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Safety and efficacy of multilevel ACDF/ACCF surgery (anterior cervical discectomy/corpectomy and fusion): retrospective comparative cohort study

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BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

**SAFETY AND EFFICACY OF MULTILEVEL ACDF/ACCF SURGERY
(ANTERIOR CERVICAL DISCECTOMY/CORPECTOMY AND FUSION):
RETROSPECTIVE COMPARATIVE COHORT STUDY**

by

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B.A., University of Southern Maine, 2013

Submitted in partial fulfillment of the
requirements for the degree of
Master of Science

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DEDICATION

I would like to dedicate this work to my parents: Juliusz and Jadwiga Cygan.

Their encouragement and wisdom are instrumental in my life.

ACKNOWLEDGMENTS

This thesis was a unique learning experience. Weeks were spent on research and writing, but also, a lot of time was devoted to a variety of additional activities, such as obtaining Institutional Review Board (IRB) approval or gaining permission to shadow surgeries at the Boston Medical Center (BMC). Completing all requirements was possible, because of the support I received from BMC staff, Boston University (BU) faculty members, as well as my family and friends.

Firstly, I would like to thank Dr. Chadi Tannoury for trusting not only in my ability to work on this research project, but also in my capability to make it useful to the Orthopaedic Surgery field. Offering me an opportunity to shadow surgeries was one of the most thrilling experiences of my life. Your leadership, insight, patience, and approach to this project have been incredibly helpful. I gained tremendous amount of knowledge about the challenges facing both health care employees as well as patients. This experience and memory would stay with me for the rest of my career.

I would like to express my gratitude to my readers, Dr. Thomas Trivison and Stacey Hess-Pino. Your continued guidance and support made completing this thesis project possible. Offering a lot of comments through the last months allowed me to view this thesis project from many angles and construct an objective view on it. Your expertise in clinical research field let me conduct this study and defeat obstacles.

I owe many thanks to the BMC Spine Surgery Team lead by Dr. Tony Tannoury (Chief of Spine Surgery), as well as nurses, technicians, and administrative employees. They all were very welcoming, patient, and put extra effort to make observation of

surgeries possible. In addition to that, I would like to highlight how insightful and supportive was Dr. Ahmed Yousry Moussa, Spine Surgery Research Fellow at BMC. He always found time to discuss various aspects of this thesis project, and offered valuable suggestions.

Furthermore, I want to thank all BU School of Medicine Clinical Investigation program instructors for providing me with a very pragmatic knowledge and experience, as well as my fellow classmates, who were very supportive throughout the conduct of this project.

Last but not least, I thank my family and friends for being patient, understanding, and for accompanying me during this study conduct.

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LILIANA MARIA CYGAN

ABSTRACT

Purpose: The goal of this thesis research project is to evaluate and compare post-operative complications among patients, who underwent short and long segment Anterior Cervical Discectomy/Corpectomy and Fusion (ACDF/ACCF).

Methods: Retrospective cohort study design allowed for evaluation of series of variables (age, sex, diagnosis, general post-operative outcome, and complications) while comparing them between the short and long segment groups.

Results: Patients within both cohorts tended to experience similar complications, except pseudarthrosis and adjacent segment disease, which both were more prevalent in the long segment group. Diagnosis or short versus long segment length did not have an effect on the general post-operative outcome. One-level ACDF patients were younger than multilevel ACDF surgery patients. Dysphagia was more likely to occur in older patients, with the risk of dysphagia incidence increased by 7% with each year of patient's age.

Conclusions: Study indicated that longer segment ACDF/ACCF does not carry higher risk of complications incidence than short segment treatment. Further studies are advised to increase generalizability of these results.

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LIST OF ABBREVIATIONS

ACCF	Anterior Cervical Corpectomy and Fusion
ACDF	Anterior Cervical Discectomy and Fusion
BMC.....	Boston Medical Center
BU	Boston University
BUSM	Boston University School of Medicine
DF	Degrees of Freedom
FET	Fisher Exact Test
IRB.....	Institutional Review Board
NSAID	Non-Steroidal Anti-Inflammatory Drug
OR.....	Odds Ratio
TDR.....	Total Disc Replacement

INTRODUCTION

Spine

The spine, or vertebral column, is the axial part of the skeletal system, linking the skull with pelvis. It plays a key role in protecting the spinal cord from mechanical injuries, and supports body mass, with a strong emphasis on balancing weight and movement of head and neck.^{1,2} The human vertebral column, depicted in Figure 1, is composed of thirty-three connected bones called vertebrae, and is divided into five regions: cervical, thoracic, lumbar, sacral, and coccygeal.¹

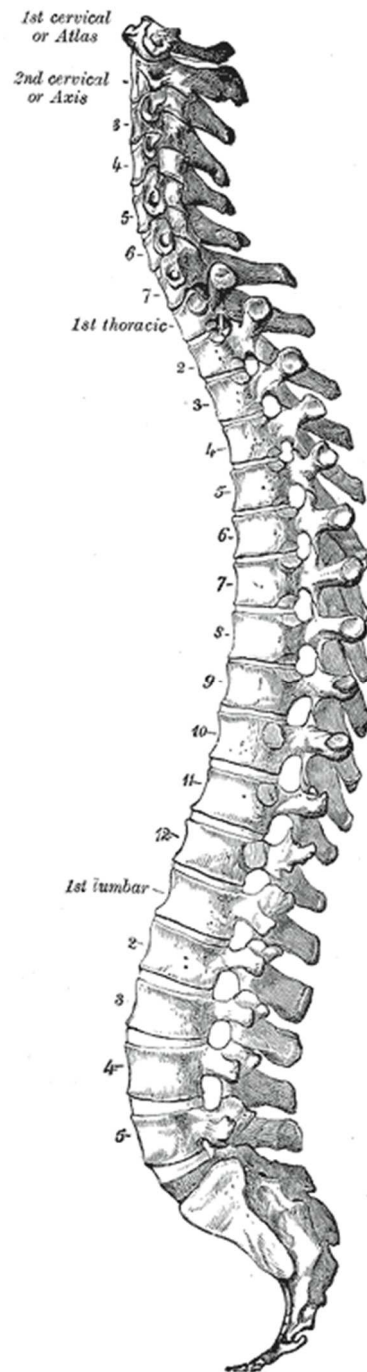


Figure 1. Vertebral Column Fig.111 (p.115) In: Gray, H *Anatomy of the Human Body*, 20th ed. Philadelphia: Lea & Febiger, 1918; New York, NY: Bartleby.com; 2000

The cervical region of the spine contains seven vertebrae, which are the smallest in the column, and, as pictured in the Figure 2, they are identified as C1 (also known as atlas,) C2 (axis,) and then C3 through C7 vertebrae.

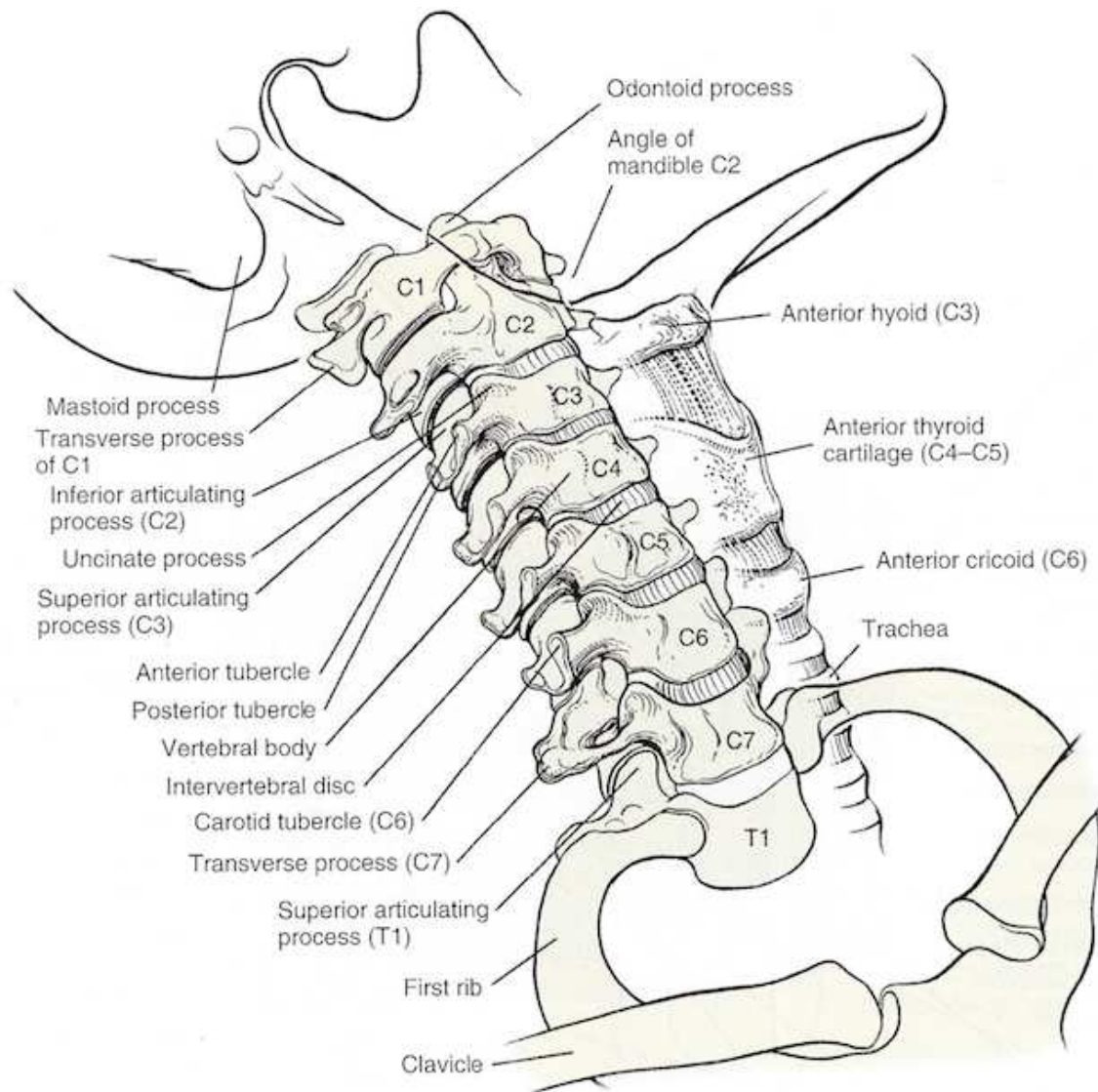


Figure 2. Anterior View of Cervical Spine In: Hoppenfeld S, DeBoer P, Buckley RE *Surgical Exposures in Orthopaedics: The Anatomic Approach*, 11th ed. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins Health; 2009

The cervical spinal vertebrae C2 to C7, and the cervicothoracic junctional segment C7-T1, are interconnected by fibrocartilagenous structures called intervertebral discs. While the spinal cord runs within the spinal canal, the cervical spinal nerves emanate from the cervical cord and exit the cervical spine through the intervertebral foramina. The cervical spinal nerves are also coded with a letter C, typically numbered from 1 to 8 (C1-C8.) They innervate various muscles of the neck and upper extremities governing crucial movements of the head, diaphragm, neck, and upper limbs.¹ Moreover, the cervical spine is in a close proximity to the thyroid gland, the esophagus, major vessels supplying the brain, and the upper parts of the respiratory system including the larynx and the trachea. Therefore, surgical approaches to address certain cervical spinal pathologies may lead to collateral injuries to the neighboring vital structures leading to significant morbidities and complications. These are being investigated in this project.

Cervical Vertebrae

With the exception of C1, all cervical human vertebrae (C2-C7) comprise two main bony structures referred to as the vertebral body anteriorly and the lamina, also known as posterior arch.

