Original Article

Clinical Predictors of Resectability of Pancreatic Adenocarcinoma

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ABSTRACT

Background/Aims: Identifying patient-related factors as well as symptoms and signs that can predict pancreatic cancer at a resectable stage, which could be used in an attempt to identify patients at an early stage of pancreatic cancer that would be appropriate for surgical resection and those at an unresectable stage be sparred unnecessary surgery. **Materials and Methods:** A retrospective chart review was conducted at a major tertiary care, university hospital in Riyadh, Saudi Arabia. The study population included individuals who underwent a computed tomography and a pancreatic mass was reported as well as the endoscopic reporting database of endoscopic procedures where the indication was a pancreatic mass, between April 1996 and April 2012. Any patient with a histologically confirmed diagnosis of adenocarcinoma of the pancreas was included in the analysis. We included patients' demographic information (age, gender), height, weight, body mass index, historical data (smoking, comorbidities), symptoms (abdominal pain and its duration, anorexia and its duration, weight loss and its amount, and over what duration, vomiting, abdominal distention, itching and its duration, change in bowel movements, change in urine color), jaundice and its duration. Other variables were also collected including laboratory values, location of the mass, the investigation undertaken, and the stage of the tumor. **Results:** A total of 61 patients were included, the mean age was 61.2 ± 1.51 years, 25 (41%) were females. The tumors were located in the head (83.6%), body (10.9%), tail (1.8%), and in multiple locations (3.6%) of the pancreas. Half of the patients (50%) had Stage IV, 16.7% stages IIB and III, and only 8.3% were stages IB and IIA. On univariable analysis a lower hemoglobin level predicted resectability odds ratio 0.65 (95% confidence interval, 0.42-0.98), whereas on multivariable regression none of the variables included in the model could predict resectability of pancreatic cancer. A CA 19-9 cutoff level of 166 ng/mL had a sensitivity of 89%, specificity of 75%, positive likelihood ratio of 3.6, and a negative likelihood ratio of 0.15 for resectability of pancreatic adenocarcinoma. **Conclusion:** This study describes the clinical characteristics of patients with pancreatic adenocarcinoma in Saudi Arabia. None of the clinical or laboratory variables that were included in our study could independently predict resectability of pancreatic adenocarcinoma. Further studies are warranted to validate these results.

Key Words: Clinical predictors, pancreatic adenocarcinoma, resectability

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It is estimated that 43,920 individuals will be diagnosed with pancreatic cancer in the United States in the year 2012,[1] with an age-adjusted incidence rate of 12.1 per 100,000.[1] Time trends have shown that there is a significant increase in the annual percentage change in the incidence (1.4%) as well as mortality (0.5%) from the year 2000 to 2009.[1] It is also estimated that 0.56% of men between the age of 50 and 70 years will develop pancreatic cancer compared with 0.40% of women.[1] Among nationals of the Gulf Cooperation Council (GCC) States, pancreatic cancer ranked as the 10th cancer for males aged 60-74 years,[2] whereas in Saudi Arabia the crude rate of pancreatic cancer between the years 1998 and 2007 in males was 10 per 100,000 and the age standardized rate (ASR) was 19 per 100,000, whereas for females the crude rate was 6 per 100,000 and the ASR was 12 per 100,000 for the same period.[2]

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There is a significant difference in the survival rates in pancreatic cancer according to the stage of the tumor, with a five-year survival of 23.3% for localized disease, 8.9% for regional disease, 1.8% for distal disease, whereas for those with unstaged disease is 3.9%.[1] Little data exists about the epidemiology of pancreatic adenocarcinoma in Saudi Arabia as well as its clinical manifestations.[3] Due to the vague symptoms associated with pancreatic cancer, unfortunately, the disease is usually discovered at an advanced stage when surgical resection is not possible and the management is mainly palliative. Although imaging technology has advanced the management of patients with pancreatic adenocarcinoma significantly, there still are limitations. A meta-analysis[4] demonstrated that the pooled sensitivity for vascular invasion for computed tomography (CT) was 71% (95% CI, 64-78%) and for magnetic resonance imaging (MRI) 67% (95% CI, 59-74%), whereas the pooled specificity was 92% (95% CI, 89-95%) and 94% (95% CI, 91-96%), respectively,[4] and there was no added benefit for MRI over CT.[4] A second meta-analysis found that helical CT had the highest sensitivity and specificity 91% and 85% when compared with regular CT, MRI, or ultrasound.[5]

Identifying patient-related factors as well as symptoms and signs that can predict pancreatic cancer at a resectable stage, or conversely those with unresectable disease, might be used in an attempt to identify patients at an early, potentially curable stage of the disease and those at an unresectable stage be sparred surgery that would add to the morbidity of patients as well as costs to the health care system at no additional benefit. More specifically, we examined the relationship between various clinical as well as laboratory findings and resectability of pancreatic adenocarcinoma with the reference of resectability being not only imaging but those who were thought to be resectable prior to surgery but intraoperatively were found to be unresectable.

