Preoperative EUS elastography: A new tool for predicting postoperative pancreatic fistulas

Original Article

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ABSTRACT

Background: Post-operative Pancreatic fistula (POPF) is one of the significant serious complications following a PancreaticoDudenectomy (PD) or Distal Pancreatectomy (DP), and its incidence ranges from 13 to 50%. Identification of patients at a greater risk could assist in tailoring the management approach, which may involve implementing different methods for anastomotic techniques, placing additional drainage, and using somatostatin analogues as a preventive measure.

Objectives: Assessing the stiffness of the pancreas using EUS elastography before surgery is an objective, quantitative, and dependable method. This detailed evaluation prior to surgery could enable surgeons to personalize and adjust the management plan in the perioperative period, leading to the best possible outcomes.

Patients and Methods: This prospective case series study was conducted in Cairo University (Kasr Al-Aini Hospital) over a 12-month period between April 2021 and March 2022. Fifty-one patients underwent pancreatic surgeries either PD or DP were enrolled into the study. EUS was done for all patients by the same operator using pentax 3870 attached to a HITACHI Avius sonographic machine. Elastography was performed for all patients in two different points of pancreas and the mean was taken for both. The reading was translated to soft, intermediate, hard texture of pancreas where soft was ≤1.40 m/s, intermediate was >1.40 m/s but ≤2 m/s, hard was >2 m/s. Amylase in drain was done at day 1, 3, 5 postoperative.

Results: A statistically significant correlation was observed between presence of pancreatic fistula and EUS findings, as soft pancreas showed higher significant prevalence of pancreatic fistula (*P=0.030*). On the other hand, grade A fistula was higher in cases with soft and intermediate stiffness but did not reach the significance level (*P=0.053*). By using ROC-curve analysis, EUS elastography can insignificantly predict postoperative pancreatic fistula in patients undergoing pancreatic surgeries at cutoff 2.0 m/s with sensitivity, specificity, PPV and NPV was 95.2%, 30.0%, 57.6% and 86.2% respectively (*P=0.514*).

Conclusion: The current research showed that pancreatic stiffness could be measured by preoperative elastography. Moreover, we discovered that the elastic ratio can be employed to detect a 'soft pancreas'. This information is valuable as it can help predict the probability of POPF following pancreatectomy.

Key Words: Distal pancreatectomy, EUS elastography, pancreatic fistulas, pancreaticoduodenectomy.

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INTRODUCTION

Pancreaticoduodenectomy (PD) is the preferred surgical option for treating tumors in the pancreatic head, with pancreatic adenocarcinoma being the most prevalent among them. Lesions in the body or tail of the pancreas (supposed to be benign or malignant), the preferred surgical procedure is distal pancreatectomy (DP). This usually includes splitting the pancreas to the left of the superior mesenteric vein/portal vein trunk, where the exact cutting point is determined based on the lesion's location. Due to the decreased frequency of pancreatic disease and delayed clinical presentation for diseases related to this part of the organ, distal pancreatectomies are less frequently performed compared to resections involving the pancreatic head[1]. As a highly destructive malignant disease, pancreatic cancer has the fourth rank among cancer-related causes of death[2].

Post-operative Pancreatic Fistula (POPF) stands out as a significant and severe complication following a PD. The incidence of POPF varies between 13% and 50%, depending on the definition of fistula used and the expertise of both the center and the surgical team. Various

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effective strategies have been implemented to decrease the risk of POPF. These approaches involve pancreatic duct stents (internal and external), using different anastomotic techniques (i.e. dunking methods and pancreatico-gastrostomy), somatostatin analogues and drains. All of the above-mentioned strategies may be helpful in anastomoses at high risk of leakage but may not be required in low-risk anastomoses[3].

