Impact of neutrophil/lymphocyte and platelet/lymphocyte ratios on patient survival in pancreatic cancer

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Abstract: Background: The value of various systemic inflammatory biomarkers has been studied across multiple cancers. These include albumin, neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR). We aimed to study multiple clinical characteristics and diagnostic tools and their correlation with overall survival time in a multiethnic community, with the goal to identify prognostic factors in patients with pancreatic cancer. **Methods:** Our study is a retrospective analysis of all patients diagnosed with histologically-proven pancreatic adenocarcinoma from 2004 to 2016 with at least 6 months of follow-up. Patients with AJCC stage I-II were labelled as early pancreatic cancer; those with Stage III-IV were grouped as advanced pancreatic cancer. The NLR was defined as the absolute neutrophil count in peripheral blood divided by the absolute lymphocyte count and PLR was defined as the platelet count divided by the absolute lymphocyte. Both ratios were calculated at time of diagnosis. **Results:** A total of 112 patients who had pancreatic duct adenocarcinoma were identified, 81 patients (72.3%) were males and 31 (27.7%) were females. The mean age at diagnosis was 55.6 ± 10.8 years. Out of the 112 patients, 34 (30.4%) were diagnoses as early pancreatic cancer and ultimately underwent surgery. The remaining 78 patients (69.6%) had advanced pancreatic disease. Mean follow up in patients with early pancreatic cancer was 2.2 ± 2.1 years; in the advanced cancer group, it was 1.3 ± 1.0 years. Undergoing an R0 resection was significantly related to improvement of overall survival in early stages while serum albumin and CA-19-9 were potential predictors of survival in advanced pancreatic cancer. **Conclusion:** We found a strong correlation between low levels of CA19-9, low CEA, high albumin and an R0 surgical resection with an improved overall patient and disease-free survivals in patients with pancreatic adenocarcinoma. NLR and PLR showed no relation to patient or disease-free survivals.

1. Introduction:

Pancreatic cancer is currently the fifth most common cancer worldwide and has the worst prognosis of all gastrointestinal cancers [1]. It is one of the leading causes of cancer related mortality and carries a poor prognosis with 5-year survival rate less than 5% [2, 3]. Various factors play a role in the prognosis including size, grade, lymph node, vascular and perineural invasion and whether or not the primary lesion is resectable[4]. In multiple studies it has been shown that inflammatory cells play a critical role in the pathophysiology of pancreatic tumors [5-7].

Chronic inflammation has been linked to cancer at many sites in the body whereby in it plays an important part in cancer growth, tissue invasion and metastasis. The tie between inflammation and cancer is an old concept first described by Virchow when he observed inflammatory cells within tumors [7]. This was later proven when a clear relationship was established between chronic pancreatitis and an increased chance in developing pancreatic cancer [8]. The value of various systemic inflammatory biomarkers has been studied across multiple cancers [9]. These include albumin, neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR) [10-12]. Due to this observed relationship between inflammation and cancer it is of interest to see to what extent this may play a role in the prognosis of patients with pancreatic cancer.

In our study, we analyzed multiple clinical characteristics and diagnostic tools and their correlation with overall survival time in a multiethnic community, with the goal to identify prognostic factors in patients with pancreatic cancer.

2. Patients and Methods:

Our study is a retrospective analysis of prospectively collected data at a tertiary hospital in

Qatar; Hamad General Hospital. The time period in our study was from March 2004 to September 2016 with at least 6 months of follow-up.

Study included patients with histologically-proven pancreatic adenocarcinoma. Patients diagnosed with pancreatic dysplasia, neuroendocrine tumors, cholangitis, and pancreatitis were excluded. Using our hepatobiliary multidisciplinary team registration database, we found 112 cases diagnosed with pancreatic cancer.

In patients who had suspected pancreatic cancer, diagnosis was done through biopsy and imaging. Staging was done using multi-detector contrast-enhanced computed tomography (MDCT) or magnetic resonance imaging (MRI) and fluorodeoxyglucose-positron emission tomography (FDG-PET). Patients were staged according to the American Joint Committee on Cancer (AJCC) staging system [13]. Patients with AJCC stage I-II were labelled as early pancreatic cancer; those with Stage III-IV were grouped as advanced pancreatic cancer [13].

