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ORIGINAL RESEARCH

Prediction of postoperative outcomes after pancreatoduodenectomy- What matters more? Radiologically assessed pancreatic morphology or body composition?

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ABSTRACT

Background Complications after Pancreatoduodenectomy (PD) are not unusual, making it worthwhile to search for factors responsible for them. Pancreatic gland morphology (PGM) and the patient's body composition (BCA) can both affect postoperative outcomes. This study was undertaken to study the differential role of PGM and BCA on postoperative outcomes after PD. **Methods** Retrospective analysis of 457 patients who underwent PD. Preoperative computed tomography scans were used to assess PGM and BCA. The impact of PGM and BCA was studied on major complications (MC) and clinically relevant pancreatic fistula (CRPF). **Results** Major complications, Clavien Dindo ≥3, were seen in 60(13.1%) patients and CRPF in 43(9.4%). On multivariable logistic regression, a high pancreatic cut surface area/main pancreatic duct (SA/MPD) was an independent predictor of MC (OR 2.842, p<0.001), along with respiratory comorbidity, preoperative cholangitis and elevated serum creatinine. Low muscle density (PMD) (OR 2.466, p=0.008) and high SA/MPD (OR 3.373, p=0.001) were risk factors for CRPF. Thirty-day mortality (30DM) was 3.9%. SA/MPD was also a risk factor for 30DM and pancreatectomy-specific complications (PSC). Visceral fat area/total abdominal muscle area was a predictor of prolonged hospital stay. **Conclusion** The parameter SA/MPD consistently predicted postoperative outcomes, predicting MC, CRPF, PSC and 30DM.

INTRODUCTION

Complications following pancreatoduodenectomy (PD) are consistently reported in all large series, in 30-40% of patients [1, 2]. Over the last few years, improvements, both in surgical techniques and postoperative care have contributed to decreasing operative mortality but the complication rates have largely remained unchanged [1, 3]. In an attempt to decrease the complications, the focus so far has been mainly on the surgical techniques to minimise pancreatic fistula rates. Due to the realisation that no further improvements have been possible by modifying the surgical techniques, the role of host factors like lean body mass and visceral fat, which are representative of the patient's physiological status, are being investigated [4]. Radiologically assessed depletion of muscle mass and quality has been reported to impact the results of surgical procedures for many gastrointestinal cancers like colorectal, colorectal liver metastases and esophageal cancer [5, 6, 7]. The effects include an increased incidence of anastomotic leak, surgical site infections, prolonged hospital stay, poor tolerance to chemotherapy and increased long-term mortality [7, 8, 9]. Patients with pancreatic cancer are anorexic and have pronounced cachexia because of fat malabsorption and cytokine-mediated systemic inflammation [10]. Therefore in the presence of muscle depletion, a major procedure like PD, is expected to be associated with increased morbidity and even increased operative mortality. However, studies of impact of lean muscle mass, visceral fat and other parameters of body composition analysis (BCA) on postoperative complications after PD have shown inconsistent and inconclusive results. This may be because of the lack of a standard index to assess muscle depletion or the lack of optimal cut-off values to define sarcopenia. We hypothesized that postoperative complications are predicted by local factors i.e. pancreatic morphology, whereas salvage rates may be predicted by depleted body composition. This study was undertaken with the primary aim to assess the impact of radiologically assessed pancreatic gland morphology (PGM) and parameters of BCA, on clinically relevant pancreatic fistula (CRPF)

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Keywords Pancreatoduodenectomy, Body composition analysis, Pancreatic gland morphology, Postoperative outcomes, Clinically relevant pancreatic fistula

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and major complications (MC) following PD. Secondary outcomes studied included 30-day mortality (30DM), pancreatectomy-specific complications (PSC) and the length of hospital stay (LOS).

MATERIALS AND METHODS

The study includes 457 patients who underwent elective PD at the Department of GI Surgery, GI Oncology, Minimal Access and Bariatric Surgery, Medanta - The Medicity, Gurugram, India, from March 2013 to October 2021. Data of patients who had an abdominal computed tomography (CT) scan performed within 3 months before surgery, whose virtual images were available, was collected from a prospectively maintained database. Patients who did not undergo a PD and for whom virtual images of CT were not available were excluded. All patients underwent a classical pylorus-sacrificing PD by the same team of experienced surgeons. Surgery included standard lymphadenectomy with reconstruction using a single jejunal loop repositioned in the supracolic compartment in a retrocolic fashion [11]. Pancreatojejunostomy was performed either by the standard duct to mucosa technique or a modified end-to-side single-layered anastomosis using interrupted delayed absorbable monofilament sutures. Patients were managed and followed as per a standardised clinical care pathway [12]. Demographic and clinical data included gender, age, body mass index (BMI), comorbid profile, American Society of Anaesthesiologist (ASA) grade, preoperative laboratory values, intra-operative events, postoperative complications, development of clinically relevant pancreatic fistula (CRPF), post pancreatectomy haemorrhage (PPH), delayed gastric emptying (DGE), intra-abdominal collection, surgical site infection (SSI), length of hospital stay (LOS) and 30-day mortality rates (30DM). The study protocol was approved by the Institutional Review Board (MICR-1397/2022) and Ethics committee approval was obtained.