Moreover, fistula occurrence may result in extended hospital stays, elevated costs, and, importantly, a substantial decline in patients' quality of life. Several factors that increase the risk of pancreatic leakage following PD have been identified. Among the most frequently reported risk factors in the literature are a soft pancreatic texture and a reduced pancreatic duct diameter (less than 3 mm)[4].

At the moment, pancreatic texture is assessed through palpation during surgery, employing a 3-parameter score (soft, medium, and hard). However, this evaluation relies on personal judgment. Hence, it is crucial to recognize a novel, unbiased objective predictor for the occurrence of POPF[5].

The International Study Group of Pancreatic Fistula (ISGPF) updated the definition of POPF in 2016 aimed to narrow the definition to only those 'associated with a clinically relevant (CR) condition related directly to the postoperative pancreatic fistula' (i.e., grade B and C). As a result, a grade A POPF has now been redefined and referred to as a 'biochemical leak', since it does not induce any alteration in the patient's clinical condition[6].

The criteria for delineating grade B and C postoperative pancreatic fistulas (POPFs) were further refined to provide clarity and enhance the differentiation between these two classifications (Table 1).

Table 1: Definitions and grades of ISGPF for POPF updated in 2016[6]

Event	BL (NO POPF)	Grade B POPF	Grade C POPF
Increased amylase activity>3 times Upper Limit of Normal (ULN)	Yes	Yes	Yes
Persisting peripancreatic drainage for more than 3 days	No	Yes	Yes
Clinically significant change in management of POPF	No	Yes	Yes
POPF percutaneous or endoscopic specific interventions	No	Yes	Yes
Angiographic procedure for POPF	No	Yes	Yes
Reoperation for POPF	No		Yes
Signs of infection related to POPF	No	Yes,without organ failure	Yes, with organ failure
POPF related organ fail	No	No	Yes
POPF related Death	No	No	Yes

PATIENTS AND METHODS:

This prospective case series study was conducted in Cairo University (Kasr Al-Aini Hospital) over a 12-month period between April 2021 and March 2022 in order to assess the role of EUS elastography in the preoperative prediction of post-operative pancreatic fistula. Fifty-one patients underwent pancreatic surgeries (PD or DP) were enrolled into the study. Informed consent - including consenting to the proposed operative procedure, its possible risks / complications, and the perioperative management protocol- was obtained from each patient before their inclusion in the study. The study protocol received approval from the institutional Ethical Committee. Patients were provided with information about potential surgical complications; along with the acknowledgment that pancreatic resection might not be feasible if undetected metastatic or locally advanced unresectable disease is identified. Patients excluded from the study if they had metastatic tumors or if their pre-operative albumin less than 2.5 mg/dl.

The study participants were assigned to either PD or DP. The allocation of patients to each group was determined based on the collective decision of the surgical team and intraoperative assessment. In instances of pancreatic proximal body tumors, the intraoperative decision was occasionally modified from PD to DP.

All patients were subjected to full preoperative evaluation. This included thorough history taking and physical examination, routine laboratory tests, Triphasic CT pancreatic protocol, endoscopic ultrasound (EUS) with elastography and biopsy from suspicious lesions and metastatic workup. Patients with a serum bilirubin concentration more than 12 mg/dl, those facing surgery delays beyond two weeks, and individuals experiencing severe pruritus or cholangitis underwent preoperative biliary drainage.

EUS was done for all patients by the same operator using pentax 3870 attached to a HITACHI Avius sonographic

machine under deep sedation with IV Propofol injection. Elastography was performed for all patients in two different points of pancreas and the mean was taken for both. The readings were translated into the soft, intermediate, and hard texture of the pancreas. Hard texture was defined as >2 m/s, intermediate as >1.40 m/s but ≤2 m/s, and Soft as ≤1.40.

