Original article

Effect of sarcopenia and visceral obesity on mortality and pancreatic fistula following pancreatic cancer surgery

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Background: **Analytical morphometric assessment has recently been proposed to improve preoperative risk stratification. However, the relationship between body composition and outcomes following pancreaticoduodenectomy is still unclear. The aim of this study was to assess the impact of body composition on outcomes in patients undergoing pancreaticoduodenectomy for cancer.**

Methods: **Body composition parameters including total abdominal muscle area (TAMA) and visceral fat area (VFA) were assessed by preoperative staging CT in patients undergoing pancreaticoduodenectomy for cancer. Perioperative variables and postoperative outcomes (mortality or postoperative pancreatic fistula) were collected prospectively in the institutional pancreatic surgery database. Optimal stratification was used to determine the best cut-off values for anthropometric measures. Multivariable analysis was performed to identify independent predictors of 60-day mortality and pancreatic fistula.**

Results: **Of 202 included patients, 132 (65·3 per cent) were classified as sarcopenic. There were 12 postoperative deaths (5·9 per cent), major complications developed in 40 patients (19·8 per cent) and pancreatic fistula in 48 (23·8 per cent). In multivariable analysis, a VFA/TAMA ratio exceeding 3·2 and American Society of Anesthesiologists grade III were the strongest predictors of mortality (odds ratio (OR) 6·76 and 6·10 respectively; both $P < 0{\cdot}001$). Among patients who developed major complications, survivors had a significantly lower VFA/TAMA ratio than non-survivors ($P = 0{\cdot}017$). VFA was an independent predictor of pancreatic fistula (optimal cut-off 167 cm^2: OR 4·05; $P < 0{\cdot}001$).**

Conclusion: **Sarcopenia is common among patients undergoing pancreaticoduodenectomy. The combination of visceral obesity and sarcopenia was the best predictor of postoperative death, whereas VFA was an independent predictor of pancreatic fistula.**

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Introduction

Pancreaticoduodenectomy is an abdominal operation commonly performed for the treatment of pancreatic head malignancies and periampullary lesions. Despite advances and standardization of the operative technique and perioperative care protocols, it still carries a high risk of postoperative morbidity and mortality, even in high-volume hospitals, mainly owing to failure of the pancreatic anastomosis[1–3].

In the past decade, the increasing number of elderly patients with multiple co-morbidities presenting for major surgery[4,5] has fuelled interest in surgical risk stratification. In fact, several prognostic scores have been suggested, including multiple perioperative factors to predict major complications or pancreatic fistula after pancreatic resection[1,6,7].

Recent reports[8–10] have shown that preoperative assessment of body composition may improve risk stratification. Depleted lean muscle mass, known as sarcopenia, and visceral obesity can be assessed precisely in a single CT slice[11]. Sarcopenia and visceral obesity have recently been described as independent predictors of the occurrence of clinically relevant pancreatic fistula in patients undergoing pancreaticoduodenectomy[8], but there is a lack of evidence of their effect on postoperative mortality.

The aim of the present study was to assess the impact of preoperative visceral obesity and sarcopenia on risk of death and pancreatic fistula following pancreaticoduodenectomy for cancer.

Methods

This study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[12] for the conduct and reporting of observational cohort studies.

Study population

All patients who underwent elective pancreaticoduodenectomy for pancreatic or periampullary cancer between January 2010 and September 2014 in a university-affiliated teaching hospital were considered eligible for inclusion in the study. The inclusion criterion was the availability of preoperative contrast-enhanced CT carried out at this institution within 30 days before scheduled surgery.