Assessment of pancreatic gland morphology and body composition

PGM was assessed by measuring pancreatic parenchymal attenuation, main pancreatic duct diameter (MPD), craniocaudal, anteroposterior diameter and surface area of the anticipated cut surface of the gland. Body composition was radiologically analysed by calculating total psoas muscle area, volume, density and total abdominal muscle area ((TPA, TPV, PMD, TAMA respectively). Body fat was assessed by calculating visceral and subcutaneous fat area (VFA and SFA) at L3 and visceral fat volume (VFV) [**Supplementary Figure 1**].

Assessment of body muscle and fat was performed using the GE Advantage Workstation Release 4.6 software (USA), on 3 mm axial cuts of non-contrast images of preoperatively performed CT scans [13]. The muscle area measurements were performed at the level of the transverse process of 3rd lumbar vertebrae, in a semi-automated manner with manual outlining of the muscle using pencil trace method, and density threshold between -30 to +110 Hounsfield units (HU)13. TPV was calculated by assessing the craniocaudal extent of the muscle by manual outlining with density threshold between -30 to +110 HU [14]. Muscle parameters studied included TAMA, TPA, expressed as mm^2, TPV expressed as mm^3 and PMD calculated in HU. TAMA included the abdominal wall and

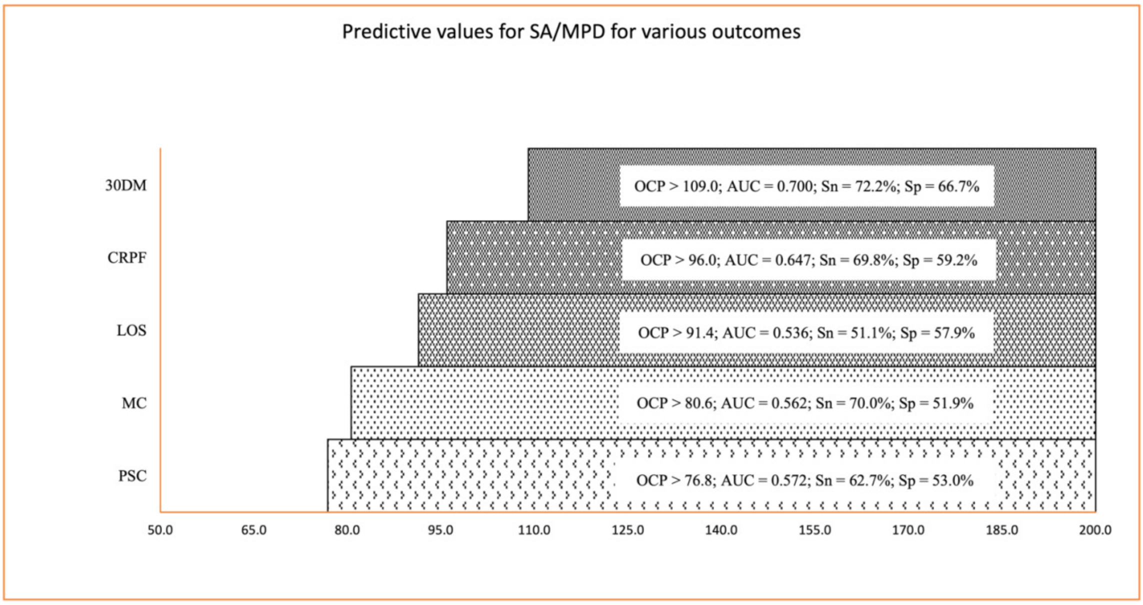

Figure 1. Predictive values of SA/MPD for various postoperative outcomes.

X axis - Values of SA/MPD in mm^2/mm, SA/MPD-Pancreatic cut surface area/main pancreatic duct diameter

Y axis- Increasing severity of outcomes- PSC-Pancreatectomy-specific complications, MC-Major complications, LOS – Length of stay, CRPF-Clinically Relevant Pancreatic Fistula, 30DM-30day mortality

OCP-Optimal cut-off point, AUC-Area under the curve, Sn-Sensitivity, Sp-Specificity

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paraspinal muscles. TAMA, TPA and TPV were normalized for height (divided by height in meters)^2 [15, 16, 17]. PMD was reported in HU, and examined fatty infiltration of the muscle.

VFA and SFA were estimated at L3, with adipose tissue thresholds of -150 to -50 HU and -190 to -30 HU respectively [16], reported as mm^2. VFV was estimated and expressed as mm3 [18]. VFA/TAMA index was also calculated, as suggested by a previous study to be a predictor of POPF [16].

