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Sarcopenia as a Risk Factor for Prosthetic Infection after Total Hip or Knee Arthroplasty

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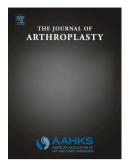
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### Sarcopenia as a Risk Factor for Prosthetic Joint Infection

- 1 Abstract:
- 2 Background:
- 3 Sarcopenia, an age-related loss of muscle mass and function, has been previously linked to an increased
- 4 risk of morbidity, mortality, and infection after a variety of surgical procedures. This study is the first to
- 5 evaluate the impact of the Psoas Lumbar Vertebral Index(PLVI), a validated marker for central
- 6 sarcopenia, on determining post-arthroplasty infection status.
- 7 Methods:
- 8 This is a case-control, retrospective review of 30 patients with prosthetic joint infection(PJI) diagnosed
- 9 by Musculoskeletal Infection Society(MSIS) criteria compared to 69 control patients who underwent a
- 10 total hip or knee arthroplasty. All patients had a recent computed tomography(CT) scan of the
- abdomen/pelvis to calculate the PLVI. PLVI was evaluated alongside age, sex, BMI, CCI, ASA, and
- smoking status to determine the predictive value for infection.
- 13 Results:
- Notably, the infected group had a large, significant difference in their average PLVI (0.736 vs. 0.963, p<
- 15 0.001). The patient's PLVI was a predictor of infection status, with a higher PLVI being protective against
- infection, OR: 0.28(95% Confidence Interval(CI): 0.109-0.715, p= 0.008). Additional predictors of
- 17 infection status were higher ASA score (OR 10.634, 95% CI: 3.112-36.345, p< 0.001) and CCI (OR: 1.438,
- 18 95% CI: 1.155-1.791, p= 0.001). Multivariate, binary logistic-regression analysis confirmed that PLVI was
- a significant independent predictor of infection status (B = -.685, p= .039).
- 20 Conclusion:
- 21 Psoas lumbar vertebral index, a marker for central sarcopenia, was demonstrated to be a risk factor for
- 22 prosthetic joint infection. Further research and consideration of sarcopenia as a screening and
- 23 optimizable risk-factor for total joint arthroplasty must be explored.

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- 24 Keywords:
- 25 Sarcopenia, Prosthetic Joint Infection, Psoas-Lumbar Vertebral Index, Arthroplasty, Screening, Risk-
- 26 factor



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# Introduction:

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Total joint arthroplasty (TJA) is one the most widely-used surgical procedures in medicine with a rapid increase in demand due to an aging population.[1–3] Unfortunately, with this increase in primary total joint arthroplasty (TJA), revision arthroplasty is expected to increase by 601% during this same time period.[3] Prosthetic joint infections (PJI) have been reported to be responsible for 19 to 30.2% of total joint arthroplasty revisions and has been observed to occur in up to 2.5% of TJA.[4-6] Some studies have even suggested that PJI may be the greatest reason for arthroplasty failure.[7] PJI is a dreaded complication after arthroplasty that produces unexpected morbidity and mortality in up to 2.5% of patients suffering from it.[4] With the increasing demand for TJA, an emphasis must be placed on patient selection and understanding the risk factors for PJI. Several studies have evaluated the correlation between health markers such as the American Society of Anesthesia (ASA) score, Charlson Comorbidity Index (CCI), and Body Mass Index and complications after TJA. Patients with higher index scores are increasingly susceptible to superficial and deep infection, untoward medical complications, and premature component failure.[8-12] Many arthroplasty centers already use these markers to risk stratify patients, however no studies have explored the effect of sarcopenia on complication rates in total joint arthroplasty. Sarcopenia was originally defined in the 1980s by Dr. Irwin Rosenberg as the age-related loss of muscle mass.[13,14] Sarcopenia has been defined in multiple different manners in the literature and the frequency at which it is being discussed has increased considerably.[13-23] The European Working Group on Sarcopenia in Older People (EGSWOP) defines sarcopenia as a 'syndrome of progressive and generalized loss of skeletal muscle mass and strength, with a risk of adverse outcomes such as physical disability, poor quality of life and death.'[14]