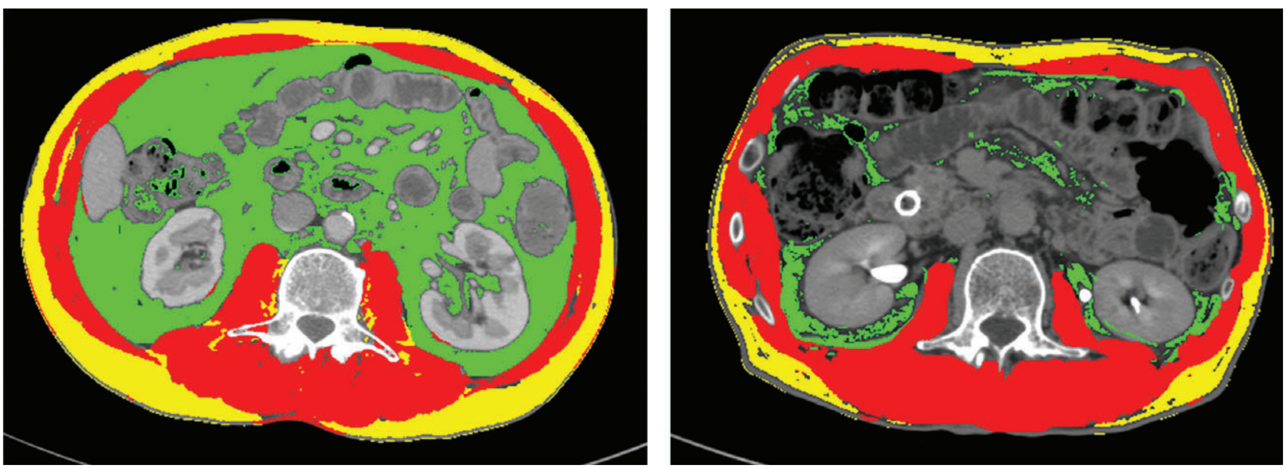
Preoperative anthropometric measurements

CT images were retrieved from digital storage in the Picture Archiving and Communication System of the Radiology Department. Two trained radiology residents supervised by a senior radiologist, unaware of postoperative patient outcomes, analysed CT images with sliceOmatic version 5.0 software (Tomovision, Montreal, Quebec, Canada), as described previously[11,13]. Two consecutive axial CT images extending upwards from the level of the third lumbar vertebra (L3), where both transverse processes were clearly visible, were processed for each patient and then averaged. Specific tissue demarcation using predefined Hounsfield unit (HU) thresholds was performed by image analysis software. Tissue boundaries were corrected manually as needed. Cross-sectional areas were computed automatically by summing tissue pixels and multiplying by pixel surface area. Total abdominal muscle area (TAMA) (cm^2) including paraspinal and abdominal wall muscles was identified and quantified by thresholds of −29 to +150 HU[14]. Cross-sectional TAMA was normalized with respect to stature and reported as cm^2/m^2. Visceral fat area (VFA) (cm^2) and subcutaneous fat area (SFA) (cm^2) were identified using the following adipose tissue thresholds: −150 to −50 HU and −190 to −30 HU respectively[15] (*Fig. 1*).

Sarcopenia was defined using predetermined sex-specific TAMA cut-off values: 52·4 cm^2/m^2 for men and 38·5 cm^2/m^2 for women[16]. The VFA/TAMA ratio was calculated for all patients.

Operative and perioperative management

Four experienced surgeons who had completed a training programme in pancreatic surgery performed all procedures[6,17]. Pylorus-preserving pancreaticoduodenectomy with standard lymphadenectomy was the routine procedure. A two-layer end-to-side pancreaticojejunostomy, end-to-side hepaticojejunostomy and double-layer



a Radiological signs of sarcopenia and visceral obesity

b No radiological signs of sarcopenia and visceral obesity

Fig. 1 CT showing third lumbar vertebra level in two patients included in the study. Subcutaneous fat area is highlighted in yellow, total abdominal muscle area (TAMA) in red and visceral fat area (VFA) in green. **a** Man with radiological signs of sarcopenia and visceral obesity (TAMA 34·4 cm^2/m^2, VFA 190 cm^2, VFA/TAMA ratio 5·5). **b** Man without radiological signs of sarcopenia or visceral obesity (TAMA 52·5 cm^2/m^2, VFA 26·8 cm^2, VFA/TAMA ratio 0·5) end-to-side duodenojejunostomy were carried out on the same jejunal loop. Two drains were usually placed close to biliary and pancreatic anastomoses. All patients were managed according to an enhanced recovery after surgery protocol and discharged after meeting predefined criteria[6,18].

