

Combined pretreatment serum CA19-9 and neutrophil-to-lymphocyte ratio as a potential prognostic factor in metastatic pancreatic cancer patients

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Abstract

The aim of this study was to explore the role of combined pretreatment serum carbohydrate antigen 19-9 (CA19-9) and neutrophil-to-lymphocyte ratio (NLR) as potential prognostic factors in metastatic pancreatic cancer patients.

We investigated pretreatment serum CA19-9 and NLR in 59 metastatic pancreatic cancer patients, determined the patients' thresholds by receiver operating characteristic curve analysis, and assessed their prognostic values by Kaplan–Meier curve and Cox regression models.

Results of multivariate analysis showed high CA19-9, high NLR, and high score (the scoring system of CA19-9 and NLR) were significantly correlated with overall survival. Area under the curve of the scoring system was higher than that of CA19-9 or NLR.

Combined pretreatment serum CA19-9 and NLR is a better prognostic biomarker of metastatic pancreatic cancer patients than CA19-9 or NLR alone.

Abbreviations: AUC = area under the curve, CA19-9 = carbohydrate antigen 19-9, CI = confidence interval, NI = not included into multivariate analysis, NLR = neutrophil-to-lymphocyte ratio, OS = overall survival, ROC = receiver operating characteristic.

Keywords: CA19-9, metastatic pancreatic cancer, neutrophil-to-lymphocyte ratio, prognostic factor

1. Introduction

Pancreatic cancer is an aggressive cancer with a 5-year survival rate of <7%.^[1] It is the seventh leading cause of cancer death worldwide.^[2] Around 80% to 85% of diagnosed patients present with locally advanced or metastatic disease, and <20% of patients can proceed with radical resection.^[3] The carbohydrate antigen 19-9 (CA19-9) is the most commonly used and best validated serum tumor marker for pancreatic cancer diagnosis in symptomatic patients and for monitoring therapy in patients with pancreatic adenocarcinoma.^[4] Several previous studies reported the relationship between the CA19-9 and survival.^[5–7] The link between inflammation and cancer was first exploited by Virchow in 1863.^[8] Several systemic inflammatory response markers have been investigated to predict survival in various cancers, such as C-reactive protein,^[9] neutrophil-to-lymphocyte ratio (NLR),^[10] and platelet-to-lymphocyte ratio.^[11] NLR has been reported to be associated with the prognosis in patients with pancreatic

cancer.^[12] It is increasingly recognized that survival of cancer patients was determined not only by tumor characteristics but also by systemic inflammatory response of the host.^[13] There have been no studies till date that have reported the prognostic role of combined detection of CA19-9 and NLR in metastatic pancreatic cancer patients and compared the combination with CA19-9 or NLR alone. Hence, the present study analyzes the prognostic utility of CA19-9 or NLR alone in metastatic pancreatic cancer patients. Further, this study determines the prediction ability of combination CA19-9 and NLR in metastatic pancreatic cancer patients.

2. Patients and methods

This retrospective analysis included 59 metastatic pancreatic cancer patients who were treated at Fujian Medical University Union Hospital between 2010 and 2015. The medical records collected in this study were: age, gender, neutrophil count, lymphocyte count, the primary pancreatic tumor location, site of metastasis, levels of CA19-9, type of treatment, follow-up, or death. NLR was calculated as the neutrophil count divided by lymphocyte count. The data was collected within 7 days before treatment. Overall survival (OS) was defined as the time from the date of diagnosis to the date of death or the date of last follow-up visit. The study was reviewed and approved by the ethical committee of the Fujian Medical University Union Hospital. According to survival time, patients were divided into subgroups to compare patients who have longer survival time than median OS with patients who had not. The receiver operating characteristic (ROC) curve was generated to evaluate the ideal cut-off values of CA19-9 and NLR for median OS prediction. The Youden index was used to determine the cut-off point. On the basis of each cutoff value, patients were dichotomized into 2

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Table 1
Characteristics of metastatic pancreatic cancer patients.

Characteristics	Values/Counts
Age, years, median (range)	65 (42–82)
Gender (male/female)	40/19
Tumor location (head/body/tail)	36/13/10
Metastatic sites (liver/other)	36/23
Serum CA19-9, U/mL, median (range)	935 (86–3640)
NLR, median (range)	4.7 (0.9–20.2)
Treatment (chemotherapy/other)	23/36
Survival time, months, median (range)	4.5 (1–10)

CA19-9 = carbohydrate antigen 19-9, NLR = neutrophil-to-lymphocyte ratio.