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Several studies have demonstrated that sarcopenia as a prognosticator can independently predict adverse outcomes.[13,16–18,21,23–27] One validated method for assessing skeletal muscle mass is calculating the psoas lumbar vertebral index (PLVI) on computerized tomography (CT) scan of the abdomen.[17,28,29] The PLVI is determined by measuring the cross sectional area of the bilateral psoas muscles and normalizing this value, by dividing it by the cross sectional area of the fourth lumbar vertebra (Equation 1).[17,28,29] Low PLVI has previously been studied as a measure of central sarcopenia and it has been found to be an independent predictor of morbidity in elderly trauma patients.[17] A decreased quantity of psoas muscle mass has also been associated with a higher mortality rate in patients undergoing elective aortic aneurysm repair, esophagectomy, hepatic resection, and liver transplantation. [18,30-32] In colon cancer patients, sarcopenia was found to act as an independent predictor of postoperative infection and need for discharge to inpatient rehabilitation.[33] Sarcopenia is a phenomenon that is increasingly discussed in the medical community, however the orthopedic literature still lags behind in this conversation. Very few studies analyze sarcopenia as a risk factor for orthopedic patients. With sarcopenia being tied to increased morbidity and mortality in several surgical specialties, this study seeks to evaluate the impact of sarcopenia in total joint arthroplasty patients. We hypothesize that sarcopenia, as measured by PLVI, correlates with an increased risk of periprosthetic infection and may warrant utilization as a screening tool in the future. Methods: The current work is a case-control, retrospective review approved by the Institutional Review Board (IRB). A retrospective chart review querying the institutional database over a two-year period (2015-2017) for the T84.5 code for periprosthetic joint infection (International Classification of Diseases Code,

10<sup>th</sup> revision, ICD-10) and also CPT codes (27090, 27091, 27134, 27137, 27138, 27486, 27487, 27488) for

removal of total hip and total knee prosthesis and revision surgeries (Current Procedural Terminology,

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73	CPT).[34] A 30 patient cohort with a history of primary total hip or knee arthroplasty, with confirmed
74	prosthetic joint infection according to the Musculoskeletal Infection Society (MSIS) criteria[35] and
75	recent computed tomography (CT) scans of the abdomen and pelvis were included in this study.
76	Exclusion criteria were a history of acute post-traumatic arthroplasty, patients with hemiarthroplasty,
77	and patients with fracture or previous fusion of their lumbar spine; 712 patients were excluded for
78	incomplete or absent CT lumbar spine imaging (Figure 1).
79	A control group of 69 patients was identified using CPT codes 27130 and 27447 for primary total hip or
80	knee arthroplasty, who had surgery from July 2015 - July 2016 and had recent CT scans of the
81	abdomen/pelvis.
82	In total 43 patients undergoing total knee arthroplasty (TKA) and 56 patients undergoing total hip
83	arthroplasty (THA) were evaluated. These patients' charts were reviewed and data were extracted
84	including: age, gender, smoking history, Body Mass Index, Charlson Comorbidity Index, American Society
85	of Anesthesiology score, length of stay (LOS) after index surgery, and discharge disposition after index
86	surgery.
87	CT scans of the abdomen/pelvis for all 99 patients were evaluated to ensure that cross-sectional area
88	(CSA) measurements of bilateral psoas muscles and the Lumbar 4 (L4) vertebral body could be made. A
89	single orthopedic investigator, blinded to infection status, calculated these values on one axial cut at the
90	level of the L4 pedicles on two separate occasions, which was averaged - shown in Figures 2&3 (ImageJ,
91	National Institutes of Health, Bethesda, MD).[36] The Psoas Lumbar Vertebral Index (PLVI) was then
92	calculated by dividing the average total surface area of the psoas by the average area of the L4
93	vertebrae - similar to a previously validated method in the literature (Equation 1).[17,29]
94	Equation 1: $PLVI = \frac{Left\ Psoas\ CSA + Right\ Psoas\ CSA}{L4\ Vetebral\ body\ CSA}$

