Original Article | Gastrointestinal Imaging

eISSN 2005-8330
https://doi.org/10.3348/kjr.2022.0277
Korean J Radiol 2022;23(11):1055-1066

Korean Journal of Radiology
KJR

Prognostic Value of Sarcopenia and Myosteatosis in Patients with Resectable Pancreatic Ductal Adenocarcinoma

Dong Wook Kim[1]*, Hyemin Ahn[1]*, Kyung Won Kim[1], Seung Soo Lee[1], Hwa Jung Kim[2], Yousun Ko[1], Taeyong Park[1], Jeongjin Lee[3]

[1]Department of Radiology and Research Institute of Radiology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea; [2]Department of Clinical Epidemiology and Biostatistics, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea; [3]School of Computer Science and Engineering, Soongsil University, Seoul, Korea

Objective: The clinical relevance of myosteatosis has not been well evaluated in patients with pancreatic ductal adenocarcinoma (PDAC), although sarcopenia has been extensively researched. Therefore, we evaluated the prognostic value of muscle quality, including myosteatosis, in patients with resectable PDAC treated surgically.

Materials and Methods: We retrospectively evaluated 347 patients with resectable PDAC who underwent curative surgery (mean age ± standard deviation, 63.6 ± 9.6 years; 202 male). Automatic muscle segmentation was performed on preoperative computed tomography (CT) images using an artificial intelligence program. A single axial image of the portal phase at the inferior endplate level of the L3 vertebra was used for analysis in each patient. Sarcopenia was evaluated using the skeletal muscle index, calculated as the skeletal muscle area (SMA) divided by the height squared. The mean SMA attenuation was used to evaluate myosteatosis. Diagnostic cutoff values for sarcopenia and myosteatosis were devised using the Contal and O'Quigley methods, and patients were classified according to normal (nMT), sarcopenic (sMT), myosteatotic (mMT), or combined (cMT) muscle quality types. Multivariable Cox regression analyses were conducted to assess the effects of muscle type on the overall survival (OS) and recurrence-free survival (RFS) after surgery.

Results: Eighty-four (24.2%), 73 (21.0%), 75 (21.6%), and 115 (33.1%) patients were classified as having nMT, sMT, mMT, and cMT, respectively. Compared to nMT, mMT and cMT were significantly associated with poorer OS, with hazard ratios (HRs) of 1.49 (95% confidence interval, 1.00–2.22) and 1.68 (1.16–2.43), respectively, while sMT was not (HR of 1.40 [0.94–2.10]). Only mMT was significantly associated with poorer RFS, with an HR of 1.59 (1.07–2.35), while sMT and cMT were not.

Conclusion: Myosteatosis was associated with poor OS and RFS in patients with resectable PDAC who underwent curative surgery.

Keywords: *Computed tomography; Muscle quality; Myosteatosis; Pancreatic ductal adenocarcinoma; Sarcopenia*

INTRODUCTION

Sarcopenia, defined as a loss of skeletal muscle mass and strength [1], is a well-known prognostic factor associated with poor prognosis in patients with various diseases [2,3]. Myosteatosis and fat deposition in the muscle are considered biomarkers of poor muscle quality [4]. Although several studies have reported the influence of myosteatosis on muscle strength and physical activity [5,6], as well as poor survival, further evidence is needed to assess the prognostic implications of myosteatosis in various diseases [7,8].

Received: April 25, 2022 **Revised:** July 15, 2022 **Accepted:** July 21, 2022
*These authors contributed equally to this work.
Corresponding author: Kyung Won Kim, MD, PhD, Department of Radiology and Research Institute of Radiology, University of Ulsan College of Medicine, Asan Medical Center, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.
• E-mail: medimash@gmail.com

Computed tomography (CT) is a common, noninvasive method of muscle assessment that measures differences in radiodensity between muscle and other tissues [9]. Sarcopenia can be diagnosed through the quantitative measurement of muscle mass, which can be segmented on CT. Muscle quality assessment for the diagnosis of myosteatosis can also be conducted by measuring the radiodensity of a segmented muscle area, given the inverse linear relationship between radiodensity and the degree of fat deposition [10].

Pancreatic ductal adenocarcinoma (PDAC) is a dismal disease with a 5-year survival rate as low as 6% [11]. It causes body composition changes and many patients develop muscle loss with disease progression [12,13]. Along with other malignancies [4], loss of muscle quality and quantity is associated with poor survival in patients with PDAC. Previous studies have reported the effects of preoperative sarcopenia and myosteatosis on overall survival (OS) and recurrence-free survival (RFS) in patients with PDAC undergoing curative-intent surgery [14-19].

Currently, the use of neoadjuvant chemotherapy in patients with advanced PDAC is increasing. The National Comprehensive Cancer Network (NCCN) proposes that non-metastatic PDAC be classified as resectable, borderline resectable, or locally advanced according to tumor-vascular contact on pretreatment imaging [20]. Curative surgery without neoadjuvant treatment remains the standard treatment only in patients with resectable PDAC. In contrast to previous studies that included all patients undergoing surgery, we believe that the selective inclusion of only those patients receiving curative surgery according to the standard treatment options would allow for a more accurate evaluation of the association between preoperative muscle status and prognosis.