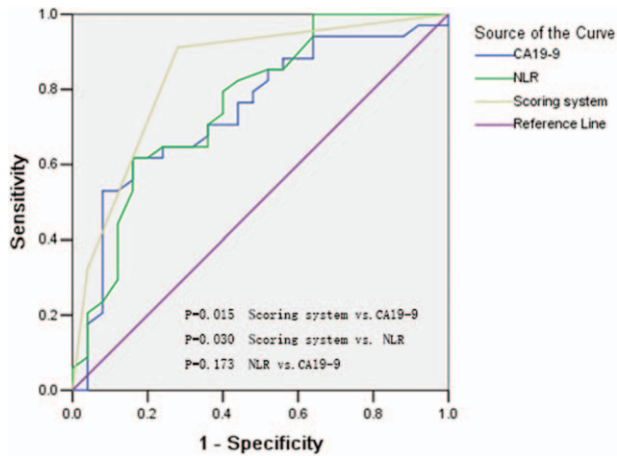


Figure 1. ROC curve analysis of CA19-9, NLR and scoring system for OS in metastatic pancreatic cancer patients. CA19-9=carbohydrate antigen 19-9, NLR=neutrophil-to-lymphocyte ratio, OS = overall survival, ROC = receiver operating characteristic.

groups. The association between CA19-9 or NLR and other parameters was evaluated by the Pearson χ^2 test. Survival data among subgroups classified by each factor were analyzed via the

Kaplan–Meier curve, the log-rank test, and Cox proportional hazard model. All variables with significant prognostic value in the univariate analysis were introduced in the final multivariate Cox proportional hazard model. $P < .05$ was considered statistically significant. Statistical analysis was performed using the SPSS software 13.0 (SPSS Inc, Chicago, IL).

3. Results

3.1. Patient general characteristics

Fifty-nine patients with metastatic pancreatic cancer diagnosis were enrolled. Of the 59 patients, 40 were males, with a median age of 65 years at diagnosis. Detailed baseline characteristics are listed in Table 1.

3.2. ROC curves of CA19-9 and NLR for median OS

The median CA19-9 was 935 U/mL (86–3640 U/mL) and the median NLR reached 4.7 (0.9–20.2). ROC curve analysis was used to evaluate cut-off values of CA19-9 and NLR to predict median OS. ROC curve analysis suggested that the cut-off value of 626 U/mL for CA19-9 and the cut-off value of 3.75 for NLR were chosen as the optimal value for evaluating median OS (area under the curve [AUC]: 0.744, 95% CI [0.614–0.874], $P = .001$, and AUC: 0.764, 95% CI [0.638–0.889], $P = .001$, respectively, sensitivity:61.76%, specificity:84.00%, Fig. 1). Furthermore, the scoring system was applied by combining CA19-9 and NLR levels: score 0 was defined as CA19-9 <626 U/mL and NLR <3.75; score 1 was defined as “CA19-9 \geq 626 U/mL with NLR <3.75” or “NLR \geq 3.75 with CA19-9 < 626 U/mL”; and score 2 was defined as CA19-9 \geq 626 U/mL and NLR \geq 3.75.

3.3. Correlations of CA19-9 and NLR with characteristics parameters

Correlations of CA19-9 and NLR with various characteristics parameters including age, gender, tumor location, and site of metastasis were analyzed. As shown in Table 2, there was no

Table 2
Characteristics of metastatic pancreatic cancer patients grouped by CA19-9 and NLR.

Variables	Sum	CA19-9, U/mL		P value	NLR		P value
		<626	\geq 626		<3.75	\geq 3.75	
Age, years				.26			.549
<65	28	14	14		13	15	
\geq 65	31	11	20		12	19	
Gender				.248			.248
Male	40	19	21		19	21	
Female	19	6	13		6	13	
Tumor location				.333			.682
Head	36	18	18		16	20	
Body	13	4	9		6	7	
Tail	10	3	7		3	7	
Site of metastasis				.687			.138
Liver	36	16	20		18	18	
Other	23	9	14		7	16	
NLR				.453			
<3.75	25	12	13		–	–	
\geq 3.75	34	13	21		–	–	
CA19-9, U/mL				.453			
<626	25	–	–		12	13	
\geq 626	34	–	–		13	21	

CA19-9 = carbohydrate antigen 19-9, NLR = neutrophil-to-lymphocyte ratio.