Considering the transection margin of pancreas to be at the left border of the porto-mesenteric axis, qualitative and quantitative assessment of the presumed pancreatic remnant was performed on non-contrast preoperative images. Qualitative assessment included parenchymal attenuation, and quantitative assessment included the MPD diameter, craniocaudal and anteroposterior diameter of the remanent pancreas cut surface. The cut surface area was calculated as the area of an elliptical surface - $\pi r_1 r_2$. A parameter defined as SA/MPD (area of the pancreatic cut surface/ mean of MPD diameter) was created to express the technical difficulty of pancreatic anastomosis.

Definitions

Postoperative complications were graded according to Clavien Dindo (CD) classification. Grades 3 and above were considered major [19]. CRPF was defined using the 2016 update of the International Study Group of Pancreatic Surgery (ISGPS) definition [20]. PPH was defined according to the 2007 definition given by the ISGPS [21]. DGE was defined using the 2007 definition by ISGPS [22]. SSI was defined as the development of erythema, induration or purulent discharge from the wound site [23]. PSC was defined as any complication, of any grade occurring as a result of pancreatic resection. Worsening of systemic diseases was excluded from this variable. LOS was defined as the number of days as an inpatient from the day of surgery to the day of planned discharge. 30DM was defined as death occurring within 30 days of surgery because of any surgical or medical cause. The primary outcome studied was the development of MC and CRPF, the secondary outcomes being 30DM, PSC and LOS.

Statistical methods

Normally distributed quantitative variables were presented as mean and standard deviation. The mean of two groups was compared using independent Student t-test. Quantitative variables which were not normally distributed were expressed as median and range. The median of two groups was compared using Mann-Whitney U test. Association between two categorical variables was studied using Chi-square test. Pearson's correlation was used to study correlations among preoperative, intra-operative and anthropometric continuous variables. Parameters of BCA were considered in a gender-specific manner. If significant at 10% on univariable analysis, cut-offs were generated per outcome by plotting receiver operating curves (ROC) and entered into multivariable logistic regression. Other continuous variables, which were not gender-specific – pancreatic morphology, lab values etc, were handled similarly. Factors significant at 10% were entered into a multivariable logistic regression to identify the influence of individual factors on the outcome variables. $P < 0.05$ was considered statistically significant. Statistical Package for the Social Sciences (SPSS) INC., Version 24.0 for Windows, was used for statistical analysis.

RESULTS

Patient cohort

Of 618 PDs performed during this period, 457 patients, whose CT scans were available on PACS (Picture Archiving and Communication System) were found eligible for the study. The mean age was 58.8±12.2 years, with 311(68.1%) men and 146(31.9%) women. Surgery was performed for malignancy in 433(94.7%) patients, with the most common tumour being ampullary (193, 42.2%) followed by pancreatic head (121, 26.5%). Twenty-eight (6.1%) surgeries were performed for benign diseases. Demographic, clinical, anthropometric parameters of the patients and postoperative outcomes have been described in **[Table 1].** As expected, TPA, TPV, TAMA, VFA, VFV, and SFA were higher in men than women, while PMD was similar **[Table 1].**

Age showed negative correlation with muscle indices (TPA r = -0.155, p=0.001, TPV r = -0.213, p=0.000, TAMA r = -0.143, p=0.002) **(Supplemental Table 1)**. Pancreatic parenchymal attenuation and SA/MPD also decreased with age suggestive of fatty replacement and gland atrophy respectively. Body mass index correlated with an increase in VFA and SFA (r=0.292 and r=0.383, both p=0.000) and a slight increase in SA/MPD (r=0.133, p=0.004) **[Supplementary Table 1].**

Major complications

Major complications were seen in 60(13.1%) patients, with CRPF at 9.4% (43/457), DGE, 32.6% (149/457) and PPH being 7.2% (33/457). When factors affecting the rate of MC were studied, none of the BCA parameters, namely, TPA, TPV, TAMA, PMD, VFA, VFV, SFA and VFA/TAMA were found to be associated, in either gender. The factors significant at 10% on univariable analysis were SA/MPD, diabetes mellitus, respiratory comorbidity, preoperative cholangitis, preoperative serum albumin, serum creatinine and estimated blood loss during surgery **(Table 2)**. Optimal cut-off points were generated for the continuous variables and data dichotomised **(Supplementary Table 2)**. On multivariable logistic regression, using the Enter Method, high SA/MPD (OR=2.842, 95% CI 1.497-5.397), respiratory comorbidity (OR=5.887, 95% CI 1.967-17.619), preoperative cholangitis (OR=3.581, 95% CI

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Table 1. Preoperative, intraoperative parameters and outcomes of all patients.

