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ORIGINAL ARTICLE

Visceral adipose tissue is a better predictor than BMI in the alternative Fistula Risk Score in patients undergoing pancreatoduodenectomy

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Abstract

Background: Muscle attenuation (MA) and visceral adipose tissue (VAT) have not yet been included in the currently used alternative Fistula Risk Score (a-FRS). The aim of this study was to examine the added value of these parameters as predictors of clinically relevant postoperative pancreatic fistula (CR-POPF) in the a-FRS after pancreatoduodenectomy compared to Body Mass Index (BMI).

Methods: A single center retrospective cohort study was performed in patients who underwent pancreatoduodenectomy between 2009 and 2018. The a-FRS model was reproduced, MA and VAT were both combined and separately added to the model instead of BMI using logistic regression analysis. Model discrimination was assessed by ROC-curves.

Results: In total, 329 patients were included of which 55 (16.7%) developed CR-POPF. The a-FRS model showed an AUC of 0.74 (95%CI: 0.68–0.80). In this model, BMI was not significantly associated with CR-POPF ($p = 0.16$). The MA + VAT model showed an AUC of 0.81 (95%CI: 0.75–0.86). VAT was significantly associated with CR-POPF (per cm^2, OR: 1.01; 95%CI: 1.00–1.01; $p < 0.001$). The AUC of the MA + VAT model differed significantly from the AUC of the a-FRS model ($p = 0.001$).

Conclusion: Visceral adipose tissue is of added value in the a-FRS compared to BMI in predicting CR-POPF in patients undergoing pancreatoduodenectomy.

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Introduction

Postoperative pancreatic fistula (POPF) after pancreatoduodenectomy occurs in approximately 10%–30% of patients and is associated with increased morbidity and mortality.[1,2] Several risk prediction models have been developed for POPF to optimize individual intra- and postoperative treatment decisions.[2–4] The alternative Fistula Risk Score (a-FRS) for pancreatoduodenectomy has been developed based on the definition of the International Study Group on Pancreatic Surgery and is the currently most used prediction model in clinical practice.[2] Besides pancreatic texture and pancreatic duct diameter, Body Mass Index (BMI) is included in the a-FRS.

The Malnutrition Universal Screening Tool, including BMI and weight loss, is commonly used in clinical practice to assess nutritional status.[5] However, in addition to BMI and weight loss, body composition can establish a patients' nutritional status in more detail. Abdominal CT scan analysis can be used to assess several body composition parameters such as muscle attenuation (MA) and visceral adipose tissue (VAT).[6] MA can indicate intramuscular fat accumulation, which is ignored when only looking at skeletal muscle mass.[7] VAT is adipose tissue surrounding the intra-abdominal organs. A higher VAT might indicate more technical difficulties during operation and is associated with postoperative inflammatory reactions.[8,9] Both

MA and VAT have been associated with POPF, but these parameters have not been included in the a-FRS.[6,7,10]

Hence, the aim of this study is to examine the added value of preoperative body composition parameters as predictors of CR-POPF in the a-FRS compared to BMI after pancreatoduodenectomy. We hypothesized that a lower MA and a higher VAT are better predictors for the risk of CR-POPF compared to BMI in the a-FRS.

Methods

Study design and population

The TRIPOD guidelines for multivariable prediction models were used for the design, internal validation and reporting of the prediction models.[11] A retrospective cohort study was performed in patients who underwent pancreatoduodenectomy in the period of January 2009 to December 2018 in the Leiden University Medical Center. Patients were included when: (i) aged ≥18 years; (ii) underwent pancreatoduodenectomy. Patients were excluded when: (i) no preoperative abdominal CT scan was available; (ii) the CT scan was dated more than two months before surgery. A waiver for informed consent was issued by the Medical Ethics Committee (G17.059) due to the retrospective nature of the study.

Data collection

Data from 2009 to 2012 were retrospectively collected from the medical charts. Data from 2013 to 2018 were requested from the mandatory, prospective and previously validated Dutch Pancreatic Cancer Audit database.[12] Relevant data included baseline, intraoperative, postoperative and histopathological characteristics. Additional data on nutritional status were obtained by preoperative abdominal CT scans.

