RELATION OF PREOPERATIVE PRE-ALBUMIN AND TRANSFERRIN TO 30-DAY RISK OF COMPLICATION IN ELECTIVE SPINE SURGICAL PATIENTS

By

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LIST OF ABBREVIATIONS

EMR	Electronic Medical Record
OHSU	Oregon Health & Science University
BMI	Body Mass Index
RR	Risk Ratio
MRN	Medical Record Number
ASA	American Society for Anesthesiologist
ICD	International Statistical Classification of Disease
MPH	Master of Public Health
ICU	Intensive Care Unit
CBC	Complete Blood Count
ANOVA	Analysis of Variance
PEM	Protein-Energy Malnutrition

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ABSTRACT

Back pain is commonly reported among adults in the U.S., it is the second most common reason adults seek medical treatment. There is steady growth in the number of older adults seeking spine surgeries, especially complex surgeries. Additionally, the number of citizens over the age of 65 is steadily increasing and will continue to increase over the next several decades. The rising number of older adults seeking spine surgery raises concern for the well-being of this population given the risk of complications in spine surgery. It is imperative for clinicians to understand all potential risk factors for their patient's undergoing surgery. Protein malnutrition is a risk factor for postoperative morbidity and mortality. While there is no universally accepted pre-operative measure of nutrition status, certain blood biomarkers are recognized as clinically important in evaluating patient's pre-surgical nutrition status. To further evaluate pre-surgical biomarkers and risk of complications we conducted a retrospective cohort study of adults aged 50 years and over undergoing elective spine surgery over the course of 12 months. After creating a case list from the electronic medical record system, data was collected on each patient fitting pre-determined inclusion and exclusion criteria. The relation between the biomarkers and risk of complications was assessed using log-binomial regression, pre-albumin and transferrin risk ratios and 95% confidence intervals were estimated. After adjusting for confounding factors, the pre-albumin relative risk of any complication was 1.1 (95% CI: 0.8-1.5), or 10% greater risk among patients with pre-albumin level above the median than the risk of those with pre-albumin level below the median. In the same model, the transferrin adjusted relative risk of any complication was 1.1 (95% CI: 0.8-1.5). In this retrospective cohort study of 211 patients, for adults aged 50 years and older, we found that preoperative nutrition, as defined by the biomarkers pre-albumin and transferrin was not an independent risk factor for medical complications within 30 days of elective spine surgery.

INTRODUCTION

Nearly 80% of the U.S. population experience neck or back pain at some time during adulthood, it is cited to be the second most common reason adults go to the doctor, many of whom ultimately pursue surgical treatment[1]. Between 1980 and 2000, the surgical treatment of spinal stenosis was the fastest growing type of lumbar surgery in the United States[2]. Not only has the number of patients seeking spine surgery increase, the rate of complex spine operations increased nearly 15 fold, from 1.3 to 19.9 per 100,000 patients from 2002-2007[2]. Specific to spinal fusion procedures, the frequency and utilization increased at a higher rate than other notable inpatient procedures from 1998-2008[3]. Likewise, the average age of patients seeking spinal fusion increased from 48 to 54 years old while the most rapid increase in utilization occurred among adults over age 60[2-4]. Largely as a result of advances in diagnostic capabilities, surgical techniques, and spinal instrumentation, the indications and frequencies of spine surgery have drastically broadened over the last several decades[5]. Concurrent with the medical advancements in this nation, quality of life expectancies have also increased, motivating an older population to seek such elective procedures[6,7]. Concomitant with the rise in rates of spine surgery, the Census Bureau predicts that the number of citizens over the age of 65 years will steadily increase over the next 30 years, from 34.6 million in 2000 to 69.4 million in 2030. The steady growth in the number of older adults seeking complex surgeries and the shift in demographics raises concern for the well-being of this population given the risk of complications in spine surgery[2].

There are many well-recognized advantages of successful spine surgery yet it's also evident that complications may lessen the likelihood of a satisfactory outcome, increase the cost of care, and potentially result in further disability or death[5]. Understanding the potential risk factors associated with developing complications in the early postoperative period following spine surgery benefits both surgeon and patient[5]. Preoperative protein-energy-malnutrition (PEM) is a well-recognized and accepted risk factor for peri- and postoperative morbidity and mortality following surgery[8]. PEM is defined as a state of nutritional insufficiency attributable to inadequate dietary intake[9]. A secondary definition can simply be

stated as any alteration in the physiology, composition, or function of an organism attributable to a diet or disease that adversely affects outcomes[10]. This can be the consequence of some diseases, age, social conditions, lack of early recognition or the absence of access to appropriate medical care, and even some cultural factors[9]. PEM is much more common in older adults than in younger populations[10,11]. Compared to well-nourished patients, the hospital stay of malnourished patients can be up to 90% longer and charges can be in excess of 37-75%[9,12]. Literature suggests that elderly and handicapped patients of who live alone without adequate familial or institutional support are at greater risk of being malnourished[8]. Moreover, PEM can contribute to a patient's decline in function and mobility and decrease quality of life[10].

In community dwelling older populations, the prevalence of malnutrition is considerably lower compared to hospitalized patients or those housed in care facilities. Malnutrition in the older adult population varies widely depending on the study setting, in community dwelling adults reports suggest the prevalence ranges from nonexistent up to 23%[13]. Whereas, 40-67% of residents in long term care institutions are reported to be malnourished[13-15]. The large majority of patients seeking elective spine surgery consist of the older community dwelling adult where the burden of malnutrition is low. Patients with a normal nutrition status have increased ability to recover from surgical procedures[16]. However, older patients may differ from younger adult patients in their reduced adaptive and regenerative capacity, making recovery more difficult[7]. Wound healing itself requires large amounts of energy because of the synthesis of the components needed for tissue repair[17]. PEM contributes to poor wound healing by prolonging the inflammation process, impairing collagen production, and increasing the risk of wound dehiscence[17].

While malnutrition is well recognized as a risk factor for postoperative complications, the nutritional status of spine surgery patients is not well understood. There are several validated gold standard screening tools recommended for nutrition screening in older patients, many of which involve time consuming assessments and questionnaires, in addition to the knowledge of how to interpret the results[18]. In a high volume surgical practice, these assessments are not practical to administer to all surgical candidates and clinicians must rely on other measures.

For these surgical evaluations, while there is no universally accepted rapid measure of nutrition status, certain blood biomarkers are recognized as clinically important in evaluating patients[9,10,16,19]. The use of these biochemical measurements allows for an objective aspect in nutritional assessments[20]. Several studies show that visceral proteins have been useful proxy for nutrition status, especially in an older population[21]. Various studies report pre-albumin and transferrin as markers of the severity of PEM; these prognostic indicators allow for better and earlier detection of PEM compared to that of other anthropomorphic markers especially given that PEM is not always accompanied by routine clinical manifestations[10,12,19,22]. Although serum albumin is commonly reported by previously published studies as an indicator of nutritional status, more recent publications indicate that pre-albumin may be a more sensitive marker of nutritional status as a result of its shorter half-life and ability to reflect more immediate nutritional changes[12,19,20]. Furthermore, the use of transferrin can aid in the detection of long term nutrition inadequacies in an objective and cost efficient manner.

Pre-albumin is used to identify malnourished patients and those at risk of malnutrition prior to major surgery, production decreases after just 14 days of consuming a diet that provides only 60 percent of the required protein[23]. Low pre-albumin levels indicate the need for nutritional assessment before surgery proceeds; clinicians recommend patients with pre-albumin levels less than 15.0 mg/dl receive a nutrition consult, while those with levels less than 10.9 mg/dl receive aggressive nutritional support[23-25]. Pre-albumin has been deemed superior to albumin as there is limited fluctuation in the plasma concentration due to hydration status change or acute changes in hepatic and renal function[23-25]. Thus, pre-albumin may be one of the earliest and most efficient laboratory indicators used as an assessment of an individual's nutrition status which remains cost-effective and objective[19,23].

Pre-albumin is a transport protein synthesized in the liver, partially catabolized by kidneys and sensitive to dietary changes, especially protein intake[23,26]. Its half-life of 2 days makes it relatively sensitive to short term changes in protein energy nutrition[23,26]. Pre-albumin is easily quantified in medical laboratories, cost-effective when included in standard of care preoperative lab tests and is an objective measure which can be applied to the general population[23]. Pre-albumin has one of the highest ratios of

essential to nonessential amino acids of any other protein in the body, making it one of the most distinct markers for protein synthesis[23]. Normal concentrations of pre-albumin range from 15-36 mg/dl, levels are not affected by hydration status like many other biomarkers; pre-albumin levels will briefly decrease in the presence of inflammation and immediately post-surgery[10,23,27]. Levels will also be chronically low in patients with certain conditions such as malignancy, cirrhosis, protein-losing enteropathy, and zinc deficiency; levels will be elevated in patients undergoing prednisone or progestational therapy[23]. A final limitation of the use of pre-albumin is the effect of binge drinking; the leakage of proteins from damaged hepatic cells may cause a brief rise in levels which will return to normal in a week after heavy drinking[23]. Although no universal standard exists in medical or research literature, pre-albumin is indicated as both a sensitive and cost-effective nutritional biomarker that can be used in identifying patients at increased risk for postoperative complications, prolonged hospital stays and, increased risk of morbidity[12,23,26].

