Analytic Morphomics, Core Muscle Size, and Surgical Outcomes

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Objective: Assess the relationship between lean core muscle size, measured on preoperative cross-sectional images, and surgical outcomes.

Background: Novel measures of preoperative risk are needed. Analytic morphomic analysis of cross-sectional diagnostic images may elucidate vast amounts of patient-specific data, which are never assessed by clinicians.

Methods: The study population included all patients within the Michigan Surgical Quality Collaborative database with a computerized tomography(CT) scan before major, elective general or vascular surgery ($N = 1453$). The lean core muscle size was calculated using analytic morphomic techniques. The primary outcome measure was survival, whereas secondary outcomes included surgical complications and costs. Covariate adjusted outcomes were assessed using Kaplan-Meier analysis, multivariate cox regression, multivariate logistic regression, and generalized estimating equation methods.

Results: The mean follow-up was 2.3 years and 214 patients died during the observation period. The covariate-adjusted hazard ratio for lean core muscle area was 1.45 ($P = 0.028$), indicating that mortality increased by 45% per 1000 mm^2 decrease in lean core muscle area. When stratified into tertiles of core muscle size, the 1-year survival was 87% versus 95% for the smallest versus largest tertile, whereas the 3-year survival was 75% versus 91%, respectively ($P < 0.003$ for both comparisons). The estimated average risk of complications significantly differed and was 20.9%, 15.0%, and 12.3% in the lower, middle, and upper tertiles of lean core muscle area, respectively. Covariate-adjusted cost increased significantly by an estimated \$10,110 per 1000 mm^2 decrease in core muscle size ($P = 0.003$).

Conclusions: Core muscle size is an independent and potentially important preoperative risk factor. The techniques used to assess preoperative CT scans, namely analytic morphomics, may represent a novel approach to better understanding patient risk.

Kerwords: risk stratification, frailty, core muscle size, analytic morphemics, preoperative assessment, surgical outcomes, costso

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Surgeons are called upon to make challenging decisions in selecting patients upon whom to perform major surgical procedures, balancing the indications for the operation with their perception of the patient's overall health and ability to recover from the operation. Although validated risk stratification tools exist to assist surgeons in evaluating patients for surgery, these tools typically only evaluate one portion of the patient's operative risk (eg, cardiovascular health) and may be inadequate to discriminate among an increasingly aged and ill patient population undergoing elective surgical procedures.[1,2] For example, the preoperative risk profile of patients undergoing aortic aneurysm repair is likely very similar, as most patients have a similar burden of cardiovascular disease. Therefore, experienced surgeons rely on a subjective assessment of each patient's vigor and physiologic reserve—a judgment that clinicians refer to as the "eyeball test." Developing techniques to objectively measure the same characteristics that form the gestalt of the "eyeball test" may provide improved means of risk stratification that can be more easily communicated to patients and communicated among providers and hospitals.

It is rare for a patient to undergo major elective surgery without an extensive radiographic workup. As radiologists and surgeons review cross-sectional images, they typically focus only on the area of pathology or the area related to the technical anatomy of the proposed procedure. However, cross-sectional images contain vast amounts of additional data specific to that patient, which is never formally assessed by clinicians. With this work, we propose a new paradigm: utilizing cross-sectional images not only for the assessment of the specific pathology of interest but also for a more global assessment of the patient. We call this approach analytic morphomics. As can be appreciated in the 2 images displayed in Figure 1, the 2 patients, though seemingly similar by conventional risk assessment, have very distinct physical characteristics evident upon cross-sectional imaging.

Our initial exploratory investigations using analytic morphomics have revealed that lean core muscle size may be an important, novel measure of patient risk.[3,4] This makes sense intuitively, considering the observed clinical relationship between loss of muscle mass, or sarcopenia, and patient frailty.[5–8] Unfortunately, very little is understood about the relationship between core muscle size and other well-known preoperative risk factors, such as age and burden of comorbid disease.[5,7,9–12] If novel measures of preoperative risk such as core muscle size represent truly independent physiological domains, then such measures will add incrementally to clinical decision-making and risk stratification. Conversely, if core muscle size is merely a proxy for measured age and previously appreciated comorbid disease, then it represents a less useful preoperative measure. Within this context, we have studied the relationship between the core muscle size, standard preoperative risk factors such as age and comorbid disease, and surgical outcomes in 1453 patients who have undergone elective general or vascular surgical procedures.