L4 Vetebral body CSA

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- 95 Source of Funding:
- 96 No funding was obtained for this project.
- 97 Statistical Analysis:

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- Patients were initially stratified into high versus low psoas lumbar vertebral index groups with a median value of .842 to identify baseline characteristic differences, a similar value and method to what has previously been described (Table 1).[17] The high PLVI cohort was defined as ≥ .842 and low psoas vertebral index cohort was defined as < .842. They were also stratified into infectious versus noninfectious groups to identify baseline characteristic differences between these two groups (Table 2). For normally distributed data, differences between demographic and clinical variables were calculated utilizing an independent samples t-test for continuous variables or chi-squared test for categorical variables, with significance level set a priori at p < .05. Data for hospital length of stay was the only variable found to be not normally distributed and a Mann-Whitney test was used for non-parametric analysis. There was missing data for discharge disposition and hospital length of stay for 13 patients, each analysis was performed on a test by test basis.
  - A univariate, binary logistic-regression analysis was then performed on categorical and continuous variables to evaluate for factors impacting infection. All variables were analyzed individually in the univariate regressions, including: demographic, health status, and postoperative information (Table 3).
- 112 A multivariate binary logistic regression analysis was subsequently performed to create a complete

  113 model of factors impacting infection while accounting for the potential confounding between variables:

Equation 2: 
$$\ln \left[ \frac{y}{(1-y)} \right] = a + b_1 x_1 + b_2 x_2 \dots + b_n x_n$$

The left side of the equation is the expected log of the odds that the outcome is present (infection status = y). Selection of variables  $(x_n)$  for inclusion in the multivariate regression were obtained from Table 2

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and included significant baseline characteristic differences between infected and uninfected groups, with a focus on previously utilized and validated health markers to stratify for risk. These established variables were BMI, CCI, ASA, Diabetes, smoking status, and each patient's PLVI was also analyzed for impact (Table 4). All variables were standardized to account for differences in scoring scales so that coefficients could be compared. Receiver operating characteristic (ROC) curve analysis was performed using R version 3.5.0 and the plotROC package. All other statistical analysis was performed with IBM SPSS Statistics Version 25.

# Results:

In total, 99 patients were included in this study, of whom 30 patients had prosthetic joint infections and 69 patients served as control with no infections within one year of surgery. Of the patient demographic and health marker differences between our low PLVI and high PLVI group, significant differences were seen in: age, sex, body mass index, CCI and ASA scores (Table 1). Patients in the low PLVI group were on average older (73.35 vs. 68.08, p= 0.015), less likely to be male (40.82% vs. 68%, p= 0.007), had a lower BMI (26.627 kg/m² vs. 31.247 kg/m², p= 0.013), and had higher CCI and ASA scores than the high PLVI group (5.04 vs. 3.84, p= 0.009 and 2.84 vs. 2.46, p= 0.003 respectively). Importantly, when patients were stratified by PLVI, the low PLVI group was found to have a much higher likelihood of having infection (p=.002).

When separated by infectious status (Table 2), there were significant differences in baseline characteristics. The infected group had a higher CCI (5.67 vs. 3.9, p= 0.001), higher ASA score (3.03 vs. 2.48, p< 0.001) and an increased rate of diabetes (26.67% vs. 21.7%, p= 0.027). Most notably, the infected group had a large, significant difference in their average PLVI (.736 vs. .963, p< 0.001). Significant correlations were also observed in available discharge disposition information after index