MATERIALS AND METHODS

A retrospective chart review was conducted at King Khalid University Hospital (KKUH), a major tertiary care and university hospital in Riyadh, Saudi Arabia. The study population included individuals who underwent a CT scan between April 1996 and April 2012 and a pancreatic mass was reported. We also reviewed the endoscopic reporting database of the endoscopy unit at the same institution for the same period for all endoscopic procedures [gastroscopies, endoscopic ultrasounds (EUS), and endoscopic retrograde cholangio-pancreatographies (ERCP)] where the indication or the impression included a pancreatic mass. We reviewed the histology reports for these patients, any patient with a histologically confirmed diagnosis of adenocarcinoma of the pancreas was included in the analysis, whereas those without a histological diagnosis or with a diagnosis other than adenocarcinoma were excluded from the analysis.

The tumor was defined as resectable when there is no extrapancreatic tumor including absence of peritoneal and hepatic metastases, patency of the superior mesenteric-portal vein confluence, and the presence of a tissue plane between the tumor and the local arterial structures, including the celiac axis, common hepatic artery, and superior mesenteric artery. Unresectable pancreatic cancer was defined when there is radiographic or clinical evidence of distant organ or peritoneal metastases, or when preoperative imaging or intraoperatively there was tumor encasement of the superior mesenteric artery or celiac axis (i.e., tumor involvement of >180° of the arterial circumference).[6]

Trained research assistants abstracted data from patients' medical records, imaging, as well as endoscopic reports. The abstracted data were entered in a standardized electronic case report form. The institution ethics review board approved the study.

Data collection

The demographic information (age, gender), height, weight, body mass index (BMI), historical data (smoking, co-morbidities), symptoms (abdominal pain and its duration, anorexia and its duration, weight loss and its amount and over what duration, vomiting, abdominal distention, itching and its duration, change in bowel movements, change in urine color), jaundice and its duration were collected. Other variables collected include laboratory values, location of the mass, the investigation undertaken, staging of the tumors, as well as the management undertaken for these patients.

No personal identification information or other personal identifiers such as address or hospital identification number were recorded to ensure patient confidentiality.

Statistical analysis

Data analysis included descriptive statistics computed for continuous variables, including means, standard deviations (SD), minimum and maximum values, as well as 95% CI. Frequencies are used for categorical variables. We used hypothesis testing, the *t* test with unequal variances, as well as Fisher's exact test where appropriate.

Univariable and multivariable logistic regressions were used to examine the association between independent variables and the dependent variable resectability of pancreatic cancer. Independent variables included age, height, weight, BMI, past history of smoking or alcohol consumption, history and duration of diabetes and hypertension, the presence of ischemic heart disease, and chronic obstructive pulmonary disease. We also included the symptoms at presentation: The presence and duration of abdominal pain, vomiting,

anorexia, jaundice, itching, weight loss and the amount of weight lost, as well as the presence of abdominal distention, ascites, and dark urine. Odds ratio (OR) and 95% CI were calculated. Characteristics of test procedure (sensitivity, specificity, likelihood ratios, receiver–operating characteristic curve, and the area under the curve) were used to evaluate the optimal cutoff value for CA 19-9.

We used the software STATA 11.2 (Stata Corp, TX, USA) in our analysis. A statistical significance threshold of $P = 0.05$ was adopted. No attempt at imputation was made for missing data.

RESULTS

Demographics and historical data

A total of 61 patients with histologically proven adenocarcinoma were included in the analysis. The basic demographic data and symptoms are presented in Table 1. The mean age was 61.2 ± 1.51 years [Figure 1], 25 (41%) females. The mean weight was 64.96 ± 2.98 kg, height 1.61 ± 0.02 m, and BMI 24.92 ± 0.98 kg/m.^{2}. History of smoking was present in 11.4%, diabetes mellitus in 52.6% with a mean duration of 3.58 ± 0.88 years, hypertension in 36.1%, and ischemic heart disease in 11.1%.

