The Correlation Analysis of Baseline Serum CA199, CEA and CA125 in Patients with Advanced Pancreatic Cancer

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Research article

Keywords: Pancreatic cancer, CA199, CEA, CA125, Correlation analysis, Prognosis

Posted Date: March 20th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-18126/v1

Abstract

Background:CA199, CEA and CA125 were the most widely used tumor markers in pancreatic cancer. However, the studies associated with the relationship between the three markers and pancreatic cancer were limited. This study aimed to explore the correlation between baseline serum CA199, CEA, CA125 levels and clinical characteristics in pancreatic cancer.

Methods:278 patients with advanced pancreatic cancer received first-line chemotherapy treatments enrolled in this research. Correlated analysis between tumor markers and disease characteristics was performed by Pearson's Chi-squared test or Fisher exact test. We used Pearson's correlation test to investigate the relationship between tumor markers and peripheral blood parameters. Univariate analysis was estimated by Kaplan-Meier method and compared using the log-rank test. Multivariate analysis and HR calculation was determined by the Cox regression model.

Results: Baseline CA199, CEA, and CA125 both positively associated with the primary tumor site (p=0.007; p=0.012; p=0.003, respectively);liver metastasis (p=0.001; p=0.001; p=0.028, respectively); number of organ metastasis (p=0.001; p=0.008;p=0.042, respectively); baseline WBC levels (p<0.001; p<0.001; p<0.001, respectively), LDH levels (p<0.001; p=0.004; p<0.001, respectively). And CA199 also correlated with years of smoking(p=0.024); diabetes and year of diabetes (p=0.012; p=0.012); baseline glycemic levels (p=0.004). CA199 and CA125 levels had the relationship with baseline neutrophil counts (p<0.001; p<0.001, respectively). Years of smoking, baseline neutrophil counts, LDH levels, CA199 levels and CA125 levels were independent prognostic factors.

Conclusion: Combinations of the four factors were also correlated with survival. It's concluded that CA199, CEA, CA125 correlated with multi-factors of clinical factors. And combinations of baseline neutrophil counts, LDH levels, CA199 levels and CA125 levels were also prognostic factor.

Introduction

Pancreatic cancer (PC) has been a serious public health problem in the worldwide, the incidence and mortality of pancreatic cancer have been rising each year[1].In2019, the related deaths of pancreatic cancer were 45,750 and the estimated new cases were 56,770 in the United States[2]. In China, the cancer incident and the cancer-related mortality of pancreatic cancer were ranked tenth and sixth respectively[3]. Both the prognosis of pancreatic cancer and the effect of treatment were not good, the morbidity and mortality were similar. The 5-year survival rate has been 3% -7%[4, 5]. Therefore, assessing patients' outcomes and early intervention was important. So, it's useful to find markers to predict the prognosis of patients.

CA 19 – 9 belongs to sialylated Lewis blood group antigen[6], the level of CA199 exceeded the upper limit of normal value above 80% in patients with advanced pancreatic cancer[7]. CEA and CA125 were also widely used in pancreatic cancer for evaluating prognosis[8, 9]. Prior studies combined different serum

tumor markers to improve the evaluating of prediction of prognosis in pancreatic cancer[10]. Some other studies combined tumor biomarkers and peripheral blood counts to estimate the prognosis of patients with pancreatic cancer[11–13]. However, the value of prognosis of these tumor markers and peripheral blood counts was different in prior studies, and the debate of prognostic validity continues in these parameters. The level of different serum tumor markers was affected by many factors, but literatures associated with the relationship between the three markers and pancreatic cancer were limited.

We collect commonly indicators in clinical in this study aim to find the connection between these indicators and select the useful prognostic factors.

Materials And Methods

Patients

278 patients with advanced or metastatic pancreatic cancer treated at the Chinese People's Liberation Army (PLA) general hospital from 2010 to 2018 were enrolled in our retrospective analysis. All patients were admitted for first-line chemotherapy. We obtain the terminal status of patients from the medical records or telephone calls. We follow up information every 3 months. The inclusion criteria were:1)The diagnosis of pancreatic cancer was confirmed by histopathology or cytological ;2)All patients without first-line chemotherapy previously were recruited; 3)The Karnofsky performance status (KPS)score of the patients' were70 or more;4)Every patients had explicit terminal status. Exclusion criteria:1) lack of baseline data;2) lost follow-up. Patients were followed up until July 30, 2018.

Laboratory measurements

Serum CA199, CEA, CA125, LDH, ALB, WBC, N, PLT, TB and glycemic levels were measured before first-line chemotherapy initiation. The cut-off values of the baseline laboratory factors were defined as the median and upper limit of normal value (ULN). The normal range of CA199, CEA, CA125 was 0.1 ~ 37 U/ml,0 ~ 5.0ug/L,0.1 ~ 35 U/ml, respectively. The normal range of WBC count, N count ,PLT, was 3.5 ~ 10 × 10^9/L,0.50 ~ 0.70,100 ~ 300 × 10^9/L, respectively. Serum LDH, serum ALB, TB, blood glycemic was 40 ~ 250U/L, 35 ~ 50 g/L, 0 ~ 21umol/L,3.4 ~ 6.1 mmol/L, respectively.

Statistical analysis

The end point was overall survival (OS). OS was defined as the time interval from the date of starting first-line chemotherapy to death or last censored follow-up. We aimed to compare the correlation between baseline characteristics, personal history, clinical outcomes, baseline blood indexes and baseline CA199, CEA, CA125, as well as the survival model based on tumor biomarker and baseline clinical characteristics. We used SPSS software (version22.0) to perform statistical analysis. And survival curves and correlation graphs are drawn with GraphPad The relationship between clinical characteristics and serum tumor markers was determined by Pearson's Chi-squared test or Fisher exact test. We used Pearson's correlation to analyze the correlation analysis of CA199, CEA, CA125.Overall survival rates were estimated by Kaplan-

Meier method and compared using the log-rank test. Multivariate analysis and HR calculation was determined by the Cox regression model. Statistical significance was defined as a twosided $P < 0.05$.

