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Original article

Both skeletal muscle index and muscle attenuation are associated with frailty in preoperative older patients with pancreatic cancer

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SUMMARY

Background and aims: Frailty and sarcopenia are associated with morbidity and mortality in older patients with cancer. The aim of this study was to examine the association of frailty with skeletal muscle index (SMI) and muscle attenuation (MA) on preoperative CT-scans in older patients with pancreatic cancer.

Methods: A single-center retrospective study was performed in patients aged ≥70 years with pancreatic cancer. Frailty was assessed by an abbreviated GA screening. Preoperative SMI and MA were determined by computed tomography (CT) scan analysis. The association of frailty and individual frailty domains with SMI and MA was assessed using linear regression analyses.

Results: 101 patients were included of which 15 (14.9 %) were frail. Frailty was associated with lower SMI (adjusted β: −5.07 cm^2/m^2; 95 % CI: −8.77–1.36) and MA (adjusted β: −5.70 HU; 95 % CI: −9.63–1.77). Both impaired functionality and risk of delirium were associated with lower SMI (adjusted β: −7.01 cm^2/m^2; 95 % CI: −11.69–2.33 and adjusted β: −4.58 cm^2/m^2; 95 % CI: −8.22–0.95, respectively). Impaired functionality was also associated with lower MA (adjusted β: −6.88 HU; 95 % CI: −11.89–1.87).

Conclusion: Frailty and impaired functionality were associated with lower SMI and MA. Risk of delirium was independently associated with lower SMI in preoperative older patients with pancreatic cancer. These results suggests that SMI and MA should be included in standard GA screening to better identify high-risk patients and enable more targeted treatment selection.

1. Introduction

The treatment of older adults with pancreatic cancer is complicated by the heterogeneous aging process [1]. The last decade has seen a surge in research establishing sarcopenia and frailty as common entities predicting morbidity and mortality in older patients with cancer. Although sarcopenia and frailty are both associated with poor outcomes, they should be seen as distinct conditions (Fig. 1) [2,3]. Sarcopenia is often considered a precursor or component of frailty, but sarcopenia does not appear to be a good biomarker to confirm the presence of frailty [2]. The relationship between sarcopenia and frailty is not yet fully characterized, and therefore disentangling both conditions is recommended to gain a better understanding of the health status of older adults [2,3].

Frailty is a common geriatric syndrome characterized by an increased vulnerability to negative health outcomes, such as loss of independence, lower quality of life, surgical complications, and

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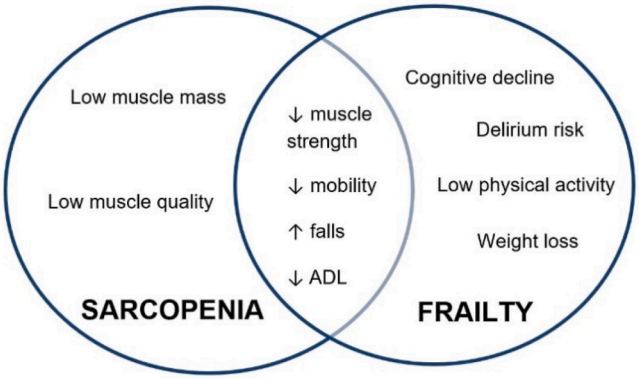

Fig. 1. The conceptual overlap between frailty and sarcopenia.

increased mortality [4]. Many frail older patients lack the physiologic reserve to recover from acute toxicities of chemotherapy or surgical complications, which may lead to functional dependency and suboptimal cancer treatment [4,5]. Therefore, frailty is commonly used in the preoperative process to guide clinical decision making for older patients with pancreatic cancer [5]. The geriatric assessment (GA) is a well-established method to assess frailty in older adults. However, it is time-consuming and there are not enough geriatric providers to assess and manage all geriatric patients. Therefore, an abbreviated GA screening is often used in clinical practice [6].

The prevalence of sarcopenia in patients with pancreatic cancer ranges from 17 % to 65 % [7]. Low skeletal muscle index (SMI), commonly referred to as sarcopenia, has been associated with disability, increased incidence of surgical complications and higher mortality in older patients with pancreatic cancer [8,9]. The wide variation in prevalence is likely due to the heterogeneous patient groups with different cancer stages and different methods of measuring sarcopenia [10]. In addition, muscle attenuation (MA), considered as a marker of muscle quality, is also an important parameter for clinical outcomes [11].

