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ORIGINAL ARTICLE

Serum levels of LDH, CEA, and CA19-9 have prognostic roles on survival in patients with metastatic pancreatic cancer receiving gemcitabine-based chemotherapy

Faruk Tas · Senem Karabulut · Rumeysa Ciftci · Fatma Sen · Burak Sakar · Rian Disci · Derya Duranyildiz

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Abstract
Purpose Serum LDH, CEA, and CA19-9 levels are important tumor markers in pancreatic cancer. The purpose of this study was to evaluate the clinical significance of serum LDH, CEA, and CA19-9 levels in metastatic pancreatic cancer (MPC) receiving gemcitabine-based chemotherapy.
Materials and methods In this retrospective study, we analyzed the outcome of 196 MPC patients who are treated with gemcitabine-based chemotherapy in our clinic.
Results Positivity rates of serum LDH, CEA, and CA19-9 were 22, 40, and 83 %, respectively. Likewise, the rates of very high serum levels of tumor markers were correlated with these positivity rates (9 % for LDH, 30 % for CEA, and 55 % for CA19-9). The serum LDH levels were significantly higher in older patients ($p = 0.05$) and also in the patients with large tumors ($p = 0.05$), hepatic metastasis ($p = 0.01$), hypoalbuminemia ($p = 0.01$), and unresponsive to chemotherapy ($p = 0.04$). However, no correlation was found between both serum CEA and CA19-9 levels and possible prognostic factors ($p > 0.05$). The significant relationships were found between the serum levels of CEA and CA19-9 ($r_s = 0.24$, $p = 0.004$), and serum LDH and CEA ($r_s = 0.193$, $p = 0.02$). But, there was no correlation between serum LDH and CA19-9 levels ($p = 0.39$). One-year overall survival rate was 12.8 % (95 % CI 8–18). Increased serum levels of all the tumor markers significantly had adverse affect on survival ($p = 0.001$ for LDH, $p = 0.002$ for CEA, and $p = 0.007$ for CA19-9). However, no difference was observed in between high levels and very high levels of serum markers for all tumor markers ($p > 0.05$). Patients with normal serum levels of all three tumor markers had better outcome than others ($p = 0.002$) and those with normal serum LDH and CEA levels (whatever CA19-9) levels had associated with better survival compared with other possible alternatives ($p < 0.001$).
Conclusion Serum levels of LDH, CEA, and CA19-9 had significant affect on survival in MPC patients.

Keywords LDH · CEA · CA19-9 · Metastatic · Pancreatic cancer

F. Tas (✉) · S. Karabulut · R. Ciftci · F. Sen · B. Sakar · R. Disci · D. Duranyildiz
Institute of Oncology, Istanbul University, Capa, 34390 Istanbul, Turkey
e-mail: faruktas2002@yahoo.com

Introduction

Nowadays, pancreatic cancer is still one of the major health problems. In USA, an estimated 45,220 new cases of pancreatic cancer were diagnosed in 2013, and 38,460 deaths are estimated to occur due to the disease [1]. It is responsible for the fourth most common mortal cancer both in men and in women [1]. Its prognosis still remains dismal. Despite all efforts at management, prognosis of patients is unsatisfactory, with 5-year survival rate only 6 % [1]. The majority (85–90 %) of patients present with advanced disease at presentation and its chemo-resistant nature lead to poor outcome.

More than half of all patients (53 %) are diagnosed as metastatic disease at presentation. Five-year survival rate of metastatic pancreatic cancer (MPC) is only 2 % [1]. Treatment options such as chemotherapy or targeted therapy have been investigated to know whether they prolong the overall survival (OS) of MPC patients. Due to moderate progress provided from chemotherapeutics, recent studies evaluated whether subgroups of patients can be identified

Table 1 Patient characteristics

Variables	*n*
No. of patients	196
Age (years)	
Median (range) 59 (32–80) −59/60+	106/90
Gender	
Male/female	122/74
Weight loss (10 %)	
Yes/no	94/35
Performance status	
0–1/2–4	125/57
Jaundice	
Yes/no	59/117
Tumor localization	
Head–neck/corpus-tail	102/79
Tumor size (4 cm)	
Small/large	86/72
Metastasis site	
Liver/bone/lung/periton	163/11/29/27
Erythrocyte sedimentation rate (ESR) (50/h)	
Normal/elevated	28/32
Serum hemoglobin level (12 g/dl)	
Normal/low	107/78
Serum white blood cell (WBC) count (10,000)	
Normal/elevated	137/49
Platelet (450,000)	
Normal/elevated	160/21
Albumin (3.5 g/dl)	
Normal/low	94/34
Chemotherapy type	
Single/combination	136/41
Response to chemotherapy	
Yes/no	27/101