Results

Patient characteristics

From January2010 to December 2017, we enrolled 278 patients with advanced or metastatic pancreatic cancer in our retrospective research. 109(39.2%) patients were male and the median age at diagnosis was 56 years (range:30–85 years). The median OS was 9.7 months (range:1.68–43.66 months).

Correlation between clinical characteristic factors and baseline tumor markers

The median values of the baseline CA199, CEA and CA125were 1180 U/ml(range:0.60-20000 U/ml),7.23ug/L(range:0.21-5033ug/L),82.56 U/ml(range:5.10–4134 U/ml), respectively. The median CA199 level was significantly correlated with years of smoking($p = 0.024$), diabetes($p = 0.012$),year of diabetes($p = 0.012$), tumor location($p = 0.007$), number of organ metastases($p = 0.001$), liver metastasis($p = 0.001$).And the median level of CEA was significantly correlated with tumor location($p = 0.012$), number of organ metastases($p = 0.008$)and liver metastasis($p = 0.001$). The medium CA125 level was significantly correlated with tumor location($p = 0.003$), number of organ metastases($p = 0.042$), liver metastasis = 0.028) (Table 1).

Table 1
Correlation between clinical characteristic factors and tumor markers

Features	CA199			CEA			CA125		
	≤ 1180	>1180	P[b] value	≤ 7.23	>7.23	P[b] value	≤ 82.56	>82.56	P[b] value
Sex			0.712			0.059			0.163
Male	56	53		61	48		59	50	
Female	83	86		75	94		77	92	
Age			0.435			0.205			0.907
≤ 56	23	121		70	74		41	103	
56	17	117		55	79		39	95	
Smoke			0.100			0.341			0.647
Yes	53	53		48	58		50	56	
No	86	86		88	84		86	86	
Year of smoking			0.024			0.556			0.688
No smoking	86	86		87	85		87	85	
1≤&≤10	2	11		4	9		5	8	
> 10	45	32		38	39		35	42	
Unknown	6	10		7	9		9	7	
No. of cigarettes [a]			0.171			0.264			0.500
0	86	86		87	85		87	85	
1≤&≤10	13	20		11	22		12	21	
> 10	37	26		32	31		32	31	
Unknown	3	7		6	4		5	5	
Diabetes			0.012			0.973			0.740
Yes	20	37		28	29		29	28	
No	119	102		108	113		107	114	
Year of diabetes			0.012			0.124			0.456

a. Number of cigarettes (No smoking; ≤10 cigarettes/day; >10 cigarettes/day)

b. Pearson chi-squared test($P < 0.05$)

Features	CA199			CEA			CA125		
	≤ 1180	>1180	P[b] value	≤ 7.23	>7.23	P[b] value	≤ 82.56	>82.56	P[b] value
No	123	105		111	117		114	114	
≤ 1	7	7		8	6		8	6	
1<&≤10	4	16		6	14		9	11	
> 10	5	11		11	5		5	11	
Jaundice			0.882			0.355			0.740
Yes	28	29		31	26		29	28	
No	111	110		105	116		107	114	
Tumor location			0.007			0.012			0.003
Head	64	42		62	44		64	42	
Body/tail	75	97		74	98		72	100	
No. of metastasis			0.001			0.008			0.042
0	32	16		31	17		31	17	
1	88	79		83	84		79	88	
≥ 2	19	44		22	41		26	37	
metastasis									
Liver			0.001			0.001			0.028
Yes	95	119		92	122		97	117	
No	44	20		44	20		39	25	
Lung			0.157			0.211			0.340
Yes	20	29		20	29		27	22	
No	119	110		116	113		109	120	
a. Number of cigarettes (No smoking; ≤10 cigarettes/day; >10 cigarettes/day)									
b. Pearson chi-squared test(P < 0.05)									

Correlation between tumor markers and different parameters

After Pearson correlation analysis, it shows that baseline WBC related to baselineCA199(r = 0.296, p < 0.001), CEA (r = 0.249, p < 0.001), CA125(0.251, p < 0.001).Baseline LDH also correlated to baselineCA199(r = 0.299, p < 0.001), CEA (r = 0.178,P = 0.004), CA125(0.239, p < 0.001). Both CA199 and CA125 related to neutrophil (r = 0.313, P < 0.001; r = 0.223, p < 0.001, respectively). Otherwise, CA199 were related to baseline glycemic (r = 0.175, p = 0.004). In addition, baseline CA199 significantly related to CEA (r = 0.207, p = 0.001) and CA125(r = 0.402, p < 0.001) (Table 2, Fig. 1).

Table 2
Correlation between tumor markers and different peripheral blood parameters

Features	CA199		CEA		CA125	
	Pearson p[c] Value correlation		Pearson p Value correlation		Pearson p Value correlation	
WBC	0.296	< 0.001	0.249	< 0.001	0.251	< 0.001
PLT	-0.087	0.149	0.050	0.407	-0.054	0.378
Neutrophil	0.313	< 0.001	0.079	0.196	0.223	< 0.001
ALB	-0.049	0.416	-0.033	0.587	-0.084	0.171
LDH	0.299	< 0.001	0.178	0.004	0.239	< 0.001
TB	-0.017	0.784	-0.023	0.712	-0.042	0.491
Glycemic	0.175	0.004	-0.014	0.823	-0.023	0.706
CEA	0.207	0.001	1		0.309	< 0.001
CA199	1		0.207	0.001	0.402	< 0.001
CA125	0.402	< 0.001	0.309	< 0.001	1	

[c] Pearson's correlation test.