Jaundice was present in 77.8%, abdominal pain in 66.8%, weight loss in 48.2%, vomiting in 29.6%, anorexia in 27.8%, itching in 25.93%, ascites in 5.6%, abdominal distention in 5.7%, and change in bowel motions in 3.7% [Figure 2]. The mean duration of jaundice was 3.67 ± 0.49 months, itching 3.44 ± 0.71 months, pain 13.95 ± 5.1 months, vomiting 6.57 ± 1.32 months, anorexia 8.29 ± 2.15 months, duration of weight loss 16.25 ± 3.75 months, and amount of weight loss was 11.3 ± 2 kg.

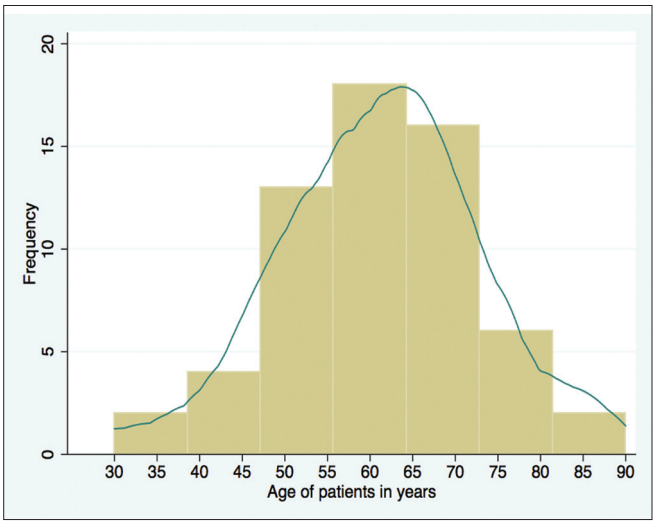

Figure 1: Age of patients

Laboratory data

The mean hemoglobin was 11.58 ± 0.28 g/dL, platelet count 257 ± 11.52 × 10^9/L, international normalized ratio 1.26 ± 0.08, total bilirubin 126 ± 19.19 µmol/L, alanine aminotransferase (ALT) 154 ± 30.21 U/L, aspartate aminotransferase (AST) 95 ± 13.88 U/L, alkaline phosphatase (ALP) 399 ± 38.41 U/L, carcinoembryonic antigen (CEA) 168 ± 145.46 ng/mL, carbohydrate antigen 19-9 (CA 19-9) 168 ± 6960 U/mL. [Table 2 and Figure 3].

Table 1: Baseline characteristics and symptoms of patients diagnosed with pancreatic adenocarcinoma

Variable	Mean	95% CI	Minimum	Maximum
Gender				
Males	59%	46.3-71.7%	NA	NA
Females	41%	28.3-53.7%	NA	NA
Age (years)	61.16	58.1-64.2	30	90
Weight (kg)	64.96	58.8-71.1	42	109
Height (m)	1.61	1.58-1.65	1.47	1.81
BMI (kg/m^2)	24.9	22.9-26.9	14.9	39.3
Smokers	11.43%	0.3-22.5%	NA	NA
Alcohol consumption	2.8%	0.0-8.4%	NA	NA
DM II	52.63%	36.0-69.3%	NA	NA
DM duration (years)	3.58	1.6-5.6	0.2	7
HTN	36.11%	19.6-52.6%	NA	NA
IHD	11.11%	0.3-21.9%	NA	NA
COPD	2.8%	0.0-8.4%	NA	NA
Symptoms				
Abdominal pain	66.7%	53.7-79.5%	NA	NA
Duration of pain[a]	6.9	4.8-9.0	1	16
Vomiting	29.6%	17.1-42.2%	NA	NA
Duration of vomiting[a]	6.6	3.7-9.4	1	16
Anorexia	27.8%	15.4-40.1%	NA	NA
Duration of anorexia[a]	8.3	3.6-12.9	1	32
Weight loss	48.2%	34.4-61.9%	NA	NA
Duration of weight loss[a]	16.3	8.0-24.5	2	48
Amount of weight loss[b]	11.3	6.8-15.8	2	22
Abdominal distention	5.7%	0.0-12.1%	NA	NA
Jaundice	77.8%	66.3-89.2%	NA	NA
Duration of jaundice[a]	3.7	2.7-4.7	1	12
Itching	25.9%	13.9-38.0%	NA	NA
Duration of itching[a]	3.4	1.8-5.1	1	8
Change in bowel movements	3.7%	0.0-8.9%	NA	NA
Ascites	5.6%	0.0-11.9%	NA	NA
Dark urine	3.3%	0.0-7.9%	NA	NA

