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Steatorrhoea is a predictor for poor survival of carcinoma in chronic pancreatitis

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Abstract
Introduction: Steatorrhea occurs when the pancreatic exocrine function is less than 10%. In CP, steatorrhea is reported in 22.9%[1]. In a survival analysis comparing carcinoma in chronic pancreatitis (CCP-Ca) and de-novo adenocarcinoma pancreas (denovo-Ca), steatorrhoea was incidentally detected as one of the poor prognostic factors impairing the survival.
Aim: To correlate steatorrhoea with overall survival and other clinical parameters in CCP-Ca and De-novo carcinoma pancreas.
Methodology: Retrospective study conducted on CCP-Ca and denovo-Ca resected between 01/01/2004 and 31/12/2013; followed-up for overall survival. The relevant statistical test including Kaplan-Meir and Cox-regression were done using SPSS-22.
Results: Among 137 patients studied, 59 (43.1%) were CCP-Ca and 78 (56.9%) were denovo-Ca. Steatorrhoea was there in 29.1% of CCP-ca and 28.2% of denovo-Ca; which was not statistically significant (p=0.901). Chi-square showed significant differences comparing diabetic status (28.8% vs 69.5%, p=0.133); serum bilirubin (p=0.009; 0.183) and serum albumin (0.45; 0.505 and hypoalbuminaemia (71.2% va 28.8%; p=0.088. 0.255; 0.026) which was more significant in CCP-Ca. On Kaplan-Meier curve it had association with survival (Log Rank test p=0.003 in CCP-Ca, p=0.084 in denovo-Ca). On Cox regression analysis steatorrhoea was poor prognostic factor impairing the survival in CCP-Ca (p=0.005; HR=2.985; 95%CI=1.392-6.404), but not in denovo-Ca.
Conclusion: Incidence of steatorrrhoea in resected cases of CCP-Ca with that of Denovo-Ca pancreas was found comparable. Patients with steatorrhoea had poor overall survival which was significant in CCP-Ca patients but not in Denovo-Ca patients. Multiple parameters which can contribute to this are correlating with steatorrhoea; including, higher tumour stage and uncontrolled diabetes.

Keywords: steatorrhoea, chronic pancreatitis, denovo carcinoma pancreas, predictors of survival, overall survival

Introduction

Steatorrhea or an increase in fat excretion in stools, is defined as more than 7 grams of fat per 100 grams of stool per day. This is one of the clinical features of fat malabsorption, observed in clinical conditions such as exocrine pancreatic insufficiency (EPI), celiac disease and tropical sprue. Examining stool by Sudan III staining for the presence of fat helps in detecting steatorrhea, confirmed by quantitative tests for fecal fat estimation. A fecal elastase-1 level <200 µg/g is diagnostic of pancreatic exocrine insufficiency. 30,000 IU of lipase delivered to the intestine with each meal would eliminate steatorrhea (Brennan *et al*., 2019) [1].

Steatorrhea is reported in 22.9% of patients with chronic pancreatitis (CP)[1]. Shandro *et al*. (2018) [3] have reported that nearly 85% of patients with advanced CP have PEI. Pancreatic exocrine insufficiency may be associated with malabsorption of the lipid-soluble vitamins A, D, E, and K. Clinical steatorrhea appears when the enzyme output is below 5–10% of normal lipase activity. Direct and indirect pancreatic function tests helps to assess the pancreatic exocrine function; direct pancreatic function tests using a hormonal secretagogue are more sensitive in diagnosing CP. In one study, the sensitivity of the secretin–cholecystokinin stimulation test showed 67% sensitivity, 90% specificity and 81% efficacy in correlating with histologically confirmed CP. Randomized controlled trials have shown that PERT improves steatorrhea, decreased stool frequency and fecal fat (Imrie, 2010). Ramesh *et al*. (2013) [4] from Kerala showed that in PEI due to CP, the treatment with pancreatin for one year was associated with significant improvements in fat absorption, nitrogen absorption, and nutritional parameters.

According to our department database on CP, the majority of the admissions were for mass lesions in the pancreas especially head of pancreas, most of them having findings highly suspicious of malignancy. Among these CP patients, steatorrhoea was seen in 35.41% of benign CP and 20.79% of malignant CP. On analysing the overall survival of resected cases of carcinoma in CP compared to the denovo carcinoma pancreas; steatorrhoea was identified as a significant parameter. Hence a comparative analysis was done with steatorrhoea as a predictor for survival in carcinoma in CP and denovo carcinoma pancreas.

Aims and objectives

Primary objective of this study was to compare the overall survival of patients with steatorrrhoea in resected cases of carcinoma arising in CP with that of de-novo carcinoma pancreas. The secondary objective was to correlate the steatorrhoea with clinical, biochemical and histopathology parameters.

