

Research Article

Utilizing Double Machine Learning to Discern Risk Factors for Preoperative Depression Among Anterior Cervical Discectomy and Fusion (ACDF) Patients

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Background

The Patient Health Questionnaire-9 (PHQ-9) is a common instrument for assessing depressive symptoms and has been validated in numerous patient populations. Cross-fitting or double machine learning (ML) is a method of variable selection that has

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gained increased attention for its potential to identify coefficients of interest. Among patients undergoing anterior cervical discectomy and fusion (ACDF), a better understanding of the factors associated with greater depressive symptoms may assist in identifying patients who could benefit the most from management of depressive symptoms prior to surgical intervention.

Purpose

In this study, we use ML to assess and identify the most significant risk factors associated with moderately severe depressive symptoms (PHQ-9 $\geq$ 15) among patients undergoing ACDF.

Methods

We prospectively collected surgical records and then conducted a retrospective review of patients undergoing single or multilevel ACDF between March 2016 and January 2019. We excluded patients if they underwent surgery due to infection, metastasis, or trauma. Demographic and baseline characteristics were recorded (Table 1). We recorded degenerative spinal diagnoses and symptoms (Table 2) and postoperative complications (Table 3). We assessed demographics, baseline characteristics, pain levels (Visual Analog Scale [VAS] arm and neck pain) and spine pathologies with a bivariate analysis to explore how much they elevated the risk of preoperative depression (Table 4). We used a cross-fit partialling-out LASSO (least absolute shrinkage and selection operator) logistic regression to estimate odds ratios (OR), confidence intervals, and to adequately control for and select significant covariates contributing to increased levels of preoperative depression (Table 5).

Results

147 patients underwent single or multilevel ACDF procedures. 58% of our patient population was older than 50 years of age. The cohort was 42% female, 63% had an elevated body mass index (BMI), and 21% had a smoking history. Other comorbidities included hypertension (29.3%), diabetes (12.2%), arm pain (49.7%), and neck pain (48.3%). The rate of moderately severe baseline depressive symptoms (PHQ-9 $\geq$ 15) was 16.3%. The most common preoperative spinal pathologies and symptoms included myeloradiculopathy (90.5%), herniated nucleus pulposus (82.3%), weakness (8.8%), and radiculopathy (6.8%). The only postoperative complication was urinary retention (1.4%). Both urinary retention cases required brief catheter replacement and were resolved prior to discharge. On bivariate analysis, significant baseline characteristics associated with higher levels of preoperative depression (PHQ-9 $\geq$ 15) included: BMI $\geq$ 30 kg/m² (OR = 2.2, p = 0.040), WC insurance (OR = 2.2, p = 0.035), VAS arm pain $\geq$ 7 (OR = 2.5, p = 0.032), and VAS neck pain $\geq$ 7 (OR = 4.1, p = 0.003). Our cross-fit partialing-out LASSO regression revealed VAS neck pain $\geq$ 7 (OR = 6.8, p = 0.002) and BMI $\geq$ 30 kg/m² (OR = 3.0, p = 0.034) as potentially significant risk factors for preoperative depression severity.

Conclusion

Our study utilized DML to identify risk factors associated with elevated levels of preoperative depression among patients undergoing single or multilevel ACDFs. The most significant risk factors associated with moderately severe depression included increased neck pain and BMI. Further investigations are needed to identify potential ACDF outcomes and complications that are most associated with increased levels of preoperative depression influences.

INTRODUCTION

Anterior cervical discectomy and fusion (ACDF) is a surgical technique that is most often used to treat myelopathy and radiculopathy of the cervical spine. Appropriate patient selection and modification of common preoperative risk factors have been observed to minimize complications and optimize patient outcomes. Machine learning (ML) is a type of artificial intelligence that has recently gained traction to

assist in improving patient outcomes in orthopedics, and in ACDF in particular (Karhade et al. 2019). ML uses algorithms to predict surgical outcomes based on a patient's medical imaging, genetics, and clinical history (Kim et al. 2018), which may reduce surgical complications. The algorithms constructed by ML have been used to gather information from a patient's medical records, including their symptoms, laboratory results, medical imaging, and physical exam to create a customized treatment plan (Lakhani

et al. 2018). In orthopaedics, ML in the form of decision trees and random forests has been used to categorize patients into groups based on osteoarthritis (OA) pathologies (Kotti et al. 2017). Additional ML techniques include nearest neighbor as applied to OA imaging (Ashinsky et al. 2017), linear regressions in knee injuries (Matić et al. 2016), and support vector machines for OA prediction (Madelin et al. 2015). Previous research has demonstrated the potential to apply ML algorithms to predict long term opioid use in patients undergoing ACDF (Karhade et al. 2019) as well as other post-surgical complications.

