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RESEARCH ARTICLE

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New onset non-alcoholic fatty liver disease after resection of pancreatic neuroendocrine tumors

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Background and Objectives: Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatis (NASH) may occur after pancreatic resection due to exocrine pancreatic insufficiency (EPI). Patients with long-term survival, such as after pancreatic neuroendocrine tumor (pNET) resection, are at risk of NAFLD/NASH. We aimed to determine the incidence and risk factors for new onset NAFLD/NASH and EPI after pNET resection.

Methods: Retrospective monocenter cohort study. Patients who underwent pNET resection (1992-2016) were assessed for new onset NAFLD/NASH and EPI. Postoperative NAFLD/NASH was determined by a blinded abdominal radiologist, who compared pre- and postoperative imaging.

Results: Out of 235 patients with pNET, a total of 112 patients underwent resection and were included with a median follow-up of 54 months. New onset NAFLD/NASH occurred in 20% and EPI in 49% of patients. Multivariate analysis showed that the only risk factor for new onset NAFLD/NASH was recurrent disease (OR 4.4, 95% CI 1.1-16.8, $P = 0.031$), but not EPI (OR 0.94, 95% CI 0.3-2.8, $P = 0.911$). The only risk factor for EPI was pancreatoduodenectomy (OR 4.3, 95% CI 1.4-13.7, $P = 0.012$).

Conclusions: New onset NAFLD/NASH is occasionally found after pNET resection, especially in patients with recurrent disease, but is not related to EPI.

KEYWORDS
exocrine pancreatic insufficiency, neuroendocrine tumors, non-alcoholic fatty liver disease, pancreas, resection

1 | INTRODUCTION

Long-term surgical complications of pancreatic surgery are especially relevant in patients with a long life expectancy after surgery, such as patients with primary neuroendocrine tumors of the pancreas (pNET). As the 5-year overall survival of these patients is 85%,[1] many of these patients may experience long-term complications, such as exocrine and endocrine insufficiency. Other complications include non-alcoholic fatty liver disease (NAFLD) and the more severe non-alcoholic steatohepatis (NASH). NAFLD/NASH may lead to

cirrhosis, hepatic failure, hepatocellular carcinoma, cardiovascular disease, and ultimately death.[2,3] Therefore, it is important to recognize NAFLD/NASH and to treat this disease in the earliest stages.

After pancreatoduodenectomy (PD), approximately 23-37% of the patients develop NAFLD/NASH.[3–7] A significant number of these patients did not suffer from metabolic syndrome preoperatively. It is likely that mechanisms underlying postoperative NAFLD/NASH differ from mechanisms underlying common metabolic NAFLD/NASH. Remarkably, hepatic steatosis following PD was related to non-obesity, lack of hyperlipidaemia or insulin resistance, indicating another cause for NAFLD/NASH than metabolic syndrome.[3,8] Still, the process leading to the NAFLD/NASH in these postoperative patients is unclear.

Some studies suggest that malnutrition or malabsorption of essential nutrients caused by exocrine pancreatic insufficiency (EPI) leads to NAFLD/NASH.[3,4,6–9] Changes in metabolism resulting in hepatic steatosis could lead to sensitivity for hepatocyte damage, inflammation, and fibrosis.[8,10] Pancreatic enzyme administration as treatment of EPI has beneficial impact on hepatic steatosis after PD, indicating that EPI could be the main cause of new onset NAFLD/NASH in these patients.[3,9] Other evidence for malnutrition in patients with EPI or after PD is the report of increase of taurine serum levels and decrease of methionine, tyrosine, albumin, cholinesterase, zinc, and total cholesterol serum levels.[3,4,6,8,10–13] Therefore, other nutrients or mechanism that not yet have been identified could cause the hepatic steatosis. Besides little evidence indicating that NAFLD/NASH could be treated with pancreatic enzyme administration, adequate treatment is not yet recognized.

The aim of this study is to determine the incidence of new onset NAFLD/NASH and EPI after resection of pNET. Risk factors for the development of NAFLD/NASH were assessed in a large cohort with relatively long-term follow-up after resection of pNET.