To the best of our knowledge, the association between preoperative frailty and sarcopenia has not been studied in patients with pancreatic cancer before. Therefore, the aim of this study was to examine the association of frailty with SMI and MA on CT-scans in preoperative older patients with pancreatic cancer. The secondary aim was to examine the association of the individual frailty domains with SMI and MA.

2. Materials and methods

2.1. Study design and population

A single-center retrospective study was performed at the Leiden University Medical Center (LUMC). The study population consisted of older patients who underwent pancreaticoduodenectomy in the period of January 2012 to December 2021 in the LUMC. Patients aged ≥70 years who underwent pancreaticoduodenectomy for pancreatic cancer were included (n = 114). Patients with no available information on frailty, no preoperative abdominal CT-scan, and CT-scan performed more than three months before surgery were excluded.

2.2. Data collection

Preoperative patient characteristics and postoperative outcome parameters were retrieved from the prospectively collected dataset of the Dutch Pancreatic Cancer Group (DPCG) [12]. The following data were retrieved from the DPCG: sex, age at time of admission for surgery, preoperative weight loss in the past three months, body mass index (BMI), American Society of Anesthesiologists (ASA) score, TNM stage (according to the 7th edition of the UICC tumor classification), type of surgery, neo-adjuvant treatment, comorbidities, surgical complications and 1-year survival. The preoperative CT-scans were collected at the department of Radiology. Data derived from the abbreviated GA screening were obtained from the electronic medical records (HIX, ChipSoft, The Netherlands). The collection of these data was part of the TENT study (Triage of Elderly Needing Treatment), a prospective study approved by the Medical Ethical Research Committee of the LUMC (NL53575.058.15).

2.3. Measurements

2.3.1. Skeletal muscle index and muscle attenuation

Skeletal muscle mass (SMM) and MA were assessed on CT-scans by measuring the cross-sectional area of a single vertebral slice at the level of the third lumbar vertebra (L3). At this level, cross-sectional skeletal muscle area is highly correlated with total body SMM [13,14]. CT-scans were preoperatively performed for diagnosis or staging of pancreatic cancer. Abdominal CT-scans closest to the date of surgery were used with oral or intravenous contrast, 120 kV and coupe thickness of 5 mm in the portal venous phase. All CT-scans were analyzed by one trained researcher (CL) using SliceOmatic (version 5.0, Tomovision, Canada) [15].

The following muscle groups were analyzed to determine the SMM: musculus rectus abdominis, musculus obliquus internus and externus, musculus transversus, musculus psoas major and minor, musculus erector spinae and musculus quadratus lumborum. Hounsfield unit (HU) thresholds were −29 to +150 HU for SMM [16]. SMI was calculated by dividing the SMM (in cm^2) by the square of height (m^2). MA was defined as the mean HU of the SMM surface.

2.3.2. Frailty

Frailty was preoperatively determined by an abbreviated GA screening; the VMS-based screening tool. VMS is a Dutch frailty assessment tool for older patients that includes four frailty domains: risk of impaired functionality, delirium, falls and undernutrition [17].

Impaired functionality was assessed using the six-item Katz activities of daily living (ADL), including bathing, toileting, dressing, eating, transferring, and continence [18]. Katz ADL score ≥2 was defined as an impaired score. Risk of delirium was assessed using three questions, including memory problems, the need for help with self-care and previously experienced confusion. Score ≥1 was considered as an increased risk of delirium [17]. Fall risk was assessed with a single question and defined as either present or absent. Risk of undernutrition was assessed with the Malnutrition Universal Screening tool (MUST). Increased risk of undernutrition was defined as MUST score ≥ 2 [19]. The cumulative risk score of the frailty domains was composed by summing the total number of deficits. Patients were defined as frail when two or more domains were impaired, pre-frail with one domain impaired and non-frail with no impairments.