BMI: Body mass index, CI: Confidence interval, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, HTN: Hypertension, IHD: Ischemic heart disease; NA: Not applicable, [a]In months, [b]In kilograms

Radiological data

All patients underwent a CT scan for staging (100%), whereas ultrasound of the abdomen was performed in 77.2%, and MRI was performed in 9.8%, EUS was performed in 56.9% [Table 3].

The majority of the patients had an ERCP performed (60.7%) and almost half of those who had an ERCP had a plastic biliary stent placement (46.0%). Metal biliary stents were inserted in 6.6% of patients, whereas duodenal metal stents were inserted in 1.6%.

The majority of the tumors in the study population were in the head of the pancreas (83.6%), 10.9% in the body, 1.8% in the tail, and 3.6% were in multiple locations.

A tissue diagnosis was obtained through fine-needle aspiration (FNA) in the majority of cases (93.2%), about half of these were through EUS (57.7%), transabdominal ultrasound in 32.7%, and CT-guided FNA in 9.6%.

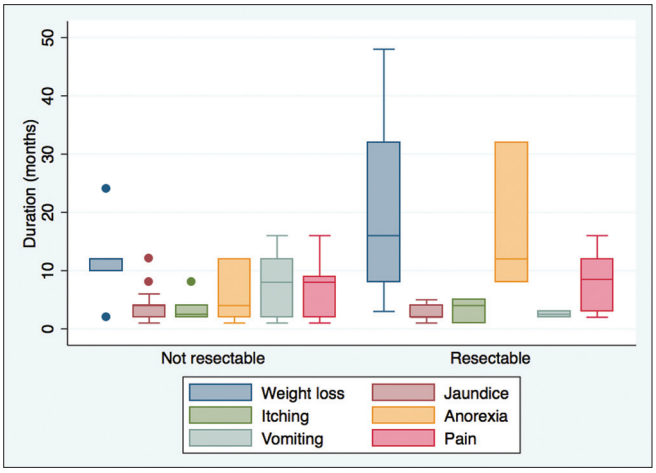

Figure 2: Various symptoms of patients who were diagnosed with pancreatic adenocarcinoma stratified by resectability of their tumors

Table 2: Laboratory values of patients diagnosed with pancreatic adenocarcinoma

Variable	Mean	95% CI	Minimum	Maximum
Hemoglobin (g/dL)	11.6	11.0-12.13	6.8	15.1
Platelets (×10³/mL)	257	234-280	117	499
INR	1.3	1.1-1.4	0.8	2.99
AST (U/L)	95	67-123	12	490
ALT (U/L)	154	93-215	19	906
ALP (U/L)	398	321-476	22	1152
Total bilirubin (μmol/L)	126	88-165	3	610
CA 19-9 (U/mL)	4477	1390-7563	2	20,000
CEA (ng/mL)	168	1-472	0	2929

ALP: Alkaline phosphatase, ALT: Alanine transaminase, AST: Aspartate aminotransferase, CA 19-9: Carbohydrate antigen 19-9, CEA: Carcinoembryonic antigen, CI: Confidence interval, INR: International normalized ratio

The portal vein was involved by the tumor in 25.9% of cases, whereas there was involvement of peritumoral lymph nodes in 42.3% and the celiac lymph nodes in 25.9%. Duodenal involvement was found in 35.7% with obstruction in 17.24% of patients. Metastasis was found in 40.5% of patients with the majority of these to the liver (88.2%) and 11.8% had metastasis to other locations.

Staging of the tumor demonstrated that half the patients (50%) were stage IV, 16.7% were stages IIB and III, whereas only 8.3% were stages IB and IIA [Table 3].

