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Sarcopenia Is an Independent Predictor of Complications Following Pancreatectomy for Adenocarcinoma

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Abstract

Background and Objectives—Sarcopenia, which is subclinical loss of skeletal muscle mass, is commonly observed in patients with malignancy. The objective of this study is to determine the correlation between sarcopenia and operative complications following pancreatectomy for cancer.

Methods—A retrospective review of a pancreatectomy database was performed. The Hounsfield Unit Average Calculation (HUAC) of the psoas muscle, a marker of muscle density and fatty infiltration, was measured from preoperative CT scans. Complications were graded and multivariate logistic regression analysis was performed.

Results—One hundred eighteen patients met criteria for analysis; the overall morbidity rate was 78.8% (n = 93). There were 31 (26.3%) patients who met criteria for sarcopenia using the HUAC. When analyzed as a continuous variable, sarcopenia was an independent predictor of major grade III complications, length of stay, intensive care unit admission, delayed gastric emptying, and infectious, gastrointestinal, pulmonary, and cardiac complications.

Conclusions—These data suggest that sarcopenia as measured with the HUAC, a value that can be obtained from a preoperative CT scan, is a significant independent predictor of surgical outcome and can be used to improve patient selection and informed consent prior to pancreatectomy in patients with cancer.

Keywords

sarcopenia; pancreatic cancer; pancreatectomy; complications

INTRODUCTION

Pancreatic resection remains the primary treatment for patients with localized pancreatic ductal adenocarcinoma (PDA) [1,2]. Despite significant improvements in operative mortality, morbidity remains commonplace following pancreatectomy [3–7]. What is unique to PDA is that operative complications may impact survival from this disease considering the importance of postoperative fitness to the timely administration of adjuvant therapy as part of multidisciplinary treatment [8–12]. Therefore, continued efforts are needed to address not only recognition and treatment of complications, but also better methods for predicting complications prior to resection [13,14]. With mild improvements in systemic therapies, the clinical pathway may change in patients deemed resectable if surgeons are able to better predict who may be at high risk for postoperative complications [8,15,16].

Determining a patient's nutritional status and level of fitness (or frailty) from physical examination and laboratory values alone can pose a challenge [17,18]. Sarcopenia is the degenerative loss of skeletal muscle mass that is quantifiable using cross sectional imaging (computed tomography) by measurement of psoas area and the muscle's density [19]. Sarcopenia has been shown to impact not only operative complications [20], but also cancer-specific outcomes following hepatic resection [21,22], colectomy [23], and pancreatic resection [24]. Sarcopenia has also shown to be prognostic in patients being treated with multimodality cancer therapies [25,26] and to be a general predictor of outcome in patients with cancer [27]. To date, sarcopenia has not been evaluated as a predictor of complications following pancreatectomy.

A particular challenge is diagnosing sarcopenia clinically in patients with obesity, who themselves are also at higher risk for complications following pancreatic resection [28,29]. In addition to using total psoas area as a measure of sarcopenia, direct measurements of muscle density have been proposed as an additional and potentially better approach [30]. The aim of this study is to determine the correlation between patient specific measurements of sarcopenia and operative complications following pancreatic resection for PDA. In order to determine accurate information about a patient's body habitus, we obtained numerous measurements of abdominal musculature and fat from high quality preoperative cross sectional imaging. We also employed the Hounsfield Unit Average Calculation, a measure of radiation attenuation that can be used to approximate muscle density and fatty infiltration, as an additional measurement of sarcopenia.

PATIENTS AND METHODS

A retrospective review of both the University of Iowa prospective pancreatectomy and American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database was performed for pancreatectomy between 2001 and 2013. Patients diagnosed with PDA underwent either pancreaticoduodenectomy (PD) or distal pancreatectomy. Patient medical records were queried for preoperative, intraoperative, and postoperative clinicopathologic and treatment-related data following Institutional Review Board approval. Postoperative complications were graded according to the Common Toxicity Criteria for Adverse Events. Pancreatic fistula and delayed gastric emptying were

graded using the International Study Group for Pancreatic Fistula and Delayed Gastric Emptying definitions.