Transferrin is similar to pre-albumin in its function as a marker of nutritional status[23]. Transferrin is a hepatic protein synthesized in the liver and acts as a transport protein for iron. The half-life of 8-10 days is slightly longer than pre-albumin which makes it less sensitive to short term changes in dietary intake[23,26]. Concentrations of transferrin are affected by liver disease, fluid status, and stress[26]. Normal concentrations of transferrin range from 200-360 mg/dl, levels normally do not decrease significantly except in the case of severe malnutrition; in monitoring for cases of mild malnutrition, pre-albumin is a superior biomarker[26]. Transferrin has not been studied as extensively as pre-albumin and other biomarkers. However, in one published study, a statistically significant relationship between serum transferrin and nutritional state has been reported, which may indicate that serum transferrin may be useful in epidemiologic studies[26,28].

Previously published research suggests an association exists between malnutrition status defined as serum albumin <3.5 mg/dl and the incidence of post-surgical complications[29-34]. However, there is little published data on nutrition status within the range of normal and the risk of complications in patients specifically undergoing spine surgery[14,31,34]. Nutrition status in spine surgery patients should be of

heightened concern as the population is often older, at greater level of physical disability, and undergo very complex surgeries[2,35].

To further evaluate the pre-surgical biomarkers and risk of complications we conducted a retrospective cohort study of adults aged 50 and over undergoing elective spine surgery over the course of 12 months. Medical centers that serve diverse populations are continually looking for strategies to optimize surgical results, improve long term patient outcomes and minimize cost of care. Examining the blood biomarkers pre-albumin and transferrin and understanding these are largely within a normal range, clinicians are now interested if there is an optimal physiologic state for patients prior to undergoing spine surgery. In other words, within this normal range, is the nutrition status of their older patient population associated with 30-day risk of medical complication. We hypothesized that patients with lower levels of pre-albumin and transferrin would have an increased risk of complication within 30 days of their surgery compared to those with higher levels of the biomarkers.

METHODS

Data Sources

Over the last year, pre-albumin and transferrin serum values have been systematically collected on patients 50 years and older electing to receive spine surgery, providing a growing database to evaluate our hypothesis. These newly collected values will aid in determining whether lower levels of pre-albumin and transferrin, used as markers of protein-energy nutrition, are associated with an increased risk of 30 day complication. We performed a retrospective cohort study by way of medical record review of the patients of four primary spine surgeons at the Oregon Health & Science University (OHSU) Spine Center. Prior to conducting any study procedures, the study protocol and procedures were reviewed and approved by the OHSU Institutional Review Board.

By querying an electronic medical record (EMR) system, all patients undergoing spine surgery were reviewed for inclusion into the cohort; primary inclusion criteria were age at admission 50 years or greater, one of four spine surgeons, and date of surgery between June 1, 2013 and June 1, 2014. The query returned 442 subjects and generated the following variables: patient name, medical record number (MRN), gender, date of birth, American Society for Anesthesiologist (ASA) score, preoperative medicine clinic visit date, primary diagnosis International Statistical Classification of Diseases (ICD) code and name, surgery type, and trauma status.

A second query was created to pull a sequential list of completed preoperative visits with the OHSU Spine Center physician assistants and clinicians. OHSU MRN, patient name, age, visit date, completed visit status, department name, primary provider, and visit type were documented from this report. The initial and secondary queries were then cross checked; any individual with a completed preoperative visit with a missing surgery date was excluded from the cohort due to the cancelled surgery. A total of 15 individuals cancelled their surgeries. Reasons for cancellation: failed nicotine screens,

incomplete bloodwork, cardiovascular issues, and at the request of the patient; none of the 15 cancellations were due to nutrition concerns.

From the case list, surgeries marked trauma, urgent, or not logged were reviewed individually for inclusion into the study; in addition, authors reviewed each primary diagnosis ICD description. Non-traumatic, non-urgent, non-infection and non-cancerous elective surgeries were included for further analysis. In total, exclusions included 60 emergency department admissions and hospital transfers, 17 cancer or tumor patients, and 11 infection patients.

Ascertainment of Patient Independent Variables

The authors manually abstracted all demographic, preoperative health status data, surgical data, and hospital data from the EMR system. The primary author, the master of public health (MPH) candidate, created an abstraction manual complete with screen shots, location of data, and hierarchy of availability and proceeded to train the individual abstracting all independent and exposure variables (Appendix A). Subjects were coded with a unique numerical identifier which was then used for data abstraction onto paper data collection forms. Patient identifying information, including name and MRN were stored in a separate protected file. Upon completion of all data collection onto paper forms, data was then entered into the electronic database.

To verify reliability of data, authors took a random 10% sample of the cohort and re-abstracted data. 50 primary variables were selected and entered into the database to be cross-checked with the data initially collected. The final percent concordance was =98%.

Demographic data collected were age, gender, race, marital status, years of education, and occupational status. Preoperative health status variables collected from the pre-operative clinic visit were smoking status, alcohol status, illicit drug use, height, weight, body mass index (BMI), blood pressure, resting heart rate, temperature, oxygen levels, temperature, primary diagnosis, comorbidities, past surgical

history, medication use, complete blood chemistry (CBC) panel, metabolic blood panel, hemoglobin A1C, and ASA grade. Surgical data variables collected from the operative and anesthesia notes included surgeon, surgical approach, number of stages, anesthesia time, operative time, estimated blood loss, number of blood products transfused, amount of fluids transfused, and number of vertebral levels operated on. Finally, collected hospital stay data were length of intensive care unit (ICU) stay and length of hospital stay. Primary exposure variables pre-albumin and transferrin were abstracted from the medical record at this time.

Ascertainment of Outcome Data

Two authors (including the MPH candidate) conducted a second independent chart review of the patient cohort and abstracted complications data (Appendix B). The authors compiled a list of major and minor medical complications likely to occur in this patient population, including wound problems, infections, morbidity, and mortality (Appendix C). Using a standardized method, the authors assessed the cohort for operative and postoperative complications, including during the hospital stay and from discharge through thirty days post-surgery. This review included any major intraoperative complication noted in the surgeon or anesthesiologist record. Hospital stay data variables included presence or absence of major or minor medical complication and finally postoperative data variables were collected from office follow-up notes with clinical staff as well as telephone calls. Upon completion of the chart review, all complications were reviewed by a third author, a board certified orthopaedic surgeon, for correct classification and confirmation. All reviewers were blinded to pre-albumin and transferrin quartile classification at the time of outcome ascertainment. Complications treated outside of OHSU could contribute to loss to follow-up bias. One way in which we aimed to decrease this bias was by reviewing phone calls made to and from OHSU clinicians within the 30 day assessment window. Furthermore, Spine Center standard of care practices mandate every surgical patient to schedule a six-week postoperative appointment. In the review of the cohort, only two patients did not return to or communicate with care staff at OHSU.

Statistical Analysis

Upon completion of independent variable collection, subjects were submitted to final inclusion/exclusion criteria. In an attempt to standardize exposure variables, authors excluded any bloodwork performed by non-OHSU laboratories. Patients who brought outside bloodwork, completed their preoperative visit via phone call, or had bloodwork from a previous surgery were all excluded from further analysis. Moreover, subjects' missing primary exposures values (pre-albumin and transferrin) were excluded from final analysis. Additionally, those patients who only underwent cervical spine surgery were considered to be a distinct surgical population and not included in this analysis. For those patients who underwent multiple surgeries within the 12 month study period, only the initial surgery was included in the cohort which led to excluding 10 additional patients. Lastly, patients without 30 day follow-up were excluded from final analysis, leaving a total of 211 subjects for analysis. A detailed version of the complete creation of the analytic cohort can be found in Figure 1.

Descriptive statistics and distributions of the exposure variables pre-albumin and transferrin were examined. Upon review of the distribution of primary exposure variables, pre-albumin and transferrin were summarized using quartiles. Pre-albumin quartile cutoffs were 24.0, 27.2, and 30.7 mg/dl; transferrin quartile cutoffs were 240.0, 263.0, and 292.0 mg/dl. Pre-albumin levels varied between 12.9 and 47.9 mg/dl while transferrin levels varied between 168.0 and 503.0 mg/dl. Quartile 1 corresponds to the lowest levels of pre-albumin and transferrin and quartile 4 corresponds to the highest levels of variables. As both pre-albumin and transferrin are markers of PEM, we examined the correlation between the two biomarkers. Additionally, we examined the correlations amongst preoperative and perioperative independent variables that had a continuous form.

Descriptive analyses were performed on all independent variables to examine distributions and normality. Continuous normally distributed variables were described as mean and standard deviations while non-normal variables were described as median values. Categorical variables were described by

frequencies. Among the four quartiles, the difference in proportions of categorical independent variables was examined and chi-square test was performed for each variable. For continuous independent variables, one-way analysis of variances for multiple means was performed.