An additional tool that has shown efficacy in reducing post-surgical complications is optimizing preoperative mental health. Recent studies investigating spine surgical outcomes have found that poor presurgical mental health (i.e., depression, anxiety, distress) is associated with worse clinical outcomes, increased post-surgical pain, and inferior postoperative recovery (Patel et al. 2019). In response to the negative impact that mental health can have on surgical outcomes, there has been an increased interest in evaluation of mental health and preoperative prehabilitation (Lundberg et al. 2019). Examples of prehabilitation include increasing physical activity, reducing anxiety, eating a balanced diet, and improving depressive symptoms (Levett and Grimmer 2019).

Preoperative mental health can be evaluated by using patient surveys and questionnaires. The Patient Health Questionnaire-9 (PHQ-9) is a validated screening tool to assess depressive symptoms. The PHQ-9 consists of nine questions, with each question carrying a weight of 0-3. A "0" signifies that the patients "never" experience a certain depressive symptom, whereas a "3" represents experiencing depressive symptoms daily. A PHQ-9 score of 5, 10, 15, and 20 indicate mild, moderate, moderately severe, and severe depression, respectively (Kroenke, Spitzer, and Williams 2001). When comparing the PHQ-9 to other depressive symptom surveys, the PHQ-9, although shorter, has equivalent specificity and sensitivity, and is based off of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) and DSM-V algorithms for the diagnosis of major depressive disorder (MDD) (Kroenke, Spitzer, and Williams 2001; Muñoz-Navarro et al. 2017). Due to its length, reliability, and validity as a depression severity tool, it can be effectively used to evaluate pre and postoperative depressive symptoms among patients undergoing ACDF.

The application of ML in spine surgery has not been extensively studied in relation to mental health. ML may help clinicians identify patients who are predisposed to poor mental health preoperatively. In this study, we use ML to assess and identify the most significant risk factors associated with moderately severe depressive symptoms (PHQ-9 $\geq$ 15) among patients undergoing ACDF.

METHODS

PATIENT POPULATION

Institutional review board approval (ORA 14051301) was obtained prior to beginning this investigation. We conducted a retrospective review of a prospectively collected surgical registry. We selected patients with surgeries between March 2016 and January 2019. Included patients underwent elective, primary, single and multilevel ACDF for degenerative spine pathologies. We excluded patients if surgery was indicated for infection, trauma, or metastasis.

DATA COLLECTION

We collected baseline and demographic variables including age, gender, BMI, smoking status, American Society of Anesthesiologists (ASA) score, Charlson Comorbidity Index (CCI) score, hypertension, preoperative levels of arm pain, neck pain, and baseline depressive symptom severity. Degenerative spinal pathology, as determined by preoperative radiographic imaging, was also recorded. Other perioperative variables collected included operative duration, and estimated blood loss (EBL). All postoperative complications that occurred during the patient's hospital stay were also recorded.

STATISTICAL ANALYSIS

Stata 16.1 (StataCorp) was used for statistical analyses and numerical calculations. We assessed descriptive characteristics and perioperative variables with means, proportions, and ranges. More than one degenerative spinal pathology may have applied for one patient. All variables were assessed as possible predictors for having moderately severe depressive symptoms as calculated by PHQ-9 score (PHQ $\geq$ 15). A cross-fit partialing-out least absolute shrinkage and selection operator (LASSO) logistic regression was used to estimate odds ratios (OR), confidence intervals, and to control for and select significant covariates contributing to increased levels of preoperative depression. The cross-fit partialing out method was used to estimate variable effects and to select for appropriate control variables. The double machine learning (DML) technique partitioned the sample into folds and then used post-LASSO calculations to estimate coefficient values for observations not included in the given fold (Chernozhukov et al. 2018). Moment conditions were solved jointly across all observations. Statistical significance was set a $p < 0.05$.

SURGICAL TECHNIQUE

The Smith Robinson approach was used to perform all ACDFs. The disc space was prepared with a burr and curette. Patients received either autograft, allograft, or bone graft substitutes to ensure adequate cage stability and placement. Following the placement of either a plate-graft construct or zero-profile device, visualization was accomplished with fluoroscopy and the wound was irrigated.

