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Drain Amylase Level as a Predictor for Postoperative Pancreatic Fistula after Pancreaticoduodenectomy for Periampullary Carcinoma

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ABSTRACT

Background: Resection of periampullary carcinoma can be performed in fifty to sixty percent of people, although pancreatic cancer resection is a viable treatment option in ten to twenty percent of cases. Periampullary carcinoma has a more favorable prognosis after surgical resection. About 0.2% of all gastrointestinal tumors are periampullary adenocarcinoma (PAAC), which involve adenocarcinoma (AC) of the pancreatic head, the distal common bile duct (CBD), the second portion of the duodenum, plus the ampulla of Vater. Although relatively uncommon, the incidence of periampullary tumors has been on the rise in recent years.

Aim of the work: This study aimed to determine the most important predictors of fistula formation after pancreaticoduodenectomy for periampullary carcinoma.

Methods: This was observational study that included 20 individuals to undergo pancreaticoduodenectomy for periampullary carcinoma in Helwan University Hospitals.

Results: There was highly significant variation among the two groups concerning drain amylase plus drain lipase**.**

Conclusion: Comprehensive care to achieve POPF reduction is essential for individuals with greater drain amylase levels, which were associated with a higher fistula risk grade. Future research must involve a multicenter investigation to validate as well as to standardize amylase levels.

Keywords: Pancreatoduodenectomy, Pancreatic fistula, Pancreatic cancer, Preoperative inflammatory biomarkers, Postoperative day 1 drains amylase values.

INTRODUCTION

Resection of periampullary carcinoma can be performed in fifty to sixty percent of people, although pancreatic cancer resection is a viable treatment option in ten to twenty percent of cases. Periampullary carcinoma has a more favorable prognosis after surgical resection, with 5-year relative longevity of 37% to 68%, compared to ten to twenty percent for resectable pancreatic adenocarcinoma & twenty-five percent to fifty-nine percent for resectable duodenal cancer [(1)].

The most reliable clinical diagnostic tools available today are computed tomography (CT) scans as well as magnetic resonance imaging cholangiopancreatography (MRCP) scans. Other diagnostic procedures, such as endoscopic ultrasonography besides endoscopic retrograde cholangiopancreatography (ERCP), both of which enable sample collection also, as a result, histological subtyping [(2)].

Several other prognostic variables, such as TNM stage, depth of infiltration (T stage), lymphovascular invasion, regional lymph node involvement (N stage), tumor differentiation, & positive surgical margins, have been postulated for relapse. Nevertheless, the majority of these prognostic factors are contested, primarily mainly because the research that mattered were either inadequately powered or excluded malignancies other than periampullary. 76.5 to 89.4% of periampullary carcinomas are amenable to curative resection. Survival at five years was 62.8%. After three years, long-term survival can be anticipated [(3)].

The purpose of the work was to determine which variables most strongly predicted recurrence after pancreaticoduodenectomy for periampullary carcinoma.

MATERIAL and METHODS

This observational research that was conducted in Helwan University hospitals comprised 20 people to undergo pancreaticoduodenectomy for periampullary carcinoma.

Inclusion criteria: Periampullary carcinoma & non-metastatic tumors.

Exclusion criteria: Malignant tumours other than periampullary carcinoma, such as pancreatic ductal adenocarcinoma, malignant intraductal papillary-mucinous neoplasm (IPMN), pancreatic islet cell carcinoma (pancreatic mucinous cystic neoplasms), distal CBD carcinoma (cholangiocarcinoma), as well as cancer of the duodenum treated by potentially curative pancreaticoduodenectomy and Metastases.

Preoperative data: The preparatory procedures that follow variables were investigated: Cancer diagnosis based on gender & age, weight, BMI, as well as performance status (WHO score) [(4)].

The following laboratory & imaging studies results were obtained from individuals files: Complete blood count, basic metabolic profile, liver function tests, coagulation profile, electrocardiogram, plus echocardiogram, tumour markers (CA 19-9, carcinoembryonic antigen (CEA), abdominal ultrasound, and high-quality computed tomography (CT). Criteria for tumour resectability evaluation necessitate thin incisions. Metastatic workup included chest CT or CXR. Besides, endoscopic ultrasound (EUS) is performed to assess if there was any vascular invasions. **Surgical procedure:** All Individuals underwent pancreaticoduodenectomy for periampullary carcinoma [(5)].

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Postoperative data: All Individuals were subjected to follow-up examinations every 3 months for 1 year. At each subsequent appointment, a thorough physical examination was performed, blood chemistry, tumor markers, and triple-phase CT for recurrence detection. If any patient dies during follow up we enrolled another one instead. Also, postoperative complications like wound infection. Post-pancreatectomy hemorrhage (PPH), postoperative pancreatic fistula (POPF), bile leak & delayed gastric emptying (DGE) was detected during hospitalization & recorded [(6)].