Definitions

Clinically relevant postoperative pancreatic fistula

CR-POPF was classified according to the International Study Group on Pancreatic Surgery definitions.[13] The classification of CR-POPF was assessed by two independent authors (JVG, JSDM) and discrepancies were resolved by consensus by a third reviewer (BAB). Since only grade B and C POPF are considered clinically relevant, CR-POPF was included as a dichotomous variable (i.e. no/grade A versus grade B/C).[13]

Pancreatic texture and pancreatic duct diameter

Pancreatic texture was defined as soft or not soft by the surgeon. Postoperative histologic diagnosis was used as surrogate to define pancreatic texture in missing values (N = 97).[14] Pancreatic duct diameter was measured by the surgeon at the head of the pancreas by assessing preoperative CT scan analysis and expressed in millimetres (mm).

Body composition

Body composition parameters included MA (in Hounsfield Units) and VAT (in cm^2). MA and VAT were determined by analysis of single slice abdominal CT scans at the third lumbar vertebra (L3 level). CT scans were only used with oral or intravenous contrast, 120 kV and coupe thickness of 5 mm in the portal venous phase. CT scans were preoperatively made for diagnosis or staging of the disease. Abdominal CT scans closest to the date of surgery were retrospectively collected through the department of Radiology. All CT scans were analysed by one trained author (CL) with SliceOmatic, version 5.0 (Tomovision, Canada).

MA was defined as the mean Hounsfield Units of the skeletal muscle mass surface. Skeletal muscle mass was determined by analysing the following muscle groups; musculus rectus abdominis, musculus transversus, musculus obliquus internus, musculus obliquus externus, musculus psoas major and minor, musculus erector spinae and musculus quadratus lumborum. Corresponding Hounsfield Units were −29 to +150 for skeletal muscle mass and −50 to −150 for VAT.[15,16] In Fig. 1, analysed CT scans at L3 level are presented with VAT stratified in quartiles.

Statistical analysis

Continuous variables are presented as means with standard deviations when data were normally distributed, and as medians with interquartile ranges when data were not normally distributed. Categorical variables are presented as frequencies with percentages.

Prediction models for CR-POPF were developed using multivariate logistic regression analysis. The a-FRS model of Mungroop et al. (2019) was created by adding pancreatic texture, pancreatic duct diameter and BMI as predictors of CR-POPF after pancreatoduodenectomy.[2] Model discrimination was assessed using receiver operating characteristic (ROC) curve analysis and the area under the curve (AUC). To examine whether MA and VAT were better predictors than BMI in the a-FRS, MA and VAT were added both separately and together to new models, the MA model, VAT model and MA + VAT model respectively, instead of BMI. MA and VAT were both included as continuous values and in quartiles. Beforehand, BMI, MA and VAT were checked for independency. The ROC curves and AUCs of the MA model, VAT model and MA + VAT model were determined again to test the added value of MA and VAT. Test of equality of ROC areas (*roccomp*) was performed to assess the difference in AUCs of the models. Internal validation was done using bootstrap resampling with 1000 replications to correct for the potential of overfitting and optimism.[17] Calibration performance of the models was assessed using Hosmer Lemeshow goodness-of-fit test. A p-value of <0.05 was considered as statistically significant. Statistical analysis was performed using Stata SE, version 16.