Hemostasis was evaluated prior to completing the surgery with a layered closure.

RESULTS

DEMOGRAPHIC AND BASELINE VARIABLES

A total of 147 patients were included in our cohort. All included patients underwent single or multilevel ACDF procedures ([Table 1](#)). The mean age was 50.2 years (range: 26.7 to 76.3), 59.2% was female, and the average BMI was 29.7 kg/m² (range 18.5 to 54.2). The vast majority of the population (84%) did not smoke. 82% of the patient population had an ASA score that was indicative of mild systemic disease or less (≤ 2), 26% of the population had a CCI score of < 1 . A minority of the population was diagnosed with diabetes (12.2%) or hypertension (29.3%). 49.7% of the population had a VAS arm pain score ≥ 7 and 48.3% had a VAS neck pain score of ≥ 7 . 16.3% of the population had moderately severe depressive symptoms (PHQ-9 ≥ 15) or worse. The three most common preoperative spinal pathologies ([Table 2](#)) were myeloradiculopathy (90.5%), herniated nucleus pulposus (82.3%), and weakness (8.8%).

PERIOPERATIVE CHARACTERISTICS

The cohort average operative duration time was 71.6 minutes (range: 29 to 722 minutes) with an average EBL of 31.5 mL (range: 15 to 200 mL). Only 2 patients in the cohort experienced postoperative complications: both experienced urinary retention that required a catheter on discharge ([Table 3](#)).

ANALYSIS OF PREDICTORS FOR MODERATELY SEVERE DEPRESSIVE SYMPTOMS

Our bivariate analysis revealed three predictors with statistically significant elevated ORs for moderately severe depressive symptoms (PHQ-9 ≥ 15) ([Table 4](#)). Increased odds were observed for BMI ≥ 30 kg/m² (OR=2.2, $p=0.040$), preoperative VAS arm pain ≥ 7 (OR=2.5, $p=0.032$), and VAS neck pain ≥ 7 (OR=4.1, $p=0.003$). The cross-fit partialing-out LASSO logistic regression revealed the most significant predictors of moderately severe depressive symptoms to be VAS neck pain ≥ 7 (OR=4.68, $p=0.024$) and BMI ≥ 30 kg/m² (OR=2.73, $p=0.045$, [Table 5](#)).

DISCUSSION

Using ML, we identified increased neck pain (VAS neck ≥ 7 , OR=4.68, $p=0.024$) and obesity (BMI ≥ 30 kg/m², OR=2.73, $p=0.045$) as significant risk factors for moderately severe symptoms of preoperative depressive symptoms (PHQ-9 ≥ 15) among patients undergoing ACDF. Our results were achieved through the application of ML, a promising application that has been used for decision making and in the identification of risk factors in a range of specialties (Lo-Ciganic et al. 2019). An important aspect of identified risk factors in our study is that they have been associated

with poor postoperative outcomes and they are both considered to be modifiable.

While PHQ-9 could be directly evaluated, identification of risk factors associated with worse preoperative depression, an objective of the present study, is of meaningful value. Chuang et al. published an article on a novel education model in *Computer Methods and Programs in Biomedicine*, demonstrating that enhanced integrative education incorporating e-learning to teach patients about their pathology and the indicated procedure reduced anxiety and alleviated stress from uncertainty among individuals undergoing cervical discectomy surgery (Chuang et al. 2016). This is founded on the well-established principle that through the communication of detailed information to patients on their healthcare, patients will gain invaluable insight that enhances their coping skills and quality of life (Brox et al. 2008; Saban and Penckofer 2007). Relaying comprehensive information preoperatively to patients has been demonstrated to improve satisfaction and decrease anxiety prior to surgery (Strøm et al. 2018). One study demonstrated that patients given more information preoperatively more promptly improved in pain outcomes, reported greater satisfaction, and experienced significantly lower state anxiety preoperatively (Sjöling et al. 2003).

Thus, while PHQ-9 scores may be directly assessed, further examination and subsequent communication to patients providing knowledge of risk factors contributing to poorer mental health may reduce worries that stem from a lack of information and empower providers and patients to together strategize mitigating such risk factors before surgery is conducted. Furthermore, by discussing such risk factors to patients who may require ACDF in the future, patients utilize this awareness to minimize modifiable factors such as obesity and pain, and potentially reduce anxiety by the immediate preoperative period.