Pathologists analysed tumours that were surgically removed. Assessment included the degree of differentiation, depth of infiltration (T stage), regional lymph node involvement (N stage), metastatic status (M stage), perineural spread, resection margin status (R0 & R1), vascular invasion and posterior margin invasion plus size of the tumor [(7)].

Ethical consideration: The research protocol was approved by Faculty of Medicine Helwan University Research Ethics Committee. All participants signed informed consents before inclusion in the study. An Informed consent was obtained from children caregivers/guardians before taking any data or doing any physical examination. All the data were strictly confidential (for research purpose only). All research procedures were carried out according to the Declaration of Helsinki.

Statistical Analysis: After collecting, reviewing, as well as coding the data, they were entered into the Statistical Package for Social Science (IBM SPSS) version 20. The quantitative data were given as mean ± standard deviations, and ranges when their distribution was found to be parametric. The qualitative data were presented as a number & a percentage of the total. The Chi-square test, or the Fisher exact test in place of the Chi-square test when the predicted count in any cell was discovered to be under 5, was utilised in order to do a comparison among two groups whose data consisted of qualitative information. The Independent t-test was used to make the comparison among two different groups, each of which had quantitative data plus a parametric distribution. It was decided that a margin of error of 5% would be acceptable, besides the confidence interval would be set to 95%. Therefore, the p-value was taken into consideration to be significant.

RESULTS

This observational study included 20 individuals to undergo pancreaticoduodenectomy for periampullary carcinoma. The mean age was 51.45 ± 8.22 years. The study included 15 men & 5 women, the mean weight was 68.00 ± 8.08 kg, the mean height was 1.58 ± 0.12 m, and the mean BMI was 27.68 ± 4.54 kg/m^2 (Table 1).

Table (1): Description of the cases according to age, sex, weight, height as well as BMI

		No.= 20
Age	Mean ± SD	51.45 ± 8.22
Sex	Female Male	5 (25.0%) 15 (75.0%)
Weight	Mean ± SD	68.00 ± 8.08
Height	Mean ± SD	1.58 ± 0.12
BMI	Mean ± SD	27.68 ± 4.54

There was no significant variance between the 2 groups regarding demographic data, co-morbidity & risk factor (Table 2).

Table (2): Comparison among non-fistula (no. =12) & fistula (no. =8) regarding demographic data, co-morbidity & risk factors

		No fistula	**Fistula**	**Test value**	**P-value**	**Sig.**
		No.= 12	**No.= 8**			
Age	Mean ± SD	49.92 ± 8.56	53.75 ± 7.61	-1.023	0.320	NS
Sex	Female Male	4 (33.3%) 8 (66.7%)	1 (12.5%) 7 (87.5%)	1.111	0.292	NS
Weight	Mean ± SD	67.00 ± 6.81	69.50 ± 10.00	-0.668	0.513	NS
Height	Mean ± SD	1.55 ± 0.11	1.63 ± 0.11	-1.552	0.138	NS
BMI	Mean ± SD	28.43 ± 4.50	26.56 ± 4.66	0.895	0.383	NS
Diabetes		2 (16.7%)	3 (37.5%)	1.111	0.292	NS
Hypertension		2 (16.7%)	2 (25.0%)	0.208	0.648	NS
Smoking		3 (25.0%)	3 (37.5%)	0.357	0.550	NS
Performance state	ECOG (0-1) ECOG (2) ECOG (3)	8 (66.7%) 3 (25.0%) 1 (8.3%)	7 (87.5%) 1 (12.5%) 0 (0.0%)	1.319	0.517	NS
Family history		3 (25.0%)	1 (12.5%)	0.469	0.494	NS

P-value >0.05: Non significant (NS); P-value <0.05: Significant(S); P-value< 0.01: highly significant (HS) *: Chi-square test, •: Independent t-test

There was significant variation in the groups concerning albumin & ALP. Also, there was no significant variance in the groups concerning HB, WBCs, platelets, ALT, AST, bilirubin, ALP & INR, CA 19-9 (U/mL) & CEA (ng/mL) (Table 3).