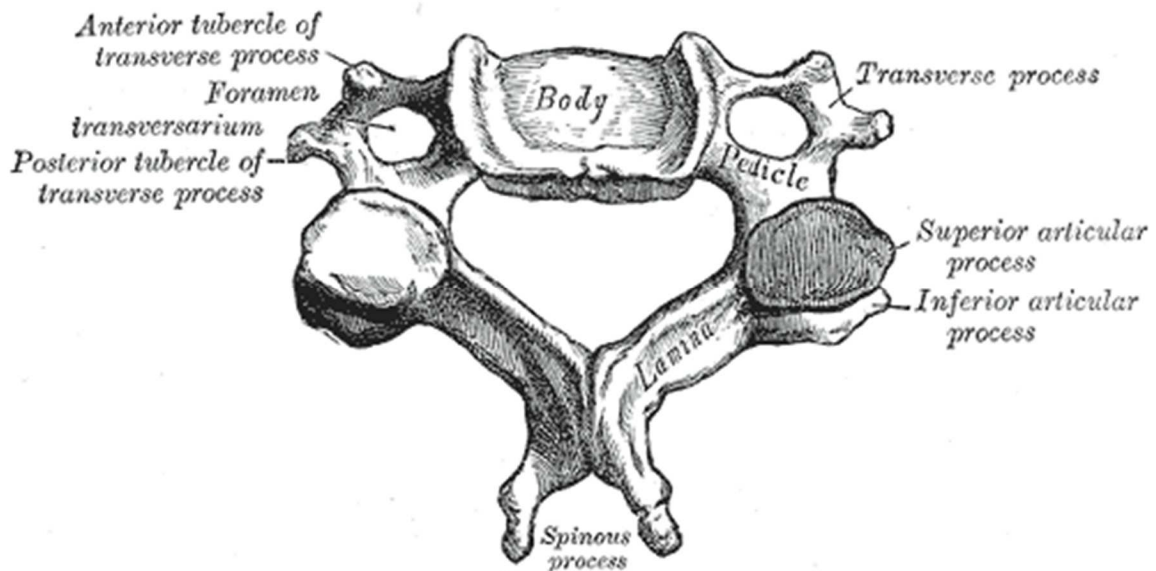


Figure 3. Cervical Vertebra Fig.84 (p.99) In: Gray, H *Anatomy of the Human Body*, 20th ed. Philadelphia: Lea & Febiger, 1918; New York, NY: Bartleby.com; 2000

The vertebral bodies are connected via the fibrocartilagenous intervertebral discs.

Although there are seven cervical vertebrae, only six cervical intervertebral discs are recognized. The top two vertebrae, atlas and axis (C1 and C2, respectively) are not joined by an intervertebral disc. Each of the intervertebral discs comprises a central soft *nucleus pulposus* surrounded by a peripheral tough *annulus fibrosus*.¹⁻³ The disc provides flexibility, mechanical support, and stability to the vertebrae column.³ The biomechanical features of intervertebral discs are possible due to the high abundance of fibrous protein; collagen.³ Due to the characteristics of that protein, however, discs undergo structural changes over time.

Disc Diseases

It is understood that disc degeneration happens naturally with aging, but it also can be facilitated by other factors such as occupation, trauma, genetics, as well as

environmental and behavioral causes like smoking. Although it might be difficult to identify a simple pathogenesis of disc degeneration in each patient, the results of that process may cause noticeable and disrupting symptoms, such as myelopathy (spinal cord compression) and radiculopathy (nerve root compression).

As noted in the Journal of Neurology, Neurosurgery, and Psychiatry, both radiculopathy and myelopathy are linked to compression of the neuroelements.⁴ While the compression may be caused by a trauma, more frequently it is the result of disc herniation or degeneration. It has been suggested that the occurrence of cervical spondylotic myelopathy is correlated with age, because over time discs undergo structural changes. The water content in the intervertebral discs decreases which leads to loss of its original height. While the *annulus fibrosus* bulges and the disc protrusion size increases, the space available for the neural elements decreases and ultimately a compression of the spinal cord and/or the spinal nerves occurs.⁴ Disc degeneration is illustrated in the Figure 4 below. On the left-hand side a healthy disc is opposed to the degenerated one on the right hand side.

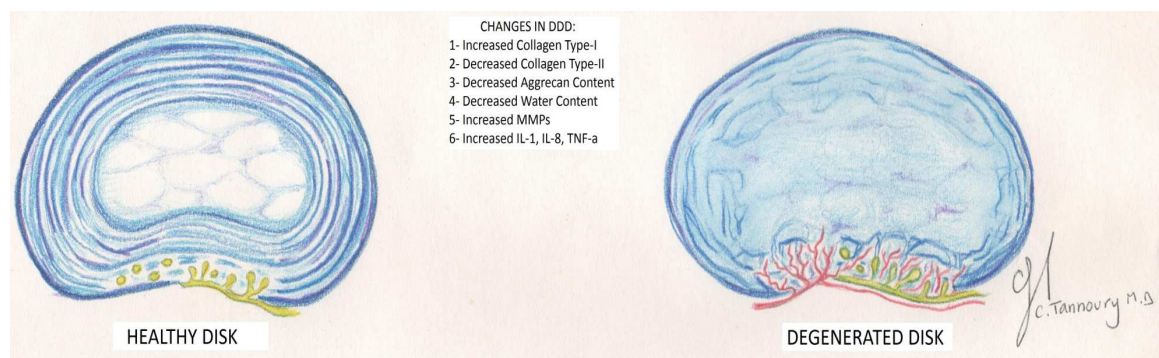


Figure 4. Healthy and Degenerated Discs.
Used with the author's permission: Dr. Chadi Tannoury.

Mechanical cord compression (myelopathy) interrupts normal nerve impulses, and triggers numbness, weakness, and pain of the shoulders, arms, hands, and fingers, as well as loss of movement precision or balance in some cases.⁵ Radiculopathy (nerve compression,) along with the structural changes of the discs, is frequently accompanied by inflammation and vascular changes, with neck and arm pain being the most typical signs.⁶ Disc degeneration may also present itself with axial neck pain, along the erector spinae muscles (muscles around the vertebrae column,) and in the periscapular (shoulder) region of the back.⁴

Surgical treatment is recommended for both, myelopathy and radiculopathy, not only to address the debilitating pain or impairing weakness, but to prevent further progression of the disease.⁴

Available Treatment

There are several treatments available for patients with myelopathy and radiculopathy. Those who suffer from cervical radiculopathy are first treated conservatively with non-steroid anti-inflammatory drugs (NSAIDs) along with physical therapy and temporary bracing. As summarized by Roth et al., it is believed that pharmaceutical approach would decrease the inflammation:

“The rationale is to counteract the neurotoxic/ proinflammatory chemicals present during cervical radiculopathy. The presence of following compounds: phospholipase, 2 nitric oxide, prostaglandin E2, and interleukin-6 have been noticed in both herniated and degenerated discs. It is thought that these agents contribute to pain by irritating nerves, altering conduction, and in some cases, causing axonal damage.”⁷ If NSAIDs are not

helpful, patients can be treated with alternative oral medications such as opioids (used with caution and for short period of time, to prevent increase of tolerance and dependence) or oral steroids. Some patients have been treated with cervical epidural steroid injections. The success rate of the mentioned conservative options has not been as high as desired.⁷ Zhang et al suggested other biological forms of treatment, such as gene and cell therapies, or even tissue engineering. However, the authors noted that these methods focus on disc restoration only, rather than pain management per se.⁸ Thus, surgical options focused on removal of entire affected discs or their parts can be most effective in addressing the underlying causes of nerve compression leading to radiculopathy. Treatment of myelopathy aims at surgically removing the compression of the spinal cord, with hope of recovering its function, and to prevent the progression of the disease.

Surgical Intervention

The surgical intervention offered to patients suffering from myelopathy or/and radiculopathy is often anterior cervical discectomy (partial or complete removal of the affected disc) and fusion (ACDF) with or without partial or complete removal of the vertebral body, known as corpectomy (ACCF). Other surgical treatment options include posterior cervical discectomy, posterior cervical laminectomy, posterior cervical laminoplasty, and posterior cervical fusion.⁴

During ACDF/ACCF surgeries, the removed parts of discs and/or vertebrae are typically reconstructed with structural bone grafts collected from the patient's own bones (auto-

graft) or from cadaveric donors (allograft), or even purely synthetic structures (intervertebral cage devices) illustrated by the x-ray in Figure 5.



Figure 5. Anterior Cervical Fusion with Fusion Cage and Plate In: Hunter, TB, Taljanovic, S Medical Devices of the Neck & Spine: Cervical Spine Instrumentation, New York, NY Cambridge University Press; 2013 available at http://medapparatus.com/NeckSpine/Spine_Page2.html#top

Although autograft use is the gold standard,⁹ some patients choose allografts in order to prevent donor site morbidities associated with graft tissue harvesting. Mariscalco et al. suggested that there is no significant difference in efficacy between autografts versus allografts.⁹ Recently, a total disc replacement (TDR) known as cervical arthroplasty is

gaining popularity because it preserves range of movement of the cervical spine, and ultimately prevents adjacent segment degeneration.⁸

While ACDF/ACCF/TDR are performed via an anterior cervical approach, laminectomy/discectomy with or without fusion, as well as laminoplasty are performed via a posterior midline approach. The anterior surgical exposure maybe considered less morbid than the posterior exposure due to less muscle dissection, which is better tolerated by patients, at least in the early postoperative period. As suggested by Cabraja et al, as well as Vishteh et al, the anterior approach to the cervical spine offers better exposure of the structures of interest (discs and vertebrae) and provides better chances of restoring natural sagittal cervical alignment.^{10,11}

Anterior cervical discectomy and fusion (ACDF) and anterior cervical corpectomy and fusion (ACCF) require splitting the platysma muscle, then bluntly developing a surgical plane between the sternocleidomastoid muscle laterally and the strap muscles medially, and more deeply between the trachea-esophageal complex medially and the carotid sheath where the following are found: the carotid artery, the jugular vein, and the vagus nerve (CN X) laterally. Further, the deep cervical and pretracheal connective tissues (fascia) are dissected, and the longus colli muscles are lifted off bilaterally to expose the cervical spine anteriorly.⁹ Once that access is gained, one or more disc levels are identified, and using specialized instruments and magnification tools, the pathologic disc along with its cartilaginous endplates are removed (discectomy). This is followed by thorough decompression of the neural elements (canal and foramina), and insertion of an interbody structural graft (autograft,

allograft, or synthetic) and securing it by anterior instrumentation with plate and screws applied to the adjacent vertebral bodies above and below the disc level(s) to be fused.



Figure 6. Plate Applied to Vertebral Bodies In: Rao, AS, Michael, ALR, Timothy, J
Surgical Technique of Anterior Cervical Discectomy and Fusion (ACDF) Procedures
Elective Orthopaedic Surgery Upper Extremity and Spine, London: Springer-
Verlag; 2012

Post-surgical Complications

Due to reported increased rates of complications with multilevel anterior cervical fusion, ACDF surgeries are commonly performed on one or two disc levels. However, some cases require addressing three or more discs. Pan et al reported that multilevel ACDF surgeries are associated with wide range of complications, including but not limited to dysphagia, voice hoarseness, vocal cord paralysis, speech impairment,

hardware failure, bleeding with hematoma formation, and esophageal injuries.¹²⁻¹⁶ Additionally, use of the gold standard autologous iliac crest bone graft carries risks of chronic pain, surgical site infection, and even stress fracture among others.¹⁷⁻¹⁹

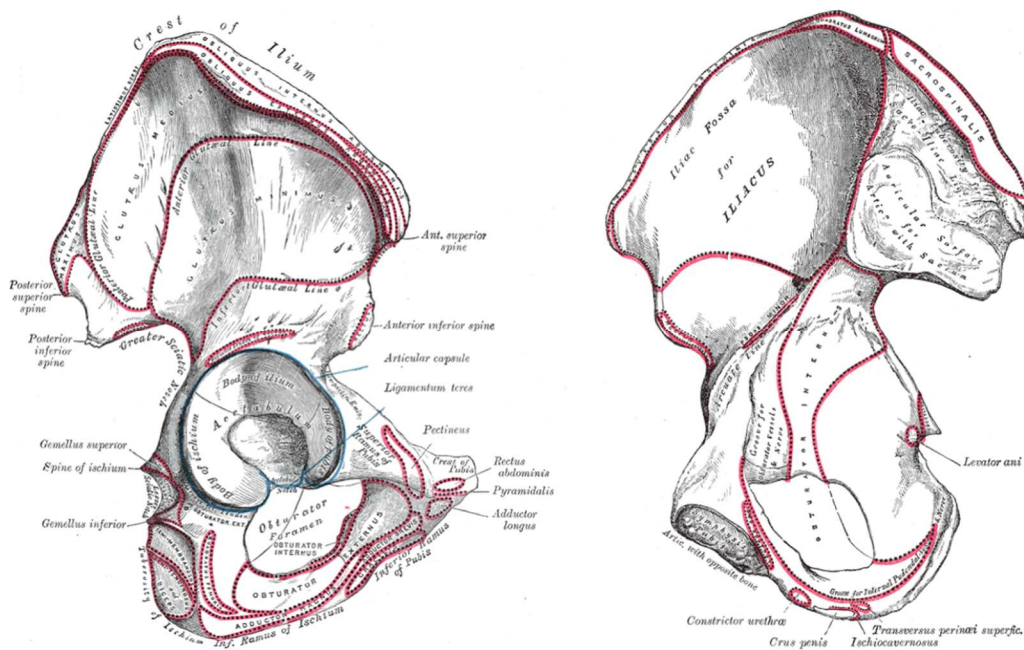


Figure 7. Iliac Crest Outlined in Hip Bone. Figures 235 and 236, Respectively In: Gray, H *Anatomy of the Human Body*, 20th ed. Philadelphia: Lea & Febiger, 1918; New York, NY: Bartleby.com; 2000