Operative procedure

Pancreaticoduodenectomy (Whipple)

A standard PD includes the removal of the pancreatic head, duodenum, the initial 15 cm of the jejunum, common bile duct, gallbladder, and a distal gastrectomy. Following resection, the pancreatic stump was reconstructed through end-to-side double-layer pancreaticojejunostomy (PJ), with a preference for duct-to-mucosa anastomosis. End-to-side hepaticojejunostomy was carried out 10-15 cm distal to PJ. Gastrojejunostomy was conducted either through stapling or hand-sewn methods, according to surgeon's preference. Two drains were positioned adjacent to the anastomosis; accompanied by a third pelvic drain.

Distal pancreatectomy

In DP, the main pancreatic duct was ligated, and the pancreatic stump was sealed in a 'fish-mouth' configuration.

In all patients, early mobilization was encouraged upon return to the surgical ward. Patients were discharged home once the following criteria were met: 'hemodynamically stable, afebrile patient/audible bowel sounds/well tolerated liquid diet/good pain control with the use of oral analgesia/ no complications'.

ASSESSMENT for occurrence of POPF was done by

(1) Clinical data: pulse, BP, Temperature, Respiratory rate.

(2) Amylase in drain at day 1, 3, 5 postoperative.

(3) The need for percutaneous or endoscopic drainage of a collection.

(4) The need for re-operation.

(5) The need for admission to ICU postoperative and signs of organ failure (such as need for intubation, hemodialysis or inotropic supports.

Statistical analysis

The collected data will be, tabulated, and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 26.0, Microsoft Excel 2016 and MedCalC program software version 19.1.

Numerical parametric data were summarized using descriptive statistics, expressed as mean±SD (standard deviation), with the range presented as the minimum and maximum values. For numerical non-parametric data, descriptive statistics included the median and the 1st and 3rd inter-quartile range. Categorical data were described using the count and percentage.Inferential analyses for quantitative variables involved employing the independent t-test for two independent groups with parametric data. In cases of two independent groups with non-parametric data, the Mann-Whitney U test was utilized.

Receiver Operating Characteristic (ROC) curve analysis was employed to assess the overall performance of the parameter and determine the optimal cut-off value, along with the identification of sensitivity and specificity at this cut-off value. Inferential analyses for qualitative data involved the use of the Chi-square test for independent groups. The significance level was set at a *P value <0.05*, indicating statistical significance; otherwise, results were considered non-significant. The *P-value* serves as a statistical measure indicating the probability that the observed results in a study could have arisen by chance.

RESULTS:

This study involved 51 patients who were candidates for pancreatic surgeries and were investigated by EUS. They were referred to the hepatobiliary Unit of Cairo University hospital. The most common age group involved was 41-60 years (74.5%). In our study, total number of diseased males was (n=24, i.e., 47.1%) and total number of diseased females was (n=27, i.e., 52. %). The majority of cases (n=47, i.e., 92.2%) underwent PD while only four cases (7.8%) underwent DP.

Despite the relatively smaller number of patients undergoing DP, we deemed it necessary to incorporate them into our study. In two patients who underwent DP, the initial pre-operative surgical plan was a PD. However, intraoperative evaluation revealed that the lesion site (located at the junction between the neck and body of the pancreas or in the proximal body of pancreas) could be effectively managed by a DP with significantly reduced morbidity and mortality rates compared to a PD.

Regarding the distribution of pancreatic fistula among the study group, twenty-one cases (n=21, i.e., 41.2%) were diagnosed to have pancreatic fistula (only 1 of these pancreatic fistula patients underwent distal pancreatecomy and it was just biochemical leak) while thirty cases (n=30, i.e., 58.8%) did not have fistula. Regarding grading of fistula, 19 cases (n=19, i.e., 37.3%) had grade A while two cases (n=2, i.e., 3.9%) (3.9%) had grade C. None of patients had grade B.