2 | MATERIALS AND METHODS

2.1 | Study design

This is a retrospective cohort study, performed in the Academic Medical Center (AMC) in Amsterdam. Patients who underwent surgery for pNET from 1992 to 2016 in the AMC were identified. Patients with hormone producing tumors and corresponding clinical symptoms (functional pNET or F-pNET) as well as patients without hormone excess or corresponding clinical symptoms (non-functional pNET or NF-pNET) were included. Operative procedures included PD (either pylorus preserving or classical Whipple), enucleations, central pancreatectomy, distal pancreatectomy (±splenectomy), central and distal pancreatectomy (±splenectomy), and total pancreatectomy.[14]

2.2 | Outcomes

EPI was defined as presence of steatorrhea, and/or pancreatic enzyme supplementation of at least 1 month, after (partial) pancreatic resection or enucleation. Postoperative somatostatin analogues (SSA) use was defined as postoperative SSA use of at least 3 months, excluding temporary SSA administration (often 7 days) during first admission.

2.2.1 | Evaluation of NAFLD/NASH

To objectify the presence of new onset hepatic steatosis or NAFLD/NASH, postoperative imaging was compared to preoperative imaging by an independent experienced radiologist, blinded to the patients' clinical course. Preoperative imaging closest to the operation and most recent postoperative imaging of at least 3 months after the operation were evaluated. Because patients with risk of metabolic, alcoholic and medication related hepatic steatosis were excluded from this study, the assumption was made that preoperative NAFLD/NASH was not present, in case preoperative imaging was not available.

Unenhanced computed tomography (CT) was used for comparison. For each patient, the average CT attenuation of two regions of interest (ROIs) of the liver were measured in Houndsfield Units (HU), avoiding macroscopic hepatic vessels and liver lesions. Hepatic steatosis was defined as an absolute hepatic attenuation of 40 HU or less.[15] In the cases that unenhanced CT was not available, magnetic resonance imaging (MRI), ultrasonography or contrast-enhanced CT were, respectively, reviewed. These latter methods of assessing NAFLD/NASH are described in previous literature.[15–20]

2.2.2 | Evaluation of nutrient and lipid household

Outcomes of regular follow-up blood tests to detect postoperative changes were analyzed. Several patients without EPI underwent these laboratory tests to monitor expected EPI development based on their type of operation. Therefore, blood tests results between the two patient groups could be compared. Blood tests included albumin, prealbumin, apolipoprotein B, HDL-, LDL-, and total cholesterol, cholinesterase, HbA1c, total serum protein, triglycerides, zinc, and amino acids.

2.3 | Exclusion criteria

Patients were excluded in case of age <18 year, another histopathological diagnosis than pNET after operation, operation and follow-up in another hospital than AMC, excessive alcohol use (>14 units a week for women and >21 units a week for men), diabetes mellitus, obesity (BMI >30), pre-existent fatty or other liver disease, daily use of steroids, death within 3 months after surgery.

2.4 | Analysis

Statistical analyses were performed using SPSS software, version 23.0 (SPSS Inc., Chicago, IL). Descriptive statistics were used for frequency analysis and for calculating measures of central tendency. Results were expressed as number with percentage, mean with standard deviation (SD) or as median with range or interquartile range (IQR) in case of an amount, a normal or a not-normal distribution, respectively. To determine the normality of our dataset, normality tests were used on

continuous numeric variables. Independent-samples *t*-test and Mann-Whitney *U*-test were used to compare continuous variables between EPI and non-EPI group, and NAFLD/NASH and non-NAFLD/NASH group. Chi-squared test or Fisher's Exact test were used to compare categorical variables between EPI and non-EPI group, and NASH and non-NASH group. Univariate logistic regression analyses were conducted to determine risk factors associated with new onset NAFLD/NASH and EPI after pancreatic resection or enucleation due to pNET. Variables with $P < 0.1$ were subsequently evaluated with multivariate logistic regression analyses and reported as odds ratio (OR) with corresponding 95% confidence interval (CI). Time to diagnosis of NAFLD/NASH was performed with Kaplan Meier method. All *P* values were based on a two-sided test. *P* values of less than 0.05 were considered to be statistically significant.