For multivariate analysis, age was categorized as 50-59 years, 60-69 years, and 70 and older. Body mass index status was categorized as obese, BMI greater than 30.0 kg/m^2, versus non-obese, BMI less than 29.9 kg/m^2. Marital status was categorized as single or married/domestic partner. Smoking status was categorized as not current smoker, current smoker, or former smoker, alcohol status was similarly classified as no current use, current use, or unknown. ASA score was classified as ASA score 1 & 2 versus ASA score 3 & 4. Systolic blood pressure was categorized as normal: systolic pressure less than 120mm Hg, pre-hypertension 120-139 mm Hg, and high blood pressure greater than 140 mm Hg. Number of surgical levels fused was categorized as no fusion, 1 level fused, 2-3 levels fused, and 4 or more levels fused. The outcome variable was categorized as a binary variable, 0 for no complication versus 1 for yes complication and measured by cumulative incidence over 30 days. Using binary variables for biomarkers pre-albumin and transferrin, risk of complication for patients with biomarker levels above the median value was compared to the risk of complication for patients with biomarker levels below the median value. The relation between the biomarkers and risk of complications was assessed using log-binomial regression, pre-albumin and transferrin risk ratios (RR) and 95% confidence intervals were estimated.

In order to identify variables associated with any complication and biomarker level, patient preoperative and perioperative characteristics were compared across pre-albumin and transferrin quartile and across the percentages of complication using one-way analysis of variance (ANOVA) for continuous variables and Pearson chi-square test for categorical variables. Variables assessed as confounders of the association between biomarker level and complication in this model were gender, age, BMI, blood pressure, ASA score, history of previous spine surgery, number of levels fused, spine fusion, perioperative blood transfusion, number of stages, total anesthesia time, and total length hospital stay.

The potential confounding variables were introduced into a regression model containing pre-albumin and transferrin where the change in risk ratio was assessed. If the RR estimates changed by at least 10% from the unadjusted model, the variable was considered a confounder and considered for retention in the final. In using this method, BMI and the number of levels fused were found to most confound the relationship between biomarker level and complication. Upon the addition of other independent variables into the multivariate model containing BMI and levels fused, the RR estimates of pre-albumin and transferrin did not change by more than 10%. Finally, we proceeded to introduce the independent variables gender, age, and ASA score, and found the RR estimates were largely unchanged. However, given the clinical importance of these variables, the final model included the variables BMI, levels fused, gender, age, and ASA score.

All analyses were performed using SAS ® software, Version 9.4 of the SAS System for OHSU (Cary, NC).

RESULTS

The final study cohort included 108 males (51%) and 103 females (49%) with a mean age of 65 (±9) years. Those adults in the lowest pre-albumin quartile (Q1, mean level 20.7 mg/dl) tended to be older, male, have a higher ASA score, and were also more likely to receive a perioperative blood transfusion as compared to those in highest pre-albumin quartile (Q4, mean level 34.7 mg/dl). Those adults in the lowest transferrin quartile (Q1, mean level 215.5 mg/dl) were significantly older, female, had a lower BMI, and lower blood pressure as compared to those in the highest transferrin quartile (Q4, mean level 322.9 mg/dl). All other demographic and perioperative characteristics were statistically similar between quartiles of pre-albumin and transferrin. Pre-albumin preoperative and perioperative characteristics are presented in Table 1 and Table 2, respectively. Transferrin preoperative and perioperative characteristics are presented in Table 3 and Table 4, respectively.

In the cohort of 211 patients, thirty-two experienced at least 1 postoperative complication. Over the 30 day time period, the cumulative incidence of complication in elective spine surgery patients was 15.2% (95% CI: 10.3%-20.0%). The most common complications were minor urinary tract infections (8 patients, 3.8%), delirium (7 patients, 3.3%), and blood loss greater than 4000mL (7 patients, 3.3%) (Figure 4). The incidence of postoperative complications was compared amongst biomarker quartiles. A similar number of patients experienced at least one complication amongst the pre-albumin quartiles (Figure 5). Similarly, a comparable number of patients experienced at least one complication amongst the transferrin quartiles (Figure 5). Those in the lowest quartile of pre-albumin experienced 6 complications (12%), patients in quartile 2 experienced 10 complications (19%), patients in quartile 3 experienced 11 complications (21%), and those in the highest quartile of pre-albumin experienced a total of 5 complications (9%). Patients in the lowest quartile of transferrin experienced 6 complications (12%), patients in quartile 2 experienced 8 complications (15%), patients in quartile 3 experienced 7 complications (13%), and those in the highest quartile of transferrin experienced a total of 11 complications (21%). Because the proportions with complications were similar in the bottom two and the

top two quartiles, we used the binary categorization (above the median, median or below) for the remaining analyses.

A separate univariate analysis was conducted to assess associations between having a major medical complication and potential pre- and perioperative characteristics. The risk of any complication varied according to patient BMI, ASA score and whether they had a previous spine surgery (yes/no) (Appendix D). Risk of complications amongst perioperative characteristics varied according to the number of vertebral levels fused, spine fusion (yes/no), transfusion (yes/no), the number of stages, anesthesia time, and the length of total stay. All other demographic, comorbidities, and surgical characteristics did not differ by a significant amount. Given that many operative variables are proxies for the length and complexity of the surgical procedures, many of the variables were highly correlated with one another. Pearson correlation coefficients confirmed the strong relationships between anesthesia time with the number of levels fused ($r=0.71$, $p<0.0001$) and total length of stay ($r=0.74$, $p<0.0001$). Additionally, the number of levels fused was strongly correlated with length of total stay ($r=0.61$, $p<0.0001$). Given the collinearity of several of the surgical variables, variables will be introduced into separate models to assess the change in RR estimates as to create the most robust model and to avoid over fitting the model.

Table 5 presents the results of the log-binomial regression models, using any complication as the outcome variable and pre-albumin and transferrin as the exposure variables. The first model included only pre-albumin, the unadjusted relative risk of any complication was 0.99 (95% CI: 0.5-1.9), the second model included only transferrin, the unadjusted relative risk of any complication was 1.27 (95% CI: 0.7-2.5). In a mutually adjusted model containing primary exposure variables, transferrin and pre-albumin, the pre-albumin RR estimate was 0.97 (95% CI: 0.7-1.3) and the transferrin RR estimate was 1.29 (95% CI: 0.7-2.4). When adjusted for BMI (obese vs. non-obese) and number of levels fused (no fusion, 1 level fused, 2-3 levels, ≥4 levels), the pre-albumin RR estimate of any complication was 1.1 (95% CI: 0-8-1.5) and the transferrin RR estimate was 1.1 (95% CI: 0.8-1.5). Introducing ASA score, gender and age into

the model containing pre-albumin, transferrin, BMI, and levels fused, the risk of complication occurring in the 30 days following elective spine surgery remained essentially unchanged near the null value of 1.0. To test for a trend in the association of the biomarkers and complication risk, we reran the foregoing analysis after replacing the categorical variables for pre-albumin and transferrin with the continuous variable for each. Consistent with the results in Table 5 there was no association of either biomarker and 30 day risk of complication. The RR (95% CI) for a unit change in pre-albumin was 1.0 (0.94-1.07) (p-trend=0.98) and for transferrin was 1.0 (0.99-1.01) (p-trend=0.50).

Finally, we compared the analytic cohort of 211 patients to the 33 patients who underwent elective thoracic, thoracolumbar, or lumbar surgery who were subsequently missing the exposure variables, pre-albumin and transferrin. All preoperative and perioperative characteristics were compared between the two groups, no characteristics significantly differed between the patient groups. For those patients missing exposure variables, the overall cumulative incidence of complication was 15.2% (95% CI: 2.9%-27.4%), nearly identical to that among the 211 patients comprising the analytic cohort. The results suggest that excluding the patients missing the biomarker variables likely did not introduce any form of selection bias.

DISCUSSION

In this retrospective cohort study of 211 elective spine surgery patients aged 50 years and older, we found that preoperative nutrition, as defined by biomarkers pre-albumin and transferrin was not an independent risk factor for medical complication within 30 days. Pre-albumin and transferrin are both established biomarkers of total body protein, and low levels of both have been previously associated with postoperative morbidity and mortality[19,23]. In our multivariate log-binomial regression model of association between complication and biomarker level, with clinical covariates chosen from the univariate analysis, neither low levels of preoperative transferrin or pre-albumin demonstrated an increased risk in complication. In multivariate models, there was virtually no difference in risk of complications between those with high versus low pre-albumin and those with high versus low transferrin. Despite the relatively small sample size and low incidence of medical complications occurring within 30 days postoperatively, this study's results still provide us information about nutrition status within the normal range and its association with risk of medical complication following elective spine surgery.

Adogwa et al found albumin to be a significantly associated with postoperative complication following elective spine fusion but not in traumatic or neoplastic spine cases[14]. Klein et al found a significant relationship between nutritional status, as measured by total lymphocyte count and serum albumin, and postoperative complications in patients undergoing elective lumbar fusion[36]. Schoenfeld et al reported serum albumin 3.5 g/dl or less to be associated with both mortality and complications in their study of 5887 patients after spinal arthrodesis[31]. Additionally, van Stijn reviewed several studies among general surgical patients and concluded that preoperative serum albumin <3.5 mg/dl may be associated with patients at higher risk of postoperative complications[7]. However, it is difficult to compare the existing literature as authors report solely on serum albumin as primary exposure variable whereas the current study used pre-albumin, for its ability to reflect more short term change in a patient's nutrition status, in addition to the measure being less subject to influence by hydration status and liver or kidney function. Moreover, these studies specifically examined a small number patients who were clinically

malnourished as defined by serum albumin <3.5 mg/dl whereas we studied pre-albumin within a normal range. There are no current publications evaluating pre-albumin and transferrin and the incidence of postoperative complications in spine surgery patients. Lourenco et al found low pre-albumin to be independently associated with morbidity and mortality in patients after an acute heart failure episode[20]. Several studies suggest pre-albumin as a useful tool in the assessment of poor nutrition and suggest it is associated with increased morbidity and mortality, but surprisingly none report on spine surgery specifically[20,37-39].

