of early-onset ASD. Asymmetry of fat at C5 was the strongest overall predictor (Coefficient: 0.06), followed by standardized CSA at C7 (Coefficient: 0.05) and percentage fat at C5 (Left- Coefficient: 0.05; Right- Coefficient: 0.05). Conversely, unadjusted CSA (Left- Coefficient: -0.05; Right- Coefficient: -0.05) and FCSA (Left- Coefficient: -0.05; Right- Coefficient: -0.05) measures at C6 were the strongest negative predictors of early-onset ASD (**Table 4**). Evaluation of selected model covariates appearing across all possible combinations of collected features suggests that the overall size, lean muscle mass, and muscle asymmetry were highly important for accurate predictions of early-onset ASD, and far exceeded the relative importance of all demographic, operative, and sagittal radiographic parameters (**Figure 3**). Under this approach, total CSA (Right), fat percentage (C7, Left), and total CSA (Left) demonstrated the strongest predictive strength when compared to all other collected variables. The final model performance had a high accuracy (96.67%) and area under the

receiver operating characteristic curve (AUC=0.967) for predicting development of early- onset ASD.

DISCUSSION

To the best of our knowledge, this is the first study to investigate the influence of quality and morphometry of posterior deep neck paraspinal muscles in predicting the development of early-onset ASD following two-level ACDF after accounting for various potential factors. The results suggest that patients with ASD are characterized by significantly smaller preoperative FCSA of deep neck extensors at the C7 level, aberrant asymmetry in preoperative TCSA at C5-C7 levels, and aberrant asymmetry in preoperative FCSA of these muscles at C6 and C7 levels. Moreover, measures of TCSA, FCSA, fatty infiltration (% and CSA), and preoperative asymmetry in deep neck extensors at the C5, C6, or C7 levels were strong predictors for postoperative development of early-onset ASD in patients undergoing two-level ACDF, far exceeding the predictive strength of baseline patient demographics and sagittal radiographic alignment parameters. These findings underscore the relation between deep paraspinal neck muscle morphometry and early-onset ASD, and provides a potential new therapeutic target for reducing risks of ASD after anterior cervical spine surgery.

Within the present study, the relationship between CSA measures and early-onset ASD suggests that the relative composition and size of deep neck paraspinal muscles may have a complex biomechanical influence on postoperative recovery of the cervical spine. Specifically, while certain measures (percentage fat composition, standardized CSA, asymmetry) were predictive of early-onset ASD, corresponding unadjusted measures (TCSA, FCSA, fat CSA) predicted an opposite outcome. This finding implies that the relative size and composition of

cervical paraspinal muscles may have significant influence, whereby those with large (though small relative to the CSA of the corresponding cervical vertebral body), lean, and symmetric musculature were less likely to develop ASD. Though our study is limited by a relatively small sample size, the overall accuracy of predictions made using these metrics suggests that consideration of paraspinal musculature is warranted in cervical spine surgery.

Previous studies have commented on the clinical importance of paraspinal muscle morphology, although few have thoroughly examined their role in predicting outcomes after surgery.[30-32] Recent literature concerning cervical paraspinal musculature has highlighted a relationship between muscle morphology and sagittal alignment.[30-33] Passias *et al*[30] demonstrated that patients with cervical deformity were more likely to present with fatty infiltration and atrophic changes in the posterior cervical extensors, and asserted that such findings could predict postoperative cervical sagittal parameters. They later demonstrated that surgical correction of such deformities could restore cervical muscle tone and mitigated minor perioperative complications and postoperative pain.[31] Further, Tamai *et al*[32] suggested that cervical paraspinal muscles could have a role in the development of cervical disc degeneration. Other investigations concerning lumbar paraspinal musculature noted similar findings, suggesting CSA measures may inherently be related to conditions such as spinal deformity, ASD, global sagittal alignment, functional outcomes, postoperative complications, and fusion rates.[18,34] These studies collectively substantiate that paraspinal musculature has a considerable, though unexplored, role in dictating outcomes after spine surgery. The present study adds to this growing body of literature by citing a "predictive" relationship between cervical musculature and early-onset ASD. Further studies should validate this association and expand upon the postoperative clinical significance of paraspinal muscles.