Preoperative characteristics	Total	Men	Women	p value
Age (in years)	58.8 ± 12.2	59.1 ± 12.2	58 ± 12	0.378
ASA Grade				
1	235 (51.4%)	164 (52.7%)	71 (48.6%)	
2	212 (46.4%)	139 (44.7%)	73 (50%)	0.453
3	10 (2.2%)	8 (2.6%)	2 (1.4%)	
Diabetes Mellitus	176 (38.5%)	127 (40.8%)	49 (33.6%)	0.136
Hypertension	174 (38.1%)	122 (39.2%)	52 (35.6%)	0.458
Cardiac Comorbidity	50 (10.9%)	43 (13.8%)	7 (4.8%)	*0.004*
Respiratory Comorbidity	17 (3.7%)	10 (3.2%)	7 (4.8%)	0.406
Obstructive Jaundice	273 (59.7%)	200 (64.3%)	73 (50%)	*0.004*
Cholangitis	22 (4.8%)	17 (5.5%)	5 (3.4%)	0.342
Preoperative stenting	34 (7.4%)	25 (8%)	9 (6.2%)	0.477
Hemoglobin (gm/dl)	11.4 ± 1.8	11.5 ± 1.9	11.2 ± 1.5	0.054
Serum Bilirubin (mg/dl)	1.7 (0.8 - 4.8)	1.8 (0.8 - 5.6)	1.3 (0.7 - 4.5)	*0.019*
Serum Albumin (gm/dl)	3.8 ± 0.4	3.8 ± 0.5	3.8 ± 0.4	0.378
Serum Aspartate Transaminase levels (U/L)	56 (36 - 89)	67 (40 - 89)	45 (33 - 87)	*0.002*
Serum Alanine Transaminase levels (U/L)	63 (37 - 93)	68 (39 - 102)	52 (34 - 88)	*0.013*
Serum Creatinine (mg/dl)	0.6 ± 0.3	0.7 ± 0.3	0.6 ± 0.2	*0.031*
Parameters of body composition analysis and pancreatic gland morphology				
BMI (Kg/m^2)	24.77 ± 3.88	24.67 ± 3.78	24.99 ± 4.08	0.411
TPA Index (mm^2/m^2)	403.99 ± 158.75	459.17 ± 150.12	286.47 ± 103.12	*0.000*
TPV Index (mm^3/m^2)	75.7 ± 29.99	85.94 ± 28.9	53.9 ± 18.46	*0.000*
Psoas muscle density (HU)	47.6 ± 17.58	47.89 ± 19.54	47 ± 12.46	0.613
TAMA Index (mm^2/m^2)	3334.38 ± 985.91	3590.14 ± 952.65	2789.59 ± 823.04	*0.000*
Visceral Fat Area at L3 (mm^2)	9767.7 (4584.7 - 15978.2)	11163.7 (5826.3 - 17897.4)	6498.85 (3425.6 - 12156.5)	*0.000*
Visceral Fat Volume (mm^3)	2870.6 (1659.4 - 4170.5)	3198.4 (1796.9 - 4433.4)	2257.2 (1349 - 3496.4)	*0.000*
Subcutaneous Fat Area at L3 (mm^2)	15266.8 (10125.8 - 21557.3)	13048.6 (8989.1 - 19083.1)	18798.5 (14738.8 - 27668.4)	*0.000*
VFA/TAMA	1.08 (0.61 - 1.71)	1.13 (0.68 - 1.76)	0.94 (0.5 - 1.63)	0.078
Pancreatic parenchymal attenuation (HU)	33.31 ± 11.68	33.33 ± 11.59	33.25 ± 11.9	0.948
Surface area/MPD (mm^2/mm)	88.02 (47.27 - 130.39)	90.28 (48.8 - 134.07)	81.68 (45.29 - 127.07)	0.251
Intraoperative events				
Soft pancreatic texture	328 (71.8%)	217 (69.8%)	111 (76%)	0.166
Pancreatic anastomosis				
Duct - Mucosa	323 (70.7%)	229 (73.6%)	94 (64.4%)	*0.043*
End - Side	134 (29.3%)	82 (26.4%)	52 (35.6%)	
Intraoperative blood transfusion	11 (2.4%)	8 (2.6%)	3 (2.1%)	0.736
Fistula risk Score				
A	47 (10.3%)	32 (10.3%)	15 (10.3%)	
B	388 (84.9%)	264 (84.9%)	124 (84.9%)	1
C	22 (4.8%)	15 (4.8%)	7 (4.8%)	
Blood loss (ml)	100 (100 - 200)	100 (100 - 200)	100 (100 - 150)	0.356
Duration of Surgery (minutes)	334 ± 60	338 ± 60	325 ± 58	*0.035*
Postoperative outcomes				
ICU readmission	36 (7.9%)	29 (9.3%)	7 (4.8%)	0.094
Delayed gastric emptying (DGE)	149 (32.6%)	111 (35.7%)	38 (26%)	*0.04*
Clinically Relevant Pancreatic Fistula (CRPF)	43 (9.4%)	30 (9.6%)	13 (8.9%)	0.8
Post Pancreatectomy Hemorrhage (PPH)	33 (7.2%)	25 (8%)	8 (5.5%)	0.324
Surgical site infection	111 (24.3%)	79 (25.4%)	32 (21.9%)	0.418