3 | RESULTS

3.1 | Patient selection

From 1992 to 2016 a total of 235 patients were assessed with pNET at our center. From these patients, 158 patients (67.2%) underwent pancreatic resection or enucleation. Since 46 patients met (multiple) exclusion criteria, the final study population consisted of 112 patients. The most common cause for exclusion was the risk of metabolic syndrome (Figure 1).

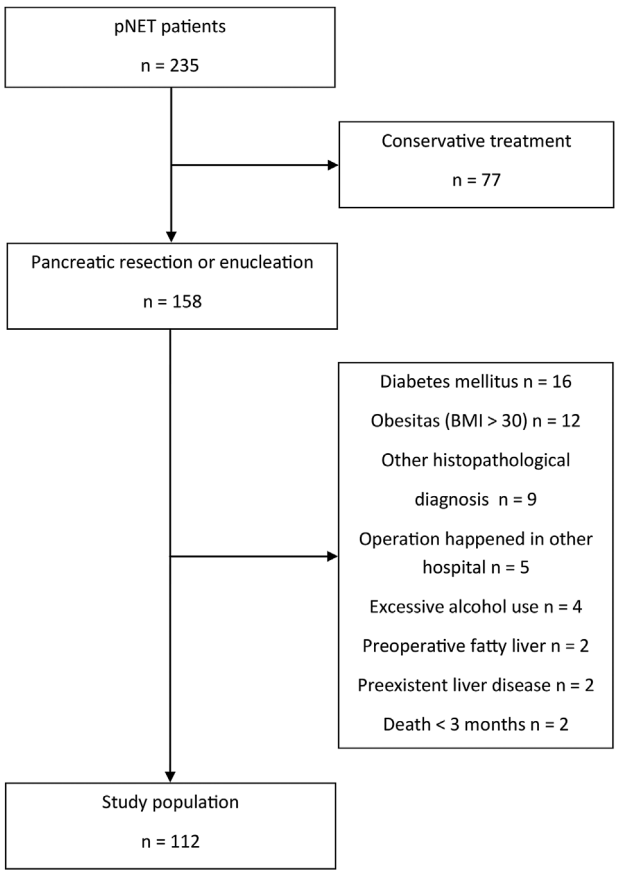

FIGURE 1 Flowchart of patient selection. pNET, pancreatic neuroendocrine tumor

TABLE 1 Baseline characteristics

Age at time of surgery (years)	53.9 (±12.4)
Male sex (*n*)	54 (48.2%)
Preoperative body weight (kg)	70.0 (49-110)
Preoperative body mass index (kg/m^2)	24.3 (±3.3)
Diagnosis (functional: non-functional) (*n*)	34:78
NF-pNET	78 (69.6%)
Insulinoma	24 (21.4%)
Gastrinoma	6 (5.4%)
Glucagonoma	2 (1.8%)
VIPoma	2 (1.8%)
Surgical procedure (*n*)	
Pancreatectomy	86 (76.8%)
Enucleation	26 (23.2%)
MEN1 syndrome (*n*)	4 (3.6%)
Metastases at diagnosis (*n*)	6 (5.4%)
Recurrent disease (*n*)	26 (23.3%)
Chemotherapy (*n*)	7 (6.3%)
Postoperative SSA (*n*)	6 (5.4%)
PRRT (*n*)	4 (3.6%)

NF-pNET, non-functional pancreatic neuroendocrine tumor; MEN1, Multiple Endocrine Neoplasia Type 1; SSA, somatostatin analogues; PRRT, peptide receptor radionuclide therapy.