Univariate and multivariate analysis of prognostic factors

We used Cox proportional hazards regression model to identify the prognostic value of clinical characteristic factors and tumor markers. In the univariate analysis, the significant prognosis factors of patients were sex(p = 0.001), smoking(p = 0.020) year of smoking(p = 0.004), number of cigarettes (p = 0.030), baseline WBC (p = 0.022) baseline neutrophil (p < 0.001), LDH(p = 0.004), the median level of baseline CA199 (p = 0.006), the median level of CEA (p = 0.003), the median level of CA125(p < 0.001) (Table 3, Fig. 2).

Table 3
Univariate and multivariate analysis of prognostic factors

Features	N	mOS (month)	Univariate		Multivariate	
			HR (95%CI)	P value	HR (95%CI)	P value
Sex				0.001		
Male	109	12.1	1			
Female	169	7.9	1.46(1.10–1.93)			
Age				0.051		
≤ 56	144	10.7	1			
56	134	9.0	1.31(1.00-1.71)			
Smoke				0.020		
No	172	11.1	1			
Yes	106	9.1	1.28(0.97–1.69)			
Year of smoking				0.004		0.025
No smoking	172	11.1	1		1	
1≤&≤10	13	7.9	2.64(1.41–4.94)		1.46(0.48–4.43)	
> 10	77	9.9	1.11(0.82–1.51)		0.90(0.37–2.20)	
Unknown	16	5.9	1.78(1.02–3.10)		1.12(0.51–2.47)	
No. of cigarettes				0.030		
0	172	11.1	1			
1≤&≤10	33	6.0	1.85(1.22–2.80)			
> 10	63	9.4	1.12(0.91–1.55)			
Unknown	10	9.2	1.14(0.55–2.33)			

c. Gem: Gemcitabine; Gem-based: Gemcitabine plus S1; Gemcitabine plus platinum;Gemcitabine plus capecitabine; TG: nab-paclitaxel plus gemcitabine; TS: nab-paclitaxel plus S1; Others: Oxaliplatin plus S1; Platinum monotherapy

Features	N	mOS (month)	Univariate		Multivariate	
			HR (95%CI)	P value	HR (95%CI)	P value
Diabetes				0.837		
No	221	9.9	1			
Yes	57	9.2	0.90(0.65–1.25)			
Year of diabetes				0.240		
No	228	9.9	1			
≤ 1	14	8.6	1.29(0.71–2.32)			
1<&≤10	20	14.0	0.61(0.35–1.05)			
> 10	16	6.0	1.03(0.56–1.89)			
Jaundice				0.135		
No	221	10.6	1			
Yes	57	7.5	1.11(0.80–1.52)			
Tumor location				0.859		
Head	106	9.8	1			
Body/tail	172	9.9	1.17(0.89–1.55)			
No. of metastasis				0.162		
0	48	12.7	1			
1	167	9.3	1.39(0.95–2.03)			
≥ 2	63	10.9	1.32(0.85–2.04)			
Metastasis						
Liver				0.077		

c. Gem: Gemcitabine; Gem-based: Gemcitabine plus S1; Gemcitabine plus platinum;Gemcitabine plus capecitabine; TG: nab-paclitaxel plus gemcitabine; TS: nab-paclitaxel plus S1; Others: Oxaliplatin plus S1; Platinum monotherapy

Features	N	mOS (month)	Univariate		Multivariate	
			HR (95%CI)	P value	HR (95%CI)	P value
No	64	12.2	1			
Yes	214	9.4	1.36(0.99–1.88)			
Lung				0.632		
No	229	9.8	1			
Yes	49	10.9	0.91(0.63–1.29)			
First-line chemotherapy [d]				0.123		
Gem	40	6.2	1			
Gem-based	43	11.0	0.70(0.44–1.22)			
TG	27	11.8	0.65(0.39–1.10)			
TS	159	9.9	0.63(0.44–0.91)			
Others	9	5.9	1.44(0.97–1.03)			
TB				0.273		
≤ULN	239	10.3	1			
>ULN	39	6.2	1.35(0.92–1.96)			
Baseline glucose				0.969		
≤ULN	168	9.8	1			
>ULN	110	9.9	0.95(0.73–1.26)			
Baseline WBC				0.022		
≤ULN	248	10.4	1			

c. Gem: Gemcitabine; Gem-based: Gemcitabine plus S1; Gemcitabine plus platinum;Gemcitabine plus capecitabine; TG: nab-paclitaxel plus gemcitabine; TS: nab-paclitaxel plus S1; Others: Oxaliplatin plus S1; Platinum monotherapy

Features	N	mOS (month)	Univariate		Multivariate	
			HR (95%CI)	P value	HR (95%CI)	P value
>ULN	30	6.7	1.51(1.00-2.27)			
Baseline PLT				0.233		
≤ULN	238	9.8	1			
>ULN	40	12.1	0.82(0.55–1.22)			
Baseline neutrophil				< 0.001		0.001
≤ULN	187	11.2	1		1.58(1.16–2.16)	
>ULN	91	7.0	2.02(1.52–2.67)			
Baseline ALB				0.075		
≤LLN	30	5.8	1			
>LLN	248	10.3	0.67(0.45–1.02)			
Baseline LDH				0.004		
≤ULN	246	10.4	1		1	0.017
>ULN	32	6.5	1.87(1.26–2.78)		1.83(1.18–2.83)	
Baseline CA199				< 0.001		0.028
≤ 1180	139	12.2	1		1	
> 1180	139	7.5	1.78(1.35–2.33)		1.47(1.08–2.01)	
Baseline CEA				0.003		
≤ 7.23	136	12.1	1			
> 7.23	142	7.9	1.50(1.14–1.96)			

c. Gem: Gemcitabine; Gem-based: Gemcitabine plus S1; Gemcitabine plus platinum;Gemcitabine plus capecitabine; TG: nab-paclitaxel plus gemcitabine; TS: nab-paclitaxel plus S1; Others: Oxaliplatin plus S1; Platinum monotherapy

Features	N	mOS (month)	Univariate	Multivariate
			HR (95%CI) P value	HR (95%CI) P value
Baseline CA125			< 0.001	0.001
≤ 82.56	136	12.7	1	1
> 82.56	142	7.4	2.13(1.61–2.81)	1.77(1.29–2.43)

c. Gem: Gemcitabine; Gem-based: Gemcitabine plus S1; Gemcitabine plus platinum;Gemcitabine plus capecitabine; TG: nab-paclitaxel plus gemcitabine; TS: nab-paclitaxel plus S1; Others: Oxaliplatin plus S1; Platinum monotherapy

Multivariate analysis showed that year of smoking, normal level of baseline WBC, neutrophil counts, baseline LDH, the medium level of CA199,CEA, CA125were independent prognostic factors (HR = 1.51,P = 0.022; HR = 2.02, P < 0.001; HR = 1.87, P = 0.004; HR = 1.78, P < 0.001; HR = 1.50, P = 0.003; HR = 2.13, P < 0.001) (Table 3).

