PREOPERATIVE NEUTROPHIL TO LYMPHOCYTE RATIO (NLR) IS ASSOCIATED WITH REDUCED DISEASE-FREE SURVIVAL FOLLOWING CURATIVE RESECTION OF PANCREATIC ADENOCARCINOMA

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ABSTRACT

INTRODUCTION: Serological proinflammatory markers, such as C-reactive protein (CRP), neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have been associated with reduced survival for many different types of cancer. This study determined the prognostic value of these markers preoperatively in patients with resectable pancreatic adenocarcinoma.

METHODS: Patients undergoing consecutive pancreaticoduodenectomies for pancreatic ductal adenocarcinoma were entered into our database from 2001 to the present day. CRP, NLR and PLR at the time of presentation were recorded as well as overall and disease-free survival.

RESULTS: Seventy-four patients were identified. Overall median survival was 35.0 months and median disease free survival was 27.0 months. Follow-up ranged from 1 month to 1 to 125.8 months. Preoperative neutrophil to lymphocyte ratio (NLR) was significantly greater in those patients who developed recurrence in the follow-up period (4.5 versus 3.1). CRP and PLR were not found to differ significantly between the two groups. Kaplan-Meier survival analysis of patients with an NLR of greater than 5 demonstrated a disease-free survival of 12 months compared with 52 months for those patients with an NLR of <5 ($P<0.001$).

CONCLUSION: Preoperative NLR offers important prognostic information regarding disease-free survival following curative resection of pancreatic ductal adenocarcinoma.

INTRODUCTION

The link between inflammation and cancer was first proposed by Virchow in 1863 (1). In addition to chronic inflammation having a direct causal relationship with tumourogenesis; malignancies in themselves incite an inflammatory response in patients which is linked to many of the deleterious effects of cancers, such as weight loss (2). Survival for advanced cancers is linked to a complex interplay of cachexia, performance status and disease progression (2,3). These findings have been exploited in developing inflammatory and nutritional-status scores (such as the Glasgow Prognostic Score) for advanced inoperable pancreatic cancer (4). An inevitable progression from these findings has been the investigation of using inflammatory markers to predict survival in operable cancers. Preoperative blood-based assays such as C-reactive protein (CRP), neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have all been associated with reduced survival for many different types of cancer (2,3). At present, there is a relative paucity of data regarding the influence of these markers on survival following resection of pancreatic and periampullary cancers. The purpose of this study was to examine the predictive role of preoperative CRP, NLR and PLR in patients undergoing curative resection for periampullary malignancies.

METHODS

Patients undergoing consecutive pancreaticoduodenectomies for pancreatic ductal adenocarcinoma were retrospectively identified and entered into our

database from 2001 to the present day. Serological values such as liver function tests, full blood count and CRP at the time of presentation were recorded. All in-hospital and 30-day mortalities were excluded from further analysis. Patterns of recurrent disease were recorded as was overall median and disease-free survival (calculated from Kaplan-Meier survival curves). Median values for serological markers were compared between the survivors and patients with recurrent disease using the Students t-test. Further analysis of identified negative prognostic factors was undertaken using Kaplan-Meier survival curves and Cox Proportional Hazards Regression. A P value of <0.05 was considered significant. Medcalc^{TM} version 9.3 was used for all statistical calculations.

RESULTS

Seventy-four patients with curative resection of pancreatic ductal adenocarcinoma were identified and preoperative serology, tumour phenotype and tumour characteristics are summarized in Table 1. Overall median survival was 35.0 months and median disease-free survival 27.0 months. Follow-up ranged from 1 to 125.8 months. Median survival following detection of recurrent disease was 5.7 months (range of 1 to 23.2 months). The majority of patients presented with recurrence at multiple sites; with liver and lung metastases being a feature in over 70% of recurrences [Table 2]. The neutrophil to lymphocyte ratio (NLR) on pre-operative serology at the time of initial presentation was significantly greater in those patients who developed recurrence in the follow-up period (3.1 versus 4.5%) [Table 3]. Other markers of inflammatory response,

such as CRP, platelet count and platelet to lymphocyte ration (PLR) were not found to differ significantly between the two groups [Table 3]. Kaplan-Meier survival analysis of patients with an NLR of greater than 5% revealed a highly significant decreased disease-free survival of 12 months compared with 52 months for those patients with an NLR of <5% [Figure 1]. Other serological markers including CRP and PLR were not found to influence survival. On Cox proportional hazard regression, no independent risk factors for reduced survival were identified.