Material and methods

This is done as a part of the ongoing single centre retrospective comparative study in the Department of

Surgical Gastroenterology, Govt. Medical College, Trivandrum, on the consecutive cases of pancreaticoduodenectomy done from 01/01/2004 to 31/12/2013 for carcinoma in CP or denovo carcinoma pancreas. The sample size (n) was calculated as 40 in each group.

Inclusion criteria were radiologically confirmed cases of CP (by CECT/ERCP/MRCP) with a mass lesion defined as an area of altered tissue attenuation or focal enlargement of the head of the pancreas other than pseudocyst/abscess on imaging were taken as suspected cases of carcinoma in CP. Among them the resected ones, histopathology confirmed cases as `adenocarcinoma pancreas associated with CP' were included in the study as Carcinoma-in CP, resected and confirmed cases of denovo ductal adenocarcinoma pancreas were also included. Tumour stage reported as TNM stage – I or II were enrolled in to this study. Exclusion criteria were CCP with dysplasia alone or other atypical cases, carcinoma pancreas with direct tumour infiltration to the adjacent structures other than duodenum or bile duct, patients with serious comorbidities and operative mortality within 30 days.

The study variables included clinical steatorrhoea, demographic details, other clinical features like duration of symptoms, pain, jaundice, loss of weight, diabetes mellitus, laboratory investigations and histopathology characteristics. The follow up details of these patients were assessed for the overall survival (in months) for plotting the Kaplan-Meier curve. The data regarding clinical parameters, histopathology and overall survival was compiled based on a structured proforma, after obtaining a documented consent from the individual patients.

Statistical analysis: Suitable parametric and non-parametric statistical tests were applied for comparing the clinical and pathological parameters. Student-t-test, Mann-Whitney U test, Chi-Square test, Kaplan and Meier survival curve and Log Rank (Mantel-Cox) test were used to assess significant differences between the two groups. Cox proportional hazard regression model used to assess the strength of association through the estimated hazard ratios, to assess the predictors of survival. Statistically significant difference was defined as the p-value <0.05. The various statistical tests were done using IBM SPSS Statistics (27.0 version).

Results

137 patients who had pancreaticoduodenectomy during this study period; among these carcinoma in CCP (CCP-Ca) was 43.1% (n=59) and de-novo carcinoma pancreas (Denovo-Ca) was 56.9% (n=78). The median age at diagnosis in CCP-Ca was 50 years and that in Denovo-Ca was 55 years, (p<0.001). The CCP-Ca group had 33 (55.9%) males and 26 (44.1%) females, Denovo-Ca group had 44 (56.4%) males and 34(43.6%) females, (p=NS). Steatorrhoea was there in 23 (29.1%) of CCP-Ca and 24 (28.2%) of Denovo-Ca; which was not statistically significant (p=NS), (Fig.1).

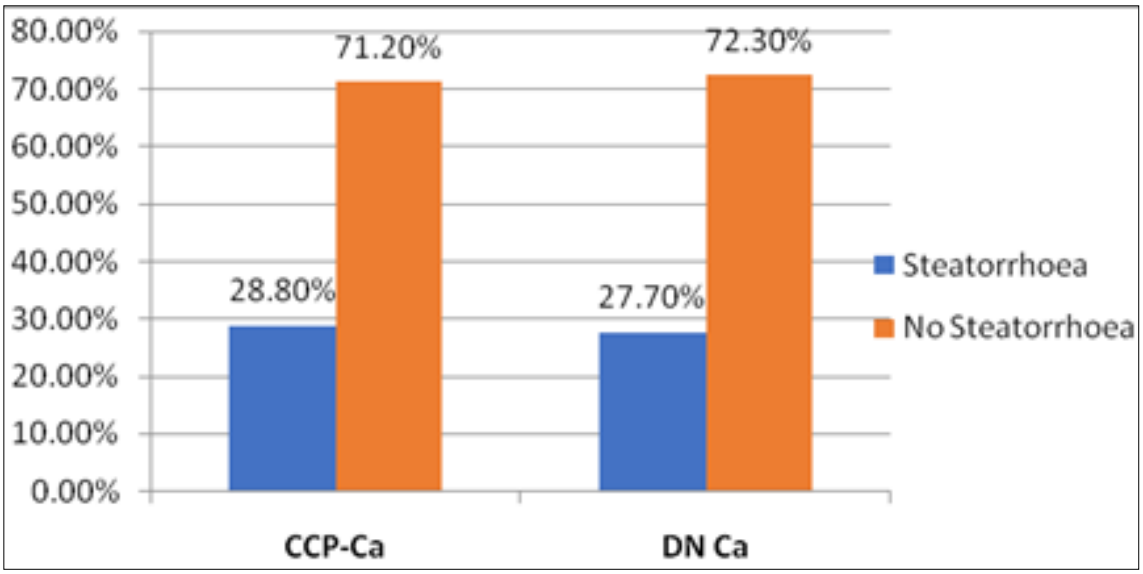

Fig 1: Steatorrhoea as the presenting symptoms in CCP-Ca and denovo-ca

Steatorrhoea and other parameters

Mean blood sugar and serum bilirubin were higher in patients with steatorrhea; serum albumin was lower in steatorrhea (p=NS). Steatorrhea had significant association with jaundice in CCP-Ca (p=0.036), but not denovo-Ca (p=0.526). Steatorrhoea showed significant differences in diabetic patients (28.8% vs 69.5%, p=0.133).