3.2 | Patient characteristics

Of the 112 included patients, 54 were male, with a mean age of 53.9 ± 12.4 years. See Table 1 for baseline characteristics. All four patients with MEN1 syndrome underwent partial pancreatic resection. Of these patients, two were diagnosed with multiple insulinomas, one with multiple gastrinomas and one with multiple NF-pNETs. Three of the four MEN1 patients had recurrent disease. Overall, 26 patients (23.2%) were identified with recurrent disease; 7 with loco-regional disease and 19 with distant recurrence. At diagnosis, three patients had lymph node metastases and three had liver metastases. Seven patients received chemotherapy after pancreatic surgery; one due to recurrent disease of NF-pNET in the liver after failure of other systemic treatment, one as adjuvant treatment due to initial suspicion of pancreatic adenocarcinoma until definitive pNET histopathology was determined and 5 due to other malignancies. SSA and peptide receptor radionuclide therapy (PRRT), were given to 5.4% and 3.6% of patients, respectively, in context of recurrent disease (Table 1). As 18 of 112 patients died, the overall mortality rate was 16.1%. Median follow-up duration was 54 months (IQR 17-97 months).

3.3 | Factors associated with postoperative new onset NAFLD/NASH

Postoperative imaging was available in 81 patients, 20 with unenhanced CT, 6 with MRI, 14 with ultrasound and 41 with

TABLES 2 Comparison between patients with or without postoperative new onset NAFLD/NASH

	NAFLD/NASH (*n* = 16)	No NAFLD/NASH (*n* = 65)	*P*-value
Male sex (*n*)	9 (56.3%)	29 (44.6%)	0.419
Postoperative body mass index (kg/m^2)	23.5 (±3.9)	22.4 (±3.2)	0.287
EPI (*n*)	7 (43.8%)	29 (45.3%)	0.911
Pancreatic enzyme use (*n*)	7 (43.8%)	33 (51.6%)	0.781
Diagnosis (*n*)			
NF-pNET	14 (87.5%)	49 (75.4%)	0.503
Insulinoma	1 (6.3%)	9 (13.8%)	0.678
Gastrinoma	1 (6.3%)	4 (6.2%)	1.000
Glucagonoma	0 (0.0%)	1 (1.5%)	1.000
VIPoma	0 (0.0%)	2 (3.1%)	1.000
Type of operation/pancreatectomy (*n*)			
Pancreatoduodenectomy	6 (37.5%)	27 (41.5%)	1.000
Enucleation	1 (6.3%)	14 (21.5%)	0.281
Central pancreatectomy	3 (18.8%)	5 (7.7%)	0.189
Distal pancreatectomy	2 (12.5%)	12 (18.5%)	0.725
Central and distal pancreatectomy	4 (25.0%)	5 (7.7%)	0.070
Total pancreatectomy	0 (0.0%)	2 (3.1%)	1.000
Recurrent disease (*n*)	10 (62.5%)	14 (21.5%)	**0.004**
Chemotherapy (*n*)	2 (12.5%)	5 (7.7%)	0.620
Postoperative SSA (*n*)	3 (18.8%)	3 (4.6%)	0.088
PRRT (*n*)	1 (6.3%)	3 (7.7%)	1.000

The bold value indicate the statistically significant *P*-values.
NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatis; EPI, exocrine pancreatic insufficiency; SSA, somatostatin analogues; PRRT, peptide receptor radionuclide therapy; Variables containing missing data: postoperative BMI 11 (13.6%), EPI 1 (1.2%), pancreatic enzyme use 1 (1.2%).

contrast-enhanced CT. Postoperative imaging on which the diagnosis NAFLD/NASH was made, was conducted after a median time of 39 months (IQR 15-80 months) after surgery. Mean time to diagnosis of NAFLD/NASH from surgery was 152 ± 11 months (95%CI 119-185). Sixteen patients (19.8%) were diagnosed with postoperative NAFLD/NASH, of which seven patients (43.8%) were suffering from EPI (OR 0.94, 95% CI 0.3-2.8, *P* = 0.911, Table 2). No difference was seen in BMI between patients who developed NAFLD/NASH and patients who did not (*P* = 0.287, Table 2). Although only 1 of 15 patients (6.7%) developed NAFLD/NASH after enucleation, this was not statistically significant (*P* = 0.281, Table 2). In contrast, four of nine patients (44.4%) after central and distal pancreatectomy (± splenectomy) developed NAFLD/NASH (*P* = 0.070, Table 2). Other types of resection, type of pNET and gender were also not statistically differing between both patient groups.

