ORIGINAL ARTICLE

Prognostic Factors in Patients with Pancreatic Adenocarcinoma and the Impact of Pancreatic Fistula on Oncologic Outcomes

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ABSTRACT

Background Pancreatic cancer prognosis remains poor despite recent advances. We aimed to determine prognostic factors associated with pancreatic cancer outcome by retrospective analysis of patients who received curative surgical treatment. **Methods** In this retrospective study, we analyzed 226 pancreatic cancer patients who received curative surgical treatment from January 2004 to December 2015. The overall survival and disease-free survival rates were determined by the Kaplan- Meier method. Univariate analysis and multivariate analysis were conducted to identify potential and independent prognostic factors. **Results** The estimated 1, 2, 3, and 5-year overall survival rates after curative resections were 35.84%, 15.48%, and 6.19% respectively. The overall pancreatic fistula rate was 30.53%. Univariate and multivariate analyses identified the following independent prognostic factors for overall survival: microvascular invasion, neutrophil/lymphocyte ratio>5, modified Glasgow prognostic score and lymph node ratio>0.3. Additionally, microvascular invasion, neutrophil/lymphocyte ratio>5 and platelet/lymphocyte ratio>160 were independent prognostic factors for disease-free survival. Pancreatic fistula was not associated with worse overall survival or disease-free survival. **Conclusion** Although pancreatic fistula remains the major cause of morbidity after pancreatic resection, it did not appear to influence overall survival and disease-free survival. Inflammation markers, microvascular invasion and lymph node ratio should be thoroughly assessed as independent prognostic factors in pancreatic cancer.

INTRODUCTION

Pancreatic cancer constitutes a small percentage of all cancers, but it is the fourth leading cause of cancer-related deaths with a five year relative survival of 8% [1,2]. With increasing incidence and mortality rates in recent years, pancreatic cancer is expected to be the second leading cause of cancer related deaths by 2030 [3]. The vast majority of pancreatic cancers are adenocarcinomas arising from exocrine glands of the pancreas [4]. Surgery remains the only therapy with curative intent. The silent nature of pancreatic cancer hinders its early-stage diagnosis despite technological advances and modern equipment. Only 20% of patients present with potentially resectable disease [5].

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Abbreviations OS overall survival; DFS disease-free survival; mGPS modified glasgow prognostic score; NLR neutrophil/lymphocyte ratio; PLR platelet/lymphocyte ratio; LMR lymphocyte/monocyte ratio; LNR lymph node ratio; AJCC American joint committee on cancer; ASA American society of anesthesiologists; PPPD pylorus-preserving pancreaticoduodenectomy; CA carbohydrate antigen; CEA carcinoembryonic antigen
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Even after curative resection and adjuvant chemo-radiotherapy, most patients will have recurrence, and the five-year survival remains at 25% [1]. Since pancreatic cancer cells metastasize early in disease development, 85% of patients eventually experience recurrence after curative resection [6]. Therefore, investigating clinicopathological factors as prognostic indicators are essential to help clinicians develop appropriate treatment strategies tailored for each patient.

The tumor marker Carbohydrate Antigen (CA) 19-9 has become the "gold standard" for diagnosing and monitoring treatment in pancreatic cancer patients over the past several decades. However, it remains insufficient for screening patients with pancreatic cancer [7]. A recent study revealed that CA 19-9 combined with another tumor marker Carcinoembryonic Antigen (CEA), could be used as prognostic predictors in these patients [8]. The lymph node ratio and the total number of positive lymph nodes were also evaluated as potential prognostic factors [9]. Furthermore, the importance of inflammation-based scores has been recently emphasized in various cancers as well as in pancreatic cancer [10-14].

Pancreatic fistula is the most common complication after pancreatic surgery, which can lead to serious adverse effects on patient outcomes. The incidence rates

of pancreatic fistula after pancreaticoduodenectomy and distal pancreatectomy range from 0% to 24% and from 5% to 28%, respectively [15]. However, there are only a few reports on the association between pancreatic fistula and long-term survival and local recurrence.

The aim of this study was to evaluate potential prognostic factors and to examine the relationship between pancreatic fistula and both overall survival and local recurrence in 226 patients with resectable pancreatic cancer, who were treated in the Agios Dimitrios General Hospital department during an 11-year interval.

