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ORIGINAL ARTICLE

CALy Prognostic Score (CEA, ALP, Lymphocyte Count) as a predictor of survival after hepatectomy for liver-only colorectal metastases

Kyriakos Neofytou[1], Alexandros Giakoustidis[1], Satvinder Mudan[1,2]

[1]Department of Academic Surgery, Royal Marsden Hospital, Fulham Road, London, UK; [2]Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, UK

Summary

Purpose: *The discovery of prognostic factors for patients who undergo hepatectomy for colorectal liver metastases (CRLM) in the era of neoadjuvant chemotherapy is imperative. This study aimed to establish a simple, cheap and easily available prognostic score for these patients.*

Methods: *Preoperative carcinoembryonic antigen (CEA), serum alkaline phosphatase (ALP), and lymphocyte count (LC) were used for the establishment of a prognostic score (CALy PS). The cut-off levels of these variables were determined by applying receiver operating curve (ROC) analysis. The final prognostic score assigned one risk point for each variable (CEA>4 ug/L, ALP>93 U/L, and LC≤1.6x10^9/L).*

Results: *One hundred and thirty-five patients were included. Two risk categories were established with 0-1 and 2-3 points, respectively. CALy 0-1 vs CALy 2-3, and CALy 2-3 were associated with decreased disease free survival (DFS) and overall survival (OS) both in univariate and multivariate analysis (DFS: HR 1.84; 95% CI 1.18-2.86; p=0.007; OS: HR 2.25; 95% CI 1.23-4.11; p=0.008). When four risk categories were established with 0,1,2,and 3 points,CALy was again associated with decreased DFS and OS both in univariate and in multivariate analysis (DFS: HR 1.37; 95% CI 1.083-1.74; p=0.009; OS:HR 1.84; 95% CI 1.31-2.59; p<0.001). Three-year DFS rates for these categories (CALy 0, CALy 1, CALy 2, and CALy 3) were 45, 38, 15 and 7%, respectively, and the 5-year OS rates were 78, 68, 32, and 24%, respectively.*

Conclusion: *This simple, cheap, and easily available risk score provides good prognostic accuracy for both DFS and OS for patients undergoing liver resection for liver-only colorectal metastases after neoadjuvant chemotherapy.*

Key words: *carcinoembryonic antigen, colorectal liver metastases, lymphocyte count, prognostic score, serum alkaline phosphatase*

Introduction

Colorectal cancer is the third most common cancer worldwide, with half of the patients developing CRLM during the course of their disease [1]. Surgical resection of CRLM in combination with systemic chemotherapy has been demonstrated to increase patient survival, with a 5-year OS ranging between 35 and 58% for resected cases [2]. Unfortunately, only 15-20% of these patients are candidates for hepatectomy. In an effort to increase this rate, the administration of neoadjuvant chemotherapy has dominated, and its main objective is the downsizing of metastases. The indications for hepatectomy have increased; in specialised centres, complex liver resections are performed with mortality below 5% [3,4].

There is still the question of the candidates that would truly benefit from hepatectomy, an intervention accompanied by morbidity reaching

Correspondence to: Kyriakos Neofytou, MD, MSc. Fulham Road, SW3 6JJ, London, UK. Tel: +44 07741749087, Fax: +44 (0)20 79354444, E-mail: kneophy2@gmail.com
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or exceeding 40% [3,4], whereas it is curative for only 16% of these patients the rest of whom will develop recurrent disease [5]. The need for new reliable prognostic factors is imperative, as traditional prognostic factors (established before the era of neoadjuvant chemotherapy and the expanded criteria for hepatectomy) either do not apply or at least are questioning [4,6]. These new prognostic factors have to demonstrate high sensitivity and specificity, but at the same time, they have to be simple, cheap and easily available.

ALP has been used in the past both for the diagnosis of CRLM and also as a prognostic factor for patients undergoing hepatectomy for CRLM [7,8]. At the same time, the prognostic value of preoperative CEA is documented in the literature [9]. Furthermore, circulating lymphocytes are the source of tumour-infiltrating lymphocytes, which are related to beneficial patient progress in various malignancies [10].

The purpose of this study was to ascertain whether a novel prognostic score based on preoperative CEA, serum ALP and LC affects the DFS and OS of patients with liver-only colorectal metastases undergoing hepatectomy after neoadjuvant chemotherapy.

Methods

We used our prospectively accumulated surgical database to identify patients who underwent liver resection at the Royal Marsden Hospital between January 2005 and December 2012. Patients who underwent liver resection for CRLM and who received preoperative chemotherapy were included for study. The exclusion criteria were as follows: a) extrahepatic disease (17 patients), b) no neoadjuvant chemotherapy (15 patients), c) incomplete resection - R2 resection (4 patients), d) death within 90 days from operation (2 patients), e) missing data for preoperative CEA, ALP or LC (3 patients), and f) missed follow-up during the first year after hepatectomy (5 patients).