In regards to EUS elastography, 23 patients (n=23, i.e., 45.1%) had intermediate stiffness with values >1.40 m/s but ≤2 m/s, 18 patients (n=18, i.e., 35.3%) had soft pancreas with SWV values ≤1.40 m/s and 10 patients (n=10, i.e., 19.6%) had hard pancreas with values were >2 m/s. The mean value of shear wave velocity (SWV) was 1.83±1.79 m/s with range from 0.10 to 8.40 m/s.

A statistically significant relationship was observed between the presence of a pancreatic fistula and the EUS findings (Table 2 and Fig. 1), as soft pancreas showed higher significant prevalence of pancreatic fistula (*P=0.030*).

On the other hand, grade A fistula was higher in cases with soft and intermediate stiffness but did not reach the significance level (*P=0.053*) as showed in (Table 3).

Table 2: Relation between EUS elastography and presence of fistula

	Soft (*n*=18) *N* (%)	Intermediate (*n*=23) *N* (%)	Hard (*n*=10) *N* (%)	Test value	*P* value
Fistula presence					
No	7 (55.6%)	14 (47.8%)	9 (90.0%)	X^2=7.01	0.030
Yes	11 (44.4%)	9 (52.2%)	1 (10.0%)		

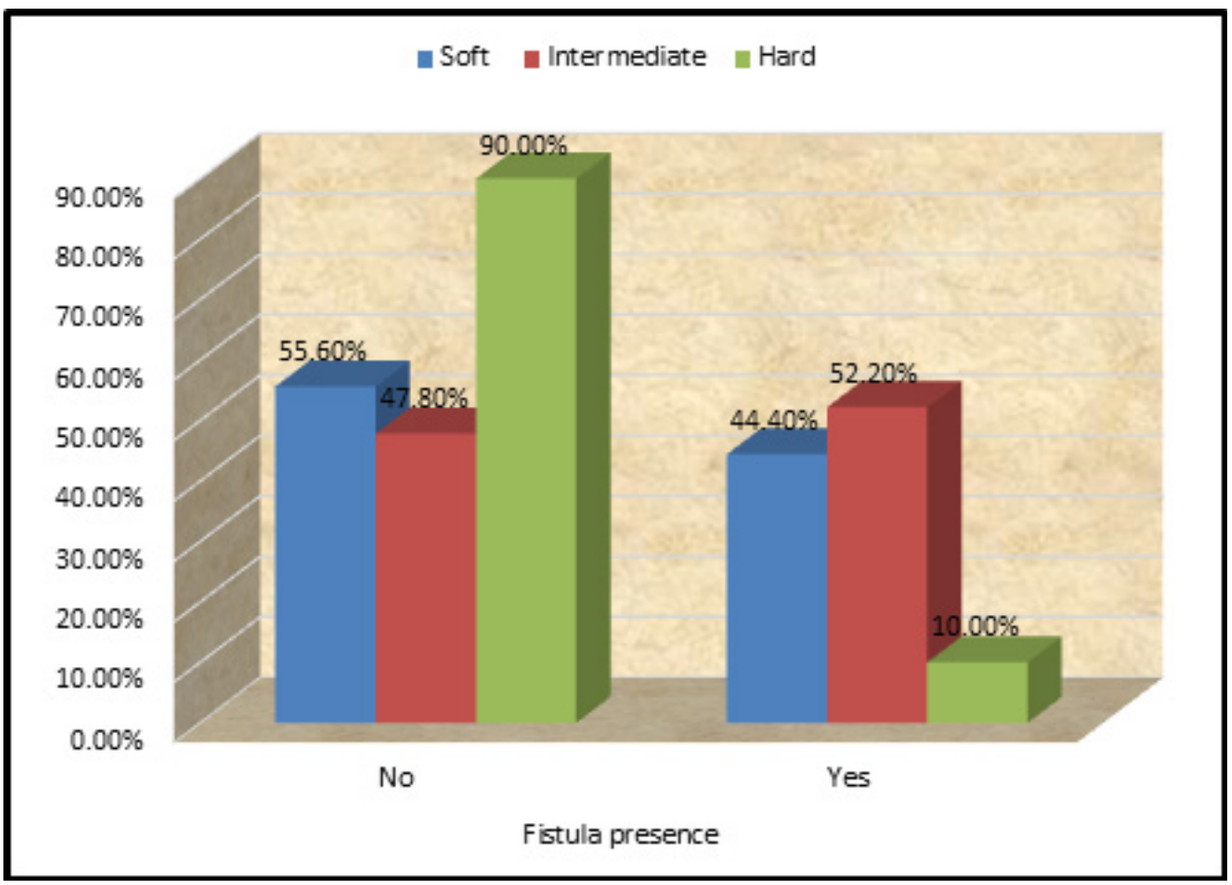

Fig. 1: Relation between EUS elastography and presence of fistula.

Table 3: Relation between EUS elastography and grade of fistula