The elevation both the serum N, LDH, CA199 and CA125 associated with poor prognosis

Multivariate analysis showed that the baseline levels of N, LDH, CA199 and CA125 were independent prognosis factors in our research. Therefore, we combine the four markers to predict the relationship between the four markers and prognosis. And if the level of N,LDH exceeded the ULN or the level of CA199 and CA125 more than the medium level was defined as a score of 1.Finally,we divided the patients into 5 groups with scores of 0,1,2,3 and 4.The survival analysis showed that the patients with higher score had shorter OS with statistic significantly(P < 0.001)(Fig. 3).The medium OS of the patients with the score from 0 to 4 was 13.7, 14.0, 9.2, 5.7, 3.2 months, respectively. The result showed that the elevation both serum N, LDH, CA199 and CA125 associated with poor prognosis.

Discussions

Most of the studies used tumor biomarkers and peripheral blood parameters to value prognosis. Nevertheless, the level of the tumor markers and blood markers may be affected by other factors. Actually, some researches showed that several tumor markers have the relationship with some clinical characteristics in other kinds of tumors[14–16]. However, few studies performed the correlation analysis of tumor markers in pancreatic cancer. Therefore, we collected the indicators which commonly used in clinical to perform the correlation analysis.

Our retrospective research explored the correlation of tumor markers and clinical factors in pancreatic cancer. We presented several major results. First, we chose the three tumor markers which most commonly used in pancreatic cancer to perform correlation analysis with clinical characteristics. Then, we analyzed the relation between tumor markers and different peripheral blood parameters. Finally, all parameters were performed survival analysis with the Cox proportional hazards regression model.

In our investigation, the CA199, CEA and CA125 had relationship with the primary tumor site and number of organ metastasis as well as liver metastasis. CA199 is a kind of cell surface glycoprotein which could participate in tumor metastasis or invasive and has relationship with cellular and adhesion[5]. The CEA which possessed cell adhesion properties is also used to performed prognostic monitoring in pancreatic cancer[17]. Prior study showed that the level of CA125 could reflect metastasis-associated burden to the patients with advanced pancreatic cancer[18]. Therefore, the commonly trait of these tumor markers formed previous results may contributed to correlation.

In our study, the level of CA199 was also associated with the year of smoking. Kawai S et al. analyzed the relationships between the levels of serum CA199 and smoking, alcohol drinking and BMI, the result shows that the smoking habit of the subjects had an effect to the serum CA199 levels, and no significant associations were observed with drinking and BMI[19]. Some studies showed that smoking could change gene expressions which involved in biomarkers[20, 21]. Hence, smoking habits could change the level of CA199.

Lots of researches demonstrated that the diabetes or medicine of diabetes had effect on the level of CA199. Our research also found that CA199 associated with diabetes and glycemic levels. Huang Y et al. compared diabetes patients with subjects without history diabetes, the result showed that the CA199 levels higher in patients with diabetes and impaired glycemic regulation than the subjects with no history diabetes[22]. Sun HK et al. demonstrated that CA199 levels could be influenced by glycemic levels[23]. The mechanism between CA199 levels had effect on the patients in pancreatic cancer with diabetes is unclear. The main reason could be that the function of pancreatic insulin secretion is dysfunction in patients with diabetes and cellular dysfunction could result in CA199 levels increase[24]. Pancreatic cancer could induce pancreatic endocrine and exocrine disorders and damaged the pancreatic cells. All these reasons generated the association between diabetes and CA199 levels.

In our results, three tumor markers (CA199, CEA, CA125) had relationship with different peripheral blood counts. The inflammatory cells mainly included WBC and neutrophil cell had effect on the three biomarkers. Inflammatory cells played an important role in the process of tumor initiation, proliferation or metastasis of tumor cells[25]. Some researches testify these inflammatory cells correlated with tumor metastasis[26]. Few studies testified that the relationship between peripheral blood counts and tumor biomarkers. Our result found that WBC and neutrophil cell counts correlated with CA199, CEA and CA125, but neutrophil cell had no relationship with CEA. Lee JH et al. had the opposite result that the CEA had no relationship with WBCs in patients with advanced rectal cancer[27]. Actually, the mechanism of the

relation between inflammatory cells and tumor markers was unknown. Maybe, the inflammatory cell changed the microenvironment of tumor cells and contributed to tumor proliferation and migration, thus, the level of tumor markers be influenced.

LDH is a pivotal enzyme that participates in the process of pyruvate to lactate in anaerobic conversion[28]. LDH would overexpress in hypoxia tumor tissues and metastatic cancer tissues[29]. The level of LDH associated with tumor invasion and metastasis[13]. Our result shows that LDH levels correlated with CA199, CEA, and CA125. Yu SL et al. found that the LDH median levels had relationship with markers of systemic inflammation, but negatively correlated with CA199 levels[30]. Other studies rarely reported relevant results. Therefore, we need multi-center studies with larger samples to explore the phenomenon.