Surgical-related complications may occur at different stages: pre-operative, intra-operative, post-operative and beyond.²⁰ While many complications are directly related to the surgical intervention and techniques, other complications are inherent to the patients and their underlying medical morbidities such as: cardiac risks (e.g. coronary artery disease, congestive heart failure, etc.), non-cardiac risks (pulmonary, renal, hepatic, etc.), anesthesia-related risks, coagulation-related risks, and the patient's immune system and

ability to heal and fight infections.²⁰ It has been documented that the post-operative complication rates vary between hospitals due to many variables including the surgical technique adopted, the surgeon's competency and experience, the patient's morbidity, and perioperative nursing care.^{13-15, 21}

Pseudarthrosis, Adjacent Segment Disease and Degeneration

Hilibrand and Robbins investigated the occurrence of “adjacent segment degeneration” and “adjacent segment disease” as the implicit result of cervical discectomy and fusion.¹⁶ Degeneration is characterized by visible radiographic changes in segments adjacent to the operated one(s). Similarly, adjacent segment disease is characterized by development of disc degeneration symptoms related to the affected adjacent segment(s).¹⁶ Some patients also develop pseudarthrosis (failed fusion) leading to recurrence of the patient's initial symptoms, which can be verified with radiographic imaging. Multilevel ACDF/ACCF, as compared to short segment fusion (one and two level) may be associated with lower adjacent segment degeneration and disease, as suggested by Hilibrand and Robbins.¹⁶ Similarly, Lee and colleagues suggested that patients treated with one or two level ACDF are more likely to develop adjacent segment pathology than those treated with 3 or more levels ACDF. The same authors predict that 22.2% of patients will require reoperation for adjacent segment disease within 10 years. Other risk factors for reoperation due to ASD were female gender and smoking.²²

The vast majority of the published studies evaluating multilevel ACDF surgeries were either based on few evaluated cases, or retrospective studies.^{23 Was 31} The overestimated rates of reported complications with multilevel ACDF/ACCF may lead to

the assumption that one or two level ACDF are significantly safer and less morbid to the patient. Not to mention the significant increase in direct and indirect health care costs associated with complicated surgeries warranting additional patient care and in some instances revision surgeries.

Rationale for Study

This retrospective cohort study investigated the characteristics of post-surgical complications among Boston Medical Center (BMC) patients who were diagnosed with radiculopathy or myelopathy, and agreed to surgical intervention with cervical discectomy/corpectomy and fusion (ACDF/ACCF). This study was designed to assess if there were statistically significant differences in the complications occurrence between those patients who underwent long segment fusion (three or more discs) with those who had only one or two discs fused during a surgery. Based on the available literature¹², the following clinical complications were of interest: surgical site infection, chronic pain, weakness, dysphagia, blood loss, hardware failure, voice hoarseness and vocal cord paralysis, infection of the iliac crest bone graft area, development of adjacent segment disease, as well as: hardware failure, pseudarthrosis, and adjacent segment degeneration. Furthermore, this study investigated if the general post-operative outcomes were better in any of the two study arms, and if it was affected by the initial diagnosis. Finally, the role of age in experiencing post-surgical complications was examined.

This research study aimed to provide further information on the characteristics of post-surgical outcomes among patients undergoing long and short segment ACDF surgeries. It was designed to establish a groundwork for further analysis of the

complications and to provide rationale for a long-term prospective clinical investigations that would aim towards assessing the best surgical intervention approach for patients with multilevel diseased cervical spine, who suffer from radiculopathy and/or myelopathy.

Thesis Questions

1. Is there a difference in complication rate between patients who underwent short segment (one and two-levels) ACDF versus long segment (three or more) ACDF/ACCF surgeries?
2. Is there a statistically significant difference in general post-operative outcome assessment between the two compared groups (short Segment ACDF versus long Segment ACDF/ACCF)?
3. Is initial diagnosis related to the length of the treated segment and does it affect the general post-operative assessment?
4. Does age correspond to higher rates of complications?

METHODS

Boston University School of Medicine Institutional Review Board (BUSM IRB) approved this thesis research prior to any investigational activity was pursued. This protocol was designated with a code H-33676 expiring on March 22nd 2016.

Study Design

This research project was designed to fit a retrospective cohort study model. Population of BMC Orthopaedic Department patients was divided into two groups: subjects who underwent short ACDF versus those who underwent long ACDF/ACCF surgery. Two study cohorts were compared in the context of post-surgical complications incidence.

Post IRB approval a BMC Orthopaedic Spine Surgery staff member provided de-identified data extracted from medical charts, surgical notes, and radiographic images. Demographic data (sex, age, height, weight) was provided along with the underlying diagnosis, post-surgical assessment grade and presence or absence of the following complications: surgical site infection, chronic pain, weakness, dysphagia, blood loss, hardware failure, voice hoarseness and vocal cord paralysis, infection of the iliac crest bone graft area, development of adjacent segment disease, as well as: hardware failure, pseudarthrosis, and adjacent segment degeneration.

Study Population

The following inclusion criteria were used to determine eligible study population:

1. History of ACDF/ACCF treatment
2. Diagnosis of radiculopathy or myelopathy

3. Lack of known serious comorbidities (e.g. tumors)
4. Timeframe of the surgery: 2011-2014
5. Availability of complications and convalescence grade information
6. Availability of information on patients' sex and age
7. Being treated by Dr. Chadi Tannoury or Dr. Tony Tannoury

In order to eliminate some of the potential confounding variables, the following exclusion criteria were employed:

1. Undergoing ACDF/ACCF due to trauma, tumors, and infections
2. Lack of clearly stated diagnosis in the patient history
3. Lack of information from the follow-up visits about patient's convalescence
4. Missing post-intervention overall assessment grade

De-identified data provided for this research pertained patients who were treated at BMC Orthopaedic Spine Surgery Department from 2011 to 2014 due to the availability of uniform records. Data pertaining ACDF/ACCF patients not treated for radiculopathy or myelopathy diseases was excluded in order to avoid confounding variables (e.g. other trauma related injuries or undergoing exhausting cancer treatments). There was no age limitation in this study. Data that was lacking the general post-operative grade as well as any information on complications was excluded from the analysis, as it would not be used for study outcome measures analysis.

Outcome Measures

The primary outcome measure was the number of each complication occurring in

patients of the two studied groups. The following post-operative complications were reported as present or absent in the post ACDF/ACCF patients:

- infection
- pain
- voice hoarseness
- iliac crest bone graft infection
- stiffness
- weakness
- dysphagia
- blood loss
- symptomatic adjacent segment degeneration
- hardware failure

Additionally, radiographic images of post ACDF/ACCF patients were evaluated to confirm presence or absence of the following potential complications:

- hardware failure
- pseudarthrosis
- adjacent segment degeneration (ASD).

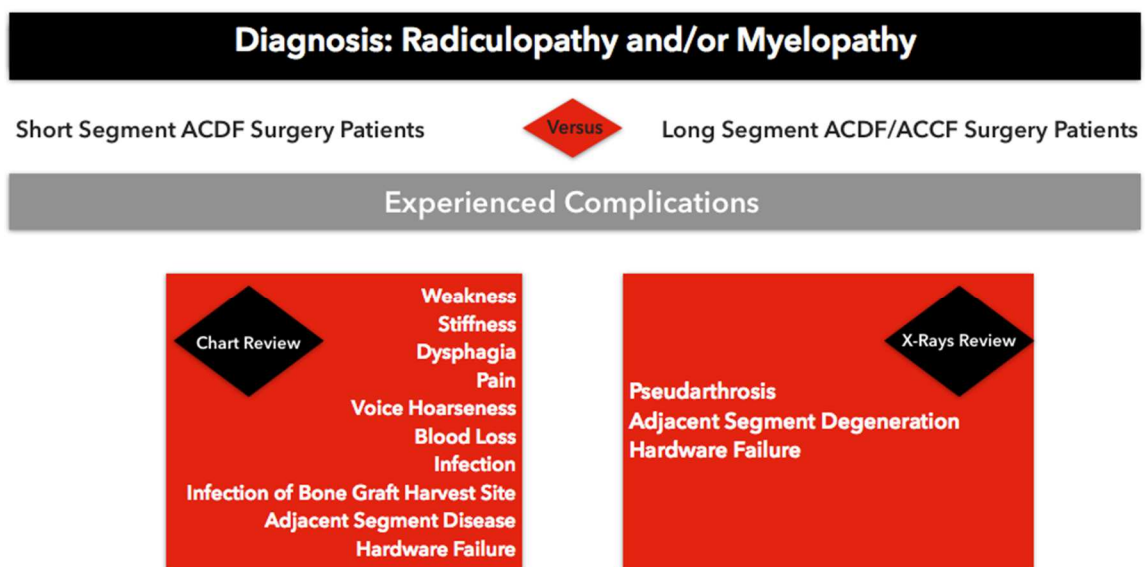


Figure 8. Primary Outcome Measures.

A secondary outcome measure, depicted in Figure 9, was post-intervention assessment grade. Odom’s Criteria was used by BMC surgeons to express patients’ post-surgical outcome rating: *POOR*, *FAIR*, *GOOD* or *EXCELLENT*, and was provided for each subject.²⁴ Additionally, the general assessment grade was paired with the initial diagnosis (radiculopathy or myelopathy).

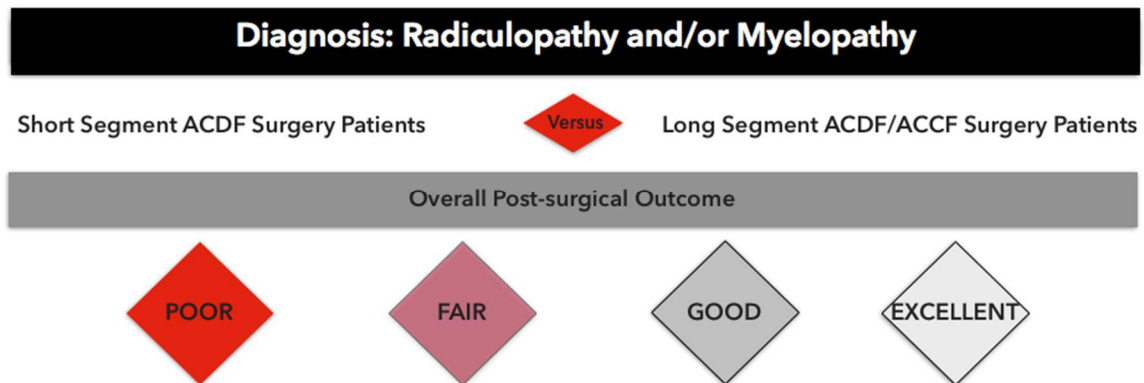


Figure 9. Other Outcome Measures.

Finally the role of age in experiencing post-surgical complications was investigated. Age mean of study subjects was stratified by the segment length (short vs. long) and ACDF/ACCF level (five independent levels), and then evaluated for each complications type, as depicted in Figure 10.

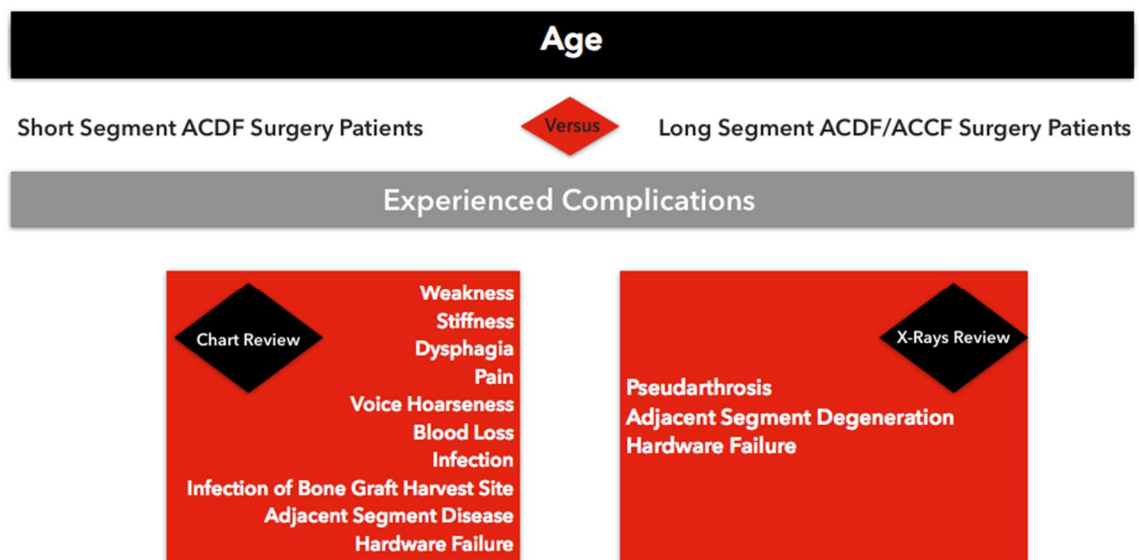


Figure 10. Additional Outcome Measures.

