

Sarcopenia is a Significant Predictor of Mortality After Abdominal Aortic Aneurysm Repair

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Abstract

Aims Repair of abdominal aortic aneurysms (AAA) decreases the incidence of rupture and death. In cancer patients, sarcopenia has been associated with increased surgical complications and mortality. The impact of sarcopenia on survival after AAA repair has yet to be described.

Methods and Results Patient demographic, laboratory, body composition measurements and survival data were obtained from patients undergoing AAA repair at the Indiana University medical campus over a 5-year period. Univariate and multivariate analyses were performed to identify factors associated with overall survival. Overall, 58.2% presented with sarcopenia. Sarcopenic patients were older (71.8±8.3 versus 66.8±8.1 years; $p<0.001$), had lower body mass index (BMI) (26.3±5.2 versus 31.5±5.9 kg/m²; $p<0.001$), higher rates of myosteatosi s (84.4% versus 52.%; $p<0.001$), greater AAA diameter (60.6±14.0 versus 57.8±11.7 mm; $p=0.016$), higher Charlson Comorbidity Index (CCI) (32.3% versus 25.1% ≥ 6 ; $p=0.034$), and increased rates of rupture (8.2% versus 3.8%; $p=0.047$). Sarcopenic and nonsarcopenic patients had no difference in 30-day morbidity (8.5% versus 8.5%; $p=0.991$) or mortality (3.7% versus 0.9%; $p=0.07$). Univariate analysis demonstrated age, sarcopenia, myosteatosi s, CCI, and BMI to be associated with long-term survival. There was no correlation between BMI and sarcopenia. Both sarcopenia and myosteatosi s resulted in decreased one-, three-, and five-year survivals compared to their counterparts. On multivariate analysis sarcopenia is independently associated with survival, conferring a 1.6-fold increase in death ($p=0.04$). The combination of sarcopenia plus myosteatosi s doubled the risk of death compared to sarcopenia alone.

Conclusions This is the first study to demonstrate that over half of all patients undergoing AAA repair are sarcopenic, a condition associated with increased mortality. Sarcopenia with myosteatosi s is associated with double the mortality of sarcopenia alone. CT scan, but not BMI, accurately identifies sarcopenia and myosteatosi s. Defining the mechanisms through which sarcopenia contributes to late death after AAA repair is critical to developing novel interventions that may improve survival in this high risk population.

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Keywords: Abdominal aortic aneurysm, Sarcopenia, Myosteatosi s, Prognosis, Survival

Received 26 October 2017 Accepted 20 February 2018

Introduction

The primary focus in improving survival in patients with abdominal aortic aneurysms (AAA) has been centered on the timing of surgical repair to prevent the catastrophic consequences of aneurysm rupture. Intensive population based studies have provided detailed guidelines for intervention that rely on factors associated with risk of rupture that include maximal transverse diameter, growth rate, aneurysm morphology, and symptoms (1). While these efforts have had a significant impact in decreasing complications from

rupture, assessing mid- and long-term outcomes post AAA repair has largely been ignored (2-5).

In recent years, body composition has emerged as a novel prognostic indicator in both malignant and non-malignant diseases (6-8). Sarcopenia, or low muscle mass for height, is a catabolic state associated with an inflammatory condition(9). Furthermore, sarcopenia has been associated with increased morbidity and mortality risk following major surgical procedures (10). Inflammation has been implicated as a driving mechanism for the development of sarcopenia(11). Tumor necrosis factor-alpha (TNF- α), interleukin-1beta (IL-1 β), and interleukin-6 (IL-6) promote muscle wasting

by increasing protein degradation and decreasing protein synthesis (12-14). Inflammation has been shown to be associated with AAA as well. Microscopic examination of AAA have shown inflammatory cells infiltrating the aneurysms (15, 16). In addition, patients with AAA have elevated levels of inflammatory cytokines, which in turn, activate matrix metalloproteinases (MMPs) (17-20). The activation of MMP favors collagen and elastin degradation leading to aortic wall weakening and aneurysm formation(20).

Cross-sectional skeletal muscle and adipose tissue masses at the level of the third lumbar (L3) vertebrae have been shown to correlate with overall body measurements of each tissue types (21). Using specifically designed software body composition measurements can be readily obtained from computed tomography (CT) scans that are a standard part of the pre-operative evaluation for patients undergoing endovascular or open AAA repair. Thus, body composition may be a predictor of post-AAA morbidity and mortality.