THE ASSOCIATION OF DEPRESSIVE SYMPTOMS

Optimization of depressive symptoms prior to surgical spine procedures may improve functionality and surgical outcomes. Researchers have observed that patients with greater levels of preoperative depressive symptoms had worse functional outcomes after ACDF (Phan et al. 2017). Similarly, greater preoperative depressive symptoms, as measured by PHQ-9, have been associated with worse post-lumbar surgery improvement in postoperative quality of life in EQ-5D (Chapin, Ward, and Ryken 2017). In addition to resulting in inferior surgical outcomes, preoperative depression is also associated with post-surgical complications, chronic opioid use, revisions, 30-day readmissions, and increased costs after lumbar surgery (O'Connell et al. 2018). Treating preoperative depression has the potential to result in greater patient satisfaction, fewer post-surgical complications, immense cost savings, and fewer revision procedures. Such findings may also assist surgeons when considering whether patients are ideal surgical candidates.

Several studies have indicated more limited effects of mental health on ACDF outcomes. Among these studies, one study investigated mental health only using short form (SF) mental health component summary (MCS) scores that

Table 1. Demographics and Perioperative Descriptors

Characteristic	n=147	Percentage	Mean (Range)
Age			50.2 (26.7 - 76.3)
≤50 years	77	52.4%	
>50 years	70	47.6%	
Gender			
Female	60	40.8%	
Male	87	59.2%	
Body mass index (BMI)			29.7 (18.5 - 54.2)
<30 kg/m ²	84	57.1%	
≥30 kg/m ²	63	42.9%	
Smoking status			
Non-smoker	124	84.4%	
Smoker	23	15.7%	
ASA Score			1.9 (1.0 - 3.0)
≤2	121	82.3%	
>2	26	17.7%	
CCI Score			1.4 (0.0 - 5.0)
<1	38	25.9%	
≥1	109	74.2%	
Hypertension			
Non-hypertensive	104	70.8%	
Hypertensive	43	29.3%	
Diabetes			
Non-diabetic	129	87.8%	
Diabetic	18	12.2%	
Preoperative VAS Arm Pain score			6.1 (0.0 - 10.0)
<7	74	50.3%	
≥7	73	49.7%	
Preoperative VAS Neck Pain score			6.3 (0.0 - 10.0)
<7	76	51.7%	
≥7	71	48.3%	
Postoperative Day of Discharge			0.6 (0.0-8.0)
POD 0	82	56.6%	
POD 1	55	37.9%	
POD 2	6	4.1%	
≥POD 3	2	1.4%	
Operative duration			71.6 (29.0 - 722.0)
≤105 minutes	141	95.9%	
>105 minutes	6	4.1%	
Estimated blood loss (EBL)			31.5 (15.0 - 200.0)
≤50 mL	139	94.6%	
>50 mL	8	5.4%	
Baseline Depressive Symptoms			7.6 (0.0 - 26.0)
PHQ-9<15	123	83.7%	
PHQ-9≥15	24	16.3%	

ASA = American Society of Anesthesiologists; CCI = Charlson Comorbidity Index; PHQ-9=Patient Health Questionnaire-9; VAS = Visual Analog Scale

were either reflective of global mental health (Mayo et al. 2017) or of depressive symptoms. These differ from the cur-

rent study in our use of PHQ-9 to specifically assess depressive symptoms. Other investigations have revealed modest

Table 2. Rates of preoperative spinal pathologies

Degenerative Disc Disease	2.7% (4)
Spondylolisthesis	1.4% (2)
Herniated Nucleus Pulposus	82.3% (121)
Radiculopathy	6.8% (10)
Myelopathy	2.0% (3)
Myeloradiculopathy	90.5% (133)
Palsy	0.7% (1)
Weakness	8.8% (13)

Table 3. Rates of postoperative complications

Postoperative Complications	Percent (n)
Urinary Retention Requiring a Catheter	1.4% (2)
Neurological Disease	0.0% (0)
Cardiac Complications	0.0% (0)
Fever	0.0% (0)
Blood Transfusion	0.0% (0)
Cardiovascular Complications	0.0% (0)
Ileus	0.0% (0)
Pseudarthrosis at 6 months	0.0% (0)
Urinary Tract Infection	0.0% (0)
Renal Failure	0.0% (0)
Aspiration	0.0% (0)
Arrhythmia	0.0% (0)
Pneumothorax	0.0% (0)
Pneumonia	0.0% (0)
Altered Mental Status	0.0% (0)
Durotomy	0.0% (0)
Surgical Site Infection	0.0% (0)

differences in physical function as measured by SF-12 PCS among those with mild and moderate levels of depression as compared to those with moderately severe depression that persisted up to 3-months after ACDF (PHQ-9<15: 38.2 versus PHQ-9 ≥ 15: 32.3, $p=0.032$) (Jenkins et al. 2020).