Statistical Analyses

Sample Size

Typically a sample size calculation for a research study would be based primarily on a literature review. However, so far, very few studies focused on evaluating post ACDF/ACCF complications. Studies published thus far included approximately 30-50 subjects, each.^{25, 26} Due to lack of sufficient groundwork to estimate a significant percent difference between studied arms, in the context of experienced complications, the sample size calculation was based on an educated guess with a knowledge of a retrospective study design characteristics. Assuming that studied groups would be statistically significantly different in complications occurrences when one of the groups had 20% of complications incidence and the second had 40% incidence of complications, then to reduce Type-I error to 5% and Type-II error to 10%, the sample size would have to include a minimum of 216 subjects (108 in each study arm). Applying a 5% α (Type I error) is a gold standard in medical studies, implying 5% probability of falsely identifying an existence of a difference between groups.²⁷ Study was powered at 0.9 to reduce the Type II error to 10%. This research project was a retrospective analysis; therefore, it carried no physical or psychological harm to the studied population. Additionally, data was de-identified, so there was no risk of a breach of subjects' personal information. Therefore, it was safe to aim at a sample size bigger than 216 suggested by a standard sample size equations. To account for exclusions of subjects with insufficient information, an approximate 15% margin was chosen to add to the calculated value. Data pertaining 250 patients was requested.

Data Set

A staff member, who was not directly involved in the patients' care and not involved in this study, extracted patient information gathered in the BMC Orthopaedic Surgery Department database. The following information was obtained: sex (male or female), age (measured in years), weight (measured in kilograms), level of ACDF surgery (one or two-levels) or ACDF/ACCF surgery (three, four or five-levels), diagnosis (radiculopathy or myelopathy), presence or absence of the listed complications (infection, pain, voice hoarseness, iliac crest bone graft infection, stiffness, weakness, dysphagia, amount of blood loss, symptomatic adjacent segment degeneration, hardware failure, pseudarthrosis), and overall clinical outcome assessed by the surgeon (*POOR, FAIR, GOOD, EXCELLENT.*)

Age and weight were the only continuous variables provided for this study. The level of ACDF/ACCF surgery was treated as an ordinal variable. For the study purpose, the levels were grouped into two categories: short segment ACDF and long segment ACDF/ACCF. This procedure aimed at gathering two groups of relatively equal size, to ensure adequate power for comparison. All complication types were described as categorical binary data. Finally, general post-surgical outcome was an ordinal variable. Identification of the types of data gathered for this research study was imperative for choosing correct statistical methods to test hypotheses and to detect any possible trends.

There were few potential confounding factors identified. Subject's weight was a major confounding variable, as studies show that overweight patients are at a higher risk of experiencing complications while and after undergoing surgical procedures.²⁸⁻³⁰

However, the effect of weight on complication incidence was not evaluated in the final statistical analysis because 30% of subjects did not have that information available in their medical documentation (69 cases.) Comorbidities were additional confounding factor, and to address this issue, subjects, who suffered from serious diseases, such as cancer, were excluded from this study. Since this research was of a retrospective nature, aimed at a certain cohort, it was impossible to reduce the confounding effects by randomization or counterbalancing.

Hypotheses and Objectives

The main objective of this study was to compare the complication incidence between patients who underwent long segment ACDF/ACCF surgery versus those treated with short segment intervention. It was suspected that patients in both study arms experienced similar numbers of complications.

H_0 – complication rates were not different between short and long ACDF/ACCF

H_A – complication rates were different between short and long ACDF/ACCF

Further analysis aimed to detect if long segment ACDF/ACCF surgery led to a worse post-treatment assessment than short segment ACDF surgery. The hypothesis was that there was no difference in post-operative outcome and segment length.

H_0 – post-operative assessment was not different between short and long ACDF/ACCF

H_A – post-operative assessment was different between short and long ACDF/ACCF

Another point of interest was detecting any dependency between initial diagnosis and need for a short or long segment intervention. The hypothesis was that there was no

difference in the necessity for short ACDF vs. long ACDF/ACCF surgery between the patients diagnosed with radiculopathy or myelopathy.

H₀ – length of segment under intervention was not dependent on initial diagnosis

H_A – length of segment under intervention was dependent on initial diagnosis

Additionally, the relationship between initial diagnosis and its potential effect on the post-treatment assessment post ACDF/ACCF surgery was investigated. The hypothesis was that there was no difference in post-operative outcome grade between the groups diagnosed with radiculopathy and myelopathy.

H₀ – post-operative assessment was not dependent on initial diagnosis

H_A – post-operative assessment was dependent on initial diagnosis

Lastly, study analysis was centered on assessing whether older age might be linked to higher incidence of experienced complications in the two studied groups.

H₀ – age was not linked to higher complications rate in the studied population

H_A – age was linked to higher complications rate in the studied population

Testing Hypotheses

Statistical analysis was done in R software versions 3.2.0 and 3.2.1. Choice of tests was based on the types of variables used in this research: numerical (age), nominal (complications, segment length, diagnosis, general post-operative outcome), ordinal (ACDF Level).

Shapiro-Wilk normality test was used to investigate whether the sample was normally distributed.

The comparison of all complication types between short segment ACDF surgery

and long segment ACDF/ACCF surgery patients was done with Fisher's exact test (FET,) primarily, because it offers more precise estimation than approximation obtained with χ^2 (Chi-square) analysis.³¹ FET is suitable for 2×2 tables, so each complication was tested separately for both study arms. Results of FET provided *p*-value, which offers estimation of probability. *P*-value, if below 0.05, indicated that evidence indicating that compared variables were associated was significant.

In addition to FET, an odds ratio was computed to estimate the probability of complication's occurrence within both of the studied groups. Long segment ACDF/ACCF was considered an "exposed" group, whereas short segment ACDF was treated as an "unexposed" group. To calculate odds ratio, firstly, a computation of the ratio of odds to the number of all exposed cases had to be done, and then calculation of the ratio of odds to number of all unexposed cases. Then the ratio of the two values could be derived, as illustrated in the following equation:

Equation 1. Odds Ratio Equation.

$$OR = \frac{\frac{Odds}{Exposed}}{\frac{Odds}{Unexposed}} = \frac{\frac{a}{a+b}}{\frac{b}{a+b}} \bigg/ \frac{\frac{c}{c+d}}{\frac{d}{c+d}} = \frac{a \times d}{b \times c}$$

Results of the Odds Ratio (OR) computation offered an estimate of the probability of association between ACDF/ACCF segment length and odds of complication's occurrence. OR equal to 1 was interpreted that complication was as likely to occur in patients undergoing short level and multilevel ACDF/ACCF surgeries. OR lower than 1 was understood as short level ACDF/ACCF patients had smaller chances of developing a complication, whereas OR higher than 1 was understood as short ACDF/ACCF surgery

was associated with higher odds of experiencing complication.³²

Chi Square analysis was performed to detect any potential relationship between length of ACDF/ACCF segment, as well as diagnosis and the general post-treatment assessment. Again, p -value below 0.05 indicated that evidence for association was significant.

Since age constitutes a numeric continuous variable Welch Two Sample t-test was used to evaluate the differences in age means between short and long segment intervention. The Welch test allowed for adjustments of variances between tested groups, which are not even.³¹ Moreover, *one-way* ANOVA was used to investigate trends between each levels of ACDF/ACCF and patients' age. The reason for switching from t-test (such as Welch test) to *one-way* ANOVA was the fact that in this analysis levels were investigated rather than just short versus long segment.³¹ *One-way* ANOVA yielded p -value, estimating the probability of the outcome occurring due to chance when the null hypothesis (no differences between the groups) was true.³³ A p -value lower than 0.05 indicated that evidence for differences between mean age of patients within each discs in treatment level (levels 1, 2, 3, 4, and 5) was significant. Furthermore, a *one-way* ANOVA computation provided an F ratio close to 1.0, if the null hypothesis was true. A higher F ratio would forecast a null hypothesis as untrue. Due to *one-way* ANOVA results (p – value < 0.05), post-hoc Tukey Honest Significant Difference (HSD) Test was performed. Although it is considered a fairly weak test, it allowed for the identification of the groups that were distinctive in the studied sample. Lastly, the effect of age and complication incidence was tested with logistic regression. Logistic regression allowed

for the testing of the continuous independent variable, such as age, and its relation to binary dependent variable, such as, in this study, complication (a variable noted as “yes” corresponding to occurrence of an event or “no” indicating its absence.) The regression model was represented by the following equation:

Equation 2. Logistic Regression Equation.

$$\ln\left(\frac{p_m}{1 - p_m}\right) = \beta_0 + \beta_1 x$$

In this formula, \ln was an expression of natural logarithm, p_m represented sample proportion, and $\beta_0 + \beta_1 x$ represented a binary outcome of a complication taking place or not. Logistic regression was, as explained by Riffenburgh, a method of using dependent variable as the log of odds ratio.³¹ When interpreting results, p -value was used to estimate the probability of relationship occurring by chance, if the null hypothesis was true.³¹ P -value lower than 0.05 would indicate strong evidence of association of the tested variables.

RESULTS

Baseline Characteristics

A well-balanced study population of two hundred and twenty-eight subjects was analyzed for this study: with 48% (109 subjects) and 52% (119 subjects) of female and male subjects, respectively. The baseline characteristics are described in the Table 1 below.

Table 1. Baseline Characteristics.

Variable	ACDF/ACCF Patients	
	Long Segment N = 112	Short Segment N = 116
Sex, N (%)		
Male	57 (51)	62 (53)
Female	55 (49)	54 (47)
Age (years), Mean (SD)	57.32 (9.47)	49.29 (11.32)

SD = Standard Deviation, ACDF =Anterior Cervical Discectomy and Fusion, ACCF =Anterior Cervical Corpectomy and Fusion

Age tested with Shapiro-Wilk normality test, yielded a W of 0.99308, and *p*-value of 0.3671. Hence sample was drawn from a normally distributed population. (Figure 11)

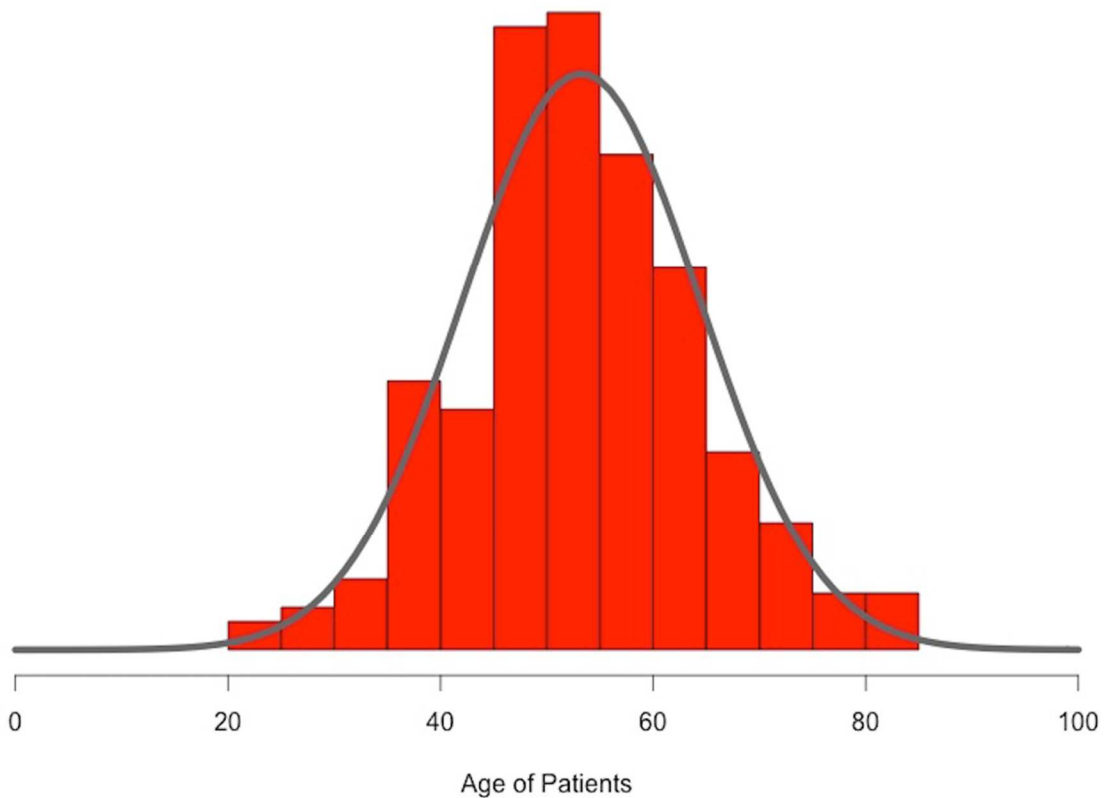


Figure 11. Age Distribution in the Study Population.