Computed Tomography Scan Measurements

Two independent reviewers analyzed preoperative dual phase contrast enhanced Computed Tomography (CT) scans to create a sarcopenia profile for each patient. All measurements from the two reviewers were then averaged. The sarcopenia profile was comprised of psoas area and density, pancreatic duct diameter, and measurements of fat thickness in various locations. The psoas area (cm²) and density (Hounsfield Units) were measured at the level of the third lumbar vertebral body (L3). Pancreatic duct diameter (mm) was taken over the portal-superior mesenteric venous confluence. Abdominal wall fat (mm) was the perpendicular distance between the left rectus abdominus and the skin at the level of the umbilicus. Hip girdle fat (mm) was denoted as the distance between the iliac plate and skin at the level of the posterior superior iliac spine. Visceral fat (mm) measurement was taken at the level of the left renal vein as the vertical distance between the left posterior renal capsule and the paraspinal musculature [29].

Sarcopenia Quantification

Sarcopenia was quantified using two approaches—the Total Psoas Index (TPI) and the Hounsfield Unit Average Calculation (HUAC). Gender specific quartiles were then generated and the lowest 25% within each approach met criteria for sarcopenia. For TPI, the psoas muscle at L3 was measured as described by others [24]. The TPI (right psoas area +left psoas area)/(height²) normalized the measured psoas area for the height of the patient.

The Hounsfield Unit is a measure of radiation attenuation that can be obtained from a CT Scan. The HUAC of the psoas muscles is a measure of muscle density and fatty infiltration. Both the right and left psoas were evaluated and the average was used for the final HUAC calculation. Right Hounsfield Unit Calculation (RHUC) =(Right Hounsfield Unit*Right Psoas Area)/(Total Psoas Area), left Hounsfield Unit Calculation (LHUC) =(Left Hounsfield Unit*Left Psoas Area)/(Total Psoas Area), and HUAC =(Right Hounsfield Unit Calculation +Left Hounsfield Unit Calculation)/2.

Statistical Analysis

To determine which perioperative variables were significantly associated with each operative complication, univariate logistic regression models were constructed. Potential predictors of complications included: age, race, gender, BMI, smoking status, COPD, diabetes mellitus, weight loss, type of surgery (PD vs. distal pancreatectomy), vascular resection, blood transfusion, TPI, HUAC, estimated blood loss, pancreatic duct diameter, amount of visceral, hip girdle, or abdominal wall fat based on CT measurements. Jejunostomy tube placement was included as a variable only included after being confirmed to have been placed as part of routine practice. Operative complications under consideration included: length of stay (≤ 10 days vs. >10 days), intensive care unit (ICU) admission, major grade III complications, pancreatic fistula (any), deep vein thrombosis or pulmonary embolism, wound complications, delayed gastric emptying, 30-day readmission, and infectious, GI, pulmonary, or cardiac complications. Perioperative variables significantly

associated with each complication on univariate analysis were considered for possible inclusion in a multivariate model. Multivariate logistic regression models were then constructed to examine the effects of the significant perioperative variables on the odds of each complication (e.g., a length of stay more than 10 days or presence of each complication) using a stepwise variable selection procedure. Estimated effects of predictors are reported as odds ratios (OR) along with 95% confidence intervals.

Since HUAC was significantly associated with several complications, we conducted a post-hoc analysis to determine if it was also associated with overall survival. Patients who died within 90 days were excluded from the analysis. A Cox proportional hazard regression model was utilized to determine if HUAC, both continuously and categorically using the gender-specific cutoffs, was univariately associated with overall survival. All tests were two-sided and tested at the 5% significance level. The data analysis was performed using SAS 9.3 (Cary, NC).