2.4. Statistical analysis

Descriptive analyses of baseline characteristics were performed for the study population. Normally distributed continuous variables were presented as mean with standard deviation (SD) and non-normally distributed variables as median with interquartile range (IQR). Normality and linearity were checked by using

histograms and scatter plots. Ordinal or categorical variables were presented as absolute numbers and percentage of total (%). Differences between the non-frail, pre-frail and frail groups were tested with the Chi–Square test for nominal data and with the Kruskal–Wallis test for ordinal and non-normally distributed continuous variables. For normally distributed continuous variables, one-way analysis of variance (ANOVA) was used. When a statistically significant difference between the groups was detected, Tukey's honestly significant difference (HSD) test was used for multiple paired comparison.

The primary outcomes were SMI and MA, and presented as continuous variables. Secondarily, all of the four frailty domains were separately analyzed to assess the associations of the individual domains with SMI and MA. Linear regression analyses were performed to assess the associations of both frailty and individual frailty domains with SMI and MA. The linear regression analyses were adjusted for age, sex, and weight (model SMI) and for age, sex, and BMI (model MA) [13,20,21]. All confounders were added to the regression models. Exposure and outcome variables, and potential confounders were complete for all patients. All analyses were performed using STATA SE 16 software. P-values of <0.05 were considered statistically significant.

3. Results

A total of 114 patients aged 70 years or older underwent pancreaticoduodenectomy for pancreatic cancer between January 2012 and March 2021. After excluding 13 patients (11.4 %) based on the predefined criteria, 101 patients were included in the present study. Figure 2 shows the flowchart of patient inclusion.

The baseline characteristics with a comparison between frailty subgroups are shown in Table 1. The mean age was 75.3 ± 3.8 years and 60 patients (59.4 %) were male. Overall, preoperative median BMI was 24.2 [IQR:4.0] kg/m^2. Most patients did not receive neoadjuvant therapy (89.9 %). The majority of patients had one or more comorbidities (82.8 %). Stage III was the most common cancer stage (56.4 %). A total of 53 patients (52.5 %) had no geriatric deficits, 33 patients (32.7 %) had one deficit, and 15 patients (14.9 %) had two or more deficits. Deficits in Katz-ADL screening were found in 8.0 %, 12.8 % were at risk of delirium, 16.2 % had experienced one or more falls in the past 6 months and 33.7 % were at risk of undernutrition.

Figure 3 shows SMI and MA of the non-frail, pre-frail and frailty group. Statistically significant differences between non-frail, pre-frail and frail patients were seen in the percentage of body weight loss, mean SMI and MA, and geriatric parameters. Tukey's HSD test showed that pre-frail and frail patients had more weight loss than non-frail patients ($p = 0.01$). Patients with frailty also had a significant lower SMI and MA than non-frail patients ($p = 0.02$ and $p = 0.04$, respectively).

Table 2 shows the associations of frailty with SMI and MA. Linear regression analyses showed that pre-frail patients had a lower SMI compared to non-frail patients. However, this result was not statistically significant. In both unadjusted and adjusted analyses, frail patients had a statistically significant lower SMI (β: −5.87 cm^2/m^2; 95 % CI:-10.03–1.72 and β: −5.07 cm^2/m^2; 95 % CI: −8.77–1.36, respectively) and lower MA (β: −5.29 HU; 95 % CI: −9.61–0.97 and β: −5.70 HU; 95 % CI: −9.63–1.77, respectively) compared to non-frail patients.

Table 3 shows the association of the individual frailty domains with SMI. Linear regression analyses showed that, in both unadjusted and adjusted models, patients with impaired functionality (Katz ≥2) had a statistically significant lower SMI (β: −8.67 cm^2/m^2; 95 % CI: −13.85–3.50 and β: −7.01 cm^2/m^2; 95 % CI: −11.69–2.33, respectively) compared to patients with a Katz score <2 points. After adjusting for age, sex, and weight, patients at risk of delirium (score ≥1) had a statistically significant lower SMI (β: −4.58 cm^2/m^2; 95 % CI: −8.22–0.95) compared to patients without risk of delirium (score 0). Patients at risk of falls (score 1) and undernutrition (MUST ≥2) also had a lower SMI in both unadjusted and adjusted analyses. However, these results were not statistically significant.

Table 4 shows the association of the individual frailty domains with MA. Linear regression analyses showed that, in both unadjusted and adjusted models, patients with impaired functionality (Katz ≥2) had a statistically significant lower MA (β: −5.62 HU; 95 % CI: −10.97–0.26 and β: −6.88 HU; 95 % CI: −11.89–1.87, respectively) compared to patients with Katz score <2. Both in unadjusted and adjusted analyses, patients at risk of delirium (score ≥1), falls (score 1) and undernutrition (MUST ≥2) also had a lower MA. However, these results were not statistically significant.