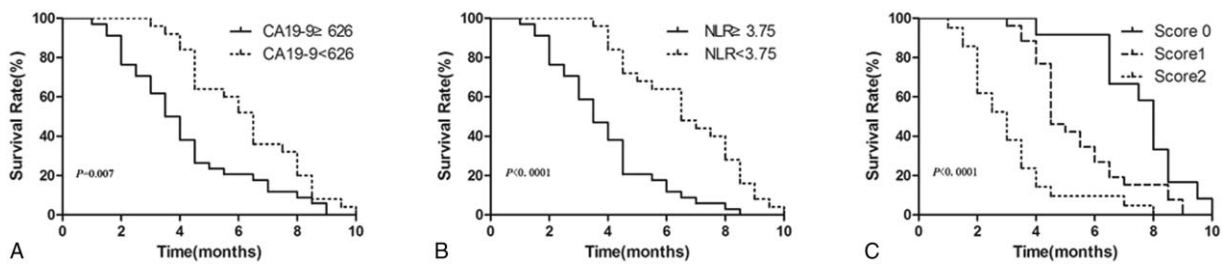


Figure 2. Kaplan–Meier survival curves for OS in metastatic pancreatic cancer patients according to CA19-9, NLR, and scoring system. CA19-9=carbohydrate antigen 19-9, NLR=neutrophil-to-lymphocyte ratio, OS = overall survival.

significant correlation observed between CA19-9 or NLR and other parameters.

3.4. Correlations of characteristics parameters with OS

To investigate whether CA19-9, NLR, and other characteristics, parameters are associated with OS, univariate and multivariate Cox proportional models were calculated. The Kaplan–Meier curves for OS reveal that high levels of CA19-9 or NLR are associated with poor prognosis in metastatic pancreatic cancer ($P=.0036$, $P<.0001$, respectively) (Fig. 2A and B). Univariate analysis identified the age of the patients at diagnosis (≥ 65 vs < 65 , $P=.0457$), CA19-9 (≥ 626 vs < 626 , $P=.0036$), NLR (≥ 3.75 vs < 3.75 , $P<.0001$), the high score of scoring system (score 1 vs score 0, score 2 vs score 0, $P=.0077$, $P<.0001$, respectively), and no chemotherapeutic treatment (no chemotherapy vs chemotherapy, $P=.0012$) were significantly associated with worse OS in

metastatic pancreatic cancer, whereas gender, tumor location, and site of metastasis were not (Table 3). All available variables significantly associated with survival in univariable analysis were introduced in a multivariate logistic regression. Multivariate analysis reveals that CA19-9 (≥ 626 vs < 626 , $P=.007$), NLR (≥ 3.75 vs < 3.75 , $P<.0001$), and the scoring system (score 2 vs score 1 vs score 0, $P<.0001$) were independent prognostic factors for OS (Table 3).

3.5. The scoring system of CA19-9 and NLR is a superior prognostic factor

To determine the independent prognostic significance of the scoring system of CA19-9 and NLR in a metastatic pancreatic cancer patient, Cox regression model and Kaplan–Meier method were performed. The univariate Cox regression and the multivariate Cox regression survival analysis showed that the

Table 3
Univariate and multivariate analysis of parameters for the prediction of overall survival in metastatic pancreatic cancer patients.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age, years						
<65	1 (referent)			1 (referent)		
≥ 65	1.812	1.011–3.247	.0457	1.388	0.784–2.457	.261
Gender						NI
Male	1 (referent)					
Female	1.714	0.8879–3.309	.1083			
Tumor location						NI
Head	1 (referent)					
Body	0.7897	0.4011–1.555	.4946			
Tail	0.7825	0.3752–1.632	.4275			
Site of metastasis						NI
Liver	1 (referent)					
Other	1.344	0.7411–2.437	0.3304			
CA19-9, U/mL						
<626	1 (referent)			1 (referent)		
≥ 626	2.364	1.325–4.218	.0036	2.22	1.240–3.976	.007
NLR						
<3.75	1 (referent)			1 (referent)		
≥ 3.75	4.214	2.265–7.838	<.0001	3.698	2.044–6.692	<.0001
Scoring system						
0	1 (referent)			2.862	1.832–4.471	<.0001
1	2.762	1.309–5.827	.0077			
2	7.286	3.051–17.40	<.0001			
Treatment						
Chemotherapy	1 (referent)			1 (referent)		
No chemotherapy	2.61	1.462–4.660	.0012	1.586	0.900–2.794	1.111