Table 3: Results of investigations performed

Variable	Mean (%)	95% CI
Ultrasound	77.2	66.0-88.4
CT	100	100-100
MRI	9.8	2.1-17.5
ERCP	60.7	48.0-73.3
With plastic stent	27.9	16.3-39.4
With metal stent	6.6	3.2-12.9
Duodenal stent	1.6	0.0-4.9
EUS	56.9	43.8-70.0
FNA	93.2	86.6-99.8
EUS guided FNA	57.7	43.8-71.6
Ultrasound guided FNA	32.7	19.5-45.9
CT guided FNA	9.6	1.3-17.9
Location of the mass		
Head	83.6	73.5-93.7
Body	10.9	2.4-19.4
Tail	1.8	0.0-5.5
Multiple locations	3.6	0.0-8.7
Portal vein involvement	25.9	8.3-43.6
Lymph node involvement	42.3	22.0-62.7
Celiac lymph node involvement	25.9	8.3-43.6
Duodenal involvement	35.7	16.8-54.6
Distant metastasis	40.5	25.0-56.0
Liver	88.2	71.2-100
Multiple locations	11.8	0.0-28.8
Cytology results		
Adenocarcinoma	93.3	86.8-99.8
Ampullary adenocarcinoma	3.7	0.0-8.0
Negative for malignant cells	1.7	0.0-5.0
Pseudocyst	1.7	0.0-5.0
Stage of disease		
I B	8.3	0.0-26.7
II A	8.3	0.0-26.7
II B	16.7	0.0-41.4
III	16.7	0.0-41.4
IV	50	16.8-83.2
Unresectable	75.4	67.3-86.5

CT: Computerized tomography, ERCP: Endoscopic retrograde cholangio-pancreatography, EUS: Endoscopic ultrasound, FNA: Fine-needle aspiration, MRI: Magnetic resonance imaging

Univariable analysis

Descriptive averages and proportions among patients with resectable versus nonresectable pancreatic adenocarcinoma are detailed in Table 4. Among the variables examined, the only variable that was found to have significant differences in univariable analysis for patients with resectable pancreatic adenocarcinoma compared with those with unresectable adenocarcinoma was the hemoglobin level OR 0.65 (95% CI, 0.42-0.98) [Table 4].

Multivariable analysis

Using stepwise multivariable regression none of the variables included in the model could predict resectability of pancreatic cancer.

Hypothesis testing

The only variables that showed statistically significant differences between resectable and unresectable pancreatic adenocarcinoma, respectively, were the duration of vomiting (2.5 months vs. 7.3 months) (P = 0.01), the level of hemoglobin (10.6 g/dL vs. 11.9 g/dL) (P = 0.05), and the CA 19-9 level (107 ng/mL vs. 5448 ng/mL) (P = 0.01) [Table 5].

Receiver–operating characteristic curve for CA 19-9

For unresectable pancreatic cancer using a CA 19-9, a cutoff level of 166 ng/mL had a sensitivity of 89%, a specificity of 75%, a positive likelihood ratio of 3.6, and a negative likelihood ratio of 0.15 with an area under the curve 88.9% (95% CI, 70.8-98.9%) [Figure 4].

DISCUSSION

Pancreatic adenocarcinoma usually carries a dismal prognosis due to the late presentation at an unresectable stage of the disease and has a 5-year survival of about 4%.[7] Although the definition of unresectable pancreatic tumor is variable between studies using a combination of criteria ranging from semicircular encasement of the peripancreatic vessels to frank invasion of the vessels or occlusion,[8] and even those with vascular invasion of the portal vein and the superior mesenteric vein have been offered resection with vascular reconstruction.[9] In this study, we used the definition by Evans *et al.*,[6] which is one of the most common definitions used in the literature.

The median survival for those with primarily unresectable locally advanced pancreatic carcinoma after neoadjuvant chemoradiotherapy is 13.3 months.[8] Although imaging modalities have helped to identify patients at an advanced stage of disease, their ability still is limited – a meta-analysis of studies assessing the performance of positron emission tomography (PET)/CT has demonstrated a sensitivity of 87% and a specificity of 83%[10] A study from the eastern province of Saudi Arabia[11] attempted to predict resectability of pancreatic head tumors based on multidetector CT and included 69 patients over almost a 4-year period; however, 37 patients (54%) were excluded from the study as they either had clearly unresectable disease or they were not candidates for surgery based on concomitant comorbidities.[11] Of those who had surgery only 25 of the 32 had histologically proven adenocarcinoma (78%), whereas the remainder had benign lesions of the head of the pancreas. Of those who were thought to be resectable, 11 (34.4%) underwent a palliative surgery and of those who had a Whipple procedure as a curative surgery three out of 21 (14.3%) had positive resection margins, thus emphasizing the importance of sparing those with an unresectable disease, an unnecessary surgery. Due to the limitation of preoperative investigations in assessing resectability of pancreatic adenocarcinoma, it