Therefore, we investigated the prognostic value of muscle quality, including myosteatosis, in patients with resectable PDAC who underwent curative surgery, using quantitative muscle measurements on preoperative CT.

MATERIALS AND METHODS

This retrospective observational study was approved by the Institutional Review Board of Asan Medical Center, which waived the requirement for informed consent owing to the retrospective study design (IRB No. 2020-1924).

Patients

Patients with PDAC admitted to our institution between January 2014 and January 2017 were retrospectively and consecutively enrolled as part of the study population in a previous study [21] evaluating the prognosis of PDAC according to the CT characteristics of the tumor. Patients meeting the following criteria were included: 1) resectable PDAC according to the NCCN criteria [20] and 2) curative-intent surgery without neoadjuvant treatment. Briefly, resectable PDAC was defined as PDAC with no arterial (celiac axis, superior mesenteric artery, or common hepatic artery) or tumor contact with the superior mesenteric or portal veins at < 180° without contour irregularity or thrombus [22].

Patients meeting the following criteria were excluded: 1) no pancreatic CT protocol before surgery, 2) palliative surgery or macroscopic residual tumor (R2) after surgery, 3) other coexisting malignancies within 5 years before PDAC diagnosis, and 4) insufficient clinical data.

CT Protocol

Multiphasic CT was performed using multidetector CT scanners (Discovery CT 750HD, GE Medical Systems and Somatom Definition AS+ or Definition Edge, Siemens), and the pancreatic CT protocol was performed according to the NCCN guidelines [20]. Unenhanced and biphasic contrast-enhanced images included the arterial phase (10 seconds after descending aorta enhancement at 100 Hounsfield unit [HU]) and portal venous phase (72 seconds after contrast administration), which were obtained after the intravenous administration of 150 mL of ioversol (Optiray 320; Guerbet) at 3 mL/s. Unenhanced axial images were reconstructed at a 5-mm thickness and 2.5–3.0 mm for the arterial and portal venous phases in the axial and coronal planes, respectively. The other scan parameters included tube voltages of 100 or 120 kVp, tube current of 200–400 mA with automatic exposure control, pitches of 0.6 or 1, and a field of view to fit.

Evaluation of Muscle Quantity and Quality on CT

Muscle quantity and quality were measured in a single slice of an axial CT image of the portal venous phase following the automatic selection of the CT slice at the inferior endplate level of the L3 vertebra (Fig. 1) [23]. All skeletal muscles (psoas, paraspinal, transversus abdominis, rectus abdominis, quadratus lumborum, internal oblique, and external oblique muscles) in the selected image were automatically segmented using a convolutional

https://doi.org/10.3348/kjr.2022.0277

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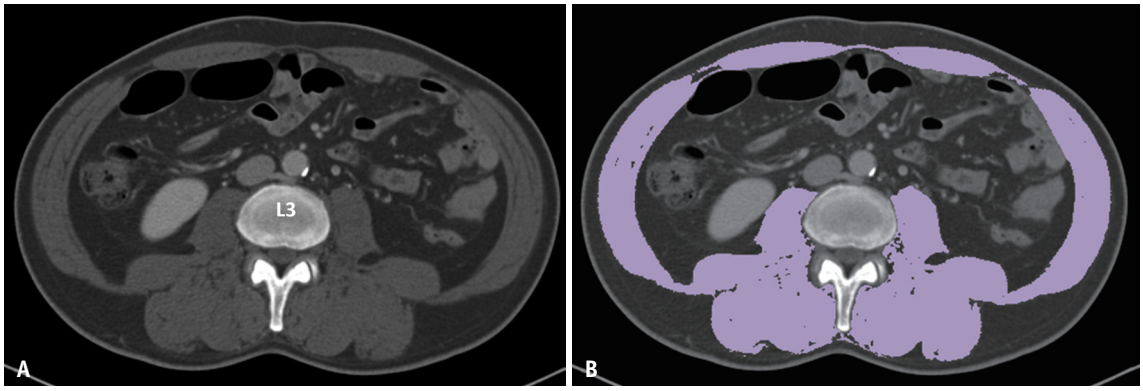

Fig. 1. Evaluation of muscle quantity and quality by CT.
A. Selection of CT slice at the L3 level. **B.** Automatic segmentation of the skeletal muscle area and measurement of the mean attenuation.

neural network (AID-U™, iAID Inc.) with a Dice similarity coefficient of 0.96–0.97 [24].

Clinicopathologic Data Collection

Demographic and laboratory data relevant to patient prognosis (i.e., patient age, sex, height, weight, and cancer antigen 19-9 level) were collected from the electronic medical records and measured within 1 month before surgery. Surgical and pathological data, including the type of surgery, cancer stage according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system (Supplementary Table 1) [25], tumor differentiation, and resection margin status (R0, negative margin vs. R1, microscopically positive margin) [26], were acquired. Adjuvant treatment, typically initiated 3–10 weeks after surgery, was also confirmed.

Data on PDAC recurrence events were collected from radiologic reports of follow-up contrast-enhanced CT scans, routinely acquired every 3 months for the first year and every 3–6 months thereafter. Data on death events were collected from the electronic medical records.