Collected date points included patient age, sex, complete blood count with differential count (neutrophil, lymphocyte, and platelet count), liver function tests (ALT, AST, ALP, serum bilirubin, and serum albumin), and tumor marker (CA19-9 and CEA). Tumor characteristics were obtained either through radiology or on final post-operative tumor pathology; regarding tumor site, size, lymphatic and vascular invasion, lymph node involvement, perineural invasion, TNM classification, and tumor margins. Blood tests were collected at the time of diagnosis.

The NLR was defined as the absolute neutrophil count in peripheral blood divided by the absolute lymphocyte count and PLR was defined as the platelet count divided by the absolute lymphocyte. Both ratios were calculated at time of diagnosis. An NLR of 5 and PLR of 200 were used as cut off values [10, 14]. A cut-off value of 200 for Ca19-9 and 5 for CEA was used; additionally, an NLR was used of 5 and a PLR of 200 [9, 11, 12, 15-17].

Our retrospective study was approved by our institutes Ethical Committee for Human Research at Hamad Medical Corporation.

Statistical Analysis:

Data were summarized as mean ± standard deviation, or frequency (percentage) as appropriate. Categorical variables were analyzed using Chi-square or Fischer's exact test when appropriate and continuous variables analyzed using Mann-Whitney U test. Kaplan-Meier curve was used to draw survival of patients, and Cox proportional hazards regression was used in identifying prognostic facts in relation to patient survival. A P-value of 0.05 was used for statistical significance. SPSS software (SPSS Inc., Chicago, US, version 22) was used for analysis.

3. Results:

A total of 112 patients who had pancreatic duct adenocarcinoma were identified, 81 patients (72.3%) were males and 31 (27.7%) were females. The mean age at diagnosis was 55.6 ± 10.8 years. Out of the 112 patients, 34 (30.4%) were diagnoses as early pancreatic cancer and ultimately underwent surgery. The remaining 78 patients (69.6%) had advanced pancreatic disease. Mean follow up in patients with early pancreatic cancer was 2.2 ± 2.1 years; in the advanced cancer group, it was 1.3 ± 1.0 years.

Both groups of early and advanced pancreatic cancer were compared regarding several factors. Between the two groups, there was no statistically significant difference in relation to patient age and gender. Additional variables of interest including liver function tests, tumor markers and biochemical inflammatory markers at the time of diagnosis are summarized in table 1.

In relation to overall survival, univariate and multivariate cox regression analysis was done with respect to multiple variables. Early pancreatic cancer and advanced pancreatic cancer patients were separated and studied separately.

Early Pancreatic Cancer:

Univariate analysis was carried though to determine prognostic factors for patient survival. Age, Gender, tumor size, and vascular invasion were not significantly associated with outcome. Of the 34 patients 25 (22.3%) underwent an R0 resection and 9 (8.0%) patients had an R1 resection. Undergoing an R0 resection was significantly related to improvement of overall survival with a hazards ratio of 0.134 (0.026-0.687).

With respect to liver function tests; serum AST, ALT, ALP, bilirubin and albumin were not found to be significantly associated with overall survival on univariate analysis. Additionally, tumor marker Ca19-9>200 at the time of diagnosis failed to demonstrate statistical significance during univariate analysis, hazards ratio of 1.387(0.467-4.117) (P= 0.556).

PLR did not demonstrate any statistical significant impact on overall survival during univariate analysis. Multiple cut off values were used for NLR ranging from 2-6; however, none displayed any statistical significance on overall survival.

A summary of the statistical significance and Hazards ratio with 95% confidence interval concerning the above mentioned clinic-pathological parameters in early pancreatic cancer can be found in Table 2.

Advanced Pancreatic Cancer:

Age, Gender, NLR, and PLR at the time of diagnosis, all failed to show statistical significance concerning overall survival on univariate analysis.

Table 1: Characteristics of patients

Characteristics	Early Pancreatic Ca, N=34	Advanced Pancreatic Ca, N=78	p-value
Age	55.06 ± 9.79	55.77 ± 11.23	0.740
Gender Male Female	 25 9	 56 22	 0.852
NLR	3.47 ± 2.44	4.69 ± 4.17	0.058
PLR	199.59 ± 93.23	195.11 ± 116.64	0.830
ALT	166.89 ± 188.74	86.93 ± 115.93	0.040
AST	107.58 ± 103.31	62.41 ± 74.51	0.038
ALP	386.46 ± 308.94	259.81 ± 214.47	0.054
Bilirubin	98.70 ± 104.54	85.82 ± 117.59	0.590
Albumin	40.11 ± 7.65	36.34 ± 6.70	0.030
Ca 19-9	309.34 ± 673.87	4109.15 ± 5749.82	0.001
AFP	2.63 ±1.18	5.16 ± 14.48	0.299