As presented in Table 2 below, the distribution of ACDF/ACCF surgeries was relatively similar across the level groups (each level corresponding to the number of discs under treatment.) Overall, only the level five ACDF/ACCF surgeries were less prevalent, with only five (4.8%) occurring. The remaining disc levels represented over 95% of the cases evaluated in this study, including: 57 (25%) one-level surgeries, 59 (26%) two-level operations, 48 (21%) three-level, and 53 (23%) four-level ACDF/ACCF surgeries, respectively.

Table 2. Distribution of ACDF Surgery Levels in the Study Population.

Levels of ACDF Surgery in Study Population		
Levels	Frequency	Percent
Short		
One Level	57	25
Two Levels	59	48
Long		
Three Levels	48	21
Four Levels	53	23
Five Levels	11	5

ACDF =Anterior Cervical Discectomy and Fusion

Complications

The number of complications in this research study is presented in Table 3. Results were divided by short and long segment intervention. Among the investigated complications, pain was the most common, affecting 21% of the studied population (48 subjects). Overall, there were 16 (7.0%) cases of dysphagia; 15 (6.6%) patients who suffered from neck stiffness; and 21 (9.2%) patients who developed symptoms of adjacent segment degeneration. The remaining complications occurred in less than ten subjects, including: seven (3.1%) who experienced infection; six (2.6%) who experienced voice hoarseness; six (2.6%) cases of infection related to the iliac crest bone graft harvest; and seven (3.1%) cases of patients with substantial blood loss during surgery (smallest noted amount was 100 ML and the largest lost amount of blood was 300 ML).

Table 3. Complications Distribution in Short Segment ACDF surgery Patients versus Long Segment ACDF/ACCF Patients.

COMPLICATIONS	ACDF/ACCF	
	Long Segment N = 112	Short Segment N = 116
Pain, N (%)	26 (23.2)	22 (19) **
Infection, N (%)	5 (4.5)	2 (1.7)
Voice Hoarseness, N (%)	3 (2.7)	3 (2.6)
Iliac Crest Bone Graft Infection, N (%)	5 (4.5)	1 (0.9)
Stiffness, N (%)	8 (7.1)	7 (6.0)
Weakness, N (%)	3 (2.7)	2 (1.7)
Dysphagia, N (%)	11 (9.8)	5 (4.3)
Blood Loss, N (%)	3 (2.7)	4 (3.4)
Hardware Failure, N (%)	0 (0)	0 (0)
Adjacent Segment Degeneration on X-Ray Image, N (%)	33 (29.5) **	23 (19.8) *
Hardware Failure on X-Ray Image, N (%)	0 (0) *	0 (0) *
Pseudarthrosis on X-Ray Image, N (%)	9 (8) *	0 (0) *
Adjacent Segment Disease, N (%)	16 (14.3)	5 (4.3)

**1 case missing in the study arm, **2 cases missing in the study arm,
ACDF = Anterior Cervical Discectomy and Fusion, ACCF = Anterior Cervical Corpectomy and Fusion*

Complications incidence among short segment ACDF patients and long segment ACDF/ACCF patients are displayed in the Figures 12 and 13 below. The visual

representation showed very similar plots for both study arms. The short segment plot appeared a bit compressed in comparison to the long segment plot, but retaining similar trends such as high incidence of pain, dysphagia and adjacent segment disease and lack of such complications like hardware failure. Long segment patients experienced few complications in counts higher than 10, whereas only two types of complications were reported with respect to the short segment study arm.



Figure 12. Long Segment ACDF/ACCF Post-surgical Complications Counts.

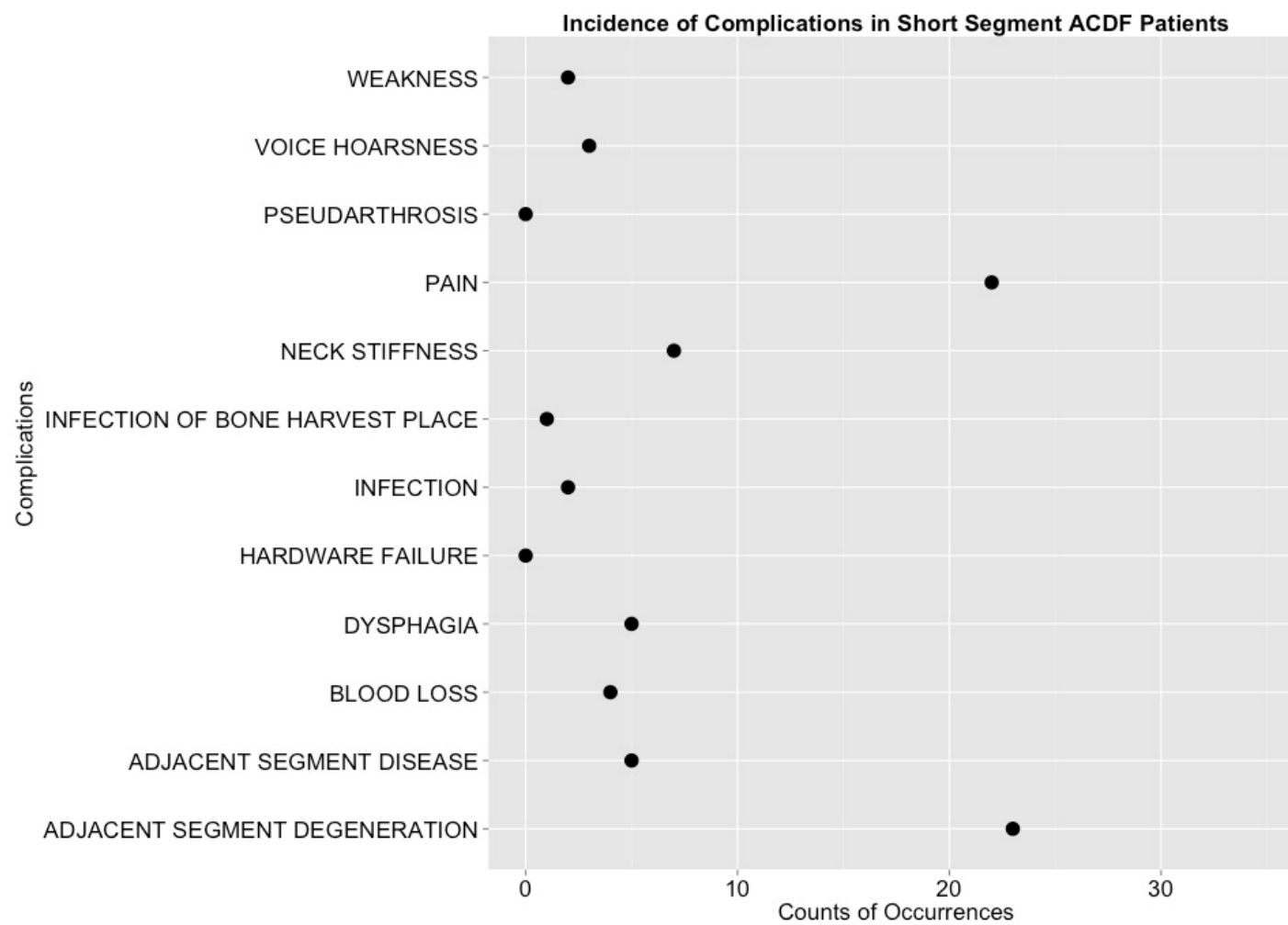


Figure 13. Short Segment ACDF Post-surgical Complications Counts.

The odds ratio of occurrences of each complication type in short segment ACDF in comparison to the long segment ACDF/ACCF patients was calculated. Only pseudarthrosis detected in radiographic imaging and symptomatic adjacent segment disease were significantly associated with multilevel ACDF/ACCF surgery. Subjects undergoing long segment ACDF/ACCF treatment were 73% more likely to develop adjacent segment disease. However, it is worth noting that none of the patients, who underwent short segment ACDF surgery demonstrated pseudarthrosis on their radiographic images, resulting in pseudarthrosis-long segment effects being implausible. A list of all subjects who experienced pseudarthrosis is presented in Appendix I. There was no statistical evidence that remaining types of complications were significantly different between the short and long segment study groups. Detailed results of the statistical analysis are provided in the Table 4.

Table 4. Odds of Complications Incidence Among Short Segment ACDF/ACCF Patients in Comparison to Long Segment ACDF Patients.

Complications	Odds ratio	Statistics	
		95% Confidence Interval	p-value
Pain	0.79	(0.39 – 1.57)	0.52
Infection	0.38	(0.04 – 2.36)	0.26
Voice Hoarseness	0.96	(0.13 – 7.36)	0.97
Iliac Crest Bone Graft Infection	0.19	(0.004 – 1.71)	0.11
Stiffness	0.84	(0.25 – 2.74)	0.79
Weakness	0.64	(0.05 – 5.69)	0.68
Dysphagia	0.42	(0.11 – 1.35)	0.12
Blood Loss	1.30	(0.21 – 9.05)	0.76
Hardware Failure	-	-	-
Adjacent Segment Degeneration on X-ray	0.58	(0.30 – 1.12)	0.09
Hardware Failure on X-ray	-	-	-
Pseudarthrosis on X-ray	0.00	(0.00 – 0.47)	0.001*
Symptomatic Adjacent Segment Disease	0.27	(0.08 – 0.82)	0.01*

*Statistically significant p-value < 0.05

Diagnosis, Segment Length, and General Post-Operative Assessment

There were no dependency trends detected between the number of discs under treatment and the surgeon's assessment of patients' progress (p -value 0.79, X^2 of 1.1 with 3 df). Lack of any relationship between the tested variables is illustrated in the mosaic plot in Figure 14 below. The grades between two groups were nearly perfectly overlapping.

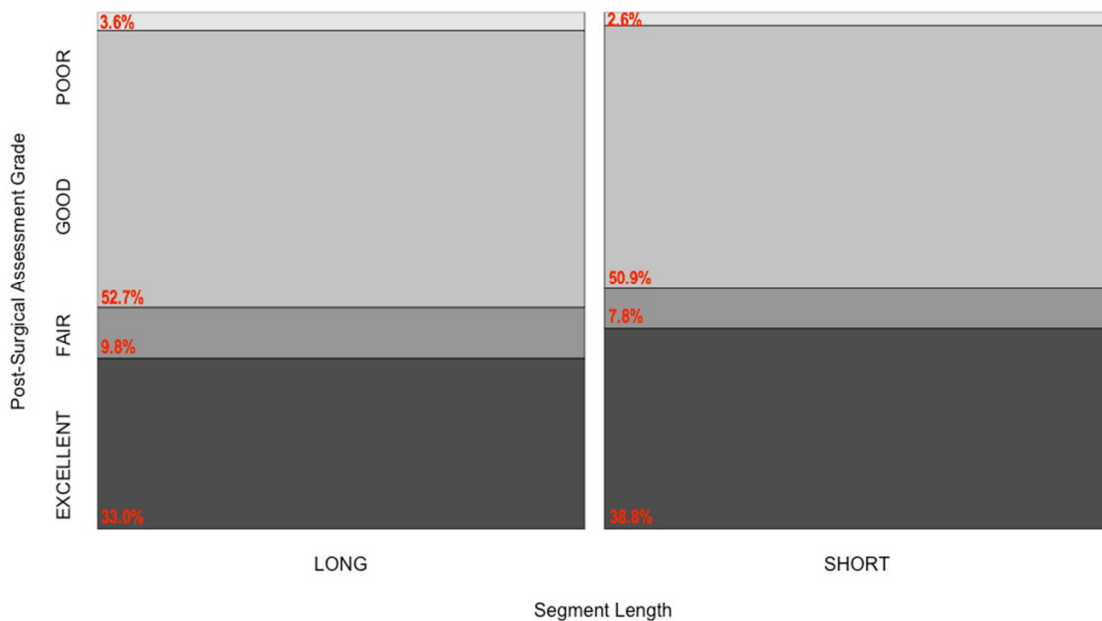


Figure 14. General Post-operative Outcome in Short ACDF Surgery Patients vs. Long ACDF/ACCF Surgery Patients.

Subjects diagnosed with radiculopathy were more likely to need just one or two level surgery ($p < 0.0001$). While subjects who were diagnosed with myelopathy, were more likely to require long segment intervention (Figure 15).