Determination of Patients with Sarcopenia and Myosteatosis

To identify patients with sarcopenia, we used the skeletal muscle index (SMI), calculated as the skeletal muscle area (SMA) divided by the height squared (cm^2/m^2) [4,27]. To identify patients with myosteatosis, we used the mean attenuation of the SMA (HU) [4].

Before determining the cutoff values for sarcopenia and myosteatosis, the patients were categorized into one of eight subgroups dichotomized by age (< 65 vs. ≥ 65 years), sex (male vs. female), and body mass index (BMI) (underweight or normal [BMI < 23 kg/m^2] vs. overweight or obese [BMI ≥ 23 kg/m^2]). The optimal cutoff values for sarcopenia and myosteatosis in each subgroup were separately derived using the outcome-based Contal and O'Quigley method [28], which is used to obtain survival-related cutoffs by calculating the maximum value of log-rank statistics. In our study, the cutoff values were determined based on the time to death.

Survival Analysis according to Muscle Type

The cutoff values for sarcopenia and myosteatosis were used to classify the patients into the following four muscle types: 1) normal muscle type (nMT), patients with neither sarcopenia nor myosteatosis, 2) sarcopenic muscle type (sMT), patients with sarcopenia but no myosteatosis, 3) myosteatotic muscle type (mMT), patients with myosteatosis but no sarcopenia, and 4) combined muscle type (cMT), patients with both sarcopenia and myosteatosis.

The primary outcome was OS, defined as the survival time between surgery and death. The secondary outcome was RFS, defined as the survival time between surgery and recurrence or death [29]. Patients without death or recurrence were excluded at the last follow-up visit. Kaplan–Meier survival curves for OS and RFS were plotted according to muscle type and the presence of sarcopenia and myosteatosis and compared using log-rank tests. The univariable and multivariable Cox proportional hazard regression analyses included muscle types and clinicopathological characteristics (i.e., serum cancer antigen 19-9 level, AJCC cancer stage, tumor differentiation, resection margin status, and adjuvant treatment), which are considered to be potentially associated with patient survival.

The associations between muscle type and clinicopathological characteristics were analyzed using

 https://doi.org/10.3348/kjr.2022.0277

Pearson's χ^2 tests. The intervals between the surgery date and the first date of adjuvant treatment were analyzed according to muscle type using one-way analysis of variance.

Statistical significance was set at $p < 0.05$. SAS (version 9.4; SAS Institute), SPSS (version 21.0; IBM Corp.), and R (version 3.6.0; R Foundation for Statistical Computing) were used to perform statistical analyses.

RESULTS

Patient Characteristics

Among the 456 patients with resectable PDAC, 410 underwent successful curative surgery (Fig. 2). Sixty-three patients were excluded because of the absence of a pancreatic CT protocol before surgery (n = 38), palliative surgery or macroscopic residual tumor (n = 5), coexisting malignancy within 5 years (n = 18), and insufficient clinical data (n = 2). Finally, 347 patients (mean age ± standard deviation, 63.6 ± 9.6 years; 202 male) were included. The patient characteristics are summarized in Table 1. The median interval between CT and surgery was 8 days (range: 1–35 days). The AJCC tumor stage was IA or IB in 124 (35.7%) patients, IIA or IIB in 164 (47.3%) patients, and III in 59 (17.0%) patients. The tumor was well differentiated in 40 (11.5%) patients, moderately differentiated in 269 (77.5%) patients, and poorly differentiated or undifferentiated in 38 (11.0%) patients. The resection margins were R0 in 259 (74.6%) patients and R1 in 88 (25.4%) patients. Adjuvant treatment was administered to 226 patients (65.1%).

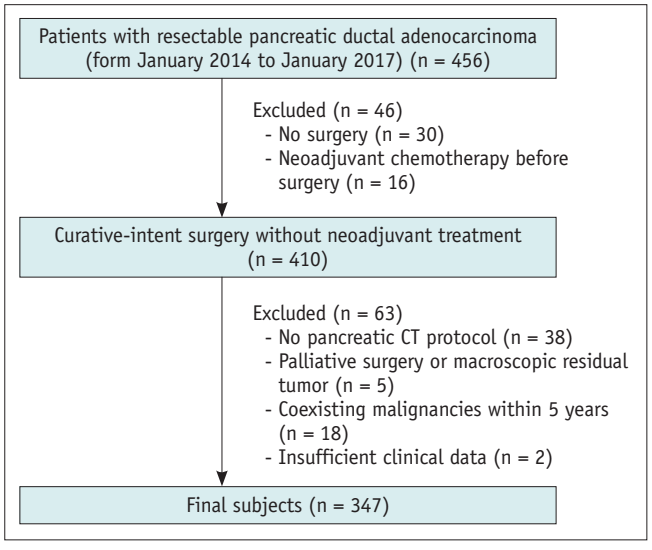

Fig. 2. Flow diagram of the study patients.