Recurrent disease was present in 10 patients (62.5%) with postoperative NAFLD/NASH (*P* = 0.004, Table 2) and was the single risk factor associated with development of NAFLD/NASH (OR 4.4, 95%CI 1.1-16.8, *P* = 0.031) from regression analysis. After exclusion of enucleations, recurrence disease was still the only risk factor identified (OR 5.1, 95%CI 1.3-20.3, *P* = 0.020).

Patients with NAFLD/NASH had lower mean asparagine levels than patients without this hepatic steatosis (35.8 vs 46.9 µmol/L; *P* = 0.056, Table 3). Other laboratory values were not different between the two patient groups (Table 3).

3.4 | Factors associated with postoperative EPI

As shown in Table 4, postoperative EPI was detected in 51 patients (49.0%). All 49 patients using pancreatic enzymes were suffering from EPI, according to our definitions. Thirty-nine patients used the enzymes on a daily basis and one to a varying extent with a minimum of several days a week. The other nine patients used the supplements sporadically or stopped treatment completely due to side effects, noncompliance or inadequate treatment effect.

Whereas the majority of NF-pNET patients developed postoperative EPI (82.4% vs 62.3%, *P* = 0.029), the majority of insulinoma patients did not (5.9% vs 34.0%, *P* < 0.001, Table 4). After PD, 30 of 39 patients (76.9%) suffered from EPI (*P* < 0.001). These patients developed EPI more often than patients who underwent enucleation and other types of pancreatic resection (OR 7.0, 95% CI 2.8-17.3, *P* < 0.001).

Multivariate analysis showed that PD was the sole independent risk factor associated with EPI (*P* = 0.012) and that diagnosis of insulinoma was the sole independent protective factor against EPI (*P* = 0.037, Table 5). Because supplementation of pancreatic enzymes is a postoperative consequence, this variable was excluded from multivariate analysis.

TABLE 3 Comparison between patients with or without postoperative new onset NAFLD/NASH

	NAFLD/NASH	No NAFLD/NASH	*P*-value
Laboratory results (*n* = 24)	(*n* = 5 of 16)	(*n* = 19 of 65)	
Albumin (g/L)	40.0 (±9.7)	446 (±3.6)	0.352
Pre-albumin (g/L)	0.2 (±0.1)	0.3 (±0.2)	0.365
Apolipoprotein B (g/L)	0.9 (±0.2)	09 (±0.4)	0.868
Total cholesterol (mmol/L)	4.9 (±1.5)	4.8 (±1.6)	0.900
HDL-cholesterol (mmol/L)	1.6 (±0.7)	1.5 (±0.4)	0.898
LDL-cholesterol (mmol/L)	2.7 (± 0.9)	2.5 (±1.4)	0.844
Cholinesterase (U/L)	7204 (±3261)	7537 (±1978)	0.775
HbA1C (mmol/mol)	45.6 (±9.1)	41.6 (±6.1)	0.257
Total serum protein (g/L)	68.8 (±14.0)	76.2 (±4.9)	0.307
Triglycerides (mmol/L)	1.6 (±1.0)	1.4 (±0.6)	0.941
Zinc (μmol/L)	11.9 (±1.9)	12.6 (±2.6)	0.585
Amino acids (μmol/L)			
Asparagine	35.8 (±4.0)	46.9 (±12.0)	0.056
Other[a]			NS

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatis; HDL, high-density-lipoprotein; LDL, low-density lipoprotein; NS, not significant.
[a]Other amino acids are taurine, aspartic acid, hydroxyproline, threonine, serine, asparagine, glutamic acid, glutamine, proline, glycine, alanine, citrulline, 2-aminobutyric acid, valine, methionine, isoleucine, leucine, tyrosine, phenylalanine, tryptophan, ornithine, lysine, histidine, and arginine.

3.5 | Patients with NAFLD/NASH

Characteristics of 16 patients with postoperative new onset NAFLD/NASH with or without EPI are illustrated in Table 6. Of these patients, six of seven with EPI had undergone PPPD, while all nine without EPI underwent other types of surgery (*P* = 0.001). Although more NAFLD/NASH patients with EPI had recurrent disease (85.7% vs 44.4%) and received postoperative SSA (42.9% vs 0%) than patients without EPI, both were not statistically significant (*P* = 0.145 and *P* = 0.063, respectively).