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138	surgery, with the prosthetic joint infection group having a greater percentage of patients going to rehab
139	and a longer length of stay after their index surgeries (p= 0.045 and p= 0.002).
140	Table 3 depicts the results of the univariate binary logistic-regression with dependent, binary variable
141	being infection status. The patient's psoas lumbar vertebral index was a large predictor of infection
142	status, with a high PLVI being protective against infection: OR: .28 (95% Confidence Interval(CI): .109-
143	.715, p= 0.008). An additional predictor of infection was increasing ASA status (OR 10.634, 95% CI:
144	3.112-36.345, p< 0.001). Higher CCI also conferred higher odds of having infection (OR: 1.438, 95% CI:
145	1.155-1.791, p= 0.001). Being in the lowest quartile of PLVI in our patient population demonstrated a
146	4.614 OR of having infection compared to the patients in the top three quartiles (p= 0.002 for a 95% CI
147	of 1.759-12.102).
148	Univariate receiver operating curve (ROC) analysis was performed for both significant variables and
149	variables of interest to depict predictive accuracy of each variable (Figure 4). PLVI, ASA, and CCI had
150	area under the ROC (AUROC) values of 0.74 (95% CI: 0.6305-0.8459), 0.74 (95% CI: 0.6595-0.826) and
151	0.72 (95% CI: 0.6148-0.8345), respectively when analyzed independently.
152	Multivariate, binary logistic-regression analysis results are depicted in Table 4 demonstrating each
153	variable's independent contribution to infection status after accounting for confounding factors. All
154	variables were standardized so that comparisons between coefficient values could be made. Once again,
155	PLVI was a factor that significantly influenced infection status, with the second largest magnitude
156	regression coefficient (B=685, p= 0.039). Higher ASA status had the largest, significant contribution to
157	likelihood of infection with a B coefficient value of 1.080 and a p value of 0.004. Variables that didn't
158	reach statistical significance after multivariate regression were BMI, CCI, Diabetes and smoking status
159	(p= 0.586, p= 0.072, p= 0.441, and p= 0.921 respectively). In logistic regression, the coefficients ( $b_n$ )

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calculated by the model demonstrate the change to the expected log odds relative to a one unit change in X<sub>1</sub> (ASA, PLVI, BMI etc.) while all other predictors are held constant.

Infection 
$$\propto \ln \left[ \frac{y}{(1-y)} \right] = -1.310 + 1.080(ASA) - .685(PLVI) ... + b_n x_n$$

- The Nagelkerke R<sup>2</sup> coefficient of fit was .415 with a classification accuracy of 76.8%. The model's chisquare value was  $\chi^2(6) = 34.354$  and the full model p value < .001.
- 164 Discussion:

Sarcopenia is a diagnosis that has gained significant traction in the world of medicine as an independent predictor of morbidity and mortality. It has even been added to the most recent ICD-10 (M62.84) acknowledging that it is an important clinical diagnosis.[37] In the orthopedic trauma literature, sarcopenia has been associated with an increased risk for fragility fractures for all patients.[13,38] Also, elderly sarcopenic patients suffering acetabular fractures have demonstrated a significantly increased one year mortality (28.6% vs. 12.3%) and likelihood for discharge to a short term nursing facility (94.7% vs. 76.9%).[24,29] Bokshan *et al.*[13] evaluated patients undergoing thoracolumbar spine surgery and found patients with sarcopenia had increased risk of in-hospital complications, longer hospital stay, and increased mortality. In contrast, our study found patients with sarcopenia had similar length of stay and discharge disposition to rehab compared to the non-sarcopenic group.