All the parameters were performed univariate analysis and multivariate analysis. The result of univariate analysis showed that sex, the habits of smoking significantly associated with prognosis of the patients with pancreatic cancer. It is same as other researchers[31, 32]. Serum baseline WBC levels, neutrophil levels, LDH, CA199, CEA and CA125 were also proved to correlate with prognosis in pancreatic cancer. Prior studies demonstrated the value of these parameters[13, 27, 33]. However, tumor location, number of organ metastasis, liver and lung metastasis had no effect on OS in pancreatic cancer. Our multivariate analysis suggested that years of smoking were the only clinical factor which could influence the prognosis. Baseline neutrophil levels, LDH, CA199 and CA125 levels were independent factors for survival. Single factor for predicting survival in pancreatic cancer was not precise. To improve accuracy of prognosis in patients with pancreatic cancer, we combined the different factors. The four factors presented tumor metabolism, systemic inflammation and tumor markers. In the four factors, every indicator increased count 1 point. The result showed that the patients who had a higher score suffered worse survival time.

Limitations

There are some limitations in our studies. Firstly, retrospective analysis may consist of selection bias. Then, the sample was small and it is a single-center study, some results need to be testified with larger sample from multi-center. Finally, in the retrospect research, some information was incomplete. Next step, we will perform multi-center studies to validate the results.

Conclusion

Our research confirmed that baseline CA199, CEA and CA125 are associated with primary tumor site, number of organ metastasis, liver metastasis, serum WBC and LDH levels. And CA199 correlated with years of smoking, diabetes, glycemic levels. Neutrophil counts levels had relationship with CA199 and CA125. Sex, years and number of cigarettes, chemotherapy regimens, baseline neutrophil levels, LDH, CA199, CEA and CA125 were independent prognostic factors. Combined analysis of baseline neutrophil levels, LDH, CA199 and CA125 levels could evaluate prognosis of pancreatic cancer well.

Abbreviations

CA199: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; CA125: Carbohydrate antigen 125; LDH: lactate dehydrogenase; ALB: albumin; WBC: white blood cell; N: Neutrophil cell; PLT: Platelet; TB: Total bilirubin; KPS: Karnofsky performance status; CI: Confidence interval; HR: Hazard ratio.

Declarations

Acknowledgements

We appreciate the all colleagues at PLA General Hospital for treating the patients with advanced pancreatic cancer in our study.

Author's contributions

GCD participated in the design of the study, collecting data, interpretation of data and drafted the manuscript. HY and ZPG participated in checking results of data. HY and SSG participated in analysis of data.

Funding

Research was supported by the National Natural Science Foundation of China (81571411). The funding body has no role in the design of the study, collection, analysis, interpretation of data, and writing of the manuscript.

Availability of data and materials

All the data and materials supporting the conclusions were included in the main paper.

Ethics approval and consent to participate

Our study was approved by the ethics committee of PLA General Hospital. All treatments were performed in accordance with institutional guidelines and regulations. Clinical data retrieved electronically from the medical records of PLA General Hospital Registry.

Consent for publication

Not applicable.

Competing interests

The authors have declared no conflicts of interest.

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018; 68(1):7-30.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019; 69(1):7-34.
3. Wanqing Chen RZ, Peter D. Baade, Siwei Zhang, Hongmei Zeng, Freddie Bray, Ahmedin Jemal, Xue Qin Yu, Jie He. Cancer Statistics in China, 2015. CA CANCER J CLIN 2016.
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA: A Cancer Journal for Clinicians. 2015; 65(1):5-29.
5. Swords DS, Firpo MA, Scaife CL, Mulvihill SJ. Biomarkers in pancreatic adenocarcinoma: current perspectives. Onco Targets Ther. 2016; 9:7459-7467.
6. Luo G, Guo M, Jin K, Liu Z, Liu C, Cheng H, Lu Y, Long J, Liu L, Xu J *et al*. Optimize CA19-9 in detecting pancreatic cancer by Lewis and Secretor genotyping. Pancreatology. 2016; 16(6):1057-1062.
7. Viviane Hess BG, Philipp Grawe, Daniel Dietrich, György Bodoky, Thomas Ruhstaller, Emilio Bajetta, Piercarlo Saletti, Arie Figer, Werner Scheithauer, Richard Herrmann. CA19-9 tumour-marker response to chemotherapy in patients with advanced pancreatic cancer enrolled in a randomised controlled trial. Lancet Oncol 2008; 9(9):132–138.
8. J. Lundin' PJR, P. Kuusela2 & C. Haglund'. The prognostic value of preoperative serum levels of CA 19-9 and CEA in patients with pancreatic cancer. Br J Cancer. 1994; 69: 515-519.
9. Luo G, Xiao Z, Long J, Liu Z, Liu L, Liu C, Xu J, Ni Q, Yu X. CA125 is superior to CA19-9 in predicting the resectability of pancreatic cancer. J Gastrointest Surg. 2013; 17(12):2092-2098.