Mechanistically, there are a number of considerations that may explain the relationship between muscle asymmetry and onset of ASD. Various neck muscles work synergistically to maintain alignment, mobility, and segmental stability of the cervical spine.[15] It has been estimated that neck muscles provide approximately 80% of total neck stability, while osseoligamentous structures contribute the remaining 20%.[17] Deep cervical extensors support neck movement and provide cervical stability.[35] Weaknesses in these muscles are associated with neck pain.[36] Any abnormal deep neck muscle function may lead to pain or instability in the neck region. Since anterior approach to the cervical spine may damage anterior neck muscles through local dissection and/or retraction, posterior deep neck extensors become the primary muscle group responsible for stability during the early postoperative period.[16] Any deficits or dysfunction of these muscles may alter spinal biomechanics and heighten the risk of developing ASD early in the postoperative period.[37] Research has shown that ACDF increased the mobility of adjacent segment cephalic to the fused construct.[38] When some segments are fused, adjacent unfused segments need to increase mobility to compensate for the reduced range of motion, which may heighten the intradiscal pressure in adjacent discs and lead to development of ASD.[39,40] Since biomechanical research has shown that the application of electrical stimulation to cervical muscles can reduce the neutral zone and range of motion in the sagittal plane of healthy and degenerative porcine cervical spines,[41] proper muscle function are crucial for the stability and mobility of the cervical spine (especially after ACDF). This may explain the close association between preoperative morphometry of deep neck extensors (but not other imaging phenotypes) and ASD development.

Historically, C5-C7 has been recognized as one of the most common vertebral segments affected by significant degenerative and arthritic change,[42] –though how paraspinal muscle

morphology and asymmetry at these levels are associated with ASD remains unclear. The present study demonstrated significant differences in fat composition, standardized CSA, and side-to-side asymmetry of deep neck paraspinal muscles in ASD patients when compared to those of non-ASD patients. These measures, particularly at C5-C7, were highly predictive of early-onset ASD, and suggests that there is likely an intimate biomechanical relationship between paraspinal musculature (especially at lower cervical levels) and cervical degeneration after an ACDF. Decreased CSA of muscles may indicate atrophy, weakness, or impairment of muscles, and may consequently affect their behavior and function at these vertebral levels.[43,44] Such considerations may underscore the necessity of further investigating the complex interactions between cervical dynamic stabilizers, degenerative changes, and the effectiveness of interventions to halt these imbalances.

Since previous studies have demonstrated that the decreased CSA of lumbar *multifidus* in patients with back pain may not spontaneously recover after pain attenuation, it is conceivable that preoperative atrophy and asymmetry in deep neck extensor muscles may persist after surgery without proper rehabilitation.[45] This condition may be worsened by altered activity of other neck muscles following surgery.[11,46] These factors together may cause persistent abnormal segmental cervical biomechanics and subsequent ASD development. Preliminary evidence has shown that strengthening exercises targeting deep paraspinal neck muscles can increase CSA and reduce fatty infiltration of the *multifidus* in patients with chronic whiplash disorders.[47] Similarly, isometric head/neck extension training in a neutral position at 20% of maximum voluntary contraction force can recruit both superficial and deep neck extensors in healthy individuals.[14] High load resistant exercises have also been shown to hypertrophize *semispinalis capitis*, *semispinalis cervicis*, and *multifidus* in asymptomatic individuals. Future research should

investigate the effects of neck strengthening exercises as a part of pre-operative physical therapy for patients with cervical radiculopathy, and the ability of these exercises to improve muscle asymmetry, lower the rate of surgical intervention, and possibly improve outcomes in patients with ACDF.[48]

Despite these findings, the utility of cervical muscle measurements may be grossly limited in clinical application without the holistic consideration of other well-validated metrics. Notably, on univariate analysis, there were relatively few cervical muscle differences between early-onset ASD and non-ASD patients. However, when accounting for other demographic, radiographic, and clinical features, cervical muscles demonstrated markedly greater predictive utility and suggests that small differences in cervical muscles may be amplified by other clinical variables. Though speculative, it stands to reason that differences in muscle CSA or asymmetry may be more clinically meaningful in patients that have concurrent sagittal alignment disturbances, additional degenerative pathology, and other comorbid features. Such considerations suggest that at minimum, the implementation of multivariate assessment is required in clinical medicine, while also implying that more robust analytical techniques (i.e. artificial intelligence, machine/deep learning) may help describe nuanced pathophysiological and biomechanical mechanisms of spine disease.