The therapeutic strategy for every patient was outlined by discussion in a multidisciplinary team meeting. For the exclusion of extrahepatic disease, all patients underwent computed tomography of the chest, abdomen and pelvis. In addition, for the same reason, most of the patients underwent fluorodeoxyglucose-positron emission tomography (FDG-PET). Portal vein embolisation was performed 4 weeks prior to surgery in cases when the future liver remnant was considered to be inadequate (future liver remnant to whole liver volume ratios <30%).

For each patient, the institutional electronic records were checked, and data were collected regarding the following: a) standard demographics, b) primary colorectal tumour, c) CRLM characteristics, d) preoperative chemotherapy, e) response to preoperative chemotherapy, f) liver resection, and g) DFS and OS.

Serum ALP and LC were measured within 10 days before surgery as part of the routine preoperative work up of the patients. CEA was measured after the completion of neoadjuvant chemotherapy.

The study was approved by the local ethics committee and Institutional Review Board.

Statistics

Statistical analyses were performed with the Statistical Package of the Social Sciences (SPSS), version 17.0. The primary end points of the study were DFS and OS. DFS was calculated from the date of hepatectomy to the date of disease recurrence and was censored at the last follow up or at the time of unrelated to cancer death if the patients remained tumour free at that time. OS was calculated from the time of diagnosis to the date of cancer-related death.

We determined the optimal cut-off levels for the CEA, serum ALP and lymphocyte count by applying ROC analysis (1). For CEA, the area under the curve was 0.57 (95% CI 0.47 to 0.67) for OS and 0.70 (95% CI 0.60 to 0.80) for DFS. The value of 4 was chosen as the cut-off level for CEA for both DFS and OS, as this value is associated with high sensitivity and specificity for DFS (0.635 and 0.718, respectively) and OS (0.620 and 0.518, respectively). For serum ALP, the area under the curve was 0.62 (95% CI 0.52 to 0.72) for OS but only 0.53 (95% CI 0.43 to 0.63) for DFS. The value of 93 was chosen as the cut-off level for serum ALP for both DFS and OS, as this value is associated with a reasonable sensitivity and high specificity for DFS (0.378 and 0.750, respectively) and OS (0.500 and 0.750, respectively).

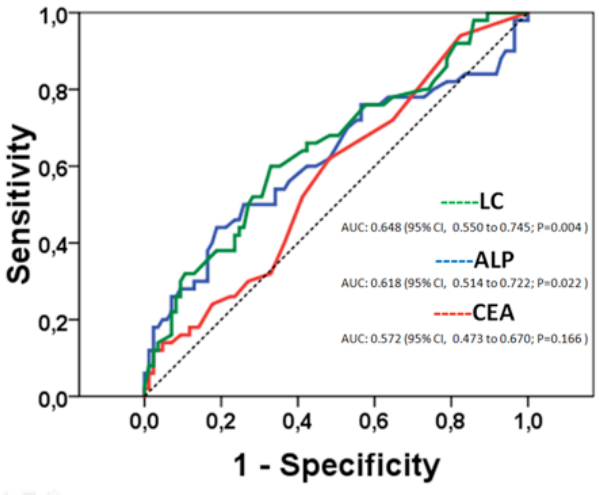

Figure 1. Receiver operating curve (ROC) for preoperative lymphocyte count (LC), preoperative alkaline phosphatase (ALP), preoperative CEA, and cancer-related death. AUC= Area Under the Curve, CI= Confidence Interval.