There were several limitations to this study that are worth noting. Given the retrospective nature of the design, we were limited to data recorded in the medical record. Several anthropometric variables were not consistently recorded or were poorly measured. Data on race, drug use, smoking status and level of alcohol use are not consistently or routinely collected as part of standard of care practices which limit our ability to adequately understand the impact of certain demographic characteristics on biomarker level and risk of complication. However, with the data available these variables were not found to confound the relationship between biomarker and risk of complication, it is highly unlikely that any of these variables are strong enough negative confounders to mask an actual association. A further limitation introduced by using data available in the EMR, is that the ascertainment of complications was limited to those who returned to OHSU for treatment of complication or who reported the complication in follow-up visits. It is possible that medical complications were treated elsewhere and were not captured. However, the short follow-up period limited the risk of patients leaving the area or seeking treatment elsewhere; only two patients did not return to OHSU or communicate with clinicians in the specific follow-up period.

Finally, the time frame in which pre-albumin and transferrin were routinely collected on all elective surgical patients was relatively short. Recent changes to clinic practices provided only 12 months' worth of data to evaluate the hypothesis of interest. Larger sample sizes over longer periods of time may allow for additional conclusions to be drawn and more robust statistical inferences to be made. Additionally, due to the small number of types of complications that occurred, for analysis purposes, all types of

complications were collapsed into a single group. Thus, a large amount of information is lost due to the diverse nature of complications studied in this cohort. Certain medical complications may be more closely related to nutrition status than others. Wound healing was of special interest, but a total of 8 wound complications precluded our ability to analyze this group separately. Generalizability may also be limited given the nature of a single center study, although as a public hospital, a diverse group of patients seek treatment. Despite these limitations we were able to draw conclusions on nutrition status and risk of complication within 30 days following elective spine surgery.

Future studies should consider a larger sample size and a more diverse cohort of patients, perhaps from multiple medical centers. Additionally, a prospective cohort study in which independent and outcome variables are collected prospectively would be a more ideal design to examine associations of nutritional biomarkers and risk of complication. Finally, given the number of studies citing the positive association between serum albumin and the risk of complication, an additional study utilizing the same patient cohort to examine serum albumin's association with 30 day risk of complications could potentially add to the body of previously published studies. Serum albumin, with a half-life of 20 days, may be reflective of longer term nutrition; whereas serum pre-albumin would reflect more recent protein intake. Thus it is of interest to explore both this association of serum albumin with the risk of complication in this patient population as well as the discordance between serum albumin and serum pre-albumin.

Elective spine surgery encompasses a diverse group of surgical procedures in regards to complexity, length, and expected outcomes. Given the high vascularization and the limited invasiveness of cervical spine procedures, we excluded patients whose primary operation occurred in the cervical spine[40]. By including all thoracic, thoracolumbar, and lumbar spine surgeries, the heterogeneous sample is strongly representative of the diversity found in the elective spine surgical field. Among this elective patient population, there was very little burden of malnutrition, and outcomes were studied within the range of normal nutrition status. These findings suggest that within the normal range of nutrition, as determined by pre-albumin and transferrin, there is no increased risk of postoperative complication within

30 days following elective spine surgery. In light of the previously published literature in support of serum albumin as prognostic tool for nutrition status, and given that serum albumin is a standard part of most chemistry blood panels, the cost of these additional biomarker labs may not be warranted. Additionally, pre-albumin and transferrin may not provide any additional information regarding nutrition status that is not already available in standard CBC and chemistry panels. However, the information provided in this study provides invaluable perspective for surgeons in evaluating their surgical patient population; while the physiologic state of elective surgical candidates widely varies, especially in regards to nutrition status, this study shows that among this normal variation there is no excess risk of medical complication within 30 days postoperatively.

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Figure Titles

Figure 1

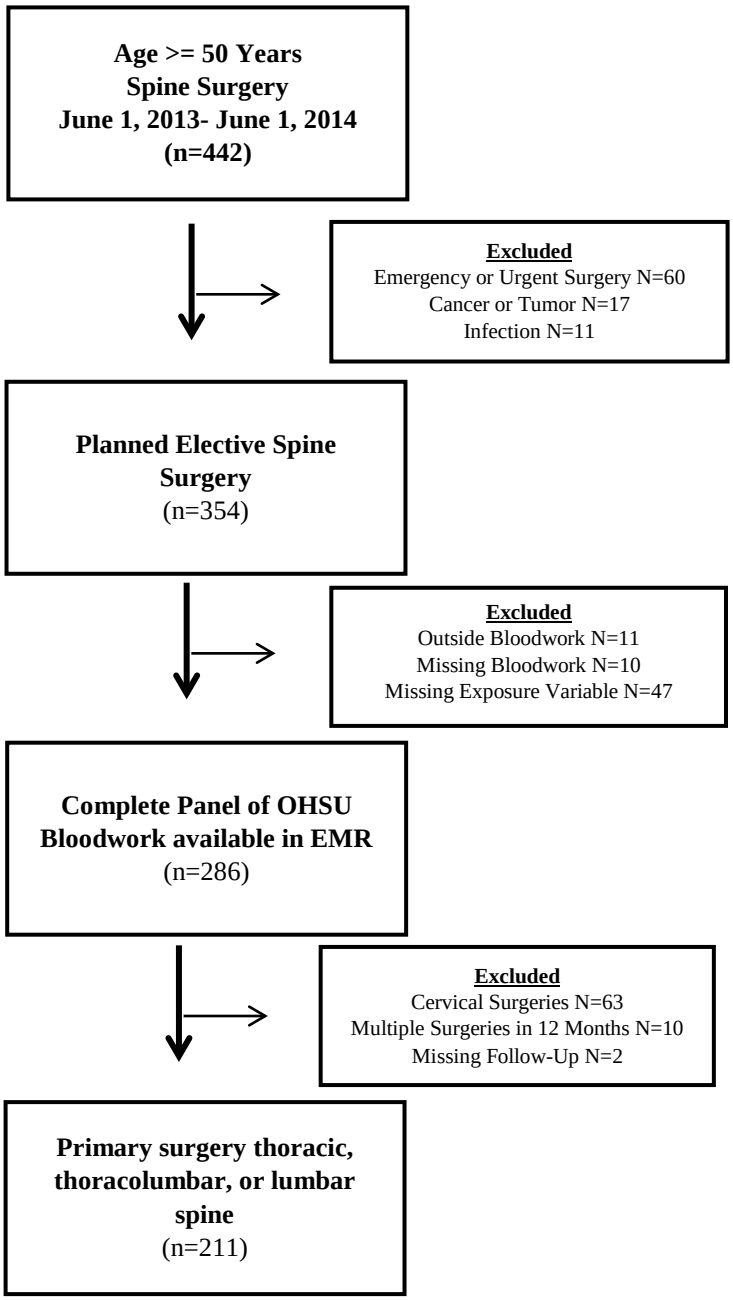

Age >= 50 Years
Spine Surgery
June 1, 2013- June 1, 2014
(n=442)
Excluded
Emergency or Urgent Surgery N=60
Cancer or Tumor N=17
Infection N=11
Planned Elective Spine Surgery
(n=354)
Excluded
Outside Bloodwork N=11
Missing Bloodwork N=10
Missing Exposure Variable N=47
Complete Panel of OHSU Bloodwork available in EMR
(n=286)
Excluded
Cervical Surgeries N=63
Multiple Surgeries in 12 Months N=10
Missing Follow-Up N=2
Primary surgery thoracic, thoracolumbar, or lumbar spine
(n=211)