Only in 2 of 16 patients (12.5%) new onset NAFLD/NASH was diagnosed during follow-up, but were not prescribed treatment or

TABLE 4 Comparison between EPI and non-EPI patient groups

	EPI (*n* = 51)	Non-EPI (*n* = 53)	*P*-value
Male sex (*n*)	25 (49.0%)	24 (45.3%)	0.844
Postoperative weight loss (kg)	7.0 (−7 to 28)	6.0 (−8 to 11)	0.264
Postoperative pancreatic enzyme use (*n*)	49 (96.1%)	0 (0.0%)	**<0.001**
Diagnosis (*n*)			
NF-pNET	42 (82.4%)	33 (62.3%)	**0.029**
Insulinoma	3 (5.9%)	18 (34.0%)	**<0.001**
Gastrinoma	3 (5.9%)	2 (3.8%)	0.675
Glucagonoma	1 (2.0%)	0 (0.0%)	0.490
VIPoma	2 (3.9%)	0 (0.0%)	0.238
Type of operation/ pancreatectomy (*n*)			
Pancreatoduodenectomy	30 (58.8%)	9 (17.0%)	**<0.001**
Enucleation	7 (13.7%)	17 (32.1%)	**0.036**
Central pancreatectomy	4 (7.8%)	6 (11.3%)	0.742
Distal pancreatectomy	5 (9.8%)	13 (24.5%)	0.069
Central and distal pancreatectomy	3 (5.9%)	8 (15.1%)	0.202
Total pancreatectomy	2 (3.9%)	0 (0.0%)	0.238

The bold values indicate the statistically significant *P*-values.
EPI, exocrine pancreatic insufficiency; NF-pNET, non-functional pancreatic neuroendocrine tumor; pancreatoduodenectomy; Variables containing missing data: postoperative weight loss 21 (20.2%).

TABLE 5 Multivariate analysis for risk factors to develop exocrine pancreatic insufficiency

	OR	95%CI	*P*-value
Diagnosis (*n*)			
NF-pNET	0.439	0.075-2.579	0.362
Insulinoma	0.102	0.012-0.871	**0.037**
Type of operation/ pancreatectomy (*n*)			
Pancreatoduodenectomy	4.343	1.377-13.697	**0.012**
Enucleation	1.145	0.284-4.623	0.849
Distal pancreatectomy	0.706	0.179-2.780	0.618

The bold values indicate the statistically significant *P*-values.
OR, odds ratio; CI, confidence interval; NF-pNET, non-functional pancreatic neuroendocrine tumor.

advised lifestyle change due to concurrent recurrent disease. Three other patients (18.8%) were advised lifestyle change, but the remaining patients died or were lost to follow-up.

4 | DISCUSSION

This is the first study evaluating the incidence of new onset NASH/NAFLD and EPI in a large cohort of patients undergoing surgery for pNET. Our results showed that 20% of patients developed NAFLD/NASH, whereas 49% of patients developed EPI. Only 7 of 16 NAFLD/NASH patients suffered from EPI after pancreatic surgery. Thus, EPI appeared not to be associated with development of hepatic steatosis during follow-up in our cohort. In addition, pancreatic enzyme use were equally distributed between patients with or without NAFLD/NASH and therefore not associated with protection against hepatic steatosis. Previous studies reported that 23-37% of patients develop NAFLD/NASH after PD,[3–7] yet other types of pancreatic surgery have not been evaluated.

