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REVIEW

Correlation Between Fatty Pancreas Disease and Pancreatic Diseases, Perioperative Complications of Pancreatic Surgery

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Abstract: Fatty pancreas disease (FPD) refers to excessive fat accumulation and fat infiltration in pancreatic tissue. Factors such as obesity, diabetes, non-alcoholic fatty liver disease (NAFLD), and alcohol consumption can contribute to the development of FPD. Patients with FPD typically lack obvious clinical symptoms or signs, and diagnosis primarily relies on imaging techniques. Currently, there is limited attention to this disease both domestically and internationally. FPD is closely associated with pancreatic-related diseases (eg, diabetes, pancreatitis, pancreatic cancer). Pancreatic cancer, characterized by high mortality and low survival rates, has been linked to FPD in terms of its occurrence, progression, and patient prognosis. FPD is considered a potential early clinical manifestation of pancreatic cancer and may promote distant metastasis. However, the mechanisms by which FPD contributes to pancreatic carcinogenesis remain unclear. Additionally, Studies have found that FPD can lead to perioperative complications (postoperative pancreatic fistula, postoperative nonalcoholic fatty liver, endoscopic retrograde cholangiopancreatography pancreatitis), which are closely related to the prognosis of patients after pancreatic surgery.Although FPD is challenging to diagnose, its instability allows for clinical management through early dietary interventions, oral medications, and, when necessary, bariatric surgery to alter disease progression. Whether targeting adipocytes, lipid metabolism, or adipocyte-related cytokines could serve as novel intervention strategies for pancreatic cancer remains a critical area for further investigation.

Keywords: fatty pancreas, non-alcoholic fatty pancreas, pancreatic fat deposition, pancreatic cancer, pancreatic fistula

Pancreatic cancer has an extremely high mortality rate. According to data released by the American Cancer Society in 2023,[1] pancreatic cancer has become the third leading cause of cancer-related deaths in the United States and is projected to rise to the second leading cause by 2030.[2,3] Radical surgery remains the only effective treatment for pancreatic cancer. However, due to its neuro-invasive and vascular-invasive growth characteristics, 50%-55% of patients are diagnosed with distant metastases, and only 15%-20%[4] are eligible for surgical intervention, with an overall survival rate of approximately 10%.[2] While a small amount of fat tissue is present in the pancreas of healthy individuals, numerous studies have shown that excessive fat accumulation and infiltration in the pancreas can promote the development and progression of pancreatic cancer. Patients with pancreatic fat infiltration have a higher risk of developing pancreatic cancer compared to healthy individuals, suggesting that this condition may be a significant risk factor for pancreatic cancer.[5–8] Moreover, this disease is closely associated with perioperative complications and patient prognosis in pancreatic cancer.[5] Therefore, early clinical detection of fatty pancreas is of great importance.

Definition, Epidemiology, and Etiology of Fatty Pancreas

As early as 1933, Ogilvie[9] conducted a study comparing 19 obese cases with 19 control cases and found that the pancreas of obese patients exhibited varying degrees of fat accumulation. This led to the proposal of the concept of " excessive pancreatic fat." Subsequently, terms like 'pancreatic fatty infiltration', 'non-alcoholic fatty pancreatic disease (NAFPD) ", and others emerged. Currently, clinical terms such as "fatty pancreas disease (FPD) ", "intra-pancreatic fat deposition (IPFD) ", and "pancreatic steatosis (PS) ' are commonly used to describe the phenomenon of excessive lipid deposition in pancreatic

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tissue. These terms are defined as a pathological condition characterized by fat accumulation within pancreatic cells or interlobular stroma exceeding normal levels due to various causes. The lack of standardized nomenclature for this condition has resulted in limited attention and hindered further research.