DISCUSSION

Despite relatively plentiful and robust data regarding proinflammatory serological markers for other types of cancers, their efficacy in determining survival for patients with periampullary malignancies has been reported to a lesser extent in the literature. Table 4 (4-16) summarises all the published data thus far. The possible clinical applications of these simple markers can be categorized into determining survival following resection; determining resectability of tumours or determining survival for patients with advanced cancers. Taken as a whole, the published studies overwhelming show that raised proinflammatory makers are linked to poor survival or unresectable disease. However, there is still considerable variation in which markers have been used and whether they have been found to be of value. Our study and Bhatti *et al* (6) did not find PLR to be associated with poorer survival, although four other studies from a single centre have found PLR to predict survival and resectability of periampullary

malignancies (5,7,8,10). The only published positive data on CRP and survival for resected pancreas cancers reported on *postoperative* CRP, which was found to influence survival.

Preoperative markers could serve a role in avoiding surgery in high-risk patients, whose blood tests place them in a poor prognostic survival group. This would require very robust data and most probably a combination of markers, such as those used in the Glasgow Prognostic Score, to exclude patients on the strength of preoperative blood test results. It would be difficult to use postoperative serological values (such as CRP) in making clinical decisions regarding the suitability of patients for surgery, although it could have an application in deriving a prognostic score determining adjuvant therapy for postoperative patients. Another possible application of CRP, PLR or NLR, could be in selecting patients for preoperative staging laparoscopy. At present, there exists significant variation between centers, with some laparoscopically staging all periampullary malignancies and others selectively staging or not staging at all. Raised NLR and PLR values have been associated with unresectablity both at open surgery (11) and at staging laparoscopy (10) and so could be used to increase the diagnostic yield of staging laparoscopy whilst avoiding unnecessary procedures in other patients.

The published data in patients with advanced periampullary cancers concentrate on CRP and NLR. Most studies report reduced survival associated with these

markers. These markers could be used to stratify patients in the context of chemotherapy trials, in addition to more traditional means such as radiological staging. They might also have a role in measuring response to treatment. Proinflammatory markers could also be used as a target for intervention rather than just a monitoring tool. Modulation of the inflammatory cascade could improve outcome or improve palliation. Pancreas cancer, in particular, is noted for the debilitating weight loss which many patients experience. Progression of the disease in patients has been noted to correlate with increasing CRP levels by up to 15mg/L per month (17). These changes accelerate as the patient approaches death and are linked with marked cachexia and a drop in performance status (17). In turn, nutritional supplements, such as fish oil administered to pancreatic cancer patients have been found to result in lower CRP levels when compared to non-treated controls (18). Such immunomodulation may reduce both weight loss and improve performance status in the palliation of patients with advanced pancreatic cancer.

CONCLUSION

NLR is associated with reduced disease-free survival in patients with resectable pancreatic adenocarcinoma. These findings are supported by other studies examining NLR and other proinflammatory markers (such as PLR and CRP) The optimum proinflammatory marker has yet to be determined and requires further study.

TABLES AND FIGURES

Table 1: Patient demographics, diagnosis, serology and tumour-related variables.

Table 2: Patterns of recurrence in resected patients.

Table 3: Comparison of serology between recurrence and non-recurrence groups.

Figure 1: Kaplan-Meier disease-free survival curves for patients with an NLR greater than 5 at diagnosis.

Table 4: Summary of published data

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			Number	%	Median	Range
Gender	Male		46	51.7	-	-
	Female		28	31.5	-	-
Age (years)			-	-	66	30 to 83
Serology at Presentation	CA19.9 (units/mL)		-	-	284	3 to 10000
	Bilirubin (µmol/L)		-	-	221	8 to 631
	WCC ($x10^9$/L)		-	-	7.8	11 to 27.9
	Lymph ($x10^9$/L)		-	-	1.5	0.05 to 3.7
	Neut ($x10^9$/L)		-	-	5.3	0.6 to 26
	NLR (%)		-	-	3.3	1.4 to 21.6
	CRP (mg/L)		-	-	11.0	<5 to 191
Tumour Characteristics	Lymph Node Status	Positive	44	59.5	-	-
		Negative	26	35.1	-	-
		No Data	4	5.4	-	-
	% Positive Lymph Nodes		-	-	12.5	0 to 61.5
	Tumour Size (mm)		-	-	30	15 to 85
	Grade	Well	9	12.2	-	-
		Moderate	32	43.2	-	-
		Poor	27	36.5	-	-
		No Data	6	8.1	-	-
	Microvessel Invasion	Yes	22	29.7	-	-
		No	42	58.1	-	-
		No Data	9.0	12.2	-	-
	Perineural Infiltration	Yes	44	39.7	-	-
		No	22	59.5	-	-
		No Data	8	10.8	-	-
	Resection Margin Positive	Yes	40	54.1	-	-
		No	27	36.5	-	-
		No Data	7	9.5	-	-
Chemotherapy Postoperatively		Yes	53	71.6	-	-
		No	9	12.2	-	-
		No Data	12	16.2	-	-