METHODS

Study Population

The observation period for this study was from 2006 to 2009. Patients were retrospectively selected from the Michigan Surgical Quality Collaborative database, assembled at the University of Michigan. The Michigan Surgical Quality Collaborative uses the basic data platform of the American College of Surgeons-National Surgical Quality Improvement Program to standardize data collection and measure outcomes. The specific methods for patient selection, data collection, and data definitions have been well described previously by our group and others.[13–17] All patients in the Michigan Surgical Quality Collaborative database who received an elective (emergency cases excluded) operation at the University of Michigan and who had a computerized tomography (CT) scan of the abdomen specifically for preoperative planning, were considered for analysis. Data were

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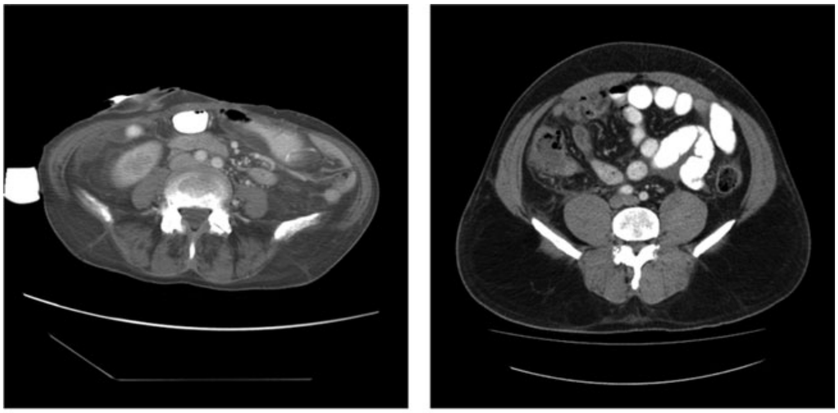


58 year old male with diabetes, previous myocardial infarction, and COPD who is pre-operative for a colostomy takedown

58 year old male with diabetes, previous myocardial infarction, and COPD who is pre-operative for a colostomy takedown

FIGURE 1. This figure demonstrates the significant variation in morphometric characteristics of patients that can be easily noted on cross-sectional images. Both of these patients are males, have similar comorbid conditions, have a similar weight, and are preparing for an elective colectomy. Significant differences in body composition, muscular density and area, and bone morphometry can be noted when comparing these 2 cross-sectional images selected at the fourth lumbar vertebra.

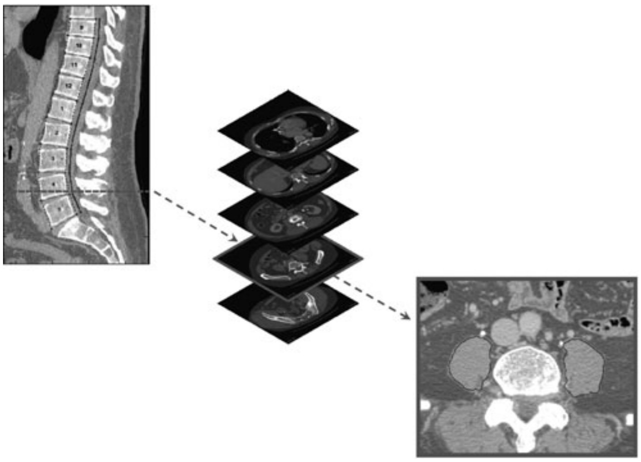


FIGURE 2. Semi-automated method used for processing of cross-sectional images and measurement of the area of the psoas muscle at the level of the fourth lumbar vertebra. Non-muscle density tissues (primarily fat density tissue) within the psoas muscle are subtracted from the area, yielding a lean psoas area.

collected on the following variables: age, sex, race, mean work relative value units as a measure of case complexity, albumin level, smoking status, functional status, previous myocardial infarction, previous cardiac surgery, congestive heart failure, preoperative angina, hypertension, previous stroke or transient ischemic attack, preoperative coma or hemiplegia, ascites, varices, diabetes, disseminated cancer, steroid use, recent weight loss, bleeding disorder, sepsis, chronic obstructive pulmonary disease, preoperative ventilator utilization, preoperative dyspnea, renal disease, and peripheral vascular disease.