RESULTS

Clinicopathologic and Treatment Related Variables

There were 118 patients with PDA who met the criteria for analysis, and the clinicopathologic and treatment-related variables are shown in Table I. Of note, most patients had PD (n =105, 89.0%) and 35 patients (31.3%) met criteria for morbid obesity (BMI ≥30). Sarcopenia was defined as a TPI or HUAC value within the lowest gender specific quartile (Fig. 1). Using these pre-defined criteria, 31 (26.3%) patients met the criteria for sarcopenia using the TPI while 29 (24.6%) patients met criteria based on the HUAC. For men, the lower quartile was 5.2 cm²/m² for the TPI and 18.8 for the HUAC. For women, the lower quartile was 4.0 cm²/m² for the TPI and 20.3 for the HUAC.

Perioperative Data and Complications

Table II summarizes perioperative outcomes and complications. The median length of stay was 9 days (range 5–77 days), with 31 patients (26.5%) requiring ICU admission. Vascular resection was performed in 12 patients (10.2%). Complications were reported in 93 patients (78.8%); with major grade III complications in 36 patients (30.5%). Infectious complications occurred in 36 patients (30.5%) with 32 patients (27.1%) having a wound complication. Gastrointestinal complications arose in 24 patients (20.3%) and delayed gastric emptying (any grade) occurred in 52 patients (44.1%). There were 8 patients who died within 90 days of resection (6.8%).

Univariate analysis was performed using 19 perioperative variables as mentioned in the Methods. On univariate analysis, there were several preoperative and intraoperative variables that were significantly predictive of complications. Length of stay was predicted by ($P < 0.05$) jejunostomy tube placement, vascular resection, TPI, and HUAC. The following factors were predictive of ICU stay—blood transfusions, age, HUAC, and visceral fat. Major grade III complications were predicted by smoking history, jejunostomy tube placement, vascular resection, blood transfusion, age, TPI, and HUAC. Delayed gastric emptying was predicted by procedure type, jejunostomy tube placement, HUAC, and

pancreatic duct diameter. There were no significant predictors of pancreatic fistula or readmission found on univariate analysis.

A multivariate logistic regression analysis was performed on the data to isolate variables that were independently predictive of complications (Table III). Factors that independently predicted length of stay include presence of a jejunostomy tube ($P=0.03$), the TPI ($P=0.02$), and the HUAC ($P=0.01$). Multivariate analysis demonstrated that receiving a blood transfusion ($P<0.01$) and the HUAC ($P<0.01$) were predictive of ICU stay. The variables that were individually predictive of major grade III complications include jejunostomy tube placement ($P<0.01$), blood transfusion ($P=0.02$), and HUAC ($P<0.01$).

The HUAC was the sole factor that was independently significant for any incidence of any complication ($P<0.01$), infectious complications ($P=0.02$), gastrointestinal complications ($P=0.03$), and cardiac complications ($P<0.01$). In summary, HUAC was a significant independent predictor of any complication, length of stay, intensive care unit stay, delayed gastric emptying, along with major grade III, infectious, gastrointestinal, pulmonary, and cardiac complications. Of note, all the odds ratios were greater than 1 indicating for each 5 unit decrease in HUAC the odds of the respective complication increased.

Impact of Sarcopenia on Postoperative Survival

When evaluated as a continuous variable, HUAC did not predict postoperative overall survival following pancreatic resection ($P=0.44$). This was also the finding when using gender specific cutoffs to compare those with sarcopenia in contrast to those without ($P=0.80$).

DISCUSSION

Morbidity following pancreatectomy for adenocarcinoma is a significant factor in the course of a patient's disease. The complications encountered postoperatively ultimately determine clinical management options and dictate the time frame for administration of adjuvant therapy. The ability to predict complication rates preoperatively can potentially improve patient selection and informed consent prior to surgical resection. Sarcopenia is the degenerative loss of skeletal muscle mass and it is an objective subclinical quantification of a patient's nutritional status, fitness level, and frailty. The HUAC is a patient-specific measurement of the spinal musculature density and fatty infiltration, thus it is reflective of the extent of a patient's sarcopenia. Our results demonstrate that the HUAC is a significant predictor of operative complications following surgical resection in patients with PDA.