Table 2 Number and percent of patients due to tumor markers

Marker	*n*	%
LDH (U/l)		
Normal (<475)	120	78
High (475–1,000)	31	20
Very high (>1,000)	3	2
CEA (ng/ml)		
Normal (<10)	103	60
High (10–100)	49	28
Very high (>100)	20	12
CA19-9 (IU/ml)		
Normal (<35)	31	17
High (35–1,000)	67	37
Very high (>1,000)	85	46

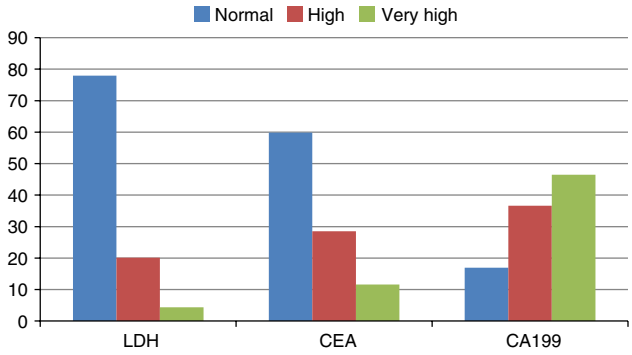

Fig. 1 Percent of patients due to tumor markers

who could benefit most from specific treatment strategies. This would lead to improvement in selection of patients with poor prognosis to be treated only with supportive care and would avoid unnecessary adverse effects and complication of systemic chemotherapy.

Certain prognostic factors are predictive of survival in MPC patients. Good prognostic factors include good performance status at diagnosis, no significant weight loss (not more than 5 %), and female gender. Moreover, biomarker discovery is a complementary research strategy that will likely improve outcomes. The goals of biomarker discovery include early detection, improved prognosis, and optimization of current therapies. So far, several tumor markers of pancreatic cancer have been reported and effective biomarkers have eluded the pancreatic cancer field [2–5]. CA19-9 is the most commonly used pancreatic cancer tumor marker in clinical practice for the evaluating of prediction of prognosis [2–5]. Moreover, early evidence suggests that also other serum tumor markers such as CEA and LDH levels might have a prognostic relevance in patients with advanced pancreatic cancer [2–5].

The present study investigated the impact of pretreatment serum CA19-9, CEA, and LDH levels on the prognosis of MPC patients.

Materials and methods

The data of 196 metastatic patients with histologically confirmed diagnosis of pancreatic cancer, treated and followed up in our clinic, were recorded from medical charts. The localization of tumor was determined surgically, endoscopically, or radiologically. Pathologic confirmation of pancreatic cancer was obtained by surgery or a fine-needle aspiration biopsy. The staging of metastatic patients was done by using various imaging modalities such as computed tomography, magnetic resonance imaging, and PET/CT scan. Patients were staged according to the International Union Against Cancer TNM classification.

Table 3 Results of comparisons between the serum markers and various clinical/laboratory parameters

Variables	LDH			CEA			CA19-9		
	Normal (*n*)	High (*n*)	*p*	Normal (*n*)	High (*n*)	*p*	Normal (*n*)	High (*n*)	*p*
Age (years)									
Young	**72**	**14**	**0.05**	58	34	0.37	15	84	0.48
Older	**48**	**20**		45	35		16	68	
Gender									
Male	79	19	0.29	68	44	0.76	23	93	0.17
Female	41	35		35	25		8	59	
Weight loss									
Yes	60	16	0.20	53	32	0.82	15	73	0.54
No	26	3		18	12		7	25	
Performance status									
Normal	77	15	0.80	66	41	0.47	24	93	0.16
Low	35	14		29	23		6	46	
Jaundice									
Yes	36	12	0.49	29	22	0.56	6	47	0.10
No	72	18		63	39		24	85	
Tumor site									
Head and neck	64	21	0.39	53	37	0.86	15	79	0.98
Body and tail	48	11		41	27		12	64	
Tumor size									
Small	**59**	**10**	**0.05**	50	25	0.30	16	66	0.30
Large	**43**	**17**		39	28		9	59	
Liver metastasis									
Yes	**94**	**33**	**0.01**	85	58	0.63	24	129	0.27
No	**25**	**1**		18	10		7	22	
Bone metastasis									
Yes	10	1	0.28	4	7	0.10	33	7	0.37
No	110	33		99	62		28	145	
Lung metastasis									
Yes	17	4	0.72	17	7	0.24	6	19	0.31
No	103	30		86	62		25	133	
Peritoneal metastasis									
Yes	13	5	0.53	14	10	0.83	2	23	0.20
No	107	29		89	58		29	128	
ESR									
Normal	21	7	0.77	18	10	0.52	3	25	0.36
High	25	7		23	9		6	25	
Hemoglobin									
Normal	69	21	0.77	57	44	0.20	17	90	0.57
Low	48	13		45	23		14	59	
WBC									
Normal	87	29	0.16	77	51	0.94	25	110	0.39
High	31	5		25	17		6	40	
PLT									
Normal	105	29	0.75	92	60	0.74	26	133	0.61
High	12	4		9	7		4	15	
Albumin									
Normal	**89**	**18**	**0.01**	69	44	0.90	22	97	0.50