Herein, we evaluated the impact of body composition on short- and long-term outcomes after AAA repair. We hypothesize that patients with sarcopenia, determined by CT derived L3 skeletal muscle measurements at the time of AAA repair, will have increased surgical complications and decreased post-operative survival when controlling for other factors. Based upon data examining 505 patients undergoing elective and urgent AAA repair at Indiana University (IU) we demonstrate that the presence of sarcopenia is a significant predictor of survival at five years post-AAA repair.

Methods

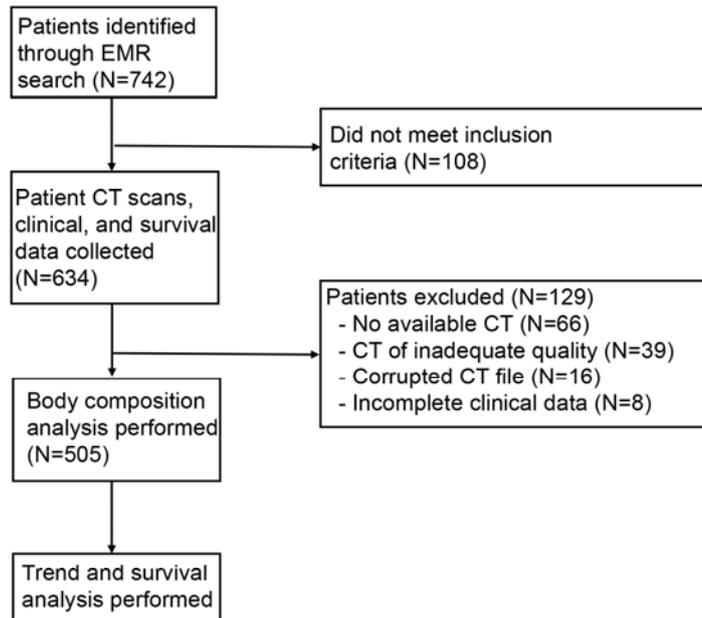
This study was approved by the Indiana University Institutional Review Board and carried out in compliance with the IU Standard Operating Procedures for Research Involving Human Subjects and therefore have been performed in accordance to the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Selection of patients is outlined in Figure 1. All patients presenting to Indiana University Methodist Hospital between January 1, 2012 and July 30, 2015 and the Richard L. Roudebush Veterans Administration Medical Center (RRVAMC) between July 1, 2005 and July 30, 2015 for repair of AAA were eligible for inclusion. Patients from RRVAMC were obtained through a query of the electronic medical record (EMR). The Vascular Quality Initiative database was used to obtain patients from IU Methodist Hospital. Together these searches identified seven hundred forty-two total patients. One hundred eight did not meet inclusion criteria. One hundred twenty-nine patients were excluded for the following reasons: sixty-six had no available CT scan, thirty-nine had CT scan of inadequate quality for analysis, sixteen had corrupted CT files that could not be analyzed, and eight had incomplete clinical data.

Body composition analysis was performed on five-hundred five patients using Slice-O-Matic® software Version 4.3 (Tomovision, Montreal, Quebec, Canada) by the following method: cross-sectional area (cm^2) was measured and recorded for skeletal muscle (SKM), visceral adipose tissue (VAT), subcutaneous adipose tissue (SCAT), and mean skeletal muscle density (SKM HU) at the level of the third lumbar vertebrae (L3)(21). Hounsfield thresholds were set at -29 to +50 for SKM, -50 to -150 for VAT, and -30 to -190 for SCAT. Two consecutive images were analyzed and the mean of the two images were normalized to height in meters squared to establish tissue specific indices (cm^2/m^2). Total muscle measurements included rectus abdominus, external and internal oblique, transversus abdominus, psoas, erector spinae, and quadratus lumborum.

Sarcopenia was defined as skeletal muscle index (SKMI) $<52.4 \text{ cm}^2/\text{m}^2$ for males and $<38.5 \text{ cm}^2/\text{m}^2$ for females (22). Myosteatosis was defined as mean skeletal muscle density <33 HU for patients with body mass index (BMI) $\geq 25 \text{ kg}/\text{m}^2$ and <41 HU for patients with BMI $<25 \text{ kg}/\text{m}^2$ (6). BMI classification was based on the World Health Organization (WHO) definitions (23). Patients meeting the criteria for sarcopenia and obesity were classified as having sarcopenic obesity. Complications were defined as any deviation from normal recovery including the need for a procedural intervention within 30 days of the index operation.