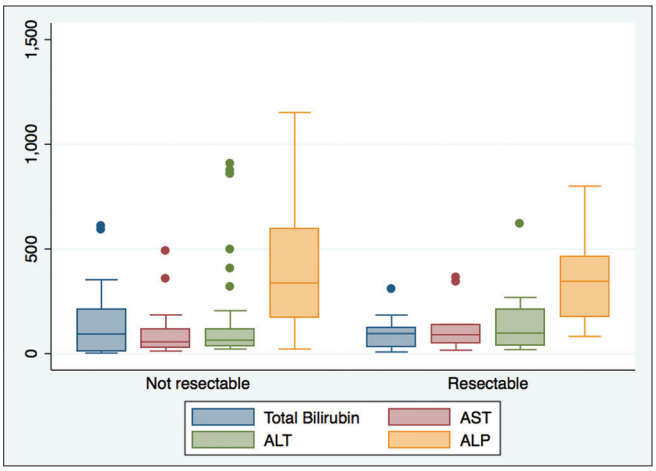

Figure 3: Total bilirubin level and liver enzymes of patients with regard to resectability of their pancreatic adenocarcinoma

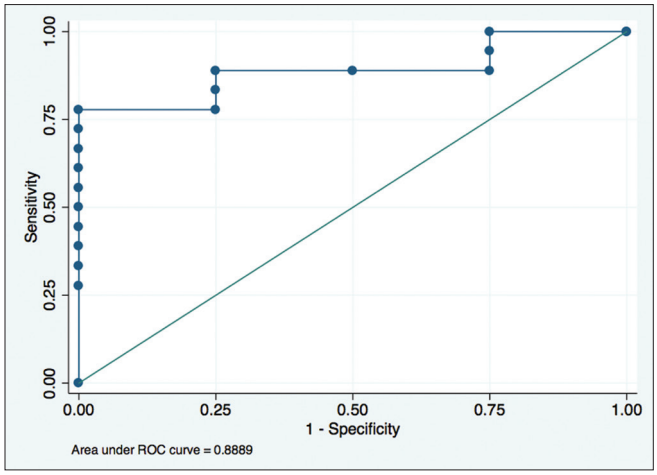

Figure 4: Receiver–operating characteristics curves (ROC) for serum CA 19-9 to distinguish between patients with resectable and unresectable pancreatic adenocarcinoma. The area under the ROC curve was 0.89. The best discriminating value in this population was 166 ng/mL

Table 4: Univariable analysis of predictors of resectability of pancreatic adenocarcinomas

Variable	Univariable analysis	
	Odds ratio	95% CI
Age	1.00	0.95-1.06
Male gender	0.94	0.24-3.58
Smoking	4	0.31-51.03
DM II	0.9	0.19-4.17
HTN	0.79	0.15-4.21
IHD	1.78	0.10-31.98
BMI	1.06	0.88-1.27
Abdominal pain	0.64	0.16-2.63
Duration of pain (months)	1.09	0.89-1.32
Vomiting	0.19	0.03-1.06
Duration of vomiting (months)	0.67	0.31-1.47
Anorexia	0.31	0.07-1.43
Duration of anorexia (months)	1.32	0.86-2.01
Weight loss	0.64	0.16-2.63
Amount of weight loss (kg)	0.87	0.62-1.22
Jaundice	3.5	0.61-20.13
Itching	2.06	0.38-11.04
Hemoglobin (g/dL)	0.65	0.42-0.98
Platelets (×10^3/mL)	1.00	0.99-1.01
INR	6.48	0.29-146.70
AST (U/L)	1.00	1.00-1.00
ALT (U/L)	1.00	0.99-1.00
ALP (U/L)	1.00	1.00-1.00
Total bilirubin (μmol/L)	1.00	0.99-1.00
CA 19-9 (U/mL)	0.99	0.98-1.00
CEA (ng/mL)	0.94	0.82-1.09

ALP: Alkaline phosphatase, ALT: Alanine transaminase, AST: Aspartate aminotransferase, BMI: Body mass index, CA 19-9: Carbohydrate antigen 19-9, CEA: Carcinoembryonic antigen, DM: Diabetes mellitus, HTN: Hypertension, IHD: Ischemic heart disease, INR: International normalized ratio