THE INFLUENCE OF PAIN ON DEPRESSION AND OUTCOME

A complex relationship exists between pain and depression. Our study, using a LASSO model, observed that patients who reported elevated preoperative neck pain (VAS neck ≥7) had an OR=4.68 for moderately severe depressive symptoms (PHQ-9 ≥ 15). Previous research has observed that individuals with neck pain in the past 12 months reported depression, as evaluated by the Zung Self-Rating Depression Scale (Rajala et al. 1995). While pain alone may have a negative effect on mental health, physical disability as a result of that pain should also be considered as a risk factor. Similarly, other studies have observed that

neck pain intensity as evaluated by VAS was significantly correlated with anxiety, while disability correlated with de-

pression, anxiety, and catastrophizing (Dimitriadis et al. 2015). The link between mental health and neck pain has further been established in a review of population-based and primary care studies demonstrated that back and neck pain was strongly associated with depression and that psychological symptoms were often present early in the natural history of the pain (Von Korff and Simon 1996). They echoed the dichotomized theories that chronic pain is either the body's somatization of unacknowledged depression, or that depression is a consequence of chronic pain (Von Korff and Simon 1996).

BMI AND DEPRESSIVE SYMPTOMS

The results of our study demonstrated a statistically significant relationship between preoperative depression (PHQ-9 scores ≥15) and having a BMI of ≥30 kg/m² in both our bivariate regression (OR = 2.2, $p = 0.040$) and the LASSO model (OR=3.0, $p=0.034$). These results are aligned with previous studies, which have found that obesity and depression have a complex reciprocal relationship (Luppino et al. 2010). Such findings suggest that obesity is associated

Table 4. Bivariate Analysis of Demographics, Baseline Characteristics, Pain and Spinal Pathologies

Characteristic	Among PHQ-9≥15 (Percent)	RR	Confidence Interval	P-Value
Age				
≤50 years	41.7%	Reference		
>50 years	58.3%	1.5	(0.7 - 3.2)	0.257
Gender				
Male	58.3%	1.0	(0.5 - 2.0)	0.926
Female	41.7%	Reference		
Body mass index (BMI)				
<30 kg/m ²	37.5%	Reference		
≥30 kg/m ²	62.5%	2.2	(1.0 - 4.8)	0.040
Smoking status				
Non-smoker	79.2%	Reference		
Smoker	20.8%	1.4	(0.6 - 3.4)	0.437
ASA Score				
≤2	83.3%	Reference		
>2	16.7%	0.9	(0.3 - 2.5)	0.887
CCI Score				
<1	25.0%	Reference		
≥1	75.0%	1.0	(0.4 - 2.4)	0.918
Hypertension				
Non-hypertensive	58.3%	Reference		
Hypertensive	41.7%	1.7	(0.8 - 3.6)	0.143
Diabetes				
Non-diabetic	87.5%	Reference		
Diabetic	12.5%	1.0	(0.3 - 3.1)	0.967
Preoperative VAS Arm Pain				
<7	29.2%	Reference		
≥7	70.8%	2.5	(1.1 - 5.6)	0.032
Preoperative VAS Neck Pain				
<7	20.8%	Reference		
≥7	79.2%	4.1	(1.6 - 10.3)	0.003
Spinal Pathologies and Signs				
Degenerative Disc Disease	4.2%	1.6	(0.3 - 8.9)	0.620
Spondylolisthesis	4.2%	3.2	(0.7 - 13.3)	0.118
Herniated Nucleus Pulposus	70.8%	0.5	(0.2 - 1.1)	0.100
Radiculopathy	4.2%	1.6	(0.3 - 8.9)	0.620
Myelopathy	4.2%	2.1	(0.4 - 10.9)	0.382
Myeloradiculopathy	91.7%	1.2	(0.3 - 4.4)	0.831
Palsy	0.0%	—	—	—
Weakness	8.3%	0.9	(0.2 - 3.6)	0.924