Figure 2

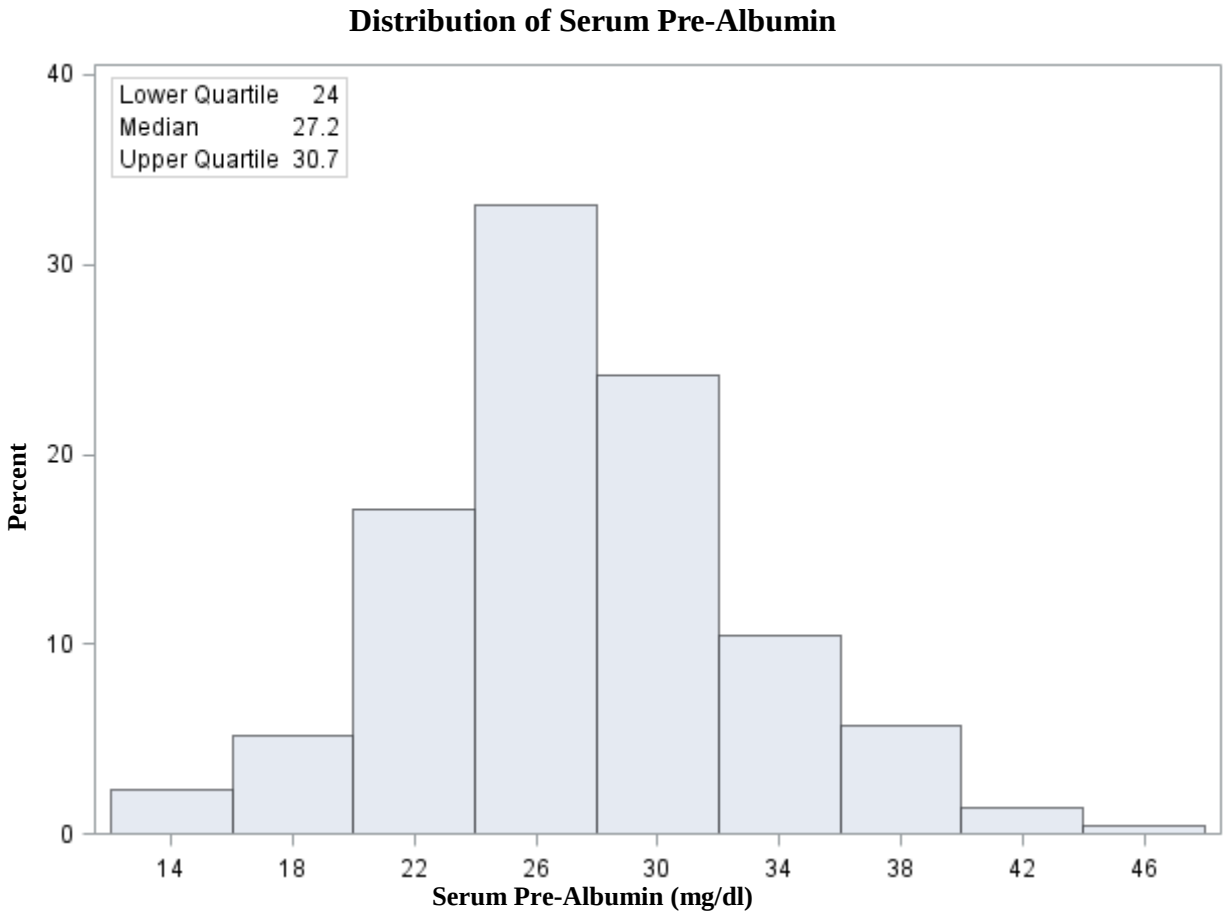

Distribution of Serum Pre-Albumin
Lower Quartile 24
Median 27.2
Upper Quartile 30.7
Percent
0
10
20
30
40
14
18
22
26
30
34
38
42
46
Serum Pre-Albumin (mg/dl)

Figure 3

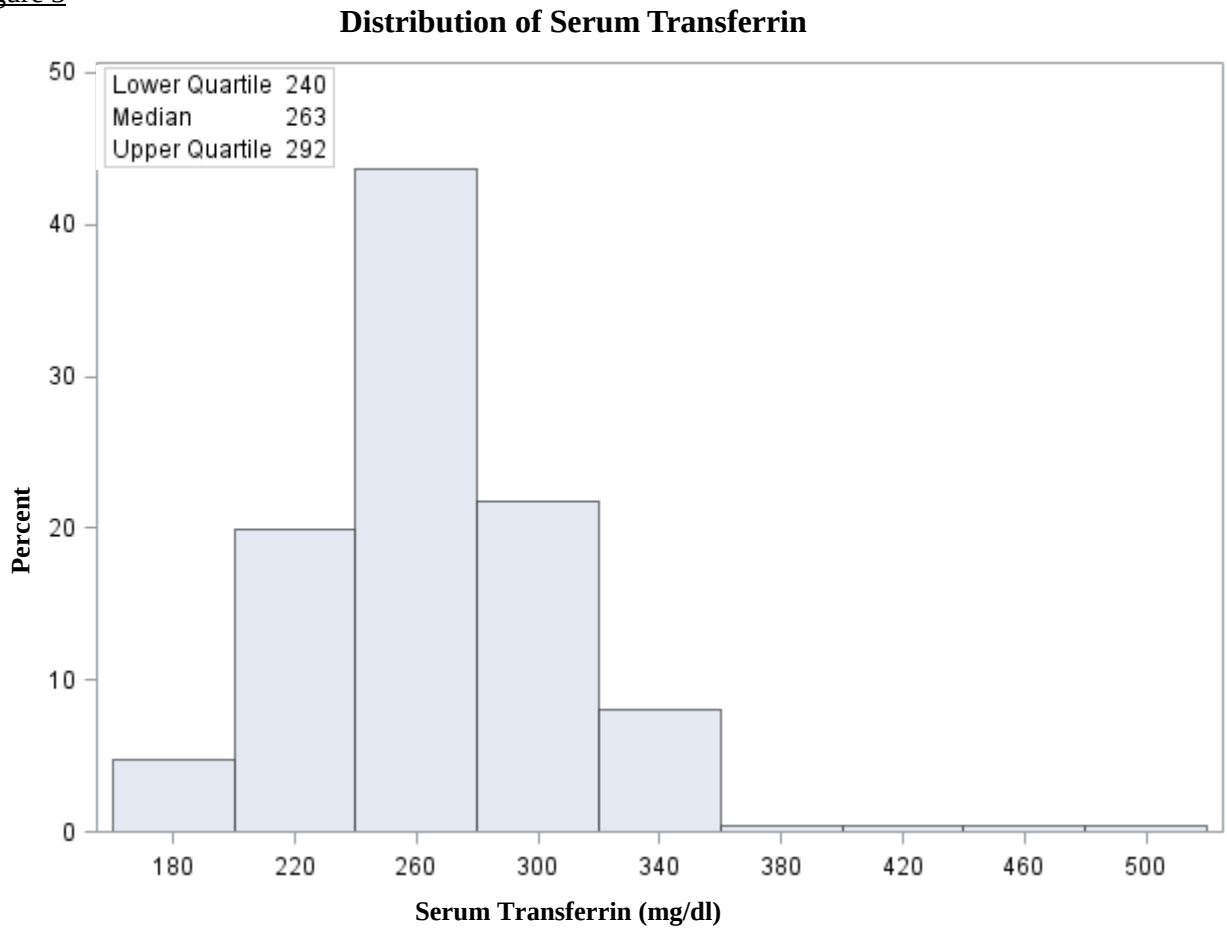
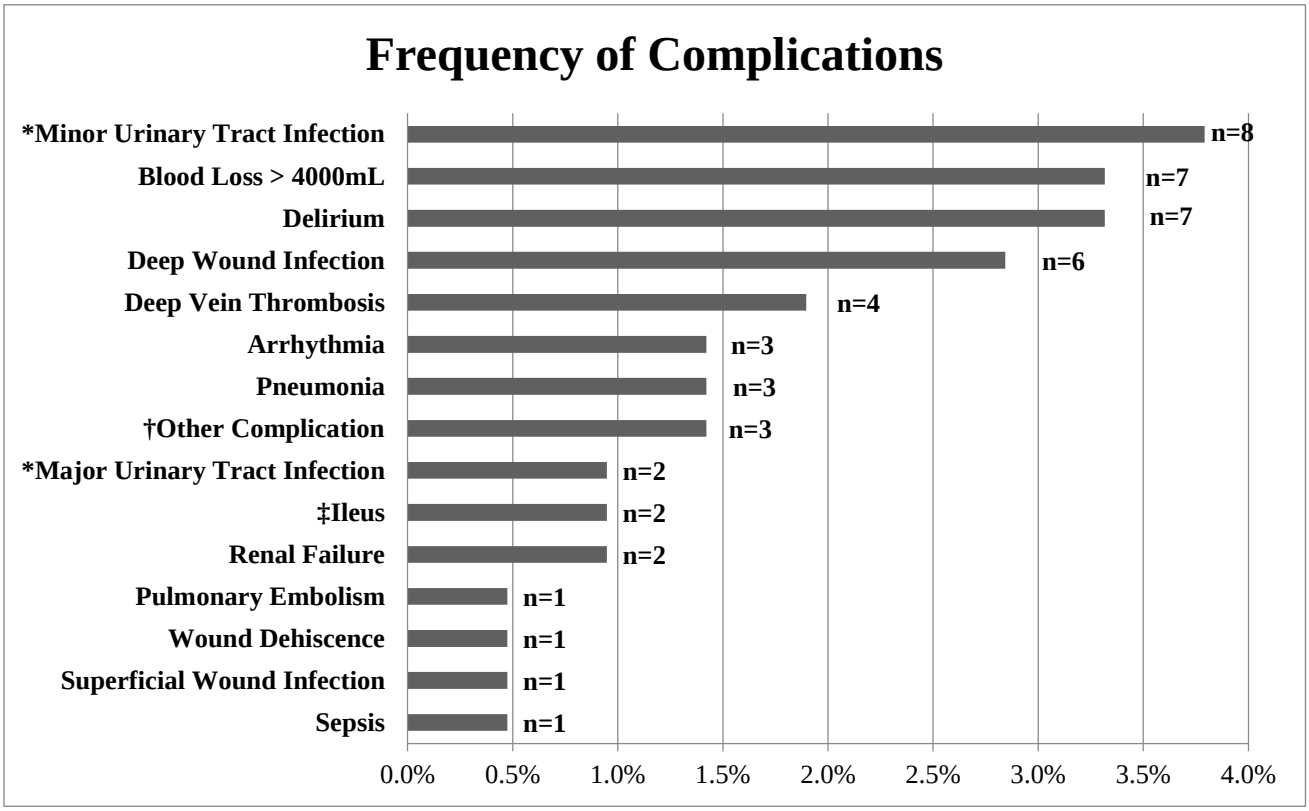