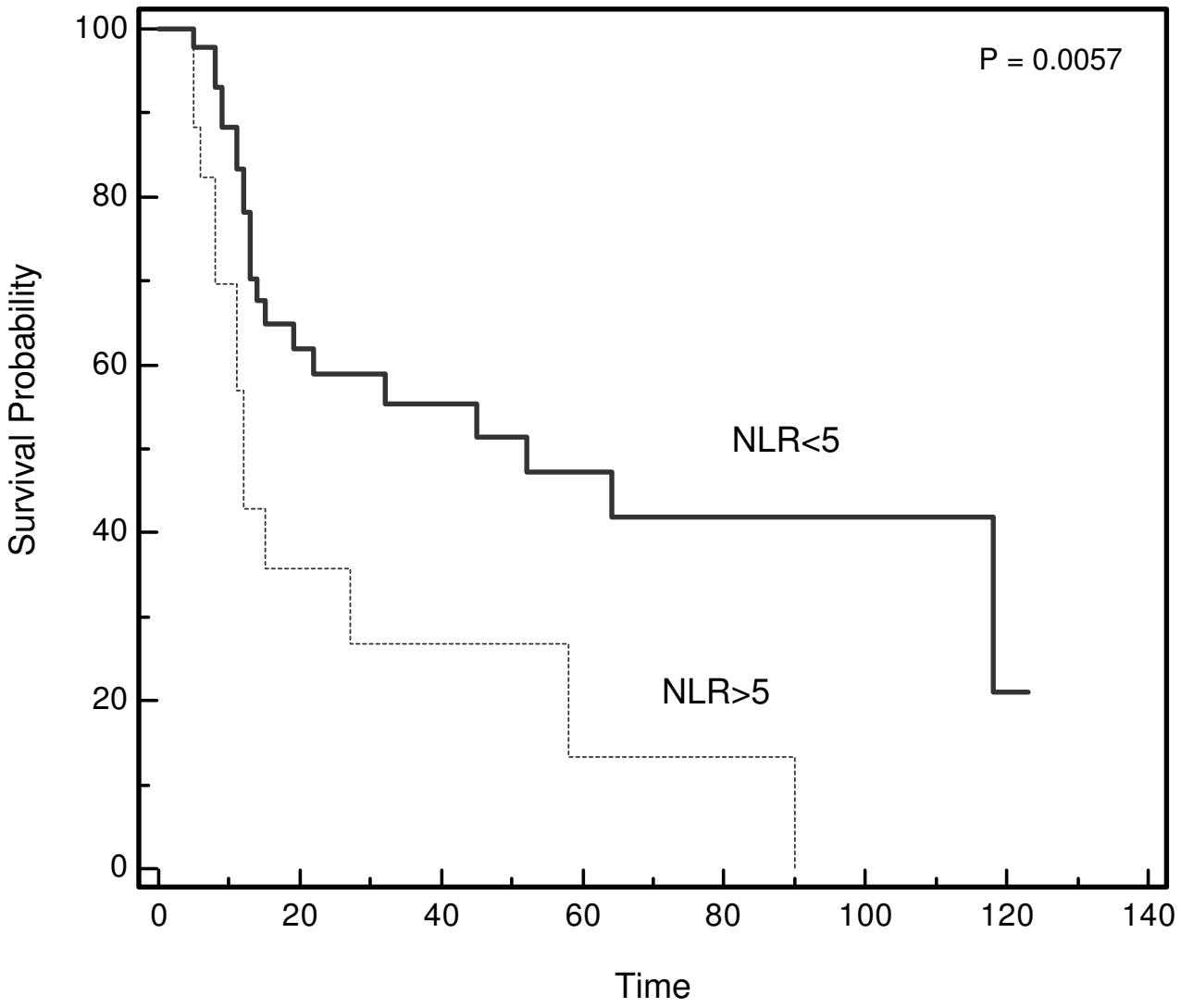
WCC= White Cell Count
Neut= Neutrophil Count
Lymph= Lymphocyte Count
NLR= Neutrophil:Lymphocyte Ratio
CRP= C-Reactive Protein
* = Includes 4 malignant mucinous cancers

		Number	Percentage
Recurrence at One Site		8	21.6
Recurrence at Multiple Sites		26	70.3
Local Recurrence Only		1	2.7
Distant Recurrence Only		22	59.5
Local and Distant Recurrence		11	29.7
Anatomical Sites of Recurrence	**Nodes**	17	45.9
	Coeliac Origin	7	18.9
	SMA Origin	9	24.3
	Retroperitoneal Margin	4	10.8
	Hepaticojejunostomy	3	8.1
	Peritoneal Metastases	8	21.6
	Ascites	7	18.9
	Portal Vein Occlusion	5	13.5
	Hepatic	19	51.4
	Pulmonary	9	24.3
	Bone	1	2.7