Uncontrolled diabetes were higher in steatorrhea in CCP-Ca p=0.059; and in Denovo-Ca p=0.013). Hypoalbuminaemia co-existed with steatorrhea in 44.1% of CCP-Ca and 29.6% of Denovo-Ca, but this was not statistically significant (p=0.088). Steatorrhoea showed association with higher tumour stage in CCP-Ca (p=0.017) and in Denovo-Ca (p=0.292); but in Denovo-Ca it was not statistically significant.

Steatorrhoea and overall survival

On Kaplan-Meier curve (Fig.2), those with steatorrhoea had poor survival which was significant in CCP-Ca patients (Log Rank test p=0.003 in CCP-Ca, p=0.084 in denovo-Ca). Chi-Square test based on the outcome had shown steatorrhoea as a variable which is significantly associated with the outcome (death/survival) in CCP-Ca. On Cox regression analysis steatorrhoea was poor prognostic factor impairing the survival in CCP-Ca (p=0.005;HR=2.985;95%CI=1.392-6.404).

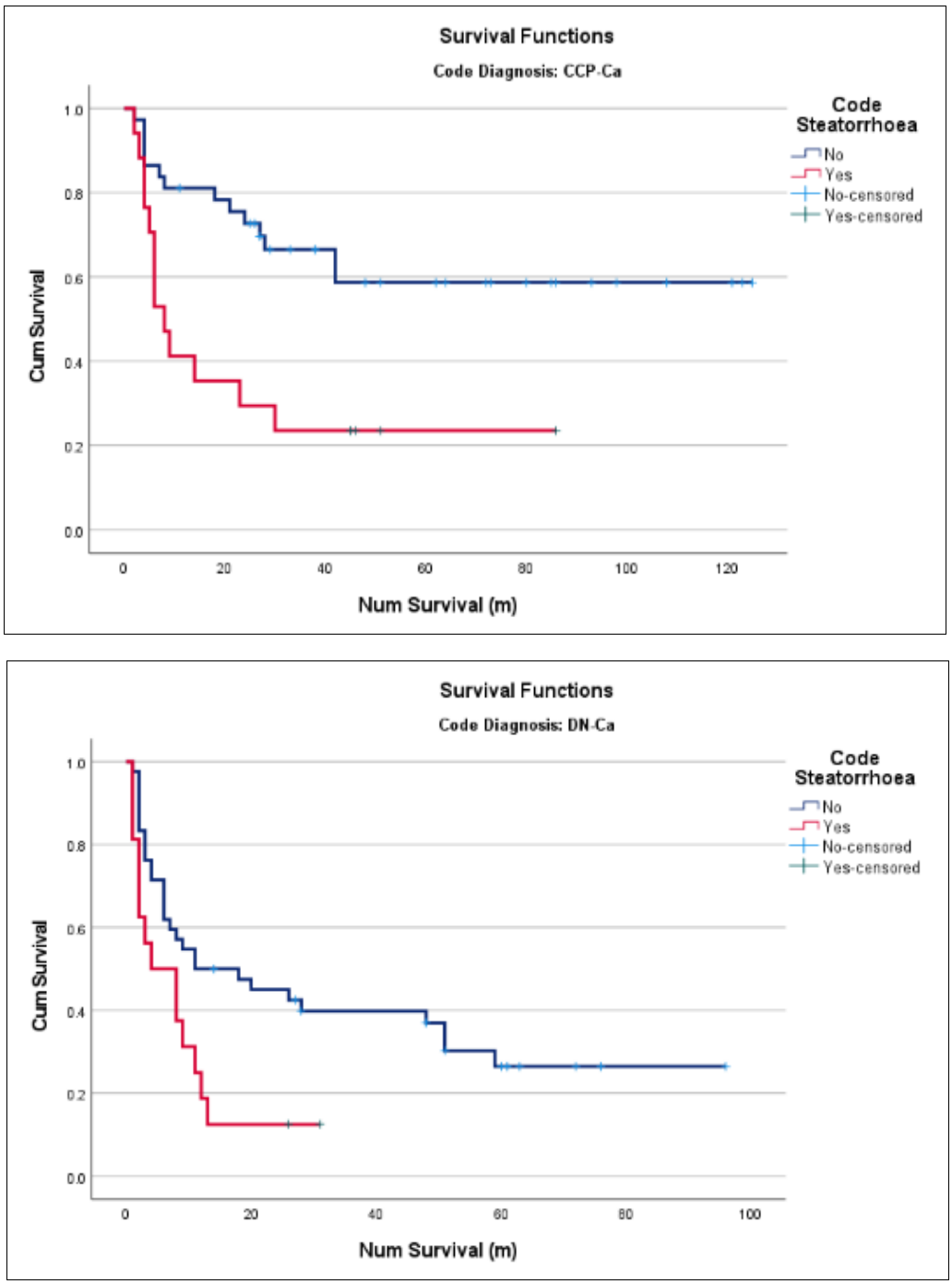

Fig 2: Kaplan-meier curve: steatorrhoea and survival in CCP-Ca and denovo-ca

In this study, steatorrhoea, was found significantly affecting the survival of the CCP-Ca patients enrolled. On analysing this variable affecting the outcome it was found to have many clinical correlations with the other various parameters studied.

Discussion

Carcinoma in CP

Bracci *et al*, (2009) [5] in a case-control study showed that CP has a 7.2 fold increased risk for pancreatic cancer. Zheng *et al*. (2019) reported that the two independent risk factors for the development of pancreatic cancer in patients with CP after surgery were; time interval to surgery [HR 1.005, 95% CI (1.002–1.008), p = 0.002] and de novo endocrine insufficiency [HR 10.672, 95% CI (2.567–44.372), p = 0.001]. Babu *et al*. (2019) [7] have reported that carcinoma occurring in chronic calcific pancreatitis (CCP) are multifocal, poorly differentiated, advanced on presentation and associated with poor overall survival.

Predictors of survival in carcinoma pancreas

Xiaodong *et al*., (2019) [8] reported in their univariate analysis showed that AJCC T and N staging, the status of resection margin, grade of tumour differentiation, perineural invasion, intravascular cancer embolus, combined vascular resection, neutrophil-to-lymphocyte ratio (NLR) ≥ 2, carcinoembryonic antigen ≥5 ng/mL, carbohydrate antigen 19-9 (CA 19-9) ≥ 400 U/mL, and without postoperative adjuvant chemotherapy were correlated with shorter DFS.

In this study, the median age at diagnosis was significantly lower in CCP-Ca (50 years) than in Denovo-Ca (55 years). The CCP-Ca patients were younger than the Denovo-Ca