This study had several limitations. First, although the sample size was small,~~.~~ ~~However, they were representative samples from a large cohort~~a number of methodological considerations were made to maximize sample utility. SVM analysis was purposely chosen to implement techniques such as regularization and cross-validation;~~,~~ thus, aiding to minimize overfitting seen with classic multivariate logistic modelling approaches.[49] Further, all patients were collected as representative samples from seven years of clinical practice at a robust orthopaedic institution.

Though a larger sample size would likely aid the development of a more accurate model, such efforts would require a concerted multicenter approach with collection of identical metrics across institutions. Second, there was no information regarding the presence or absence of unilateral pain at the preoperative or postoperative stage. It is possible that the problem of deep neck paraspinal muscle asymmetry is more prevalent among patients with unilateral cervical radiculopathy. Third, the cervical range of motion, daily activity level, and information regarding medical or physiotherapy treatment were not documented, which might affect the structure of cervical muscles. Fourth, the current study only involved data from a single institution. Future prospective multicenter studies should be conducted to validate and extend our findings. While other factors (e.g., fear avoidance behavior, psychological distress, or frailty) may affect the cervical muscle control that may alter cervical biomechanics, these preoperative or postoperative factors were not considered in the current study given the limitation of retrospective review of medical record, future studies should consider the impact of psychological and/or physical factors on the motor control of neck muscles and subsequent ASD development.[50] Lastly, we have presented the persuasive motivation for developing a detailed biomechanical model of cervical spine that would allow prediction of the muscle activation with surgical intervention such as short or multilevel fusion on the mobility of adjacent levels, stress and strain fields within the disc constituents, and possible mechanisms of disc degeneration process. We acknowledge that the neural contribution and control synergies should be considered alongside this approach to fully exploit the treatment strategy for the phenotypes of high risk patients for proper training and rehabilitation before and after surgery to reduce the human suffering and economic burden of this disorder/disease. In addition, this work provides a framework to integrate the assessment of deep paraspinal neck muscles in predictive modelling for more

precision-based spine care for patients with cervical spine disorders that necessitate surgical intervention.

CONCLUSIONS

This is the first study to identify the morphology, composition, and asymmetry in preoperative deep neck extensors at the lower cervical spine to be predictors for early-onset ASD following ACDF after considering various demographic and radiographic factors. Our results highlight that clinicians and researchers should be aware of the importance of deep paraspinal neck muscle morphology and the association with radiographic evidence of ASD development early after ACDF. Future prospective research should investigate whether certain physical and physiological characteristics of deep neck muscles affect the prognosis of ASD or functional recovery following ACDF. Furthermore, this study has laid the foundation to further assess the impact of such paraspinal neck muscles alongside a full spectrum of risk profile phenotypes (e.g. alignment, additional degenerative findings, etc.), further employing the benefits of machine learning algorithms to robustly guide predictive modelling for direct clinical use.

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FIGURE LEGENDS

Figure 1. Lateral plain radiographs of a patient that underwent anterior cervical discectomy and fusion with plate fixation at C5-C7. **(A)** Preoperative images. **(B)** Postoperative images demonstrating adjacent segment degeneration at C4-C5, proximal to the fused construct.

Figure 2: Postoperative axial magnetic resonance images of the cervical spine of two patients, illustrating evaluation of the paraspinal muscles. **(A)** Images illustrate adjacent segment degeneration at C6-C7. **(B)** Images illustrate no adjacent segment degeneration at a similar level.

Figure 3: The final machine learning model had high accuracy (96.67%) and area under the curve (AUC) was 0.967 for receiver operating characteristics in predicting outcomes of early-onset adjacent segment degeneration.