Distribution of Serum Transferrin
Lower Quartile 240
Median 263
Upper Quartile 292
Percent
50
40
30
20
10
0
180
220
260
300
340
380
420
460
500
Serum Transferrin (mg/dl)

Figure 4



*Major UTI altered the course of hospital stay or developed into further condition; minor UTI requires basic antibiotic treatment

†Other complications: cardiac rhythm anomaly requiring conduction block & pacemaker; unplanned return to ICU for hypertension; rhabdomyolysis

‡ Ileus: blockage of the intestine caused by a lack of peristalsis altering course of hospital stay

Figure 5

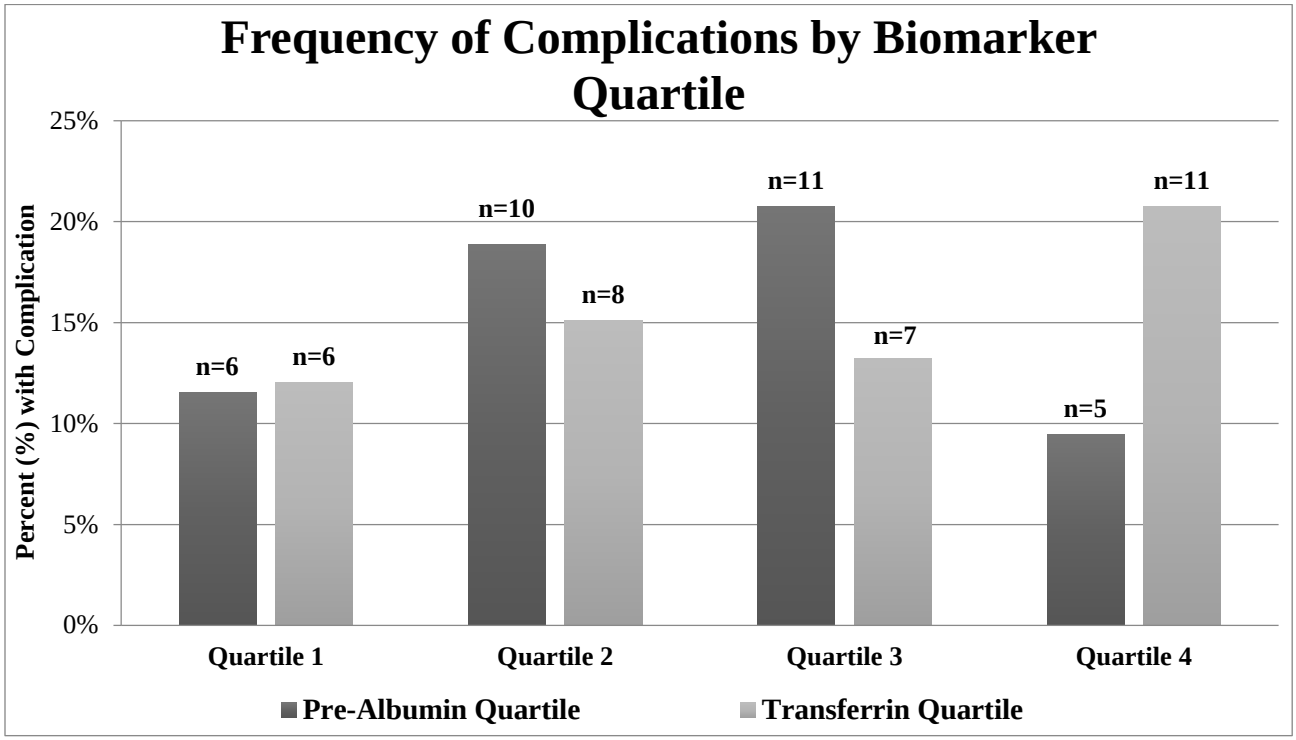

Frequency of Complications by Biomarker Quartile
Percent (%) with Complication
25%
20%
15%
10%
5%
0%
n=6
n=6
n=10
n=8
n=11
n=7
n=5
n=11
Quartile 1
Quartile 2
Quartile 3
Quartile 4
Pre-Albumin Quartile
Transferrin Quartile

Table 1: Distribution of Preoperative Characteristics among 211 Adult Elective Spine Surgery Patients According to Pre-Albumin Quartile 2013-2014*

	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	
Pre-Albumin (mg/dl; mean ± SD)	20.70±2.8	25.5±0.90	28.9±1.1	34.7±3.5	
Pre-Albumin (mg/dl; range)	(12.9-23.8)	(24.0-27.1)	(27.2-30.6)	(30.7-47.9)	
Number	52	53	53	53	***P***
Age at Admission (mean ± SD)	66.8±8.0	66.2±7.7	62.6±9.5	65.5±8.8	*0.05*[a]
Age 50-59	11 (19)	11 (19)	22 (37)	15 (25)	*0.25*[b]
Age 60-69	21 (26)	22 (27)	17 (21)	22 (27)	
Age 70+	20 (29)	20 (29)	14 (20)	16 (23)	
Gender					*<0.01*[b]
Male (n, %)	36 (33)	27 (25)	26 (24)	19 (18)	
Female (n, %)	16 (16)	26 (25)	27 (26)	34 (33)	
Current BMI in kg/m^2 (mean ± SD)	31.7±7.3	31.8±6.8	31.7±6.7	29.5±5.6	*0.18*[a]
Normal; BMI: 18.5-24.9 (n, %)	8 (23)	7 (20)	8 (23)	12 (34)	*0.86*[b]
Overweight; BMI: 25.0-29.9(n, %)	18 (23)	20 (26)	19 (25)	20 (26)	
Obese; BMI: ≥30.0 (n, %)	26 (26)	26 (26)	26 (26)	21 (21)	
Marital Status					*0.60*[b]
Single (n, %)	17 (30)	15 (27)	12 (21)	12 (21)	
Married/Domestic Partner (n, %)	34 (23)	37 (25)	38 (25)	41 (27)	
Smoking Status					*0.48*[d]
Not Current Smoker (n, %)	25 (26)	22 (23)	21 (22)	28 (29)	
Current Smoker (n, %)	6 (26)	3 (13)	7 (30)	7 (30)	
Former Smoker (n, %)	21 (23)	28 (31)	24 (26)	18 (20)	
Alcohol Status					*0.13*[b]
No Current Use (n, %)	28 (30)	23 (25)	24 (26)	17 (18)	
Current Use (n, %)	17 (19)	26 (30)	18 (20)	27 (31)	
Unknown (n, %)	7 (23)	4 (13)	11 (35)	9 (29)	
ASA Score*					*0.05*[b]
Scores 1 & 2 (n, %)	17 (17)	25 (25)	31 (31)	28 (28)	
Scores 3 & 4 (n, %)	35 (32)	28 (25)	22 (20)	25 (23)	
Systolic Blood Pressure (mean ± SD)	131.2±16.1	130.4±15.9	133.2±19.3	135.3±18.9	*0.48*[a]
Systolic BP < 120 mm Hg (n, %)	14 (29)	14 (29)	8 (16)	13 (27)	*0.54*[b]
Systolic BP: 120-139 mm Hg (n, %)	22 (24)	25 (28)	24 (27)	19 (21)	
Systolic BP>140 mm Hg (n, %)	16 (22)	14 (19)	21 (29)	21 (29)	
Previous Spine Surgery					*0.40*[b]
No (n, %)	20 (21)	23 (24)	25 (26)	29 (30)	
Yes (n, %)	32 (28)	32 (26)	28 (25)	24 (21)	

[a]*P-value using one-way analysis of variance*

[b]*P-value using chi-squared test*

[c]*P-value using Kruskal-Wallis one-way analysis of variance*

[d]*P-value using Fisher's exact test*

**Patient cohort includes 211 people ages 50-89 years who underwent elective spine surgery between June 2013 and June 2014 at Oregon Health & Science University in Portland, Oregon*

Table 2: Distribution of Perioperative Characteristics among 211 Adult Elective Spine Surgery Patients According to Pre-Albumin Quartile 2013-2014*