4. Discussion

Our study demonstrated that frailty was associated with a lower SMI and MA in preoperative older patients with pancreatic cancer. Impaired functionality (Katz ≥2) was independently associated with a lower SMI and MA. After adjusting for age, sex, and weight, risk of delirium was associated with a lower SMI. These results suggests that SMI and MA should be included in standard screening to better identify high-risk patients and enable more targeted treatment selection.

The current study showed that frailty was associated with a lower SMI in preoperative patients with pancreatic cancer. Our

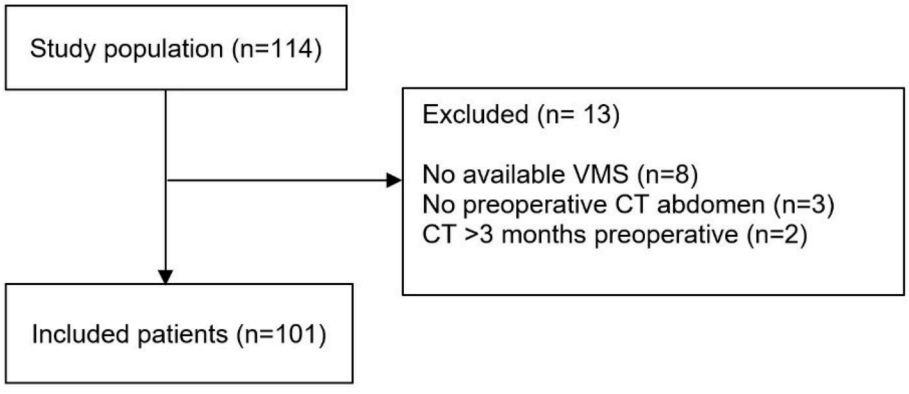

Fig. 2. Flowchart of patient inclusion.

Table 1
Comparison of patient characteristics between frailty subgroups.

