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ORIGINAL PAPER

High preoperative serum CA19-9 level is predictive of poor prognosis for patients with colorectal liver oligometastases undergoing hepatic resection

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Abstract Oligometastasis is defined as a transitional state between localized and widespread systemic metastatic cancers. In colorectal cancer, the prognostic factors and prognostic value of preoperative serum carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) for patients with colorectal liver oligometastases (CLOM) undergoing hepatic resection have not been well explored. Therefore, the present study included 141 patients with CLOM (≤5 liver metastases) who underwent R0 resection from 2005 to 2012. The association of clinicopathological factors including preoperative CA19-9 and CEA levels with overall survival (OS) was analyzed with univariate and multivariate analyses. Kaplan–Meier analysis showed that patients with high CA19-9 levels tended to have poorer OS than those with low levels (median OS 21.5 vs. 64.0 months, $P = 0.002$). Preoperative CEA levels were not significantly associated with OS ($P > 0.05$). Univariate and multivariate analyses demonstrated that larger tumor size of liver metastases (HR 1.911; 95 % CI 1.172–3.114; $P = 0.009$), bilobar distribution (HR 1.776; 95 % CI 1.097–2.873; $P = 0.019$), and higher preoperative CA19-9 levels (HR 1.954; 95 % CI 1.177–3.242; $P = 0.010$) were independent predictors of poor OS for patients with CLOM. Our study identified tumor size, distribution, and preoperative CA19-9 levels as independent prognostic factors for OS of patients with CLOM. In particular, measurement of preoperative CA19-9 levels offers an easy tool that could help identify high-risk patients and aid in improving the management of patients with CLOM.

Keywords Colon cancer · Oligometastasis · Hepatectomy · CA19-9 · Prognosis

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide, with an estimated 1.4 million new cases and 0.7 million deaths each year based on data from GLOBOCAN [1, 2]. Nearly one-fourth of patients present with synchronous liver metastases at the time of initial diagnosis of colorectal cancer. Approximately 50 % of patients develop metachronous liver metastases after resection of the primary tumor [3]. Hepatic resection is the most effective and potentially curative treatment for colorectal liver metastases (CLM) [4–6]. The 5-year overall survival rate following curative hepatic resection ranges from 28 to 58 % [7–10]. Nevertheless, the incidence of postoperative recurrence remains high, and 60–85 % of patients relapse within 2 years after resection of CLM [11].

The identification of relevant prognostic factors will help to establish and optimize therapeutic strategies for CLM. Serum levels of tumor markers such as carcinoembryonic

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antigen (CEA) are widely used to predict prognosis in patients with CLM [12–14]. Preoperative CEA has been incorporated into many useful prognostic scoring systems for stratifying the risk of recurrence, including the clinical risk scores (CRS) [7, 8]. Carbohydrate antigen 19-9 (CA19-9) is another tumor marker often used in combination with CEA. However, the utility of CA19-9 in predicting prognosis remains controversial [14–16].

The concept of oligometastases was first proposed by Hellman and Weichselbaum [17] as a sequel to the spectrum theory of cancer metastasis. With advances in understanding the mechanisms underlying cancer metastasis, oligometastasis is now defined as a transitional state ($\leq$5 metastases) between localized and widespread systemic metastatic cancers in which local therapy could achieve prolonged survival or even cure [17, 18]. In recent years, there is accumulating preclinical and clinical evidence which implies the existence of oligometastasis in various types of cancer. In CRC, liver oligometastases disease has been shown to be a distinct subgroup that may benefit from aggressive management [10, 19]. In the latest version of ESMO Consensus Guidelines, mCRC were classified into oligometastatic disease (OMD) and metastatic disease [20]. For patients with OMD confined to liver, a potentially curative approach exists. However, the prognostic factors for patients with colorectal liver oligometastases (CLOM) undergoing hepatic resection have not been well explored. Specifically, the prognostic value of serum tumor markers is needed to be clarified.