In this study, we identified a significant difference in average psoas lumbar vertebral index between the prosthetic joint infection cohort (.736) and the non-infected cohort (.964), indicating that patients developing infection had much less central skeletal muscle mass. The current study uses a median value to divide patients into high vs. low PLVI groups that was comparable to previously published values and methods (.842 vs. .84 [17]). When looking at PLVI as a continuous variable through univariate analysis,

having a higher PLVI provided a protective impact against periprosthetic infection. After multivariate

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regression accounted for the potential confounding variables such as BMI, CCI, ASA, Diabetes, and smoking status, PLVI continued to be a significant predictor of periprosthetic joint infection. Receiver operating curve analysis demonstrated the predictive value of PLVI for infection with an area under the curve value of 0.74, illustrating that PLVI alone provides good discrimination between infected and noninfected patients. This study is the first to identify PLVI, a marker for central sarcopenia, as an independent risk factor for prosthetic joint infection. One limitation of this study was the small sample size for both infected and uninfected cohorts. The combination of a low incidence of PJI in addition to only a small percentage of arthroplasty patients undergoing CT scans of the abdomen or lumbar spine for a variety of reasons (workup for: abdominal 190 pain, back pain, aortic aneurysm, malignancy, fever, hip pain, etc.) made this difficult to overcome. However, post-hoc power analysis using the mean and standard deviation values for our infected (.736 +/- .242) and uninfected groups (.964 +/- .274), and an alpha value of .05, demonstrated adequate power of 98.5%. Duration of infection prior to imaging likely impacts skeletal muscle mass measurements, as chronic inflammatory conditions can lead to a catabolic state.[39] Twenty-eight out of 30 patients in our PJI cohort had acute infectious processes, while 2/30 had more chronic infectious histories. Of these two patients, one had a PLVI within one standard deviation above our cutoff value for sarcopenia and the second patient had a PLVI within one standard deviation below the cutoff for sarcopenia, so the overall confounding impact is likely negligible. Measuring psoas lumbar vertebral index is only one method of determining skeletal muscle mass and assessing sarcopenia. The purpose of this study is not to advocate for CT-scans of the abdomen/pelvis 202 for all prospective or even high-risk patients, but instead to investigate and recognize the contribution of sarcopenia to adverse outcomes after arthroplasty. Prospective studies including various functional

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204	testing for sarcopenia is necessary and likely the most practical way to implement routine testing and
205	risk stratification in the preoperative setting in the future. These analyses can include gait speed, timed
206	get up and go test, stair-climbing and more easy to reproduce tests in the office like grip strength and
207	peak expiratory flow.[14,40] However, a clear correlation between these tests and adverse outcome in
208	the TJA patient must be demonstrated. Higher risk patients can then be further analyzed if necessary
209	with CT-scan or with much less radiation-generating dual energy x-ray absorptiometry (DEXA), which is
210	considered the gold standards for estimating muscle mass.[14,41]
211	Over the years, more conscientious efforts to help patients achieve more optimal risk profiles prior to
212	surgery have been undertaken. Such efforts include, but are not limited to, weight-loss and optimizing
213	body mass index, smoking cessation, and improved nutritional status as measured by albumin or
214	prealbumin.[8,11,12,42] Interestingly, recent studies have shown that BMI may have limited predictive
215	value of perioperative complications independent of sarcopenia. [43]
216	Sarcopenia is a treatable entity and may be a very relevant modifiable risk factor. The American Medical
217	Directors Association has released evidenced-based guidelines for the prevention and improvement of
218	sarcopenia. Their research demonstrated that sufficient protein intake (>1.2g/kg/day) slows loss of
219	muscle mass and leucine-enriched amino acids can enhance muscle strength.[44–46] Furthermore,
220	resistance exercise has been established as a reliable treatment option for sarcopenia. Churchward et al.
221	found that there were no non-responders to resistance exercise regimens, with sarcopenia always
222	improving in a cohort of 110 patients.[47]
223	Prosthetic joint infections (PJI) place a huge burden on both the patient and the healthcare system. The
224	annual cost of PJI revisions in the US is projected to exceed \$1.62 billion by 2020.[3] The responsibility to
225	minimize this burden on both patients and the healthcare system falls on the orthopedic practitioner.
226	An aging population confers an increasing demand for total hip and knee arthroplasty; utilizing

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- 227 previously established risk factors for infection and continuing to explore new ways to quantify risk is
- 228 the only way to mitigate the impact of this devastating outcome.
- Conclusion: 229

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There is a paucity of research on sarcopenia in orthopedic surgical patients and as a result it is underdiagnosed and under-recognized. Psoas lumbar vertebral index, a marker for central sarcopenia, was demonstrated to have good predictive capacity for prosthetic joint infection status in this study. Similar 232 233 to modifiable risk factors like BMI and nutritional status, sarcopenia is a treatable entity. Further research and consideration of sarcopenia as a screening and optimizable risk-factor for total joint 235 arthroplasty, and orthopedics in general, must be explored.