Data collection

Prospectively collected data were retrieved from the institutional electronic pancreatic surgery database. Before surgery, demographic details, co-morbidities, American Society of Anesthesiologists (ASA) grade, body mass index (BMI), serum levels of glucose and albumin, and haemoglobin level were recorded for all patients. Duration of surgery, operative blood loss, need for blood transfusion, and surgeon assessment of main pancreatic duct diameter and pancreatic stump texture were also recorded.

A pancreaticoduodenectomy-specific major complication risk score was calculated, as described in a previous study[6]. Postoperative 60-day follow-up to record morbidity, mortality and readmissions was carried out by a clinician not directly involved in patient care.

Outcome measures

The primary endpoint of the study was postoperative mortality at 60 days, as suggested by previous research[19]. The secondary endpoint was occurrence of pancreatic fistula defined according to International Study Group on Pancreatic Fistula criteria[20].

Postoperative complications were defined *a priori* according to a previous study[21], and graded according to the Clavien–Dindo classification[22], which was validated in pancreatic surgery[23]. Complications requiring surgical, endoscopic or radiological intervention, or requiring intensive care, or causing death were considered as major (grade III–V). Haemorrhage was defined according to International Study Group of Pancreatic Surgery criteria[24]. Microbiological analysis and positive culture proved all infectious complications.

Statistical analysis

Normality was assessed by inspection of frequency histograms. Continuous data are reported as mean(s.d.) or median (range), and were compared by Student's t test or the non-parametric Mann–Whitney U test. Categorical variables were analysed using χ^2 test or Fisher's exact test, as appropriate. Correlations between continuous measures were demonstrated using Pearson's (r) or Spearman's (ρ) correlation, as appropriate.

Cut-off values for significant anthropometric measures with the best predictive ability for a binary outcome (mortality or pancreatic fistula) were determined using optimal stratification to find the most significant P value and the highest odds ratio (OR) in univariable logistic regression analysis[25]. ORs are reported with 95 per cent c.i.

To assess the independent contribution of each variable to 60-day mortality and pancreatic fistula, multivariable logistic regression analysis was performed with inclusion of candidate predictors that were significant at $P < 0{\cdot}100$ in the univariable analyses. Backward stepwise elimination with internal validation using 200 bootstrap samples[26] was used to determine final significant predictors, and variables significant at $P < 0{\cdot}050$ were retained in the final multivariable model. Unit increases for continuous anthropometric measure variables were also obtained by dividing the range of each continuous variable into six intervals of equal proportions.

Multicollinearity was assessed by inspecting correlation matrices of independent variables and by calculating the variance inflation factor (VIF). VIF values exceeding 10 are regarded as indicating serious multicollinearity, and values greater than 4 may be a cause for concern[27]. The results of multicollinearity testing for the logistic regression models in this study can be found in *Tables S1–S3* (supporting information).

The discriminative power of the logistic model equations was determined by constructing a receiver operating characteristic (ROC) curve, and by calculating the concordance index. To determine the goodness-of-fit of the models, the Hosmer–Lemeshow test was used to assess whether the model differed significantly from a perfect prediction model.

All statistical tests were two-sided; $P < 0{\cdot}050$ was considered to indicate statistical significance. Statistical analyses were performed using Stata® version 13.1 (StataCorp LP, College Station, Texas, USA) and SPSS® version 20 (IBM, Armonk, New York, USA).

Results

Two hundred and eighty-four consecutive patients were considered eligible for the study (*Fig. 2*). The 202 patients included in the study underwent preoperative cancer staging CT at a median of 9 (range 1–28) days before surgery. There were no missing data for primary or secondary study outcomes, or for the main co-variables considered in the analysis.