Measurement of Psoas Muscle Area

Our primary exposure variable for this analysis is lean core muscle size. As previously described, we used semiautomated methods to measure the area of the psoas muscle (Fig. 2).[3,4] More specifically, the cross-sectional area and density of the left and right psoas muscles at the level of the fourth lumbar vertebra (L4) were measured in our study population. To adjust for fatty infiltration of the psoas muscle, the average density in Hounsfield Units of the psoas muscle within these regions was also measured and used to calculate the total cross-sectional area of the psoas muscles, excluding fatty infiltration (lean core muscle size). These steps were completed in a semiautomated fashion using algorithms programmed in MATLAB v13.0.

Outcomes

The primary outcome measure for this analysis included overall mortality. Patient death was determined by assessment of the Social Security Death Master File. Additional outcomes included patient complications (within 30 days of surgery). These major complications (defined by the American College of Surgeons-National Surgical Quality Improvement Program) included the following: postoperative sepsis, surgical site infection, prolonged ventilation, pneumonia, bleeding, venous thromboembolism, myocardial infarction, stroke, and acute renal failure, among others.[14,18,19] Financial outcomes are reported as hospital revenue (estimated payments to the University of Michigan in 2010 US$) using a previously validated approach.[20–23]

Analysis

Descriptive statistics were computed for the study cohort. Continuous variables were summarized by the mean, standard deviation, and histogram, whereas frequency tables were produced for categorical variables. Linear regression was performed to examine the relationship between lean core muscle size and other patient characteristics.

Patients began follow-up at the time of the elective surgical procedure and were followed until death or loss to follow-up. The Kaplan-Meier method was used to estimate survival probability by lean core muscle size tertile, which wascompared using the Gehan-Wilcoxon test. The covariate-adjusted effect of lean core muscle size on postoperative mortality was ascertained through the Cox proportional hazards regression model. Initial models estimated the average effect of lean core muscle size on the postoperative death rate (ie, hazard); a given hazard ratio from such models would be interpreted as a weighted average over the follow-up time distribution. We also fitted time-dependent Cox (also known as "non-proportional hazards") models, which allowed the effect of core muscle size to depend on time since surgery.

The covariate adjusted effect of lean core muscle size on surgical complications was examined through a logistic regression model.

Generalized estimating equations methods were used to fit a linear regression model to examine the covariate-adjusted relationship between core muscle size and insurer payments to the University of Michigan.[24] Unlike the typical linear regression model, generalized estimating equations do not require that the response be normally distributed, and uses robust (also known as "sandwich") standard errors, which are accurate even if the model is misspecified.

Relationships between burden of comorbid disease, age, and core muscle size were further assessed. Patients were ranked on the basis of age, lean core muscle size, and comorbidity. The ranking for lean core muscle size was gender adjusted. Patients were assigned a point for each comorbidity (detailed earlier). Three groups of patients were selected: the 10% oldest, the 10% with the smallest lean core muscle size, and the 10% with the most comorbidities. These groups were compared using a Venn diagram.

A significance level of $\alpha = 0.05$ was used. All analysis was performed using SAS v9.2 (SAS Institute; Cary, NC).

RESULTS

All patients in the Michigan Surgical Quality Collaborative database who received an elective (emergency cases excluded) operation at the University of Michigan and who had a CT scan of the abdomen, specifically for preoperative planning, were considered for analysis. Over the observation period, there were about 7204 major operations detailed in the database. Only 1453 of these patients had a preoperative CT scan fulfilling the criteria specified earlier. Descriptive and clinical characteristics for the study group (N = 1453) are detailed in Table 1. The case mix included the following: 144 liver cases (9.9%), 273 major vascular cases (18.8%), 408 pancreas cases (28.1%), and 629 cases categorized as "other" major general surgery (43.3%). The mean follow-up was 2.3 years, and 214 patients died during the observation period. Lean core muscle area was approximately normally distributed for both males (mean area, 2138 ± 687 mm^2) and females (mean area, 1356 ± 430 mm^2) (Fig. 3).