Table 3 continued

Variables	LDH			CEA			CA19-9		
	Normal (*n*)	High (*n*)	*p*	Normal (*n*)	High (*n*)	*p*	Normal (*n*)	High (*n*)	*p*
Low	**23**	**13**		24	16		6	37	
Response to chemotherapy									
Yes	**23**	**1**	**0.04**	15	8	0.84	6	18	0.32
No	**66**	**19**		62	30		16	82	
Serum LDH level									
Normal	–	–	–	73	42	0.31	19	96	0.44
Higher	–	–		16	14		3	25	
Serum CEA level									
Normal	73	16	0.31	–	–	–	22	79	0.68
Higher	42	14		–	–		7	58	
Serum CA19-9 level									
Normal	19	3	0.44	22	7	0.07	–	–	–
Higher	96	25		79	58		–	–	

Significant *p* values (<0.05) are highlighted in bold

Chemotherapy was given to the majority of the MPC patients ($n = 177$, 90 %). These patients were treated with various chemotherapy regimens as a single-agent or combination therapy. Regimens of single or combination chemotherapy were selected based on performance status of the patients and extension of disease. Drug schemes were applied as follows: gemcitabine alone ($n = 133$, 75 %, combination of gemcitabine with platinum ($n = 26$, 15 %) and capecitabine ($n = 5$, 3 %), capecitabine alone ($n = 3$, 2 %), or 5-FU with folinic acid and cisplatin ($n = 10$, 6 %). Response to chemotherapy was evaluated radiologically after 2–3 cycles of chemotherapy according to international RECIST criteria. Non-responder patients to chemotherapy were treated with second-line chemotherapy if they had a good performance status. Chemotherapy was continued until disease progression or unacceptable toxicity.

The possible prognostic variables were selected based on those identified in previous studies. Serum CEA and CA19-9 levels were determined by microparticle enzyme immunoassay (Abbott Diagnostics, Chicago, IL, USA). Serum LDH levels, albumin, and hemoglobin were measured at presentation in our biochemical laboratory. Serum LDH activity was determined immediately after collection by the kinetic method on a Targa-3000 autoanalyzer (Pointe Scientific Inc., Lincoln Park, MI, USA) at 37 °C. The laboratory parameters were evaluated at diagnosis within the normal ranges of our institution. The upper limits of normal serum tumor marker were 475 U/l for LDH, 10 ng/ml for CEA, and 35 IU/ml for CA19-9. Positivity rates used in this study merely indicated the percentages of patients with a marker level above the normal (cutoff) level.

SPSS software (SPSS 16, Chicago, IL, USA) was used for statistical analyses. The Pearson's Chi square test or Fischer's exact test was used to assess the difference in the distribution of the clinicopathological parameters in the MPC disease. For correlations among tumor markers, Spearman's correlation coefficient with two-tailed significance was used. Overall survival was determined as the time elapsed between the time of histological diagnosis and the date of death or the date of last follow-up visit or the date of point of study if the patient was still alive at this time. Time-dependent variables and OS were estimated by using Kaplan–Meier methods, and their differences were evaluated by the log-rank test. A level of $p \leq 0.05$ was considered as statistically significant.

Results

Demographic, laboratory, and clinicopathological features of patients are listed in Table 1. In this retrospective study, we analyzed the outcome of 196 patients with MPC treated and followed up in our clinic. There were 122 (62 %) male with a median age of 59 years, range 32–80 years. Majority of the patients had good performance status (PS 0–1) (69 %), weight loss than more than 10 % (73 %), head and neck localization (56 %), hepatic metastasis (83 %), and no jaundice (66 %). However, minority have been found as anemic (42 %), leukocytosis (26 %), and hypoalbuminemic (27 %). Single-agent chemotherapy (mostly gemcitabine) was given to majority of the patients (77 %), and response rate to chemotherapy was 22 %.

The positivity rates of serum tumor markers are listed in Table 2 and Fig. 1. Positivity rates of serum LDH, CEA, and CA19-9 were 22, 40, and 83 %, respectively. Likewise, the rates of very high serum levels of tumor markers were correlated with these positivity rates (2/22, 9 % for LDH; 12/40, 30 % for CEA; and 46/83, 55 % for CA19-9).

Table 3 shows the correlation between the serum levels of tumor markers and various clinicopathological factors.