Table 5: Comparison of demographic and clinical characteristics of patients with resectable and unresectable pancreatic adenocarcinoma

Variable	Resectable	Nonresectable	*P* value
Age	58.5	62.0	0.26
Male sex	8	28	0.76
Smoking	2	2	0.56
DM II	5	15	1.00
HTN	3	10	0.72
IHD	1	3	1.00
BMI	26.1	24.3	0.33
Abdominal pain	9	27	0.54
Duration of pain (months)	8.3	6.4	0.46
Vomiting	2	14	0.10
Duration of vomiting (months)	2.5	7.3	0.01
Anorexia	3	12	0.52
Duration of anorexia (months)	17.3	5.8	0.26
Weight loss	9	17	0.37
Amount of weight loss (kg)	8.0	12.1	0.25
Jaundice	13	29	0.47
Dark urine	2	0	0.06
Itching	4	10	1.00
Ascites	0	3	0.55
Hemoglobin (g/dL)	10.6	11.9	0.05
Platelets (×103/mL)	272	252	0.49
INR	1.4	1.2	0.67
AST (U/L)	124	86	0.31
ALT (U/L)	154	154	1.00
ALP (U/L)	351	414	0.42
Total bilirubin (μmol/L)	96.6	135.1	0.27
CA 19-9 (U/mL)	107	5448	0.01
CEA (ng/mL)	5.7	196	0.28

ALP: Alkaline phosphatase, ALT: Alanine transaminase, AST: Aspartate aminotransferase, BMI: Body mass index, CA 19-9: Carbohydrate antigen 19-9, CEA: Carcinoembryonic antigen, DM: Diabetes mellitus, HTN: Hypertension, IHD: Ischemic heart disease, INR: International normalized ratio

would be important to identify variables, or a combination of variables that would be predictive of resectable pancreatic adenocarcinoma.

In our study we used the strict criterion of a histological diagnosis of adenocarcinoma. The majority of the cases were diagnosed through EUS-guided FNA (57.7%) and ultrasound-guided FNA (32.7%). EUS-guided FNA is an attractive modality for the diagnosis of pancreatic lesions given that it is a relatively safe and less invasive procedure compared with other modalities but one of its major drawbacks is that it requires dedicated training and might not be a wide spread technique in the Gulf Cooperation Council region. A study from Oman that attempted to describe the sensitivity of EUS-guided FNA in the evaluation of pancreatic masses included only 27 cases with adenocarcinoma of the pancreas from a single center over a 6-year period,[12] whereas a second similar study from Saudi Arabia only included 11 cases over 3 years.[13] However, neither of these studies[12,13] described the clinical characteristics of these patients within their case series.

The mean age of patients with pancreatic head masses in the cohort by Aziz *et al*.,[11] was 53 years, which is much less compared with our cohort (61 years) but that is expected as they excluded patients with significant comorbidities. A second paper[14] from the same institution and overlapping the same time period[11] described the presentation, characteristics, and the perioperative complications of patients who underwent a pancreatoduodenectomy for both benign and malignant conditions but only included 14 cases with pancreatic cancer. The largest cohort reported from the region to date is from AlGhamdi *et al*.,[3] which included 179 patients with pancreatic tumors over a 10-year period; 132 of those had adenocarcinomas. The median age in the cohort was 63 years and despite that the cohort of AlGhamdi *et al*.,[3] had similar characteristics to ours with regard to the gender of the patients and the prevalence of smoking (16.2% vs. 11.4%) and diabetes (57.5% vs. 52.6%), respectively; our cohort presented more frequently with abdominal

pain (66.7% vs. 39.1%), jaundice (77.8% vs. 15.6%), weight loss (48.2% vs. 16.2%), and the tumor being located in the head of the pancreas (83.6% vs. 68.2%) but were less likely to have stage III/IV disease (66.7% vs. 74.7%), respectively. The main aim of the study of AlGhamdi *et al*.[3] was to determine factors associated with an increased median overall survival, whereas that of ours was to find clinical predictors of resectability. Nonetheless, the paper by AlGhamdi *et al*.[3] adds important information to the presentation of patients with pancreatic tumors in Saudi Arabia.