Therefore, the aim of this study was to evaluate the prognostic factors for prediction of overall survival in patients with CLOM. Accordingly, whether preoperative CA19-9 and CEA levels could predict prognosis was also investigated.

Materials and methods

Patients and data collection

A total of 141 patients who underwent curative surgery for their primary colorectal tumors and synchronous/metachronous liver metastases from 2005 to 2012 at Sun Yat-sen University Cancer Center (SYSUCC) were enrolled in the study. The inclusion criteria of patients in this study were as follows: (1) colorectal liver oligometastases ($\leq$5 metastases); (2) R0 resection; (3) no evidence of extrahepatic metastasis; and (4) no percutaneous ablation treatment before hepatic resection.

The present study was approved by the Institutional Review Board of SYSUCC. Written informed consent was obtained from all the members who participated in this study. For each patient, the institutional medical records were checked and information was collected from a prospectively maintained database regarding the following: demographic, clinical, operative, pathological, and follow-up data.

Preoperative blood tests including tumor markers at the time of diagnosis was carried out within 2 weeks before operation. Preoperative imaging to evaluate the extent of liver disease and to exclude extrahepatic disease included contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis. Fluorodeoxyglucose positron emission tomography (FDG-PET) was performed selectively to confirm extrahepatic metastatic disease.

All patients had agreed multidisciplinary team meetings. The decision of timing for resection of liver metastases was made by the multidisciplinary team. Intraoperative ultrasound was performed in all patients, and surgical plan was modified accordingly. Overall survival (OS) was calculated from the date of hepatic resection to the date of death, or the date was censored at the last follow-up.

Statistical analysis

Values were presented as mean $\pm$ SD, median (range), or percentage, as appropriate. The Student's t test, Chi-square test, or Fisher's exact test were used for analyzing the differences between groups. The survival probabilities were estimated by the Kaplan–Meier method and compared with the log-rank test. Univariate and multivariate analyses with Cox proportional hazard regression model were performed to determine the hazard ratio of each prognostic factor. Covariates with P values <0.05 on univariate analysis were subjected to multivariate analysis. All statistical analyses were performed with the IBM SPSS Statistics 20 software (IBM, New York, NY) and GraphPad Prism 5.0 software (GraphPad Software, San Diego, CA). A P value of less than 0.05 was considered statistically significant.

Results

Baseline patient characteristics

The median age of the 141 patients was 60 years (range 20–82 years), with 92 (65.2 %) males and 49 (34.8 %) females. In this cohort, 80 (56.7 %) patients had colon cancer and 61 (43.3 %) patients had rectum cancer. Overall, 33 (23.4 %) patients had right-sided colon cancer (proximal to the splenic flexure) and 108 (76.6 %) patients had left-sided colon cancer (distal to the splenic flexure). In 69 (48.9 %) patients, the primary tumors involved lymph nodes metastasis. Of these 141 patients, 88 (62.4 %)

presented with solitary liver metastases and 53 (37.6 %) had multiple (range 2–5) tumors. The median size of each patient's largest tumor was 2.6 cm (range 0.3–12.1 cm). Sixty-six patients (46.8 %) underwent synchronous surgery of primary tumor and liver metastases. Regarding perioperative chemotherapy, 52 (36.9 %) received preoperative chemotherapy before undergoing hepatic resection and 102 patients (72.3 %) received postoperative chemotherapy. There was no perioperative death within 30 days after surgery.

Stratification of preoperative serum CA19-9 and CEA level

The median preoperative serum CA19-9 and CEA levels of all 141 patients were 24 U/ml (range 0.6–4846) and 11.1 ng/ml (range 0.7–2480), respectively. Among the 141 patients, 54 (38.3 %) patients had ≥35 U/ml (above the normal level), 29 (20.6 %) had ≥100 U/ml, and 21 (14.9 %) had ≥200 U/ml of preoperative CA19-9 levels. Also, 91 (64.5 %) patients had ≥5.0 ng/ml (above the normal level), 40 (28.4 %) had ≥30 ng/ml, and 20 (14.2 %) had ≥100 ng/ml of preoperative CEA levels. By using different cutoff values of preoperative CA19-9 (35, 100, and 200 U/ml) and CEA (5, 30, and 100 ng/ml), all patients were divided into high-level and low-level groups for further analysis.