Linear regression using core muscle size as the response variable demonstrated a strong relationship between age and lean core muscle area among males ($y = -20.8x + 3352.2$, $r = 0.485$, $P < 0.0001$, Fig. 4A) and females ($y = 12.0x + 2039.3$, $r = 0.481$, $P < 0.0001$, Fig. 4B). Worth noting is the significant variation of core muscle area within each age group.

TABLE 1. Patient Characteristics (N = 1453)

Demographic Characteristics	Mean ± SD (or Percent)
Age	58.9 ± 16.2
Height (cm)	170.2 ± 12.7
Weight (kg)	81.9 ± 22.1
Body mass index	28.3 ± 6.3
Sex (male)	52.8%
Race (nonwhite)	16.2%
Lean psoas area (mm^2)	1742.4 ± 680.0
Clinical Characteristics	
Preoperative albumin (g/dL)	4.0 ± 0.7
Diabetes	17.9%
Smoker	15.8%
Nonindependent function status	4.2%
Chronic obstructive pulmonary disease	6.5%
Cancer diagnosis	7.7%
Recent transient ischemic attack	3.2%
Taking perioperative steroids	7.6%
Currently receiving systemic chemotherapy	3.0%
Currently receiving radiation therapy	2.2%
Preoperative sepsis	2.2%
Peripheral vascular disease	4.3%
Myocardial infarction within 30 days of surgery	0.9%
Ascites	0.9%

Linear regression using core muscle size as the response variable indicated that sex ($P < 0.0001$), age ($P < 0.0001$), weight ($P < 0.0001$), diabetes ($P = 0.0421$), functional status ($P < 0.0001$), chronic obstructive pulmonary disease ($P = 0.002$), renal disease (0.0419), steroid use ($P < 0.0001$), preoperative sepsis (0.0006), and peripheral vascular disease (0.0048) were significantly correlated with core muscle area. Correlations between core muscle area and such covariates would not introduce bias into our main analysis because the Cox, logistic, and generalized estimating equation models adjusted for each of the associated covariates. Considering the strong relationship between lean core muscle size and gender ($P < 0.0001$), models were stratified by gender.

Lean Core Muscle Size and Mortality

To initially describe the effect of lean core muscle area on postoperative survival, patients were stratified into tertiles by lean core muscle area (Fig. 5). Patients in the upper lean core muscle area tertile had 1-year survival probability of 95% and 3-year survival of 91%. Correspondingly, 1-year and 3-year survival was estimated at 87% and 79%, respectively, for lower lean core muscle area tertile patients ($P = 0.033$ comparing these groups).

Cox regression revealed that covariate-adjusted mortality increased significantly as lean core muscle area decreased. Specifically, the covariate-adjusted hazard ratio for lean core muscle area was estimated at hazard ratio = 1.45 ($P = 0.028$), indicating that mortality increases by 45% per 1000 mm^2 decrease in lean core muscle area. This model was repeated after stratifying by specific procedure category (liver, major vascular, pancreas, and "other" major general surgery) and the hazard ratio = 1.60 ($P = 0.009$). Furthermore, when procedure types were entered into the model as covariates, there was no statistically significant relationship between procedure type and mortality.

Table 2 lists hazard ratios for various lean core muscle areas. The reference lean core muscle area (hazard ratio = 1) is 1640 mm^2, which was the median area in our study population. The hazard ratio for a patient with lean core muscle area, 820 mm^2, was 1.35; that is, a patient with a muscle area at the fifth percentile has a covariate-adjusted postoperative mortality rate that is 35% greater than a patient at the median lean core muscle area. Other values in Table 2 can be interpreted similarly.

A second Cox model (this time, a nonproportional hazards model) revealed that the effect of lean core muscle area decreased significantly ($P = 0.0019$) as follow-up time increased. This model assumes that the log hazard ratio for lean core muscle area was a function of log follow-up time, which may be difficult to interpret. Therefore, we fitted a third Cox model, this time allowing for 3 follow-up time interval-specific lean core muscle area effects (the first postoperative year postsurgery, the second postoperative year, and beyond the second post-operative year). Results of this model are depicted in Figure 6, revealing that the core muscle area hazard ratio is estimated to be 1.96 ($P = 0.002$) for the first postoperative year, 0.96 ($P = 0.85$) for the second postoperative year, and 1.06 ($P = 0.84$) for the time beyond the second postoperative year. Hence, the impact of lean core muscle area on mortality appears to be heavily concentrated in the first year postsurgery. Among patients who survive 1-year postsurgery, the subsequent death rate appears not to depend on lean core muscle area (Fig. 5).

