Evaluation Of Diagnostic Performance Of Amylase And Lipase In Pre-Operative Pancreatic Ductal Adenocarcinoma

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Abstract :

Background: CEA and CA 19.9 are most common markers used in clinical practice in management of PDAC. Preoperative serum CA19-9 and CEA level are closely related with survival time in PC patients and therefore may be used for evaluating the prognosis for PDAC. Now, the question posed in this study was whether the pancreatic enzymes lipase and amylase add significance towards increasing diagnostic and prognostic efficacy of PDAC furthermore. Thus, this study is planned to explore whether measured amylase and lipase can lead to statistically significant improvement in the diagnostic and prognostic efficacy of PDAC.

Methods : The study includes 50 clinically diagnosed and confirmed cases of PDAC. 50 age and sex matched healthy volunteers were selected and used for comparison of result. ROC analysis of CA-19.9 and CEA was the major statistical analysis to find cut-off. Sensitivity, specificity, accuracy, PPV and NPV of CEA, CA19.9, amylase and lipase were calculated in PDAC to know their diagnostic efficacy.

Results : Increased serum lipase and amylase with increased LAR indicates pancreatic duct blockage while decreased serum lipase and serum amylase with increased LAR may hint for pancreatic insufficiency.

Conclusions : Preoperative amylase and lipase levels and the calculation of the LAR at the time of localized pancreatic cancer diagnosis might be helpful in the risk assessment in surgically resectable pancreatic cancer.

Keywords : Carcinoembryonic antigen, Carbohydrate Antigen 19–9, Pancreatic Ductal Adenocarcinoma, Amylase, Lipase etc.

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INTRODUCTION :

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive malignancy. It is the most deadly among all gastrointestinal cancers.(1) As per Globocan 2022, pancreatic cancer remains 23rd in incidence with 13,661 new cases (0.97 % of all cancer cases). It remains 18th in rank in terms of mortality with 12,759 deaths. (1.4 % of all cancer deaths).(2-4)

The 5-year survival rate for all stages of PDAC is only 7% due to late diagnosis and dismal prognosis. Only potentially curative treatment option is surgical resection, partly combined with neo-adjuvant and/or adjuvant chemotherapy or radiotherapy. However, only 15%–20% of all patients are eligible for this treatment option as at the time of diagnosis the disease is in advanced stage.(5) Only a small number of parameters, apart from radiological examinations are currently employed to predict clinical outcome of disease. Currently, serum carbohydrate antigen 19-9 (CA 19.9) is the most common and validated diagnostic tumor marker for PDAC used in clinical practice. There are many studies that shown a correlation between the level of CA19-9 and the survival rate of patients with advanced disease.(6,7) However, it has some limitations due to its poor predictive value in patient with no symptoms. On other hand, CA 19-9 can be elevated in acute cholangitis, pancreatitis, obstructive jaundice and liver cirrhosis. Additionally, Lewis-negative blood type patient do not produce CA 19-9 levels, thus contributing to false negativity. (8,9)

CEA is overexpressed in 30-60% of patients with PDAC. There are many studies that suggested CEA as an independent predictor of poor survival rates in patients with PDAC.(10). However, due to its poor sensitivity, it is inferior to CA 19.9 in prediction of treatment response and prognostication of PDAC. Many clinicians prefer to use CA 19.9 and CEA in combination to increase diagnostic and prognostic efficacy of PDAC. (11,12)

Now, the question posed in this study was whether the pancreatic enzymes lipase and amylase add significance towards increasing diagnostic and prognostic efficacy of PDAC furthermore.

Elevated serum levels of pancreatic enzymes are frequently used for the diagnosis of pancreatic diseases especially acute pancreatitis. However, alterations in their serum level are also possible with other pancreatic conditions. Further, their significance with respect to cancer patients is hardly considered yet. Thus, this study is planned to explore whether measured amylase and lipase levels can lead to a statistically significant improvement in the diagnostic and prognostic efficacy of PDAC.

