Diagnostic Role of Platelet Lymphocyte Ratio(PLR) in Pancreatic Head Masses

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Received: 18 January 2011 / Accepted: 4 March 2012 / Published online: 27 March 2012
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Abstract Masses in and around pancreas constitute an important clinical entity in gastrointestinal surgical practice. Most common being adenocarcinoma of head of pancreas followed by inflammatory masses due to chronic pancreatitis. Accurate diagnosis is of central importance as therapeutic strategies range from observation to complete surgical removal including total pancreatectomy. Several tumor markers are available which could help in prognostication and diagnosis of carcinoma pancreas. Carbohydrate antigen 19-9(CA 19-9) is traditionally accepted best marker available. The role of new tumor marker platelet lymphocyte ratio (PLR) has been defined recently in prognostication of carcinoma pancreas. Role of PLR in diagnosing and its efficacy after combining it with CA 19-9 is not known. The aim of study was to assess the demographics of histologically proven neoplastic and inflammatory pancreatic head masses in our department. To assess the role of CA19-9 and platelet lymphocyte ratio(PLR) in determining nature of pancreatic head mass. Data consisted of histologically proven 45 patients .23 having head mass due to chronic pancreatitis and 22 because of neoplastic lesions. Demographics in terms of age, sex, previous pain episodes, presence of jaundice, history of alcohol intake were compared in both groups. Also tumor markers CA 19-9 and PLR individually and in combination were compared in both groups. Cancer pancreas significantly ($p<0.001$) occurred in older age

group, was significantly associated with jaundice ($p=0.005$) and weight loss ($p<0.001$). Accuracy in diagnosis of cancer pancreas was similar with CA 19-9 and PLR (68.89 %), where as combining CA 19-9 with PLR showed increased sensitivity(81.82 %) and accuracy(71.11 %) in diagnosing cancer pancreas. Other combinations showed no advantage. PLR is at least as good as CA 19-9 as diagnostic marker to differentiate between malignant and inflammatory head mass of pancreas.

Keywords Pancreatic head mass · Platelet lymphocyte ratio · PLR · CA 19-9

Introduction

Masses in and around the pancreas constitute an important clinical entity in gastrointestinal surgical practice. Most common being adenocarcinoma of the head of pancreas followed by the inflammatory masses due to chronic pancreatitis.

Accurate diagnosis is of central importance, as therapeutic strategies range from observation to complete surgical removal including total pancreatectomy. Several tumor markers are available that can help in prognostication and diagnosis of pancreatic cancer.

Carbohydrate antigen 19–9 (CA19-9) is traditionally accepted as the best marker available. In recent review, median sensitivity of CA19-9 for pancreatic cancer was 79 % (70–90 %), whereas the median specificity was 82 % (68–91 %) [1]. Goonnetilleke and Siriwardena [1] stated that CA19-9 should be used “in contemporary algorithms for the diagnosis of pancreatic cancer”. The diagnostic role in assessing the accuracy of CA19-9 in differentiating inflammatory head masses in chronic pancreatitis from superimposed carcinomas on chronic pancreatitis has recently been assessed in 84 consecutive patients who had mass lesions in chronic pancreatitis. The sensitivity and specificity of CA19-9 was

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68 % and 70 %, respectively which is less than the values observed in carcinoma developing in normal pancreas [2].

The role of new tumor marker platelet lymphocyte ratio (PLR) has been defined recently in prognostication of carcinoma pancreas [3]. This is based on the fact that pancreatic cancer causes thrombocytosis and lymphocytopenia.

Lymphocytopenia occurs due to systemic inflammation caused by cancers that release a number of inhibitory immunologic mediators, most notably interleukin-10 (IL-10) and transforming growth factor-beta. These result in significant immunosuppressive effect with consequent impaired lymphocyte function [4]. Pancreatic cancer cells directly secrete these two (IL-10 & TGF β) inhibitory cytokines [5].

Lymphocytopenia has been shown previously to be associated more strongly with pancreatic adenocarcinoma when compared with gastric and colorectal cancer [6], suggesting that pancreatic malignancy is associated with a more marked host inflammatory response than other gastrointestinal cancers.

A reduced number of tumor-infiltrating lymphocytes in resected pancreatic adenocarcinoma specimens have also been found to be associated with poorer survival rates after surgery [7]. Lymphocyte trapping within peritumoral fibrous tissue is believed to be an additional factor by which pancreatic cancer cells evade immune surveillance [10].