Table 1. Baseline Patient & Operative Characteristics

		Overall (n = 62)	ASD (n = 32)	Non-ASD (n = 30)	*P* values
		Demographics			
Age (years)		52.4 ± 10.9	52.4 ± 12.0	52.3 ± 9.9	0.970
Gender (% male)		45.2% (n = 28)	43.8% (n = 14)	46.7% (n =14)	0.818
Body mass index		28.4 ± 5.5	29.1 ± 5.0	27.7 ± 6.0	0.298
Smoking (% smoker/ ex-smoker)		46.8% (n = 29)	53.1% (n = 17)	40.0% (n = 12)	0.535
Comorbidity		67.7% (n = 42)	65.6% (n = 21)	70.0% (n = 21)	0.713
		Preoperative Clinical Presentation			
Neck pain		90.3% (n = 56)	90.6% (n = 29)	90.0% (n = 27)	0.934
Arm pain		80.0% (n = 48)	80.7% (n = 25)	79.3% (n = 23)	0.897
Myelopathy		27.1% (n = 16)	31.0% (n = 9)	23.3% (n = 7)	0.567
Neck pain intensity (1-10)		6.4 ± 3.5	6.4 ± 3.6	6.4 ± 3.7	0.982
Neck Disability Index (0-100)		42.6 ± 21.4	47.0 ± 23.2	38.2 ± 20.0	0.430
Arm pain intensity (1-10)		4.5 ± 3.9	3.4 ± 4.0	5.7 ± 3.6	0.277
		Operative variables			
Fusion level					
	C3-C5	9	4	5	0.302
	C4-C6	20	13	7	
	C5-C7	33	15	18	
		Postoperative Clinical Presentation			
Cephalic ASD					
	C3	4	4	0	<0.001
	C4	9	9	0	
	C5	11	11	0	
Caudal ASD					
	C6	2	2	0	<0.001
	C7	7	7	0	
	T1	5	5	0	
Neck pain intensity (1-10)		2.4 ± 2.8	1.6 ± 1.7	3.6 ± 3.6	0.369
Neck Disability Index (0-100)		20.8 ± 18.9	12.6 ± 10.3	31.0 ± 22.6	0.035
Arm pain intensity (1-10)		2.6 ± 3.5	0.9 ± 1.7	4.9 ± 4.1	0.035

ASD: Adjacent Segment Degeneration

Table 2. Cervical Spine Imaging Phenotypes

	Overall (n = 62)	ASD (n = 32)	Non-ASD (n = 30)	*P* values
Lordosis				
C2-C7 (degrees)	5.4 ± 11.4	6.3 ± 10.1	4.5 ± 12.8	0.560
Fusion segment (degrees)	0.3 ± 7.9	0.5 ± 7.7	0.1 ± 8.3	0.855
Proximal adjacent segment (degrees)	1.5 ± 7.5	1.1 ± 7.4	1.9 ± 7.8	0.917
Distal adjacent segment (degrees)	3.9 ± 5.8	4.9 ± 6.4	2.6 ± 4.8	0.541
Disc displacement				
C2-C3	15.0% (n = 9)	19.4% (n = 6)	10.3% (n = 3)	0.329
C3-C4	52.5% (n = 31)	58.1% (n = 18)	46.4% (n = 13)	0.371
C4-C5	68.3% (n = 41)	71.0% (n = 22)	65.5% (n = 19)	0.650
C5-C6	90.0% (n = 54)	93.6% (n = 29)	86.2% (n = 25)	0.343
C6-C7	88.3% (n = 53)	83.9% (n = 26)	93.1% (n = 27)	0.266
C7-T1	18.3% (n = 11)	16.1% (n = 5)	20.7% (n = 6)	0.648
Disc narrowing				
C2-C3	3.3% (n = 2)	3.2% (n = 1)	3.5% (n = 1)	0.962
C3-C4	11.7% (n = 7)	6.5% (n = 2)	17.2% (n = 5)	0.193