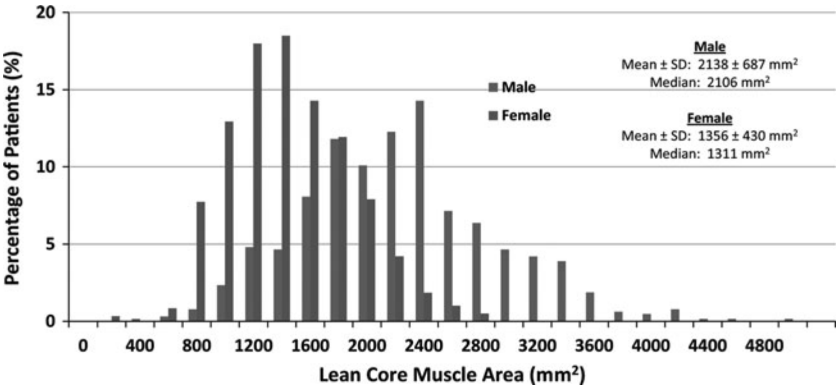


FIGURE 3. Distribution of lean core muscle area among male and female patients undergoing elective major general and vascular surgical procedures. Note that muscle area is normally distributed among both populations and that male mean lean core muscle area is greater than that of females ($P < 0.0001$).

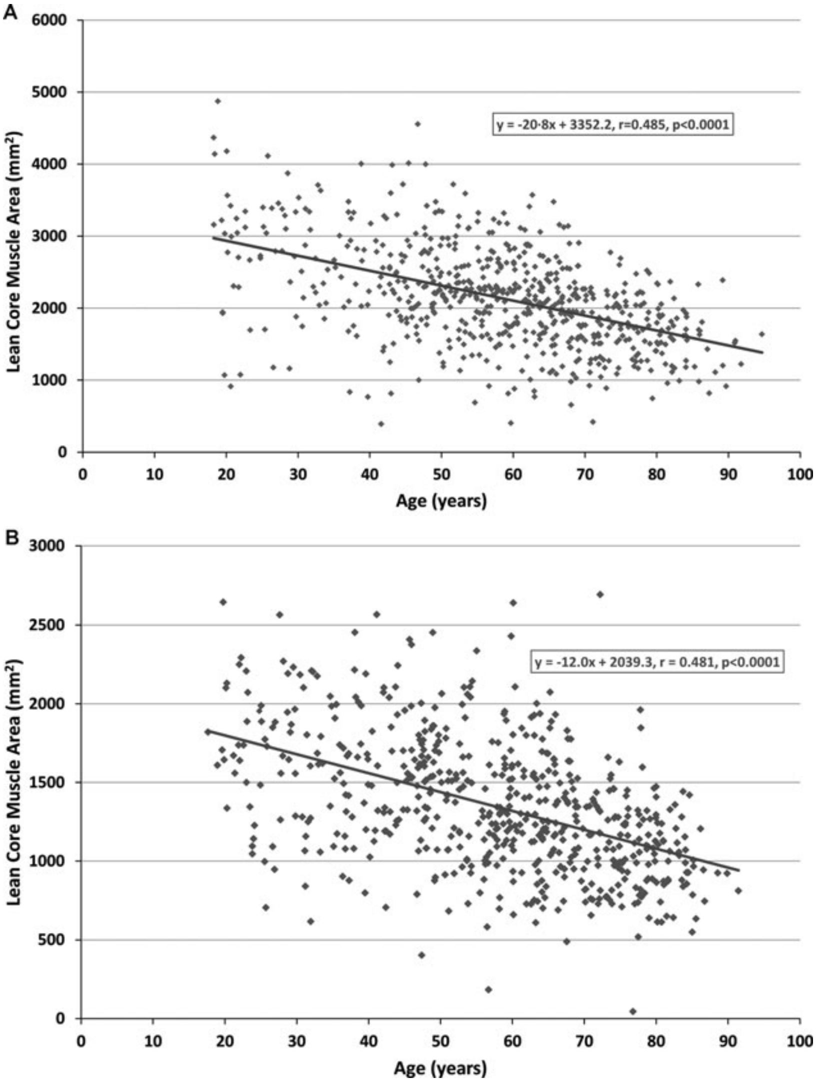
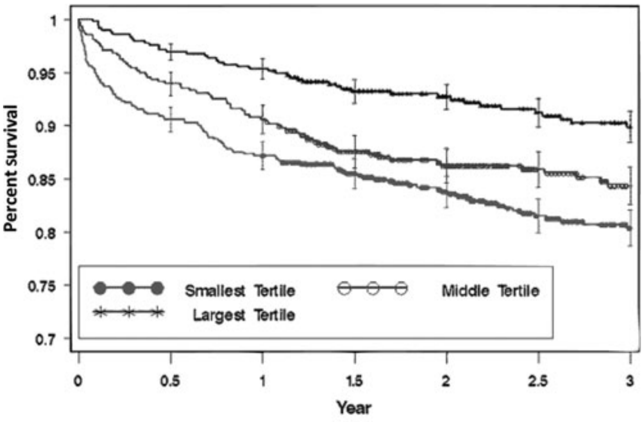