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Major complications (CD Grade 3,4,5)	60 (13.1%)	45 (14.5%)	15 (10.3%)	0.216
Thirty day mortality	18 (3.9%)	15 (4.8%)	3 (2.1%)	0.156
Pancreatectomy specific complications	276 (60.4%)	193 (62.1%)	83 (56.8%)	0.288
Length of hospital stay	9 (7 - 12)	9 (7 - 13)	8 (7 - 11)	*0.03*
Tumour location				
Ampullary	211 (46.5%)	136 (44%)	75 (51.7%)	0.345
Bile duct - Lower end	57 (12.6%)	39 (12.6%)	18 (12.4%)	
Duodenum	40 (8.8%)	31 (10%)	9 (6.2%)	
Head of pancreas	146 (32.2%)	103 (33.3%)	43 (29.7%)	

ASA – American Society of Anesthesiologists, BMI – Body Mass Index, TPA – Total psoas muscle area, TPV – Total Psoas Muscle Volume, TAMA – Total Abdominal Muscle Area, VFA/TAMA – Visceral fat area/total abdominal muscle area, ICU – Intensive Care Unit

Significant values have been italicized.

Table 2. Univariable and multivariable analyses of potential predictors of major complications after pancreatoduodenectomy.

Parameters	Major Complications (n=60)	No Major Complications (n=397)	Univariable p value	Multivariable analysis Odd's Ratio (95% Confidence Interval)	Multivariable p value
SA/MPD (mm^2/mm)	99 (59.5 - 145.4)	86.1 (47.3- 127.1)	0.075	2.842 (1.497 - 5.397)	*0.001*
Diabetes Mellitus	29 (48.3%)	147 (37.0%)	0.095	1.435 (0.797 - 2.482)	0.228
Respiratory comorbidity	7 (11.7%)	10 (2.5%)	0.002	5.887 (1.967 - 17.619)	*0.002*
Preoperative Cholangitis	7 (11.7%)	15 (3.8%)	0.012	3.581 (1.307 - 9.811)	*0.013*
Preoperative Serum Albumin levels (gm/dl)	3.7 ± 0.5	3.8 ± 0.4	0.042	1.429 (0.791 - 2.582)	0.237
Preoperative Serum Creatinine levels (mg/dl)	0.8 ± 0.3	0.6 ± 0.2	0.000	1.995 (1.104 - 3.604)	*0.022*
Estimated intra-operative blood loss (ml)	100 (100 - 300)	100 (100 - 200)	0.001	1.321 (0.735 - 2.376)	0.352

SA/MPD – Pancreatic cut surface area/ main pancreatic duct diameter

Significant values have been italicized

1.307-9.811) and elevated serum creatinine (OR=1.995, 95% CI 1.104-3.604) were associated with an increased risk of MC **[Table 2]**.

Clinically relevant pancreatic fistula

Forty-three patients developed CRPF. On univariable analysis, low PMD, high SFA and high VFA/TAMA were associated with an increased incidence of CRPF in the female gender. Other factors significant at 10% were the presence of preoperative respiratory comorbidity, elevated preoperative serum bilirubin levels, serum creatinine levels, intraoperative blood loss, duration of surgery and SA/MPD **(Table 3, Supplementary Table 3)**. On multivariable logistic regression, SA/MPD (OR 3.373, 95% CI 1.673–6.800, p=0.001) emerged as a stronger predictor than PMD (OR 2.466, 95% CI 1.267–4.801, p=0.008), while SFA and VFA/TAMA got eliminated **[Table 3].**

Thirty-day mortality

The 30DM rate was 3.9%(18/457). On gender-wise univariable analysis of BCA parameters, low PMD was found significant at 10% in the male gender (p=0.014). At the same time, paradoxically a high TAMA was seen in the female gender (p=0.011) **[Table 4, Supplementary Table 4].** Other parameters significant in univariable analyses were a high SA/MPD, diabetes mellitus, cardiovascular disease, preoperative biliary stenting, presence of a vascular anomaly, elevated serum bilirubin, AST and ALT levels. SA/MPD (>109 mm^2/mm) and preoperative biliary stenting were two factors most predictive of 30DM (OR=5.580, 95% CI 1.582-19.685, and, OR=6.794, 95% CI 1.925-23.974, respectively)**[Table 4].** Though TAMA index emerged as a strong predictor, there were only 3 women in the cohort who died and therefore, this statistical result cannot be considered robust or clinically relevant. When the analysis was restricted to the 60 patients with MC, 42 could be rescued, while 18 died (Failure to rescue 30%,18/60). On comparing the parameters of BCA and PGM, SFA was significantly higher in men who died vs those who could be salvaged (16470.5±8155.9, vs 12129.2±5615.1, p=0.042). The median SA/MPD, was also higher in the FTR group (135(183.6–100.1) vs 88(119.8–36.5), p=0.016) (irrespective of the gender). Since the sample size for failure to rescue was small, generating gender-specific optimal cut-off for the parameters of BCA would not have revealed meaningful results, and, therefore not reported.