Table 2: Association between clinic-pathologic parameters and overall survival in patients with early pancreatic cancer

Variable	HR (95%CI)	P-value
Age	0.989 (0.943-1.035)	0.640
Gender	0.862 (0.465-1.259)	0.871
R0 Resection	0.134 (0.026-0.687)	0.016
NLR>5	1.081 (0.909-1.285)	0.378
PLR>200	1.003 (0.998-1.008)	0.252
ALT	0.999 (0.996-1.002)	0.653
AST	1.001 (0.995-1.006)	0.760
ALP	1.001 (0.999-1.002)	0.448
Bilirubin	0.999 (0.994-1.004)	0.621
Albumin	1.023 (0.950-1.102)	0.548
Ca 19-9>200	1.387 (0.467-4.117)	0.556
AFP	1.139 (0.597-2.174)	0.693

Table 3: Association between clinic-pathologic parameters and overall survival in patients with advanced pancreatic cancer

Variable	Univariate Analysis		Multivariate Analysis	
	HR (95%CI)	P-value	HR (95%CI)	P-value
Age	1.014 (.994-1.035)	0.177		
Gender	0.971 (0.575-1.639)	0.912		
NLR>5	1.022 (0.974-1.073)	0.377		
PLR>200	1.001 (0.999-1.003)	0.237		
ALT	1.000 (0.998-1.002)	0.707		
AST	1.001 (0.998-1.004)	0.609		
ALP	1.000 (0.999-1.001)	0.846		
Bilirubin	1.001 (0.999-1.003)	0.552		
Albumin	0.953 (0.914-0.994)	0.027	0.967 (0.918-1.019)	0.212
Ca 19-9>200	1.456 (1.066-1.989)	0.018	1.198 (0.646-2.220)	0.566
AFP	1.006 (0.983-1.030)	0.602		

With respect to liver function tests, AST, ALT, ALP and bilirubin did not show any statistical significance in relation to patient survival. However, serum albumin at time of diagnosis showed statistical significance on univariate analysis, carrying a hazards ratio of 0.953(0.914-0.994).

Ca19-9 > 200, at the time of diagnosis, was associated with worse overall survival on univariate analysis, hazards ratio of 1.456(1.066-1.989).

Multivariate analysis:

Factors identified during univariate analysis were examined together under multivariate analysis, seeking significance concerning their prognostic value on patient survival.

Serum albumin levels failed to show statistical significant on multivariate analysis; hazards ratio of 0.967(0.918-1.019), (P =0.212). Additionally, tumor marker Ca19-9 >200 lost its significance; with a hazards ratio of 1.198(0.646-2.220), (P = 0.566). A summary of the statistical significance and Hazards ratio with 95% confidence interval concerning the above mentioned clinic-pathological parameters in advanced pancreatic cancer can be found in Table 2.

4. Discussion:

It is well known that pancreatic cancer has the worst prognosis among all gastrointestinal tumors. The survival outcome of pancreatic cancer patients is dependent not only on tumor characteristics but also on various patients' related factors. Relevant prognostic factors for pancreatic cancer includes; tumor size, stage and grade, surgical resection margins, serum tumor marker levels, and lymph node involvement [13, 14, 18].

In addition to the above mentioned factors, over the last few years interest has arisen surrounding systemic inflammatory markers and their prognostic value in different cancers including pancreatic cancer [9, 10]. The view that neutrophil to lymphocyte and platelet to lymphocyte ratio as predictors of prognosis have particularly peaked interest among inflammatory markers [10]. A few studies has focused upon NLR specifically; typically focusing on either operable cases only or advanced cases of pancreatic cancer [10-12, 15].

Pancreatic cancer approached via curative resection is noted to provide improved patient survival and decreasing morbidity and mortality. In a study by Lim JE et al they demonstrated that an R0 resection provided statistically significant improvement of overall survival; in addition they supported that tumor characteristics such as histological grade, tumor size, and lymph node metastasis all held statistically significant prognostic value [13]. The importance of an R0 resection is well known in literature and it has been demonstrated in several studies that surgical resection with clear margin status with or without small tumor size was associated with a better survival rate [19-21]. Collectively these all support our finding in our study that amongst patients undergoing resection, an R0 resection had a strong association with overall survival in concordance with the literature.