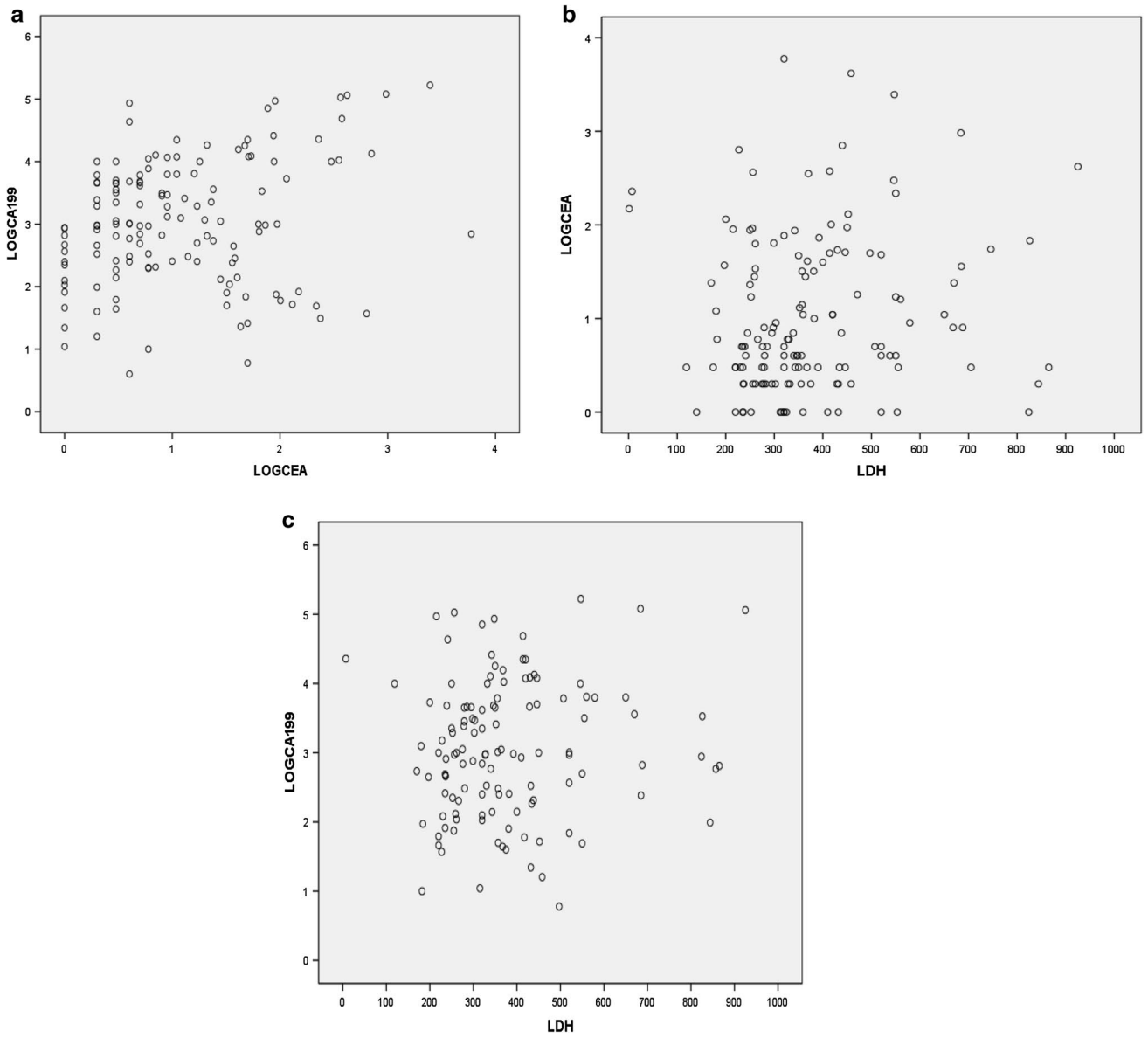

Fig. 2 **a** Correlation between serum CEA and CA19-9 levels in patients ($r_s = 0.24$, $p = 0.004$). **b** Correlation between serum LDH and CEA levels in patients ($r_s = 0.193$, $p = 0.02$). **c** Correlation between serum LDH and CA19-9 levels in patients ($r_s = 0.078$, $p = 0.39$)

The serum LDH levels were significantly higher in older patients (42 vs. 19 %, $p = 0.05$) and also in the patients with large tumors (40 vs. 17 %, $p = 0.05$), hepatic metastasis (35 vs. 4 %, $p = 0.01$), hypoalbuminemia (57 vs. 20 %, $p = 0.01$), and unresponsive to chemotherapy (29 vs. 4 %, $p = 0.04$). The distributions of prognostic factors depend on both serum CEA and CA19-9 levels and were almost identical; no relation was found ($p > 0.05$).