In healthy individuals, the pancreas contains minimal fat, with magnetic resonance imaging (MRI) studies suggesting normal pancreatic fat content ranges between 1.8%-10.4%. Typically, pancreatic fat content exceeding 10.4% is considered indicative of fatty pancreas.[10,11] Domestic cross-sectional studies have reported the incidence of fatty pancreas in China to be between 2.7% and 35.0%,[12,13] while its prevalence in the general population abroad ranges from 16.0% to 35.0%.[14] A recent meta-analysis incorporating 18 studies[15] reported an overall prevalence of FPD at 21.1% (95% CI: 11.04–36.58). The study also highlighted significant variations in prevalence depending on the diagnostic method used: MRI, computed tomography (CT), and transabdominal ultrasound showed prevalence rates of 17.53% (95% CI: 16.20–18.95), 30.05% (95% CI: 24.14–36.70), and 21.23% (95% CI: 8.52–43.88), respectively.

Factors such as obesity, metabolic syndrome, alcohol consumption, non-alcoholic fatty liver disease, hormonal levels, low birth weight, urea, and ferritin are all associated with the occurrence of fatty pancreas.[14,16,17]

Diagnosis of Fatty Pancreas Disease

The clinical manifestations of fatty pancreas disease (FPD) are nonspecific and often imperceptible. Shen[18] conducted a study involving 25 FPD patients and reported common symptoms including abdominal distension (44.0%), weight loss (24.0%), abdominal pain (16%), and diarrhea (12%). Since the pancreas is located deep retroperitoneum and its shape is irregular, it is difficult to quantify FPD by invasive operation in clinical work, and non-invasive imaging examination is needed to detect and diagnose FPD.

Imaging examinations are generally required to detect and diagnose FPD. On ultrasound, FPD typically appears as hyper echogenicity. However, due to the thick subcutaneous fat layer in obese patients and the retroperitoneal location of the pancreas, coupled with interference from surrounding organs such as the stomach and duodenum, misdiagnosis is common. On computed tomography (CT), FPD manifests as low-density regions, with decreasing CT values correlating with increasing pancreatic fat content. Clinically, the CT values of the pancreatic head, body, and tail are measured and compared with those of the spleen. A pancreas-to-spleen density ratio of <0.7 is used as a diagnostic criterion for FPD.[19] A retrospective study of 62 postoperative pancreatic patients[20] demonstrated a significant correlation between the pancreas-spleen density ratio on CT and histological pancreatic fat fraction.

Unlike ultrasound and CT, magnetic resonance imaging (MRI) allows for quantitative assessment of FPD. Chemical shift encoded MRI is now considered to be the first choice and the gold standard for non-invasive adipatic quantification of abdominal organs.[21,22] Pancreatic fat content exceeding 10.4% is used as a diagnostic threshold for FPD.[10] However, challenges such as the small volume of the pancreas relative to surrounding structures, as well as the effects of vascular, pancreatic duct, and abdominal fat signal artifacts, limit the precision of MRI. MR mDixon-Quant imaging technology offers higher accuracy in fat quantification compared to MRS, providing direct fat percentages and covering the entire organ's fat range (0–100%) with minimal motion artifacts, making it more suitable for small organs like the pancreas.[23,24] Gu [25] measured an average pancreatic fat content of 3.33% in 237 healthy volunteers, confirming its reliability in pancreatic fat quantification. However, comparative studies between mDixon-Quant and MRI remain lacking.

At present, histopathological examination is the gold standard for diagnosis and discovery of fatty pancreas. As early as 1978, Olsen TS suggested that steatosis is the deposition of adipose tissue cells in the pancreas and is a common histological change in the pancreas. Postmortem examination by Stamm BH on 112 patients with pancreatic diseases found that there were different degrees of adipose, of which 23% of the patients had a quarter of the pancreatic parenchymal tissue replaced by adipose tissue, and pointed out that the degree of fat deposition in the pancreas increased with the age of patients. Schmitz-Moormann P revealed the relationship between pancreatic adipose tissue content, age and body weight by using morphometrics and statistics, and found that there were significant differences in fat deposition in the pancreas.[26–28] As mentioned in the above studies, histopathological examination is autopsy, and invasive pancreatic puncture is often associated with the risk of collateral organ injury, post-puncture bleeding and infection. Sampling error exists in local puncture, which cannot effectively indicate the degree of overall pancreatic fat infiltration, so histopathological examination cannot be widely used in clinical practice.