Table 1. Patient Characteristics

Characteristics	Values
Age, year	63.6 ± 9.6
Male:female	202:145
Height, m	162.0 ± 8.6
Body mass index, kg/m^2	23.2 ± 2.9
Cancer antigen 19-9 level, U/mL*	81 (22.2–322.6)
Tumor location	
Head	216 (62.3)
Body	65 (18.7)
Tail	66 (19.0)
AJCC tumor stage	
IA	36 (10.4)
IB	88 (25.3)
IIA	17 (4.9)
IIB	147 (42.4)
III	59 (17.0)
Tumor differentiation	
Well-differentiated	40 (11.5)
Moderately differentiated	269 (77.5)
Poorly differentiated or undifferentiated	38 (11.0)
Resection margin	
R0	259 (74.6)
R1	88 (25.4)
Adjuvant treatment	226 (65.1)

Unless otherwise specified, data are presented as mean ± standard deviation for continuous variables and numbers (percentages) for categorical variables. *Median with an interquartile range in parenthesis. AJCC = American Joint Committee on Cancer

Table 2. Cutoff Values for Sarcopenia (SMI) and Myosteatosis (Mean Attenuation of SMA) according to Using the Contal and O'Quigley Methods

Body Mass Index	Age (Year)	SMI (cm^2/m^2)		Mean Attenuation of SMA (HU)	
		Male	Female	Male	Female
Underweight or normal (< 23 kg/m^2)	< 65	45.25	37.39	51.71	49.05
	≥ 65	48.86	38.85	44.73	48.82
Overweight or obese (≥ 23 kg/m^2)	< 65	54.89	44.90	49.72	40.33
	≥ 65	49.66	49.84	49.36	43.89

HU = Hounsfield unit, SMA = skeletal muscle area, SMI = skeletal muscle index

https://doi.org/10.3348/kjr.2022.0277

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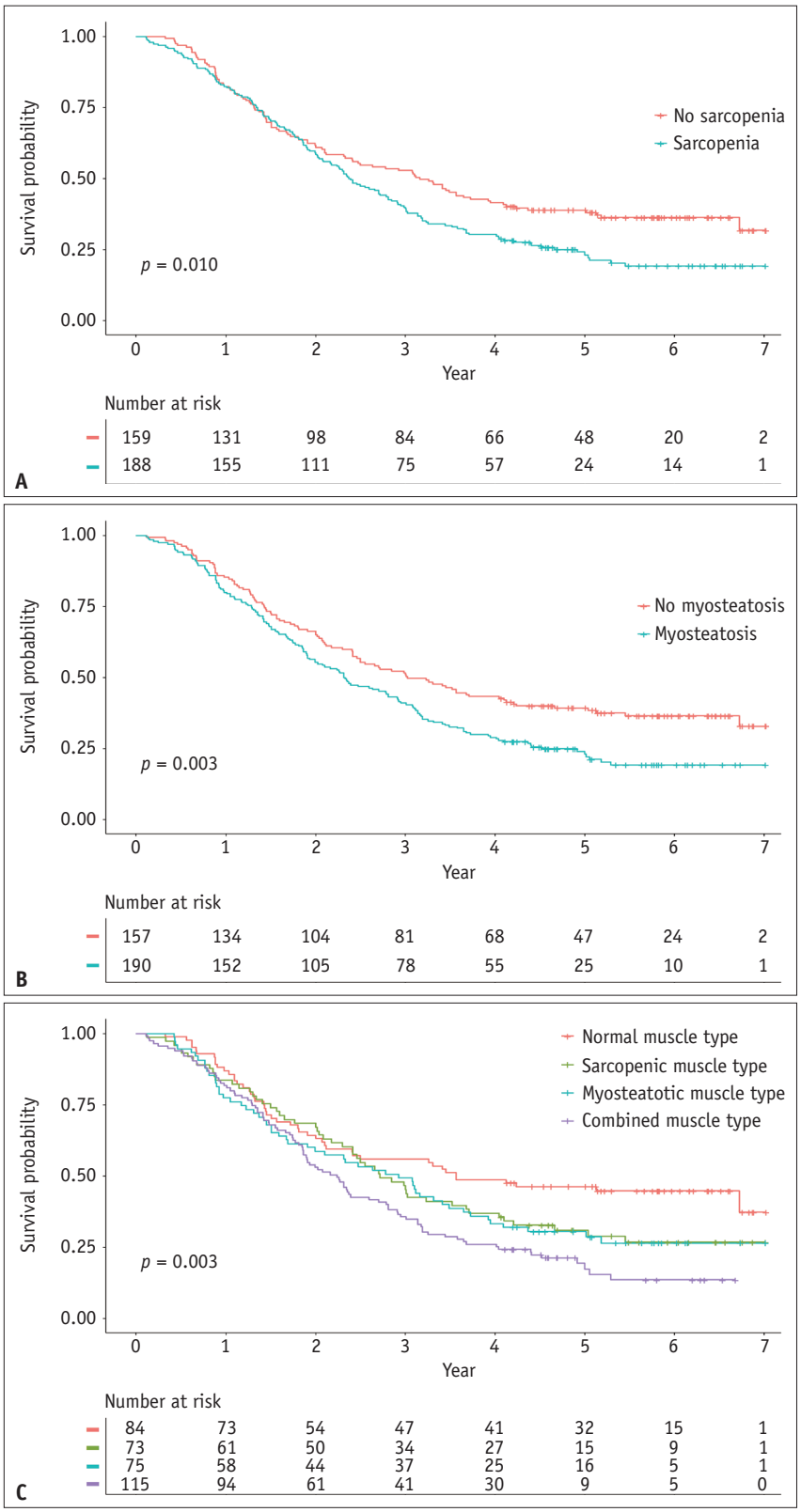

Fig. 3. Kaplan–Meier curves of the OS according to the presence of sarcopenia (A) and myosteatosis (B) and according to the muscle types (C).