The significant relationships were found between the serum levels of CEA and CA19-9 ($r_s = 0.24$, $p = 0.004$), and serum LDH and CEA ($r_s = 0.193$, $p = 0.02$) (Fig. 2a, b). Contrarily, no correlation between serum LDH and CA19-9 levels ($r_s = 0.078$, $p = 0.39$) was found (Fig. 2c).

The median follow-up time was 174.3 days (range 2–715 days). The median survival for all patients was 159 ± 17.1 days (95 % CI 125.3–192.6). Six-month and 1-year OS rates were 45.4 % (95 % CI 38–52) and 12.8 % (95 % CI 8–18), respectively. As expected, older age ($p = 0.04$), poor performance status ($p = 0.004$), presence of jaundice ($p = 0.01$), leukocytosis ($p = 0.02$), and unresponsiveness to chemotherapy ($p = 0.02$) were associated with worse outcome (Table 4). Likewise, increased serum levels of all the tumor markers significantly had adverse affect on survival ($p = 0.001$ for LDH, $p = 0.002$ for CEA, and $p = 0.007$ for CA19-9) (Table 4). However, survival values of all tumor markers were identical ($p = 0.19$)

Table 4 Univariate analyses of survival

Variables	Median survival (±SE) (days)	*p*
Age (60 years)		
Young	**166.0 (35.5)**	**0.04**
Older	**150.0 (17.9)**	
Gender		
Male	155.0 (20.2)	0.59
Female	166.0 (25.3)	
Weight loss		
Yes	171.0 (22.3)	0.20
No	155.0 (56.3)	
Performance status		
Normal	**193.0 (25.5)**	**0.004**
Low	**117.0 (25.4)**	
Jaundice		
Yes	**117.0 (22.2)**	**0.01**
No	**188.0 (22.7)**	
Tumor site		
Head and neck	159.0 (16.1)	0.48
Body and tail	132.0 (34.2)	
Tumor size		
Small	168.0 (13.0)	0.35
Large	132.0 (39.9)	
Liver metastasis		
Yes	157.0 (13.9)	0.36
No	212.0 (76.6)	
Bone metastasis		
Yes	179.0 (87.5)	0.62
No	157.0 (16.9)	
Lung metastasis		
Yes	212.0 (36.1)	0.59
No	149.0 (15.6)	
Peritoneal metastasis		
Yes	227.0 (58.1)	0.24
No	155.0 (15.9)	
ESR		
Normal	211.0 (25.7)	0.56
High	179.0 (15.5)	
Hemoglobin		
Normal	171.0 (30.9)	0.41
Low	141.0 (13.8)	
WBC		
Normal	**235.0 (38.5)**	**0.02**
High	**141.0 (14.1)**	
PLT		
Normal	164.0 (20.4)	0.75
High	157.0 (18.9)	
Albumin		
Normal	171.0 (21.7)	0.19
Low	125.0 (12.6)	
Response to chemotherapy		
Yes	258.0 (17.6)	**0.02**
No	215.0 (21.9)	
Serum LDH level (475 U/l)		
Normal	**193.0 (22.1)**	**0.001**
Higher	**91.0 (44.1)**	
Serum CEA level (10 ng/ml)		
Normal	**212.0 (25.1)**	**0.002**
Higher	**119.0 (22.8)**	
Serum CA19-9 level (35 IU/ml)		
Normal	**238.0 (53.6)**	**0.007**
Higher	**141.0 (16.1)**	

Significant *p* values (<0.05) are highlighted in bold

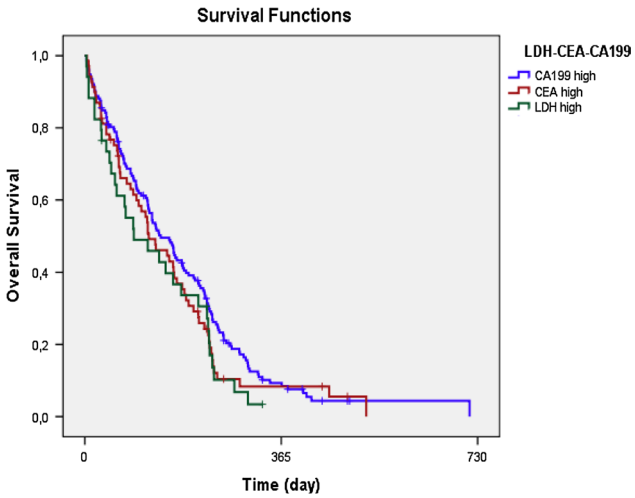

Fig. 3 Overall survival curves of all elevated serum tumor markers ($p = 0.19$)

(Fig. 3). Table 5 also shows the analyses of survival values of all of the tumor markers according to three variables (normal/high/very high serum levels) instead of two variables (normal/high serum levels). Similar significant OS values were found in these analyses ($p = 0.003$ for LDH, $p = 0.009$ for CEA, and $p = 0.01$ for CA19-9 (Fig. 4a–c). However, no difference was observed in between high levels and very high levels of serum markers for all tumor markers ($p > 0.05$).