None of the historical variables evaluated in the study could predict resectability of pancreatic adenocarcinoma. Although this finding my well be due to being underpowered, a cohort of 355 patients studied by Raptis *et al*.[7] did not find much effect for the duration of symptoms where they only found a marginal survival benefit when assessing the time from the beginning of symptoms to referral to a specialist with a hazard ratio (HR) of 1.001 (95% CI, 1.001-1.002) ($P = 0.02$).[7] This finding might suggest that the duration of symptoms do not correlate with the stage of disease.

The same study did not find any effect on the probability of survival based on gender or age, nor on the presentation with jaundice, abdominal pain, or weight loss.[7] A second study comprised of 214 patients with histologically proven pancreatic adenocarcinoma found that those who had undergone resection tended to be younger (62.1 vs. 64.0, $P = 0.047$), and less symptomatic (97.8% vs. 99.8%, $P = 0.018$)[15] but as the values suggest, these appear to be of statistical rather than clinically significant differences.

A case–control study from Mayo Clinic comprised of 736 cases and 1875 controls found a higher proportion of new-onset diabetes in patients diagnosed with pancreatic adenocarcinoma compared with controls up to 3 years prior to the diagnosis of pancreatic cancer.[16] In their study, they did not find any association between resectability and the presence or the duration of diabetes, thus in keeping with the results by Souza *et al*.,[17] where they found no association between the presence of diabetes or its duration with the stage or resectability of pancreatic adenocarcinoma.

In our study, the only variable that was found to have a prognostic value in assessing the resectability of pancreatic adenocarcinoma was the hemoglobin level OR 0.65 (95% CI, 0.42-0.98) with a higher value predicting unresectability. Although this finding might be a mere statistical one there is data in the literature that might explain this finding and shed light on its biological plausibility. A study looking at the serum levels of erythropoietin in patients with pancreatic ductal adenocarcinoma found that higher levels of erythropoietin had a worse prognosis regardless of the stage of the disease,[18] but the study did not find a negative effect associated with the hemoglobin level.[18] A study by Ruiz-Tovar *et al*.[19] found that preoperative levels of hemoglobin <12 g/dL as well as the presence of abdominal pain were associated with a poor prognosis and although this finding may differ from ours but so does the patient population included in this study as the cohort described had undergone surgery, which indicates that these were all thought to be resectable tumors. This was also replicated in another cohort of 302 patients with pancreatic adenocarcinoma.[20] These studies might implicate that the finding that a higher level of hemoglobin is associated with unresectable disease is plausible as higher levels of erythropoietin have been proved to be associated with a worse prognosis but has not been studied in the prediction of resectability. Nonetheless, this variable was only significant on univariable analysis and not on multivariable analysis, which might indicate a hidden confounder and thus warrants further investigation.

Numerous investigators have attempted to use tumor markers in the prediction of resectability of pancreatic cancer. A study by Kim *et al*.[21] attempted at assessing the use of CA 19-9 in predicting the resectability of pancreatic adenocarcinoma and estimated that a CA 19-9 level of ≤92.77 U/mL in addition to tumor size best predicted resectability. And, a second group from Taiwan found that a CA 19-9 level of 37 U/mL was an independent predictor of resectability.[15] In a group of 51 patients who were initially thought to have resectable disease based on imaging but only a third were found to be resectable, a CA 19-9 level of 256.4 U/mL was found to have a specificity of 92.3% and a sensitivity of 82.4%.[22] A study by Fujioka *et al*.[23] found that when both CA 19-9 and CEA were negative, the OR for curative resection was 4.43. Our data demonstrated that a CA 19-9 value of 166 ng/mL had a sensitivity of 89%, specificity of 75%, positive likelihood ratio of 3.6 and a negative likelihood ratio of 0.15 for the prognostication of resectability of pancreatic adenocarcinoma. This figure lies in the range reported by many studies.

There are potential reasons for limitations of these markers in practice. A high serum bilirubin level can confound measurements of CA 19-9[24] as well as 5-10% of patients with pancreatic cancer have normal CA 19-9 serum levels due to their Sialyl-Lewis negative state.[24] Furthermore, elevated CA 19-9 levels have been found in non-malignant conditions.[25]

The study does have a number of limitations, some of which are inherited due to the study design being retrospective in nature limiting some of the information that might contribute to residual confounding. Also, we lack clinical outcomes of these patients with regards to morbidity as well as mortality and survival.

CONCLUSION

None of the clinical or the laboratory variables that were included in our study could predict resectability of pancreatic adenocarcinoma on multivariable analysis. Further studies are warranted to validate these results.

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