Thrombocytosis occurs because of the fact that pancreatic cancer commonly causes a hypercoagulable state resulting in a predisposition to thromboembolic events [8]. A number of proinflammatory mediators (notably IL-1, IL-3, and IL-6) are known to stimulate megakaryocyte proliferation [11]; therefore, the association between a relative thrombocytosis and adverse overall survival in pancreatic cancer might be explained on the basis that the platelet count reflects an additional index of systemic inflammation elicited by the tumor.

Smith et al. [3] in their retrospective study suggested that preoperative PLR reflects an index of tumor invasiveness and merits prospective evaluation as an adjunct to CA19-9 in determining the requirement for laparoscopic staging in patients with potentially resectable periaampullary malignancy.

Same authors [9] also evaluated preoperative PLR as an independent significant prognostic marker in periaampullary carcinoma, as higher values of PLR were associated with lower median survival.

PLR is being recognized as a systemic marker to predict invasiveness of the tumor.

Combining both CA19-9 and PLR may increase the positive predictive value of the resectability of the pancreatic tumor.

Its role in differentiating benign from malignant lesions remains unknown.

Aim

1. To assess the demographics of histologically proven neoplastic and inflammatory pancreatic head masses in our department.
2. To assess the role of CA19-9 and PLR in diagnosis and management of pancreatic head masses.

Methods

Prospective study conducted in period ranging from June 2008 to May 2010. The patients admitted in Surgical Gastroenterology ward of Bangalore Medical College and Research institute were included.

Inclusion criteria were as follows:

- Impression of mass of pancreatic head on imaging indicated by the presence of abrupt focal change in gland thickness or thickness more than 2 cm of pancreatic head (2 cm being widely accepted as normal thickness of pancreatic head).

Exclusion criteria were as follows:

- Patients having clinical or biochemical evidence of cholangitis.
- Head masses where pathological evidence of the nature of the mass is not available.

(This would include inflammatory head masses where conservative management is considered to be adequate.)

Demographics of the admitted patients were noted. Relevant history such as jaundice, weight loss (>10 % in the last 3–6 months considered significant), previous attack of pancreatitis, significant alcohol intake were noted (equivalent of 80 g or more of ethanol/day for at least 5 years).

Patients admitted with a mass in the head of pancreas were subjected to blood investigations.

- Complete blood count
- Liver function tests
- CA19-9
- PLR
- Immunoglobulin G4 (IgG4) – where indicated

The following imaging studies were performed:

- Transabdominal ultrasound
- Doppler to see the status of vessels – where indicated.
- Contrast enhanced computed tomogram (CECT) abdomen (pancreas protocol CT), that is, triphasic CT with arterial, pancreatic parenchymal, and portal phase.
- MRI/MRCP – where indicated; for example, for diagnostic dilemma where CT cannot be done due to poor renal status or in conditions like pregnancy.
 - Upper gastrointestinal endoscopy – end/side viewing scopy.

- Endoscopic retrograde cholangiopancreatography (ERCP) – where indicated; for example, for diagnostic dilemma and where stenting is needed for palliation.
- Endoscopic ultrasound (EUS) – where indicated; for example, where diagnostic dilemma about the nature of pancreatic head mass is present with other imaging techniques and EUS-guided fine needle aspiration cytology (FNAC) can be taken.
- FNAC – Endoscopic ultrasound guided or CT guided percutaneous for masses of indeterminate etiology and metastatic tumors where chemotherapy would require pathologic confirmation.

All the patients were subjected to ultrasound and CECT (pancreas protocol) and upper GI endoscopy. Other tests were selectively used where indicated.

Statistical Methods

A descriptive statistical analysis was carried out in the present study. Results on continuous measurements were presented on mean $\pm$ SD (min-max) and results on categorical measurements were presented in number (%). Significance was assessed at 5 % level of significance. Student *t* test (two-tailed, independent) was used to find the significance of study parameters on continuous scale between two groups. Intergroup analysis chi-square/Fisher Exact test was used to find the significance of the study parameters on categorical scale between two or more groups. Diagnostic statistics viz. sensitivity, specificity, PPV, NPV, and accuracy were computed to find the correlation of cancer of pancreas. ROC curve analysis of CA19-9 and PLR was carried out to establish the diagnostic marker of these with the cancer of pancreas.

The statistical softwares, namely SPSS 15.0, Stata 8.0, MedCalc 9.0.1, and Systat 11.0 were used for the analysis of the data.