A-C. The Kaplan–Meier curves indicate a worse OS in patients with sarcopenia compared to the OS in patients without sarcopenia (median, 28.7 vs. 38.1 months; $p = 0.010$; **A**) and in patients with myosteatosis compared to the OS in patients without myosteatosis (median, 28.0 vs. 36.5 months; $p = 0.003$; **B**). The Kaplan–Meier curves differed significantly according to muscle type ($p = 0.003$; **C**). OS = overall survival

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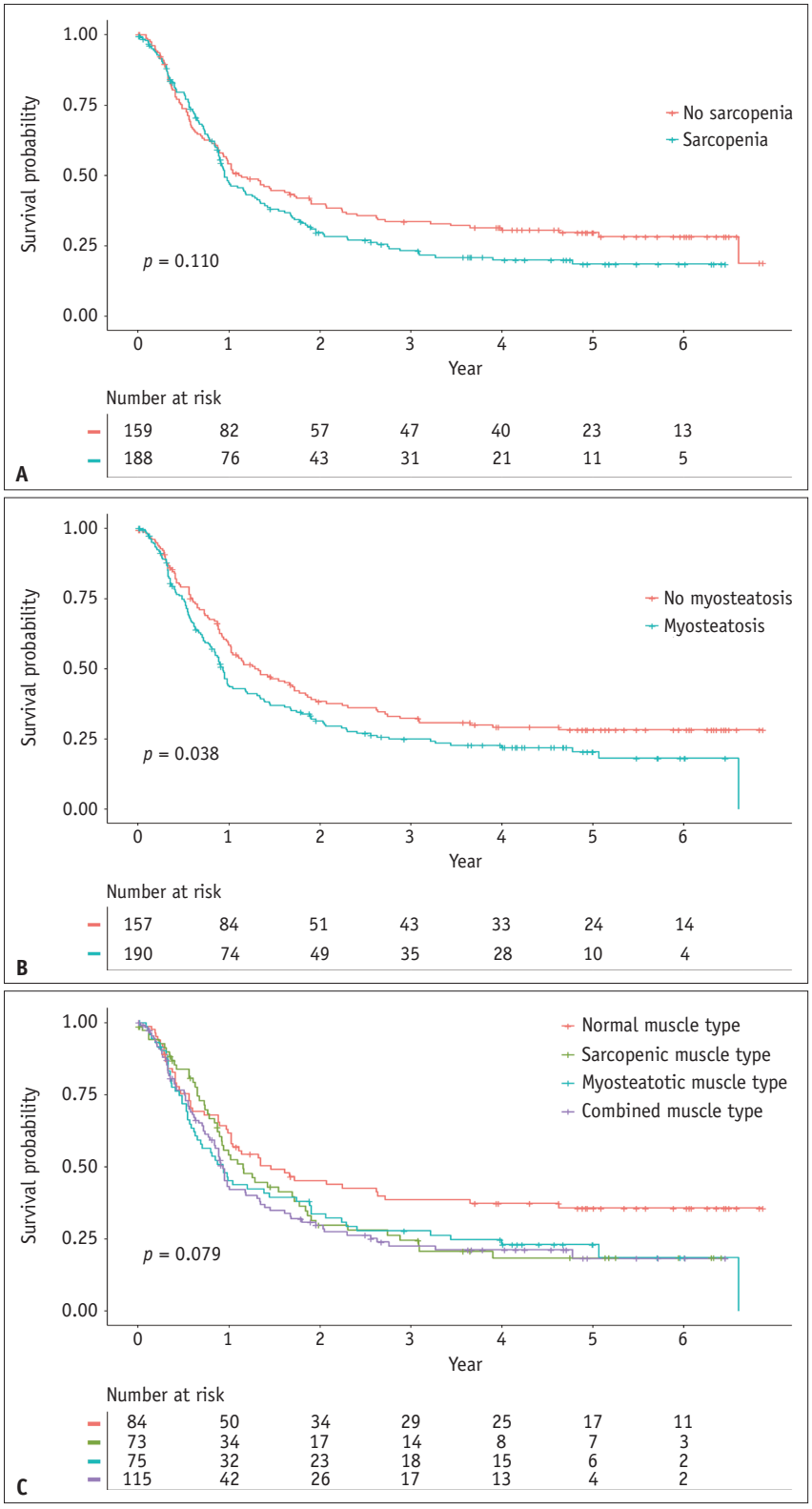

Fig. 4. Kaplan–Meier curves of the RFS according to the presence of sarcopenia (A) and myosteatosis (B) and muscle types (C).
A-C. RFS and sarcopenia showed no significant association (median, 11.5 vs. 13.8 months; $p = 0.110$; **A**). In contrast, the Kaplan–Meier curves showed a worse RFS in patients with myosteatosis compared to that in patients without myosteatosis (median, 11.3 vs. 16.0 months; $p = 0.038$; **B**). Although the Kaplan–Meier curves did not differ significantly according to muscle type ($p = 0.079$; **C**), normal muscle type was associated with a better RFS compared to that in the other muscle types (median RFS: 17.6 months for normal muscle type vs. 14.0 months for sarcopenic muscle type, 11.3 months for myosteatotic muscle type, and 11.3 months for combined muscle type). RFS = recurrence-free survival

https://doi.org/10.3348/kjr.2022.0277

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Muscle Measurement and Determination of Sarcopenia and Myosteatosis

The mean SMA and SMI were 124.0 ± 27.2 cm^2 and 48.9 ± 7.6 cm^2/m^2, respectively. The mean value of the mean attenuation of SMA was 46.3 ± 8.1 HU.