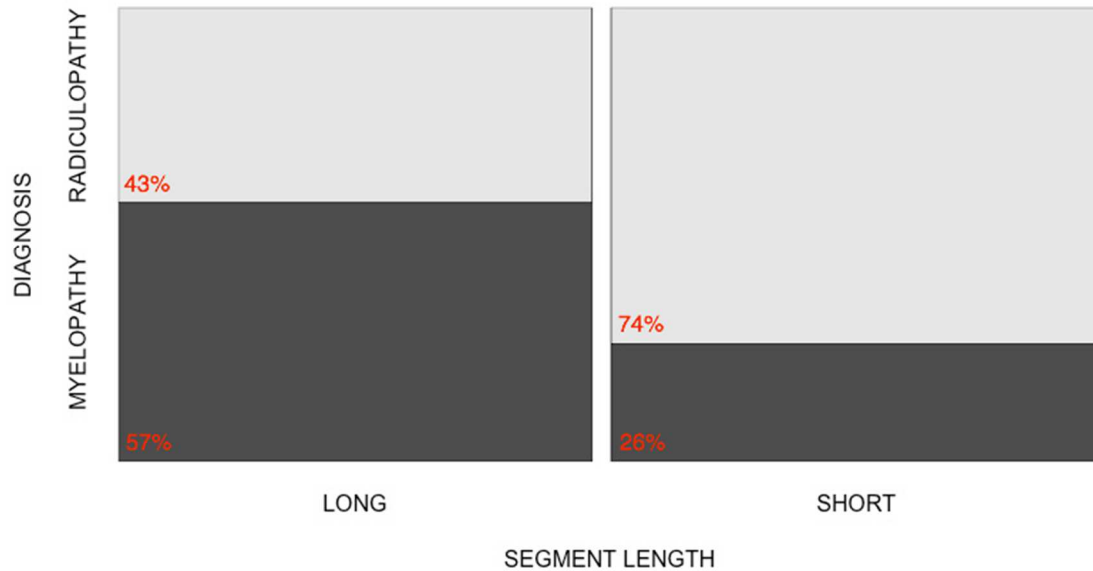


Figure 15. Diagnosis and Length of the Cervical Spine Segment under Treatment.

With respect to subject diagnosis and general post-surgical outcomes, statistical analysis produced weaker, but existent trends with Fisher's Exact Test yielding $p = 0.0189$. Subjects originally diagnosed with radiculopathy showed more often an *EXCELLENT* post-surgical outcome (59) than those suffering from myelopathy (23). Also, it was noted that a few more radiculopathy subjects (62) received a *GOOD* grading versus those with myelopathy (57.) Outcomes, such as *FAIR* and *POOR* were very similarly distributed among myelopathy and radiculopathy groups (10 to 10 and 4 to 3, respectively).

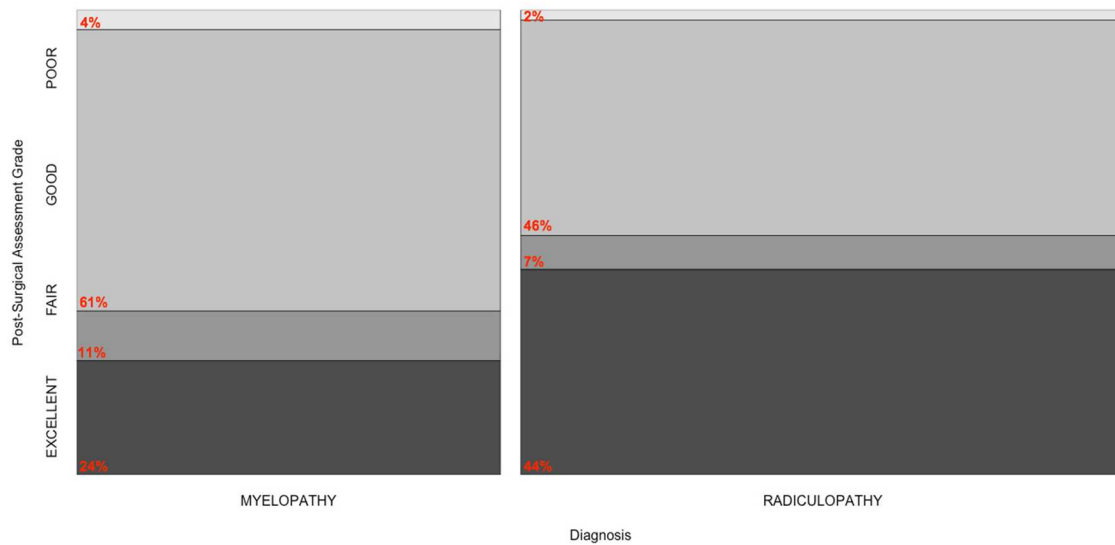


Figure 16. General Post-Operative Assessment in Patients Diagnosed with Myelopathy versus Radiculopathy.

Age, Segment Length and Complications

Welch Two Sample t-test yielded a t of 5.8 at 221.6, and p -value <0.0001 , with the 95% Confidence Interval of 5.3 – 10.7. The mean age values for both study cohorts are presented in Table 5. The short segment patients were relatively younger than those who underwent long segment intervention. On average, patients who visited BMC to undergo short segment ACDF were 8 years younger than those who sought multilevel ACDF/ACCF intervention.

Table 5. Differences in Mean Age of Short Segment ACDF Surgery Patients versus Long Segment ACDF/ACCF Surgery Patients.

	Age Differences [Years]	
	Long Segment N = 112	Short Segment N = 116
Mean	57.32	49.29
Standard Deviation	9.47	11.32
Standard Error of the Mean	0.89	1.05
Lower 95%	55.55	47.21
Upper 95%	59.1	51.38

The box plot (below) illustrates that the two groups differed in mean age.

Although there were few outliers in both groups, the long segment group was relatively older in comparison with the short segment group. Fifty percent of patients treated with a long ACDF/ACCF surgery were between 50 and 65 years of age, whereas 50% of patients who underwent short segment ACDF surgery were between 40-55 years of age.

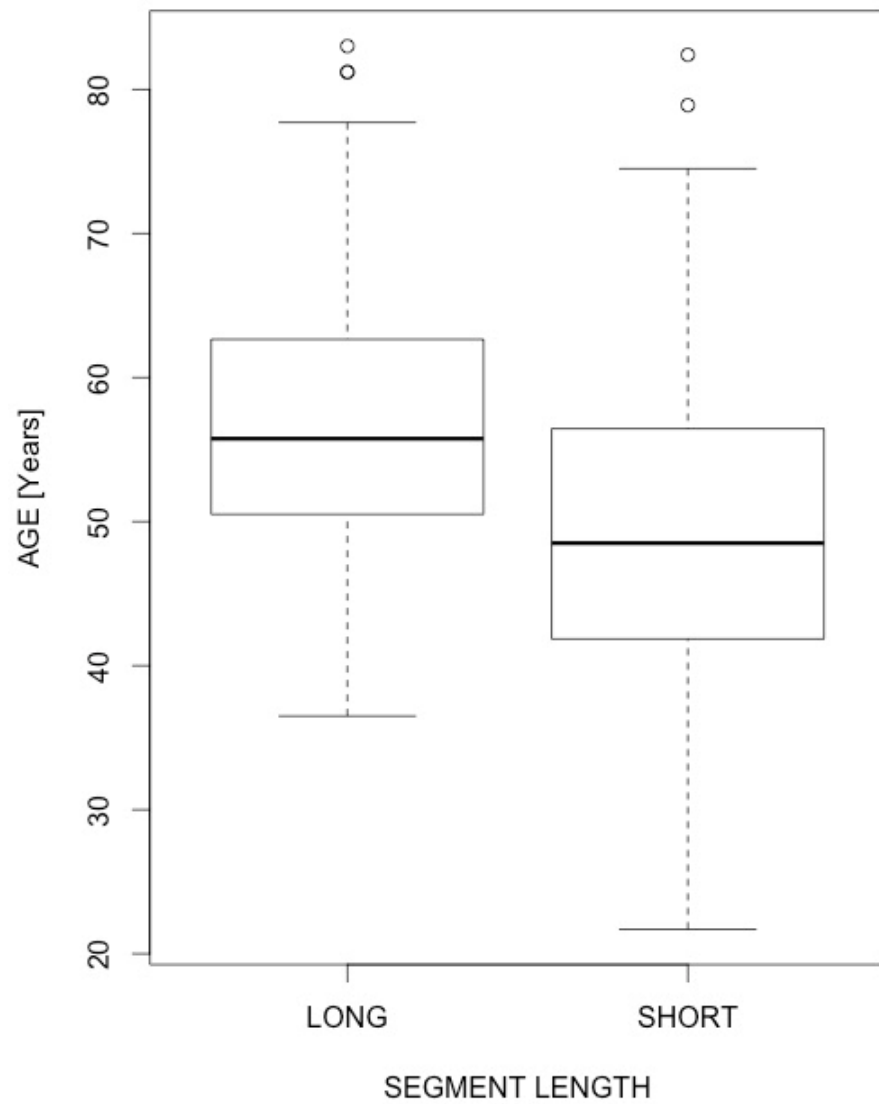


Figure 17. Age of Short Segment ACDF Patients versus Long Segment ACDF/ACCF Patients.

Since there was a significant difference in means between age of short ACDF surgery patients and long segment ACDF/ACCF surgery patients, the next step was to investigate trends between age means and each level of ACDF/ACCF surgery. Average age of subjects, who needed 5 Level intervention (five discs fused) was 60.52 years, which is over 13 years more in comparison with patients, who received 1 Level treatment (one disc fused). Overall, average age within each group seemed to increase along with the segment length undergoing surgical treatment. The only exception was transition from Level 4 to Level 5 – average age was nearly identical in those two groups. Table 6 provides additional details on age characteristics of subjects within each group.

Table 6. Age within Each ACDF/ACCF Level.

Level (Number of Discs)	Number of Cases	Mean	Std Error	Lower 95%	Upper 95%
1	57	46.93	1.36	44.25	49.61
2	59	51.58	1.33	48.95	54.21
3	48	54.64	1.48	51.73	57.56
4	53	59.08	1.41	56.31	61.86
5	11	60.52	3.09	54.42	66.61

Std = Standard

Box plot, shown in Figure 18, confirms that the median age was different between the groups. Subjects who had only one disc fused were relatively younger than those who had ACDF/ACCF surgery on more levels. Again, levels 4 and 5 were similarly distributed, as patients appeared to be in similar age (mean of 59.08 and 60.52, respectively). To summarize, the box plot suggests that being older corresponded to the levels of disc fusion surgery.

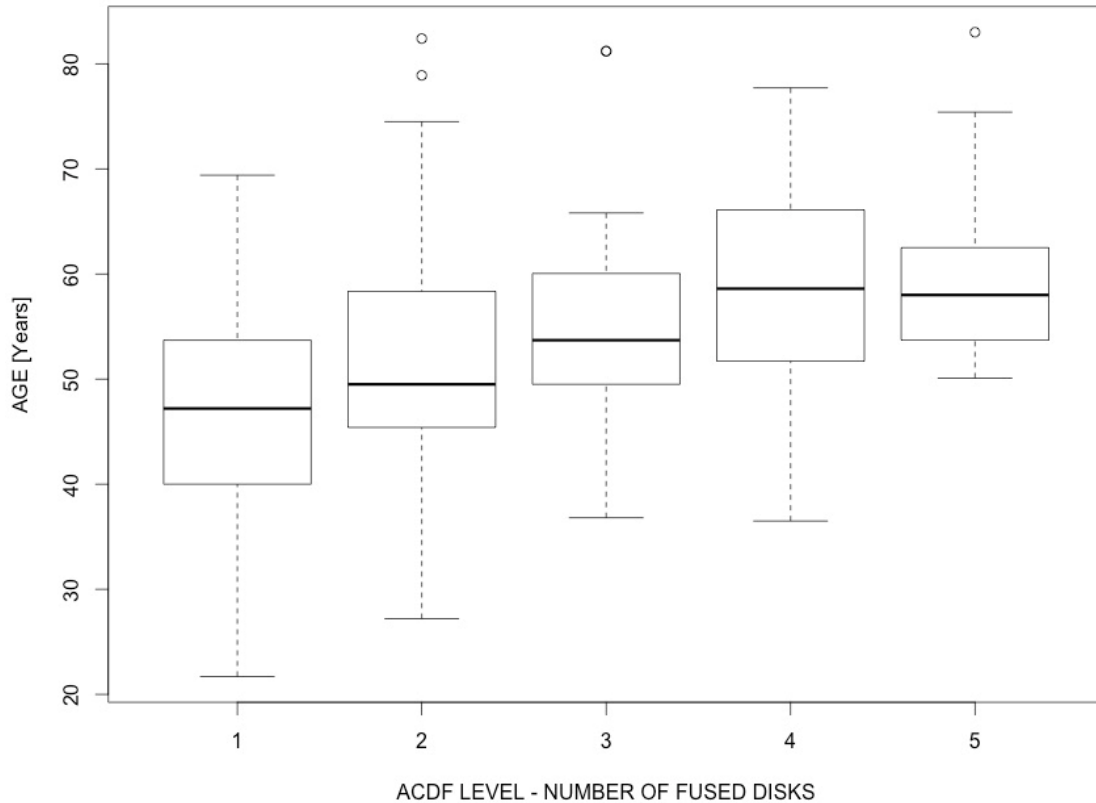


Figure 18. Age Trends within each Level (Number of Discs) Treated with ACDF and/or ACCF Surgery.