METHODS

Study Population

Between 2004 and 2015, 226 (65.7%) patients with resectable pancreatic adenocarcinoma underwent macroscopic complete resection in the "Agios Dimitrios" General Hospital department of surgery. Resectable pancreatic cancers were defined as stage I or II disease according to the sixth American Joint Committee on Cancer (AJCC) [16]. Curative surgical procedures included pancreaticoduodenectomy (including subtotal stomach-preserving pancreaticoduodenectomy and Pylorus-Preserving Pancreaticoduodenectomy, PPPD), distal pancreatectomy and total pancreatectomy.

Data Collection

After surgery, follow-up information was updated by hospital visits, written correspondence, and telephone interviews. The patients were followed periodically until death, loss of contact, or the end of the study, which was May 2018. OS time, was defined as the time period from the date of surgery to the date of last follow-up or death. Recurrence status and site, including local recurrence, liver metastases, para-aortic lymph nodes metastases, lung metastases, and peritoneal carcinomatosis, were examined to analyze the DFS. For each patient, the following information was collected: demographic data including age, sex, lifestyle factors including smoking, and alcohol consumption, presence of diabetes mellitus, abdominal pain, comorbidity index according to the American Society of Anesthesiologists (ASA) risk classification system, tumor staging based on the Union Internationale Contre le Cancer classification, tumor characteristics, including location, histological type, and differentiation, resection margin status, and infiltration of the lymph nodes, perineural, and vascular structures, postoperative complications, pancreatic fistula development and early postoperative mortality.

We also evaluated the number of the positive lymph nodes and the LNR by dividing the number of the positive lymph nodes with the number of all lymph nodes that were examined, to evaluate their prognostic value in OS and DFS. Additionally, to investigate the roles of inflammation scores in pancreatic cancer prognosis, we evaluated the Modified Glasgow Prognostic Score (mGPS) which incorporates the C-reactive protein and albumin values, the Neutrophil/Lymphocyte Ratio(NLR), the Platelet/ Lymphocyte Ratio(PLR), and the Lymphocyte/Monocyte Ratio(LMR) for each patient.

Statistical Analysis

Clinical characteristics were analyzed using Pearson's chi-square or Fisher's exact test for categorical and dichotomous variables, and Student's t test for continuous variables. OS was calculated from the date of initial surgical treatment to the date of occurrence of either death from any cause or last contact. DFS was defined as the period from initial surgical treatment to disease recurrence. The Kaplan–Meier method was used to create survival curves, and differences were assessed with the log-rank test. Statistical significance was assumed for a two-tailed p-value of<0.05. To determine independent factors for OS and DFS, the Cox proportional hazards model it was used to determine potential factors, which were entered into a forward regression procedure for the final identification of independent prognostic factors.

RESULTS

Study Patients' Characteristics

We included 226 patients with resectable pancreatic adenocarcinoma in this retrospective study. The median age was 71 (31-89) years, and the male/female ratio was 1.2:1. The presenting symptoms were jaundice and abdominal pain in 65.93% and 47.35% patients, respectively. In the study cohort, 116 (51.33%) patients were smokers, and 41 (18.14%) patients consumed alcohol. Diabetes mellitus was diagnosed preoperatively in 72 (31.19%) patients, and 44 (19.47%) patients were prescribed metformin as diabetes mellitus therapy. Detailed information on major demographic and clinic-pathological characteristics of the study cohort is presented in **(Table1)**.

Intra-operative Parameters

In all study cohort patients, the indication for surgery was suspicion of malignancy. Specifically, 226 patients who were found to have a resectable tumor at exploratory laparotomy underwent subsequent curative pancreatectomy. Among these, 156 (69.03%), 39 (17.26%), 23 (10.18%), and 8 (3.54%) patients underwent PPPD, classic Whipple, distal pancreatectomy, and total pancreatectomy, respectively. Partial resection of the portal vein was necessary in 26 (11.5%) of patients **(Table 1).**

Morbidity and Mortality Rates

The perioperative mortality in the first 30 postoperative days was 2.65% (6/266) for the entire cohort. The mean length of hospital stay for the entire cohort was 11.34 (2- 80) days. During the post-operative course, 33.62% (76/226) of the patients in the study cohort developed one or more complications. Additionally, 69 (30.53%) patients developed pancreatic fistula after pancreatectomy. Specifically, pancreatic fistulas developed in 27.18% (53/195) and 69.57% (16/23) of the patients after

Table 1. Demographic characteristics and clinical data of the cohort patients (n=226).