10. Liu L, Xu H, Wang W, Wu C, Chen Y, Yang J, Cen P, Xu J, Liu C, Long J *et al*. A preoperative serum signature of CEA+/CA125+/CA19-9 >/= 1000 U/mL indicates poor outcome to pancreatectomy for pancreatic cancer. Int J Cancer. 2015; 136(9):2216-2227.
11. Michael Haas RPL, Petra Stieber , Stefan Holdenrieder , Christiane J. Bruns , Ralf Wilkowski , Ulrich Mansmann , Volker Heinemann , Stefan Boeck. Prognostic relevance of CA 19-9, CEA, CRP, and LDH kinetics in patients treated with palliative second-line therapy for advanced pancreatic cancer. Tumor Biol. 2010; 31:351–357.
12. Chen Y, Wang YR, Deng GC, Dai GH. CA19-9 decrease and survival according to platelet level in patients with advanced pancreatic cancer. BMC Cancer. 2019; 19(1):860.
13. Wang Y, Xiao X, Wang T, Li L, Zhu Y, Xu H, Chu Y, Jiao F, Cui J, Wang L. A Survival Model in Locally Advanced and Metastatic Pancreatic Ductal Adenocarcinoma. J Cancer. 2018; 9(7):1301-1307.
14. Song J, Huang X, Chen Z, Chen M, Lin Q, Li A, Chen Y, Xu B. Predictive value of carcinoembryonic antigen and carbohydrate antigen 19-9 related to downstaging to stage 0-I after neoadjuvant chemoradiotherapy in locally advanced rectal cancer. Cancer Manag Res. 2018; 10:3101-3108.
15. Zhou W, Yang F, Peng J, Wang F, Lin Y, Jiang W, Yang X, Li L, Lu Z, Wan D *et al*. High pretreatment serum CA19-9 level predicts a poor prognosis for patients with stage III colon cancer after curative resection and adjuvant chemotherapy. J Cancer. 2019; 10(16):3810-3818.
16. WeiYu Xu HZ, Xiaobo Yang, Yi bai, JianZhen Lin, JunYu Long, JianPing Xiong, JunWei Zhang, XinTing Sang, HaiTao Zhao. Prognostic significance of combined preoperative fibrinogen and CA199 in gallbladder cancer patients. World J Gastroenterol. 2018; 24(13):1451-1463.
17. Hammarstrom S. The carcinoembryonic antigen CEA family: structures, suggested functions and expression in normal and malignant tissues CANCER BIOLOGY. 1999; 9:67-81.
18. Liang Liu H-XX, Wen-Quan Wang , Chun-Tao Wu1,2,3, Jin-Feng,Xiang,Chen Liu, Jiang Long, Jin Xu, De-Liang Fu, Courtney W. Houchen, Russell G. Postier, Min Li, Xian-Jun Yu, Quan-Xing Ni. CA125 is a novel predictive marker for pancreatic cancer metastasis and correlates with the metastasis-associated burden. Oncotarget. 2016; 7(5).
19. Kawai S, Suzuki K, Nishio K, Ishida Y, Okada R, Goto Y, Naito M, Wakai K, Ito Y, Hamajima N. Smoking and serum CA19-9 levels according to Lewis and secretor genotypes. Int J Cancer. 2008; 123(12):2880-2884.
20. Philibert RA, Ryu GY, Yoon JG, Sandhu H, Hollenbeck N, Gunter T, Barkhurst A, Adams W, Madan A. Transcriptional profiling of subjects from the Iowa adoption studies. Am J Med Genet B Neuropsychiatr Genet. 2007; 144B(5):683-690.
21. van Leeuwen DM, Gottschalk RW, van Herwijnen MH, Moonen EJ, Kleinjans JC, van Delft JH. Differential gene expression in human peripheral blood mononuclear cells induced by cigarette smoke and its constituents. Toxicol Sci. 2005; 86(1):200-210.
22. Huang Y, Xu Y, Bi Y, Xu M, Lu J, Wang T, Li M, Chen Y, Liu Y, Huang F *et al*. Relationship between CA 19-9 levels and glucose regulation in a middle-aged and elderly Chinese population. J Diabetes. 2012; 4(2):147-152.

23. Kim SH, Baek CO, Lee KA, Park TS, Baek HS, Jin HY. Clinical implication of elevated CA 19-9 level and the relationship with glucose control state in patients with type 2 diabetes. Endocrine. 2014; 46(2):249-255.
24. Yu H, Li R, Zhang L, Chen H, Bao Y, Jia W. Serum CA19-9 level associated with metabolic control and pancreatic beta cell function in diabetic patients. Exp Diabetes Res. 2012; 2012:745189.
25. Ocana A, Nieto-Jimenez C, Pandiella A, Templeton AJ. Neutrophils in cancer: prognostic role and therapeutic strategies. Mol Cancer. 2017; 16(1):137.
26. Zhou B, Deng J, Chen L, Zheng S. Preoperative neutrophil-to-lymphocyte ratio and tumor-related factors to predict lymph node metastasis in nonfunctioning pancreatic neuroendocrine tumors. Sci Rep. 2017; 7(1):17506.
27. Lee JH, Jeong JU, Kim SH, Nam TK, Lee JH, Jeong S, Yu M, Jang HS. Nadir/pre-chemoradiotherapy ratio of white blood-cell count can predict tumor response and recurrence-free survival in locally advanced rectal cancer: a multi-institutional analysis. International Journal of Colorectal Disease. 2018; 34(1):105-112.
28. Markert CL. Lactate Dehydrogenase Isozymes Dissociation and Recombination of Subunits. Science. 1963; 140:1329–1330.
29. Maftouh M, Avan A, Sciarrillo R, Granchi C, Leon LG, Rani R, Funel N, Smid K, Honeywell R, Boggi U *et al*. Synergistic interaction of novel lactate dehydrogenase inhibitors with gemcitabine against pancreatic cancer cells in hypoxia. Br J Cancer. 2014; 110(1):172-182.
30. Yu SL, Xu LT, Qi Q, Geng YW, Chen H, Meng ZQ, Wang P, Chen Z. Serum lactate dehydrogenase predicts prognosis and correlates with systemic inflammatory response in patients with advanced pancreatic cancer after gemcitabine-based chemotherapy. Sci Rep. 2017; 7:45194.
31. Chen Yuan VM-O, Ana Babic, Clary B. Clish, Peter Kraft, Ying Bao, Zhi Rong Qian, Douglas A. Rubinson, Kimmie Ng, Edward L. Giovannucci, Shuji Ogino, Meir J. Stampfer, John Michael Gaziano, Howard D. Sesso, Barbara B. Cochrane, JoAnn E. Manson, Charles S. Fuchs, and Brian M. Wolpin. cigarette smoking and pancreaticcancer survival. J Clin Oncol. 2017; 35(16).
32. Yu2 S-HZG-FLX-FLLLS-N. Efficacy of different chemotherapy regimens in treatment of advanced or metastatic pancreatic cancer: A network meta-analysis.pdf. J Cell Physiol 2018. 2018; 233:3352–3374.
33. Piotr Hogendorf Aleksander Skulimowski AD, Anna Kumor, Grahyna PoznaNska, Aleksandra OleVna, Joanna Rut, and Janusz Strzelczyk. A Panel of CA19-9, Ca125, and Ca15-3 as the Enhanced Test for the Differential Diagnosis of the Pancreatic Lesion. Disease Markers 2017.