Table (3): Analogy amongst non-fistulas (no =12) & fistula (no. =8) regarding lab investigations, CA 19-9 (U/mL) plus CEA (ng/mL)

		No fistula	Fistula	Test value•	P-value	Sig.
		No.= 12	No.= 8			
HB	Mean ± SD	9.94 ± 0.88	10.60 ± 0.73	-1.754	0.096	NS
Wbcs	Mean ± SD	5.78 ± 1.33	6.25 ± 1.78	-0.406	0.689	NS
Platelets	Mean ± SD	134.75 ± 4.75	148.50 ±56.85	-0.605	0.553	NS
Albumin	Mean ± SD	3.88 ± 0.68	3.25 ± 0.62	2.111	0.039	S
ALT	Mean ± SD	42.67 ± 5.54	36.13 ± 5.55	0.480	0.637	NS
AST	Mean ± SD	27.92 ± 5.89	39.13 ± 8.66	-1.128	0.274	NS
Bilirubin	Mean ± SD	6.17 ± 1.75	7.38 ± 1.20	-1.367	0.189	NS
ALP	Mean ± SD	190.00 ± 11.04	204.08 ± 16.84	-2.270	0.036	S
INR	Mean ± SD	1.17 ± 0.21	1.33 ± 0.34	-1.238	0.232	NS
CA 19-9 (U/mL)	< 37 > 37	7 (58.3%) 5 (41.7%)	1 (12.5%) 7 (87.5%)	4.201	0.060	NS
CEA (ng/mL)	< 5 > 5	8 (66.7%) 4 (33.3%)	3 (37.5%) 5 (62.5%)	1.650	0.199	NS

There was no significant distinction between the groups as regards CA 19-9 (U/mL), CEA (ng/mL) & radiological investigations (Table 4).

Table (4): Analogy among non-fistula (no. =12) & fistula (no. =8) regarding radiological investigations

		No fistula		Fistula		Test value*	P-value	Sig.
		No.	%	No.	%			
ERCP	CBD dilatation <7 ml	0	0.0%	2	25.0%	3.333	0.088	NS
	CBD dilatation > 7 ml	12	100.0%	6	75.0%			
EUS finding						–	–	–
Tumor	Yes	12	100.0%	8	100.0%	NA	NA	–
	No	0	0.0%	0	0.0%			
CT finding						–	–	–
LN enlargement	Yes	7	58.3%	3	37.5%	8.333	0.361	NS
	No	5	41.7%	5	62.5%			
Perimpullary mass	Yes	9	75.0%	6	75.0%	0.000	1.000	NS
	No	3	25.0%	2	25.0%			
MRI finding						–	–	–
MPD dilatation<5 mm		2	16.7%	3	37.5%	1.111	0.292	NS
MPD dilatation> 5mm		10	83.3%	5	62.5%			
Perimpullary mass	Yes	12	100.0%	8	100.0%	NA	NA	–
	No	0	0.0%	0	0.0%			
Ultrasound	Dilated CBD	12	100.0%	8	100.0%	NA	NA	–

There was no significant disparity in the groups regarding time of operation, blood loss & type of pancreatic anatomists (Table 5).

Table (5): Analogy among Non fistula (no. =12) & Fistula (no. =8) regarding Intra Operation Events

Intra Operation Events		No fistula No.= 12	Fistula No.= 8	Test value	P-value	Sig.
Time of operation	Mean ± SD	6.30 ± 1.01	6.11 ± 1.01	0.406	0.690	NS
Blood loss	Mean ± SD	671.66 ± 182.97	534.62 ± 135.29	3.269	0.087	NS
Type of pancreatic anatomists	Duct to mucosa with stenting	5 (41.7%)	5 (62.5%)	0.833	0.361	NS
	Duct tomucosa Without stenting	7 (58.3%)	3 (37.5%)			

There was highly significant variance found among groups regarding drain amylase & drain lipase (Table 6).

Table (6): Analogy among Non-fistula (no. =12) & Fistula (no. =8) regarding Drain Amylase

		No fistula No.= 12	Fistula No.= 8	Test value•	P-value	Sig.
Drain Amylase				–	–	–
Day 1	Mean ± SD	118.33 ± 44.48	618.75 ± 192.61	76.872	0.001	HS
Day 3	Mean ± SD	83.75 ± 41.29	950.00 ± 478.09	40.051	0.001	HS
Day 5	Mean ± SD	69.58 ± 21.58	5062.50 ± 1781.60	96.918	0.001	HS

DISCUSSION

Ampullary cancer is extremely uncommon, making up only 0.5% of GI tumours & 30% of tumours that necessitate a PD. Because of its proximity to the ampulla, ampullary cancer tends to present with relatively few symptoms or signs, making for easier discovery as well as diagnosis than other periampullary malignancies. There is a high recurrence probability of up to 50% after surgical resection of ampullary cancer, although even in T1 disease, there is a 30% rate of lymph node (LN) metastases [8]. The goal of the work was to determine the most important predictors of fistula formation after pancreaticoduodenectomy for periampullary carcinoma.

In our research we identified 4 people (20 %) with +ve family history of pancreatic cancers. Similarly, study done by **Tersmette *et al.*** [9] Showed that as much as 10% of individuals with pancreatic cancer report a family history of pancreatic cancer.