	Sex (Male/Female)	124 (54.87%)/102(45.13%)
	Age (Years)	71 (31-89)
	Mean hospital stay (Days)	11.34 (2- 80)
	Preoperative diabetes mellitus (Yes/No)	72 (31.19%)/154 (68.14%)
	Obstructive jaundice (Yes/No)	149 (65.93%)/ 77 (34.07%)
	Alcohol abuse (Yes/No)	42 (18.58%)/184 (81.42%)
	Nicotine abuse (Yes/No)	116 (51.33%)/110 (48.67%)
ASA Classification	I	59/226 (26.11%)
	II	103/226 (45.58%)
	III	62/226 (27.43%)
	IV	2/226 (0.89%)
AJCC Stage	IA	13/226 (5.75%)
	IB	48/226 (21.24%)
	IIA	42/226 (18.58%)
	IIB	113/226 (50%)
	III	7/226 (3.01%)
	IV	3/226 (1.33%)
	Surgical method Pancreaticoduodenectomy (Whipple)	39 (17.26%)
	Pylorus Preserving Pancreaticoduodenectomy (PPPD)	156 (69.03%)
	Distal pancreatectomy	23 (10.18%)
	Total pancreatectomy	8 (3.54%)
	Portal vein resection	26 (11.5%)
Tumor Differentiation	G1	20 (8.85%)
	G2	129 (57.08%)
	G3	77 (34.07%)
R Status	Ro	188 (83.19%)
	R1	30 (13.27%)
	R2	8 (3.54%)
N Status	NO	113 (50%)
	N1	113 (50%)
	Perineural Invasion	148 (65.49%)
Microvascular Invasion	Positive	100 (44.25%)
	Negative	126 (55.75%)
	Morbidity rate	76/226 (33.62%)
	Mortality rate	6/226 (2.65%)
	Total pancreatic fistula rate	69/226 (30.53%)
	Grade A	41 (50.42%)
	Grade B	24 (34.78%)
	Grade C	4 (5.8%)
	Perioperative blood transfusion	63 (27.88%)

pancreaticoduodenectomy and distal pancreatectomy, respectively. Finally, 63 (27.88%) patients received blood transfusions **(Table 1).**

Pathological Features

Most of the patients with resectable tumors had AJCC stage IIb (50%) and stage Ib (21.24%) disease. The pathologic evaluation of the surgical specimens revealed R0, R1, and R2 resection in 188 (83.19%), 30 (13.27%), and 8 (3.54%) patients, respectively. The pancreatic adenocarcinoma was well-differentiated, moderated-differentiated and poorly differentiated in 20 (8.85%), 129 (57.08%), and 77 (34.07%) patients, respectively. The median number of the excised lymph nodes was 14.38 (5-32), and the lymph nodes were positive in half the patients. Perineural invasion was identified in 148 (65.49%) patients, whereas vascular invasion was found in 100 (44.25%) patients **(Table 1)**.

Survival and Prognostic Factors Analysis

The median OS of the entire cohort was 23.129 months, with 1, 3 and 5-year OS rates of 35.84%, 15.48%, and 6.19%, respectively **(Figure 1)**.

We analyzed all variables to determine prognostic factors associated with survival using the Kaplan–Meier method with the log-rank test. Among these parameters, PLR>160 ($p=0.097$, $p>0.05$), LMR<3 ($p= 0.173$, $p>0.05$), CA 19-9>100 U/ml ($p=0.274$, $p>0.05$), CEA>10 mg/dl ($p=0.823$, $p>0.05$), R resection status ($p=0.203$, $p>0.05$), pancreatic fistula ($p=0.818$, $p>0.05$), blood transfusion ($p=0.666$, $p>0.05$) had no statistically significant association with OS. In contrast, age>65 years ($p=0.004$, $p<0.05$), poorly differentiated tumor type ($p<0.001$, $p<0.05$), tumor staging ($p<0.001$, $p<0.05$), perineural invasion ($p<0.001$, $p<0.05$), microvascular invasion ($p<0.001$, $p<0.05$), NLR>5 ($p=0.019$, $p<0.05$), mGPS score