Length of hospital stay and pancreatectomy-specific complications

The median LOS was 9 days, IQR – 7-12 days. After excluding the patients who died, 182 (41.5%) were discharged on the 9th postoperative day. The only factor predictive of a prolonged LOS (>9 days) was VFA/TAMA (OR 1.59, 95% CI 1.007-2.372, p=0.021). PSC occurred

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Table 3. Univariable and multivariable analyses of potential predictors of clinically relevant pancreatic fistula after pancreatoduodenectomy.

Parameters		Clinically Relevant Pancreatic Fistula (n=43)	No Clinically Relevant Pancreatic Fistula (n=414)	Univariable p value	Multivariable analysis Odd's Ratio (95% Confidence Interval)	Multivariable p value
Psoas Muscle Density (HU)	Male	52.1 ± 28.9	47.4 ± 18.3	0.232	2.466 (1.267 - 4.801)	*0.008*
	Female	39.4 ± 7.5	47.7 ± 12.6	0.003		
SFA (mm^2)	Male	13034.2 (7144.1 - 17704)	13048.6 (9084.5 - 19248.6)	0.296	1.374 (0.707 - 2.669)	0.349
	Female	23059.7 (16023.8 - 35921.7)	18515.7 (14738.8 - 27256.3)	0.099		
VFA/TAMA	Male	1.3 (0.8 - 1.9)	1.1 (0.7 - 1.7)	0.474	1.591 (0.800 - 3.164)	0.185
	Female	1.4 (1 - 2.2)	0.9 (0.5 - 1.6)	0.098		
SA/MPD (mm^2/mm)		107 (84.6 - 195.1)	84.9 (46.8 - 126.2)	0.000	3.373 (1.673 - 6.800)	*0.001*
Respiratory comorbidity		4 (9.3%)	13 (3.1%)	0.053	3.843 (1.103 - 13.379)	*0.034*
Preoperative Serum Bilirubin levels (gm/dl)		2.1 (0.8 - 8.4)	1.6 (0.8 - 4.6)	0.028	1.581 (0.797 - 3.135)	0.190
Preoperative Serum Creatinine levels (mg/dl)		0.7 ± 0.3	0.6 ± 0.3	0.013	1.219 (0.628 - 2.367)	0.558
Intra-operative blood loss (ml)		100 (100 - 200)	100 (100 - 300)	0.009	1.658 (0.823 - 3.341)	0.157
Duration of Surgery (minutes)		316.5 ± 53.5	335.3 ± 60	0.049	1.564 (0.779 - 3.140)	0.208

SFA – Subcutaneous fat area, SA/MPD – Pancreatic cut surface area/ main pancreatic duct diameter

Significant values have been italicized

Table 4. Univariable and multivariable analyses of potential predictors of thirty-day mortality after pancreatoduodenectomy.

Parameters		Thirty-day Mortality (n=18)	Alive at thirty days (n=439)	Univariable p value	Multivariable analysis Odd's Ratio (95% Confidence Interval)	Multivariable p value
Psoas muscle density (HU)	Male	39.8 ± 8.5	48.3 ± 19.9	0.014	1.300 (0.382 - 4.426)	0.675
	Female	49.4 ± 11.4	47 ± 12.5	0.742		
TAMA Index (mm^2/m^2)	Male	3850.7 ± 1293.1	3577.0 ± 933.1	0.277	4.861 (1.410 - 16.761)	*0.012*
	Female	4649.6 ± 1672.6	2750.6 ± 760.1	0.011		
Age (years)		64.4 ± 11.8	58.5 ± 12.1	0.047	4.306 (1.148 - 16.145)	*0.030*
SA/MPD (mm^2/mm)		135.3 (100.1 - 183.6)	86.1 (46.8 - 127.1)	0.027	5.580 (1.582 - 19.685)	*0.008*
Diabetes Mellitus		11 (61.1%)	165 (37.6%)	0.052	1.077 (0.318 - 3.653)	0.905
Cardiovascular comorbidity		6 (33.3%)	44 (10.0%)	0.004	3.537 (0.890 - 14.051)	0.073
Preoperative Endobiliary Stenting		12 (66.7%)	146 (33.3%)	0.006	6.794 (1.925 - 23.974)	*0.003*
Vascular anamoly		7 (38.9%)	64 (14.6%)	0.009	3.339 (0.982 - 11.353)	0.053
Preoperative Serum Bilirubin levels (gm/dl)		3.9 (2.4 - 5.8)	1.5 (0.8 - 4.6)	0.075	4.939 (1.258 - 19.397)	*0.022*
Preoperative Serum Aspartate Transaminase levels (U/L)		99 (53 - 135)	55 (36 - 88)	0.002	3.534 (0.654 - 19.087)	0.142
Preoperative Serum Alanine Transaminase levels (U/L)		79 (63 - 150)	62 (37 - 93)	0.002	1.037 (0.171 - 6.269)	0.969