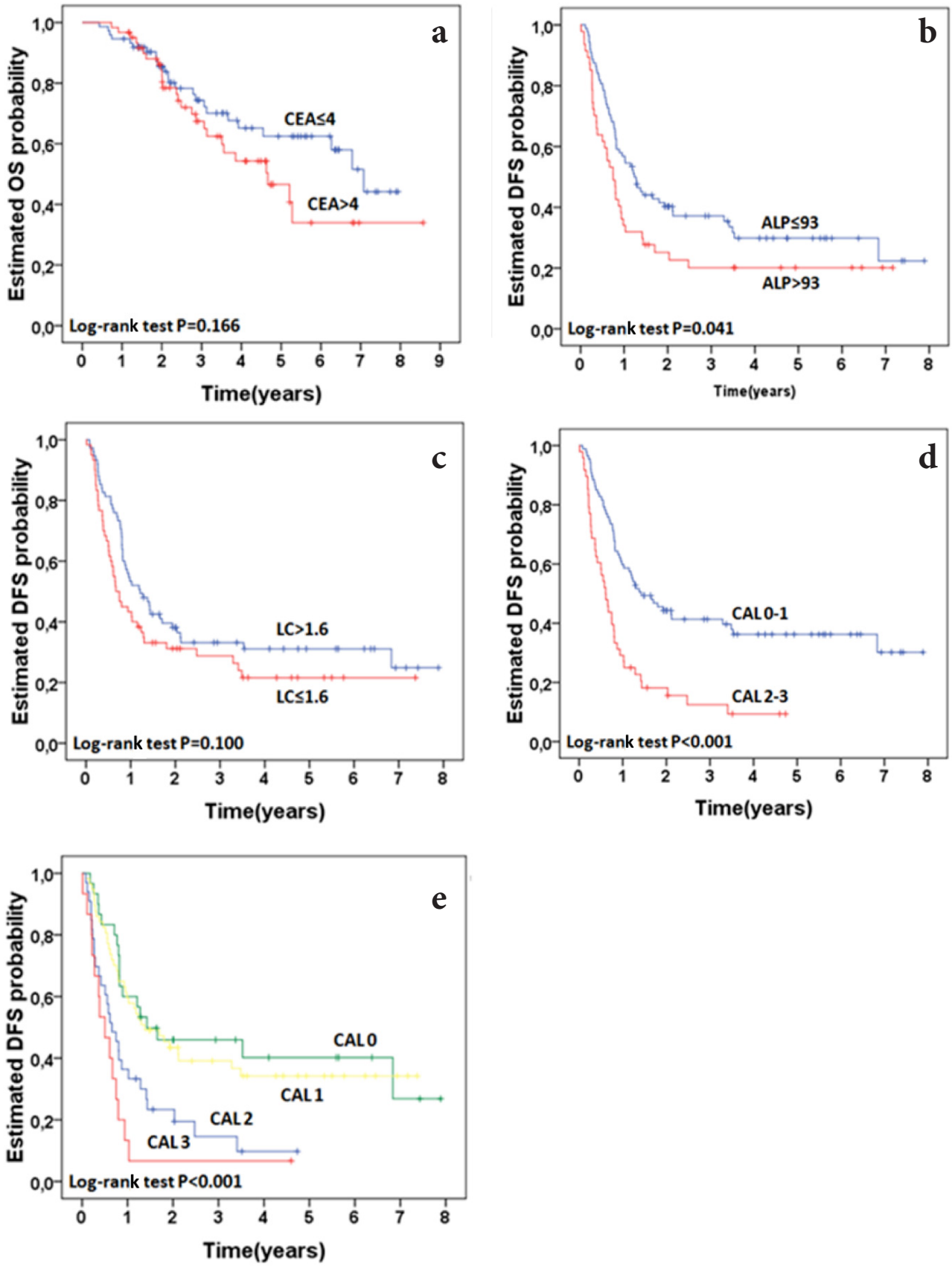

Figure 2. DFS and **a)** Preoperative CEA, **b)** Preoperative alkaline phosphatase (ALP), **c)** Preoperative lymphocyte count (LC), **d)** CALy 0-1 vs CALy 2-3, **e)** CALy 0 vs CALy 1 vs CALy 2 vs CALy 3.

Table 1. Baseline clinicopathologic characteristics and their association with DFS and OS in univariate analysis