The cutoff values for sarcopenia and myosteatosis in each subgroup are summarized in Table 2. Based on the cutoff values, 188 (54.2%) patients were diagnosed with sarcopenia and 190 (54.8%) with myosteatosis. Regarding muscle types, 84 (24.2%), 73 (21.0%), 75 (21.6%), and 115 (33.1%) patients were classified as nMT, sMT, mMT, and cMT, respectively.

Univariable Survival Analysis

A total of 247 (71.2%) patients died during follow-up, with a median OS of 31.8 months (range, 1.4–84.8 months). The Kaplan–Meier curves showed a worse OS in patients with sarcopenia compared to that in patients without sarcopenia (median, 28.7 vs. 38.1 months; $p = 0.010$) (Fig. 3A) and in patients with myosteatosis compared to patients without myosteatosis (median, 28.0 vs. 36.5 months; $p = 0.003$) (Fig. 3B). The Kaplan–Meier curves also revealed a significant difference between muscle types ($p = 0.003$) (Fig. 3C).

Tumor recurrence occurred in 238 (68.6%) patients, with a median RFS of 12.3 months (range, 0.1–82.9 months). RFS and sarcopenia were not significantly associated (median, 11.5 vs. 13.8 months; $p = 0.110$) (Fig. 4A). In contrast, the Kaplan–Meier curves showed a worse RFS in patients with myosteatosis compared to that in patients without myosteatosis (median, 11.3 vs. 16.0 months; $p = 0.038$) (Fig. 4B). Although the Kaplan–Meier curves did not differ significantly according to muscle type ($p = 0.079$) (Fig. 4C), nMT tended to be associated with a better RFS compared to that in the other muscle types (median RFS: 17.6 months for nMT vs. 14.0 months for sMT, 11.3 months for mMT, and 11.3 months for cMT).

Multivariable Survival Analysis

Table 3 summarizes the results of the univariable and multivariable Cox proportional analyses of OS and RFS according to the muscle types and clinicopathologic characteristics (also see the representative cases in Supplementary Figs. 1, 2). In the univariable analysis, mMT (hazard ratio [HR], 1.49; 95% confidence interval [CI], 1.01–2.21; $p = 0.046$) and cMT (HR, 1.92; 95% CI, 1.35–2.74; $p < 0.001$) were associated with a significantly

Table 3. Univariable and Multivariable Cox Proportional Hazard Analyses of the Muscle Type and Clinicopathologic Characteristics

Parameter	Overall Survival				Recurrence-Free Survival			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Muscle type								
Normal muscle type	1 [reference]		1 [reference]		1 [reference]		1 [reference]	
Sarcopenic muscle type	1.41 (0.95–2.09)	0.090	1.40 (0.94–2.10)	0.098	1.39 (0.94–2.06)	0.096	1.43 (0.96–2.13)	0.076
Myosteatotic muscle type	1.49 (1.01–2.21)	0.046	1.49 (1.00–2.22)	0.049	1.49 (1.02–2.18)	0.040	1.59 (1.07–2.35)	0.020
Combined muscle type	1.92 (1.35–2.74)	< 0.001	1.68 (1.16–2.43)	0.006	1.56 (1.09–2.22)	0.014	1.35 (0.93–1.96)	0.116
Cancer antigen 19-9 level	1.00 (1.00–1.00)	< 0.001	1.00 (1.00–1.00)	0.096	1.00 (1.00–1.00)	0.063	1.00 (1.00–1.00)	0.100
AJCC tumor stage								
IA or IB	1 [reference]		1 [reference]		1 [reference]		1 [reference]	
IIA or IIB	1.98 (1.47–2.66)	< 0.001	1.99 (1.47–2.71)	< 0.001	2.19 (1.61–2.97)	< 0.001	2.05 (1.50–2.82)	< 0.001
III	2.72 (1.88–3.93)	< 0.001	2.78 (1.88–4.11)	< 0.001	2.87 (1.97–4.19)	< 0.001	2.80 (1.89–4.16)	< 0.001
Tumor differentiation								
Well-differentiated	1 [reference]		1 [reference]		1 [reference]		1 [reference]	
Moderately differentiated	2.11 (1.32–3.39)	0.002	2.10 (1.30–3.39)	0.002	2.65 (1.59–4.42)	< 0.001	2.53 (1.49–4.28)	< 0.001
Poorly differentiated or undifferentiated	3.55 (2.01–6.28)	< 0.001	4.41 (2.45–7.91)	< 0.001	3.95 (2.12–7.34)	< 0.001	5.28 (2.77–10.08)	< 0.001
Resection margin (R1)	1.61 (1.22–2.12)	< 0.001	1.29 (0.96–1.72)	0.086	1.62 (1.22–2.15)	< 0.001	1.36 (1.01–1.82)	0.043
Adjuvant treatment	0.59 (0.46–0.76)	< 0.001	0.53 (0.40–0.69)	< 0.001	0.68 (0.52–0.90)	0.006	0.60 (0.45–0.80)	< 0.001