ASA = American Society of Anesthesiologists; CCI = Charlson Comorbidity Index; RR = Relative Risk; VAS = Visual Analog Scale

with depression in the same way that depression is associated with obesity (Luppino et al. 2010). Another theory linking depression and BMI is that the association between the two is non-linear (de Wit et al. 2009). This U-shaped association indicates that being both underweight and overweight are correlated with depressive symptoms. Ultimately, the relationship between obesity and depressive symptoms is complex, and some researchers believe the

link between the two is weak (Atlantis and Baker 2008). Biologically, obesity and depression may be linked due to increased activation of the hypothalamic–pituitary–adrenal (HPA) axis, which releases cortisol (Milaneschi et al. 2019). Although increased cortisol in obesity has been established, there are still gaps in research connecting the hormone to depression (Milaneschi et al. 2019).

Table 5. Cross-fit Partialing-out LASSO logistic regression to estimate

Risk Factor	Odds Ratio	95% CI	*p-value†
VAS Neck Pain ≥ 7	4.68	1.23 – 17.85	0.024
BMI ≥ 30 kg/m ²	2.73	1.02 – 7.32	0.045

BMI = Body Mass Index; LASSO = least absolute shrinkage and selection operator; VAS = Visual Analog Scale; 95% CI = 95% Confidence Interval

***Boldface** indicates statistical significance

†p-value calculated using backwards stepwise Poisson regression with robust error variance

Elevated BMI has been associated with numerous effects among spine surgery patients including increased levels of disk generation (Teraguchi et al. 2014), lower back pain (Samartzis et al. 2011), sciatica, and the overall incidence of undergoing spine surgery indicated by disc herniation (Shiri et al. 2010). Likewise, obesity has been associated with postoperative complications including longer operative time durations, increased costs, higher rates of surgical site infections, cardiovascular complications, and an overall higher rate of mortality. Although the influence of BMI has been elaborated in multiple dimensions centered on spine surgery, few studies have focused on risk factors that are most commonly associated with preoperative depression.

The association of BMI preoperative comorbidities, whether musculoskeletal or psychiatric, is often hypothesized to be straightforward. For example, it is intuitive that disc degeneration could occur more often among those with elevated BMI due to greater mechanical loads imposed on the spine (Jackson and Devine 2016). However, more recently, a complex set of multifactorial associations may underlie disc degeneration (Samartzis et al. 2013). Obesity has been increasingly associated with a “chronic inflammatory state” (Samad and Ruf 2013). While adipocytes are the body’s fat-building cells, they also are associated with the release of leptin. Leptin is a member of a group of hormones known as adipokines. Investigators have observed that adipokines are associated with increased rates of osteoarthritis in multiple joints. Furthermore, adipokines appear to increase the disc tissue matrix deterioration within the vertebral column (Zhao et al. 2008). In addition to the emerging nuanced effects that obesity appears to have over common musculoskeletal pathologies, other biomolecular etiologies related to obesity may also be associated with psychiatric disorders such as depression.

While musculoskeletal comorbidities may be related to an interplay of leptin with structural tissue production, increased depressive symptoms, however, may be associated with another adipokine known as adiponectin (Everson-Rose et al. 2018). The circulating level of adiponectin is diminished in obese individuals (Everson-Rose et al. 2018). Furthermore, the amount of adiponectin in circulation has been observed to correlate inversely with increased depressive symptoms as measured by PHQ-9 scores ($p=0.006-0.048$) (Herder et al. 2018). Adiponectin can increase insulin sensitivity and regulate glucose and fatty acid metabolism (Forny-Germano, De Felice, and Vieira 2019). Adiponectin has well-reported anti-inflammatory effects (Liu et al. 2015), and can facilitate antidepressant effects, both after acute and chronic administration (Nico-las et al. 2018).

STEPS TOWARD MODIFICATION

One of the most important reasons to focus on modifiable risk factors associated with depressive symptoms and poor surgical outcomes is because of the potential to modify them and to optimize surgical candidates. Recommending that patients receive appropriate nutrition, exercise, and psychological care is imperative. For example, the increased focus on integrative medicine and use of nutrition in the perioperative setting has been used to target pain, healing, and mood. Certain diets, such as those that are high in fruit, fish, olive oil, vegetables, and low in animal foods appear to be associated with reduced levels of depression (Li et al. 2017). Although multidisciplinary approaches can raise short term cost, long term benefits may outweigh this upfront cost, and other approaches are underway to create programs such as including mindfulness (Hearn and Finlay 2018) and cognitive behavioral therapy (Strøm et al. 2019).