Several studies showed the prognostic value of histological grade of tumor, tumor size, and lymph node metastasis in pancreatic cancer[13, 22, 23]. In our study we found on univariate analysis that tumor size had no statistical significance on patient outcome.

With relation to tumor markers in a study by Sperti el[16] they found that patients with a preoperative CA19-9 level < 200 U/mL had a significantly better prognosis than those with CA19-9 > 200 U/mL and noted that it was an important independent prognostic parameter [16], similarly we used a cutoff value of 200. Various other studies have also supported the role of Ca19-9 as a prognostic factor, including a study by Maisy NR et al [24]. In a paper published by Ni et al, they reported that in addition to higher concentrations of CA19-9, CEA was also related to advanced pancreatic cancer and an overall poor prognosis for patients. Our study was in concordance with previous studies and we found that Ca 19-9 was a statistically significant prognostic indicator of overall survival in patients with advanced pancreatic cancer; however, lost its significance during multivariate analysis.

In respect to liver function tests their values generally held no statistically significant value in patients with early and advanced pancreatic cancer; however, serum albumin was significant in patients with advanced pancreatic cancer. Serum albumin continues to play an important role as a prognostic factor, and as seen in a study by Smith et al we too found a high serum albumin at time of diagnosis and follow up level to be associated with increased overall survival in patients with advanced pancreatic cancer[25]. Although among other liver function tests, we found no statistically significance in relation to AST, ALT, ALP and Bilirubin levels for patient with advanced pancreatic cancer. This is in disconcordance with other studies that too reported a prognostic value of ALP in patients with advanced pancreatic cancer [26].

The role of NLR and PLR has recently been brought under light as holding possible prognostic value, especially as inflammation is seen to play an integral role in tumor pathophysiology; albeit a multifactorial theory is hypothesized to explain the presumable changes seen in neutrophil, lymphocyte, and platelet counts. The changes seen are theorized to be in part due to an increase in granulocyte colony-stimulating factors, IL 1, IL 2, IL 6, IL 10, tumor necrosis factor A, transforming growth factor B; all of which are believed to eventually lead to neutrophilia, thrombocytopenia, and leukopenia [15]. This ultimately would lead to increased NLR and PLR ratios.

In a study by Asari et al it was demonstrated that in patients with pancreatic cancer a higher preoperative NLR and PLR were significantly associated with a poorer prognosis[17]. In multiple

studies carried out by Smith RA et al they demonstrated similarly to Asari that preoperative PLR was an independent predictor of survival [25, 27]. Our results are more in line with a study by Bhatti et al. in which we did not find a statistically significant value for PLR in its association with poorer survival [15]. Likewise, in our study NPR was not correlated with overall survival across neither early nor advanced pancreatic cancer.

Multiple papers use an NLR ratio of greater than 5 as a cutoff value when studying its prognostic value [11, 12, 15, 17]. In a paper by Guthrie et al, they reviewed multiple papers on the relationship between inflammatory markers and multiple types of cancers, the findings put forth was that different authors had used different cut off values to attain statistical significance [15]. We used 5 separate cut off values when studying NLR (2 to 6); however, we still did not attain a statistically significant relation with overall survival across either group.

In our study while we found statistical significance in key elements such as R0 resection, Albumin, and Ca 19-9; the lack of statistical significance found in our study pertaining to inflammatory markers brings to question of whether and/or how a positively NLR and PLR would have altered patient care and ultimately if there is clinical significance to these markers.

The value may however be in the additional use of NLR and PLR in companionship with multiple clinic-pathological, radiological, and biochemical markers in helping predict the resectability of pancreatic cancer. A prospective study though difficult may help in addressing if inflammatory markers can aid in predicting resectability of pancreatic cancer.

A weakness to our study was its retrospective nature. In addition it is noteworthy to mention our early starting point of 2004 and relatively recent end point of September 2016, which can play an important role in selection bias due to shorter follow up time of some patients.

Conclusion:

Conclusion: We found a strong correlation between low levels of CA19-9, low CEA, high albumin and an R0 surgical resection with an improved overall patient and disease-free survivals in patients with pancreatic adenocarcinoma. NLR and PLR showed no relation to patient or disease-free survivals.

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4/29/2019