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Table 1: PLVI				
	Average or % of			
(n included for each	patients	Low PLVI (n = 49)	High PLVI (n = 50)	
evaluation)	(number)	< .842 ≥ .842		P-Value
Age in years (99)	70.69			0.015
Male (99)			68% (34)	0.007
BMI kg/m <sup>2</sup> (99)	29.772 26.267 31.247		0.013	
Diabetes Mellitus				
(99)	23.23% (23)	24.49% (12) 22% (11)		0.150
Smoking History (99)	12.12% (12)	2.12% (12) 16.33% (8) 8% (4)		0.20439
Nasal MRSA (99)	3% (3)	% (3) 4% (2) 2% (1)		0.546
CCI (99)	4.43	5.04 3.84		0.009
ASA (99)	2.65	2.84 2.46		0.003
		46.15% (18/39	55% (26/47	
Discharge Home (86)	51.16% (44)	available)	available)	0.397
			44.68% (21/47	
Discharge Rehab (86)	<b>Discharge Rehab (86)</b> 48.83% (42)		available)	0.397
Length of Stay (87)	3.64	3.77 (39 available) 3.54 (48 available) 0.975		0.975
Infection (99) 30% (30) 44.9% (22) 16% (8)		16% (8)	0.002	

Table 1: Baseline characteristic differences for high vs. low psoas lumbar vertebral index

Table 2: Infection Status				
	Average or %			
(n included for each	patients	Non-Infected (n =		
evaluation)	(number)	69)	Infected (n = 30)	P-Value
Age - years (99)	70.69	70.48 71.17		0.764
Male (99)	54.55%	6 50.72% 63.33%		0.247
BMI - kg/m <sup>2</sup> (99)	29.772 30.539 28.0		28.009	0.055
Diabetes (99)	23.22% (23)	21.7% (15)	26.67% (8)	0.027
Smoker (99)	12.12% (12)	10.14% (7)	16.67% (5)	0.361
Nasal MRSA (99)	3% (3)	3% (3) 3% (2) 3% (1		0.908
CCI (99)	4.43	3.9	3.9 5.67	
ASA (99)	2.65	2.48	3.03 < 0.0	
Discharge Home (86)	51% (44)	57% (39)	29% (5/17) <b>0.045</b>	
Discharge Rehab (86)	<b>(86)</b> 49% (42) 43% (30) 71% (12/17)		71% (12/17)	0.045
		3.46 (for 69	4.33 (for 18	
Length Of Stay (87)	3.64	patients)	ents) patients) 0.002	
PLVI (99)	0.895	0.964	0.736	< 0.001