patients. There were no difference regarding the gender of the patients in these groups. The percentage of patients having steatorrhoea as their presenting symptoms was similar in both the groups; 29.1% in CCP-ca and 28.2% in Denovo-Ca. The two subtypes of carcinoma pancreas were found comparable in this regard.

On analysing the entire cohort; the steatorrohea found higher among diabetics, and those who had jaundice or hypoalbuminaemia. However these were not statistically significant. Metabolic disorder like diabetes can affect the different organs including the exocrine pancreas to produce steatorrhoea. High grade biliary obstruction in malignancy also found associated with steatorrhoea. Hypoalbuminaemia could be a result of steatorrhoea as well.

On comparing CCP-Ca and Denovo-Ca patients; steatorrhoea had significant association with jaundice in CCP-Ca, but not in Denovo-Ca. CCP is a chronic disease which can lead to exocrine and endocrine deficiency; the higher incidence of steatorrhoea may be due to the underlying CP also. On analysing the diabetic patients in both the groups uncontrolled diabetes was higher in patients having steatorrhea in both CCP-Ca and in Denovo-Ca. Hypoalbuminaemia co-existed with steatorrhea in CCP-Ca and Denovo-Ca though the difference was not statistically significant. On analysing the histopathology, steatorrhoea was found significantly more among higher tumour stage in CCP-Ca; but it had no significance in Denovo-Ca group. Other tumour characteristics including tumour differentiation and lymph node positivity had no relation with steatorrhoea in the two groups.

Survival analysis by Kaplan-Meier curve had shown that those with steatorrhoea has poor overall survival which was significant in CCP-Ca patients but not in Denovo-CA patients. Multiple parameters which can contribute to this are correlating with steatorrhoea; including, higher tumour stage and uncontrolled diabetes. Log Rank test, Chi-Square test and Cox regression analysis shows steatorrhoea as a poor prognostic factor impairing the survival in CCP-Ca.

Conclusion

The incidence of steatorrrhoea in resected cases of carcinoma arising in CP with that of de-novo carcinoma pancreas was found comparable. Patients with steatorrhoea had poor overall survival which was significant in CCP-Ca patients but not in Denovo-Ca patients. Multiple parameters which can contribute to this are correlating with steatorrhoea; including, higher tumour stage and uncontrolled diabetes.

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