			DFS		*OS*	
Parameter	*N*	*%*	*HR (95% CI)*	*p value*	*HR (95% CI)*	*p value*
Age at operation (years)						
≤ 70	104	77	1 (referent)		1 (referent)	
>70	31	23	1.35 (0.85-2.15)	0.19	2.15(1.17-3.95)	0.013
No. of metastases at diagnosis						
≤ 3	105	77.8	1 (referent)		1 (referent)	
>3	30	22.2	2.03 (1.29-3.19)	0.002	1.72 (0.91-3.25)	0.091
Distribution of lesions						
Unilobar	91	67.4	1 (referent)		1 (referent)	
Bilobar	44	32.6	2.24 (1.46-3.43)	<0.001	2.65 (1.50-4.69)	0.001
Size of largest metastases (cm)						
≤ 5	106	80.3	1 (referent)		1 (referent)	
>5	26	19.7	1.33 (0.82-2.15)	0.233	1.13 (0.58-2.22)	0.708
Timing of metastasis						
Synchronous	92	68.1	1 (referent)		1(referent)	
Metachronous	43	31.9	0.91 (0.59-1.41)	0.691	0.88 (0.48-1.59)	0.674
PVE						
No	123	91.1	1 (referent)		1 (referent)	
Yes	12	8.9	2.82 (1.52-5.24)	0.001	1.97 (0.77-5.01)	0.154
Type of neoadjuvant chemotherapy						
Oxaliplatin-based	88	66.2	1 (referent)		1 (referent)	
Irinotecan- based	45	33.8	1.35 (0.89-2.06)	0.153	1.20 (0.66-2.19)	0.547
Preoperative administration of Bevacizumab						
No	86	63.7	1 (referent)		1 (referent)	
Yes	49	36.3	1.31 (0.86-1.97)	0.196	1.00 (0.56-1.78)	0.999
Response to neoadjuvant chemotherapy						
Responders[+]	121	89.6	1 (referent)		1 (referent)	
Progression	14	10.4	3.79 (2.09-6.85)	<0.001	2.40 (1.06-5.42)	0.034
No. of segments removed						
≤ 3	69	51.1	1 (referent)		1 (referent)	
>3	66	48.9	1.28 (0.86-1.92)	0.221	1.34 (0.77-2.35)	0.296
Primary tumour *in situ* at the time of hepatectomy						
No	112	83	1 (referent)		1 (referent)	
Yes[++]	23	17	1.66 (1.01-2.75)	0.045	1.07 (0.50-2.28)	0.860
Adjuvant chemotherapy						
Yes	102	75.6	1 (referent)		1 (referent)	
No	33	24.4	2.41 (1.54-3.78)	<0.001	3.19 (1.77-5.74)	<0.001
Preoperative CEA						
≤4	74	54.8	1 (referent)		1 (referent)	
>4	61	45.2	2.15 (1.43-3.24)	<0.001	1.48 (0.84-2.60)	0.168
Preoperative ALP						
≤ 93	88	65.2	1 (referent)		1 (referent)	
>93	47	34.8	1.53 (1.01-2.31)	0.043	2.34 (1.34-4.09)	0.003
Preoperative lymphocyte count						
>1.6	75	55.6	1(referent)		1 (referent)	
≤ 1.6	60	44.4	1.39 (0.93-2.02)	0.102	2.57 (1.46-4.55)	0.001
CALy prognostic score						
0-1	87	64.4	1 (referent)		1 (referent)	
2-3	48	35.6	2.45(1.62-3.69)	<0.001	2.88 (1.64-5.06)	<0.001
CALy prognostic score						
0	30	22.2	1 (referent)		1 (referent)	
1	57	42.2	1.10 (0.62-1.94)		2.10 (0.77-5.71)	
2	33	24.5	1.54 (1.13-2.09)		1.96 (1.19-3.23)	
3	15	11.1	1.56 (1.22-2.00)	<0.001	1.79 (1.24-2.59)	<0.001

DFS: disease-free survival, OS: overall survival, HR: hazards ratio, CI: confidence interval, PVE: portal vein embolisation.
[+]Radiologic complete response or radiologic partial response or stable disease (according to RECIST)
[++]16 patients underwent synchronous resection of primary tumour and CRLM, and 7 patients were managed with a 'liver first' approach.

Table 2. Relationships between baseline clinicopathologic characteristics and CALy

Parameter	*CALy* 0-1 N (%)	2-3 N (%)	*p value*
Age at operation (years)			
≤ 70	71 (81.6)	33 (68.8)	
>70	16 (18.4)	15 (31.3)	0.089
No. of metastases at diagnosis			
≤ 3	70 (80.5)	35 (72.9)	
>3	17 (19.5)	13 (27.1)	0.313
Distribution of lesions			
Unilobar	61 (70.1)	30 (62.5)	
Bilobar	26 (29.9)	18 (37.5)	0.366
Size of largest metastases (cm)			
≤ 5	69 (81.2)	37 (78.7)	
>5	16 (18.8)	10 (21.3)	0.734
Unknown	2	1	
Timing of metastasis			
Synchronous	61 (70.1)	31 (64.6)	
Metachronous	26 (29.9)	17 (35.4)	0.509
PVE			
No	82 (94.3)	41 (85.4)	
Yes	5 (5.7)	7 (14.6)	0.084
Type of neoadjuvant chemotherapy			
Oxaliplatin-based	55 (63.2)	33 (68.8)	
Irinotecan- based	30 (24.5)	15 (31.3)	
Other	2 (2.3)		0.636
Preoperative administration of Bevacizumab			
No	53 (60.9)	33 (68.8)	
Yes	34 (39.1)	15 (31.3)	0.365
Response to neoadjuvant chemotherapy			
Responders	81 (93.1)	40 (83.3)	
Progression	6 (6.9)	8 (16.7)	0.075
Primary tumour *in situ* at the time of hepatectomy			
No	72 (82.8)	40(83.3)	
Yes	15 (17.2)	8(16.7)	0.932

PVE: portal vein embolisation

For the preoperative LC, the area under the curve was 0.65 (95% CI 0.55 to 0.75) for OS and 0.56 (95% CI 0.46 to 0.66) for DFS. The value of 1.6 was chosen as the cut-off level for LC for both DFS and OS, as this value is associated with high sensitivity and specificity for DFS (0.469 and 0.715, respectively) and OS (0.600 and 0.588, respectively).