Figure 1



Statistical Analysis

The primary outcome measured was overall survival calculated from the time of surgery to the time of death or last follow up. The main prognostic factor was presence of pre-operative sarcopenia, however secondary prognostic factors included age, sex, AAA diameter, pre-operative myosteator, BMI classification, and CCI. Age and AAA diameter were treated as continuous variables for Cox proportional models. CCI was divided into the following three categories: ≤ 3 , 4-5, and ≥ 6 for Kaplan-Meier and Cox proportional models. Sarcopenia, myosteator, and sex were treated as categorical variables for Kaplan-Meier and Cox proportional models. Kaplan-Meier analyses are reported as median survival in months with log-based p values. Cox proportional models are reported as hazard ratios with 95% confidence intervals with p values.

Mean age, BMI, SKMI, SKM HU, AAA, and estimated blood loss (EBL) were compared between sarcopenic and non-sarcopenic groups by independent t-test. Sex, repair method, myosteator, complications (overall), race, and rupture were compared between groups using Pearson's chi-squared test. CCI and American Society of Anesthesiologist (ASA) score were compared between groups using Mann-Whitney U test. SKMI measurements between BMI categories were compared by sex by ANOVA. All p values are two-sided.

Multivariate analysis was performed using Cox proportional models. All variables found to be significantly associated with survival on univariate analysis were included in the model. Two models were

created; one which included BMI and excluded sarcopenia and myosteator while the second model included sarcopenia and myosteator and excluded BMI. Two models were required due to the BMI's dependence on body composition. Sarcopenia and myosteator are classifications of body composition. BMI is therefore influenced by sarcopenia and myosteator status. All variables in a multivariate model must be independent or the model will not be accurate, thus the need for two models. Age and CCI were treated as a continuous variable for both models. BMI was treated as a categorical variable and was categorized by WHO classification.

All statistical analyses were performed using IBM SPSS Statistics for Windows version 23.0 (Chicago, IL). Images for Kaplan-Meier curves and graphs were created using GraphPad Prism version 7 (GraphPad software, La Jolla, CA). Significance was set at $p < 0.05$ for all results.

Results

Baseline patient characteristics are summarized in Table 1. Using values of sarcopenia determined for cancer patients (22), we observed that 58.2% of patients had sarcopenia compared to 41.2% without. Sarcopenic patients were older (71.8 ± 8.3 vs. 66.8 ± 8.1 years; $p < 0.001$), had larger AAA diameter (60.6 ± 14.0 vs. 57.8 ± 11.7 mm; $p = 0.01$), increased comorbidities (32.3% vs. 25.1% CCI ≥ 6 ; $p = 0.03$), and increased rates of rupture (8.2% vs. 3.8% ; $p = 0.05$) than non-sarcopenic patients. With regards to body composition analyses sarcopenic

patients had lower BMI (26.3 ± 5.2 vs. 31.5 ± 5.9 kg/m²; $p < 0.001$), lower SKMI (43.7 ± 6.7 vs. 58.7 ± 8.3 cm²/m²; $p < 0.001$), less dense skeletal muscle (28.5 ± 11.1 vs. 33.0 ± 7.1 HU; $p < 0.001$), and higher rates of myosteatosi s (84.4% vs. 52.1% ; $p < 0.001$). There was no difference in 30-day post-operative morbidity rate (8.5% vs. 8.5% ; $p = 0.99$) or 30-day post-operative mortality rate (0.9% vs. 3.7% ; $p = 0.07$) between patients with sarcopenia and those without sarcopenia.

Univariate Kaplan-Meier survival analysis showed that sarcopenic patients had significantly decreased overall survival from non-sarcopenic patients (Figure 2A), along with decreased one, three, and five-year survivals (Figure 2B). Patients with myosteatosi s also had significantly decreased overall survival than patients without myosteatosi s (Figure 2C) and decreased one, three, and five-year survivals (Figure 2D).