The single risk factor for development of NAFLD/NASH was recurrent disease. Recurrent disease has not been identified as risk factor previously, most likely because available studies rarely report outcomes on pNET patients with a long follow-up period, but mainly include pancreatic adenocarcinoma patients with worse prognosis and higher mortality rate.[3,5–7,9,21,22] First, treatment of pNET recurrence with SSA, PRRT or chemotherapy may possibly be related to development of hepatic steatosis. This is not supported by our findings. Additionally, chemotherapeutic agents that are especially found to have a relation with NAFLD are fluorouracil (5-FU) and tegafur/gimeracil/oteracil (S-1) based regimens.[23,24] Only 2 of 7 patients with chemotherapy in this cohort developed NAFLD/NASH, of which both regimens were not 5-FU or S-1 based. Second, location of recurrence could be of influence of NAFLD/NASH development. However, because similar recurrence localizations were seen in the NAFLD/NASH group and the non-NAFLD/NASH group, no association between location of recurrence, especially liver metastasis, and hepatic steatosis could be made. Perhaps an association between hepatic steatosis and location and/or treatment of recurrence was not found due to the limited number of patients in. Therefore, this finding should be investigated with more patients and attention in future studies.

Whereas more patients with postoperative SSA treatment (18.8% vs 4.6%) and after central and distal pancreatectomy ± splenectomy (25.0% vs 7.7%) developed NAFLD/NASH, no statistical association was found. This can probably be explained by the small sample size.

TABLE 6 Characteristics of 16 patients with postoperative NAFLD/NASH ± EPI

	EPI	Gender	Diagnosis	Type of operation	Recurrent disease	Treatment
1	+	F	NF-pNET	Pancreatoduodenectomy	Liver, abdomen, rib	Chemotherapy
2	+	M	NF-pNET	Pancreatoduodenectomy	Liver	No
3	+	F	NF-pNET	Pancreatoduodenectomy	Liver, lymph node, hip	SSA
4	+	M	NF-pNET	Pancreatoduodenectomy	Liver	No
5	+	M	NF-pNET	Pancreatoduodenectomy	Liver	SSA
6	+	M	NF-pNET	Pancreatoduodenectomy	No recurrence	No
7	+	F	NF-pNET	Distal pancreatectomy	Loco-regional	Chemotherapy and SSA
8	–	M	NF-pNET	Enucleation	No recurrence	No
9	–	M	NF-pNET	Central pancreatectomy	No recurrence	No
10	–	F	NF-pNET	Central pancreatectomy	No recurrence	No
11	–	M	Gastrinoma	Central pancreatectomy	Liver	PRRT
12	–	F	Insulinoma	Distal pancreatectomy	Loco-regional	No
13	–	M	NF-pNET	Distal pancreatectomy	Liver, stomach, retroperitoneum	No
14	–	F	NF-pNET	Distal pancreatectomy	No recurrence	No
15	–	F	NF-pNET	Distal pancreatectomy	No recurrence	No
16	–	M	NF-pNET	Distal pancreatectomy	Lymph node	No

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatis, EPI; exocrine pancreatic insufficiency; F, female; M, male; NF-pNET, non-functional pancreatic neuroendocrine tumor; SSA, somatostatin analogues; PRRT, peptide receptor radionuclide therapy.

Nevertheless, these results suggest a possible relation and future research is warranted with increased amount of patients.

After enucleation, only one patient (6.7%) developed hepatic steatosis. This may be explained by the fact that significant less patients had recurrent disease after enucleation (1 of 25) and recurrence is the sole risk factor for NAFLD/NASH.

In contrast to the literature, only 6 of 33 PD patients (18%) from this cohort developed NAFLD/NASH. Most likely, an underestimation of patients with NAFLD/NASH is made in this study due to evaluation of imaging studies instead of the golden standard (liver biopsy).[15–18,20] If multiple imaging modalities were available, the imaging study with highest accuracy for detection of NAFLD/NASH was used; unenhanced CT, MRI, ultrasonography and contrast-enhanced CT, respectively. Specificity for unenhanced CT for detection of NAFLD/NASH was 88.1-94.6%.[16] With MRI, hepatic steatosis can be accurately diagnosed both qualitatively and quantitatively.[17] Ultrasonography has overall 85% sensitivity and 94% specificity for hepatic steatosis.[18] Calculating blood-subtracted hepatic attenuation on contrast enhanced CT-images has increasing accuracy as the threshold level of hepatic steatosis increases. Sensitivity ranged from 62.1% to 87.5% in one study[19] and specificity from 86.2-100% in two studies.[19,20] It is likely that the number of patients with postoperative new onset NAFLD/NASH after pancreatic resection was underestimated in this study, especially if the hepatic steatosis was of a mild degree, and because of the moderate to high sensitivity and specificity for all imaging studies.