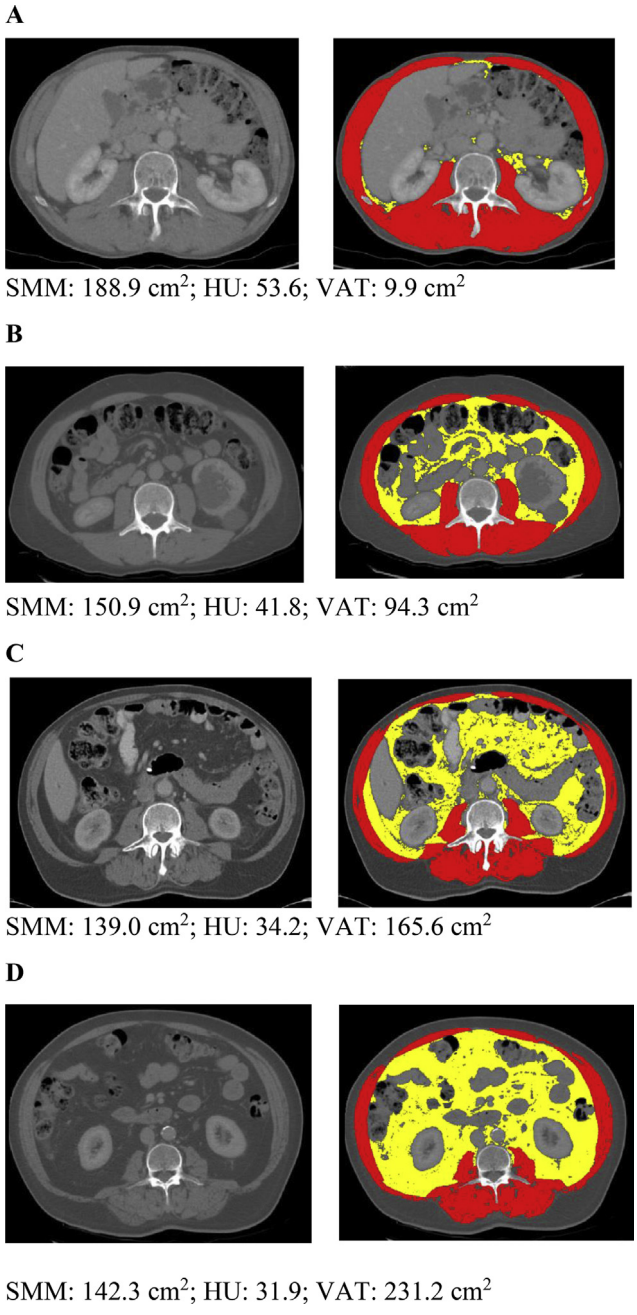

Figure 1 a–d. Analysed CT scans on L3 level with VAT stratified in quartiles

Results

A total of 329 patients were included in this study. Patient characteristics are presented in Table 1. A flowchart of patient inclusion is shown in Fig. 2.

Fifty-five patients (16.7%) developed a CR-POPF and were more often males (65.5%). Mean age was 65 years. Overall, patients had a preoperative median BMI of 24.6 kg/m^2. Patients with CR-POPF experienced less weight loss and had a higher VAT compared to patients without CR-POPF. Most patients were diagnosed with pancreatic ductal adenocarcinoma (54.1%) and T3 tumors (69.5%). Patients with CR-POPF more often had a soft pancreatic texture and a smaller pancreatic duct diameter compared to patients without CR-POPF (45.5% versus 31.4% and 2.0 mm versus 4.0 mm, respectively). In total, most of the patients did not receive neoadjuvant therapy (96.7%) and frequently had comorbidities (84.7%).

Fig. 3 shows the prevalence of CR-POPF stratified in quartiles of BMI, MA and VAT. The prevalence of CR-POPF increased linearly for VAT in contrast to BMI and MA. Results of the a-FRS model, MA model, VAT model and MA + VAT model are shown in Table 2. The models including MA and VAT in quartiles are attached in the supplementary data. Fig. 4a shows an ROC curve of the a-FRS model with an AUC of 0.74 (95%CI: 0.68–0.80). Pancreatic duct diameter (per mm, OR: 0.67; 95%CI: 0.57–0.79; $p < 0.001$) was found as significant predictor of CR-POPF. Soft pancreatic texture and BMI were not significantly associated with CR-POPF.

The MA model included MA instead of BMI. Fig. 4b shows a ROC curve with an AUC of 0.73 (95%CI: 0.68–0.79). MA was not found as a significant predictor of CR-POPF. No significant difference was found between the AUC of the MA model and the AUC of the a-FRS model ($p = 0.546$).