Univariate Cox proportional modeling showed increasing age, sarcopenia, myosteatosi s, increasing CCI, and BMI to each be associated with increased risk of mortality (Table 2). Multivariate model 1 showed sarcopenia and increasing CCI to be independently associated with increased risk of mortality (Table 2, Model 1). Sarcopenia had the greatest influence on mortality in this model carrying a 1.6 fold increased risk of death (Table 2, Model 1). Furthermore, sarcopenia was identified in eighty-four of the one-hundred fifteen patient deaths, representing 73% of deaths (Figure 3A), while myosteatosi s was identified in ninety-four, or 82%, of all patient deaths (Figure 3B). Patients with sarcopenia plus myosteatosi s had shorter overall survival than

patients with sarcopenia alone or myosteatosi s alone (Figure 3C). In fact, the combination of sarcopenia plus myosteatosi s doubled mortality (Figure 3D). Multivariate model 2 (Table 2, Model 2) showed increasing age, increasing CCI, and BMI classification of underweight to be significantly associated with increased mortality, while BMI classification of overweight was associated with decreased mortality.

Kaplan-Meier survival analysis comparing obese patients with sarcopenia (sarcopenic obesity) to obese patients without sarcopenia shows significant difference in survival (Figure 4A). Cox proportional modeling show sarcopenic obesity confers a 3.5 fold increased risk of mortality compared to patients with nonsarcopenic obese patients (HR=3.5; 95% CI=1.6-7.9).

Mean BMI for patients with sarcopenia is significantly lower than those without sarcopenia (26.3 vs. 31.5 kg/m²) (Figure 4B). SKMI measurements were compared among BMI categories for both males (Figure 4C) and females (Figure 4D). All BMI categories had significantly different SKMI measurements for both sexes. Furthermore, 87.1%, 64.9%, and 34% of males in the normal, overweight, and obese BMI categories had SKMI measurements that qualified as sarcopenic, while 85.7% and 37.5% of females in the normal and overweight BMI categories had SKMI measurements which qualified as sarcopenic. Overall, 85.7% of underweight, 86.9% of normal, 62.6% of overweight, and 33.3% of obese BMI patients had SKMI measurements that fell into the sarcopenic category.

Table 1. Baseline Patient Characteristics

Variable	Overall (n=505)	No Sarcopenia (n=211)	Sarcopenia (n=294)	P
Age, yrs (SD)	69.7 (8.6)	66.8 (8.1)	71.8 (8.3)	<0.001
Sex (%)				
Male	467 (92.5)	191 (90.5)	276 (93.9)	0.158
Female	38 (7.5)	20 (9.5)	18 (6.1)	
Repair Method (%)				
Open	181 (35.8)	70 (33.2)	111 (37.8)	0.290
EVAR	324 (64.2)	141 (66.8)	183 (62.2)	
BMI, kg/m² (SD)	28.5 (6.1)	31.5 (5.9)	26.3 (5.2)	<0.001
SKMI, cm²/m² (SD)	49.8 (10.6)	58.7 (8.3)	43.7 (6.7)	<0.001
Mean SKM HU (SD)	30.3 (9.9)	33.0 (7.1)	28.5 (11.1)	<0.001
Myosteatosis (%)				
Yes	357 (70.1)	110 (52.1)	248 (84.4)	<0.001
No	148 (29.3)	101 (47.9)	46 (15.6)	
AAA diameter, mm (SD)	59.4 (13.1)	57.8 (11.7)	60.6 (14.0)	.016
EBL, mL (SD)	656.9 (906.2)	649.2 (918.8)	662.4 (898.6)	0.872
30-Day Complications (%)	43/505 (8.5)	18/211 (8.5)	25/294 (8.5)	0.991
No Complication	462	193	269	
Endoleak	19	8	11	
LE ischemia	6	4	2	
Bleeding	10	2	10	
Graft Infection	1	1	0	
Wound infection/dehiscence	4	1	3	
Colonic ischemia	1	0	1	
Renal artery aneurysm	2	2	0	
Groin pseudoaneurysm	1	0	1	
30-Day Mortality (%)	13 (2.6)	2 (0.9)	11 (3.9)	0.07
Race (%)				
Asian	1 (0.2)	0 (0)	1 (0.3)	0.603
Black/African-American	32 (6.3)	17 (8.1)	15 (5.1)	
Native Hawaiian/Pacific Islander	2 (0.4)	1 (0.5)	1 (0.3)	
White	456 (90.3)	188 (89.1)	268 (91.2)	
Unknown	14 (2.8)	5 (2.4)	9 (3.1)	
CCI (%)				
≤ 3	154 (30.5)	77 (36.5)	77 (26.2)	0.034
4-5	203 (40.2)	81 (38.4)	122 (41.5)	
≥ 6	148 (29.3)	53 (25.1)	95 (32.3)	
ASA (%)				
2	6 (1.1)	5 (2.4)	1 (0.3)	0.177
3	272 (53.9)	117 (55.5)	155 (52.7)	
4	216 (42.8)	86 (40.8)	130 (44.2)	
5	8 (1.6)	2 (0.9)	6 (2.0)	
Unknown	3 (0.6)	1 (0.5)	2 (0.7)	
Rupture (%)				
Yes	32 (6.3)	8 (3.8)	24 (8.2)	0.047
No	473 (93.7)	203 (96.2)	270 (91.8)	