	Total sample (n = 101)	No frailty (n = 53)	Pre-frailty (n = 33)	Frailty (n = 15)	P-value
Sex male, N (%)[a]	60 (59.4)	33 (62.3)	19 (57.6)	8 (53.3)	0.80
Age (years), mean±SD[b]	75.3 ± 3.8	75.2 ± 4.2	75.4 ± 3.5	75.5 ± 2.7	0.94
Age range (years)	70–85	70–85	70–81	70–81	–
Weight loss (%), mean±SD[b]	6.3 ± 3.9	5.0 ± 3.7[e]	7.6 ± 3.8[e]	7.6 ± 4.0[e]	**0.01**
BMI (kg/m^2), median [IQR][c]	24.2 [4.0]	24.5 [3.9]	23.4 [4.0]	23.1 [7.4]	0.07
Skeletal muscle area (cm^2), mean±SD[b]	126.8 ± 28.3	131.8 ± 29.2	123.5 ± 24.1	116.4 ± 31.7	0.13
Skeletal muscle index (cm^2/m^2), mean±SD[b]	42.5 ± 7.4	44.2 ± 8.0[e]	41.7 ± 5.6	38.3 ± 6.9[e]	**0.02**
Muscle attenuation (HU), mean±SD[b]	33.0 ± 7.6	33.7 ± 7.2[e]	33.8 ± 7.9	28.4 ± 7.4[e]	**0.04**
Albumin (g/L), mean±SD[b,d]	37.8 ± 4.9	38.8 ± 4.4	37.2 ± 4.6	33.0 ± 6.0	**0.05**
CRP (mg/L), median [IQR][c,d]	8.0 [16.5]	8.0 [10.9]	9.8 [21.0]	29.0 [43.0]	**0.01**
GPS score, N (%)[c,d]					**0.04**
0	22 (21.8)	14 (26.4)	7 (21.2)	1 (6.7)	
1	12 (11.9)	6 (11.3)	5 (15.2)	1 (6.7)	
2	6 (5.9)	0 (0.0)	4 (12.1)	2 (13.3)	
ASA class, N (%)[c]					0.28
1	8 (7.9)	4 (7.5)	3 (9.1)	1 (6.7)	
2	63 (62.4)	37 (69.8)	19 (57.6)	7 (46.7)	
3	30 (29.7)	12 (22.6)	11 (33.3)	7 (46.7)	
TNM stage, N (%)[c]					0.28
Tis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
T1	25 (24.8)	15 (28.3)	7 (21.2)	2 (13.3)	
T2	18 (17.8)	11 (20.8)	5 (15.2)	2 (13.3)	
T3	57 (56.4)	27 (50.9)	18 (54.5)	11 (73.3)	
T4	1 (1.0)	0 (0.0)	1 (3.0)	0 (0.0)	
Type of surgery, N (%)[a]					0.38
Classic Whipple	25 (24.8)	11 (20.8)	11 (33.3)	3 (20.0)	
PPPD	76 (75.2)	42 (79.2)	22 (66.7)	12 (80.0)	
Neoadjuvant therapy, N (%)[c]					0.80
No	80 (89.9)	41 (91.1)	26 (86.7)	13 (92.9)	
Chemotherapy	6 (6.7)	3 (6.7)	2 (6.7)	1 (7.1)	
Chemoradiotherapy	3 (3.4)	1 (2.2)	2 (6.7)	0 (0.0)	
Adjuvant therapy, N (%)[a]	46 (45.5)	27 (50.9)	15 (45.5)	4 (26.7)	0.46
Biliary drainage, N (%)[a]	53 (52.5)	27 (50.9)	17 (51.5)	9 (60.0)	0.82
Comorbidities, N (%)[f a]	72 (82.8)	40 (87.0)	21 (72.4)	11 (91.7)	0.35
Vascular disease	27 (40.3)	15 (40.5)	5 (15.2)	7 (77.8)	
Gastrointestinal disease	21 (34.4)	11 (37.9)	7 (30.4)	3 (33.3)	
Diabetes mellitus	21 (26.6)	10 (25.0)	6 (22.2)	5 (41.7)	
Neurological disease	15 (25.9)	9 (30.0)	2 (10.0)	4 (50.0)	
Pulmonary disease	13 (27.3)	9 (27.3)	2 (8.3)	2 (25.0)	
Surgical complications N (%)[g a]	36 (58.1)	17 (54.8)	11 (52.4)	8 (80.0)	0.30
Bleeding	15 (17.9)	11 (25.6)	3 (11.1)	1 (7.1)	
Wound-infections	14 (21.5)	6 (18.8)	4 (19.0)	4 (33.3)	
Gastroparesis	16 (20.3)	5 (12.5)	3 (11.5)	8 (61.5)	
Pancreatic fistula	13 (14.6)	8 (17.8)	4 (13.8)	1 (6.7)	
1-Year mortality, N (%)[a]	33 (32.7)	17 (32.1)	12 (63.6)	4 (26.7)	0.80
Geriatric characteristics, N (%)[a]					
Katz-ADL ≥2	8 (8.0)	0 (0.0)	1 (3.1)	7 (46.7)	**<0.001**
Risk for delirium	12 (12.8)	0 (0.0)	5 (16.7)	7 (50.0)	**<0.001**
Fall risk	16 (16.2)	0 (0.0)	3 (9.7)	13 (86.7)	**<0.001**
Risk for undernutrition	34 (33.7)	0 (0.0)	24 (72.7)	10 (66.7)	**<0.001**

SD: standard deviation; IQR: interquartile range; HU: Hounsfield unit; BMI: Body Mass Index; CRP: C-reactive protein; GPS: Glasgow Prognostic Score; ASA: American Society Anesthesiology; PPPD: pylorus-preserving pancreatoduodenectomy.
Statistical significant differences are in bold ($p < 0.05$).
[a] P-value for any difference between non-frail, pre-frail, and frail groups, calculated with Chi–Square test.
[b] P-value for any difference between non-frail, pre-frail, and frail groups, calculated with one-way ANOVA.
[c] P-value for any difference between non-frail, pre-frail, and frail groups, calculated with Kruskal Wallis test.
[d] Missing data: albumin (N = 50), CRP (N = 24), GPS score (N = 61).
[e] Multiple pairwise comparison using Tukey's HSD test: $p < 0.05$.
[f] Multiple comorbidities possible.
[g] Multiple surgical complications possible.