Figures

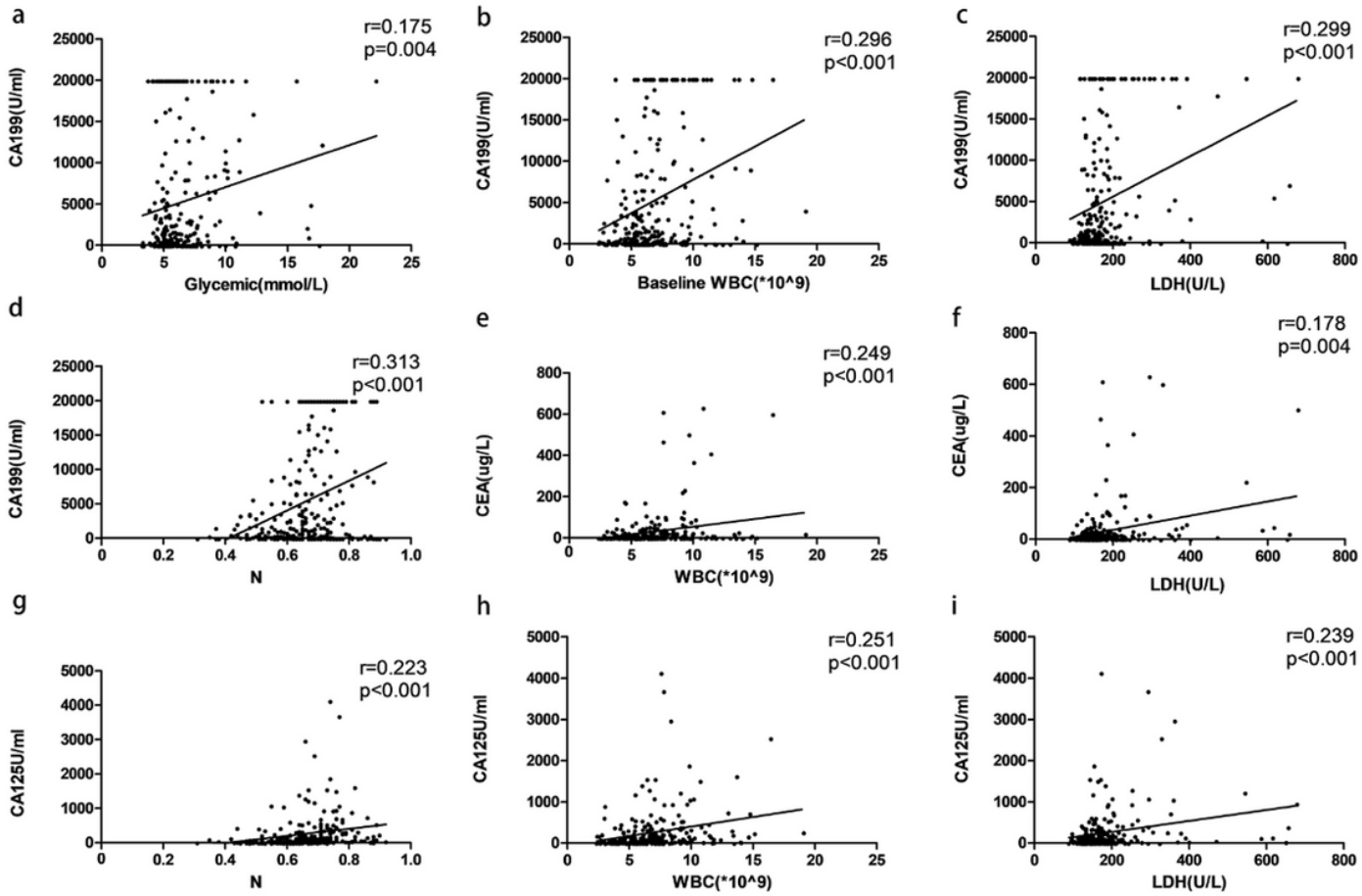

Figure 1

Correlation between the three tumor markers and different peripheral blood parameters in advanced pancreatic cancer.