Table 2. Survival Analysis by Cox Modeling

Model 1				
Variable	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age	1.06 (1.04-1.09)	<0.001	1.03 (0.99-1.05)	0.06
Sarcopenia	1.94 (1.28-2.93)	0.002	1.59 (1.03-2.45)	0.04
Myosteatosis	1.97 (1.21-3.19)	0.01	1.32 (0.77-2.23)	0.29
Charlson Comorbidity Index	1.38 (1.25-1.51)	<0.001	1.32 (1.18-1.47)	<0.001

Model 2				
Variable	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age	1.06 (1.04-1.09)	<0.001	1.03 (1.00-1.06)	0.03
Charlson Comorbidity Index	1.38 (1.25-1.51)	<0.001	1.32 (1.18-1.47)	<0.001
Body Mass Index				
Normal	Reference		Reference	
Underweight	5.59 (2.17-14.37)	<0.001	5.90 (2.29-15.23)	<0.001
Overweight	0.70 (0.45-1.09)	0.11	0.74 (0.47-1.15)	0.18
Obese	0.49 (0.30-0.80)	0.005	0.56 (0.34-0.92)	0.02

Table 2 presents the variables associated with mortality in univariate and multivariate analysis. Two models were created due to the dependence of body mass index on muscle mass. Model 1 shows when controlling for other factors sarcopenia increases all-cause mortality 1.59 fold and incremental increases in Charlson Comorbidity Index (CCI) by 1.32 fold. Incremental increases in age trended towards being significantly associated with all-cause mortality. Model 2 replaces CT derived body morphometric measurements with body mass index categories. Incremental increases in age and CCI, along with underweight category correlate with increased risk of all-cause mortality, while obesity confers a decreased risk of all-cause mortality.