The HUAC can be readily obtained from preoperative cross-sectional imaging that is part of the routine staging workup preceding pancreatectomy. The measurement of the HUAC is easy and reproducible and takes only a few minutes so can be easily performed in most clinical scenarios. As a continuous variable, it is an excellent representation of the extent of a patient's sarcopenia. As we have shown, sarcopenia is predictive of complications independent of the patient's body habitus. In some instances, obesity may make it difficult for clinicians to appreciate frailty or muscle wasting due to body habitus. This would make

an evaluation of sarcopenia potentially more valuable in these patients using the HUAC obtained from preoperative imaging.

Sarcopenia that is secondary to malignancy presents as muscle atrophy in the absence of necrosis with a decrease in the size and number of muscle cells, which may be reversible [31]. Given the potential for a decrease in a patient's extent of sarcopenia via clinical intervention, a predictive model of post-operative complications based on this parameter can guide clinical decision-making. Patients who are at a higher risk for complications may undergo neoadjuvant chemotherapy while receiving concurrent therapy to improve their sarcopenia profile prior to surgical resection (e.g., nutrition and exercise optimization). This approach may ultimately decrease complication rates following pancreatectomy resulting in a better outcome that can potentially alter prognosis [32].

While the focus of our study is the correlation between sarcopenia and surgical outcomes, its association with survival has been previously studied. Skeletal muscle radiation attenuation, a component of the HUAC, has been shown to be independently associated with survival in patients with cancer [31]. More specifically, it has also been shown to predict survival following resection of PDA—sarcopenia, as a categorical variable, was associated with a 63% increased risk of death at 3 years following pancreatectomy [24]. Our results did not show that TPI or HUAC in our cohort predicted survival in resectable PDA, which may reflect complication management and timely introduction of adjuvant therapy in most patients. It may also be due to the study sample size.

Our results are clinically applicable to patients with resectable PDA who are candidates for treatment with pancreatic resection. The database from which our results were analyzed consisted of operations performed by numerous surgeons, which introduces the potential for inconsistency in operative complications from one surgeon to the next that is independent of a patient's body habitus. Our results may be skewed depending on which surgeon performed the operation and variations in individual technique, such as routine drainage or jejunostomy tube placement. Furthermore, only CT was utilized in this study. There are data now that support the use of Magnetic Resonance Imaging (MRI) in staging and operative planning in patients with PDA; MRI has been previously used to quantify sarcopenia and therefore could potentially be utilized preoperatively to perform this function [33]. Despite the study limitations, these data may be applicable to patients being evaluated for pancreatic resection for PDA in most high volume centers.

For future studies, it would be valuable to explore the HUAC prospectively as a method of quantifying sarcopenia. The definition of sarcopenia as a categorical variable is not concrete. A commonly used convention is that a patient is diagnosed with sarcopenia if their TPI lies within the lowest gender-specific quartile [24]. The HUAC is representative not only of psoas area but also radiation attenuation, which accounts for both muscle density and fatty infiltration. Sarcopenia could be more clearly quantified and analyzed using this parameter, rather than the TPI. Moreover, sarcopenia is a feature of body habitus that can be altered over time. There is a need for development of a therapeutic strategy to increase a patient's muscle mass in order to favorably alter their sarcopenia profile and decrease their risk for

operative complications. If such a protocol was developed, physicians may contemplate the use of such a therapy prior to resection.

CONCLUSION

The HUAC, a measure of the extent of sarcopenia, is a significant predictor of operative complications following pancreatectomy for PDA. This value is a patient-specific factor that can be readily obtained from preoperative imaging. Given the ease with which the HUAC can be obtained and its association with a host of complications, it can be widely used to assist in prediction of patient morbidity, potentially alter the course of clinical action in patients with sarcopenia, and lower complication rates postoperatively. The HUAC may improve patient selection for pancreatectomy, decisions regarding adjuvant versus neoadjuvant therapy, and the informed consent process.

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Fig. 1.

Gender-specific distribution of BMI and sarcopenia endpoints in patients with resected pancreatic ductal adenocarcinoma. Note that the Hounsfield Unit Average Calculation correlated more with BMI distribution than with that of the Total Psoas Index.