MATERIALS AND METHODS :

The present cross-sectional study was conducted at Government Medical College and Cancer Hospital, Chhatrapati Sambhajinagar. The study population included 50 clinically diagnosed and confirmed cases of pancreatic ductal adenocarcinoma (PDAC). 50 age and sex matched healthy volunteers between age 18 to 60 were selected and used for comparison of result. The blood samples of PDAC patients admitted in ICU or Wards at Government Medical College and Cancer Hospital, Chhatrapati Sambhajinagar were collected after diagnosis but before surgical resection. The estimation of carbohydrate antigen 19.9 and CEA were carried out on fully automated chemiluminescent immune analyzer using principle of CLIA while estimation of amylase and lipase were carried out on fully automated chemistry analyzer.

Estimation of CA 19.9 : Estimation of CA19.9 was carried out on fully automated chemiluminescent immune analyzer working on principle of two site sandwich chemiluminescent immunoassay (CLIA). In first step, test sample, paramagnetic micro-particles coated with monoclonal anti-CA 19.9 antibody and monoclonal anti-CA 19.9 antibody-alkaline phosphate conjugate were added into a reaction cuvette. After incubation, CA 19.9 present in the test sample binds to both anti-CA 19.9 antibody coated micro-particles and anti-CA 19.9 antibody-alkaline phosphate conjugate to form a sandwich complex. Micro-particle was magnetically captured while other unbound substances were removed by washing. In second step, the substrate solution was added to reaction cuvette. The substrate was catalyzed by anti-CA 19.9 antibody-alkaline phosphatase conjugate in the immune-complex retained on the micro-particle. The resulting chemiluminescent reaction was measured as relative light units (RLUs) by the photomultiplier built into the system. The amount of CA 19.9 present in the test sample was proportional to relative light units (RLUs) generated during the reaction. The CA 19.9 concentration determined via a calibration curve and produced automatically by the instrument.

Estimation of CEA :. Estimation of CEA was carried out on fully automated chemiluminescent immune analyzer working on principle of two site sandwich chemiluminescent immunoassay (CLIA). In first step, test sample, paramagnetic micro-particles coated with monoclonal anti-CEA antibody and monoclonal anti-CEA antibody-alkaline phosphate conjugate were added into a reaction cuvette. After incubation, CEA present in the test sample binds to both anti-CEA antibody coated micro-particles and anti-CEA antibody-alkaline phosphate conjugate to form a sandwich complex. Micro-particles were magnetically captured while other unbound substances were removed by washing. In second step, the substrate solution was added to reaction cuvette. The substrate was catalysed by anti-CEA antibody-alkaline phosphatase conjugate in the immune-complex retained on the micro-particle. The resulting chemiluminescent reaction was measured as relative light units (RLUs) by the photomultiplier built into the system. The amount of CEA present in the test sample is proportional to relative light units (RLUs) generated during the reaction. The CEA concentration can be determined via a calibration curve.

Estimation of Amylase : Serum amylase activity was estimated by using System Pack on fully automated clinical chemistry analyzer. Serum amylase act on substrate, 2-Chloro-4-nitrophenol-α-maltotrioside (CNP-G3) to form colored chromophore, 2-Chloro-4-nitrophenol. The kinetic of color formation (production of chromophore, 2-Chloro-4-nitrophenol) was directly proportional to amylase activity and measured at 415

nm. The results were calculated automatically by the instrument. The results were expressed in U/L.

Estimation of Lipase : Serum lipase activity was estimated by using System Pack on fully automated clinical chemistry analyzer. Pancreatic lipase cleaves colorimetric substrate 1,2-o-dilauryl-rac-glycero-3-glutaric acid – (6-methylresorufin)-ester to produce chromophore methylresorufin. The kinetic of color formation (production of chromophore methylresorufin) was directly proportional to lipase activity and measured at 580 nm. The results were calculated automatically by the instrument. The results were expressed in U/L.

Inclusion criteria: Patients with age between 18 to 60, both sex, tobacco addicts, tobacco non-addicts, alcoholics but diagnosed with pancreatic ductal adenocarcinoma were included in the study.

Exclusion criteria: Patients with age < 18 and > 60, patients with any other type of cancer and other pancreatic conditions such as acute and chronic pancreatitis were excluded from the study group.