	Soft (*n*=11) *N* (%)	Intermediate (*n*=9) *N* (%)	Hard (*n*=1) *N* (%)	Test value	*P* value
Fistula grade					
Grade A	9 (81.8%)	9 (100%)	1 (100%)	X^2=2.01	0.733
Grade B	0 (0.0%)	0 (0.0%)	0 (0.0%)		
Grade C	2 (18.2%)	0 (0.0%)	0 (0.0%)		

The occurrence of pancreatic fistula following DP is observed to be lower compared to the incidence following pancreatoduodenectomy. However, caution must be exercised in drawing definitive conclusions from these findings, as the DP group exhibits a small sample size as illustrated in (Table 4).

Table 4: Relation between type of pancreatic surgery and fistula

	Distal pancreatectomy (*n*=4) *N* (%)	Pancreaticoduodenectomy (*n*=47) *N* (%)
Fistula presence		
No	3 (75.0%)	27 (57.4%)
Yes	1 (25.0%)	20 (42.6%)
Fistula grade		
Grade A	1 (25.0%)	18 (38.3%)
Grade B	0 (0.0%)	0 (0.0%)
Grade C	0 (0.0%)	2 (4.3%)

By using ROC-curve analysis (Fig. 2), EUS elastography can insignificantly predict POPF in patients undergoing pancreatic surgeries at cutoff 2.0 m/s with sensitivity, specificity, PPV and NPV was 95.2%, 30.0%, 57.6% and 86.2% respectively (*P=0.514*).

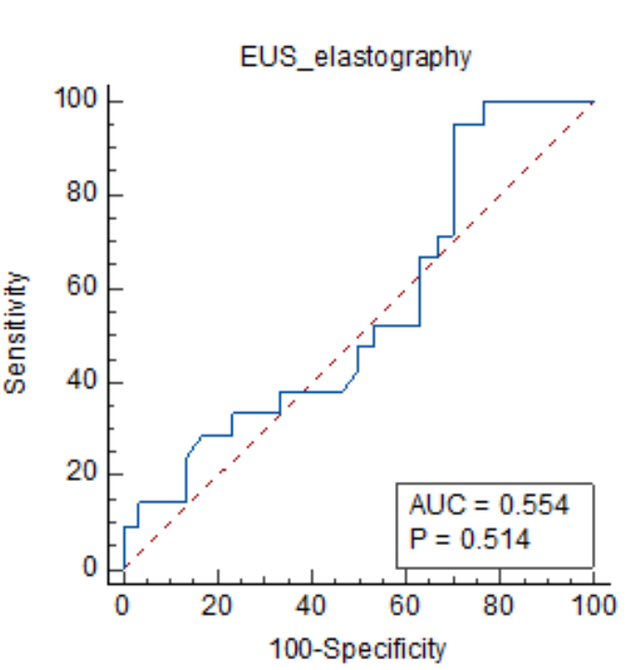

Fig. 2: ROC curve of EUS elastography in prediction of postoperative pancreatic fistula in patients undergoing pancreatic surgeries.