The final prognostic score assigned one risk point for each variable (CEA>4 ug/L, ALP>93 U/L, LC ≤ $1.6x10^9$/L). Initially, two risk categories were established with 0-1 and 2-3 points (CALy 0-1 vs CALy 2-3, respectively). Thereafter, four risk categories were established with 0,1,2, and 3 points (CALy 0, CALy 1, CALy 2, and CALy 3, respectively).

The Chi-square test was used for calculating the association between clinicopathologic characteristics and dichotomised CEA, serum ALP, LC, and CALy PS. The impact of these features on DFS and OS was analysed using the Kaplan-Meier method. Survival outcomes between groups were compared with the log-rank test. P value of less than 0.05 was considered statistically significant. The factors associated with the DFS or the OS (p >0.1) in univariate analysis were used for the multivariate Cox regression analysis.

Results

A total of 135 patients were enrolled. The

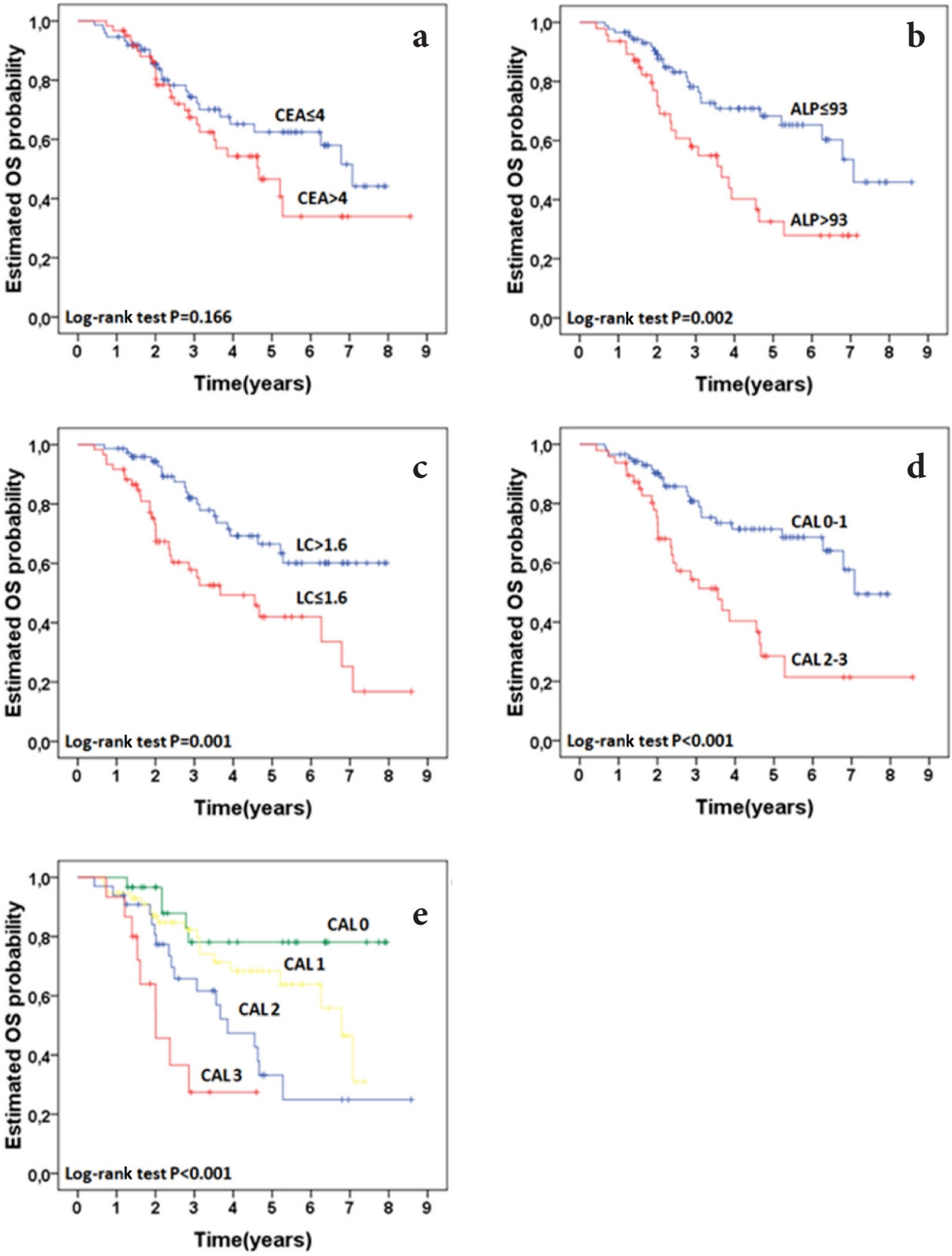

Figure 3. OS and **a)** Preoperative CEA, **b)** Preoperative alkaline phosphatase (ALP), **c)** Preoperative lymphocyte count (LC), **d)** CALy 0-1 vs CALy 2-3, **e)** CALy 0 vs CALy 1 vs CALy 2 vs CALy 3.