results are not directly comparable with other studies, since this is the first study that examined the associations of frailty, based on the abbreviated GA screening, with SMI and MA in preoperative older adults with pancreatic cancer. However, the results of two other studies that investigated the association between frailty and SMI in older patients with head and neck cancer, support our findings [22,23]. In contrast to our study, Williams et al. (2018) reported a weak association between frailty, based on G8-questionnaire, and low SMI in adults with cancer [13]. Dunne et al. (2019) were unable to find an association between frailty, based on the Carolina Frailty Index, and SMI in older adults with cancer [24]. This could be attributed to differences in the study population and frailty assessment. Previous studies examined adults with multiple cancers [13,24], whereas we specifically focused on older adults with operable pancreatic cancer. In addition, previous studies used different screening tools to measure frailty, which reflects the lack of a standardized approach. The association of frailty with a lower SMI might partly be explained by the physical domain, as we showed that impaired functionality was significantly associated with a lower SMI in older patients

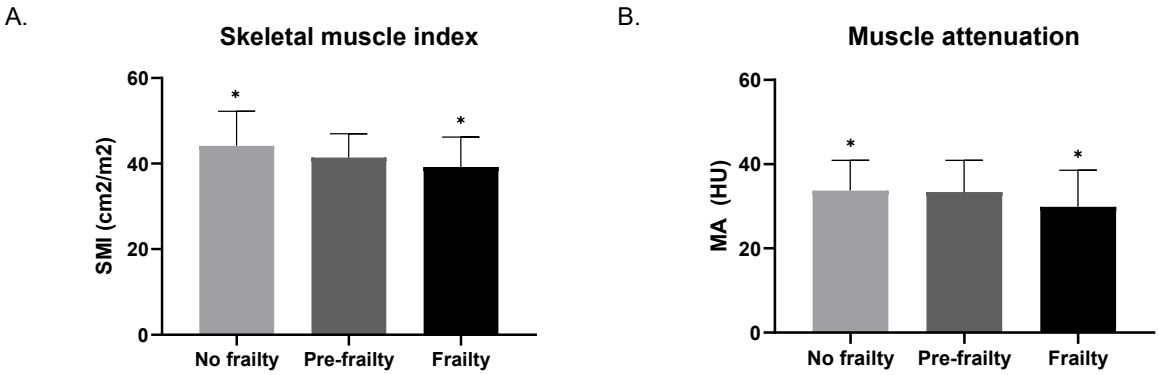

Fig. 3. SMI (A) and MA (B) of non-frail, pre-frail and frail groups.

Table 2
The association of frailty with SMI and MA in preoperative older patients with pancreatic cancer.

	Crude model			*Adjusted model*		
	β	95%CI	P-value	β	95%CI	P-value
SMI (cm^2/m^2)						
No frailty	Ref	Ref	Ref	Ref	Ref	Ref
Pre-frailty	−2.48	−5.63–0.66	0.12	−1.51	−4.38–1.35	0.30
Frailty	−5.87	−10.03–1.72	**0.01**	−5.07	−8.77–1.36	**0.01**
MA (HU)						
No frailty	Ref	Ref	Ref	Ref	Ref	Ref
Pre-frailty	0.12	−3.15–3.39	0.94	−0.91	−3.95–2.12	0.55
Frailty	−5.29	−9.61–0.97	**0.02**	−5.70	−9.63–1.77	**0.01**

SMI: Skeletal Muscle Index; MA: Muscle Attenuation; HU: Hounsfield unit β: beta coefficient; 95 % CI: 95 % confidence interval, Ref: reference.
SMI (cm^2/m^2) = SMM (cm^2)/height (m^2).
Adjusted model SMI: age, sex, and weight.
Adjusted model MA: age, sex, and BMI.
Statistical significant differences are in bold ($p < 0.05$).

Table 3
The association of individual frailty domains with SMI in preoperative older patients with pancreatic cancer.