FIGURE 4. Relationship between lean core muscle area and age among male (A) and female (B) patients, demonstrating significant variation of core muscle area within each age group. A strong trend toward decreasing core muscle area with advancing age exists for both males ($y = -20.8x + 3352.2$, $r = 0.485$, $P < 0.0001$) and females ($y = 12.0x + 2039.3$, $r = 0.481$, $P < 0.0001$).

Lean Core Muscle Size and Complications

Logistic regression revealed that the covariate-adjusted odds of complications increased by a significant 67% per 1000 mm^2 decrease in lean core muscle area; with an odds ratio of 1.67 ($P = 0.005$). In a second logistic model, we grouped lean core muscle area into tertiles. Relative to the middle tertile, patients in the lowest core muscle area tertile had a 49% increase in the odds of complications (odds ratio = 1.49; $P = 0.052$), whereas patients in the highest tertile experienced a 47% decrease (odds ratio = 0.53; $P = 0.019$). Figure 7 presents an application of this mode, in which we compare 3 hypothetical groups of patients, with each patient in all 3 groups being at the reference level of each adjustment covariate (so that the only discrepancy lies in their



Time 0: n=586 for tertile 1, 450 for tertile 2, 449 for tertile 3
Time 1 year : n=505 for tertile 1, 406 for tertile 2, 426 for tertile 3
Time 3 years: n=223 for tertile 1, 170 for tertile 2, 207 for tertile 3

FIGURE 5. Patient survival after major general and vascular surgery stratified by tertile of lean core muscle size. These nonadjusted survival rates were calculated by the method of Kaplan-Meier. The group of patients in the smallest tertile of muscle area had significantly inferior survival compared to the group in the largest tertile (*P* < 0.033).

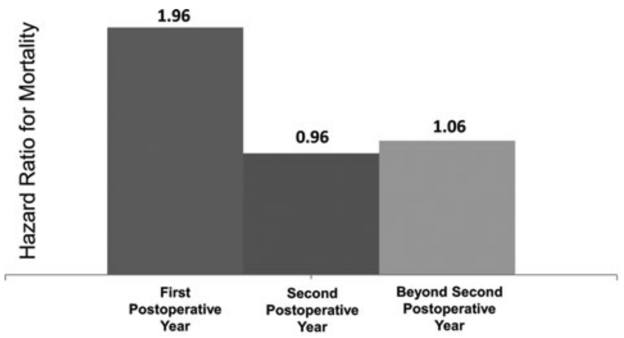
TABLE 2. Hazard Ratio for Mortality, Calculated From the Main Effects (No Interaction) Cox Model With Continuous Lean Core Muscle Size

Lean Core Muscle Size (1000 mm^2)	Percentile	Hazard Ratio
0.04	Minimum	1.81
0.82	5th	1.35
1.23	25th	1.16
1.64	Median (50th)	1
2.18	75th	0.82
3.03	95th	0.60
4.87	Maximum	0.30

lean core muscle areas). The estimated average risk of complications is approximately 20.9%, 15.0%, and 12.3% in the lower, middle, and upper tertiles of lean core muscle area, respectively.