Table 3. Multivariate analysis of factors affecting disease free survival and overall survival

	DFS		*OS*	
Parameter	*HR (95% CI)*	*p value*	*HR(95% CI)*	*p value*
Age at operation >70			1.80 (0.92-3.53)	0.084
>3 metastases at diagnosis	1.37 (0.79-2.40)	0.257	1.09 (0.52-2.28)	0.815
Bilobar distribution of lesions	1.71 (1.03-2.83)	0.035	2.36 (1.17-4.74)	0.015
PVE	1.27 (0.60-2.67)	0.524		
Disease progression during neoadjuvant chemotherapy	2.85 (1.47-5.55)	0.002	1.61 (0.65-3.99)	0.296
Primary tumour *in situ*	1.28 (0.75-2.18)	0.360		
No adjuvant chemotherapy	1.65 (1.00-2.71)	0.048	1.84 (0.96-3.53)	0.066
CALy 2-3	1.84 (1.18-2.86)	0.007	2.25 (1.23-4.11)	0.008

DFS: disease free survival, OS: overall survival, HR: hazards ratio, CI: confidence interval, PVE: portal vein embolisation

demographic characteristics of the patients, the characteristics of CRLM at diagnosis, and the treatment of patients are shown in Table 1. The preoperative serum ALP was >93 (high) in 47 patients (34.8%). The CEA was >4 (high) in 61 patients (45.2%), and the LC was <1.6 (low) in 60 patients (44.4%). The CALy was 0-1 in 87 (64.4%) patients (low risk) and 2-3 in 48 patients (high risk).

The median follow-up period was 34 months (range 5-103). For the entire study population, the 1-, 3- and 5-year DFS rates were 49, 31 and 26%, respectively, whereas the 1-, 3- and 5-year OS rates were 96,71 and 56%, respectively.

As demonstrated in Table 2, there was no significant difference in clinicopathologic characteristics or given treatment between patients with CALy 0-1 and CALy 2-3. In addition, there was no difference in clinicopathologic characteristics between patients with high and low CEA or high and low LC (data not shown). Regarding ALP, high ALP was significantly associated with a bilobar distribution of CRLM and preoperative PVE (p=0.029 and p=0.015, respectively). Furthermore, there was no association between the variables composing CALy (CEA, ALP, and LC) (Supplementary Table 1).

During the follow-up period, 96 patients (71.1%) developed tumour recurrence and 50 (37%) died because of progressive disease.

Supplementary Table 1. Relationships between the components of CALy

	CEA >4	*ALP >93*
ALP >93	0.522*	
Lymphocytes ≤ 1.6	0.176*	0.258*

*p-value (chi-square test)

Within the group of patients with CALy 2-3, the recurrence rate was much higher, with 42 (87.5%) of the 48 patients developing tumour recurrence. The corresponding rate for the group of patients with CALy 0-1 was 62.1% (87.5 vs 62.1%, p=0.002). Cancer-related death occurred in 27 of 48 (56.3%) patients with CALy 2-3 and in 23 of 87 (26.4%) patients with CALy 0-1 (p=0.001).

The results of univariate analyses demonstrated that more than 3 liver metastases at diagnosis (HR 2.03; 95% CI 1.29-3.19, p=0.002), bilobar distribution of lesions (HR 2.24; 95% CI 1.46-3.43; p<0.001), preoperatively portal vein embolisation (HR 2.82; 95% CI 1.52-5.24; p=0.001), disease progression during neoadjuvant chemotherapy according to RECIST criteria [11] (HR 3.79; 95% CI 2.09-6.68 ; p<0.001), primary tumour *in situ* at the time of hepatectomy (HR 1.66; 95% CI 1.01-2.75; p=0.045), not administrating adjuvant chemotherapy (HR 2.41; 95% CI 1.54-3.78; p<0.001), and CALy 2-3 (HR 2.45; 95% CI 1.62-3.69; p<0.001) were associated with a decreased DFS (Table 1). The patients with CALy 2-3 displayed a median DFS of 7.3 months compared with the DFS of 17.1 months of the patients with CALy 0-1 (Figure 2). The 3- and 5-year DFS rates were 12 and 9%, respectively, in patients with CALy 2-3 and 41 and 36%, respectively, in patients with CALy 0-1.