AJCC = American Joint Committee on Cancer, CI = confidence interval, HR = hazard ratio

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Table 4. Association between the Muscle Types and Clinicopathologic Characteristics

Characteristics	Muscle Type				*P*
	Normal Muscle Type (n = 84)	Sarcopenic Muscle Type (n = 73)	Myosteatotic Muscle Type (n = 75)	Combined Muscle Type (n = 115)	
AJCC tumor stage					0.971
IA or IB	31 (36.9)	26 (35.6)	25 (33.3)	42 (36.5)	
IIA or IIB	37 (44.0)	37 (50.7)	37 (49.3)	53 (46.1)	
III	16 (19.0)	10 (13.7)	13 (17.3)	20 (17.4)	
Tumor differentiation					0.694
Well-differentiated	10 (11.9)	7 (9.6)	8 (10.7)	15 (13.0)	
Moderately differentiated	63 (75.0)	57 (78.1)	63 (84.0)	86 (74.8)	
Poorly differentiated or undifferentiated	11 (13.1)	9 (12.3)	4 (5.3)	14 (12.2)	
Resection margin (R1)	18 (21.4)	25 (34.2)	14 (18.7)	31 (27.0)	0.131
Adjuvant treatment	66 (78.6)	49 (67.1)	47 (62.7)	64 (55.7)	0.009

Data are presented as numbers (percentages). AJCC = American Joint Committee on Cancer

worse OS compared to nMT. In the multivariable analysis, mMT (HR, 1.49; 95% CI, 1.00–2.22; $p = 0.0496$) and cMT (HR, 1.68; 95% CI, 1.16–2.43; $p = 0.006$) were associated with significantly worse OS compared to nMT after adjusting for clinicopathologic characteristics. AJCC tumor stage ($p < 0.001$), tumor differentiation ($p < 0.001$), and adjuvant treatment ($p < 0.001$) were significantly associated with OS.

Meanwhile, the univariable analysis indicated that mMT (HR, 1.49; 95% CI, 1.02–2.18; $p = 0.040$) and cMT (HR, 1.56; 95% CI, 1.09–2.22; $p = 0.014$) were related to a significantly worse RFS compared to nMT. In the multivariable analysis, mMT was associated with a significantly worse RFS compared to nMT (HR, 1.59; 95% CI, 1.07–2.35; $p = 0.020$). However, sMT (HR, 1.43; 95% CI, 0.96–2.13; $p = 0.076$) and cMT (HR, 1.35; 95% CI, 0.93–1.96; $p = 0.116$) were not related to RFS. In addition, AJCC tumor stage ($p < 0.001$), tumor differentiation ($p < 0.001$), resection margins ($p = 0.043$), and adjuvant treatment ($p < 0.001$) were significantly associated with RFS.

Association between Muscle Types and Clinicopathologic Characteristics

Table 4 summarizes the associations between muscle type and clinicopathological characteristics, demonstrating a significant association between adjuvant treatment and muscle type ($p = 0.009$). Patients undergoing adjuvant treatment with available information (n = 184), showed significant differences between the intervals from the date of surgery to the first date of adjuvant treatment (mean interval ± standard deviations; 38.8 ± 15.5 days for nMT, 45.8 ± 19.5 days for sMT, 49.1 ± 20.1 days for mMT, and 45.5 ± 16.5 days for cMT; $p = 0.04$). The other clinicopathological characteristics, including AJCC tumor stage ($p = 0.971$), tumor differentiation ($p = 0.694$), and resection margin ($p = 0.131$), were not significantly associated with muscle type.

DISCUSSION

The results of our study revealed that muscle types with myosteatosis, regardless of the presence of sarcopenia (i.e., mMT and cMT), were linked to poor OS in patients with resectable PDAC (HR vs. nMT, mMT = 1.49 [95% CI, 1.00–2.22] and cMT = 1.68 [95% CI, 1.16–2.43]). In addition, mMT and cMT were associated with RFS in the univariable analysis; however, only mMT was associated with a significantly higher tumor recurrence rate than nMT in the multivariable analysis (HR, 1.59; 95% CI, 1.07–2.35).

Our results indicated that myosteatosis is a disease entity distinct from sarcopenia and plays an independent prognostic role. This finding is supported by previous studies reporting that myosteatosis, but not sarcopenia, was associated with poor survival in patients with pancreatic or periampullary cancers [30,31]. This result could be attributed to the different mechanisms of sarcopenia and myosteatosis that contribute to nutritional and immunologic disturbances [32]. Unlike sarcopenia, myosteatosis (fat deposition within muscles) leads to the accumulation of lipid intermediates (i.e., diacylglycerol and ceramide) and insulin resistance [8]. It is also associated with increased systemic inflammation and oxidative stress [33,34]. Indeed, myosteatosis is associated with elevated levels of serum inflammatory markers (albumin, white blood cell count, neutrophil-to-lymphocyte ratio, and

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C-reactive protein) [30,31]. In addition, Stretch et al. [35] reported that myosteatosis and sarcopenia were associated with different body compositions, gene expression, and metabolites.