Preoperative characteristics and body composition parameters for the overall series are shown in *Table 1*,

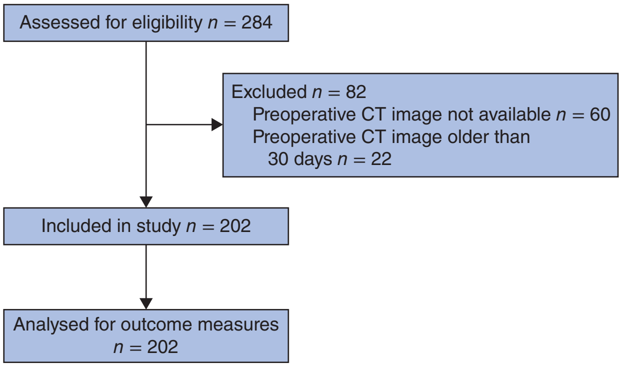


Fig. 2 Flow chart for the study

Table 1 Demographic and preoperative data for all patients

	No. of patients* ($n = 202$)
Age (years)†	66·8(10·7)
Sex ratio (M : F)	108 : 94
Body mass index (kg/m^2)†	23·6(3·7)
< 18·5	16 (7·9)
18·5–24·9	121 (59·9)
25·0–29·9	55 (27·2)
≥ 30·0	10 (5·0)
Weight loss (% bodyweight)	
5–10	51 (25·2)
>10	42 (20·8)
ASA grade	
I–II	137 (67·8)
III	65 (32·2)
Pre-existing co-morbidity	
Cardiovascular disease	33 (16·3)
Hypertension	80 (39·6)
COPD	7 (3·5)
Diabetes	45 (22·3)
Insulin therapy	21 (10·4)
Preoperative biliary drainage	90 (44·6)
Preoperative chemotherapy	42 (20·8)
Haemoglobin (g/dl)†	12·0(1·5)
< 115	78 (38·6)
Serum albumin (g/l)†	37·2(5·2)
< 35	62 (30·7)
TAMA (cm^2/m^2)†	43·3(8·4)
M	47·3(7·9)
F	38·6(6·4)
VFA (cm^2)†	105·0(72·8)
SFA (cm^2)†	148·9(80·0)
VFA/TAMA ratio†	2·43(1·72)

*With percentages in parentheses unless indicated otherwise; †values are mean(s.d.). ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; TAMA, total abdominal muscle area; VFA, visceral fat area; SFA, subcutaneous fat area.

and intraoperative and oncological data in *Table 2*. Patients excluded from the study had similar characteristics to those included (*Table S4*, supporting information). According to predefined sex-specific cut-offs, 79 men (73·1 per cent) and

Table 2 Operative and pathology variables in all patients.

	No. of patients* ($n = 202$)
Duration of operation (min)†	349(75)
Soft pancreatic texture	90 (44·6)
Small pancreatic duct (≤ 3 mm)	83 (41·1)
Operative blood loss (ml)†	544(352)
≥ 700	59 (29·2)
Blood transfusion	73 (36·1)
Amount per patient (units)‡	2 (1–2)
Vascular resection	18 (8·9)
Major complication risk score	
0–3	57 (28·2)
4–7	93 (46·0)
8–11	41 (20·3)
12–15	11 (5·4)
Pathology	
Pancreatic adenocarcinoma	166 (82·2)
Periampullary malignancy	36 (17·8)
TNM stage	
I	15 (7·4)
II	167 (82·7)
III	13 (6·4)
IV	7 (3·5)
Resection margin	
R0	129 (63·9)
R1	73 (36·1)

*With percentages in parentheses unless indicated otherwise; †values are mean(s.d.) and ‡median (i.q.r.).

53 women (56 per cent) were sarcopenic. The correlations between different anthropometric factors and preoperative nutritional indices are summarized in *Table S5* (supporting information). As expected, VFA and SFA showed significant positive correlation with BMI ($r = 0·581$ and $r = 0·728$ respectively; $P < 0·001$). Mean VFA was similar in patients with a soft *versus* hard pancreatic texture (102·1 *versus* 107·3 cm^2; $P = 0·627$), and small *versus* larger pancreatic duct diameter (100·4 *versus* 113·2 cm^2; $P = 0·228$). No significant correlation was found for the major complication risk score with TAMA ($r = –0·029$, $P = 0·530$) or VFA ($r = 0·092$, $P = 0·128$).