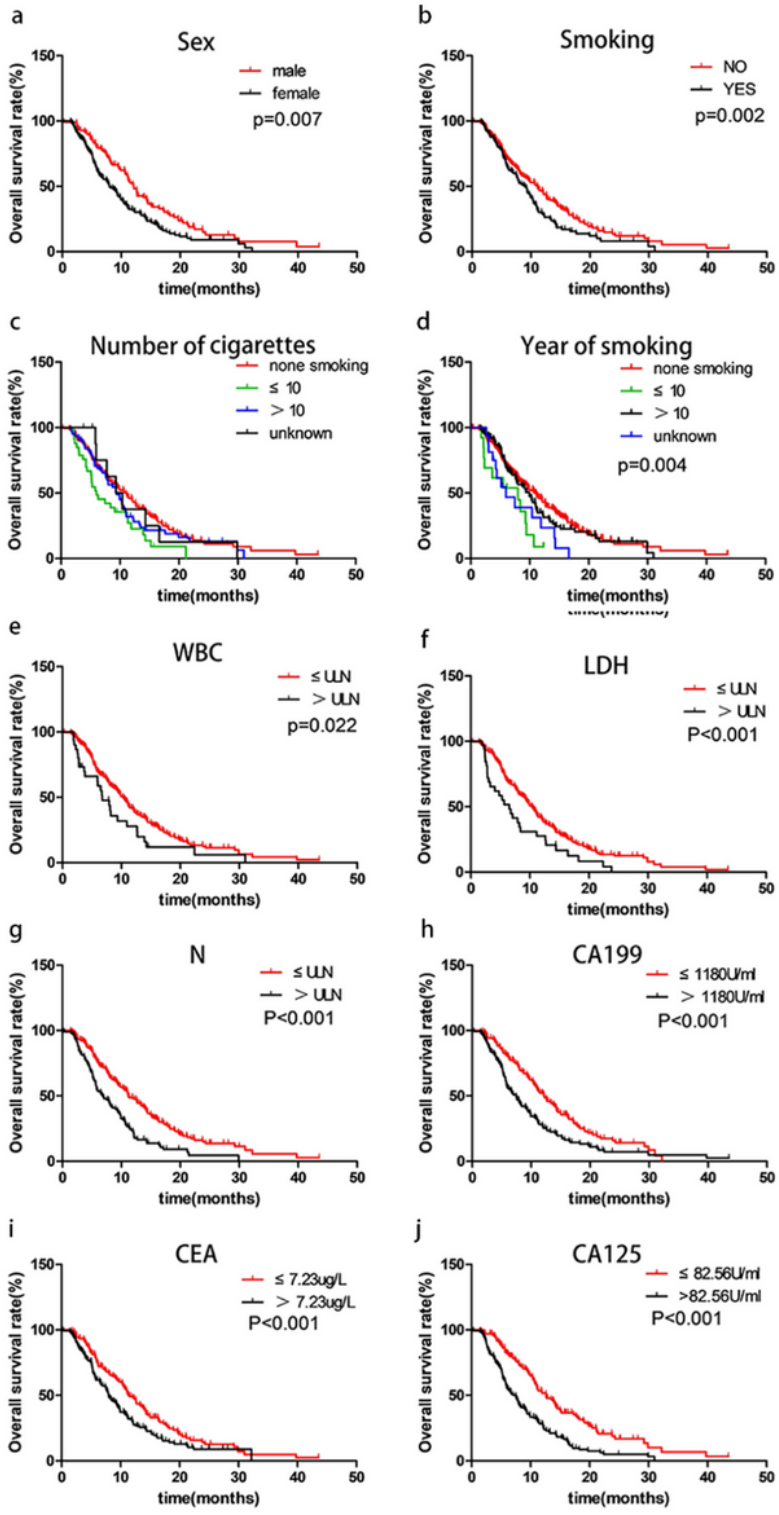

Figure 2

Kaplan-Meier overall survival curves according to the level of different clinical characteristics. a. Sex with overall survival; b. Smoking with overall survival; c. Number of cigarettes ; d. Year of smoking; e. Baseline WBC levels; f. Baseline LDH levels; g. Baseline N counts levels; h. Baseline the median level of serum CA199; i. Baseline the median level of serum CEA; j. Baseline the median level of serum CA125.

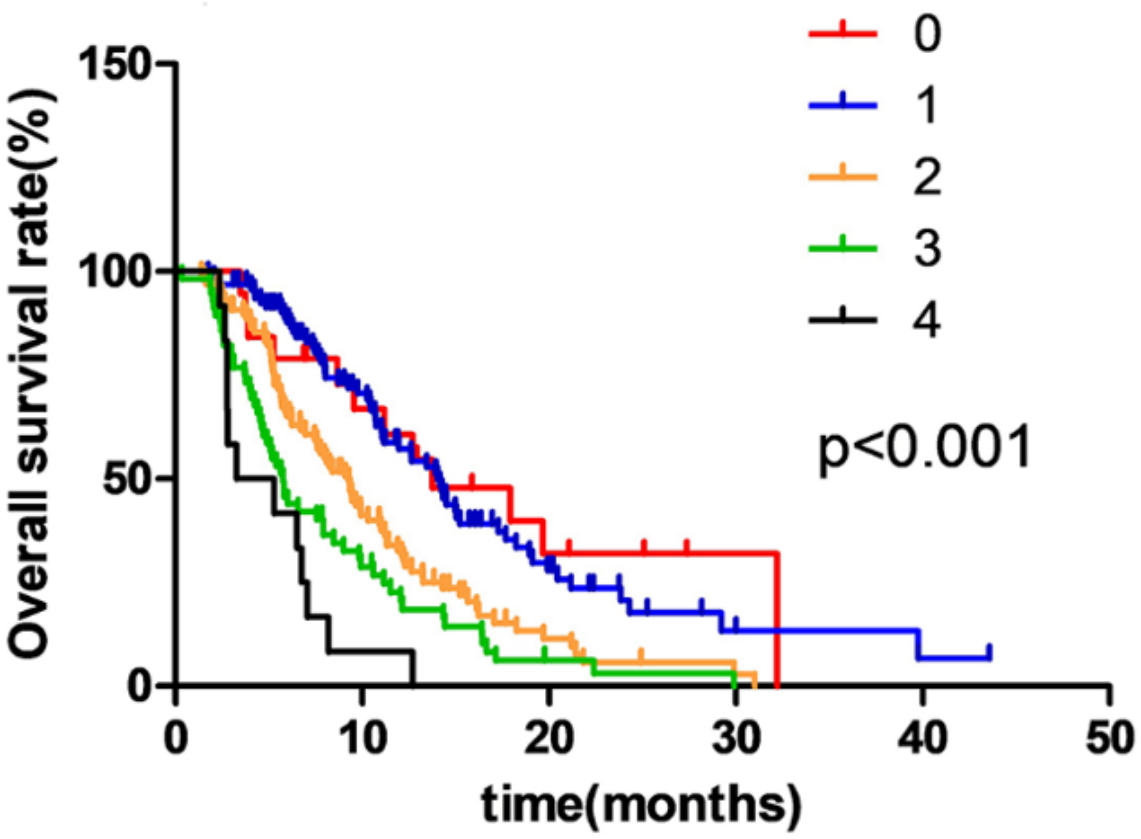

Figure 3

Kaplan-Meier overall survival curves for 278 patients with advanced pancreatic cancer stratified by different scores combining baseline serum N, LDH, CA19-9, and CA125 levels.