in 276(60.4%) patients and SA/MPD remained the only predictor of PSC (OR 1.665, 95% CI 1.120–2.475, p=0.012) on multivariable analysis **[Supplementary Tables 5, 6, 7, 8].**

Pancreatic cut surface area/ main pancreatic duct ratio (SA/MPD)

When various quantitative parameters of PGM, namely the mean of MPD diameter, the area of the pancreatic cut surface, anteroposterior and craniocaudal diameter and SA/MPD ratio, were plotted as ROC curves for the risk of CRPF, SA/MPD emerged as a reliable predictor with AUC at 0.65 **[Supplementary Figure 2].** The various predictive values of SA/MPD for various postoperative outcomes were further analysed. Increasing SA/MPD was associated with increasing severity of outcomes with SA/MPD>109 mm2/mm as a respectably accurate predictor of

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30DM (AUC=0.700, sensitivity=72.2%, specificity=66.7%) **[Figure 1].**

DISCUSSION

Outcomes after PD may be influenced by the technical expertise of the surgical team and center, pancreatic gland morphology and the patient's general health. Traditionally most emphasis has been on studying and modifying the technical aspects of the procedure. Despite all these improvements, the complication rates have not reduced beyond a point, which has nudged the surgeons to look at other possible contributors. One of the subjects worth investigating is how a patient's body composition affects both the causation and the outcomes of complications after PD. There is increasing awareness that frailty is an adverse factor for both short-term and long-term outcomes in cancer surgery and evidence exists that frail patients tolerate postoperative complications poorly. Not only do frail patients have a lower chance of being salvaged after a postoperative complication but they also experience a significant decline in their functional status. Sarcopenia has been reported as a predictor of poor outcomes after surgical procedures for many gastrointestinal cancers [5, 6, 7]. As mentioned, the results of most previous studies discussing the impact of sarcopenia on peri-operative outcomes following pancreatectomies have been contradictory. One of the reasons for this may be a disagreement on the ideal parameter to assess sarcopenia. Muscle area has most commonly been assessed at L3, with TPA being one of the most used parameters [24, 25, 26, 27], but with conflicting results [14, 28, 29]. Total psoas volume, TAMA, VFA and SFA have also been studied previously as predictors of postoperative outcomes [14, 15, 16, 17, 25, 28, 29, 30, 31]. This disparity is reflected across literature and highlighted in a publication from New Zealand, where the discrepancy in results was found when different parameters were used to assess sarcopenia [29,32]. Another problem is the lack of consensus in deciding the cut-off points for various parameters of BCA, or the best index to study frailty33. Body composition in Asians is bound to be different from that of Caucasians because of differences in ethnicities and lifestyles [33,34] and therefore, using defining values from studies conducted in a different ethnic group may not be relevant [17, 33, 35, 36]. Awareness of these divergent insights prompted us to include measurements of multiple radiological parameters of BCA (muscle mass measurements and body fat analyses) in this study. Pre-defined gender-specific cut-offs from previous literature were not used, instead, values were generated per outcome using ROC analysis. In addition, the radiological assessment of PGM was performed, to ascertain their relative contribution to adverse postoperative events **[Supplementary Figure 1].** Pancreatic gland morphology, when studied as SA/MPD emerged as a more consistent predictor of postoperative complications than any parameter of BCA.

It makes sense to be able to predict postoperative complications at a time when preventive or outcome-altering measures can be executed. Therefore, the best time is in the preoperative period, when patients can be selected, preoperative care optimized, and the surgical execution can possibly be stratified as per the patients' risk assessment. Traditionally, probable factors contributing to pancreatic leak have been ascertained intra-operatively, e.g., blood loss, and/or are subjective, e.g., pancreatic texture, and MPD size [37]. At this point, the surgical process is beyond the point where preventive measures can be incorporated. Therefore, an objective assessment of such risks preoperatively, if possible, would be ideal. In a 'physiologically' fit patient with a high-risk pancreas, certain preventive measures can possibly help, like the placement of drains, use of octreotide, and adding a tube jejunostomy as access for postoperative enteral feeding.