	Crude model			*Adjusted model*		
SMI (cm^2/m^2)	β	95%CI	P-value	β	95%CI	P-value
Frailty domains						
Impaired functionality						
Katz <2	Ref	Ref	Ref	Ref	Ref	Ref
Katz ≥2	−8.67	−13.85–3.50	**0.001**	−7.01	−11.69–2.33	**0.004**
Risk for delirium						
Score 0	Ref	Ref	Ref	Ref	Ref	Ref
Score ≥1	−4.04	−8.23–0.15	0.06	−4.58	−8.22–0.95	**0.01**
Fall risk						
Score 0	Ref	Ref	Ref	Ref	Ref	Ref
Score 1	−2.50	−6.53–1.53	0.22	−2.99	−6.54–0.57	0.10
Risk for undernutrition[a]						
MUST <2	Ref	Ref	Ref	Ref	Ref	Ref
MUST ≥2	−0.24	−1.19–0.71	0.62	−0.55	−1.42–0.31	0.21

SMI: Skeletal Muscle Index; β: beta coefficient; 95 % CI: 95 % confidence interval, Ref: reference.
SMI (cm^2/m^2) = SMM (cm^2)/height (m^2).
Adjusted model SMI: age, sex, and weight.
Statistical significant differences are in bold ($p < 0.05$).
[a] Adjusted for age and sex.

Table 4
The association of individual frailty domains with MA in preoperative patients with pancreatic cancer.

	Crude model			*Adjusted model*		
MA (HU)	β	95%CI	P-value	β	95%CI	P-value
Frailty domains						
Impaired functionality						
Katz <2	Ref	Ref	Ref	Ref	Ref	Ref
Katz ≥2	−5.62	−10.97–0.26	**0.04**	−6.88	−11.89–1.87	**0.01**
Risk for delirium						
Score 0	Ref	Ref	Ref	Ref	Ref	Ref
Score ≥1	−4.34	−8.78–0.10	0.06	−2.94	−7.11–1.23	0.17
Fall risk						
Score 0	Ref	Ref	Ref	Ref	Ref	Ref
Score 1	−3.11	−7.13–0.92	0.13	−3.12	−6.83–0.59	0.10
Risk for undernutrition[a]						
MUST <2	Ref	Ref	Ref	Ref	Ref	Ref
MUST ≥2	−0.20	−1.18–0.77	0.68	−0.47	−1.41–0.48	0.33

MA: Muscle Attenuation; HU: Hounsfield unit β: beta coefficient; 95 % CI: 95 % confidence interval, Ref: reference.
Adjusted model MA: age, sex, and BMI.
Statistical significant differences are in bold ($p < 0.05$).
[a] Adjusted for age and sex.

with pancreatic cancer. In literature, impaired physical function and disability are the most apparent features of sarcopenia and frailty [25–27].

Our study also demonstrated that frailty was associated with a lower MA in preoperative patients with pancreatic cancer. This finding is consistent with other studies [20,22,28]. With aging, lipid droplets infiltrate, muscle fibers become thinner and connective tissue increases [11,28]. These changes suggest a lower MA in older adults [11]. Low MA is independently associated with impaired muscle strength and mobility loss [11,29]. Fried et al. (2001) conceptualized loss of muscle strength as a core component of frailty [30]. However, the general concept of frailty goes beyond physical factors and includes physiological and social domains as well [31].

Impaired functionality was also associated with a lower MA. This is in line with Williams et al. (2018), who also reported an association between lower MA and physical function impairments [13]. Reduced MA reflects an increase in lipid content, which is associated with insulin resistance and decreased muscle activity [32–34]. This could lead to mobility limitations and lower muscle strength [32,33]. The impact of muscle fat content on strength and physical performance may explain the association between impaired functionality and MA in older adults with pancreatic cancer. Furthermore, we showed a significant independent association between risk for delirium and SMI. This is in line with Mosk et al. (2018), who showed a significant association between preoperative low SMI and postoperative delirium in older patients with colorectal cancer [35]. A meta-analysis by Persico et al. (2018) concluded that frailty significantly predisposes older adults to subsequent delirium [36]. The pathophysiological mechanisms

underlying the association between frailty and delirium have not yet been fully elucidated. However, this association appears to be multifactorial and involves complex interactions of systemic inflammation, metabolic stress, neurodegeneration, and vascular factors contributing to the relationship between delirium and frailty [36,37]. Although delirium risk assessment, based on the abbreviated GA screening, has not yet been validated, it is promising that this three-item risk assessment was also predictive of postoperative delirium in patients with cancer [21].