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Pre-Albumin (mg/dl; mean ± SD)	20.70±2.8	25.5±0.90	28.9±1.1	34.7±3.5	
Pre-Albumin (mg/dl; range)	(12.9-23.8)	(24.0-27.1)	(27.2-30.6)	(30.7-47.9)	
Number	52	53	53	53	***P***
Number of Levels Fused (mean ± SD)	3.0 ± 4.1	2.2 ± 3.3	2.1 ± 3.0	1.9 ± 3.2	*0.38*[c]
No Spine Fusion (n, %)	14 (23)	18 (30)	8 (13)	21 (34)	*0.06*[b]
1 Level Fusion (n, %)	13 (18)	14 (20)	26 (37)	18 (25)	
2-4 Level Fusion (n, %)	12 (29)	11 (26)	12 (29)	7 (17)	
4+ Levels Fusion (n, %)	13 (35)	10 (27)	7 (19)	7 (19)	
Surgical Approach					*0.29*[d]
Posterior Only (n, %)	39 (23)	47 (27)	41 (24)	46 (27)	
Anterior Only (n, %)	1 (100)	0 (0)	0 (0)	0 (0)	
Anterior-Posterior (n, %)	12 (32)	6 (16)	12 (32)	7 (19)	
Number of Stages					*0.16*[d]
One (n, %)	46 (23)	50 (25)	52 (26)	51 (26)	
Two (n, %)	6 (50)	3 (25)	1 (8)	2 (17)	
Estimated Blood Loss					*0.29*[c]
Total Milliliters (median)	500.0	375.0	400.0	350.0	
Blood Transfusion					*0.10*[b]
No (n, %)	36 (21)	45 (27)	46 (27)	42 (25)	
Yes (n, %)	16 (38)	8 (19)	7 (17)	11 (26)	
Length of Hospital Stay;					*0.37*[c]
Total days (median)	4.0	3.0	3.0	3.0	
Anesthesia Time					*0.14*[c]
Total hours (median)	5.1	4.4	4.6	3.9	

[a]*P-value using one-way analysis of variance*

[b]*P-value using chi-squared test*

[c]*P-value using Kruskal-Wallis one-way analysis of variance*

[d]*P-value using Fisher's exact test*

**Patient cohort includes 211 people ages 50-89 years who underwent elective spine surgery between June 2013 and June 2014 at Oregon Health & Science University in Portland, Oregon*

Table 3: Distribution of Preoperative Characteristics among 211 Adult Elective Spine Surgery Patients According to Transferrin Quartile 2013-2014*

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Transferrin (mg/dl; mean ± SD)	215.5±16.8	250.0±6.7	275.1±8.0	322.9±39.2	
Transferrin (mg/dl; range)	(168-239)	(240-262)	(263-291)	(292-503)	
Number	52	53	53	53	***P***
Age at Admission (mean ± SD)	66.7±8.1	67.2±8.9	65.3±9.2	61.6±7.4	*<0.01*[a]
Age 50-59	11 (17)	12 (20)	14 (24)	23 (39)	*0.05*[b]
Age 60-69	23 (28)	18 (22)	21 (26)	20 (24)	
Age 70+	19 (27)	23 (33)	18 (26)	10 (14)	
Gender					*0.07*[b]
Male (n, %)	20 (19)	25 (23)	33 (31)	30 (28)	
Female (n, %)	32 (31)	28 (27)	20 (19)	23 (22)	
Current BMI in kg/m^2 (mean ± SD)	30.0±6.4	29.9±6.4	31.9±7.2	32.4±6.5	*0.13*[a]
Normal; BMI: 18.5-24.9 (n, %)	10 (29)	9 (26)	11 (31)	5 (14)	*0.02*[b]
Overweight; BMI: 25.0-29.9(n, %)	22 (29)	26 (34)	10 (13)	19 (25)	
Obese; BMI: ≥30.0 (n, %)	20 (20)	18 (18)	32 (32)	29 (29)	
Marital Status					*0.61*[b]
Single (n, %)	12 (21)	15 (27)	12 (21)	17 (30)	
Married/Domestic Partner (n, %)	40 (27)	37 (25)	39 (26)	34 (23)	
Smoking Status					*0.36*[d]
Not Current Smoker (n, %)	27 (28)	19 (20)	23 (24)	27 (28)	
Current Smoker (n, %)	5 (22)	4 (17)	8 (35)	6 (26)	
Former Smoker (n, %)	20 (22)	30 (33)	22 (24)	19 (21)	
Alcohol Status					*0.73*[b]
No Current Use (n, %)	19 (21)	25 (27)	24 (26)	24 (26)	
Current Use (n, %)	26 (30)	18 (20)	23 (26)	21 (24)	
Unknown (n, %)	7 (23)	10 (32)	6 (19)	8 (26)	
ASA Score*					*0.30*[b]
Score 1 & 2 (n, %)	29 (29)	28 (28)	23 (23)	21 (21)	
Scores 3 & 4 (n, %)	23 (21)	25 (23)	30 (28)	32 (29)	
Systolic Blood Pressure (mean ± SD)	127.8±16.4	131.6±17.6	137.0±18.0	133.7±17.5	*0.05*[a]
Systolic BP < 120 mm Hg (n, %)	16 (33)	12 (24)	10 (20)	11 (22)	*0.13*[b]
Systolic BP: 120-139 mm Hg (n, %)	23 (26)	27 (30)	17 (19)	23 (26)	
Systolic BP>140 mm Hg (n, %)	13 (18)	14 (19)	26 (36)	19 (26)	
Previous Spine Surgery					*0.41*[b]
No (n, %)	29 (30)	22 (23)	22 (23)	24 (25)	
Yes (n, %)	23 (20)	31 (27)	31 (27)	29 (25)	

[a]*P-value using one-way analysis of variance*

[b]*P-value using chi-squared test*

[c]*P-value using Kruskal-Wallis one-way analysis of variance*

[d]*P-value using Fisher's exact test*

**Patient cohort includes 211 people ages 50-89 years who underwent elective spine surgery between June 2013 and June 2014 at Oregon Health & Science University in Portland, Oregon*

Table 4: Distribution of Perioperative Characteristics among 211 Adult Elective Spine Surgery Patients According to Transferrin Quartile 2013-2014*

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Transferrin (mg/dl; mean ± SD)	215.5±16.8	250.0±6.7	275.1±8.0	322.9±39.2	
Transferrin (mg/dl; range)	(168-239)	(240-262)	(263-291)	(292-503)	
Number	52	53	53	53	***P***
Number of Levels Fused (mean ± SD)	2.0 ± 2.7	2.6±4.2	2.0±3.1	2.5±3.5	*0.66*[a]
No Spine Fusion (n, %)	18 (30)	18 (30)	15 (25)	10 (16)	*0.35*[b]
1 Level Fusion (n, %)	13 (18)	17 (24)	19 (27)	22 (31)	
2-4 Level Fusion (n, %)	12 (29)	6 (14)	13 (31)	11 (26)	
4+ Levels Fusion (n, %)	9 (24)	12 (32)	6 (16)	10 (27)	
Surgical Approach					*0.57*[d]
Posterior Only (n, %)	44 (25)	45 (26)	43 (25)	41 (24)	
Anterior Only (n, %)	1 (100)	0 (0)	0 (0)	0 (0)	
Anterior-Posterior (n, %)	7 (19)	8 (22)	10 (27)	12 (32)	
Number of Stages					*0.55*[d]
One (n, %)	49 (25)	48 (24)	51 (26)	51 (26)	
Two (n, %)	3 (25)	5 (42)	2 (17)	2 (17)	
Estimated Blood Loss					*0.46*[c]
Total Milliliters (median)	400.0	350.0	350.0	500.0	
Blood Transfusion					
No (n, %)	44 (26)	43 (25)	43 (25)	39 (23)	*0.54*[b]
Yes (n, %)	8 (19)	10 (24)	10 (24)	14 (33)	
Length of Hospital Stay					*0.26*[c]
Total days (median)	3.0	3.0	3.0	4.0	
Anesthesia Time					*0.24*[c]
Total hours (median)	4.5	4.3	4.1	5.8	

[a] *P-value using one-way analysis of variance*

[b] *P-value using chi-squared test*

[c] *P-value using Kruskal-Wallis one-way analysis of variance*

[d] *P-value using Fisher's exact test*

**Patient cohort includes 211 people ages 50-89 years who underwent elective spine surgery between June 2013 and June 2014 at Oregon Health & Science University in Portland, Oregon*

Table 5: Risk Ratios of Complications within 30 days among adults undergoing elective spine surgery according to pre-surgical level of pre-albumin and transferrin

	Pre-Albumin Level			Transferrin Level		
Outcome Measures	<27.2mg/dl	≥27.2mg/dl		<263.0mg/dl	≥263.0mg/dl	
Mean (mg/dl)	23.12	31.78		232.76	298.96	
Range (mg/dl)	(12.9-27.1)	(27.2-47.9)		(168.0-262.0)	(263.0-503.0)	
Total N	105	106		105	106	
No. Complications (%)	16 (15%)	16 (15%)		14 (13%)	18 (17%)	
Model	**RR (95% CI)**		**P**	**RR (95% CI)**		**P**
Unadjusted	1.0 (Referent)	1.0 (0.5-1.9)	0.9	---	---	
Unadjusted	---	---		1.0 (Referent)	1.3 (0.7-2.4)	0.5
Mutually Adjusted	1.0	1.0 (0.7-1.3)	0.9	1.0	1.3 (0.7-2.3)	0.5
*Model 1	1.0	1.1 (0.8-1.5)	0.5	1.0	1.1 (0.8-1.5)	0.5
**Model 2	1.0	1.1 (0.7-1.5)	0.7	1.0	1.1 (0.8-1.5)	0.6

* Variables modeled are pre-albumin level, transferrin level, body mass index (<30 kg/m2, >= 30 kg/m2) and number of levels fused (no fusion, 1 level fused, 2-3 levels fused, ≥4 levels fused)