SMA= Superior Mesenteric Artery

		Median	Range	P Value
CA19.9 (units/mL)	No Recurrence	243	3 to 1000	ns
	Recurrence	254	7 to 1000	
Bilirubin (µmol/L)	No Recurrence	262	12 to 631	ns
	Recurrence	220	8 to 430	
WCC (x10^9/L)	No Recurrence	7.2	1.1 to 27.9	ns
	Recurrence	9.0	4.2 to 21.6	
Neut (x10^9/L)	No Recurrence	4.9	0.6 to 26.1	ns
	Recurrence	6.62	4.3 to 17.7	
Lymph (x10^9/L)	No Recurrence	1.47	0.1 to 3.2	ns
	Recurrence	1.43	0.7 to 3.7	
NLR	No Recurrence	3.1	1.4 to 9.0	P= 0.02
	Recurrence	4.7	1.6 to 12.9	
CRP (mg/L)	No Recurrence	11	<5 to 116	ns
	Recurrence	9	<5 to 191	
Platelets	No Recurrence	281	48 to 778	ns
	Recurrence	309	166 to 491	
Platelet to Lymphocyte Ratio	No Recurrence	200.1	95 to 1222	ns
	Recurrence	203.1	87 to 542	
Albumin	No Recurrence	40	16 to 48	ns
	Recurrence	36	25 to 47	

WCC= White Cell Count
Neut= Neutrophil Count
Lymph= Lymphocyte Count
NLR= Neutrophil:Lymphocyte Ratio
CRP= C-Reactive Protein
ns= Not significant


P = 0.0057
NLR<5
NLR>5
Survival Probability
Time
0
20
40
60
80
100
120
140

Study	Year	Number of Patients	Use of Marker	Pathology	Serological Marker	Findings	
Bhatti *et al* [6]	2010	83	Predicting following curative resection of periampullary malignancy	PDA	Preoperative PLR & NLR	NLR ≤ 3	13.7 months overall survival
						NLR of 3 to 4	17 months overall survival
						NLR >4	4.9 months overall survival
						No association with PLR and survival	
Smith *et al* [7]	2009	110		PDA	Preoperative PLR	PLR ≤150	19.7 months overall survival
						PLR of 151 to 300	13.7 months overall survival
						PLR >300	5.8 months overall survival
Sakka *et al* [5]	2009	34		PM*	Preoperative PLR	Preoperative PLR > 300 associated with decreased survival	
Smith *et al* [8]	2008	34		AM	Preoperative PLR	Preoperative PLR in combination with CA19-9 found to predict postoperative survival	
Jamieson *et al* [9]	2005	65		PDA	Postoperative CRP	CRP ≤10 mg l(-1)	21.5 months median survival
						CRP >10 mg l(-1)	8.4 months median survival
Smith *et al* [10]	2008	263	Determining resectability	PM	Preoperative PLR	PLR ≤150	PPV, NPV, sensitivity, and specificity of 81%, 38%, 51%, and 72%, respectively, at staging laparoscopy for resectability
Ong *et al* [11]	2008	113		PDA	Preoperative NLR	NLR significantly higher in patients undergoing bypass at exploration for potentially curative carcinoma	
Pine *et al* [12]	2009	199	Predicting survival for advanced or inoperable tumours	PDA	Pretreatment CRP	Raised CRP independently associated with reduced survival, only in non-resected patients	
Müller *et al* [13]	2008	136		PDA	Pretreatment CRP	Not associated with survival	
Tingstedt *et al* [14]	2007	119		PDA	Pretreatment CRP	CRP independent risk factor for survival	
Glen *et al* [4]	2006	187		PDA	Pretreatment CRP	CRP (as part of a prognostic factor) linked with poor survival	
Aliustaoglu *et al* [15]	2010	65		PDA	Pretreatment NLR	Pretreatment NLR >5 associated with poor survival	
An *et al* [16]	2010	95		PDA	Pretreatment NLR	NLR >5 independent risk factor for shortened survival	

PDA= Pancreatic Ductal Adenocarcinoma
PM= Periampullary Malignancy
AM= Ampullary Malignancy
* Including Neuroendocrine Malignancy
NPV= Negative Predictive Value
PLR= Platelet to Lymphocyte Ratio
CRP= C-reactive Protein
NLR= Neutrophil to Lymphocyte Ratio
PPV= Positive Predictive Value