Mortality

Twelve patients (5·9 per cent) died within 60 days of surgery (*Table 3*); the deaths occurred at a median of 18 (range 4–45) days after operation. Ten patients died during the primary hospital stay, and two after initial discharge during hospital readmission. In ten patients (5·0 per cent) death followed a surgical complication, and was caused by sepsis-related multiple organ failure (4), pancreatic fistula-related bleeding (3), sepsis-related heart failure (2) and sepsis-related pulmonary embolism (1). Two patients (1·0 per cent) had a sudden cardiac arrest within the

Table 3 Postoperative outcomes in all patients

	No. of patients* ($n = 202$)
30-day mortality	7 (3·5)
60-day mortality	12 (5·9)
No complications	52 (25·7)
Complications (Clavien–Dindo grade)	
I–II	110 (54·5)
III	24 (11·9)
IV	4 (2·0)
Pancreatic fistula (ISGPF grade)	48 (23·8)
A	12 (5·9)
B	23 (11·4)
C	13 (6·4)
Haemorrhage (ISGPS grade)	19 (9·4)
A	2 (1·0)
B	7 (3·5)
C	10 (5·0)
Cardiorespiratory complications	25 (12·4)
Delayed gastric emptying	24 (11·9)
Wound infection	23 (11·4)
Bile leak	14 (6·9)
Length of hospital stay (days)†	12 (10–17)
Hospital readmission	28 (13·9)

*With percentages in parentheses unless indicated otherwise; †values are median (i.q.r.). Some patients may have had more than one complication. ISGPF, International Study Group on Pancreatic Fistula; ISGPS, International Study Group of Pancreatic Surgery.

first week after surgery unrelated to any other surgical complication.

The results of univariable and multivariable analyses for predictors of postoperative 60-day mortality are presented in *Table 4*. The optimal cut-off value for VFA/TAMA ratio in predicting postoperative mortality obtained by means of optimal stratification was 3·2. Independent predictors of postoperative mortality identified by multiple logistic regression analysis were: VFA/TAMA ratio over 3·2, ASA grade III and soft pancreatic texture. The ROC curve showing the discriminative power of the multivariable model including significant predictors is shown in *Fig. 1a* (supporting information) (concordance index 0·871, 95 per cent c.i. 0·800 to 0·943). When VFA/TAMA ratio was divided into six consecutive clusters in this multivariable analysis, a dose–effect relationship with mortality was found (OR 1·95 (95 per cent c.i. 1·18 to 3·23) for each 1·6-unit increment; $P = 0{\cdot}009$). Limiting the mortality prediction model to preoperative factors (VFA/TAMA ratio and ASA grade) yielded a concordance index of 0·822 (95 per cent c.i. 0·732 to 0·912) (*Fig. 1b*, supporting information).

Complications

Major complications occurred in 40 patients (19·8 per cent). The pancreatic fistula rate was 23·8 per cent (48 of 202); clinically relevant pancreatic fistula (grades B and C) developed in 36 patients (17·8 per cent). Reoperation was necessary in 18 patients (8·9 per cent). Reasons for reoperation were: late bleeding (9), sepsis (7), early bleeding (1) and wound dehiscence (1). When patients were stratified

Table 4 Univariable and multivariable analyses of potential predictors associated with 60-day postoperative mortality after pancreaticoduodenectomy in patients with cancer