C4-C5	21.7% (n = 13)	25.8% (n = 8)	17.2% (n = 5)	0.421
C5-C6	56.7% (n = 34)	58.1% (n = 18)	55.2% (n = 16)	0.821
C6-C7	45.0% (n = 27)	38.7% (n = 12)	51.7% (n = 15)	0.311
C7-T1	13.3% (n = 8)	19.4% (n = 6)	6.9% (n = 2)	0.156
Black disc				
C2-C3	78.3% (n = 47)	77.4% (n = 24)	79.3% (n = 23)	0.859
C3-C4	78.3% (n = 47)	74.2% (n = 23)	82.8% (n = 24)	0.421
C4-C5	75.0% (n = 45)	77.4% (n = 24)	72.4% (n = 21)	0.655
C5-C6	78.3% (n = 47)	74.2% (n = 23)	82.8% (n = 24)	0.421
C6-C7	73.3% (n = 44)	71.0% (n = 22)	75.9% (n = 22)	0.668
C7-T1	58.3% (n = 33)	64.5% (n = 20)	51.7% (n = 15)	0.315
Typical endplate abnormalities				
C2-C3	8.1% (n = 5)	9.4% (n = 3)	6.7% (n = 2)	0.696
C3-C4	21.0% (n = 13)	18.8% (n = 6)	23.3% (n = 7)	0.658
C4-C5	9.7% (n = 6)	9.4% (n = 3)	10.0% (n = 3)	0.934
C5-C6	9.7% (n = 6)	9.4% (n = 3)	10.0% (n = 3)	0.934
C6-C7	9.7% (n = 6)	3.1% (n = 1)	16.7% (n = 5)	0.710
C7-T1	8.1% (n = 5)	9.4% (n = 3)	6.7% (n = 2)	0.696
Atypical endplate abnormalities				
C2-C3	1.6% (n = 1)	0.0% (n = 0)	3.3% (n = 1)	0.298
C3-C4	4.8% (n = 3)	3.1% (n = 1)	6.7% (n = 2)	0.516
C4-C5	4.8% (n = 3)	6.3% (n = 2)	3.3% (n = 1)	0.593
C5-C6	16.1% (n = 10)	9.4% (n = 3)	23.3% (n = 7)	0.135
C6-C7	14.5% (n = 9)	18.8% (n = 6)	10.0% (n = 3)	0.328
C7-T1	3.2% (n = 2)	6.3% (n = 2)	0.0% (n = 0)	0.164
Modic changes				
C2-C3	8.1% (n = 5)	6.3% (n = 2)	10.0% (n = 3)	0.588
C3-C4	12.9% (n = 8)	9.4% (n = 3)	16.7% (n = 5)	0.392
C4-C5	17.7% (n = 11)	25.0% (n = 8)	10.0% (n = 3)	0.122
C5-C6	25.8% (n = 16)	21.9% (n = 7)	30.0% (n = 9)	0.465
C6-C7	17.7% (n = 11)	15.6% (n = 5)	20.0% (n = 6)	0.652
C7-T1	8.1% (n = 5)	3.1% (n = 1)	13.3% (n = 4)	0.140
Osteophyte	83.9% (n = 52)	84.4% (n = 27)	83.3% (n = 25)	0.911
Spondylolisthesis	10.0% (n = 6)	9.7% (n = 3)	10.3% (n = 3)	0.931
Spinal cord/canal CSA				
C2 spinal cord (mm^2)	256.8 ± 50.1	252.4 ± 50.4	261.7 ± 50.7	0.573
C2 spinal canal (mm^2)	861.9 ± 133.6	830.9 ± 111.1	889.8 ± 148.2	0.242
C2 spinal cord/canal ratio	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.0	0.072
C7 spinal cord (mm^2)	198.2 ± 35.9	203.9 ± 36.9	193.0 ± 35.2	0.357
C7 spinal canal (mm^2)	729.6 ± 167.0	664.1 ± 139.0	788.5 ± 171.1	0.020
C7 spinal cord/canal ratio	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	0.041