It was our hypothesis that pancreas-related factors cause a complication while patient-related factors determine whether a patient will tolerate the complication or not. This has been described as a failure to rescue – the death of a patient who developed a major complication [38, 39]. The present study partially supports our theory and shows that SA/MPD reliably predicts the postoperative course after PD. Increasing values have a graded contribution to the severity of complications **[Figure 1, PSC -> CRPF -> 30DM].** However, none of the BCA parameters seemed to have a meaningful impact on postoperative outcomes, except for PMD being a predictor of CRPF. Muscle density or attenuation is an infrequently studied parameter of BCA, which inversely correlates with intra-muscular adiposity [40]. Muscle mass depletion is said to cause a decrease in muscle attenuation which parallels decreased muscle strength, and function and negatively impacts surgical outcomes [41]. It has been shown to independently predict infectious and gastrointestinal complications and was associated with the development of CRPF [31, 42]. It would have been helpful to study factors predicting failure to rescue, however because of small numbers, generating optimal cut-offs would not have been statistically robust. Noticeably, the median VFA was higher in patients who could not be rescued as compared to those who did develop a complication and were salvaged (13946.7 (8898.7-24696) vs 10350 (5587.6-13906.1), p=0.044). Similarly, the mean SFA was higher in men who could not be salvaged. Because of the physiological differences between men and women, a differential contribution of muscle mass and body fat can be expected, and therefore gender-specific univariable analyses of BCA parameters were performed. A high value of SA/MPD, >/=109 mm^2/mm emerged as a predictor of mortality, with an OR of 5.580. A high TAMA was paradoxically found to be predictive of 30DM, this statistical result is not reliable as only 3 women died, who had relatively high TAMA values. Nevertheless, the lack of benefit of high

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muscularity on postoperative outcomes, as shown by our results, was consistent with the findings of a meta-analysis studying the impact of sarcopenia on outcomes following pancreatic resections [32]. One can dare to infer from these results that high adiposity is probably a better predictor of poor outcomes than low muscularity. However, to accurately study mortality at a rate of 3%, with a precision of 1% and 95% confidence interval, a sample size of over 1150 is required.

Based on the radiological assessment of PGM and patients' BCA, we propose a classification which divides the patients into one of four types. Low-risk pancreas – fit patient, high-risk pancreas – fit patient, low-risk pancreas – frail patient and high-risk pancreas – frail patient. It is probably, the last group of patients who are most at risk, as they have a higher chance of developing an adverse postoperative event and possibly a lower chance of rescue. A reasonable parameter which can objectively identify a high-risk pancreas on a preoperative CT seems to be the SA/MPD. What constitutes a frail patient, and which parameter should be used to reliably predict failure to rescue remains a matter of debate and warrants larger, multicenter studies.

The retrospective nature of our study is an obvious disadvantage. The data comes from a single high-volume centre, which may limit the widespread applicability of these morphometric values. Though the data is derived from a prospectively maintained database, some amount of reporting bias vis-a-vis postoperative outcomes can't be ruled out. Nevertheless, this is the first study to consider almost all parameters of BCA and has generated optimal cut-offs per outcome, instead of relying on pre-defined values derived from data of another ethnic group. The study also considers the morphometric assessment of pancreas and attempts to convert a subjective intra-operative assessment into an objective preoperative identification of a 'difficult' pancreas. Though preoperative PGM has been studied previously by considering the remanent pancreatic volume and found to be a risk factor for CRPF, performing pancreatic volumetry is a tedious task. SA/MPD is relatively a simpler tool and can be easily measured and reported on pre-operative scans [30]. Pancreatic stump width ≥8 mm and MPD diameter ≤2 mm has been previously reported as risk factors for CRPF [43], but the study reported a relatively high rate of CRPF at 28%. In the present study, SA/MPD was preferred over the use of pancreatic stump width or MPD alone as the AUC for SA/MPD was higher than any other parameter **[Figure 1].** Pancreatic attenuation was studied as an objective marker of the 'functionality' of the gland or the amount of 'juice' in the pancreas. The fatty replacement may occur with age as signified by correlations **[Supplementary Table 1]** but also decreases the tensile strength of the gland so the sutures may hold poorly. However, this PGM parameter was not a predictor of CRPF or any other adverse event. The effect of pancreatic morphology and some aspects of a patient's body composition in affecting postoperative outcomes after PD are suggested by our study. The entrenched views of technical refinements being the sole determinants of good outcomes seem irrational, a patient's body composition does play a substantial, though not yet fully understood role.

CONCLUSION

Pancreatic morphology, studied as SA/MPD was a more consistent predictor of adverse postoperative outcomes after PD than BCA. A high SA/MPD was predictive of PSC, MC, CRPF and 30DM. Fatty replacement of the muscle, represented as decreased PMD was predictive of CRPF and a high SFA was associated with a higher chance of 30-day deaths in male patients.

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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