Correlation Between Fatty Pancreatopathy and Pancreatic Disease

A recent meta-analysis found that compared with people without FPD, patients with FPD were more likely to suffer from endocrine diseases such as diabetes, elevated blood sugar, and exocrine diseases related to acute pancreatitis and pancreatic cancer.[15] A 10-year prospective cohort study by Chan[29] found that fat pancreas was independently associated with the subsequent development of Diabetes mellitus (DM) (adjusted hazard ratio, 1.81; 95% CI, 1.10–3.00; P = 0.02), each percentage increase in pancreatic fat was associated with a 7% increased risk of DM (adjusted hazard ratio, 1.07; 95% CI, 1.01–1.13; P =0.016). Dong[30] conducted a prospective cohort study on 42,599 cases of general population in the UK biological database and found that patients with higher levels of IPFD had a higher risk of developing pancreatic diseases. A significant correlation was found between high levels of IPFD and DM (HR 1.221, 95% CI 1.132–1.318,P=0.001). There was also a significant association between FPD and acute pancreatitis (HR 1.337, 95% CI 1.122–1.593, P= 0.001).

At present, the etiology of pancreatitis includes cholelithiasis, ethanol, hypertriglyceridemia, drugs, endoscopic retrograde cholangiopancreatography (ERCP), trauma, but whether FPD can cause pancreatitis has not received much attention. Sbeit W[31] further discussed the relationship between FPD and acute pancreatitis. Case-control studies were conducted based on whether people had ever suffered from pancreatitis, and it was found that univariate analysis [odds ratio (OR), 5.14, P = 0.006] OR multivariate analysis (OR, 10.78; 95%Cl, 3.75–30.89; P < 0.0001) have demonstrated that FPD is closely associated with acute pancreatitis. Subsequently, Sbeit W[32] further proved the occurrence of acute pancreatitis with high score of fatty pancreas and Systemic Inflammatory Response Syndrome (SIRS) through retrospective study of 409 patients with acute pancreatitis. It is suggested that fatty pancreas may be a predictor of the severity of acute pancreatitis. Dong[30] not only found that high levels of IPFD and FPD were closely related to DM, but also found a significant correlation between high levels of IPFD and acute pancreatitis (HR 1.513, 95% CI 1.179–1.941,P=0.001). There was also a significant association between FPD and acute pancreatitis (HR 3.982, 95% CI 2.192–7.234, P=0.001).

In 2018, Tahtac-M conducted a cohort study on 43 patients with pancreatic steatosis and 48 patients without pancreatic steatosis, and found that pancreatic steatosis would cause pancreatic exocrine insufficiency.[33] A study of 1458 volunteers undergoing pancreatic MRI showed[34] that magnetic resonance proton density fat fraction (MRI-PDFF) of pancreas was negatively correlated with fecal elastase. Gopi S[35] found that fecal elastase could be used as evidence of exocrine insufficiency through a real-world study of 147 patients. This further demonstrated an association between fat pancreas and impaired exocrine function in chronic pancreatitis.

In a systematic review and meta-analysis of 13 studies,[36] Sreedhar UL reported for the first time that 52% of patients with pancreatic cancer or precancerous lesions had pancreatic fat deposition, and believed that the increase of pancreatic fat deposition was closely related to the risk of pancreatic cancer or precancerous lesions. Subsequently, Lipp M further recommended precancer screening and follow-up for patients with fatty pancreas through systematic review and meta-analysis of 2956 patients.[37]

However, the mechanism of adipocyte involvement in pancreatic cancer remains unclear.[38] Hori[39] proposed in 2014 that FPD might represent an early stage of pancreatic ductal adenocarcinoma (PDAC). They suggested that the FPD promotes tumor cell proliferation, metastasis, and angiogenesis through specific cytokines. Rebours[40] evaluated the data of CT and postoperative pancreatic histomorphology and pathology and found that FPD is one of the risk factors for pancreatic precancerous lesions, and fatty infiltration of pancreatic lobules is an independent risk factor for pancreatic intraepithelial neoplasia (PanIN).