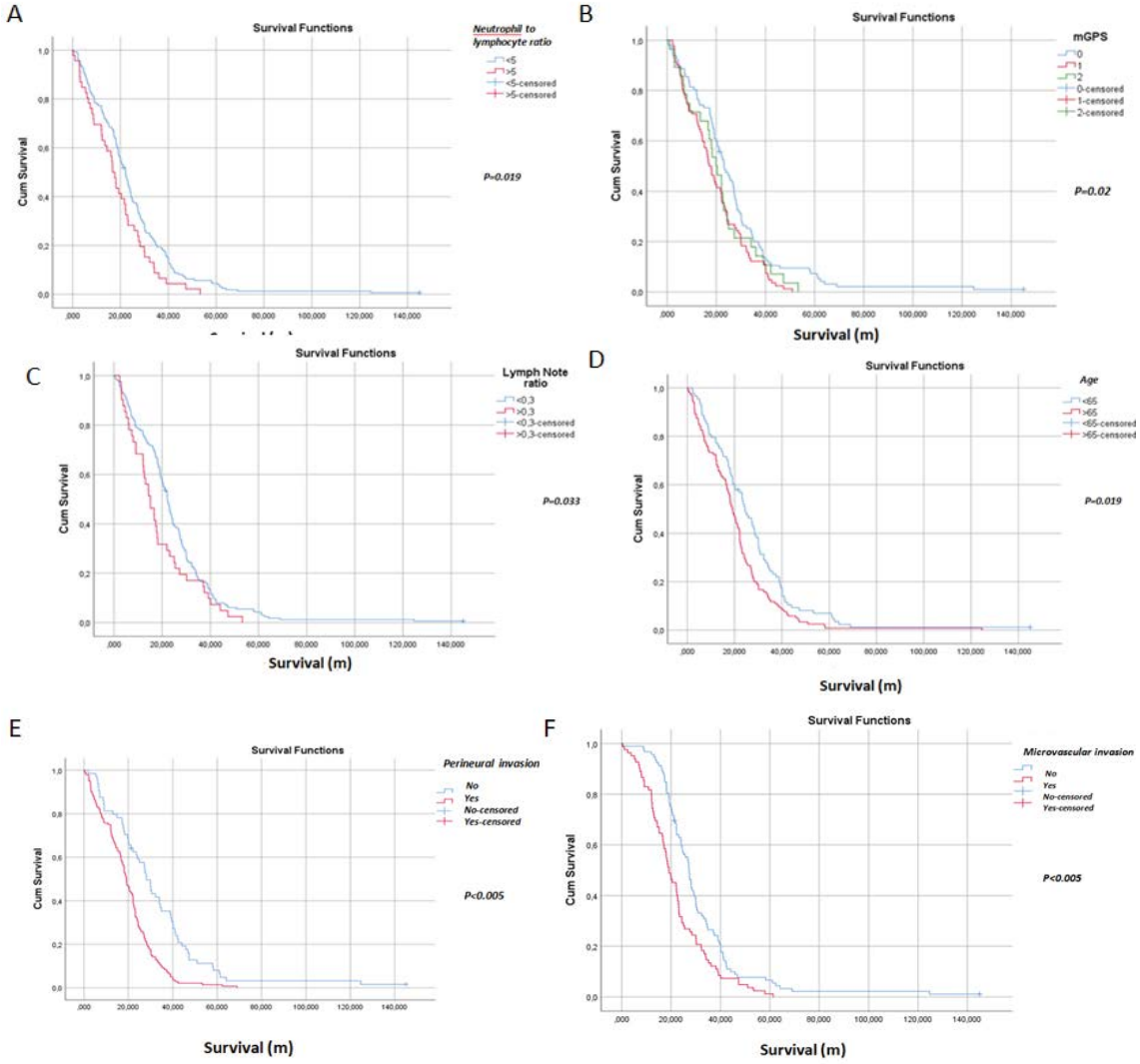

Figure 1. Overall survival (Kaplan-Meier) curves for study population of 226 patients with pancreatic adenocarcinoma who underwent pancreas resection. A: Patients with NLR>5 had a median survival of 18.5 months vs 24.5 months in patients with NLR<5 (p=0.019). B: Patients with mGPS score 0 had a median survival of 26.8months vs 21months and 19 months in patients with mGPS1 and mGPS2 respectively (p=0.02). C: Patients with lymph nodes ratio>0.3 had a median survival of 18.3months vs 24.5 months in patients with LNR<0.3 (p=0.033). D: Patients older than 65 years had a median survival of 20.4 months vs 27 months in patients younger than 65 years (p=0.004). E: Patients with microvacular invasion had a median survival of 21.6 months vs 31 months in patients without microvascular invasion (p<0.001). F: Patients with perineural invasion had a median survival of 19.5 months vs 32.2 months in patients without perineural invasion.