Table 2: Baseline characteristic differences between infected/noninfected group

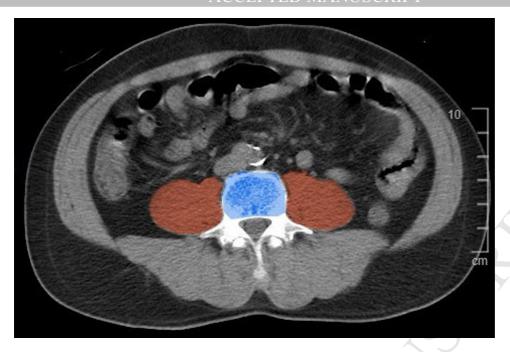
Table 3: Univariate Regression Analysis			
	OR	95% CI	P-Value
Age	1.006	(0.967-1.047)	0.771
Male	1.678	(0.696-4.045)	0.249
ВМІ	0.929	(0.860-1.002)	0.057
Diabetes	1.734	(0.771-3.900)	0.183
Smoker	1.771	(0.514-6.109)	0.365
Nasal MRSA	1.155	(0.101-13.249)	0.908
ССІ	1.438	(1.155-1.791)	0.001
ASA	10.634	(3.112-36.345)	< 0.001
Discharge Home	0.321	(0.102-1.009)	0.052
Discharge Rehab	3.12	(0.991-9.821)	0.052
LOS	1.201	(0.948-1.522)	0.13
PLVI High vs. Low (≥ .842 vs. <			
.842)	0.28	(0.109-0.715)	0.008
PLVI 1st Quartile (Top 25%)	0.254	(0.069-0.930)	0.039
PLVI 2nd Quartile	0.49	(0.164-1.460)	0.2
PLVI 3rd Quartile	1.112	(0.419-2.955)	0.831
PLVI 4th Quartile (Bottom 25%)	4.614	(1.759-12.102)	0.002

Table 3: Univariate Binary Logistic Regression analyzing odds ratios for each variable, with outcome being infection.

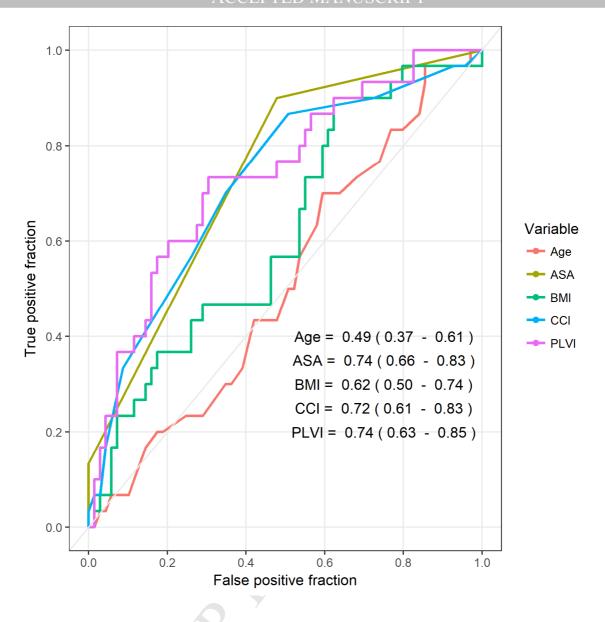
Table 4: Multivariate Regression Analysis					
	В	P value	Exp(B)	95% C.I. for EXP(B)	
		T Value	EXP(D)	Lower	Upper
ВМІ	0.170	0.586	1.185	0.643	2.184
CCI	0.570	0.072	1.768	0.951	3.288
ASA	1.080	0.004	2.945	1.398	6.202
Diabetes	0.198	0.441	1.219	0.736	2.020
Smoking	0.026	0.921	1.026	0.620	1.697
PLVI	-0.685	0.039	0.504	0.263	0.966
Constant	-1.310	0.000	0.270	-	

Table 4: Multivariate Binary Logistic Regression Analysis









- Figure 1: 99 total patients meeting inclusion/exclusion criteria for this study
- Figure 2: Cross sectional cut at L4 of a nonsarcopenic patient with a PLVI of 1.38
- Figure 3: Cross sectional cut at L4 of a sarcopenic patient with a PLVI of 0.4855
- Table 1: Baseline characteristic differences for high vs. low psoas lumbar vertebral index
- Table 2: Baseline characteristic differences between infected/noninfected group
- Table 3: Univariate Binary Logistic Regression analyzing odds ratios for each variable, with outcome being infection
- Figure 4: Univariate area under receiver operating curve (AUROC) demonstrating predictive capacity for infection of each variable. Area under curve values listed for each variable.
- Table 4: Multivariate Binary Logistic Regression Analysis