				Multivariable analysis	
	Alive after 60 days ($n = 190$)	Died within 60 days ($n = 12$)	Univariable P‡	Odds ratio†	P
Age (years)*	66·3(10·7)	74·5(7·9)	0·010§		
ASA grade III	57 (30·0)	8 (67)	0·021	6·10 (2·74, 13·58)	< 0·001
Cardiovascular disease	28 (14·7)	5 (42)	0·030		
Preoperative weight loss > 10%	39 (20·5)	3 (25)	0·717		
Body mass index (kg/m^2)*	23·6(3·7)	24·8(4·3)	0·281§		
< 18·5	15 (7·9)	1 (8)	1·000		
≥ 25·0	59 (31·1)	6 (50)	0·206		
Preoperative biliary drainage	84 (44·2)	6 (50)	0·769		
Sarcopenia	122 (64·2)	10 (83)	0·224		
VFA (cm^2)*	101·7(70·9)	157(85·7)	0·010§		
SFA (cm^2)*	146·1(77·1)	194·0(111·4)	0·044§		
TAMA (cm^2/m^2)*	43·5(8·5)	39·9(6·1)	0·152§		
VFA/TAMA ratio*	2·33(1·59)	4·02(2·51)	< 0·001§	6·76 (2·41, 18·99)¶	< 0·001
Soft pancreatic texture	81 (42·6)	9 (75)	0·037	4·25 (1·42, 12·69)	0·010
Small pancreatic duct	75 (39·5)	8 (67)	0·075		
High operative blood loss (≥ 700 ml)	53 (27·9)	6 (50)	0·113		

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.) and †values in parentheses are 95 per cent c.i. ‡Fisher's exact test, except §Student's t test. The variables sex, diabetes, chronic obstructive pulmonary disease, haemoglobin level below 11·5 g/dl, low serum albumin (less than 35 g/l), preoperative chemotherapy, tumour stage, duration of operation and blood transfusion were not predictive in univariable analysis ($P \geq 0{\cdot}112$). All variables with $P < 0{\cdot}100$ in univariable analysis were considered in the multivariable stepwise logistic regression analysis. Visceral fat area (VFA)/total abdominal muscle area (TAMA) ratio and not VFA was included in the multivariable analysis because of its higher odds ratio and lower P value in the univariable analysis, and the risk of collinearity of the two variables (*Tables S1* and *S2*, supporting information). ¶Odds ratio for death if VFA/TAMA ratio exceeds 3·2 (value obtained by means of optimal stratification). SFA, subcutaneous fat area.

Table 5 Univariable and multivariable analyses of potential predictors associated with pancreatic fistula

				Multivariable analysis	
	No pancreatic fistula ($n = 154$)	Pancreatic fistula ($n = 48$)	Univariable P‡	Odds ratio†	P
Age (years)*	66·0(10·5)	69·4(11·1)	0·052§		
ASA grade III	49 (31·8)	16 (33)	0·844		
Body mass index (kg/m^2)*	23·6(3·7)	23·9(3·6)	0·638§		
≥ 25·0	49 (31·8)	16 (33)	0·844		
Preoperative biliary drainage	66 (42·9)	24 (50)	0·385		
Sarcopenia	102 (66·2)	30 (63)	0·635		
VFA (cm^2)*	95·9(67·7)	134·1(81·3)	0·001§	4·05 (1·85, 8·84)¶	< 0·001
SFA (cm^2)*	145·1(78·6)	161·0(84·1)	0·231§		
TAMA (cm^2/m^2)*	43·2(8·3)	43·5(9·1)	0·827§		
VFA/TAMA ratio*	2·22(1·52)	3·12(2·09)	0·002§		
Soft pancreatic texture	54 (35·1)	36 (75)	< 0·001	4·76 (2·14, 10·60)	< 0·001
Small pancreatic duct	50 (32·4)	33 (69)	< 0·001	2·52 (1·25, 5·07)	0·010
High operative blood loss (≥ 700 ml)	40 (26·0)	19 (40)	0·062		

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.) and †values in parentheses are 95 per cent c.i. ‡Fisher's exact test or χ^2 test, except §Student's *t* test. Pancreatic fistula was defined according to the International Study Group on Pancreatic Fistula criteria. The variables sex, weight loss, diabetes, cardiovascular disease, chronic obstructive pulmonary disease, haemoglobin level below 11·5 g/dl, low serum albumin (less than 35 g/l), preoperative chemotherapy, tumour stage, duration of operation and blood transfusion were not predictive in univariable analysis ($P \geq 0{\cdot}143$). All variables with $P < 0{\cdot}100$ in univariable analysis were considered in the multivariable stepwise logistic regression analysis. Visceral fat area (VFA) and not VFA/total abdominal muscle area (TAMA) ratio was included in the multivariable analysis because of its higher odds ratio and lower P value in the univariable analysis, and the risk of collinearity of the two variables (*Table S3*, supporting information). ¶Odds ratio for developing pancreatic fistula if VFA exceeded 167 cm^2 (value obtained by means of optimal stratification). SFA, subcutaneous fat area.

according to the presence or absence of sarcopenia, no significant difference was found with regard to postoperative outcomes (*Table S6*, supporting information).