Observations and Results

Study comprised 45 patients. Of them 23 patients had pancreatic head mass due to chronic pancreatitis and 22 patients had head mass due to neoplastic lesions of the pancreas.

Demographics of study population are shown in Table 1. In this study, pathological diagnosis was present in all the patients. Of the 23 patients with chronic pancreatitis, diagnosis was confirmed by Frey's procedure in 20 and through pancreaticoduodenectomy in 2 because of the diagnostic dilemma. In 1 patient, diagnosis was confirmed using EUS-guided biopsy and by follow-up CECT that showed decrease in the size of the head mass (Table 2).

Table 1 Demographics of study population

Age in years	Number of patients	Cancer of pancreas	%	Chronic pancreatitis	%
18-20	2	0	0.0	2	8.7
21-30	8	1	4.5	7	30.4
31-40	6	3	13.6	3	13.0
41-50	13	5	22.7	8	34.8
51-60	8	5	22.7	3	13.0
61-70	8	8	36.4	0	0.0
Total	45	22	100.0	23	100.0
Male	32	15	68.2	17	73.9
Female	13	7	31.8	6	26.1

Of the 22 patients with cancer of pancreas, biopsy confirmation was done in 10 resectable patients using pancreaticoduodenectomy, in 8 patients with locally advanced carcinoma head of pancreas (LA Ca HOP), triple bypass was done and intraoperative core biopsy was taken from pancreatic head mass.

Of the 4 patients with metastatic disease, 3 were subjected to CT-guided FNAC from liver metastasis and in 1 patient intraoperative biopsy from pancreatic head mass and peritoneal nodule was taken (Table 3).

Various variables were studied between two groups (Table 4) that included platelet, neutrophil, and lymphocyte count along with values of tumor markers CA19-9 and PLR.

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of various tumor markers were studied (Table 5).

- CA19-9 was seen with various cutoffs.
- PLR at >150 , marked thrombocytosis ($>4 \text{ L/mm}^3$)
- Marked lymphocytopenia ($<1000/\text{mm}^3$)
- Combination of PLR with CA19-9.

The results showed mean lymphocyte count as $1730.77 \pm 715.80/\text{mm}^3$ in cancer of pancreas, which was lower than the value in chronic pancreatitis, that is, $1996.30 \pm 523.13/\text{mm}^3$. Although the absolute count was lower, difference did not attain statistical significance ($P=0.161$).

Marked lymphopenia (<1000) was seen in 3 (13.6 %) patients. All were having neoplastic lesions. One with locally advanced carcinoma of head of pancreas, one with

Table 2 Management in headmass due to chronic pancreatitis

Chronic pancreatitis	N=23
Frey's	20
pancreaticoduodenectomy	2
Observation with EUS guided biopsy	1

Table 3 Management in headmass due to cancer pancreatitis

LA AdenoCa HOP	8	Triple Bypass with core tissue biopsy
AdenoCa HOP	6	Pancreaticoduodenectomy
Ampullary adeno Ca infiltrating duodenum	2	Pancreaticoduodenectomy
Metastatic Ca HOP	4	CT guided FNAC from Liver nodules with CBD stenting in 3 and Triple Bypass with intraoperative biopsy in 1
Mucinous Neoplasm HOP	1	Pancreaticoduodenectomy
NET Of HOP	1	Pancreaticoduodenectomy

resectable carcinoma of head of pancreas, and one with ampullary carcinoma invading duodenum.

Mean platelet count was $2.76 \text{ L} \pm 1.06 \text{ L/mm}^3$ in the cancer group as compared with $2.58 \text{ L} \pm 1.38 \text{ L/mm}^3$ in the chronic pancreatitis group, difference being statistically insignificant ($P=0.625$).

Marked thrombocytosis ($>4 \text{ L}$) was seen in 8 patients. Of them 4 were patients with chronic pancreatitis and 4 (18 %) were cancer patients.

PLR (when cutoff taken as 150) was taken as the marker to differentiate cancer from chronic pancreatitis. Sensitivity, specificity, PPV, NPV, and accuracy were 63.64 %, 73.91 %, 70.00 %, 60.00 %, and 68.89 %.

CA19-9 was seen in this study at various cutoff levels to see its effect.

Sensitivity, specificity, PPV, NPV, and accuracy at a cutoff 37 U/mL was 59.09 %, 78.26 %, 72.22 %, 66.67 %, and 68.89 % ($P=0.011$).