The relationship between older age and the need for a higher level disc replacement surgery was further examined with a *one-way* ANOVA test, Table 7. Analysis of variance yielded a *p*-value lower than 0.0001, demonstrating that there were differences in mean ages between patients of different surgery levels. Patients undergoing a lower number of disc fusion levels were younger than those who required more levels to be treated with ACDF/ACCF surgery. Box-plot analysis and one-way ANOVA indicate that short level disc fusion patients were relatively younger in comparison with those who had long segment intervention.

Table 7. One-way ANOVA Test Results Evaluating Differences in Age of Patients who underwent Various Numbers of Discs Replacement and Fusion (ACDF/ACCF Level).

	Df	Sum Sq	Mean Sq	F Value	Pr (>F)
Level	1	4845	4845	46.57	<0.0001***
Residuals	22	23514	104		
	6				

Significance Codes: 0 '*' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1**

Once it was revealed that short segment patients tended to be younger in comparison to those undergoing long segment surgery, further analysis was performed to identify which levels of ACDF/ACCF treatment were linked to differences in mean age at the statistically significant level. Results of Tukey Honest Significant Difference test are shown in Table 8, and highlight that patients undergoing one disc ACDF surgery were statistically younger than those, who required three, four, or five levels ACDF.

Table 8. Tukey HSD Test Results – Significant Difference between the Age of 1 Level ACDF Patients and the Age of Multilevel ACDF/ACCF Patients.

ACDF Levels (# of Discs)	5 Level ACDF	4 Level ACDF	3 Level ACDF
1 Level ACDF	4.30*	6.78*	2.19*

***Significant Difference: Pairs of Positive Values**

ACDF = Anterior Cervical Discectomy and Fusion

Table 9 features details of all of the pairs of short level ACDF surgery and long level ACDF/ACCF surgery with a statistically significant difference in average number of years of age. Overall, subjects undergoing a 1 Level intervention were substantially younger than those who underwent Levels 3, 4, and 5 ACDF/ACCF surgeries. Also, subjects undergoing two discs fusion were noticeably younger than those undergoing four discs surgery.

Table 9. Characteristics of ACDF Level Pairs Significantly Different between each other in Age of Patients.

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
5	1	13.59	3.38	4.30	22.87	0.0007*
4	1	12.16	1.96	6.77	17.54	<.0001*
3	1	7.71	2.01	2.19	13.24	0.0015*
4	2	7.51	1.94	2.17	12.84	0.0013*

**Significant Difference, Std Err Dif = Standard Error Difference, Lower CL = Lower Confidence Limit, Upper CL = Upper Confidence Limit*

Because of this evident trend suggesting that older age may be linked to multilevel ACDF/ACCF surgeries, the relationship between age and complications incidence was tested. To capture any potential association between age and complications, odds ratio of complications' incidence was tested in both study arms: short and long segment. It turned out that only one complication, in the context of aging, yielded results statistically significant. In the long segment arm evidence suggests that dysphagia was significantly associated with age ($p < 0.05$). An Odds Ratio of 1.07, with a 95% Confidence Interval between 1.01 and 1.15, confirmed that this association was plausible. Age was a risk factor in experiencing dysphagia in patients undergoing multilevel ACDF/ACCF surgery. With every year, the risk of developing dysphagia after long segment ACDF/ACCF increased by 7%. None of the other investigated complications seemed to be linked to a patient's age neither in short nor long segment intervention. Detailed results of logistic regression analysis are listed in Table 10 below.

Table 10. Age and Odds of Complications Incidences in ACDF/ACCF Patients

Complications	Age and Odds of Complications Incidence in ACDF/ACCF Patients							
	Short Segment ACDF				Long Segment ACDF/ACCF			
	Estimate	Standard Error	PR>Chi Sqr	Odds Ratio	Estimate	Standard Error	PR>Chi Sqr	Odds Ratio
Pain	0.04	0.02	0.11	1.04	-0.01	0.02	0.662	0.99
Infection	0.01	0.06	0.88	1.01	0.01	0.05	0.1	1.01
Bone Harvest Place Infection	-0.03	0.09	0.76	0.97	0.07	0.05	0.22	1.08
Voice Hoarseness	-0.03	0.05	0.61	0.97	0.07	0.06	0.22	1.07
Stiffness	0.05	0.03	0.13	1.05	0.02	0.04	0.63	1.02
Weakness	0.01	0.06	0.86	1.01	0.05	0.06	0.35	1.05
Dysphagia	0.05	0.04	0.23	1.05	0.07	0.03	0.033*	1.07
Blood Loss	0.08	0.04	0.06	1.08	-0.005	0.06	0.94	0.99
Adjacent Segment Degeneration	0.02	0.02	0.26	1.02	0.02	0.02	0.39	1.02
Adjacent Segment Disease	0.03	0.04	0.49	1.03	-0.05	0.03	0.10	0.95
Pseudarthrosis	-	-	-	-	0.05	0.04	0.18	1.05
Hardware Failure	-	-	-	-	-	-	-	-

* Significance Code of 0.05, PR = Probability, Chi Sqr = Chi Square, - = Lack of Computation due to Lack of Cases, ACDF = Anterior Cervical Discectomy and Fusion, ACCF = Anterior Cervical Corpectomy and Fusion

To summarize, patients who underwent long segment ADCF/ACCF surgery incurred more pseudarthrosis and adjacent segment disease than patients who underwent short segment ACDF surgery. There were no differences in incidence of other complications between the two study arms. Pain was the most common complication in each study cohort. Furthermore, segment length did not affect the overall post-operative assessment of patient convalescence. However, subjects diagnosed with radiculopathy were more likely to undergo a short segment fusion in comparison with those who were treated for myelopathy. Additionally, those treated for radiculopathy more often seemed to be graded with an *EXCELLENT* mark in the follow-up period. Subjects undergoing 1 Level ACDF surgery were younger with respect to those who needed three or more discs addressed. Finally, older study subjects were more likely to experience dysphagia, if undergoing long segment intervention. In that study arm, the risk of dysphagia increased by 7% with each year of patient's age. The remaining complications did not seem to be affected by the subject's age.

DISCUSSION

This retrospective cohort study aimed to evaluate and compare post-surgical outcomes of patients who underwent long segment ACDF and/or ACCF surgery (three, four or five discs removed and fused) with those who were treated with single or two-level segment ACDF surgery. Data used in this thesis project was extracted from BMC Orthopaedic Surgery Department, and included occurrences of complications, post-operative outcomes, initial diagnosis, as well as demographic information. Sample size was large, with a normal age distribution.

The primary objective was to assess whether long segment surgeries were associated with more complications than short segment surgeries. This assessment was based on the comparison of complications in each of the study cohort.

Secondary outcomes aimed to:

1. Evaluate whether short segment ACDF surgeries versus long segment ACDF/ACCF surgeries led to different post-operative outcomes;
2. Investigate if there was an association between the initial diagnosis and the final general assessment;
3. Examine if the initial diagnosis with respect to segment length that needed intervention affected the overall post-surgical assessment;
4. Assess the role of age and the number of post-surgical complications between groups.

All outcome measures were studied with de-identified data sets provided by BMC employee.

Short and Long Segment Patients' Complications

Overall, complications did not differ significantly between the short and long segment surgery cohorts. The most common post-surgical complication in both groups was pain, with 26 subjects in the long segment surgery cohort, and 22 subjects in the short segment surgery group experiencing pain, respectively. Such a result was not unanticipated, and was consistent with previous research conducted on post-surgical pain. In the PAIN[®] journal, Stephen Schug discussed results of a large epidemiologic post-operative pain study, and reiterated that approximately 18% of the 2000 investigated patients experienced persistent post-surgical pain.²¹ Another study, which focused on evaluating pain before and after the short segment ACDF surgery, revealed that pain after the procedure increased from 6.2% to 10.1% and 15.9% of study subjects (depending on the area of the pain: radicular pain, neck pain, and headache.)³⁴ Results of this study corresponded to epidemiologic studies on post-operative pain, as well as research focused on pain as an ACDF surgery outcome. Based on this research, as well as available literature, experience of pain may be an inevitable consequence of major surgical treatment.³⁵ However, due to pain's relatively high prevalence post ACDF/ACCF surgeries, an effective pain prevention and management plan could be outlined for spine surgery patient. Currently available pain relieve strategies tend to be too challenging for patients, as reported by Nielsen et al, and induce high opioid intake.³⁵ Effective pain alleviating techniques, designed for spine surgery patients and addressing most commonly affected regions (such as neck, shoulders, lower extremities), should be identified to address the problem. The remaining complications occurred in much lower

counts, similarly distributed between the two groups. However, two types of complications occurred more commonly among those patients who had three or more discs treated with ACDF/ACCF surgery: adjacent segment disease and pseudarthrosis.

In this study, sixteen patients who underwent long segment surgery developed symptoms of adjacent segment disease, the second most prevalent complication amongst BMC ACDF surgery patients. It is important to note that adjacent segment disease is common among patients undergoing ACDF surgery. However, studies show contradicting results. Some suggest that the greater number of discs needing fusion was not associated with higher likelihood of adjacent segment disease.⁴⁴ On the other hand, van Eck et al. demonstrated that only 11% of patients needing one-level disc surgery developed adjacent segment disease, while 100% of patients requiring four-level disc surgery developed adjacent segment disease.³⁶ Others reported female gender, smoking, and history of 1 or 2 levels ACDF as risk factors increasing probability of adjacent segment pathology development.²² Therefore, findings of this study with regard to multilevel disc surgery patients who developed adjacent segment disease, are in discordance with Hilibrand's and Lee's reports,^{16,22} yet in accord with van Eck's reports.³⁶ Accordingly, results (from this study), demonstrating that adjacent segment disease was more likely to occur in patients that needed intervention on more than one disc was not unanticipated. BMC patients, who underwent multilevel ACDF, were more likely to develop adjacent segment disease. In the context of primary focus of this research, it is an important result, because it highlights a complication type that had one of the most significant implications for the patient. Many patients, after developing

adjacent segment disease, have to undergo further revision surgeries, in fact, 12 % and 25% of patients undergoing high level disc surgery required a second and third ACDF surgery, respectively.^{23, 44} Undergoing multiple surgeries understandably conveys further risk to the patient, and may ultimately undermine the initial purpose of treating all affected discs at the same time, if patients have to undergo revision surgeries after the multi-level disc surgery. Although it is not clear, if degeneration of the discs adjacent to the fused segments is a potential consequence of the ACDF/ACCF surgery, or possibly one's propensity for this disease, perhaps the focus should be shifted to preventive measures for these patients. For example, arthrodesis (surgical bone immobilization) should include all the necessary levels to prevent further degeneration.⁴⁴

Pseudarthrosis (failed fusion) is another complication worth noting as it occurred only in patients who underwent three or more segments ACDF/ACCF surgery.

Pseudarthrosis is linked to impaired healing process in a patient.^{40, 45} Schwab and other experts pointed out that failed fusion can be caused by patient's poor ability to heal, as well as secondary factors, such as infections, comorbidities such as diabetes, excessive motions during convalescence period, and poor surgical techniques.⁴⁰ Similar to what was found in this study, other authors reported increased risks of pseudarthrosis with multilevel ACDF. Wang et al. found 30% pseudarthrosis rate in 3-level ACDF surgery compared to 20% in 2-level ACDF surgery, and almost 10% in one level ACDF surgery.^{24, 42} Despite the statistical significance, the rate of pseudarthrosis in this multilevel ACDF series is still very low (8%) compared to the literature (about 30%). Moreover, a recent meta-analysis study reported increased incidence of pseudarthrosis

with use of allograft (4.8% rate) when compared to autologous bone graft use (0.9%).³⁹ Additionally, patients who smoke are 33% more likely to develop pseudarthrosis.⁴⁵ Although we noted lower rates of pseudarthrosis with multilevel ACDF compared to the previously reported literature this complication should be seriously taken by prospective patients, as it can cause need for a revision surgery. Subjects with known comorbidities, who have to undergo multilevel ACDF/ACCF, or those who are or were smokers, should therefore be counseled and optimized prior to surgery (asked to stop smoking, control their diabetes status, should opt for an autograft instead of allograft), and they should be monitored more carefully in the convalescence period. In addition, extracorporeal bone stimulators and pharmaceutical agents assisting in bone healing could be carefully used during the surgery (e.g. bone morphogenetic proteins) or prescribed in the postoperative recovery period in order to avoid pseudarthrosis.^{21, 25, 42-43, 45}

Overall, BMC patients experienced relatively small numbers of post ACDF/ACCF complications with the cohorts differing only in the rate of adjacent segment disease and pseudarthrosis. Although these two complications affected a reasonably small number of patients, they should be taken into consideration when counseling the patient and choosing the levels and extent of fusion.