The VAT model included VAT instead of BMI. A ROC curve of the VAT model with an AUC of 0.81 (95%CI: 0.75–0.86) is shown in Fig. 4c. VAT (per cm2, OR: 1.01; 95%CI: 1.00–1.01; $p < 0.001$) was significantly associated with CR-POPF. The AUC of the VAT model differed significantly from the AUC of the a-FRS model ($p = 0.001$). In quartile analysis, the highest two quartiles of VAT were also significantly associated with CR-POPF (Supplementary Table 1) and showed incremental odds (OR: 7.69; 95%CI: 2.08–28.37; $p < 0.002$ and OR: 10.86; 95%CI: 3.02–39.07; $p < 0.001$, respectively) compared to BMI and MA.

The MA + VAT model included both MA and VAT instead of BMI. Fig. 4d shows a ROC curve with an AUC of 0.81 (95%CI: 0.75–0.86). Multivariate analysis showed that significant predictors of CR-POPF were pancreatic duct diameter (per mm, OR: 0.67; 95%CI: 0.56–0.80; $p < 0.001$) and VAT (per cm^2, OR: 1.01; 95%CI: 1.00–1.01; $p < 0.001$). The AUC of the MA + VAT model also differed significantly from the AUC of the a-FRS model ($p = 0.001$).

The Hosmer–Lemeshow goodness-of-fit test was used to further evaluate calibration performance of the models. The results showed $p = 0.3454$, $p = 0.0924$, $p = 0.6059$ and $p = 0.6979$ for a-FRS model, MA model, VAT model and MA + VAT model, respectively. These data indicated that the difference between the predicted and observed values of the models were not statistically significant, and all models had good calibration ability.

Discussion

The aim of this study was to investigate the added value of preoperative body composition parameters as predictors of CR-

Table 1 Patient characteristics

	Total cohort (N = 329)	CR-POPF[a] (N = 55)	No CR-POPF[b] (N = 274)
Gender male, N (%)	169 (51.4)	36 (65.5)	133 (48.5)
Age (years), mean ± SD	65.1 ± 11.1	65.0 ± 10.7	65.1 ± 11.2
Weight loss[c] (%), median [IQR]	6.2 [10.8]	3.1 [9.7]	6.5 [10.2]
BMI (kg/m^2), median [IQR]	24.6 [4.9]	25.9 [5.0]	24.3 [4.7]
Skeletal muscle mass (cm^2), mean ± SD	133.1 ± 31.7	142.1 ± 34.8	131.2 ± 30.8
Muscle attenuation (HU), mean ± SD	36.7 ± 9.5	35.7 ± 7.4	36.9 ± 9.9
Muscle attenuation (HU), N (%)			
0–30	79 (24.0)	14 (25.5)	65 (23.7)
30–37	87 (26.4)	18 (32.7)	69 (25.2)
37–43	76 (23.1)	12 (21.8)	64 (23.4)
≥43	87 (26.4)	11 (20.0)	76 (27.7)
Visceral adipose tissue (cm^2), median [IQR]	124.8 [134.5]	191.3 [152.8]	105.0 [130.0]
Visceral adipose tissue (cm2), N (%)			
0–60	82 (24.9)	3 (5.5)	79 (28.8)
60–125	83 (25.2)	8 (14.5)	75 (27.4)
125–195	82 (24.9)	19 (34.5)	63 (23.0)
≥195	82 (24.9)	25 (45.5)	57 (20.8)
ASA classification score, N (%)			
1	34 (10.3)	3 (5.5)	31 (11.3)
2	237 (72.0)	42 (76.4)	195 (71.2)
3	58 (17.6)	10 (18.2)	48 (17.5)
Soft pancreatic texture, N (%)	111 (33.7)	25 (45.5)	86 (31.4)
Pancreatic duct diameter (mm), median [IQR]	4.0 [4.0]	2.0 [2.0]	4.0 [4.0]
Pathology, N (%)			
Pancreatic ductal adenocarcinoma	178 (54.1)	16 (29.1)	162 (59.1)
Cholangiocarcinoma	23 (7.0)	8 (14.5)	15 (5.5)
Ampullary carcinoma	42 (12.8)	11 (20.0)	31 (11.3)
Duodenal carcinoma	15 (4.6)	4 (7.3)	11 (4.0)
Chronic pancreatitis	10 (3.0)	1 (1.8)	9 (3.3)
Neuroendocrine neoplasm	17 (5.2)	5 (9.1)	12 (4.4)
IPMN	19 (5.8)	6 (10.9)	13 (4.7)
Other	25 (7.6)	4 (7.3)	21 (7.7)
T-stage[d], N (%)			
Tis	1 (0.3)	1 (6.3)	–
T1	21 (6.4)	–	21 (12.3)
T2	31 (16.6)	3 (18.8)	28 (16.4)
T3	130 (69.5)	11 (68.8)	119 (69.6)
T4	4 (2.1)	1 (6.3)	3 (1.8)
Type of surgery, N (%)			
Classic Whipple	63 (19.3)	7 (13.0)	56 (20.5)
PPPD	259 (79.2)	45 (83.3)	214 (78.4)
PRPD	5 (1.5)	2 (3.7)	3 (1.1)
Type of pancreatic anastomosis, N (%)			
Duct-to-mucosa pancreatojejunostomy	96 (30.8)	21 (41.2)	75 (28.8)
Dunking pancreatojejunostomy	214 (68.6)	29 (56.9)	185 (71.2)