Modifiable risk factors for depression determined by our study include obesity with BMI ≥ 30 kg/m² and pain scores. For reduction of BMI, preoperative weight loss techniques may be recommended years prior to ACDF surgery. Fock et al. highlight mainstays in management of obesity, including diet control and exercise augmented with cognitive behavior therapy (Fock and Khoo 2013). Franz et al. conducted a systematic review and meta-analysis and demonstrated an average loss of 5-8.5 kg (5%-9%) in weight secondary to low-calorie diet and exercise (Franz et al. 2007). In some patients, weight-reduction surgery may provide substantial benefits. Malik et al. utilized PearlDiver to analyze outcomes among patients with vs without bariatric surgery 2-years prior to ACDF surgery, demonstrating that patients who underwent weight-reduction surgery demonstrated significantly decreased complication and readmission events (Malik et al. 2020). A separate study found that the majority of patients suffering from cervical and lumbar disease and receiving bariatric surgery did not require inpatient care for their spinal pathology by 6-months following the weight-loss surgery (Passias et al. 2021). While aforementioned studies provide important methods to reduce BMI before surgery, a lack of consensus and uniformity in preoperative weight reduction strategies remains among spinal surgeons. Further studies are required to address this shortcoming in literature.

In order to reduce the risk factors of greater preoperative pain scores, providers may consider nonconservative measures aimed at reducing pain. Methods that may demonstrate promise in pain reduction include cervical collar, physiotherapy, or medications (Persson, Carlsson, and

Carlsson 1997; Eubanks 2010). Such nonoperative methods may be of use in patients with modest myelopathy; however, symptoms should be carefully followed in case of progression of pathology (Rhee et al. 2013). Moreover, since myelopathy progresses overtime, and there is paucity of evidence to support sole use of nonoperative treatment, patients suffering from significant myelopathy may not benefit from prolonged conservative care (Rhee et al. 2013). In a systematic review, Rhee et al. demonstrated superior outcomes in patients undergoing surgery vs conservative measures in two separate studies, further illustrating this trend (Rhee et al. 2013). Ultimately, more research is required to determine novel methods to mitigate preoperative pain scores prior to cervical fusion.

STRENGTHS AND LIMITATIONS

The findings of this study must be interpreted in the context of its strengths and limitations. While ML has been observed to complete tasks faster than physicians in some environments, ML algorithms have limited transparency (The Lancet Respiratory Medicine 2018). Although ML techniques allow for an openly accepting user inputs, and for outputting interpretable results, their methods are criticized as opaque and overly complex (Schwartz et al. 2019). The mechanisms that underlie ML algorithm behavior can be difficult to interpret. Another limitation of this investigation is that it was conducted among patients that were all treated by one surgeon at a single institution. While a strength of this design is that it implicitly controls for potential confounding from using operative information from multiple surgical providers, it also may limit the generalizability of our findings to other procedures or different patient populations. A further potential limitation is that data analysis was conducted in a retrospective manner. This may have threatened our analysis by introducing selection bi-

ases that favored including certain groups of patients over others. Our use of PHQ-9 may have limitations in that there is no substitute for a clinical diagnosis of major depressive disorder (MDD). However, questionnaire instruments are helpful in their ability to convey a standardized and patient-centered evaluation of subjects that is less influenced by provider biases (Call and Shafer 2018). Additionally, it was not possible to evaluate patients for a treatment and medication history related to depression or other psychiatric disorders. Further details could have provided more information related to the preoperative risk factors in this study.

CONCLUSION

Our investigation utilized DML to identify risk factors that may influence moderately severe levels of depressive symptoms ($\text{PHQ} \geq 15$) among patients undergoing single or multilevel ACDFs. Patient characteristics including higher levels of VAS neck pain (≥ 7) and a BMI of $\geq 30 \text{ kg/m}^2$ were the most significant risk factors associated with moderately severe depression. Our findings indicate that patients who have greater levels of neck pain or increased BMI may warrant screening for preoperative depression. Although BMI, neck pain, and preoperative depression have all been associated with poor postsurgical outcomes, they are also considered modifiable risk factors. Our study provides momentum for providers to address modifiable risk factors before patients undergo ACDF in order to optimize postoperative outcomes.

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