Lean Core Muscle Size and Costs

On the basis of our linear regression analysis, covariate-adjusted cost increases significantly by an estimated $10,110 per 1000 mm^2 decrease in lean core muscle size. When we fitted a second linear model with lean core muscle size broken into tertiles, it was found that average cost was estimated to be $9730 ($P = 0.003$) higher for the patients in the lower lean core muscle area tertile compared to those in the higher tertile, covariate-adjusted. We then compare 3 hypothetical groups of patients, with each patient in all 3 groups being at the reference level of each adjustment covariate (so that the only discrepancy lies in their lean core muscle areas). The estimated average payments from insurers to the University of Michigan was $57,109, $55,707, and $47,379 in the lower, middle, and upper tertiles of lean core muscle area, respectively.



First year: N=1408, event=132
Second year: N=1356, event=44
Beyond second year: N=941, event=38

FIGURE 6. Hazard ratio of mortality by time from surgery. The Hazard ratio = 1.96 ($P = 0.001$) during the first postoperative year, Hazard ratio = 0.96 ($P = 0.84$) for the second postoperative year, and Hazard ratio = 1.06 ($P = 0.84$) beyond the second postoperative year.

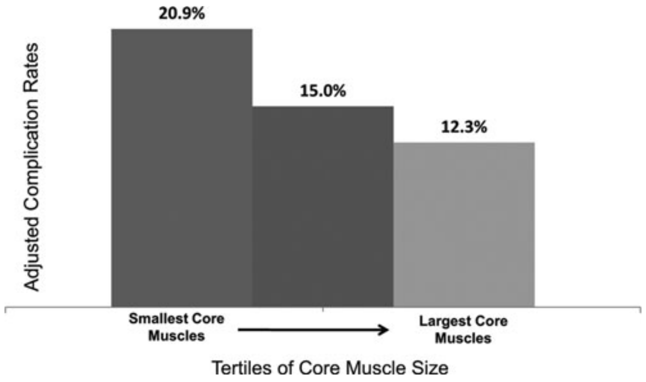


FIGURE 7. Adjusted complication rates stratified by tertile of lean core muscle size. Patients with the smallest core muscle area had a complication rate of 20.9%, which was higher than the group of patients in the middle range of core muscle area (15.0%, $P = 0.052$) and the patients with the largest core muscle size (12.3, $P = 0.02$). The rates were calculated using a logistic regression model stratified by sex, and adjusted for age, race, height, weight, albumin, case complexity, and all clinical comorbidities detailed in Table 1.

Lean Core Muscle Size as an Independent Domain of Risk

As mentioned previously, there was a significant correlation between lean core muscle size, age, and comorbidities. Furthermore, it has been demonstrated that for each age, there is significant variation in lean core muscle size (Figs. 4A, B). In an effort to further elucidate these relationships, we used a standard Venn diagram to compare the 10% (N = 145) of patients with the smallest core muscle size (gender adjusted), the 10% (N = 145) of patients with the most total comorbidities, and the 10% (N = 145) oldest patients (Fig. 8). We noted that 59.2% of patients with the smallest core muscle area were not present in the group with the highest age and/or largest comorbid disease burden.

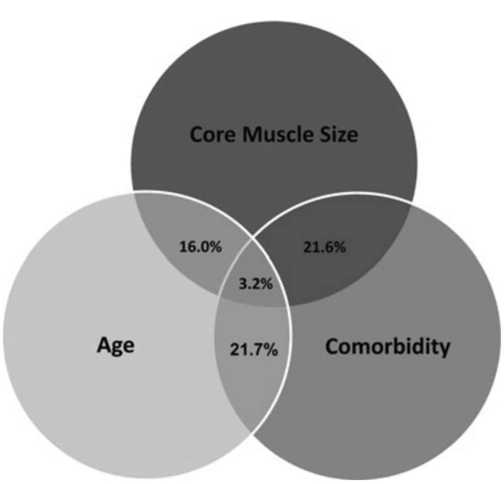


FIGURE 8. Venn diagram of lean core muscle size, age, and comorbid disease. We compared the 10% (N = 145) of patients with the smallest core muscle size (gender adjusted), the 10% (N = 145) of patients with the most total comorbidities, and the 10% (N = 145) oldest patients. The majority (59.2%) of patients with the smallest core muscle size are not included in either the group of the oldest patients, or those with the greatest comorbid disease.