Table 1 (*continued*)

	Total cohort (N = 329)	CR-POPF[a] (N = 55)	No CR-POPF[b] (N = 274)
Dunking pancreatogastrostomy	1 (0.3)	1 (2.0)	–
Neoadjuvant therapy[e], N (%)			
No	172 (96.6)	16 (100.0)	156 (96.3)
Chemotherapy	5 (2.8)	–	5 (3.1)
Chemoradiotherapy	1 (0.6)	–	1 (0.6)
Comorbidities[f], N (%)	255 (84.7)	44 (84.6)	211 (84.7)
Vascular disease	94 (43.1)	17 (44.7)	77 (42.8)
Gastrointestinal disease	97 (45.1)	17 (45.9)	80 (44.9)
Diabetes mellitus	76 (24.6)	13 (25.5)	63 (24.4)
Neurological disease	41 (21.4)	9 (28.1)	32 (20.0)
Cardiac disease	50 (15.2)	10 (18.2)	40 (14.6)
Pulmonary disease	42 (12.8)	12 (21.8)	30 (10.9)

CR-POPF: clinically relevant postoperative pancreatic fistula; SD: standard deviation; IQR: interquartile range; BMI: Body Mass Index; ASA-classification score: American Society of Anesthesiology classification score; IPMN: intraductal papillary mucinous neoplasm; PPPD: pylorus-preserving pancreatoduodenectomy; PRPD: pylorus ring-resection pancreatoduodenectomy.
[a] Grade B or C POPF.
[b] No or grade A POPF.
[c] Weight loss in past 3 months.
[d] 7th edition of the Union for International Cancer Control (UICC) TNM classification.
[e] Only patients with pancreatic ductal adenocarcinoma.
[f] Multiple comorbidities possible.