ASD: Adjacent Segment Degeneration; CSA: Cross-sectional area

Table 3. Cervical Paraspinal Muscle Cross-sectional Area Measurements

		Overall (n = 59)		ASD (n = 29)		Non-ASD (n = 30)		*P* values	
Total cross-sectional area of deep neck paraspinal muscles									
Total cross-sectional area (mm^2)		Left	Right	Left	Right	Left	Right	Left	Right
	C3	269.82 ± 61.26	257.06 ± 61.09	269.61 ± 65.80	251.32 ± 67.93	270.03 ± 57.65	262.60 ± 54.27	0.979	0.483
	C4	359.58 ± 73.56	349.11 ± 75.96	345.64 ± 80.45	345.64 ± 80.45	357.64 ± 80.45	352.46 ± 72.57	0.826	0.733
	C5	401.46 ± 85.25	398.89 ± 80.08	404.16 ± 96.49	398.14 ± 89.25	398.85 ± 74.48	399.61 ± 71.65	0.813	0.945
	C6	466.16 ± 107.32	461.69 ± 106.01	460.00 ± 101.44	448.57 ± 100.54	472.32 ± 114.36	474.79 ± 111.42	0.666	0.351
	C7	498.32 ± 130.29	486.30 ± 111.96	473.51 ± 110.13	455.71 ± 85.87	516.88 ± 145.45	526.88 ± 127.30	0.149	0.036
Average TCSA (mm^2)									
	C3	263.44 ± 58.29		260.47 ± 63.82		266.31 ± 53.34		0.704	
	C4	354.35 ± 72.34		353.69 ± 77.82		354.98 ± 67.95		0.947	
	C5	400.18 ± 77.76		401.15 ± 85.61		399.23 ± 70.81		0.925	
	C6	463.92 ± 104.00		454.29 ± 97.16		473.56 ± 111.30		0.485	
	C7	485.32 ± 103.23		464.61 ± 93.82		506.78 ± 109.71		0.124	
Average adjusted TCSA ratio*									
	C3	0.83 ± 0.21		0.81 ± 0.20		0.85 ± 0.21		0.460	
	C4	1.09 ± 0.28		1.10 ± 0.29		1.09 ± 0.28		0.868	
	C5	1.13 ± 0.28		1.17 ± 0.30		1.10 ± 0.26		0.332	
	C6	1.21 ± 0.37		1.17 ± 0.34		1.27 ± 0.40		0.288	
	C7	1.17 ± 0.35		1.10 ± 0.39		1.24 ± 0.29		0.118	
TCSA asymmetry (%)									
	C3	14.41 ± 10.43		17.49 ± 11.37		11.44 ± 8.61		0.025	
	C4	9.75 ± 7.05		10.77 ± 8.18		8.76 ± 5.72		0.276	
	C5	11.27 ± 8.87		14.74 ± 10.08		7.92 ± 5.96		0.003	
	C6	8.46 ± 6.90		10.67 ± 8.04		6.24 ± 4.71		0.014	
	C7	8.14 ± 8.25		12.66 ± 8.53		3.62 ± 4.86		<0.001	
Aberrant TCSA asymmetry**									
	C3	47.5% (n = 28)		58.6% (n = 17)		36.7% (n = 11)		0.120	
	C4	35.6% (n = 21)		41.4% (n = 12)		30.0% (n = 9)		0.422	
	C5	39.0% (n = 23)		55.2% (n = 16)		23.3% (n = 7)		0.017	
	C6	20.7% (n = 12)		37.9% (n = 11)		3.4% (n = 1)		0.002	
	C7	24.1% (n = 14)		41.4% (n = 12)		6.9% (n = 2)		0.005	
Functional cross-sectional area of deep neck paraspinal muscles									
Functional cross-sectional area (mm^2)		Left	Right	Left	Right	Left	Right	Left	Right
	C3	217.88 ± 58.11	203.56 ± 56.69	211.01 ± 61.55	196.48 ± 64.55	224.52 ± 54.79	210.39 ± 48.03	0.377	0.353
	C4	316.05 ± 71.41	309.35 ± 75.91	316.60 ± 81.15	303.29 ± 81.84	315.50 ± 61.97	315.20 ± 70.62	0.953	0.551
	C5	353.59 ± 89.98	350.42 ± 81.57	351.92 ± 103.35	345.36 ± 88.75	355.20 ± 76.65	355.31 ± 75.17	0.891	0.645
	C6	394.36 ± 98.68	395.80 ± 97.33	384.46 ± 98.20	380.44 ± 97.23	404.26 ± 99.88	411.15 ± 96.66	0.450	0.233
	C7	400.44 ± 118.79	408.35 ± 113.42	366.55 ± 87.20	377.88 ± 90.91	434.33 ± 136.90	438.82 ± 98.20	0.028	0.040

Average FCSA (mm^2)					
	C3	210.72 ± 54.81	203.75 ± 53.81	217.45 ± 49.58	0.341
	C4	312.70 ± 71.41	309.95 ± 78.99	315.35 ± 64.50	0.774
	C5	352.00 ± 81.33	348.64 ± 90.22	355.25 ± 73.12	0.759
	C6	395.08 ± 95.49	382.46 ± 94.28	407.71 ± 96.65	0.318
	C7	398.88 ± 102.87	372.22 ± 84.37	426.49 ± 114.06	0.045
Average adjusted FCSA ratio*					
	C3	0.66 ± 0.16	0.63 ± 0.16	0.69 ± 0.16	0.168
	C4	0.96 ± 0.26	0.96 ± 0.28	0.96 ± 0.25	0.983
	C5	1.00 ± 0.26	1.02 ± 0.29	0.97 ± 0.24	0.501
	C6	1.03 ± 0.32	0.98 ± 0.29	1.10 ± 0.34	0.156
	C7	0.95 ± 0.30	0.87 ± 0.31	1.04 ± 0.26	0.029
FCSA asymmetry (%)					
	C3	16.50 ± 14.92	19.68 ± 18.49	13.42 ± 9.76	0.113
	C4	10.05 ± 9.37	11.70 ± 11.83	8.46 ± 5.94	0.193
	C5	12.17 ± 11.11	14.61 ± 13.34	9.83 ± 7.96	0.099
	C6	9.56 ± 8.11	11.52 ± 9.54	7.61 ± 5.93	0.067
	C7	11.57 ± 10.16	13.22 ± 11.13	9.92 ± 8.98	0.219
Clinically-meaningful FCSA asymmetry**					
	C3	55.9% (n = 33)	58.6% (n = 17)	48.5% (n = 16)	0.795
	C4	30.5% (n = 18)	31.0% (n = 9)	30.0% (n = 9)	1.000
	C5	33.9% (n = 20)	44.8% (n = 13)	23.3% (n = 7)	0.103
	C6	24.1% (n = 14)	44.8% (n = 13)	3.4% (n = 1)	<0.001
	C7	22.4% (n = 13)	37.9% (n = 11)	6.5% (n = 2)	<0.001