Statistical analysis : In this study, receiver operating characteris AUC = 0.958 s of CA-19.9 and CEA were the major statistical analysis to find diagnostic efficacy of CEA and CA19.9 in PDAC in order to know whether CEA in combination with CA19.9 helps in early detection of PDAC and helps to reduce dismal prognosis. The area under curve (AUC) was calculated for each marker using ROC curve. Other statistical parameters were calculated by appropriate statistical formulae.

RESULTS :

The mean, median and standard deviation for CA19.9 and CEA are provided in table 1 while mean, median and standard deviation for amylase and lipase are provided in table 2.

Expression of CA 19.9 and CEA in PDAC

In our study, we estimated levels of CA 19.9 and CEA in both PDAC patients and healthy controls. We found that with compared to controls, level of CEA get less significantly ($p<0.1$) elevated in PDAC patients.(Table-1)

Cases	CA 19.9 (U/ml)			CEA (ng/ml)		
	Mean	Median	SD	Mean	Median	SD
PDAC (n=50)	444.44	75.06	980.61	33.76	5.23	121.2
Control (n=50)	15.54	17.30	10.61	2.94	3.36	1.54

Table 1. Serum levels of CEA and CA 19.9 in normal controls and PDAC

However, compared to controls, level of CA 19.9 get significantly ($p<0.001$) elevated in PDAC patients.(Table-1)

Expression of Amylase and Lipase in PDAC

We also estimated levels of amylase and lipase in both PDAC patients and healthy controls. We found that with compared to controls, level of amylase get significantly ($p<0.0001$) elevated in PDAC patients.(Table-2)

Cases	Amylase (U/L)			Lipase (U/L)		
	Mean	Median	SD	Mean	Median	SD
PDAC (n=50)	90.7	87.5	39.52	114.34	117	36.47
Control (n=50)	48.08	43.5	17.64	39.18	38	12.34

Table 2. Serum levels of amylase and lipase in normal controls and PDAC

Similarly, compared to controls, level of lipase also get significantly ($p<0.0001$) elevated in PDAC patients.(Table-2)

Diagnostic performance of CEA and CA19.9 are shown in table 3 while that of amylase and lipase are shown in table 4.

Diagnostic efficacy of CA 19.9 and CEA in PDAC

Now, to find diagnostic efficacy of CEA and CA19.9, receiver operator characteristic (ROC) curves for CA 19.9 and CEA for PDAC versus healthy controls are obtained by plotting sensitivity versus 1-specificity.

To measure diagnostic performance of CEA, we used a cut-off of 5.00 ng/ml. At this cut-off, area under curve (AUC) found 0.876 (Asymptotic 95 % CI, 0.770-0.982). With this cut-off, sensitivity of CEA we found from study is 56.00 % (95 % CI, 41.25 % to 70.01 %) while specificity we found is 98.00 % (95 % CI, 89.35 % to 99.95 %). The positive predictive value stands 96.55 %

(95 % CI, 79.84 % to 99.50 %) while negative predictive value stands 69.01 % (95 % CI, 61.91 % to 75.32 %). (Table-3)

Marker	Sensitivity	Specificity	Accuracy	AUC	Positive Predictive Value	Negative Predictive Value
CA 19.9	76.00 %	94.00 %	85.00 %	0.911	92.68 %	79.66 %
CEA	56.00 %	98.00 %	77.00 %	0.876	96.55 %	69.01 %

Table 3. Diagnostic performance of CEA and CA 19.9

Now, to measure diagnostic performance of CA 19.9, we used a cut-off of 30.4 U/ml. At this cut-off, area under curve (AUC) found 0.911 (Asymptotic 95 % CI, 0.850- 0.971).

With this cut-off, sensitivity of CA 19.9 we found from study is 76.00 % (95 % CI, 61.83 % to 86.94 %) while specificity we found is 94.00 % (95 % CI, 83.45 % to 98.75 %).The positive predictive value stands 92.68 % (95 % CI, 80.70 % to 97.46 %) while negative predictive value stands 79.66 % (95 % CI, 70.41 % to 86.57 %). (Table-3)

The diagnostic accuracy of CA 19.9 is found 85.00 % (95 % CI, 76.47 % to 91.35 %) while that for CEA found 77.00 % (95 % CI, 67.51 % to 84.83 %).