TABLE I

Clinical and Treatment-Related Variables of 118 Patients Treated With Pancreatectomy for Pancreatic Ductal Adenocarcinoma

Variable	N (%) Median (Range)
Procedure	
Pancreaticoduodenectomy	105 (89.0)
Distal pancreatectomy	13 (11.0)
Male gender	75 (63.6)
Race	
White	104 (88.1)
Other	14 (11.9)
Neoadjuvant therapy	15 (13.0)
Diabetes mellitus	31 (26.3)
Tobacco use	34 (29.1)
COPD	6 (5.1)
Weight loss	46 (39.0)
Body mass index	
Underweight/Normal	41(36.6)
Overweight	36 (32.1)
Obese	35 (31.3)
Total Psoas index	
Gender specific lower quartile	87 (73.7)
<Gender specific lower quartile	31 (26.3)
HU average calculation	
Gender specific lower quartile	89 (75.4)
<Gender specific lower quartile	29 (24.6)
Patient imaging parameters	
Visceral fat (mm)	14.7 (1.8–61.6)
Abdominal wall fat (mm)	23.1 (7.8–59.2)
Hip girdle fat (mm)	49.1 (12.1–97.6)
Pancreatic duct diameter (mm)	5.4 (3.0–16.9)

TABLE II

Operative and Treatment Related Variables and Complications Following Pancreatectomy for Pancreatic Ductal Adenocarcinoma

Variable	N (%) or Median (Range)
Length of stay	
>10 days	43 (36.4)
10 days	75 (63.6)
30 day readmission	23 (19.5)
Estimated blood loss	400 (50–7,030)
Jejunostomy tube	22 (18.6)
Perioperative blood transfusion	29 (24.6)
Vascular resection	12 (10.2)
ICU stay	31 (26.5)
Any complication	93 (78.8)
Major grade III complication	36 (30.5)
Pancreatic fistula (any)	16 (13.6)
Infectious complications	36 (30.5)
Gastrointestinal complications	24 (20.3)
Pulmonary complications	20 (17.0)
Cardiac complications	24 (20.3)
DVT/PE	6 (5.1)
Wound complications	32 (27.1)
Delayed gastric emptying	52 (44.1)
90-day mortality	8 (6.8)

TABLE III

Multivariate Analysis of Variables Associated With Operative Outcomes*

Complication	Variable (Units)	Odds ratio (95% CI)	P
Length of stay	Jejunostomy tube (Yes vs. No)	3.11 (1.14–8.51)	0.03
	Total Psoas index (1.5 cm/m ² decrease)	1.75 (1.10–2.78)	0.02
	HU average calculation	2.00 (1.22–3.33)	0.01
Intensive care unit admission	Blood transfusion (Yes vs. No)	6.88 (2.55–18.57)	
	HU average calculation	2.33 (1.32–4.00)	
Any complication	HU average calculation	2.78 (1.47–5.26)	
Major Grade III complication	J tube (Yes vs. No)	7.08 (2.28–22.00)	
	Blood transfusion (Yes vs. No)	3.47 (1.24–9.71)	0.02
	HU average calculation	3.45 (1.82–6.67)	
Infectious complications	HU average calculation	1.69 (1.08–2.70)	0.02
Gastrointestinal complications	HU average calculation	1.75 (1.06–2.94)	0.03
Pulmonary complications	Blood transfusion (Yes vs. No)	3.01 (1.02–8.84)	0.05
	HU average calculation	2.56 (1.43–4.76)	
Cardiac complications	HU average calculation	2.70 (1.54–4.76)	
Wound	BMI (5 unit increase)	1.60 (1.06–2.40)	0.02
Delayed gastric emptying	J tube (Yes vs. No)	9.15 (2.26–36.69)	
	Pancreatic duct diameter (3 mm decrease)	2.44 (1.35–4.35)	
	HU average calculation	2.33 (1.19–4.35)	0.01

* Values provided for the HU Average Calculation reflect a 5 unit decrease.