In normal pancreatic tissues, acinar and endocrine cells contain lipids in the form of triglycerides and esters. Under conditions such as hypoxia or inflammation, the highly plastic acinar cells can undergo transdifferentiation into adipocytes.[22] Mesenchymal stem cells support this transformation through lipid peroxidation pathways following the death of pancreatic parenchymal cells.[41] Pancreatic stellate cells, which serve as the primary lipid storage cells in the pancreas, lose their lipid content when activated by cytokines such as TNF-α and IL-6, transitioning into cancer-associated fibroblasts and laying the foundation for the development of PDAC.[22,42]

Research by Takahashi[43,44] suggested that the microenvironment of FPD itself promotes the occurrence and progression of PC. Adipocytes and inflammatory cells, such as macrophages, aggregate in the acinar tissues of FPD and release multiple adipokines and cytokines, including leptin, IL-6, and TNF-α. These factors exacerbate local inflammation in pancreatic

tissues, activate the KRAS pathway, and upregulate downstream genes such as NF-KB and ERK, leading to atypical proliferation of pancreatic ductal epithelium, PanIN formation, and ultimately the development of PC.

Petrov[45] proposed the "PANDORA hypothesis" suggesting that intrapancreatic fat deposition is a crucial driver of pancreatic diseases, forming a vital component of the pancreatic microenvironment. According to this hypothesis, inflammation triggered by fat deposition leads to lipotoxicity, with the degree of fat accumulation being closely associated with sporadic PC risk. Yamazaki[46] conducted a prospective observational study using MRI-measured FPD data and Mendelian randomization analysis of genetic data related to FP. They identified FPD as a risk factor for PDAC development, attributing it to local inflammation caused by adipocytes within the pancreas. They further suggested FP as a non-invasive biomarker for PDAC, providing partial support for the PANDORA hypothesis and highlighting a statistically significant relationship between FPD and PC. Dong[30] not only found a correlation between high levels of IPFD and FPD and pancreatitis, but also found a correlation between IPFD and pancreatic cancer (HR1.365, 95% CI 1.058–1.762, P=0.017). The association between FPD and pancreatic cancer (HR 1.976, 95% CI 1.054–3.704, P=0.034) further supports the hypothesis that pancreatic diseases originate from intra-pancreatic fat (PANDORA).

Mathur[47] conducted a case-control study on pathological examination of lymph nodes after resection in 40 patients with pancreatic cancer, and found that compared with patients with negative lymph nodes, patients with positive lymph nodes had significantly more pancreatic fat cells (46.4±8.7 vs 21.4±4.8; $p < 0.02$), at the same time, the average survival time of patients with positive lymph nodes decreased, so it can be considered that fat pancreas promotes lymph node metastasis in patients with pancreatic cancer, and the increase of pancreatic fat will promote the spread of pancreatic cancer.[48] A meta-analysis[49] indicated that dietary total fat and saturated fatty acid intake were positively correlated with the risk of PC, and found that fat in the pancreas was unstable, and reversal of fat pancreas through diet control and bariatric surgery was feasible in principle.[22]

Therefore, it can be considered that Fatty pancreas disease (FPD) and Intra-pancreatic fat deposition (IPFD) lead to pancreatic-related diseases, which may even be the early clinical manifestations of pancreatic cancer. In the clinical face of such patients, patients should be asked to check regularly, do clinical screening and clinical follow-up. Early identification, clear diagnosis and active intervention are of great clinical significance for preventing the occurrence and development of pancreatic diseases and improving the survival rate of patients.

Fatty Pancreas in Perioperative Pancreatic Complications

Patients with FPD may also suffer from metabolic disorders such as diabetes, hypertension, and hyperlipidemia. These metabolic conditions often increase the risk of perioperative cardiovascular events, postoperative infections, and surgical complications. Preoperative evaluation by surgeons should comprehensively assess factors such as cardiopulmonary function, thrombosis risk, and infection risk, with timely corrections as needed.