To determine the optimal classification of the preoperative CA19-9 and CEA levels, the OS was compared between the high-level group and the low-level group at each cutoff point by using the univariate Cox regression model. The value with the highest HR was regarded as the optimal critical point of classification. Each of the cutoff points and HRs is presented in Fig. 1. Among the CA19-9 cutoffs tested, preoperative CA19-9 100 U/ml obtained the highest HR (2.162; 95 % CI 1.308–3.575; $P = 0.002$), although dichotomization with a broad range of CA19-9 levels gave significantly discriminative log-rank P values (Fig. 1a). Thus, the critical cutoff value of the CA19-9 level was set as 100 U/ml. However, by using the same method, no significant differences in OS were found between the high-level CEA group and low-level CEA group, although the P values were marginal (Fig. 1b).

Relationships between preoperative CA19-9 levels and patient characteristics

The relationships between preoperative CA19-9 levels and patient characteristics were further analyzed. The most discriminative cutoff point (100 U/ml) of preoperative CA19-9 was subjected to divide patients. As shown in Table 1, preoperative CA19-9 was strongly associated with tumor size of liver metastases (≥5 vs. <5 cm, $P = 0.021$). Similarly, preoperative CA19-9 was also strongly associated with preoperative CEA levels (≥5 vs. <5 ng/ml, $P = 0.002$). No significant differences were found between preoperative CA19-9 levels and other patient clinicopathological factors including age, gender, primary site (colon/rectum, or right-sided/left-sided), pT category (T1 + T2/T3 + T4), primary lymph node metastasis (no/yes), no. of liver metastases (1/>1), distribution (unilobar/bilobar), timing of resection (synchronous/metachronous), extent of liver resection (minor/major), perioperative chemotherapy (no/yes), and other preoperative laboratory data.

Overall survival according to preoperative CA19-9 levels

The median follow-up time after hepatic resection was 38 months (range 2–128) for all 141 patients. Overall, 78

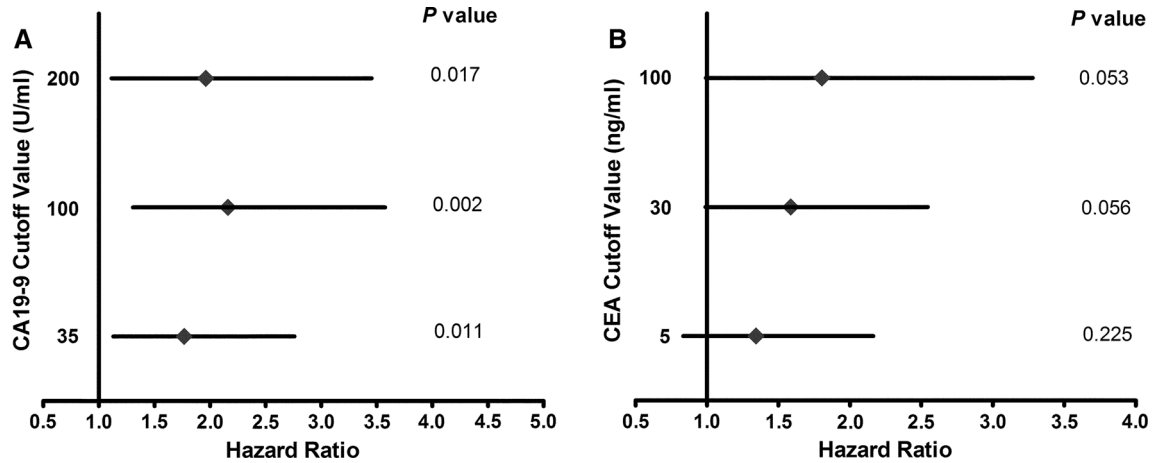

Fig. 1 Hazard ratio comparison of putative **a** CA19-9 and **b** CEA cutoff values entered separately in the univariate Cox regression model. HR, hazard ratio; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen

Table 1 Relationships between preoperative CA19-9 levels and patient clinicopathological characteristics

Characteristics	CA19-9 level		*P* value
	<100 U/ml ($n = 112$)	≥100 U/ml ($n = 29$)	
Age (years) (<60/≥60)	54/58	16/13	0.504
Gender (male/female)	76/36	16/13	0.201
Primary site			
Colon/rectum	65/47	15/14	0.541
Right-sided/left-sided	26/86	7/22	0.917
pT category (T1 + T2/T3 + T4)	17/95	6/23	0.572
Primary lymph node metastasis (no/yes)	57/55	15/14	0.936
Maximum tumor size (cm) (<5/≥5)	89/23	17/12	**0.021**
No. of liver metastases (1/>1)	70/42	18/11	0.966
Distribution (unilobar/bilobar)	86/26	20/9	0.385
Timing of resection (synchronous/metachronous)	52/60	14/15	0.859
Extent of liver resection (minor/major)	80/32	19/10	0.535
Perioperative chemotherapy			
Neoadjuvant (no/yes)	67/45	22/7	0.111
Adjuvant (no/yes)	31/81	8/21	0.992
Preoperative laboratory data[a]			
White blood cell ($\times 10^9$/l)	6.5 ± 2.5	6.6 ± 1.8	0.826
Hemoglobulin (g/l)	124.4 ± 21.6	126.8 ± 19.5	0.590
Platelet ($\times 10^9$/l)	223.6 ± 92.3	234.2 ± 118.4	0.604
ALT (U/l)	29.3 ± 37.7	31.5 ± 59.9	0.809
AST (U/l)	30.3 ± 37.1	35.3 ± 50.8	0.554
Albumin (g/l)	41.9 ± 4.2	41.2 ± 4.9	0.447
Total bilirubin (μmol/l)	11.2 ± 4.6	11.7 ± 5.2	0.567
CEA (ng/ml) (<5/≥5)	47/65	3/26	**0.002**

Statistically significant values are given in bold

CA19-9 carbohydrate antigen 19-9, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CEA* carcinoembryonic antigen

[a] Mean ± SD

(55.3 %) patients died during this study. The estimated median OS of the whole group of patients was 44.8 months, and the 1-, 3-, and the 5-year OS rates were 89.8, 59.1, and 45.9 %, respectively.

To evaluate the prognostic value of preoperative CA19-9 levels in patients with CLOM, overall survival curves were constructed by Kaplan–Meier method and compared by the log-rank test. The results showed that there were significant differences in OS between patients with high-level CA19-9 (≥100 U/ml) and those with low-level CA19-9 (<100 U/ml) (Fig. 2a). High preoperative CA19-9 levels were associated with shorter overall survival of patients with CLOM. The estimated median OS of patients with high CA19-9 levels was 21.5 months, compared with 64.0 months in the low-level group. The 1-, 3-, and 5-year overall survival rate in the high-level group was 69.0, 36.5, and 23.2 %, respectively, compared with 95.4, 65.1, and 51.8 %, respectively, in the low-level group (log-rank test, $P = 0.002$). In addition, when using different cutoff values, there were still significant differences in OS between patients with high preoperative CA19-9 levels and those with low CA19-9 levels (Fig. 2b, c). Thus, patients with CLOM who had higher preoperative CA19-9 levels tended to have poorer overall survival.