Our study showed 12 (60%) people with elevated CA 19-9 more than 37 (U/mL). Also, there was 9 individuals (45%) with CEA more than 5 (ng/mL). **Park *et al.*** [10] illustrated that the percentage of people with periampullary cancer plus increased serum CA 19-9 & CEA concentrations was 65.2% and 24.1% correspondingly. Similarly, **Song *et al.*** [8] found that EUS had a higher rate of correct T staging than MR (87.8%) as well as a lower rate of under-staging (2.4%) in individuals included in their study.

Regarding CT finding, LN enlargement was present in 75.0% among recurrence group. Regarding regional lymph node involvement, 50 % were positive by histopathology.

The current research showed that average operative period was 6.23 ± 0.99 hours, however in study done by **Dang *et al.*** [11], the mean operative time was 250 ± 50 mins. In other study done by **Wang *et al.*** [12], a total of 427 minutes were spent in surgery on average. Also, this short operative time may be because of these types of surgery done by well-trained doctors in high volume centers. According to **Junrungsee *et al.*** [13] who looked at the results of surgery for periampullary cancer as well as identified characteristics predictive of individual survival. They reported that majority of recurrent individuals had poor performance status after recurrence was detected.

In our research, there was no significant variance in no-recurrence & recurrence groups regarding CA 19-9. **Zakaria *et al.*** [14] sought to determine the role of various clinicopathological parameters playing in post-PD survival for PAAC. According to their findings, increased CA 19-9 (> 400 U/ml) posed a risk for poor survival in univariate analysis, which was consistent with those of prior research. It's possible that this is because our study only followed them for a year. **Smeenk *et al.*** [15] reported prognostic variables following R-0 resection for malignancies of the pancreatic head & ampulla. Fifty-five percent of those diagnosed with intrapancreatic perineural growth also experienced preoperative discomfort, while 41% of those diagnosed with preoperative pain had perineural growth. These results imply that intrapancreatic perineural development is not necessarily the root cause of discomfort. In fact, discomfort is sometimes regarded as a sign of advanced tumour growth beyond the limits of the pancreas since it is thought to originate from tumour infiltration into extrapancreatic (retropancreatic) splanchnic nerves.

After surgery, depth of tumour infiltration has been reported to be a predictive indicator for ampulla of Vater malignancies [3]. **Zhao *et al.*** [16] stated in their research that after pancreatic head resection, perineural infiltration was found to be a major prognostic factor that was linked to local failure. There was a strong

correlation among perineural invasion & death within a year [17]. **Zakaria *et al.* [14]** reported that, a significant independent risk factor for poor overall survival (OS) was the presence of perineural invasion.

This research demonstrated that there was no significant variance between groups regarding posterior margin invasion. The present research showed that there was no significant variance between groups regarding size of tumor. **Junrungsee *et al.* [13]** mentioned that the high-risk people from their research refer to the individuals who had poor prognostic factors such as large tumor size of more than 2 cm. Other research found that tumour size was a significant predictor of patient survival [12]. The poor OS mentioned in the research by **Al-Jumayli *et al.* [18]** was probably caused by the rapid spread of tumours. The likelihood of a complete microscopic clearance decreases as the tumour advances along pancreatic nerves as well as infiltrates distally to follow an artery channel [19]. Consistent with the findings of other authors' survival analyses, this one found that people whose original tumours were particularly big (pT3/4), low-grade (pN1), or highly malignant (pM1) had a much higher probability of passing away [20].

Regarding the pancreatic anastomosis, 50 % were duct to mucosa with stinting as well as 50 % were duct to mucosa without stinting. The present research showed no statistically significant variance in postoperative pancreatic fistula (POPF) in stenting & non-stenting group. According to **Zhao *et al.* [16]**, although the meta-analysis showed no significant difference in postoperative complication rates among PD with internal & PD with exterior stents, the use of internal stents may be preferable during drainage tube management in the postoperative period. Additionally, internal stents may aid digestion by decreasing the loss of digestive fluids.

Early detection of pancreatic fistula is important in our study we used drain amylase level for early prediction of POPF. We found that drain amylase level in post-operative day 1 more than 500 U/l was highly significant of fistula. Also, in day 5 eliminate amylase level more than 5000 U/l was highly significant of fistula. **Teixeira *et al.* [21]** showed that the amylase value in drain fluid obtained early after pancreatoduodenectomies can be used to both predict the development of pancreatic fistula as well as correlate with the severity of this complication. Because it helps direct postoperative care and identify individuals who need to be treated under close observation, this simple test should be used consistently in hospitals that do this operation.

CONCLUSIONS

In individuals whose drain amylase was associated with a greater fistula risk grade, a holistic approach to POPF prevention is essential. In the future, there will likely be a need for multicenter research to validate as well as to standardize amylase levels**.**

DECLARATIONS

- **Consent for Publication:** All authors agreed to submit the manuscript.
- **Availability of data & material:** Available.
- **Competing interests:** None.
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- **Conflicts of Interest:** Authors declare no conflicts of interest.

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