Regarding OS, the results of univariate analyses revealed that an age greater than 70 years (HR 2.15; 95% CI 1.17-3.95; p=0.013), bilobar distribution of lesions (HR 2.65; 95% CI 1.50-4.69; p=0.001), disease progression during neoadjuvant chemotherapy according to RECIST criteria [24] (HR 2.40; 95% CI 1.06-5.42; p=0.034), not administering adjuvant chemotherapy (HR 3.19; 95% CI 1.77-5.74; p<0.001), and CALy 2-3 (HR 2.88; 95%

CI 1.64-5.06; p<0.001) were associated with decreased OS (Table 1). Patients with CALy 2-3 displayed a median OS of 43 months compared with the OS of 85 months of the patients with CALy 0-1. (Figure 3). The 3- and 5-year OS rates were 55 and 28%, respectively in patients with CALy 2-3 and 81 and 71%, respectively, in patients with CALy 0-1.

Multivariate analysis for DFS was adjusted for the number of CRLM, distribution of CRLM, preoperatively portal vein embolisation (PVE), response to neoadjuvant chemotherapy, presence of primary colorectal tumour *in situ* at the time of hepatectomy, and administration of adjuvant chemotherapy. For OS, the multivariate analysis was adjusted for age at hepatectomy, number of CRLM, distribution of CRLM, response to neoadjuvant chemotherapy, and administration of adjuvant chemotherapy.

In the multivariate analysis, the CALy 2-3 remained significant for both DFS (HR 1.84; 95% CI 1.18-2.86; p=0.007) and OS (HR 2.25; 95% CI 1.23-4.11; p=0.008) (Table 3).

Regarding the components of CALy (CEA, ALP, LC), as demonstrated in Table 1, in univariate analyses, CEA >4 was associated with decreased DFS (HR 2.15; 95% CI 1.43-3.24; p<0.001). ALP>93 was associated with decreased DFS (HR 1.53; 95% CI 1.01-2.31; p=0.043) and OS (HR 2.34; 95% CI 1.34-4.09; p=0.003), and LC ≤1.6 was associated with decreased OS (HR 2.57; 95% CI 1.46-4.55; p=0.001). In multivariate analysis (Supplementary Table 2), CEA >4, but not ALP >93, remained significant for DFS (HR 1.63; 95% CI 1.04-2.55; p=0.031), whereas both ALP >93 (HR 1.96; 95% CI 1.09-3.54; p=0.025) and lymphocytes ≤1.6 (HR 2.63; 95% CI 1.46-4.74; p=0.001) were associated with decreased OS.

By creating four groups with 0, 1, 2, and 3 unfavourable prognostic factors (CALy 0: 30 patients, CALy 1: 57 patients, CALy 2: 33 patients, CALy 3: 15 patients), the CALy was still associated with decreased DFS and OS both in univariate analysis (HR 1.62; 95% CI 1.29-2.03; p<0.001, and HR 2.04; 95% CI 1.47-2.82; p<0.001, respectively) and in multivariate analysis (HR 1.37; 95% CI 1.083-1.74; p=0.009, and HR 1.84; 95% CI 1.31-2.59; p<0.001, respectively) (Figures 2,3). Three-year DFS rates for these categories (CALy 0, CALy 1, CALy 2, and CALy 3) were 45, 38, 15 and 7%, respectively, and the 5-year OS rates were 78, 68, 32, and 24%, respectively. However, the difference in DFS and OS between CALy 0 and CALy 1 categories and also between CALy 2 and CALy 3 categories did not reach significance (DFS: CALy 0 vs CALy 1: p = 0.729; CALy 2 vs CALy 3: p = 0.197; OS: CALy 0 vs CALy 1: p = 0.142; CALy 2 vs CALy 3: p = 0.051).

Discussion

In this study, we presented a simple, cheap and easily available risk score for patients with liver-only colorectal metastases undergoing liver resection after neoadjuvant chemotherapy. Using the serum ALP levels, the CEA levels and the LC, we checked the prognostic value of two risk scores, one with 2 risk categories (0-1 and 2-3 unfavourable points; CALy 0-1 and CALy 2-3, respectively) and one with 4 risk categories (0, 1, 2, and 3 unfavourable points; CALy 0, CALy 1, CALy 2, and CALy 3, respectively). Both of these risk scores had a significant prognostic value for DFS

Supplementary Table 2. Multivariate analysis of factors (including the components of CALy) affecting disease free survival and overall survival