Diagnostic efficacy of amylase and lipase in PDAC

To measure diagnostic performance of amylase and lipase, upper limit of normal range is considered. The upper normal limit considered for amylase and lipase are 80 U/L and 100 U/L respectively.

Marker	Sensitivity	Specificity	Accuracy	Positive Predictive Value	Negative Predictive Value
Amylase	56.00 %	94.00 %	75.00 %	90.32 %	68.12 %
Lipase	68.00 %	100.00 %	84.00 %	100.00 %	75.76 %

Table 4. Diagnostic performance of amylase and lipase

By considering these levels as cut-off, the sensitivity and specificity of amylase are 56.00 % (95 % CI, 41.25 % to 70.01 %) and 94.00 % (95 % CI, 83.45 % to 98.75 %) while the sensitivity and specificity of lipase are 68.00 % (95 % CI, 53.30 % to 80.48 %) and 100.0 % (95 % CI, 92.89 % to 100.00 %). Positive predictive value (PPV) and negative predictive value (NPV) of amylase stands 90.32 % (95 % CI, 75.20 % to 96.64 %) and 68.12 % (95 % CI, 60.79 % to 74.64 %) respectively. Positive predictive value (PPV) and negative predictive value (NPV) of lipase stands 100 % (95 % CI, 92.89 % to 100.00 %) and 75.76 % (95 % CI, 67.60 % to 82.40 %) respectively. (Table-4)

The diagnostic accuracy of amylase is found 75.00 % (95 % CI, 65.34 % to 83.12 %) and while that for lipase is found 84.00 % (95 % CI, 75.32 % to 90.57 %). The lipase amylase ratio (LAR) found in PDAC is 1.36 (Range 1.3-2.23) while that in control is 0.83 (Range 0.69-1.05).

DISCUSSION :

Sensitivity is the proportion of true positive results out of all subjects with a disease selected for study. Thus, it is the ability of a test to yield a positive result for a subjects that has that disease. On other hand, specificity is the proportion of true negative results out of all subjects who do not have a disease selected for study. In other words, it is the ability of the test to obtain normal range or negative results for a person who does not have that disease.(13-15)

Jacob Shreffler and Martin R. Huecker denoted that sensitivity and specificity are inversely related: as sensitivity increases, specificity tends to decrease, and vice versa.(16)

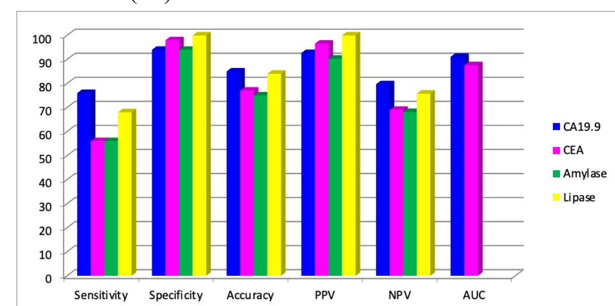

Figure 1: Diagnostic Performances of CA19.9, CEA, Amylase and Lipase in PDAC

Our results matches with opinion of Jacob Shreffler and Martin R. Huecker. In our result, CA 19.9 is more sensitive than CEA but CEA is more specific than CA 19.9.(Figure-1,Table-3)

Now, highly sensitive tests will lead to positive findings for patients with a disease, whereas highly specific tests will leads to finding of patients with no disease.(16) Thus, sensitivity and specificity together provide a holistic picture of a diagnostic test. For a test to be novel marker, it should be highly sensitive as well as highly specific.

Now, similar to previous study in this study also, we found CA 19.9 is more sensitive than CEA (Sensitivity 76.00 % vs 56.00 %). While CEA is more specific than CA 19.9 (Specificity 98.00 % vs 94.00 %) (Figure-1).