The most common complications of pancreatic surgery include delayed gastric emptying, postoperative bleeding, and postoperative pancreatic fistula (POPF). Among these, POPF is the most life-threatening complication, potentially leading to intra-abdominal infection and hemorrhage.[50] POPF is often associated with prolonged hospital stays and increased economic burden. Mathur[51] conducted blind histopathological examinations of patients undergoing pancreaticoduodenectomy and found significant pancreatic fat cell infiltration in individuals who developed POPF, with fat content higher than those without POPF. A prospective study by Rosso[52] revealed that a pancreatic fat content exceeding 10% significantly increases the risk of POPF following pancreaticoduodenectomy. The proposed mechanism involves fat cell infiltration into pancreatic tissues, causing long-term aseptic inflammation that alters tissue structure and reduces tissue rigidity. These changes make pancreaticojejunostomy technically challenging during surgery, leading to poor healing of the anastomosis. Additionally, compared to pancreatic fibrosis, fatty pancreas results in significantly decreased exocrine pancreatic function. During the perioperative period, exocrine function in FP may be normal or slightly reduced, increasing the risk of pancreatic fistula due to elevated pancreatic juice secretion. Xing[53] demonstrated through univariate and multivariate analyses that pancreatic duct diameter ≤3 mm, increased severity of fatty pancreas, and decreased pancreatic fibrosis are independent risk factors for POPF. Tranchart[54] evaluated the prognosis of pancreaticoduodenectomy by assessing pancreatic fat infiltration using preoperative CT and intraoperative pathology. Kusafuka[55] calculated the CT value ratio of pancreatic-visceral fat after CT scan of 298 patients undergoing pancreaticoduodenectomy, and

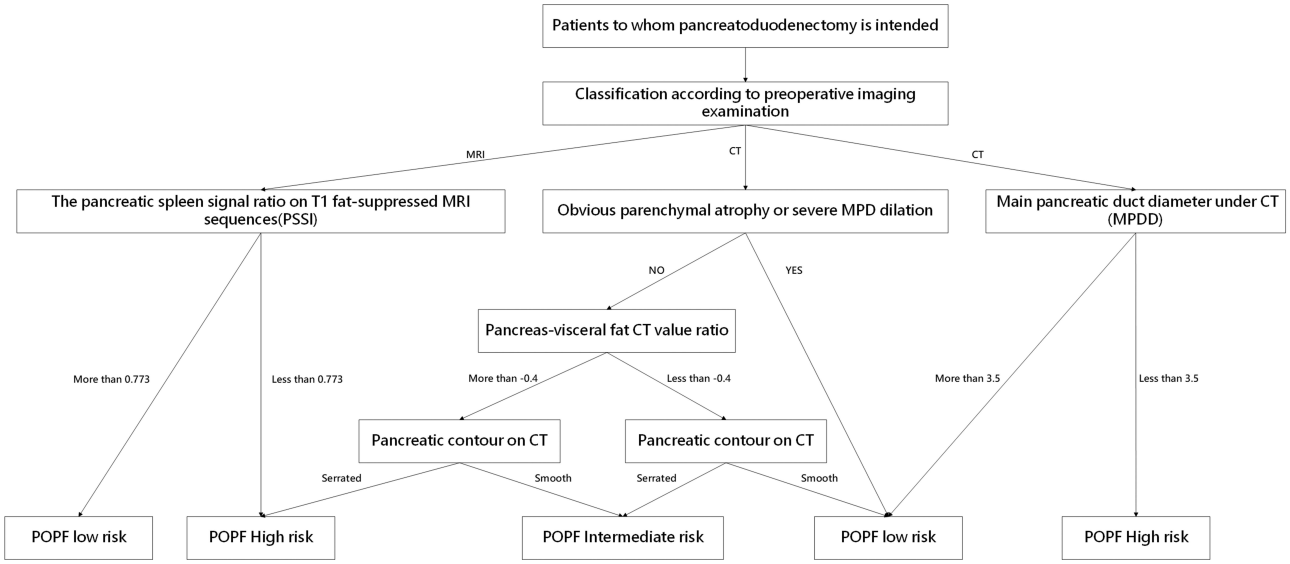

Figure 1 Strategy model for accurately predicting POPF before operation.

concluded that a high CT value ratio of pancreatic-visceral fat (>0.4) was an independent risk factor for postoperative pancreatic fistula. The high CT ratio of pancreatic to visceral fat, the serrated pancreas and the above combination may be related to pancreatic fistula. Zou[56] calculated that the best cutoff value of pancreatico-spleen signal ratio in MRI sequence of T1 fat suppression was 0.773 and the best cutoff value of pancreatic duct diameter under CT was 3.5mm by conducting magnetic resonance examination and CT examination of 205 patients undergoing pancreaticoduodenectomy. It is also suggested that higher PSSI and thicker Pancreatic duct diameter reduce the risk of postoperative pancreatic fistula (Pancreatic spleen signal ratio on T1 fat-suppressed MRI sequences, PSSI). Finally, a strategy model for accurately predicting POPF before surgery was developed based on the above views (Figure 1).