of 0(p=0.02, p<0.05), LNR>0,3 (p=0.033, p<0.05) were associated with better OS **(Table 2).**

Multivariate Survival Analysis

Factors that were significantly associated with OS in univariate survival were entered into a multivariate analysis using the Cox proportional hazards model with forward regression. Accordingly, the following variables were identified as independent factors for prognosis: age>65 years, tumor staging, microvascular invasion, NLR>5 (p=0.091, p<0.2), mGPS of 0 (p=0.073, p<0.2), and LNR>0,3 (p=0.091, p<0.2) **(Table 2)**.

Analysis of the DFS Rates

The median DFS was 25.73 (2.45-145) months, and 1,3 and 5-year DFS rates were 64.6%, 14.16% and 4.87% respectively **(Figure 2)**. The most frequent relapse type was local recurrence (65.04%), followed by liver metastases (41.59%) and peritoneal carcinomatosis (22.57%). Additionally, 63.77% of the patients with pancreatic fistula after pancreatectomy had local recurrence, whereas local recurrence occurred in 65.6% of the patients without fistula (p=0.670).

In the univariate analyses, poorly differentiated tumor type (p<0.001, p<0.05), tumor staging (p<0.001, p<0.05), perineural invasion (p<0.001, p<0.05), microvascular invasion (p=0.001, p<0.05), NLR>5 (p=0.017, p<0.05), PLR>160 (p=0.03, p<0.05), CA 19-9>100 U/ml (p=0.037, p<0.05) were significantly associated with the DFS. In contrast, LMR (p=0.110), CEA>10 mg/dl (p=0.639), R-resection status (0.097), pancreatic fistula (p=0.634), mGPS of 0 (p=0.084), LNR>0.3 (p=0.052), blood transfusion (p=0.744) were not significantly associated with DFS.

The multivariate analysis revealed that only microvascular invasion, NLR>5, and PLR>160 were independent prognostic factors for DFS **(Table 3).**

Table 2. Univariate and multivariable Cox regression analyses for OS.

Variables	HR	95% CI	p value	HR	95% CI	p value
Age>65 years	0.02	17.615-31.105	0.004	0.772	0.539-1.105	0.191
Tumor Differentiation G1	0.00	20.712-50.005		0.656	0.331- 1.302	0.386
Tumor Differentiation G2	0.01	22.563-29.085	<0.001	0.719	0.460-1.124	0.275
Tumor Differentiation G3	0.018	14.552-19.320		-	-	0.205
Staging I	0.11	24.83-67.676	<0.001	0.451	0.42-4.817	0.036
Staging II	0.02	26.281-35.247		0.635	0.63-6.422	0.176
Perineural Invasion	0.01	17.556-21.622	<0.001	0.534	0.534-1.269	0.411
Microvascular Invasion	0.05	18.862-24.480	<0.001	0.726	0.481-1.094	0.133
NLR>5	0.022	14.865-22.063	0.019	0.896	0.527-1.524	0.091
PLR>160	0.016	18.778-23.872	0.097	0.859	0.579-1.273	0.327
LMR<3	0.016	18.754-23.997	0.173	0.851	0.568-1.276	0.851
CA 19-9>100 U/ml	0.012	19.365-24.335	0.274	1.143	0.771-1.695	0.619
CEA>10 mg/dl	0.032	16.472-27.260	0.823	1.042	0.615-1.768	0.681
LNR Ratio>0.3	0.034	14.170-22.357	0.033	1.033	0.627-1.701	0.091
Blood Transfusion	0.00	18.616-29.439	0.66	1.129	0.729-1.747	0.322
Pancreatic Fistula	0.01832	19.445-26.602	0.818	1.046	0.695-1.575	0.901
mGPS of 0	0.07	22.456-31.239	0.02	1.354	0.706-2.599	0.073
R0 *vs.* R1 Resection	0.01	21.089-26.524	0.203	1.136	0.614-2.103	0.535
	0.00	14.332-24.818				

*Performed using the Kaplan–Meier analysis model and the log-rank test; values of p<0.05 in the univariate analysis were entered into a multivariate analysis.
† Performed using Cox proportional hazards models with the forward likelihood method.