At cutoff 100 U/mL these values were 50.00, 95.65, 91.67, 66.67, and 73.33 ($P=0.001$).

At cutoff 300 U/mL these values were 40.91, 100.0, 100.0, 63.89, and 71.11 ($P=0.001$).

Combination of CA19-9 and PLR was evaluated. With this combination Sensitivity, Specificity, PPV, NPV, and

accuracy of 81.82 %, 60.87 %, 66.67, 77.78, and 71.11, respectively ($P=0.003$).

Discussion

An inflammatory mass due to chronic pancreatitis and masses due to pancreatic carcinoma are the two most common causes of mass formation of head of pancreas.

Various parameters such as elderly patient, history of significant weight loss, and high bilirubin level have been described to differentiate malignant from inflammatory head mass of the pancreas.

Similar results were found in current study where age, weight loss, and bilirubin level were highly significant in differentiating both the conditions.

Other hematological parameters that were assessed in the two groups in this study were platelet and lymphocyte counts.

Taking only the absolute lymphocyte count and platelet count into consideration yielded poor results as tumor markers. Even marked lymphocytopenia and marked thrombocytosis cannot be used as tumor markers because of poor accuracy.

Combining both the hematologic indices as Platelet lymphocyte ratio (PLR) reflects a novel marker.

Initially evaluated by Smith et al. in 2008 [3], this marker is being used for prognostic purpose in the cancer of pancreas. In their study to evaluate whether the preoperative PLR improve the predictive value of CA19-9 levels in stratifying a patient group with suspected periampullary malignancy who do not require staging laparoscopy, they observed that in 263 patients, the positive and negative predictive values for resectability, sensitivity, and specificity for CA19-9 levels $<150 \text{ kU/L}$ were 83 %, 36 %, 51 %, and 73 %, respectively. For PLR <150 , these levels were 81 %, 38 %, 51 %, and 72 %, respectively.

Table 4 Variables studied between two groups

Study variables	Chronic pancreatitis	Cancer of pancreas	P value
Age in years, mean $\pm$ Sd	37.43 $\pm$ 12.57	53.36 $\pm$ 11.64	<0.001
Gender; male : Female	17:6	15:7	0.672
Alcoholic; No (%)	13 (56.5%)	6(27.3 %)	0.047
Jaundice; No (%)	5(21.7 %)	15(68.2 %)	0.005
Prev. attack of pancreatitis; No (%)	14(60.9 %)	0	<0.001
Weight loss; No (%)	3(13.0 %)	20(90.9 %)	<0.001
Bilirubin,(mg/dl) mean $\pm$ Sd	1.48 $\pm$ 1.41	9.95 $\pm$ 9.32	<0.001
Lymphocytes,(count/cumm) mean $\pm$ Sd	1996.30 $\pm$ 523.13	1730.77 $\pm$ 715.80	0.161
Platelet,(Lakhs/cumm) mean $\pm$ Sd	2.58 $\pm$ 1.38	2.76 $\pm$ 1.06	0.625
Neutrophils,(count/cumm) mean $\pm$ Sd	5528.65 $\pm$ 1756.99	6053.23 $\pm$ 2257.55	0.388
CA19-9(U/L) mean $\pm$ Sd	28.94 $\pm$ 9.60	36.83 $\pm$ 2054.54	0.076
PLR mean $\pm$ Sd	125.22 $\pm$ 16.74	191.25 $\pm$ 26.29	0.038

Table 5 Sensitivity, Specificity, positive predictive value and negative predictive value of various tumor markers at various cut off levels and combination of various tumor markers in differentiating carcinoma pancreas from chronic pancreatitis

	Sensitivity	Specificity	PPV	NPV	Accuracy	P value
a)CA19-9						
>37U/ml	59.09	78.26	72.22	66.67	68.89	0.011
>100	50.00	95.65	91.67	66.67	73.33	0.001
>200	50.00	95.65	91.67	66.67	73.33	0.001
>300	40.91	100.0	100.0	63.89	71.11	0.001
b)PLR > 150	63.64	73.91	70.00	60.00	68.89	0.011
c)Platelet > 4 L/cumm	18.13	82.61	50.00	51.33	51.11	1.000
d)Lymphocytes < 1000/cumm	13.64	100.00	100.00	54.76	57.78	0.109
e) CA19-9 & PLR	81.82	60.87	66.67	77.78	71.11	0.003

When combining the requirement for both CA19-9 levels and PLR to be <150 ($n=38$ of 183), both positive predictive value (95 %) and specificity (96 %) were improved.