The dual impact of postoperative pancreatic insufficiency and fatty pancreas often results in an imbalance of pancreatic exocrine and endocrine functions. Postoperative exocrine insufficiency may lead to nonalcoholic fatty liver disease (NAFLD) due to impaired absorption of essential amino acids, such as choline. Choline deficiency reduces plasma apolipoprotein B levels, a critical component of very-low-density lipoprotein (VLDL), impairing VLDL secretion from the liver and causing triglyceride (TG) retention, which can result in NAFLD and, in severe cases, postoperative liver failure.

Endocrine dysfunction can cause postoperative blood glucose fluctuations, impairing the healing of surgical anastomoses and incisions and increasing the risk of infection.[57] Partelli et al[58] found that when the acinar content at pancreatic resection margins exceeds 60%, the secretion of digestive enzymes by acinar cells is closely associated with acute pancreatitis. However, there is a lack of research on acute pancreatitis following pancreatic surgery in the context of fatty pancreas and acinar cell replacement.

It is well known that the common complication of endoscopic retrograde cholangiopancreatography is postoperative acute pancreatitis. Above, we found that fat pancreas is a risk factor for pancreatitis. Some scholars have also explored whether fat pancreas is a risk factor for endoscopic retrograde cholangiopancreatography pancreatitis. Park CH ‘s cohort study included 354 patients with fatty pancreatitis among 858 patients.[59] Among them, 28 patients (7.9%) in the adipose-pancreas group and 13 patients (2.6%) in the adipose-free pancreas group developed Post-endoscopic retrograde cholangiopancreatography pancreatitis(PEP) was found to be significantly associated with the development of PEP (odds ratio [OR] [95% confidence interval [CI] 2.38 [1.16–4.87]). Subsequently, Chung MJ[60] continuously included 786 patients receiving ERCP for the first time through a multicenter prospective experiment, and found that diabetes and hypertension were more common in the fat pancreas group than in the non-fat pancreas group. In addition, the risk of PEP was higher in the fat pancreas group (odds ratio, 2.09; 95% confidence interval, 1.08–4.03), suggesting that the adipose pancreas should be evaluated well before ERCP, and measures to prevent PEP should be taken in advance, emphasizing the necessity of imaging examination of adipose pancreas.

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Conclusion

In summary, we know that FPD is a key factor leading to the occurrence of many pancreatic diseases and may be the early clinical manifestations of pancreatic cancer. Relevant examinations need to be improved, and early diagnosis is particularly important. FPD is unstable, and the clinical outcome of patients can be changed through intervention and control of the intake of total dietary fat and saturated fatty acids in the early daily life of patients, low-calorie diet, and even bariatric surgery.[61] Based on the PANDORA hypothesis proposed above, Currently, hypoglycemic drugs (glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter-2 inhibitors) have been found to reduce fat deposition in the pancreas. Moreover, fatty pancreas can promote lymphatic metastasis of pancreatic cancer, so timely detection of fatty pancreas is of great significance for the treatment of pancreatic cancer patients. Whether early lymph node metastasis of pancreatic cancer can be avoided through the intervention of fatty pancreas, and whether the treatment of adipocyte, lipid metabolism or adipocell-related cytokines can be used as a new intervention measure for pancreatic cancer is still lacking in relevant studies. At the same time, fat pancreas will lead to perioperative complications of pancreas. We should fully conduct relevant risk assessment before surgery, control and manage the underlying diseases of patients, reduce the preoperative risks, and actively prevent the occurrence of pancreatic fistula, abdominal hemorrhage, abdominal infection, pancreatitis and other complications after surgery. However, it is still necessary to conduct prospective studies to improve the long-term impact of fat pancreas on pancreatic cancer and its prognosis.

Disclosure

The authors report no conflicts of interest in this work.

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