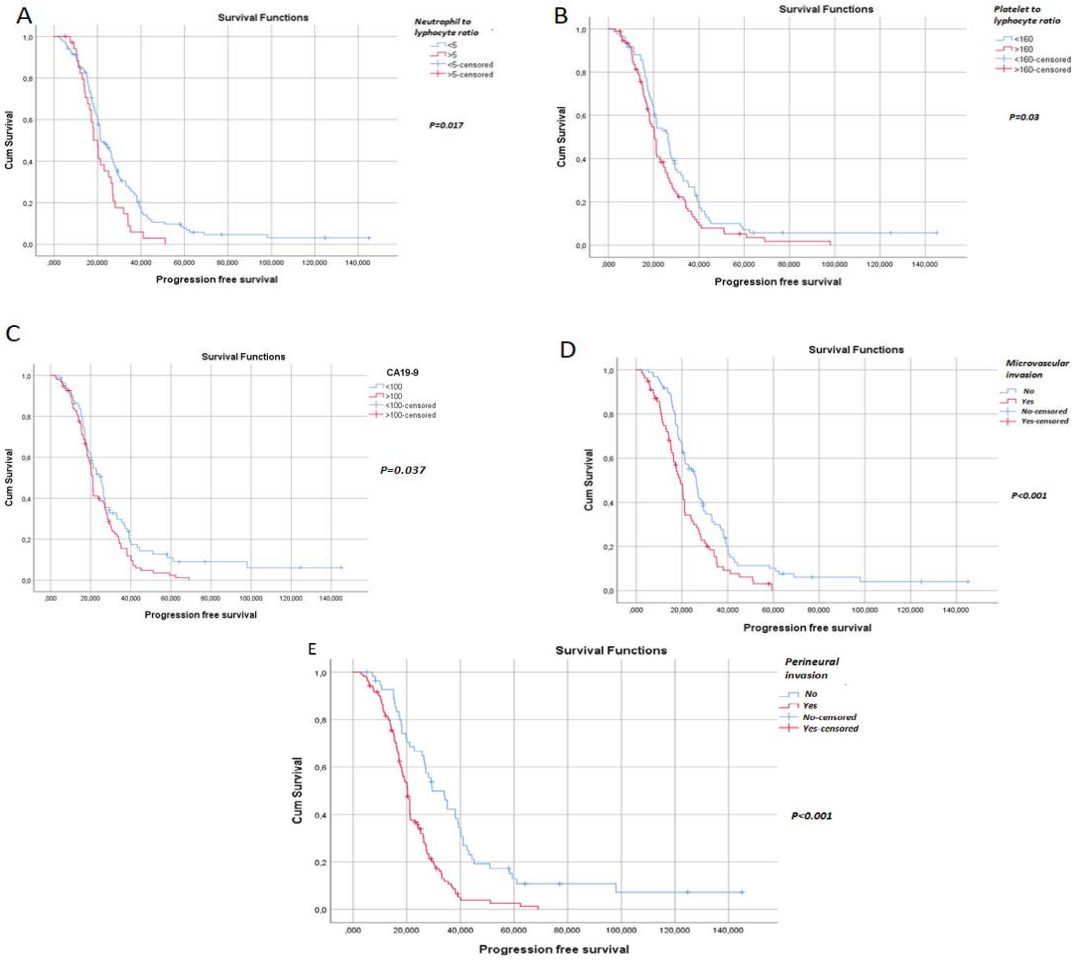

Figure 2. Disease free survivall (Kaplan-Meier) curves for study population of 226 patients with pancreatic adenocarcinoma who underwent pancreas resection.

A: Patients with NLR>5 had a median DFS of 21.4 months vs 30 months in patients with NLR <5 (p=0.017).
B: Patients with PLR<160 had a median DFS of 32.6 months vs 24.3 months in patients with PLR>160 (p=0.03).
C: Patients with CA 19-9 <100 U/ml had a median DFS of 34.1months vs 23.8months in patients with CA 19-9>100 U/ml (p=0.037).
D: Patients with microvascular invasion had a median DFS of 21.5months vs 33.1 months in patients without microvascular invasion (p=0.001).
E: Patients with perineural invasion had a median DFS of 22.1 months vs 40.8 months in patients without perineural invasion (p<0.001)

Table 3. Univariate and multivariable Cox regression analyses for DFS.