FCSA/TCSA ratio of deep neck paraspinal muscles

FCSA/TCSA ratio		Left	Right	Left	Right	Left	Right	Left	Right
	C3	0.81 ± 0.12	0.79 ± 0.12	0.78 ± 0.12	0.78 ± 0.12	0.83 ± 0.11	0.81 ± 0.12	0.078	0.381
	C4	0.88 ± 0.06	0.88 ± 0.07	0.87 ± 0.06	0.87 ± 0.08	0.89 ± 0.06	0.89 ± 0.06	0.175	0.266
	C5	0.88 ± 0.07	0.88 ± 0.07	0.86 ± 0.07	0.86 ± 0.08	0.89 ± 0.06	0.89 ± 0.06	0.086	0.123
	C6	0.85 ± 0.09	0.86 ± 0.08	0.83 ± 0.10	0.84 ± 0.08	0.86 ± 0.08	0.87 ± 0.07	0.360	0.271
	C7	0.81 ± 0.11	0.84 ± 0.08	0.78 ± 0.11	0.83 ± 0.08	0.83 ± 0.11	0.86 ± 0.08	0.092	0.158
FCSA/TCSA ratio asymmetry									
	C3	9.85 ± 8.39		10.93 ± 8.56		8.80 ± 8.23		0.333	
	C4	5.34 ± 5.15		6.01 ± 6.43		4.68 ± 3.50		0.332	
	C5	4.79 ± 3.89		4.90 ± 4.31		4.68 ± 3.50		0.830	
	C6	6.13 ± 5.36		6.94 ± 5.39		5.31 ± 5.30		0.250	
	C7	8.53 ± 10.35		11.05 ± 13.20		6.00 ± 5.56		0.065	

ASD: Adjacent Segment Degeneration; TCSA: Total Cross-sectional Area; FCSA: Functional Cross-sectional Area (lean muscle cross-sectional area)

* Adjusted cross-sectional area measures were normalized to the vertebral body cross-sectional area at each given vertebral level.[33]

** Clinically-meaningful asymmetry was identified if the percentage of between-side differences in cross-sectional area measures exceeded 12.8%.[34]

Table 4. Intra-rater reliability (and confidence intervals) of total cross-sectional area (CSA), and functional cross-sectional area of cervical paraspinal muscles from C3 to C7 levels.

ICC	Total CSA					Functional CSA				
	C3	C4	C5	C6	C7	C3	C4	C5	C6	C7
Right	0.94 (0.75-0.98)	0.93 (0.70-0.98)	0.90 (0.63-0.98)	0.95 (0.82-0.99)	0.94 (0.75-0.99)	0.91 (0.66-0.98)	0.90 (0.61-0.98)	0.93 (0.71-0.98)	0.95 (0.80-0.99)	0.95 (0.81-0.99)
Left	0.96 (0.74-0.99)	0.94 (0.79-0.99)	0.92 (0.66-0.98)	0.95 (0.68-0.99)	0.94 (0.72-0.99)	0.93 (0.72-0.98)	0.91 (0.67-0.98)	0.91 (0.66-0.98)	0.92 (0.66-0.98)	0.94 (0.80-0.99)

ICC = intra-class correlation coefficient. All calculated ICC values had $P < 0.05$.