Figure 2

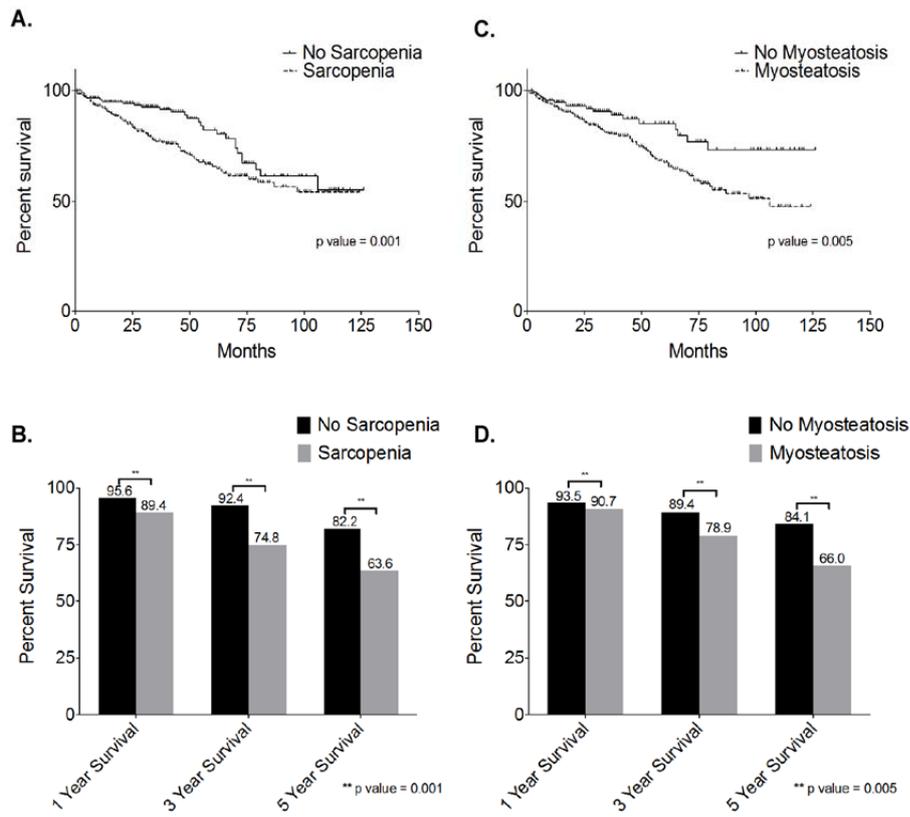


Figure 3

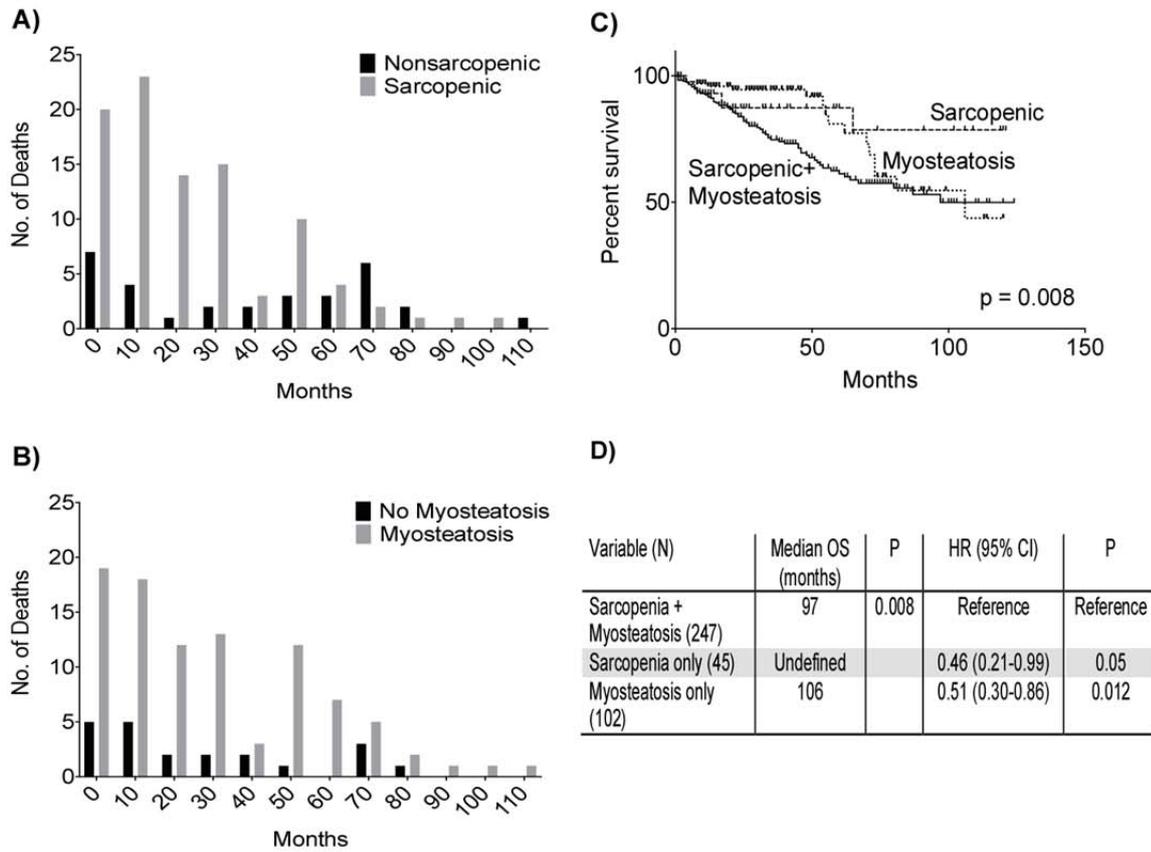
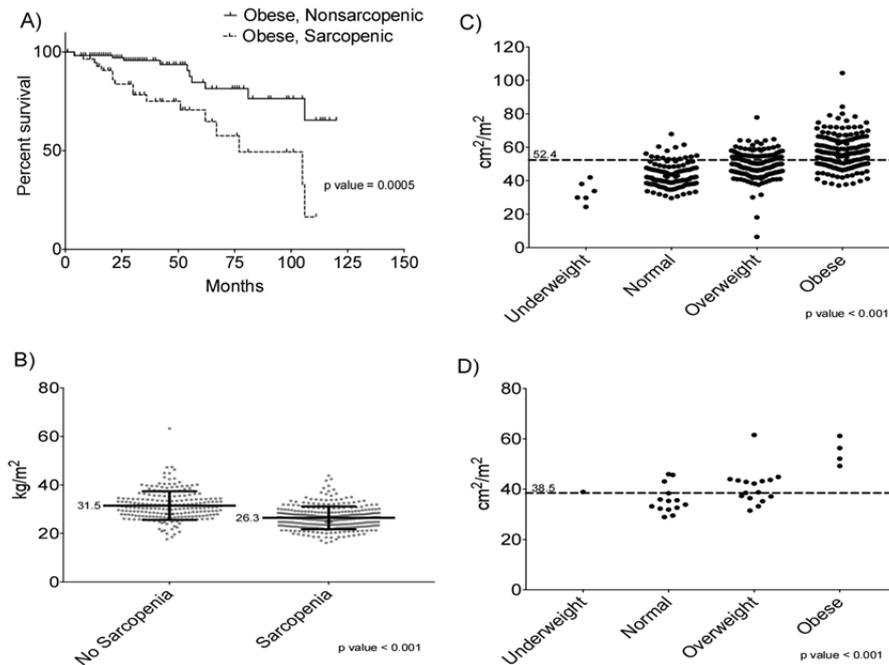