The domain 'risk of undernutrition' was not independently associated with SMI and MA, despite undernutrition is an important risk factor for loss of SMI in older adults with pancreatic cancer [9,38]. Risk of undernutrition was assessed with the MUST screening tool, which has been validated in patients with cancer [29]. However, this tool shows worse performance in sensitivity and validity compared to Nutritional Risk Screening 2002 (NRS 2002) [39–41]. In addition, MUST is a screening tool to identify adults at risk of undernutrition, but not to diagnose undernutrition [19].

The current study has important strengths. This is the first study that examined the association of frailty with SMI and MA in operable older adults with pancreatic cancer. We purposefully chose to analyze SMI as a continuous variable due to lack of consensus on defining sarcopenia within oncology. This approach enables a more thorough understanding of the association of geriatric deficits with SMI without making erroneous assumptions regarding relevant cut-off points. Another strength of our study is the completeness of the data. Our data were systematically extracted from the prospective DPCG, which has been validated for data accuracy [42]. Lastly, CT-scan analysis was used to assess the SMI and MA, which is seen as the gold standard for the evaluation of body composition in frail patients [43]. We only included CT scans in the portal venous contrast-enhanced phase. This phase is recommended for studies describing the association between skeletal muscle density and outcome measures to improve comparability of studies, since the portal venous contrast-enhanced phase is routinely performed in cancer patients [44].

Our study also has several limitations. The main limitation of our study was the relatively small sample size. However, other studies that investigated the association of frailty with SMI and MA in patients with cancer had similar sample sizes of 100–150 patients [13,23,24,45]. We chose to include only operable older patients with pancreatic cancer, which introduces the potential for selection bias towards patients with more aggressive disease or selection of more frail older adults. Omitting these patients limits the generalizability of our results to patients with unresectable tumors. Furthermore, no causal relationship between frailty sumscore and SMI and MA can be inferred due to the cross-sectional design of this study. Lastly, we note that the abbreviated GA screening tool should be used to determine the individual's risk of frailty and does not replace a comprehensive GA.

The association of frailty with SMI and MA suggests that these parameters should be included in standard screening. A low SMI and MA can identify high risk patients and indicate the need for a comprehensive GA and interventions. This may allow better selection of patients for intensive therapy, especially since these parameters are more objective than the frailty screening tools. This information can be used by clinicians in their treatment decisions in the context of frailty and its accompanying outcomes. As sarcopenia is partly potentially modifiable with early identification and intervention, it is key that clinicians understand their role in prognosis and complication. Prehabilitation with nutritional and exercise management is crucial for the treatment of sarcopenia [46]. Prospective longitudinal multicenter studies should be performed to demonstrate how preoperative screening for frailty is related to the prognosis of older patients with pancreatic cancer. Specific cut-off values for SMI and MA in older adults with pancreatic cancer are also needed to gain a better insight in both sarcopenia and frailty and its effect on treatment outcomes in these patients.

In conclusion, this study showed that frailty is significantly associated with lower SMI and MA in preoperative older patients with pancreatic cancer. Both impaired functionality and risk of delirium were independently associated with lower SMI, whereas impaired functionality was also associated with lower MA.

Ethics approval and consent to participate

The Medical Ethics Committee of the Leiden University Medical Center waived the need for informed consent. This study was performed in accordance with the Declaration of Helsinki.

Credit author statement

No one eligible for authorship has been excluded from the list of authors.

Study concepts: CJL, FvdB.

Study design: CJL, YZ, FvdB.

Data acquisition: CJL, YZ, AD, BAB, ALV, NM, SSF, ETDS, JEAP, JSDM, FvdB.

Quality control of data and algorithms: JEAP, JDSM, FvdB.

Data analysis and interpretation: CJL, YZ, JEAP, JDSM, FvdB.

Statistical analysis: CJL, YZ.

Manuscript preparation: CJL, YZ.

Manuscript editing: CJL, YZ.

Manuscript review: CJL, YZ, AD, JEAP, JSDM, FvdB.

Data sharing statement

The data supporting this study are owned by the research group of the TENT study. Access to the data may be granted by the research group upon reasonable request and are subject to institutional approval.

Declaration of generative AI and AI-assisted technologies

No generative AI and AI-assisted technologies were used in the writing process.

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Declaration of interest

None.

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