Our results showing a significant association between adjuvant treatment and muscle type suggested that patients with impaired muscle function were less likely to receive adjuvant treatment compared to patients with normal muscle function owing to their poor postoperative health status, which may have significantly contributed to their poor survival [36]. Consistent with our results, a previous study reported an association between myosteatosis and incomplete adjuvant chemotherapy [37]. Although we could not investigate this further in our retrospective study, a higher risk of postoperative complications and longer hospital stay may also contribute to poor outcomes in patients with sarcopenia and myosteatosis [8,38].

Several reports have shown the effect of preoperative sarcopenia or myosteatosis on the survival of patients with PDAC [14-19]; however, their findings were contradictory and contrary to our results. For example, some studies showed that sarcopenia and myosteatosis were associated with poor survival [14,17,19], while other studies reported that sarcopenia only was a prognostic factor for poor survival [15,16]. The variation in study results may be attributed to differences in study populations. Our study showed the effect of preoperative sarcopenia and myosteatosis in selected patients with resectable PDAC (according to the NCCN guidelines) requiring curative surgery without neoadjuvant treatment and, therefore, has clinical utility. Moreover, variations in the methods used for muscle measurement and the cutoff values for sarcopenia and myosteatosis may have contributed to the difference between our results and those of previous studies. Unlike previous studies, in which the cutoffs were arbitrarily determined using the lowest tertile [16,18] or survival outcomes at fixed time points [15,17], our results revealed the prognostic value of sarcopenia and myosteatosis when determining the optimal cutoffs in consideration of patient survival based on the Contal and O'Quigley methods.

Our results indicated that the preoperative diagnosis of myosteatosis may be crucial for risk stratification after surgery and for determining management requirements [14,39]. For example, resistance training is the most important element of exercise programs [40,41]. In addition, nutritional support, including vitamin D, β-hydroxy β-methyl butyrate, and omega-3 fatty acids, improves muscle mass and quality in cancer patients [41,42].

Our study has several limitations. First, the reason for the lack of any significant association between cMT and poor RFS in the multivariable analysis (HR 1.35, 95% CI 0.93–1.96, $p = 0.116$) is unclear. Considering the low prevalence of adjuvant treatment in cMT, the presence of adjuvant treatment may have been a confounder in the statistical analysis, undermining the association between cMT and poor RFS. Second, we calculated the cutoff values for the diagnosis of sarcopenia and myosteatosis based on a relatively small number of patients from a single institution. Therefore, validation and generalization of these cutoff values require further investigation across various somatotypes and ethnicities. Third, we measured muscle quantity and quality at a single time point on preoperative CT images. The effect of longitudinal interval changes in the muscle after surgery may also be an important prognostic factor for survival; however, data on this were not available in our study because postoperative imaging was conducted at various time points and using various CT protocols. Finally, unlike the pooled results from previous meta-analyses [43,44], margin status was not identified as an independent factor for OS. However, our results are understandable because the prognostic value of margin status was largely affected by the study design, including the definition of R0, the anatomic location of the tumor, the location of the positive margin, and the presence of adjuvant treatment [43,45-47].

In conclusion, preoperative myosteatosis was associated with poor OS and RFS after curative surgery in patients with resectable PDAC. Preoperative assessment of muscle quality may be valuable for treatment planning and optimization of nutritional support and physical therapy.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2022.0277.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

Seung Soo Lee who is on the editorial board of the *Korean Journal of Radiology* was not involved in the editorial

evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Author Contributions

Conceptualization: Dong Wook Kim, Kyung Won Kim, Seung Soo Lee. Data curation: Dong Wook Kim, Seung Soo Lee. Formal analysis: Dong Wook Kim, Hyemin Ahn, Hwa Jung Kim. Funding acquisition: Kyung Won Kim, Yousun Ko. Investigation: Dong Wook Kim, Hyemin Ahn. Methodology: Dong Wook Kim, Hyemin Ahn, Kyung Won Kim, Hwa Jung Kim. Project administration: Kyung Won Kim. Resources: Kyung Won Kim. Software: Taeyong Park, Jeongjin Lee. Supervision: Kyung Won Kim. Visualization: Dong Wook Kim, Hyemin Ahn. Writing—original draft: Dong Wook Kim, Hyemin Ahn. Writing—review & editing: Dong Wook Kim, Hyemin Ahn, Kyung Won Kim.

ORCID iDs

Dong Wook Kim
https://orcid.org/0000-0001-7887-657X
Hyemin Ahn
https://orcid.org/0000-0002-8151-8949
Kyung Won Kim
https://orcid.org/0000-0002-1532-5970
Seung Soo Lee
https://orcid.org/0000-0002-5518-2249
Hwa Jung Kim
https://orcid.org/0000-0002-2227-6775
Yousun Ko
https://orcid.org/0000-0002-2181-9555
Taeyong Park
https://orcid.org/0000-0002-7523-8975
Jeongjin Lee
https://orcid.org/0000-0001-9676-271X

Funding Statement

This study was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI18C1216).

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