When we assessed the survival analyses according to various tumor marker combinations in the same patients, it seems that the patients with normal serum levels of all three tumor markers had better outcome than others ($p = 0.002$) (Table 6a; Fig. 5a). The patients with normal serum LDH and CEA levels (whatever CA19-9 levels) had associated

Table 5 Survival values according to all tumor markers

Marker	Median survival (±SE) (days)	*p*
LDH		
Normal	193.0 (22.1)	**0.003**
High	91.0 (39.1)	
Very high	179.0 (72.6)	
CEA		
Normal	212.0 (25.1)	**0.009**
High	119.0 (33.2)	
Very high	116.0 (49.3)	
CA19-9		
Normal	238.0 (56.3)	**0.01**
High	131.0 (35.6)	
Very high	159.0 (19.5)	

Table 6 Survival values according to various marker combinations

LDH	CEA	CA19-9	*n*	Median survival (±SE) (days)	*p*
(a)					
Normal	Normal	Normal	15	311.0 (83.5)	
Normal	Normal	High	58	220.0 (21.9)	
High	High	High	13	164.0 (62.4)	**0.002**
Normal	High	High	37	131.0 (32.6)	
High	Normal	High	11	76.0 (40.1)	
(b)					
Normal	Normal	Normal	15		
Normal	Normal	High	58	237 (15.2)	
High	High	High	13		**<0.001**
Normal	High	High	37	117 (20.5)	
High	Normal	High	11		