In an analysis restricted to the 40 patients who developed major complications, VFA/TAMA ratio was the only risk factor that was significantly higher in patients who eventually died compared with survivors (4·02(2·49) *versus* 2·32(1·71); $P = 0{\cdot}017$). A VFA/TAMA ratio exceeding 3·2 significantly predicted mortality in this subgroup (OR 6·33, 95 per cent c.i. 1·37 to 29·21; $P = 0{\cdot}018$).

Results of univariable and multivariable analyses for factors associated with development of postoperative pancreatic fistula are shown in *Table 5*. The specific cut-off value for VFA associated with pancreatic fistula obtained by means of optimal stratification was 167 cm^2. Multiple logistic regression analysis confirmed that high VFA had an independent impact in predicting pancreatic fistula, along with soft pancreatic texture and a small pancreatic duct. The multivariable model including significant predictors had a concordance index of 0·800 (95 per cent c.i. 0·708 to 0·872; Hosmer–Lemeshow $P = 0{\cdot}222$). When VFA was divided into six consecutive clusters in the multivariable analysis, a dose–effect relationship with pancreatic fistula was evident (OR 1·61 (95 per cent c.i. 1·25 to 2·05) for each 50-unit increment; $P < 0{\cdot}001$). Mean VFA was similar in patients with grade A pancreatic fistula and those with a clinically relevant fistula (132(94) *versus* 134(80) cm^2 respectively; $P = 0{\cdot}953$).

Discussion

In this study, the combination of visceral obesity and sarcopenia was the best predictor of postoperative mortality together with high ASA grade and pancreatic stump texture. Moreover, high VFA was an independent predictor of pancreatic fistula. The findings suggest that visceral obesity and sarcopenia assessment should become part of the preoperative evaluation in patients undergoing pancreaticoduodenectomy for cancer.

Pancreaticoduodenectomy still represents the only chance of radical cure for pancreatic head malignancies. Despite standardization of perioperative processes and efforts to centralize pancreatic surgery[28], recent reports have pointed out that mortality rates still exceed 5 per cent even in high-volume institutions[1]. With the population ageing, the number of elderly patients scheduled for elective major surgery is increasing[5]. Elderly patients are at higher risk of postoperative death, and about half of survivors experience a significant decline in functional status[29]. This has encouraged the development of scores[1,6] to estimate the risk of poor outcome and target interventions to optimize patients undergoing pancreatic surgery[30]. However, little has been reported on emerging predictors, such as patient frailty and visceral obesity, which can be estimated through analytical morphomics[31].

Sarcopenia represents an objective and measurable feature of the frailty syndrome[32], and has consistently been reported as an indicator of poor prognosis in patients with gastrointestinal and hepatopancreatobiliary cancers[33,34]. Peng and colleagues[10] identified sarcopenia as a risk factor for 3-year mortality after resection for pancreatic adenocarcinoma, but it had no impact on short-term morbidity and mortality. Recent studies in patients undergoing liver resection and colectomy also found sarcopenia to be associated with postoperative major complications[35] and delayed recovery[36]. In the present series of patients with pancreatic cancer, which adopted predefined TAMA cut-offs, a very high incidence of sarcopenia was found. The VFA/TAMA ratio represented the strongest predictor of postoperative death after pancreaticoduodenectomy. In other words, the combination of visceral fat, a source of proinflammatory cytokines[37], and sarcopenia, which is associated with low muscle protein availability[32], increased the likelihood of surgery-related mortality. The discriminative power of the multivariable model that included only preoperative predictors (VFA/TAMA and ASA grade) was high, even in comparison with more complex models reported previously that included up to 13 predictive variables[38]. Among patients who developed major complications, VFA/TAMA ratio remained the only independent predictor of death, suggesting that this measure is a potential prognostic factor for failure to rescue in patients undergoing pancreaticoduodenectomy for cancer.