As per this study, comparing diagnostic efficacy of CA 19.9 (AUC = 0.911, accuracy = 85%) and CEA (AUC = 0.876, accuracy = 77.00 %), it is found that CA 19.9 have slightly higher diagnostic accuracy than CEA. (Figure-1)

As sensitivity and specificity together provide a holistic picture, CEA and CA 19.9 combination can provide better diagnostic accuracy than used any alone. On other hand, CA 19.9 has some limitations due to its poor predictive value while CEA get less significantly ($p<0.1$) elevated in PDAC patients in early stages but its level correlate with tumor size and increases as tumor size increases. Thus, if used in combination can provide better diagnostic accuracy.

We found lipase is more sensitive as well as specific than amylase (Sensitivity 68.00 % vs 56.00 % and Specificity 100.00 % vs 94.00 %). We found this contrary to opinion of Jacob Shreffler and Martin R. Huecker.(Figure-1). Further, lipase also have more accuracy than amylase. Anil Kumar and Sangeeta Kapoor in their study shown that sensitivity and specificity of amylase were 62.8% and 99.2% while that of lipase were 96.1% and 99.1% respectively in diagnosis of acute pancreatitis. Further, they shown that serum lipase had better diagnostic accuracy as compared to serum amylase in diagnosis of acute pancreatitis.(17) However, there is a scarcity of data indicating that a measurement of either lipase or amylase or both can be used as a diagnostic or prognostic tool in pancreatic cancer patients. Gultepe et.al. have shown that lowered lipase levels close to zero might represent a potential indicator for pancreatic cancer. (18) On other hand, Ventrucci et. al. found a highly variable enzyme behavior with low serum lipase levels (10%) and high serum lipase levels (25%) in patients with pancreatic cancer and thus they concluded that pancreatic enzymes might have no added diagnostic value in pancreatic cancer patients.(19-20) Our result matches with opinion of Anil Kumar and Sangeeta Kapoor and we find that serum lipase has better diagnostic accuracy as compared to serum amylase but in PDAC. However, use of amylase and lipase for diagnosis of PDAC is doubtful. This is because similar to Ventrucci et al., we find serum lipase and serum amylase increased in few patients while decreased in others. Some patients also show no alteration in their serum levels.

Now, increased CA 19.9 level especially, increased CEA with increased CA 19.9 level is correlated with tumor size. We found increased amylase and lipase in some patients with increased CEA while in some patients we found amylase and lipase decreased with increased CEA. Thus, we found there is no any specific correlation between CEA and amylase or CEA and lipase. Now, an increase in amylase and lipase in PDAC found primarily due to obstruction of pancreatic duct by growing tumor causing enzyme backup and leakage into the bloodstream. Sometimes, the increase may due to production of these enzymes by tumor cell itself (paraneoplastic effect). On other hand, decrease in amylase and lipase in PDAC found due to pancreatic atrophy and fibrosis caused by PDAC that leads to reduction in overall number of healthy acinar cells, which are the specific cells responsible for producing amylase and lipase.

As the tumor grows and invades the pancreas, it replaces healthy, enzyme-producing tissue with non-functional cancerous and connective tissue. This physical destruction diminishes overall capacity of pancreas to synthesize and secrete digestive enzymes.(21)

When lipase amylase ratio (LAR) is considered, we found that LAR in every healthy individual found below 1.0. The mean ± SD of LAR in healthy individual was 0.82 ± 0.48. Now, LAR in every PDAC individual found above 1.0. The mean ± SD of LAR in PDAC was 1.36 ± 1.83.

Many researcher have shown that fluctuation in lipase is greater than amylase. In case of elevation, elevation in lipase level is greater than elevation in amylase as former is more sensitive. In case of decreased level, decrease in lipase is more than decrease in amylase level. Some researcher already shown that low lipase levels close to zero may be an indication of pancreatic cancer.

CONCLUSION :

Our study found that, the non-invasive measurement of preoperative amylase and lipase levels and the calculation of the LAR at the time of localized pancreatic cancer diagnosis might be helpful in the risk assessment in surgically resectable pancreatic cancer. Increased serum lipase and serum amylase with increased LAR indicates pancreatic duct blockage while

decreased serum lipase and serum amylase with increased LAR may hint for pancreatic insufficiency. However, worth exploration is required for clearing exact role of LAR in pancreatic cancer as individual role of serum amylase and lipase for monitoring PDAC is not still clear.

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