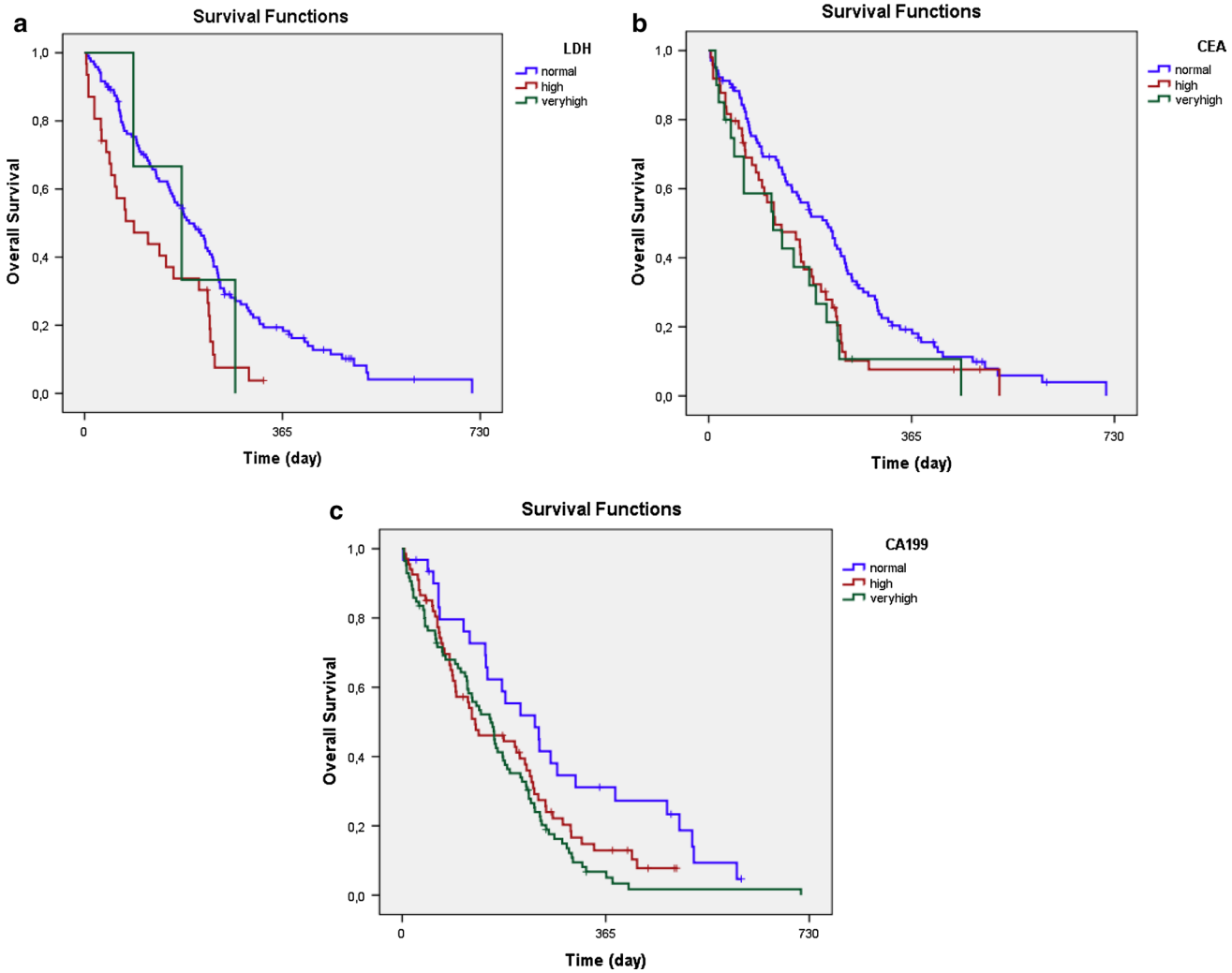

Fig. 4 **a** Survival curves in patients according to LDH levels (normal–high–very high) ($p = 0.003$). **b** Survival curves in patients according to CEA levels (normal–high–very high) ($p = 0.009$). **c** Survival curves in patients according to CA19-9 levels (normal–high–very high) ($p = 0.01$)

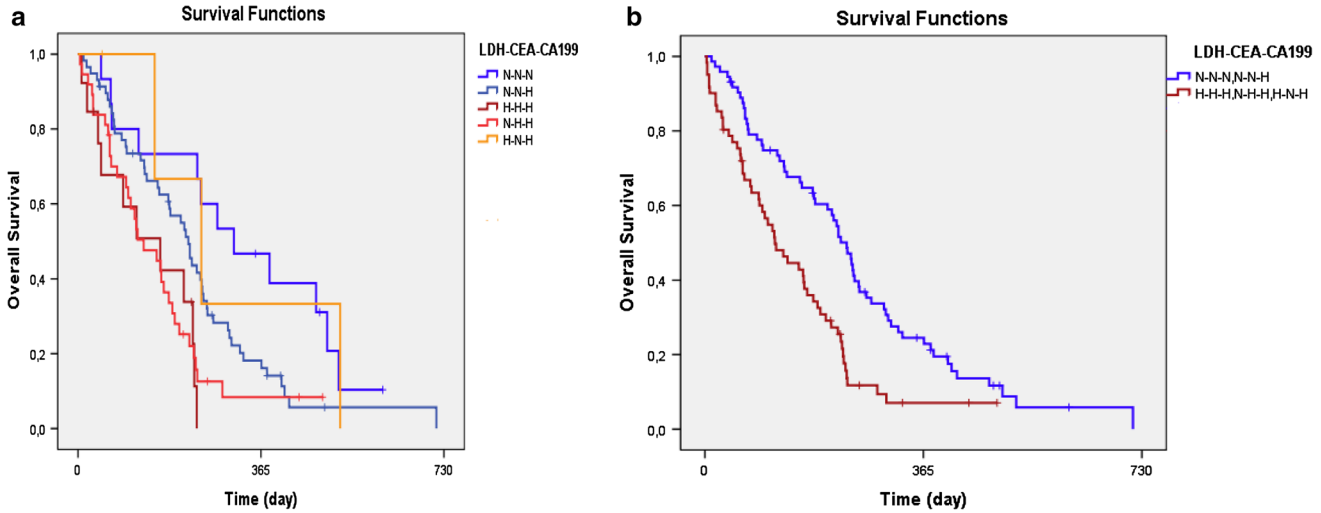

Fig. 5 Survival curves in patients according to various marker combinations. *N* normal serum level, *H* higher serum level. **a** ($p = 0.002$), **b** ($p < 0.001$)

with better survival compared with other possible alternatives ($p < 0.001$) (Table 6b; Fig. 5b).

Discussion

In this retrospective study, we investigated the clinical significance and the prognostic role of three serum biochemical variables in 196 pancreatic cancer patients with limited metastatic disease. We found that the positivity rates of serum LDH, CEA, and CA19-9 were 22, 40, and 83 %, respectively. Moreover, the rates of very high serum levels of these tumor markers were correlated with these positivity rates (9 % for LDH, 30 % for CEA, and 55 % for CA19-9). The serum LDH levels were significantly higher in the patients with large tumors ($p = 0.05$), hepatic metastasis ($p = 0.01$), hypoalbuminemia ($p = 0.01$), and unresponsive to chemotherapy ($p = 0.04$). However, no similar relationships were determined for both serum CEA and CA19-9 levels. As expected, older age ($p = 0.04$), poor performance status ($p = 0.004$), presence of jaundice ($p = 0.01$), leukocytosis ($p = 0.02$), and unresponsiveness to chemotherapy ($p = 0.02$) were associated with worse outcome. Likewise, increased serum levels of all the tumor markers significantly had adverse affect on survival ($p = 0.001$ for LDH, $p = 0.002$ for CEA, and $p = 0.007$ for CA19-9). However, survival values of all tumor markers were identical ($p = 0.19$). Similarly, no difference was observed in between high levels and very high levels of serum markers for all tumor markers ($p > 0.05$). The patients with normal serum levels of all three tumor markers had better outcome than others ($p = 0.002$). Additionally, the patients with normal serum LDH and CEA levels (whatever CA19-9 levels) had associated with better survival compared with other possible combination alternatives ($p < 0.001$).