DISCUSSION

Elastography, a recent advancement allowing real-time visualization of tissue elasticity, has proven valuable in diverse medical areas for tumor diagnosis and differential diagnosis. While its application in gastroenterology for assessing liver fibrosis and diagnosing chronic pancreatitis and pancreatic tumors using EUS has been documented, its use in surgery remains unexplored. An objective evaluation of pancreatic stiffness as a predictive risk factor for POPF can assist in selecting intraoperative surgical techniques and planning postoperative management strategies[7].

The primary objective of this study was to evaluate the utility of EUS elastography as a preoperative predictor for the occurrence of POPF.

The current study showed that as regard distribution of pancreatic fistula among the study group. Twenty-one cases (41.2%) were diagnosed to have pancreatic

fistula while 30 cases (58.8%) did not have fistula. Regarding grading of fistula, 19 cases (90.48%) had grade A while two cases (9.52%) had grade C. None of patients had grade B.

In Hatano *et al*.'s 2015 study, POPF occurred in 11 individuals (36.7%) in the PD group and in 7 individuals (63.6%) in the DP group according to the ISGPF criteria. The majority of POPF cases were classified as grade A[8].

Moreover, in the study by Kuwahara *et al*. in 2017, out of the 59 patients examined, clinically significant POPF according to ISGPF grade B or higher was observed in 19 patients, accounting for 32.2%. Interestingly, the proportion of patients with Pancreatic Ductal Adenocarcinoma was lower in the group with POPF compared to the group without POPF (*P<0.001*)[9].

Pancreatic stiffness evaluated intraoperatively serves as a crucial predictor of POPF, with a firmer pancreas exhibiting an inverse relationship with POPF. However, the intraoperative assessment is constrained by surgeon bias and lacks objectivity. Objective evaluation of pancreatic stiffness could aid in predicting the risk of POPF before the procedure. Identifying high-risk patients could facilitate the customization of the management strategy, involving the preemptive use of somatostatin analogs, alterations in anastomotic techniques and additional drain placement. Various modalities for preoperative assessment of pancreatic stiffness involve MRI elastography and EUS elastography[10].

All ultrasound scanners are currently equipped with elastography capabilities. Hence, ultrasound shear wave elastography (USWE) emerges as a valuable tool for measuring pancreatic parenchymal stiffness. However, existing studies on the role of USWE in predicting the risk of POPF are constrained by relatively small sample sizes and the heterogeneity of pancreatic surgeries[11].

In the study in our hands as regards EUS elastography, 23 patients (45.1%) had intermediate stiffness with values >1.40 m/s but ≤2 m/s, 18 patients (35.3%) had soft pancreas with SWV values ≤1.40 m/s and 10 patients (19.6%) had hard pancreas with values were >2 m/s. The mean value of shear wave velocity (SWV) was 1.83±1.79 m/s with range from 0.10 to 8.40 m/s.

In the study by Kuwahara *et al*. (2017), the group with POPF had a higher proportion of patients with a soft pancreas (74%) compared to the group without POPF, where it was 30% (*P=0.006*). Histologically, pancreatic fibrosis was classified as normal in 19 patients, severe in 12, moderate in 13, and mild in 15. Pancreatic fatty infiltration was pathologically classified as normal in 29 patients, severe in four, moderate in eight, and mild in 18. The extent of pancreatic fibrosis was significantly less in patients with POPF (*P<0.001*) than in those without POPF. However, the degree of pancreatic fatty infiltration did not exhibit a statistically significant difference between the two groups (*P=0.289*)[9].

The present study showed that there was statistically significant relation between presence of pancreatic fistula and EUS findings as soft pancreas showed higher significant prevalence of pancreatic fistula (*P=0.030*). On the other hand, grade A fistula was higher in cases with soft and intermediate stiffness but did not reach the significance level (*P=0.053*).