Figure 4



Discussion

According to the Society of Vascular Surgeons (SVS), approximately 200,000 individuals will be diagnosed with abdominal aortic aneurysms each year, and 40,000 endovascular and open repairs are performed annually to prevent rupture (24). This study identifies sarcopenia, a condition of abnormally low skeletal muscle mass, to be an independent predictor of mortality after AAA repair. Sarcopenic patients were found to have decreased one, three, and five-year survival compared to non-sarcopenic patients, and was present in 73% of all deaths. More alarming was the fact that the combination of sarcopenia with myosteatorsis doubled the mortality over sarcopenia alone.

The current study is the largest, most comprehensive study specifically examining body composition and outcomes after AAA repair. There is a growing body of literature on the negative effect of sarcopenia on surgical outcomes and mortality. Both Lee et al. and Drudi et al. demonstrated increased risk of mortality after AAA repair with decreasing total psoas muscle (25, 26). However, both studies defined sarcopenia based on the lowest tertile within the study group, making their definition susceptible to selection bias. Our study uses an established, validated, sex-specific definition of sarcopenia which did not rely on the current patient population being studied, thus eliminating any selection bias (22). The results, however, are consistent with Lee et al. and Drudi et al. We establish sarcopenia is a major prognostic indicator for

patients who have undergone AAA repair, but does not appear to influence 30-day outcomes. The data provides sex-specific values that clinicians can use clinically to identify patients with sarcopenia that are at high risk of death following successful repair. This study also identifies the combination of sarcopenia plus myosteatorsis as a significant risk factor, doubling the risk of mortality after AAA repair compared to sarcopenia alone.

The presence of sarcopenia is a risk factor independent of other known risk factors in AAA patients. Age, congestive heart failure, cerebral vascular disease, and diabetes mellitus have all been shown to increase the risk of mortality after AAA repair (27). This study, which included congestive heart failure, cerebral vascular disease and diabetes mellitus by proxy by utilizing the CCI, found that sarcopenia had significant, independent association with mortality by multivariate analysis.

Based on these results, any evaluation of a patient for AAA repair should monitor for sarcopenia and myosteatorsis, as well as the other clinical factors that have been associated with poor outcomes. Targeting these patients, ideally before, and surely after AAA repair, may prove to be beneficial, thus the mechanisms mediating death in these patients need to be elucidated to aid in developing methods to reduce the risk.