We analyzed earlier the outcome of 127 patients with pancreatic cancer treated and followed up in our clinic [2]. We found that only elevated serum CEA levels were predominant in metastatic group compared with serum CA19-9 and LDH levels ($p = 0.04$). In 56 metastatic cases, only patients with elevated LDH levels had a shorter survival outcome compared with those with normal values (10 vs. 39 months, $p = 0.0001$). Similarly such a survival advantage was not shown in patients with higher CA19-9 and CEA serum levels.

Data from 291 advanced pancreatic cancer patients [243 patients (84 %) had metastatic disease], using the predefined CA19-9 cutoff of 1,000 U/ml, a significant correlation with time to progression (TTP), was observed (6.1 vs. 4 months, $p = 0.002$) [3]. Moreover, CA19-9 values below 1,000 U/ml were linked with an improved OS, regardless of all CA19-9 values (10.5 vs. 8 months, $p = 0.006$). Additionally, a highly significant correlation of baseline CA19-9 as continuous variable with both TTP and OS was observed through all subgroups. Serum CEA values below or above a cutoff of 4.5 ng/ml showed a significant correlation with TTP (6.1 vs. 3.5 months, $p < 0.001$), and comparable results were seen when log CEA was analyzed as continuous variable (HR 1.11, $p = 0.004$). However, the correlation of baseline CEA values with OS did not reach a level of statistical significance. Among laboratory parameters, normal LDH values (<250 U/l) had a prognostic significance for both TTP (5.4 vs. 3.4 months, $p < 0.001$) and OS (9.9 vs. 5.9 months, $p < 0.001$). When LDH was analyzed into a Cox proportional hazard regression model, the level of significance remained with a HR of 1.65 ($p = 0.004$) for

TTP and a HR of 1.93 $p < 0.001$) for OS. In a multivariate Cox model for TTP, only serum CA19-9 showed independent statistical significance among tumor markers (HR 1.18, $p < 0.001$). However, none of the tumor markers was an independent prognostic value for OS.

A retrospective review of 187 patients with pancreatic cancer [71 (38 %) locally advanced, 74 (39.6 %) advanced disease], elevated serum CA19-9 (>37 U/ml) and CEA (>5 ng/ml) levels were observed in 77.2 and 40.7 % of patients with advanced pancreatic cancer at diagnosis, respectively [4]. There was no association between CA19-9 level and tumor stages ($p = 0.15$), but CEA increased as tumor sizes and stages progressed ($p = 0.001$ and $p = 0.005$, respectively). In these 145 patients with advanced disease, both the median progression-free survival (PFS) and OS values of the normal and elevated CA19-9 group were identical (4.6 vs. 5.3 months, $p = 0.735$, and 8.4 vs. 11.6 months, $p = 0.597$, respectively). However, the median PFS and OS between the normal and elevated CEA cases were significantly different (6.3 vs. 3.7 months, $p = 0.012$ and 13.4 vs. 8.2 months, $p = 0.003$, respectively).

The meta-analytic data from 653 advanced pancreatic cancer consist of 436 (67 %) metastatic patients analyzed for many (a total of 34) prognostic factors including serum CA19-9, CEA and LDH [5]. Among these tumor markers, serum CA19-9 (median survival 6.3 vs. 4.6 months, $p = 0.028$) and LDH levels (median survival 5.2 vs. 2.1 months, $p < 0.001$) were found to be highly significant and influential prognostic factors.

These contradicting results of these several studies might be attributable to several factors. In many cases, these studies heterogenous group included a small number of patients, mostly not limited to specific disease stage and treatment modality, or applied a wide range of cutoff levels. To determine whether these serum tumor markers can be generally applicable prognostic markers of pancreatic cancer, the use of these biomarkers should be tested in a large number of patients with various stages of pancreatic cancer.

In conclusion, we found that all serum tumor markers consist of CA19-9, CEA and LDH were prognostic value in patients with MPC. Further studies with much large-scale, prospective, homogenous staged and standard cutoff level are needed to determine the exact role of these serum tumor marker levels in terms of clinical significance in these cancer patients.

Conflict of interest None declared.

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