Post-Surgical Assessment of Short and Long Segment Patients

It is a common procedure for an orthopaedic surgeon to conduct a patient evaluation during follow-up visits after surgical intervention. Patients in this study received their final assessment grade typically at the third follow-up visit (6 to 12 months postoperatively). It was extrapolated that if study cohorts differed in overall post-surgical

convalescence, then some light would be shed on the effect of multiple complications occurring in a single patient post ACDF surgery. It turned out that there was no statistical evidence indicating that short segment ACDF patients were recovering faster than those who underwent multilevel ACDF/ACCF surgery. The grades corresponding to general post-surgical outcomes had nearly identical distributions between the two study groups. There are studies providing evaluations of satisfaction in the recovery process for treatments of radiculopathy and myelopathy.⁴² However, there is lack of literature providing similar analyses that would compare the final convalescence assessment for different ACDF segment lengths; therefore it is not possible to provide any comparison. However, knowing that overall healing process is equally satisfactory across the study groups could help some patients in deciding whether to undergo one or few levels ACDF surgery. Since the overall convalescence was similar in both study groups, it could be postulated that complications, although with slightly different incidence between short and long segment patients, are less relative to the overall success of the treatment. However, it had to be investigated, whether other factors could also affect such similar results in terms of overall patient's recovery from the ACDF surgery.

Diagnosis, Segment Length, and Overall Post-surgical Assessment

Radiculopathy and myelopathy differ in the symptoms at presentation, as radiculopathy is linked vastly to nerve root pain, and myelopathy results in decline of fine motor skills and is associated with weakness. Therefore, the warranted intervention and the general outcome could be affected by the underlying diagnosis. Since myelopathy results from spinal cord compression (commonly at multiple levels) and possible

scarring, the postoperative outcome is likely more guarded than in patients undergoing ACDF for radiculopathy (nerve root compression, commonly at 1 or 2 levels). Statistical analysis provided strong evidence that subjects diagnosed with radiculopathy were more likely to show overall excellent improvement in the general post-surgical assessment. BMC patients undergoing ACDF for radiculopathy were more likely to receive only one or two discs arthrodesis. In those cases shorter segment required intervention, thus, the area requiring healing (vertebral body and graft border) was smaller and may have taken shorter time to heal.⁴⁴ Unfortunately, due to very limited availability of literature on the topic²⁶, such a hypothesis would need thorough exploration. Furthermore, other factors, such as age or weight, potentially contributing to the overall successful recovery, need to be evaluated in this context as well.

Age Differences between short and long Segment Patients

Age is considered one of the major factors contributing to disc diseases, and, ultimately one of the main causes resulting in reconstructive surgeries such as ACDF and ACDF/ACCF. Therefore, the age of subjects in the two study arms was evaluated, as well as potential effect of the patient's age on the complications they experienced. It turned out that short segment ACDF patients were relatively younger than those who had to be treated with a multilevel surgery, with an average age of 49 years old versus 57 in these two groups respectively. Such a result fostered investigation of age correlation to each of the ACDF level. Therefore, differences in age between patients of all five ACDF/ACCF levels were studied. Further analysis yielded consistent results. Those undergoing more than one-level ACDF surgeries were statistically older. Since it was known that patients

who needed treatment targeting multiple levels were older, it was suspected that experiencing complications could be related to age, not necessarily to the number of discs undergoing replacements. Multiple studies indicated that spine surgery satisfaction decreases among patients who underwent treatment in an older age.³⁸ However, evaluation of age as a confounding variable in complications after spine surgeries studies were not found. As a result, hypothesis stating that age could be the underlining cause of ACDF complications rather than segment length would need further verification. It should be noted, however, that older age corresponded to dysphagia in long segment patients. A vast part of the study population consisted of subjects 50 years or older, which corresponded to the average age of patients in other spine surgery studies.^{12, 17, 38, 42} On the other hand, dysphagia constitutes a common problem encountered in subjects over 50 years old and it tends to worsen with age, irrelevant to the presence or absence of a surgical treatment.³⁷ As retrospective study design does not allow for any causal relationship inferences, it cannot be confirmed if age or segment length affected the incidence of dysphagia. Nonetheless it was clear that these three variables were associated with each other.

The lack of evidence between age and experiencing pseudarthrosis in the long segment patients was surprising.^{24,39-42} As former research suggested: “Age older than 55 years at surgery showed a significantly higher pseudarthrosis incidence.”³⁷ The healing process is considerably more tedious in the older population. Therefore, senior patients undergoing ACDF/ACCF surgery would be expected to develop pseudarthrosis more often than younger individuals undergoing the same procedure. Although previous

studies revealed that failed fusion was more prevalent among older patients,⁴⁰ this study did not shed any light on this matter.

Summarizing the study results, it appeared that long segment ACDF/ACCF surgery might affect the rate of considerable complications such as pseudarthrosis and adjacent segment disease. However, there is lack of strong evidence showing that segment length is the principle factor leading to these complications outcome. This research did not evaluate between complications interactions, as well as confounding factors other than age or initial diagnosis.

Study Limitations

We identified many limitations in this research project. With respect to the study design, the dimensions of data were not formulated to answer the study questions. Instead, study problems were answered with patient information that was already available in the BMC database. Hence, there were some confounders unaccounted for, such as weight, differences in the follow up period and post-surgery activity level. Data could not be stratified by weight of patients, because 30% of study population was missing that information. Furthermore, between patients differences in the length of follow up period were not extracted for the purposes of this study. Also, it was not known how subjects spent their post-surgery recovery time, for example if they returned to physical activity quickly, or if they have applied more sedentary lifestyle with limited amount of movement, which could affect their overall outcome and experiencing of such complications like pain or pseudarthrosis. Furthermore, the inclusion criteria were very broad (past history of ACDF/ACCF surgery, follow-up note, radiographic images present

in the patient's documentation), and additional confounders could not be accounted for, such as specific pre-existing conditions, other than tumors. For example, hemophilia would increase likelihood of a blood loss.²⁰ All of these factors could potentially influence a subject's recovery process while enhancing the treatment effect or diminishing it while causing some complications to continue. Stratification would help in managing those confounding factors, but due to lack of influence on the data collection, it was not possible.

In addition to that, one can fear that the provided data was affected by an observer bias. Data made available for this research was extracted from numerous patient charts, surgical notes, as well as radiographic images. The individual responsible for collecting information for this study might have made errors when obtaining it. This bias could have affected the study results and contribute to the lower number of reported complications, if the person who extracted data made some exclusions. Some minor incidents might have been inadvertently omitted thereby affecting the final outcome and swaying the statistical significance. Consequently, the actual difference between groups could be masked and results underestimated, suggesting no differences between the studied arms. Additionally, it has to be remembered that medical charts can be inconsistent in offering details due to being created by multiple staff members. Therefore, some medical histories might have offered more thorough descriptions and details, when others might have presented some exclusions of information. In the long run, the observer bias or incomplete source documents could have weakened the results of this study.

Furthermore, subject bias could have occurred in the source data extracted for this

research. Criteria for complications could not be customized a priori because of the retrospective nature of this study. An important aspect of identification of complications must have been patient's statement and patient's behavior at the follow up visit. Because individuals subjectively experience discomfort or pain, some of the patients could simply have ignored symptoms perceived as mild, whereas others could have overstated their complaints. This has the potential to negatively influence the internal validity of the study, as it could either underestimate or overestimate the results, depending on the feedback provided by the study individuals over the course of their treatment at BMC.

Another limitation was that the effect between dependent variables (complications) was not taken into account. More specifically, the number of complications experienced by each patient was not analyzed. This could be an important factor, because some subjects might have been more prone to suffer from many complications at once, whereas others would might not. Thus, in the end, the disparity between the studied groups could be even smaller.

Finally, this was a single institution study, which could have been perceived as a limitation as well as study advantage. The downside was the fact, that there was no possibility to test outcome measures in the broader context, such as on the national (or global) level. If investigated post-surgical complications were performed at only one hospital, and by one surgical team, we could have run into additional confounding factors, such as use of some effective and pioneered techniques or, on the opposite spectrum, lack of training that is nowadays common in the field but for some reasons not employed at the institution under investigation. On the other hand, however, single

institution study offered a naturally controlled environment and uniform operating procedures – it was extrapolated that all study subjects underwent relatively similar treatment. To sum up, the external validity of this study was somewhat impaired by lack of a broader comparison, as the results should be generalized just for the future potential BMC Orthopaedic Surgery patients.

The flaws of a retrospective study design might have influenced this project's results. Most importantly, study questions had to be formulated in a way to accommodate available data, instead of creating data set based strictly on the studied problems. Secondly, there might have been an observer, as well as a subject bias, which could have masked the true incidence of complications. Furthermore, some of the identified confounding variables, such as patient's weight, could not have been accounted for, again, due to the retrospective character of the study design. The major weakness of the study came from the fact that between variables effect was not accounted for. Finally, external validity was somewhat impaired by conducting investigation at a single institution. Despite the listed limitations, the study results should not be underestimated.

Recommendations for Future Studies

This study aimed to establish groundwork for further exploration of post-surgical complications between short segment ACDF surgery and long segment ACDF/ACCF surgery. Using a retrospective study allowed for taking into account a relatively large sample size, which increased the power of the tested effects. Furthermore, the retrospective design offered no threat to subjects' health, and using de-identified data posed no risk to patients' confidential information. In addition to that, this was an

inexpensive study. Finally, the follow up period already has taken place, therefore, no time had to be spent on waiting for the end of subjects' participation. Although retrospective study design carries substantial imperfections, the ultimate goal of studying incidence of complications between short and long segment ACDF patients was achieved. The next step would be to introduce a prospective cohort study design to combine knowledge gained from this study with addressing some of the current model's limitations.

Conducting a prospective cohort study would allow investigators to measure the most desired data points. In the prospective model investigators would ensure that each subject's weight is measured, because weight is a risk factor for complications incidence.²⁹ An orthopaedist can identify the comorbidities that would most likely influence the overall outcome. Standardized scales could be used to measure each of the complications. It would be beneficial to use pre-existent or new, but uniform, instruments to measure post-operative outcomes. Additionally, the strict follow up time should be set up. Once subjects agreed to participate in the study, they could volunteer and commit to examination at the fixed visits, for example 2 weeks after the treatment, one month, three months, six months, and at year 1 and year 2 post surgery. With such a standardized arrangement of measurements not only confounding variables would be controlled for, but also observer and subject bias may be minimalized, which ultimately increases the internal validity of the study.

A uniform and a priori designed system of measuring study outcomes would also address the problem of lower external validity of the current retrospective study. A

multicenter study could be conducted. Some of the tests could even be performed over the phone, which would lower the dropout rates and would accommodate older population that may be less mobile, as well as subjects living in the rural areas, farther from the research institutions. Moreover, appropriate stratification during statistical analysis phase could highlight interesting but currently unknown trends. For example, study sites with surprisingly low number of complications could be using some excellent, but not widely known surgical methods, which then could be popularized. Multicenter prospective study model, accompanied by a battery of standardized tools and a large sample size would yield results generalizable to a broader population and provide more definite standing on the safety of short versus long segment ACDF surgeries.

CONCLUSIONS

This thesis research was designed to evaluate and compare complications post short and long segment Anterior Cervical Discectomy and Fusion. Most post-surgical complications were similarly distributed between the two study cohorts. Pain was the most prevalent across entire study population, indicating need for an effective pain management strategy that could be offered to patients. The long segment ACDF/ACCF patients were more likely to experience pseudarthrosis and adjacent segment disease than short segment ACDF patients. Since these two complications are posing risk of revision surgery, more preventive measures should be taken before surgery (e.g. lifestyle changes) and during surgeries (e.g. applying morphogenetic proteins). General post-operative assessment was not linked to short or long segment intervention, confirming overall similarity of the study cohorts. However, patients with radiculopathy were more likely to undergo short segment ACDF than myelopathy patients, and more often they showed excellent recovery. Thus, more exploration is needed to identify factors contributing to the best postsurgical outcomes. While older population more often underwent multi-level ACDF/ACCF than short segment ACDF, aging as a risk factor of complications was detected only in cases of dysphagia. Older patients preparing for multilevel ACDF/ACCF surgery should be prepared to address this potential complication (e.g. liquid food available to patient immediately after returning home). Overall, cohorts seemed relatively similar with just few differences reminding about careful pre- and postoperative patient's assessment. Further investigation is advised to confirm that long segment ACDF/ACCF surgeries are in general as safe as the short segment ACDF surgeries.

APPENDIX I

Table 12. Age of Subjects Experiencing Pseudarthrosis post ACDF/ACCF Surgery.

SEGMENT	LEVEL	AGE
LONG	3	53.4
LONG	3	53.7
LONG	5	53.7
LONG	3	55.7
LONG	3	62.6
LONG	4	63
LONG	4	65.2
LONG	4	69
Total:	9 cases	

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