CA19-9=carbohydrate antigen 19-9, CI=confidence interval, HR=hazard ratio, NI=not included into multivariate analysis, NLR=neutrophil-to-lymphocyte ratio.

scoring system was an independent prognostic factor (Table 3). The results of Kaplan–Meier method are presented in Figure 2C. The result of ROC showed that AUC of the scoring system was 0.843 (95% CI 0.737–0.949, $P < .0001$), which was higher than that of CA19-9 and NLR (Fig. 1). These results implied that the scoring system as a significant prognostic biomarker that can be superior to either CA19-9 or NLR alone.

4. Discussion

In this study, based on the results of ROC analysis, the cut-off value of 626 U/mL for CA19-9 and the cut-off value of 3.75 for NLR were chosen. A cut-off value of CA19-9 < 1000 U/mL was reported in Chen et al's^[14] study of advanced pancreatic cancer, and was > 230 U/mL in Asaoka et al's^[15] study of resectable pancreatic head cancer.^[15] Cut-off value of NLR was < 5 was reported in Piciocchi et al's^[12] study of metastatic pancreatic cancer,^[12] and was > 2.5 in Watanabe et al's^[16] study of resectable pancreatic cancer.^[16] The optimal cut-off values have remained controversial. The differences of cut-off value are likely due to different stage of pancreatic cancer and the number of patients. The cut-off values of serum CA19-9 and NLR should be validated in a large prospective multiinstitutional study.

In pancreatic cancer, CA19-9, the only biomarker currently recommended for clinical use by the National Comprehensive Cancer Network guidelines for pancreatic cancer, is recognized as the most clinically useful marker, which fittingly reflects the tumor burden and positively correlates with the malignancy of tumor cell.^[17] A more previous study reported that CA19-9 is reliable as a possible prognostic marker of pancreatic cancer.^[18–20] A change in CA19-9 level between initial and post concurrent chemoradiotherapy was a significant prognostic marker for overall survival in locally advanced pancreatic cancer treated with concurrent chemoradiotherapy.^[18] CA19-9 was an independent prognostic factor for patients with pancreatic cancer treated by chemotherapy or concurrent chemoradiotherapy.^[19,20] Preoperative CA19-9 was an independent predictive factor for recurrence of resectable pancreatic cancer and poor survival of pancreatic cancer.^[5,15,21] The systemic inflammatory response from cancer cells may play an important role in cancer progression and malignant transformation.^[22] As one of inflammatory markers, NLR is getting more attractive, because NLR is readily measurable in peripheral blood and directly reflects the systemic host inflammatory response. The prognostic significance of NLR was reported by previous study.^[23–25] NLR provided independent prognostic information about patients with pancreatic cancer, regardless of the undergoing therapeutic modality.^[23] Inoue et al's^[24] study showed that NLR had prognostic value in a large Japanese pancreatic cancer cohort. A systematic review and meta-analysis showed that high pretreatment blood NLR could be an adverse prognostic indicator for advanced tumor.^[25] Our present study verified the results of previous studies and demonstrated that elevated CA19-9 and NLR were independent prognostic factors for poor survival of metastatic pancreatic cancer. These studies together suggest that CA19-9 and NLR offer significant prognostic information associated with survival of pancreatic cancer. Furthermore, the role of combined detection of CA19-9 and NLR in the prognosis of metastatic pancreatic cancer was assessed. As shown in Table 3 and Figure 2C, the scoring system of CA19-9 and NLR was an independent prognostic biomarker and a better predictor of prognosis than CA19-9 or NLR alone. The scoring system not

only represents the tumor characteristics but also reflects the inflammatory and immune status of the patient and therefore is considered as a good prognostic marker.

There are some limitations in this study. First, the study is subject to selection bias due to retrospective. Second, the data was from a single institution. Third, the number of patients included is relatively small. At last, potential selection bias should not be omitted in this study.

In conclusion, combined pretreatment serum CA19-9 and NLR is a better prognostic biomarker of metastatic pancreatic cancer patients than CA19-9 or NLR alone. Further studies are needed to validate the result.

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