	DFS		*OS*	
Parameter	*HR (95% CI)*	*p value*	*HR (95% CI)*	*p value*
Age at operation >70			2.01(1.04-3.88)	0.036
>3 metastases at diagnosis	1.37(0.79-2.37)	0.263	1.46(0.70-3.03)	0.303
Bilobar distribution of lesions	1.78(1.07-2.96)	0.025	2.02(0.98-4.14)	0.055
PVE	1.22(0.58-2.57)	0.587		
Disease progression during neoadjuvant chemotherapy	2.92(1.50-5.69)	0.002	1.84(0.74-4.56)	0.185
Primary tumour *in situ*	1.16(0.67-1.99)	0.580		
No adjuvant chemotherapy	1.57(0.95-2.61)	0.078	1.97(0.99-3.93)	0.053
CEA>4	1.63(1.04-2.55)	0.031		
ALP>93	1.24(0.80-1.94)	0.325	1.96(1.09-3.54)	0.025
Lymphocytes ≤1.6			2.63(1.46-4.74)	0.001

For abbreviations see footnote of Table 3

and OS. Regarding risk scores with 4 risk categories, the 3-year DFS ranged from 45% for patients with no unfavourable points to 7% for patients with 3 unfavourable points. Accordingly, the 5-year OS ranged from 78 to 24%. The discriminatory ability of the risk score with the 4 risk categories was low between CALy 0 and CALy 1 categories and also between CALy 2 and CALy 3 categories, both for DFS and OS. Regarding risk score with 2 risk categories, the presence of 2 or 3 points was an independent dismal prognostic factor of decreased DFS and OS.

Finding usable prognostic factors for patients undergoing hepatectomy in the era of the wide predominance of neoadjuvant chemotherapy is required. Currently, the changing of both the therapeutic strategies and of the clinicopathologic characteristics of patients undergoing liver resections has put into question the traditional prognostic factors [4,6].

ALP, an enzyme mainly derived from the liver and bones [12], has been used in the past both for the diagnosis of CRLM but also as a prognostic factor for patients undergoing hepatectomy for CRLM [7,8]. The widespread use of more reliable tools to serve the above purpose (CT, MRI, PET, etc.) has put into disuse the use of ALP as a prognostic factor in patients with CRLM. The low cost and the easy availability of ALP makes it a suitable candidate for its review as a prognostic factor, and recent studies have dealt with this issue [13]. Although increased levels of ALP may be due to a plurality of pathological conditions [14], in patients with CRLM, the levels of ALP could be attributed to the tumour burden of the liver. This was demonstrated in this study, in which patients with ALP >93 most often presented bilopar liver metastases. Recent studies attributed prognostic value of ALP levels in patients with metastatic prostate cancer, non-small cell lung cancer, oesophageal cancer, nasopharyngeal carcinoma, etc [15-18].

LC has been used extensively in recent years primarily for finding inflammation-related prognostic factors (neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and lymphocyte to monocyte ratio) for a variety of malignancies, including CRLM [19-21]. The roles of lymphocytes as basic and necessary components of immunosurveillance and immunoediting are well-recognised [22]. In addition, it is recognised that lymphopenia can most likely lead to inadequate immune reactions to the tumour [23,24]. In addition, many studies conclude that strong lymphocytic infiltration of various malignancies is associated with significant increase in life expectancy of cancer patients [10].

CEA, a colorectal tumour-related marker, is used mainly in the follow-up care of colorectal cancer patients [25,26], and its elevated levels are associated with the presence of liver metastases in these patients [27]. Furthermore, recent studies have demonstrated the prognostic value of preoperative level of CEA in patients undergoing hepatectomy for CRLM [9].

The main limitation of this study is that it is retrospective and inherent biases cannot be fully excluded. To minimise the selection bias, we attempted to make the population under study as homogeneous as possible regarding the severity of the disease and the treatment received by excluding patients with extrahepatic disease and those who did not receive neoadjuvant chemotherapy. We believe that this homogeneity of the population under study in combination with the prolonged follow-up is the main strength of this study. Another limitation of this study is the relative small number of enrolled patients. We believe that this is the main reason for the low discriminatory ability of the risk score with the 4 risk categories between categories CALy 0 and CALy 1 and between categories CALy 2 and CALy 3, both for DFS and OS.

In summary, we propose a simple, cheap and easily available prognostic score for patients with liver-only colorectal metastases undergoing curative liver resection. The prognostic value of all three variables that compose this prognostic score was demonstrated either directly (ALP and CEA) or indirectly (neutrophil to lymphocyte ratio) in patients with CRLM [8,9,21]. In this study, we demonstrated that the combined use of these variables leads to the creation of a prognostic score with sensitivity, specificity and accuracy greater than that demonstrated by the individual use of each variable separately as a prognostic factor. Prognostic factors such as this could possibly lead to implementing more individualised treatments for each patient and, in the case of CRLM, a better selection of candidates for hepatectomy, restricting major intervention only for patients with good prognosis.

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