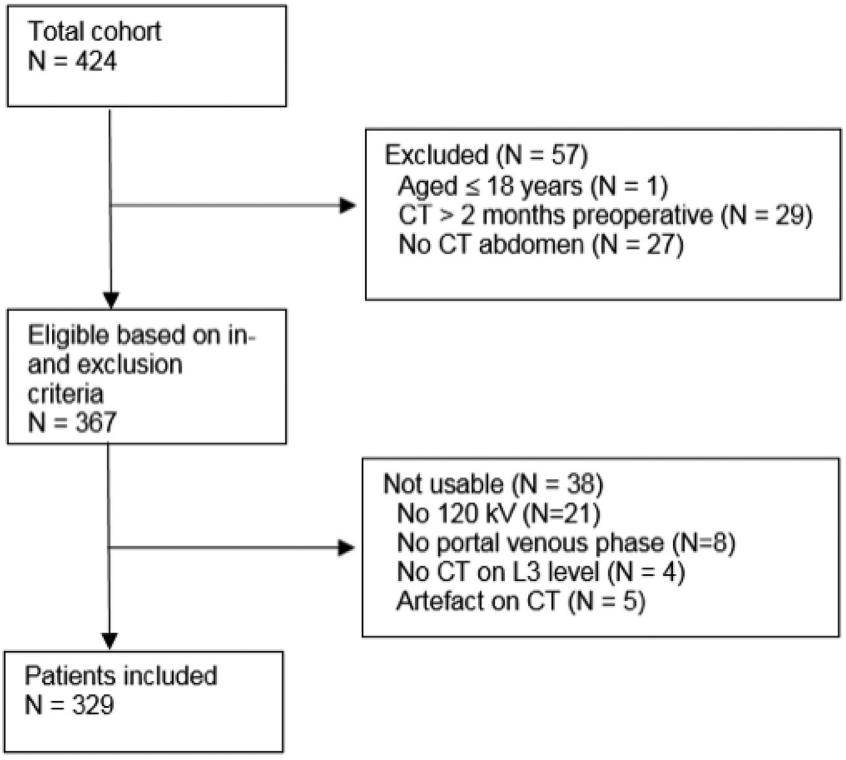

Figure 2 Flowchart of patient inclusion

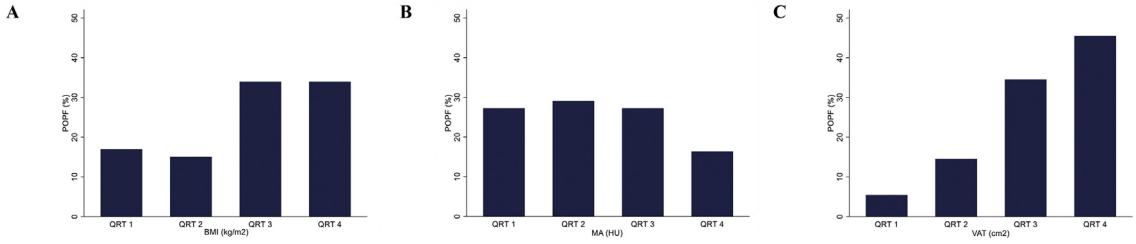

Figure 3 a–c. Prevalence of CR-POPF stratified in quartiles of BMI, MA and VAT

POPF in the a-FRS compared to BMI. Our study showed that including VAT in the a-FRS provides a significantly better model discrimination compared to BMI in predicting CR-POPF (AUC of 0.81 versus 0.74, respectively, p = 0.001).

Our results are in line with Jin et al. (2021), who also found that VAT was a significant predictor of CR-POPF.[18] However, they reported a lower median VAT compared to our study (82 cm^2 and 124.8 cm^2, respectively). This could have been caused by differences in ethnicity (Asian versus Caucasian population) and BMI (22 kg/m^2 versus 24.6 kg/m^2).[18] Several other studies developed a prediction model for CR-POPF not using VAT, but a parameter related to VAT. Yamamoto et al. (2011) found an intra-abdominal thickness, which is the distance from the linea alba to the abdominal aorta, of 65 mm or more as one of the predictors of CR-POPF.[19] A fatty pancreas is often found to be a predictor of CR-POPF, which is independently associated with a higher VAT.[20,21] However, VAT has proven to be a better parameter of a fatty pancreas than BMI.[21] This may explain why VAT and not BMI emerged as significant predictor of CR-POPF in our study. In addition, previous findings showed that BMI is not sensitive to predict clinical outcomes after pancreatoduodenectomy, whereas VAT is able to better identify high risk patients.[9,22]

Furthermore, we used the a-FRS to compare our results with, since it is widely used to predict CR-POPF.[2] The a-FRS was derived from the FRS including gland texture, pathology, pancreatic duct diameter and intraoperative blood loss as predictors of POPF.[23] Both models showed an adequate model discrimination (AUC of 0.750 and 0.942, respectively).[2] In the current study, the a-FRS model of Mungroop was reproduced resulting in only pancreatic duct diameter as a significant predictor of POPF. The discrepancy in results could be due to a lower prevalence of soft pancreatic texture and the smaller sample size used in our study. MA was not found as significant predictor in this study. These findings are not in line with Linder et al. (2019), who did find a significant different MA in patients with and without POPF.[7]

The rationale for Mungroop et al. to include only BMI to their model was that CT scan analysis might be time consuming and impracticable in clinical practice.[24] However, CT scan analysis is increasingly performed in standard patient care in our center by trained dietitians to gain insight in patients' preoperative body composition. The more experienced the dietician, the less time consuming it is to analyse a CT scan. Moreover, it is expected that in the near future improvement of software by artificial intelligence will provide automatic analysis making parameters of body composition by CT scan analysis more readily available.