In a recent consecutive series of 177 patients undergoing pancreaticoduodenectomy[8], low TAMA and high VFA were identified as stronger predictors of clinically relevant pancreatic fistula than traditional risk factors such as pancreatic texture, pancreatic duct diameter and BMI. Here, VFA, but not TAMA, correlated closely with the occurrence of pancreatic fistula, confirming that visceral adiposity is more useful than BMI in discriminating obese patients at risk of intraoperative and postoperative morbidity[8,9,39]. Visceral obesity is considered a major component of the metabolic syndrome[40], and is associated with chronic inflammation and insulin resistance[37], which may explain its negative effects on surgical outcomes. Notably, VFA was unrelated to pancreatic texture, showing an independent effect. Pancreatic texture is a subjective binary estimation, whereas visceral adiposity can be calculated objectively during preoperative staging and provides a progressive risk factor with no ceiling effect. In contrast to the present findings, a previous study[9] failed to identify any influence of visceral obesity on pancreatic fistula or mortality, but found that visceral obesity was an independent risk factor for postoperative pulmonary complications. However, that study used an arbitrary VFA cut-off value to define visceral obesity within a Japanese population, which cannot be reproduced in Western countries as the body fat distribution differs significantly among races[41]. The VFA cut-off value of 167 cm^2 obtained here by means of optimal stratification appears higher than previously adopted values[9,39], but may represent a reference for future research in similar populations.

The present study has various limitations. First, its retrospective cohort design precluded further assessment of potentially useful measures of functional capacity and frailty. Second, the relatively small sample size may limit the applicability of these findings to other populations, especially the use of VFA and VFA/TAMA ratio cut-off values. Additionally, the use of 60 days for assessment of postoperative mortality in this analysis may be criticized. Sixty-day mortality was chosen, as suggested by previous research[19], to avoid missing late postoperative or postdischarge deaths and to minimize the chance of including patients who died from early cancer recurrence. Assessing mortality at 30 days would have missed five late deaths (nearly half of all postoperative deaths) from septic or haemorrhagic complications; similarly, recording only in-hospital mortality would have missed two patients who experienced fatal complications after discharge. Recently published data suggest that 90 or 120 days represent ideal cut-offs to assess surgery-related mortality following pancreatectomy[42].

Body composition measures can be obtained easily and rapidly from a single cross-sectional image[11]. All patients with cancer routinely undergo CT staging before surgery, so there is no additional exposure to ionizing radiation or extra cost involved for the institution. Assessing visceral fat and muscle areas before surgery may help the surgeon adequately to counsel the patient and family regarding the risks of operation. Future studies should investigate strategies to optimize patients at higher risk of postoperative adverse outcomes[43], such as patient prehabilitation programmes focusing on improving co-existing morbid conditions, and delivering effective nutritional therapy and physical exercise[44].

Disclosure

The authors declare no conflict of interest.

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Supporting information

Additional supporting information may be found in the online version of this article:

Fig. S1 Receiver operating characteristic (ROC) curves for multivariable logistic regression models predicting 60-day mortality after pancreaticoduodenectomy (Word document)

Table S1 Multicollinearity testing for postoperative mortality: multivariable linear regression for candidate predictors of 60-day postoperative mortality (Word document)

Table S2 Final multivariable linear regression for candidate predictors of 60-day mortality after eliminating visceral fat area (Word document)

Table S3 Multivariable linear regression for candidate predictors of pancreatic fistula, testing for multicollinearity (Word document)

Table S4 Demographics, preoperative and operative data for excluded patients (Word document)

Table S5 Correlation matrix for body composition measures and preoperative variables (Word document)

Table S6 Postoperative outcomes in patients with and without sarcopenia (Word document)