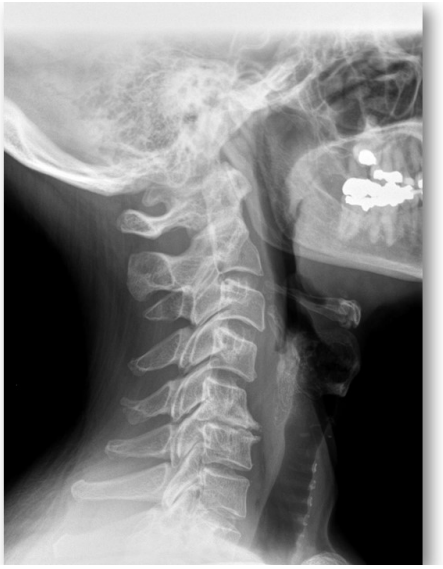

Figure 1. Lateral plain radiographs of a patient that underwent anterior cervical discectomy and fusion with plate fixation at C5-C7. (A) Preoperative images.

338x190mm (96 x 96 DPI)

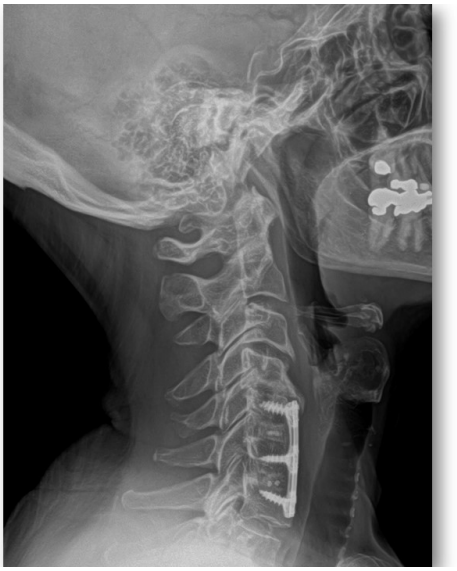

Figure 1. Lateral plain radiographs of a patient that underwent anterior cervical discectomy and fusion with plate fixation at C5-C7. (B) Postoperative images demonstrating adjacent segment degeneration at C4-C5, proximal to the fused construct.

338x190mm (96 x 96 DPI)

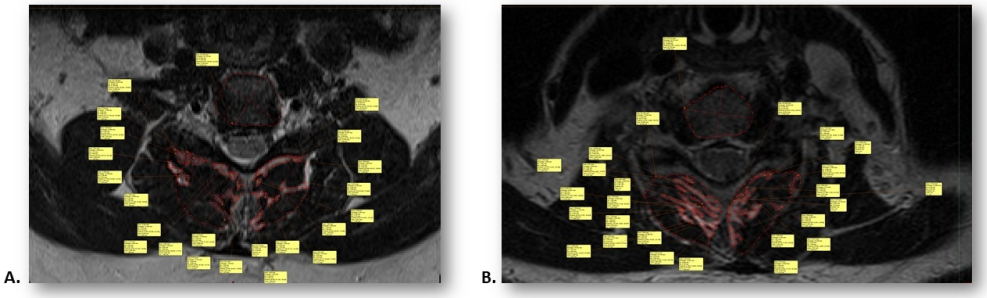

Figure 2: Postoperative axial magnetic resonance images of the cervical spine of two patients, illustrating evaluation of the paraspinal muscles. (A) Images illustrate adjacent segment degeneration at C6-C7. (B) Images illustrate no adjacent segment degeneration at a similar level.

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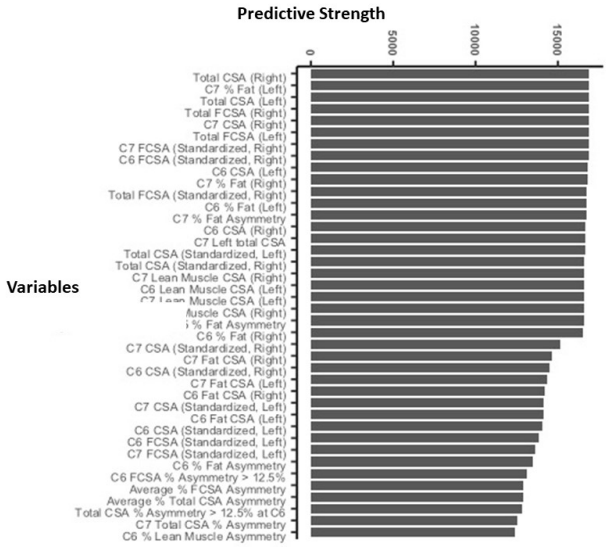

Figure 3: The final machine learning model had high accuracy (96.67%) and area under the curve (AUC) was 0.967 for receiver operating characteristics in predicting outcomes of early-onset adjacent segment degeneration.

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