Future research should be conducted on effective interventions to promote improvement of MA and loss of VAT in patients undergoing pancreatoduodenectomy. A previous retrospective study showed that maintenance of MA with decrease of VAT is possible during neo-adjuvant therapy which offers therapeutical opportunities.[25] Strategies like a low-calorie diet and resistance training could be integrated as a part of prehabilitation in patients treated with neo-adjuvant therapy.[26] In order to improve dietary guidance, the focus should be placed more on body composition and less on bodyweight and BMI in clinical practice.

Table 2 Multivariate logistic regression models including pancreatic texture, pancreatic duct diameter, BMI, MA and VAT as predictors of CR-POPF

	OR	95%CI	P-value
a-FRS model			
Soft pancreatic texture	0.98	0.51–1.90	0.95
Pancreatic duct diameter (mm)	0.68	0.57–0.81	<0.001
Body Mass Index (kg/m^2)	1.05	0.98–1.12	0.16
MA model			
Soft pancreatic texture	1.04	0.54–2.01	0.90
Pancreatic duct diameter (mm)	0.66	0.55–0.79	<0.001
Muscle attenuation (HU)	0.98	0.95–1.01	0.20
VAT model			
Soft pancreatic texture	1.14	0.58–2.26	0.70
Pancreatic duct diameter (mm)	0.67	0.56–0.80	<0.001
Visceral adipose tissue (cm^2)	1.01	1.00–1.01	<0.001
MA + VAT model			
Soft pancreatic texture	1.15	0.58–2.28	0.69
Pancreatic duct diameter (mm)	0.67	0.56–0.80	<0.001
Muscle attenuation (HU)	1.00	0.96–1.03	0.82
Visceral adipose tissue (cm^2)	1.01	1.00–1.01	<0.001

BMI: Body Mass Index; MA: muscle attenuation; VAT: visceral adipose tissue; CR-POPF: clinically relevant postoperative pancreatic fistula; OR: odds ratio; 95% CI: 95% confidence interval.