DISCUSSION

This study demonstrates that core muscle size, as measured by lean psoas muscle area, is a significant and potentially important independent preoperative risk factor. Low lean core muscle size strongly predicts postoperative mortality, and this effect seems to be concentrated in the first postoperative year. Decreased lean core muscle size is associated with an increased risk of major postoperative complications and increased hospital costs. These effects of lean core muscle size are independent of other preoperative patient characteristics, and patients identified with the lowest core muscle size are not merely the oldest patients, or those with the greatest burden of comorbid disease. The techniques used in this study to assess preoperative CT scans, analytic morphomics, may represent a novel approach to better understanding patient risk. Our impression is that the measurement of core muscle size may provide an objective metric that represents the subjective assessment of the patient's ability to withstand major surgery, imitating the surgeon's "eye ball test."

When a clinician comments that a patient appears "older than the stated age," one envisions a frail patient who would be a high risk for a major surgical procedure. The concept of frailty seems to intuitively correlate with the idea of the surgeon's "eye ball test," and has motivated our interest in refining the measurement of preoperative risk. *Frailty* is defined as "a biologic syndrome of decreased reserve and resistance to stressors," and an important component of frailty is muscle loss.[7,8] Importantly, sarcopenia, the loss of muscle mass typically associated with aging, which may be accelerated in chronic disease states, has also been correlated with survival and functional status, and now with postoperative mortality.[3,4,8,11] Additional work is needed to better understand the relationship between core muscle size, frailty, age, and surgical outcomes.

Core muscle size seems to represent a unique domain of surgical risk, when compared to age and current measures of comorbidity. Core muscle size was observed to decrease with age, but importantly, there was a wide distribution of core muscle size at each age (Figs. 4A, B). Obese patients represented another interesting group of patients, as they're frequently not judged as frail by clinicians. Considering that we have developed novel methods to measure the lean muscle mass, cross-sectional imaging may offer a unique opportunity to characterize the overall health of obese patients. Furthermore, although we highlighted a significant correlation between the burden of comorbid disease and core muscle size, we were surprised at the modest overlap between these 2 groups of patients (Fig. 8). Unlike standard risk factors (such as diabetes), core muscle size and potentially other objective measures, available on the preoperative CT scans, may highlight potentially remediable preoperative risks. Moreover, core muscle size may represent an important marker of a patient who may benefit from specific preoperative intervention such as strength training, endurance training, and respiratory rehabilitation.[25–28] Future work by our group will focus on such preoperative interventions.

There are some important limitations of this work. First, there is a potential selection bias in that we only analyzed patients who had a CT scan before major elective surgery. Not all patients get a preoperative CT scan, especially those undergoing minor surgery. More specifically, in our study, only 1453 of 7204 patients in the Michigan Surgical Quality Collaborative database fulfilled study criteria as an elective case with a CT scan ordered for preoperative planning. Furthermore, this study was conducted retrospectively on patients from a single hospital, and future work will need to focus on broader patient populations. In addition, this work is not designed to attribute causality between small core muscle size and poor surgical outcomes. Finally, there are countless possible important physiological markers of preoperative risk besides lean core muscle. We have focused on core muscle size because of a concomitant interest in patient frailty. Current analytic morphomic techniques need further development to allow for high throughput data capture and elucidation of these additional morphometric characteristics.

Better understanding the complex milieu of preoperative risk factors offers opportunities for risk stratification, patient preparation, and broader efforts to improve surgical quality. Using preoperative cross-sectional images, we describe the relationship between lean core muscle size, other well-known preoperative risk factors, mortality, morbidity, and costs. This study demonstrates the potential benefit of quantifying lean core muscle size as an objective method of risk stratification and emphasizes the rich source of additional data contained in preoperative imaging studies. It is possible that in time, surgeons will use imaging studies as a routine part of the preoperative evaluation of fitness for surgery.

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