A second significant finding is related to obesity and sarcopenia. Obesity has been reported to increase the risk of mortality after AAA repair; however, the data herein contradict these previous findings (28). A break down of SKMI measurements by BMI category showed that BMI is not an accurate reflection of lean body mass, specifically the absence or presence of sarcopenia. The majority of patients with normal BMIs (87%) and overweight BMIs (63%) met the criteria for sarcopenia. Even patients with BMI's that categorize them as obese had 33% rate of meeting the criteria for sarcopenia. Further comparison showed obese patients with sarcopenia had significantly decreased survival than obese patients without sarcopenia. This suggests that lower rates of sarcopenia are the reason that obesity had a protective effect in this study and further demonstrates the adverse effects of sarcopenia. These data suggest abandoning BMI as a useful measure for AAA patients in lieu of sarcopenia measurements.

Only twenty-two percent of patients did not have sarcopenia, myosteatorsis, or a combination of the two. The high rate of muscle abnormalities among all patients in this study suggests disruption of normal muscle metabolism in patients with AAA that is associated with death and is strikingly similar to the patterns of cachexia seen in cancer patients. While it has been shown in certain populations that muscle mass and function can be improved with exercise and supplemental protein, the muscle wasting in cancer cachexia, by definition, is resistant to reversal by conventional nutritional support (29-31). Several cytokines have been linked to the muscle wasting seen in cancer cachexia including tumor necrosis

factor-alpha (TNF- α), interleukin (IL)-1, IL-6, and interferon-gamma (IFN- γ) (32-38). TNF- α , IL-1 β , IL-6, and IFN- γ are produced by AAA (39,40). Patients with AAA have also been shown to have elevated circulatory serum levels of TNF- α , IL-1 β , IL-6 and these cytokines have been implicated in the pathogenesis of AAA (17, 39). During repair the aneurysmal tissue is not excised, and like cancer, may act as a non-healing wound, continuing to drive inflammation and production of cachexia-associated cytokines. This study highlights the importance of identifying the mechanism and correcting the muscle metabolism disruption in AAA patients. This hopefully may result in significantly increased long-term survival after repair.

While this is the largest, most comprehensive study of its kind, there are still some limitations. This is a single-institution, retrospective study, and although the results should be generalizable due to the magnitude of the cohort, the cohort was largely male Caucasians; application of the results to females and minorities populations should be done with caution. There was also an age difference between the sarcopenic and non-sarcopenic groups. The authors do not believe this to be a limitation, however, because when controlling for age in the multivariate analysis sarcopenia remained a significant negative prognostic factor.

For various reasons, thirty-two percent (237/742) of patients who presented to the institution for AAA repair were not able to be included in the study. It would be unlikely that inclusion of these patients would have a significant effect on the results, as the patient cohort of five-hundred five patients still represents a very large patient population. The authors believe that inclusion of these patients would only strengthen the results observed.

Despite these limitations, this study demonstrates sarcopenia as a common comorbidity in AAA patients undergoing repair that is independently associated with long-term all-cause mortality. It is imperative for sarcopenia to be integrated into all patient evaluations prior to open or endovascular AAA repair. The presence of sarcopenia should not exclude a patient from undergoing repair of an AAA, but rather be used to identify a subset of patients who are vulnerable to poor outcomes. Sarcopenic patients may benefit from pre- and post-operative interventions targeted at improving muscle mass and quality.

Acknowledgements

None

Sources of Funding

This work was funded in part by grants to LGK from the NIH (R01DK096167) and the Lilly Endowment, Inc.

Conflicts of Interest Statement

Joshua K. Kays, Tiffany W. Liang, Teresa A. Zimmers, Daniel P. Milgrom, Hamzah Abduljabar, Andrew Young, Bradford J. Kim, Teresa M. Bell, Andres Fajardo, Michael P. Murphy and Leonidas G. Koniaris certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing

arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

The authors certify that they comply with the ethical guidelines for authorship and publishing of the Journal of Cachexia, Sarcopenia and Muscle-Clinical Reports (von Haehling S, Ebner N, Morley JE, Coats AJS, Anker SD. Ethical guidelines for authorship and publishing in the Journal of Cachexia, Sarcopenia and Muscle-Clinical Reports. *J Cachexia Sarcopenia Muscle Clinical Reports* 2016; 1:e28:1-2.

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