Secondly, EPI after pancreatic surgery was investigated. In a study of Nakagawa et al[7] prevalence of postoperative EPI after PD was 65%. In our analysis, enucleations, total pancreatectomy and central and/or distal pancreatic pancreatectomy were also included. As the extent of resection might play a role in the development of EPI, this possibly explains the difference in prevalence of EPI. This is supported by the fact that the majority of patients after enucleation (70.8%) did not develop EPI while the majority of patients after PD (76.9%) did develop EPI.[7] Multivariate analysis showed that PD is an independent predictor for the development of EPI. It is known that EPI is associated to remnant pancreatic volume and results in endocrine and exocrine insufficiency in case of total pancreatic resection.[25,26] The same theory applies for distal pancreatic pancreatectomy after which the majority did not develop EPI (13 of 18, $P = 0.069$). While, in accordance with literature, an association between extent of resection and EPI is demonstrated with enucleation and PD patients from this cohort, this was not the case for total and distal resection. The statistical insignificance in the cases of total and distal pancreatectomy is most likely caused by the small number of patients who underwent these procedures. A larger cohort is needed to prove these associations.

Diagnosis of insulinoma was recognized as the only independent protective factor against EPI. Previous studies do not report this finding, as pNETs are rarely investigated in this context. We hypothesize that the relatively indolent and innocuous nature of this tumor does not affect the healthy adjacent pancreatic tissue compared to more malignant tumors, and therefore may be protective against EPI.

The range of time in which the blood tests were performed varied between patients from several weeks to several years postoperatively and only from 24 patients (21.4%), of which five in NAFLD/NASH group, blood tests were acquired. Just recently it became standard care to test pNET patients after pancreatic resection with (suspicion of) EPI for nutrient deficiencies or changes in the lipid metabolism. Relevant conclusions cannot be drawn and more laboratory results, especially in the NAFLD/NASH group, are required to identify changes in nutrient or lipid household between the patient groups. Possibly thereafter, patients that are likely to develop NAFLD/NASH in the future could be recognized by their blood test results and a lead for future treatment could be established.

To a lesser extent, this timeframe limitation due to our retrospective design also applies to all available imaging studies. Although the majority of patients were followed in accordance with the guidelines,[27,28] a significant amount of data were missing, most likely due to loss to follow-up and death.

Mean time to diagnosis of NAFLD/NASH in this cohort was 152 months after pancreatic surgery. In the 16 patients in whom postoperative imaging demonstrated new onset NAFLD/NASH, median shortest follow-up time until diagnosis was 39 months (IQR 15-80 months) after pancreatic surgery. Tanaka et al. described that median time to develop hepatic steatosis after PD was 6 months (range 4-12 months).[3] As NAFLD/NASH can lead to serious liver- and cardiovascular related complications, this should be assessed in all pNET patients approximately 1 year after pancreatic resection. Controlled attenuated parameter (CAP) has proven to be an accurate non-invasive alternative to liver biopsy for diagnosis of NAFLD/NASH[29–31] and could be used in the pre- and postoperative assessment of hepatic steatosis. Therefore we suggest that further research with long-term follow-up should focus on prospective pre- and postoperative liver evaluation with CAP.

5 | CONCLUSIONS

This is the first study that investigated development of EPI and NASH/NAFLD in pNET patients after resection or enucleation ($n = 112$) with long follow-up period. Forty-nine percent of these patients developed EPI after pancreatic surgery, mostly after PD. New onset NAFLD/NASH after pNET resection is occasionally seen, especially in patients with recurrent disease. EPI was not a risk factor for development of NAFLD/NASH in our patient cohort. Due to suboptimal imaging studies to detect NAFLD/NASH, likely there is an underestimation of NAFLD/NASH in this cohort and a clear explanation for current results was not found. Therefore, future (prospective) large studies are warranted to assess associations with hepatic steatosis after pancreatic surgery more accurately.

CONFLICTS OF INTEREST

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