By using ROC-curve analysis, EUS elastography can insignificantly predict POPF in patients undergoing pancreatic surgeries at cutoff 2.0 m/s with sensitivity, specificity, PPV and NPV was 95.2%, 30.0%, 57.6% and 86.2% respectively (*P=0.514*).

In line with our study results were the findings of Hatano *et al*. (2015), the elastic ratio was significantly associated with POPF in patients who underwent PD. In response to this observation, various surgical approaches, including modified anastomosis of pancreatico-jejunostomy, were adopted in the PD procedure. However, in patients undergoing DP, although there was a tendency for the POPF-positive group to have a lower elastic ratio, no significant association was observed. Given the procedural heterogeneity between PD and DP, further investigations involving multiple centers and a larger sample size are needed for additional clarification[8].

In the previous study, the optimal cut-off values for Main Pancreatic Duct (MPD) diameter and elastic ratio to predict POPF in the PD group were determined through ROC analysis. The cut-off values were found to be 3.2 mm (sensitivity 0.909, specificity 0.579) for MPD diameter and 2.09 for the elastic ratio (sensitivity 0.909, specificity 0.526), with corresponding Areas Under the Curve (AUCs) of 0.77 and 0.739, respectively. Univariate analysis revealed that MPD diameter <3.2 mm and elastic ratio <2.09 were significant risk factors for POPF (*P=0.009* and *P=0.02*, respectively). However, in multivariate analysis, neither variable was identified as an independent factor[8].

Ganjoux *et al*., 2010 investigated whether soft pancreas and fat tissue content exceeding 10% in the pancreatic parenchyma (confirmed by

histopathological examination) were independent risk factors for POPF. However, they found no correlation between soft pancreas and fat tissue content. In this study, the association between the elastic ratio and histopathologic findings of the pancreas was explored. The results indicated that the elastic ratio was significantly lower in pancreas rich in exocrine gland tissue. This suggests that a 'soft pancreas,' reflected by a low elastic ratio, exhibits high exocrine gland content on histopathology. Although the exact mechanisms linking POPF and exocrine gland content require further investigation, it is speculated that a large amount of pancreatic juice could be one of the elements contributing to the occurrence of POPF[12].

Additionally, Sushma *et al*., 2020, found that POPF and clinically relevant POPF (CRPOPF) occurred in 22 (44%) and 7 (14%) patients, respectively. Soft pancreas was identified as an independent predictor of CRPOPF (*p, 0.04*). The mean Ultrasound Shear Wave Elastography (USWE) value was significantly lower in patients with CRPOPF compared to those without CRPOPF (9.7 Kpa vs. 12.8 Kpa, *p, 0.016*). In ROC curve analysis, a USWE value of 12.65 Kpa yielded sensitivity and specificity of 100% and 47%, respectively, for predicting CRPOPF. USWE demonstrated a significant correlation with intraoperative pancreatic texture (*p, 0.001*)[7].

Given the robust connection between a soft pancreas and CRPOPF, the evaluation of pancreatic stiffness using preoperative USWE emerges as an objective, quantitative, and dependable method. This precise preoperative evaluation using USWE offers surgeons the opportunity to tailor and adjust perioperative management for optimal outcomes. Moreover, USWE demonstrated a significant positive correlation with intraoperative pancreatic stiffness assessment, making it a tool that is more objective and less prone to inter observer variation[13].

To summarize, this study underscores the feasibility of quantifying pancreatic stiffness through preoperative elastography. The elastic ratio, identifying a 'soft pancreas,' serves as a valuable predictor for the probability of POPF following pancreatectomy. A significant risk factor for POPF in this patient cohort was an elastic ratio less than 2.0. For patients exhibiting a soft pancreas or a lower elastic ratio, comprehensive efforts are essential to mitigate the risk of POPF, involving enhancements in surgical techniques and perioperative patient care.

CONFLICT OF INTEREST

There were no conflicts of interest.

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