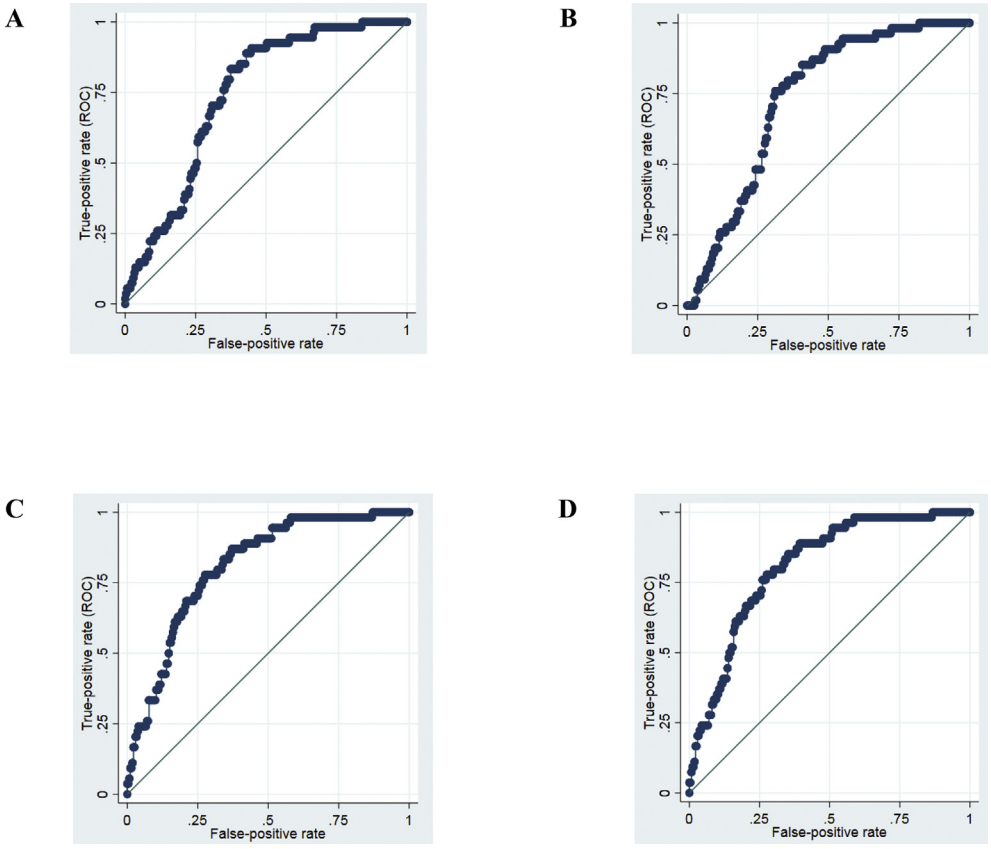

Figure 4 a–d. ROC curves of the a-FRS model (a), MA model (b), VAT model (c) and MA + VAT model (d) with AUCs of respectively 0.74 (95%CI: 0.68–0.80), 0.73 (95%CI: 0.68–0.79), 0.81 (95%CI: 0.75–0.86) and 0.81 (95%CI: 0.75–0.86)

Our results should be interpreted considering some limitations. The main limitation of this study was the relatively small sample size. Nonetheless, this study provided a clear benefit of incorporating body composition in the a-FRS over BMI. A multicenter study would be recommended to obtain a larger dataset and develop a more powered and externally validated model. Second, part of the data was retrospectively collected which holds the risk of information and classification bias. However, the rest of our data were extracted from the prospective Dutch Pancreatic Cancer Audit which has been validated for data accuracy.[13] Third, pancreatic texture was missing in 29% of patients. While pancreatic texture is mostly assessed by the surgeon, a uniform method is lacking.[27] In this study, the histologic diagnosis was used to define pancreatic texture in case of missing data, which is an objective and widely used indicator.[15,27] Fourth, CT scans were analysed by one trained author. Since the intra-observer variability is very low in CT scan analysis, this does not limit the generalizability of the results.[28] Finally, magnetic resonance imaging (MRI) will be performed more often in the future as results are promising regarding diagnosis and staging of pancreatic cancer. Mitsiopoulos et al. (1998) reported similarly good results between MRI and CT scan analysis versus cadaver analysis for skeletal muscle mass and adipose tissue.[29] This indicates that MRI analysis would be a reliable method for body composition analysis as well. When comparing CT and MRI regarding muscle attenuation, MRI shows the best contrast between adipose and muscle tissue.[30,31] MRI also has a better visibility of anatomical details and a higher sensitivity for detecting early fat infiltration in muscles and loss of muscle mass before an observed decline in functional tests than CT.[32–35] MRI shows a high accuracy for VAT as well compared to CT.[36] Nevertheless, a standardized assessment protocol for determination of body composition with MRI is still lacking and should be topic of future research.[31,37]

To our best knowledge, this is the first study to include MA and VAT in a pancreatic fistula prediction model for the Caucasian population. A multicentre study should be performed to externally validate the results of this study. CT scan analysis was used to determine body composition, which is validated as a reliable method and seen as the reference method.[16,38]

In conclusion, VAT is of added value in the a-FRS instead of BMI as predictor of CR-POPF. A fistula risk score including body composition can improve the pancreatic fistula risk stratification in patients undergoing pancreatoduodenectomy and hence optimize individual pre-, intra- and postoperative management.

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.

Author contribution

Study conception and design, acquisition of data, or analysis and interpretation of data: CJL, JVG, MHA, EB, BAB, EL, SSF, ALV, AD, JSDM.

Manuscript drafting or revising: CJL, JVG, MHA, EB, BAB, EL, SSF, ALV, AD, JSDM.

Manuscript approval: CJL, JVG, MHA, EB, BAB, EL, SSF, ALV, AD, JSDM.

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Conflicts of interest

None.

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Appendix A. Supplementary data

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