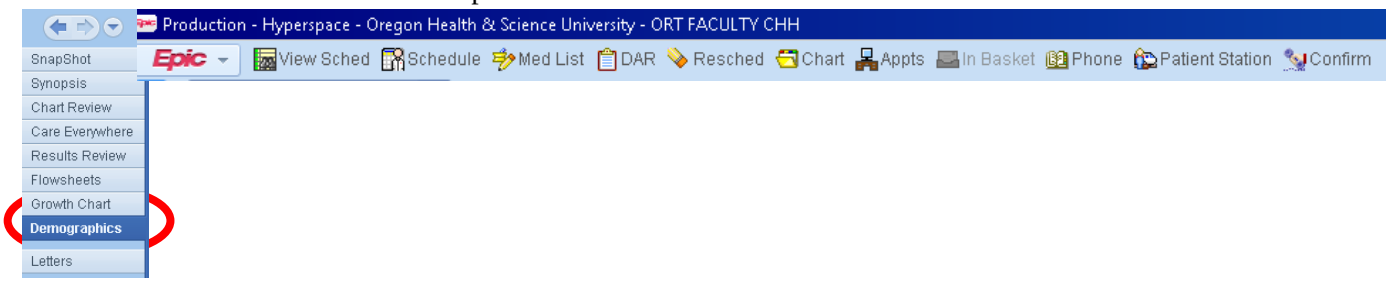
** Variables modeled include those in model 1 plus age group (50-59 years, 60-69 years, >=70 years), sex (female, male), and ASA score (1-2 points, 3-4 points)

--- indicates not fit in this model

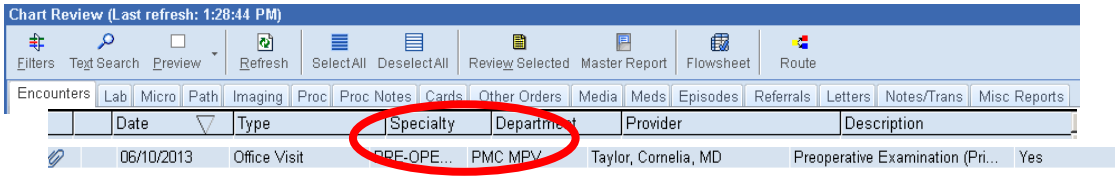
Appendix A: Independent Variable Data Collection Procedure

All independent variable collection will be completed by a single trained individual. The individual will collect data onto paper forms. Upon completion of all pre-operative and operative data, the same individual will enter all data into a single master Excel data file. A 10% sample will be randomly selected and chart reviews will be repeated. Percent concordance will be assessed.

1. With both case lists and EPIC open, start with basic demographics available under Demographics Tab. Use the MRN listed to open chart. Confirm the name matches the chart.



2. Under the Encounter tab, open the PMC visit date indicated by the Cognos report; collect all PMC data variables.



*If any values are missing, make note of unavailable and leave blank

3. Under the Encounter tab, locate the pre-operative visit with the Spine Center closest to the date of surgery. For Dr.'s Hart, Ching and Yoo this visit will be with PAs Tannia Fleming or Kara Berent, Dr. Hiratzka completes his own pre-op visits. The visit's description should be "other pre-operative visit". Collect all Spine Center pre-op data variables

   Past medical history (including previous spine surgeries and comorbidities) may be a collective list from the spine center and the PMC clinic pre-operative visits. Given that most patients have an extensive list of medications, medication use will be copy/pasted directly into electronic data collection form. Review for vitamin use and list those separately. Record all social history available, although many items may be missing. The vital signs along with height and weight are collected by the MA and located under encounter vitals listed mid-way through the visit summary.

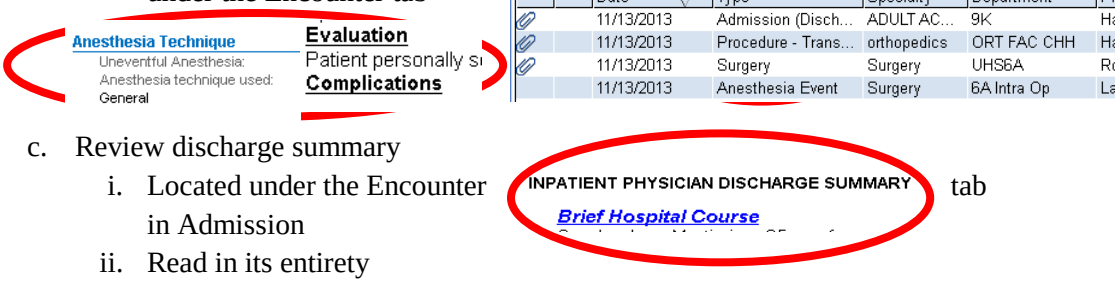
4. Under the LAB tab in EPIC; locate blood work collected the same day as the PMC pre-operative visit. Collect all blood work to include CBC, chemistry panel, metabolic panel, pre-albumin, and transferrin labs. If any blood panels are missing record this. If any blood panels are from outside OHSU facilities do not collect the values as outside bloodwork will not be used in this project. Mark the date of each lab test and the level of the test that was completed (with or without differential, and basic or complete metabolic panel).

5. Finally, under the Encounter Tab or the Proc Notes tab, open the anesthesia note and the operative note. It is likely you will have to use both the resident's report and the attending surgeon's note to complete the surgical portion of the chart review. Pay special attention to possible staged procedures; which may occur hours to weeks apart. Time should be recorded in military time for ease of calculation; include dates where indicated. For intra-op fluids record NS (normal saline) and LR (lactated ringers) as two separate values but in the same space. For EBL and transfusion records, only use anesthesia records for consistency. Additionally record any blood products (PRBC, platelets, plasma, cryo) and the number of units of each product.

Appendix B: Outcome Variable Collection Procedures

Collection of the outcome variables will be conducted by two trained reviewers independently of one another. The entire cohort will be reviewed for the occurrence of adverse events regardless of if the exposure variable (pre-albumin & transferrin) are available or not. Half of the cohort will be reviewed by Reviewer #1 and the other half reviewed by Reviewer #2, all complications will be confirmed and classified by an orthopaedic surgeon. Both reviewers will be standardized to the following review procedure.

1. For each patient, record surgery date, calculate 30 day post-op window
    a. For staged surgeries done during the same hospitalization, the latest surgery date will be used to calculate the 30 day window
2. Pull Mortality & Morbidity report for June 2013-July2014 from Ortho X-drive
    a. Download Hart, Yoo, Hiratzka, Ching medical complications
    b. Match with appropriate research subject
    c. Check if occurred in 30 day post-op window
    d. Confirm with Dr. Yoo for complication classification
3. Chart review:
    A. Under the Encounter Tab locate the Anesthesia Event, Admission, and Surgery Notes
        a. Review operative note
            i. Resident/fellow portion and surgeon notes
        b. Review anesthesia note
            i. Scroll to the bottom of the Anesthesia Event found under the Encounter tab



        c. Review discharge summary
            i. Located under the Encounter tab in Admission

            ii. Read in its entirety

        d. From surgical data collection variables collect any blood loss for a single procedure over 4000mL

    B. Review standard of care 2-week post-op visit with Spine Center Physician Assistant or for Dr. Hiratzka this again will be himself
    C. Review any phone calls made to / from the Spine Center in the 30 day window
    D. Record any medical complications
    E. Upon completion of outcome ascertainment, 3rd reviewer, Dr. Yoo, will confirm and classify adverse events

Appendix C: Comprehensive List of Potential Medical Complications

Infection Yes ☐ No ☐	Deep ☐ Sepsis ☐ Superficial ☐ UTI ☐ Other ☐
Wound Problems Yes ☐ No ☐	Dehiscence ☐ Erythema/Drainage ☐ Hematoma ☐ Seroma ☐
Morbidity Yes ☐ No ☐	Anemia ☐ Cardiac arrest ☐ Congestive Heart failure ☐ CVA/stroke ☐ DVT ☐ Intraop blood loss >4000mL ☐ Ileus ☐ Liver (other) ☐ Myocardial infarction ☐ Pleural effusion ☐ Pneumonia ☐ Pancreatitis ☐ Pulmonary (other) ☐ Pulmonary embolism ☐ Renal (other) ☐ Arrhythmia ☐ Renal failure ☐ Sepsis ☐ Stress induced cardiomyopathy ☐ Unplanned return to the OR ☐ Reason: _____ Other ☐ Please list: _____
Mortality Yes ☐ No ☐	Cause of death: _____

Appendix D: Potential Confounding Variables Associated with 30 Day Risk of Complication and Exposure Status Among Patients Undergoing Elective Spine Surgery at a Single Institution

	Pre-Albumin	Transferrin	Any Complication
Preoperative Variables			
Gender	**X**	**X**	--
Age	**X**	**X**	--
BMI	--	**X**	**X**
Blood Pressure (systolic)	--	**X**	--
ASA Score	**X**	--	**X**
Previous Surgery	--	--	**X**
Perioperative Variables			
Levels Fused	**X**	--	**X**
Spine Fusion	--	--	**X**
Transfusion	**X**	--	**X**
Number of Stages	--	--	**X**
Anesthesia Time	--	--	**X**
Total Hospital Stay	--	--	**X**