	Univariate*			Multivariate†	
Variables	**HR**	**95% CI**	**p value**	**HR**	**P value**
Age>65 years	0.00	21.213-31.017	0.93	0.793	0.301
Tumor Differentiation G1	0.00	30.085-73.864	<0.001	-	0.291
Tumor Differentiation G2	0.00	25.677-34.787	-	0.641	0.174
Tumor Differentiation G3	0.05	16.127-20.745	-	0.700	0.157
Staging I	0.00	39.846-96.905	<0.001	0.478	0.296
Staging II	0.06	28.376-39.706	-	0.668	0.408
Perineural Invasion	0.06	19.881-24.346	<0.001	0.818	0.407
Vascular Invasion	0.08	18.552-24.545	0.001	0.709	0.172
NLR>5	0.00	18.140-24.781	0.017	0.902	0.14
PLR>160	0.06	20.825-27.913	0.03	0.842	0.176
LMR<3	0.03	21.437-27.447	0.11	0.821	0.978
CA 19-9>100 U/ml	0.00	21.174-26.542	0.037	1.135	0.637
CEA>10 mg/dl	0.04	18.192-29.561	0.639	1.025	0.556
LNR Ratio>0.3	0.00	16.006-25.951	0.052	1.019	0.234
Blood Transfusion	0.04	21.279-34.502	0.744	1.205	0.481
Pancreatic Fistula	0.05	23.260-32.321	0.634	1.011	0.916
	0.00	25.996-40.025	0.084	-	0.349
mGPS 0 *vs.* mGPS1.2	0.07	20.006-26.605	-	1.396	-
	0.00	17.950-27.976	-	1.518	-
	0.00	24.973-33.811	0.097		0.36
R0 *vs.* R1 resection	0.00	16.057-27.699	-	1.178	-

*Performed using the Kaplan–Meier analysis model and the log-rank test; values of p<0.05 in the univariate analysis were entered into a multivariate analysis.

† Performed using Cox proportional hazards models with the forward likelihood method

DISCUSSION

Pancreatic cancer is one of the most lethal malignancies. Surgery remains the only curative treatment option, and there are no long term survivors among patients with unresectable tumors [17]. The five-year survival rate after curative resection varies form 15-25% based on the most recent series [18-20]. However, despite curative resection the actual survival rates remain disappointing, ranging from 4.3% to 10.1%, as reported by two large population-based studies [21,22]. In the current study elucidated outcomes and prognostic factors in 226 patients with pathologically verified pancreatic adenocarcinoma who were treated between 2004 and 2015. In the current series, only 14/226 (6.19 %) patients survived for more than five years, and the median survival was 23.129 months.

Our study revealed that age, tumor stage, and tumor differentiation were negatively associated with prognosis, consistent with the previous studies findings [23,24]. Furthermore, perineural and microvascular invasion were associated with worse OS and DFS, and microvascular invasion was an independent prognostic factor for OS and DFS by the multivariate analysis, while perineural invasion was identified in 65.49% of patients and microvascular invasion in 44.25% of patients. In accordance with previous studies, we found that although microvascular invasion is less frequent than perineural invasion, it has a more severe effect on survival. The reason could be that microvascular invasion is responsible of metastatic recurrence of disease and could lead to earlier metastasis, whereas perineural invasion is responsible of local recurrence which is not directly related to patient death [25,26].

Although postoperative mortality in pancreatic cancer has declined significantly over the last decade, with current rates less than 5% in certain specialized pancreatic centers, the morbidity remains high, ranging from 25% to 50% [23,24]. However, the impact of pancreatic fistula on survival is controversial. In a retrospective analysis of 184 patients, Nagai et al., found that the rate of peritoneal recurrence was significantly increased in patients with pancreatic fistulas. However, this increase in the risk of peritoneal recurrence did not translate into worse survival [27]. Assifi et al. conducted a retrospective analysis of 221 patients with pancreatic cancer after pancreaticoduodenectomy and found that pancreatic fistulas did not affect local recurrence rates [28]. In the current study, pancreatic fistulas developed in 69 (30.53%), 53 (27.18%), and 16 (69.57) of the patients who underwent pancreatectomy, pancreaticoduodenectomy, and distal pancreatectomy, respectively. We found no statistically significant impact of pancreatic fistulas on local recurrence (p=0.67) and the univariate and multivariate analyses did not detect an effect of pancreatic fistulas on OS or DFS.