They also observed that increasing T stage ($P=0.005$), vascular invasion ($P<0.001$), perineural invasion ($P=0.008$), and resection margin involvement ($P<0.001$) were all associated with greater preoperative PLR in resected periampullary adenocarcinoma.

In another study [9], the authors resected pancreatic ductal adenocarcinoma in 110 patients with periampullary carcinoma.

They observed that preoperative PLR was a more significant prognostic marker for overall survival ($P=0.001$) than either the lymphocyte count ($P=0.007$) or platelet count ($P=0.068$) on univariate Cox survival analysis.

The median overall survival in patients with a PLR of 150 or less ($n=48$) was 19.7 months, 13.7 months in those with a PLR of 151–300 ($n=43$), and 5.8 months in patients with a value of greater than 300 ($n=19$) (log-rank, $P=0.006$).

The preoperative PLR retained significance on multivariate analysis ($P<0.001$), along with tumor size ($P=0.010$) and lymph node ratio ($P=0.013$).

They also evaluated neutrophil-lymphocyte ratio as prognostic marker, but found it insignificant, although others like Bhatti et al. [12] found it better than PLR.

In the present study, PLR (when cutoff was taken as 150) was taken as the marker to differentiate cancer from chronic pancreatitis.

To the best of our knowledge, this is the first study that is using this parameter for this purpose.

The carbohydrate antigen 19–9 (CA19-9) has been a useful marker, both in diagnosis as well as follow-up of pancreatic cancer.

However, CA19-9 is also elevated in inflammatory lesions of the pancreas.

It is the most widely used serum marker for pancreatic cancer diagnosis. It has been reported to have a sensitivity of 70–90 % and a specificity of 70–98 % in various studies. Mostly, cutoff is considered at 37 U/mL. On increasing this

cutoff value, sensitivity of the test decreases, but specificity increases.

Similar results were seen in the present study. It was observed that on increasing the cutoff value specificity and PPV goes up, but sensitivity decreases and the overall accuracy also comes down.

Accuracy with all the cutoff levels was less than 80 % making it only a fair not a good test for diagnosing carcinoma pancreas.

Similar results were shown by Ramesh et al. [2]. In their study, sensitivity%, specificity%, PPV, and NPV of CA19-9 levels at various cutoff levels were assessed to differentiate between benign and malignant masses in chronic pancreatitis. The results of the study were as follows:

At 37 U/mL – 68, 70, 61, and 76; at 100 U/mL – 41, 86, 67, 68; at 300 U/mL – 15, 100, 100, 63, respectively.

CA19-9 levels can increase in presence of cholangitis. So, all the patients with clinical or biochemical evidence of cholangitis were excluded from the present study.

In this study, CA19-9 was elevated in 17.4% patients of chronic pancreatitis.

Results showed that there is a trend towards increase in sensitivity and increase in overall accuracy when PLR is combined with CA19-9 as compared with either tumor marker alone. When PLR alone was compared with CA19-9, it showed similar accuracy to CA19-9 as a tumor marker.

Hence, there is a case for combining CA19-9 with PLR to improve sensitivity for diagnosing cancer of pancreas. Also, PLR is a good replacement for CA19-9, which is a costly tumor marker.

Such combination has not been tried to diagnose cancer of the pancreas.

Hence, it was shown in the study that combining PLR and CA19-9 gave the most accurate result in diagnosing carcinoma of pancreas, although this should be confirmed through larger studies.

Combining PLR and CA19-9 also has a potential of diagnosing the development of carcinoma in the setting of preexisting chronic pancreatitis and differentiating malignant mass from inflammatory mass in such cases. This is

because altered ratio of platelets to lymphocytes is due to the factors that are released only in malignancy and not in benign condition.

This needs to be confirmed in well-designed larger studies.

Conclusion

In our study of 45 patients, 23 having head mass due to chronic pancreatitis and 22 having neoplastic head masses, we were able to show that new tumor marker, that is, PLR, which has been used for prognostic purpose till now, also has a diagnostic value.

PLR is at least as good as CA19-9 as diagnostic marker to differentiate between malignant and inflammatory head mass of pancreas.

Combining CA19-9 and PLR may increase the accuracy.

Role of PLR may be more useful in detecting carcinoma that developed over chronic pancreatitis, as CA19-9 is not very sensitive in these cases, but this aspect should be explored in further studies.

All the results of this study should be confirmed by additional studies involving larger sample size.

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