"As the gold standard" tumor marker for monitoring and diagnosing pancreatic cancer patients, CA19-9, provides valuable information to assist in the therapeutic decision-making especially for surgeons. Numerous studies demonstrated that elevated CA 19-9 was associated with poor prognosis [29,30]. Our study established that DFS was lower in patients with CA 19-9 level above 100 U/ml. Conversely, CEA, better known for its utility in colorectal cancer, has been evaluated for pancreatic cancer as well.

While the results suggest that CEA's susceptibility was unacceptably low in pancreatic cancer, recent studies demonstrated CEA as an independent prognostic factor for pancreatic cancer [31,32]. However, we could not demonstrate a strong association between CEA and OS or DFS.

Improvements in pathological evaluation methods for pancreatic cancer have increased the R1 resection rate from 20% to 80% [33]. The influence of resection status on survival is controversial. In the present study, R1 resection was established in 13.27% of the patients after pathological examination. The median OS (23.8 m *vs.* 19.5 m) and the DFS (29.3 m *vs.* 21.8 m) were better in patients who underwent R0 resection compared with those who underwent R1 resection. However, our univariate and multivariate analyses failed to show an association between the resection status and OS or DFS.

Lymph node involvement remains the most important prognostic factor of survival in pancreatic cancer. LNR provides information on the number of positive lymph nodes as well as the total number of resected lymph nodes. LNR's prognostic value in pancreatic cancer has been established by numerous recent studies [34-36]. However, there is no consensus on the best cutoff value for LNR. We used as a cut-off LNR of 0.3 in the current study and found that an LNR>0.3 was an independent negative prognostic factor on OS.

An interaction between pancreatic cancer cells and host immune system, leading to a reduction in the lymphocyte ratio, was recently documented [37]; therefore, we also explored the potential associations of the inflammation markers NLR, PLR, and LMR with OS and DFS in the current study. NLR as a marker of active, cancer-associated inflammation was demonstrated to be an important prognostic factor in several cancers, such as colorectal, gastric, and hepatocellular cancer [38-40]. A recent retrospective study showed that an elevated preoperative NLR was an important prognostic factor for early TNM-stage pancreatic cancer. In the current study, we evaluated NLR with a cut-off value of five, based on previous reports and found that NLR>5 was an independent prognostic factor for OS as well as DFS, by univariate and multivariate analyses. PLR as an inflammation marker was recently shown to be a predictor of worse mid-term outcomes in patients with borderline resectable pancreatic cancer [41]. Yu et al. conducted a retrospective analysis and found that a PLR>150 was an independent predictive risk factor for postoperative long-term prognosis in pancreatic cancer [42]. In the current study, PLR>160 was associated with poor postoperative DFS after curative resection in pancreatic cancer patients. Finally, LMR's prognostic impact on pancreatic cancer outcomes remains unclear. A recent meta-analysis of 1,795 patients showed that an elevated LMR predicts favorable survival [43]. Unfortunately, the current study failed to demonstrate a similar effect of LMR on OS or DFS.

In addition to reflecting an upregulation of inflammatory response, mGPS, which combines CRP with hypoalbuminemia, also reflects the nutritional decline of pancreatic cancer patients [42]. Few studies, thus far, analyze the relationship of mGPS with survival in pancreatic cancer. Most reports implicate mGPS as a strong prognostic factor of recurrence and survival [44-48]. Our results indicating mGPS is an independent prognostic factor of OS are consistent with these findings**.**

CONCLUSION

Despite recent systemic treatment advances, the prognosis of patients with advanced PDAC remain poor. Surgery continues to be the only curative therapy and is associated with statistically better survival rates after curative resection. Currently, few predictive factors can identify patients who will benefit the most from available treatment options. We identified microvascular invasion, NLR, mGPS, and LNR as independent prognostic OS factors and microvascular invasion, NLR, and mGPS as independent prognostic factors of DFS. Furthermore our analysis showed that elevated CA 19-9 was a negative prognostic factor for DFS, whereas R1 resection and pancreatic fistula did not have a significant impact on survival or recurrence.

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Conflicts of Interest

The authors report no conflict of interest.

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