Prognostic factors for overall survival

For patients with CLOM undergoing hepatic resection, univariate analysis revealed that larger tumor size of liver metastases (HR 2.145; 95 % CI 1.323–3.479; $P = 0.002$), bilobar distribution of lesions (HR 2.029; 95 % CI 1.257–3.275; $P = 0.004$), and higher preoperative CA19-9 levels (≥100 U/ml) (HR 2.162; 95 % CI 1.308–3.575; $P = 0.002$) were associated with decreased OS (Table 2). However, other clinicopathological characteristics including age, gender, primary site, pT category, primary lymph

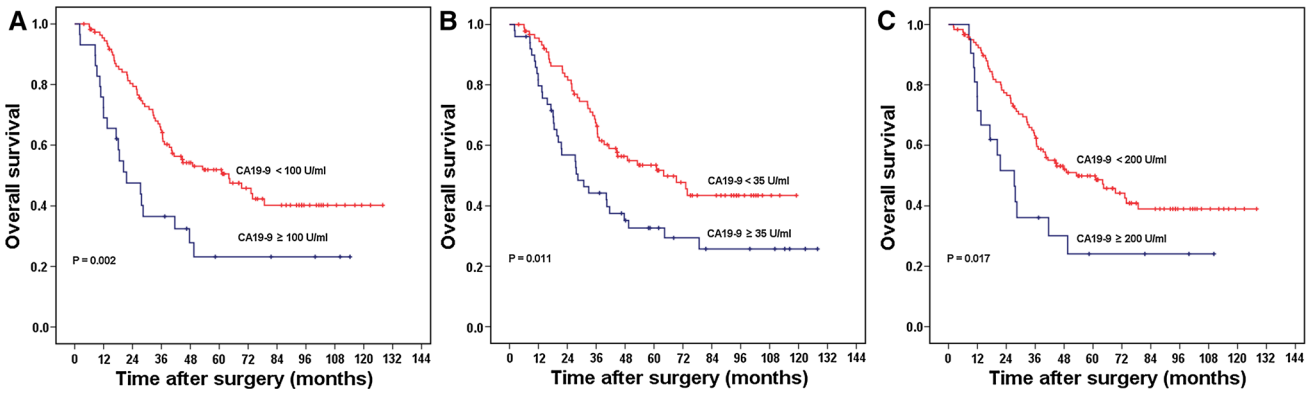

Fig. 2 Comparisons of overall survival between two groups stratified by **a** the preoperative CA19-9 cutoff value of 100 U/ml (log-rank $P = 0.002$), **b** 35 U/ml (log-rank $P = 0.011$), and **c** 200 U/ml (log-rank $P = 0.017$). Kaplan–Meier method and log-rank test were used for survival analysis

node metastasis, no. of liver metastases, timing of resection, extent of liver resection, and perioperative chemotherapy were not significantly associated with OS in the univariate analysis (Table 2).

A further multivariate Cox proportional hazard model was used to analyze the prognostic factors which were significantly associated with OS in the univariate analysis. This multivariate analysis demonstrated that larger tumor size of liver metastases (HR 1.911; 95 % CI 1.172–3.114; $P = 0.009$), bilobar distribution of lesions (HR 1.776; 95 % CI 1.097–2.873; $P = 0.019$), and higher preoperative CA19-9 levels (HR 1.954; 95 % CI 1.177–3.242; $P = 0.010$) were all independent predictors of poor OS for patients with CLOM undergoing hepatic resection (Table 2).

Discussion

In colorectal cancer with liver metastases, total number of liver lesions is not a contraindication but a prognostic factor for surgery if R0 resection can be achieved. Less tumor number in liver often indicates better survival and less recurrence after hepatic resection. Liver oligometastases (≤5 metastases) is regarded as a unique subgroup

Table 2 Univariate and multivariate Cox regression analyses for overall survival

Variable	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	*P*	HR (95 % CI)	*P*
Age (≥60 vs. < 60 years)	1.450 (0.927–2.270)	0.104		
Gender (male vs. female)	1.337 (0.826–2.165)	0.238		
Primary site				
Rectum versus colon	1.137 (0.727–1.776)	0.574		
Right-sided versus left-sided	1.041 (0.608–1.783)	0.883		
pT category (T3 + T4 vs. T1 + T2)	1.220 (0.645–2.310)	0.541		
Primary lymph node metastasis (yes vs. no)	1.406 (0.899–2.199)	0.135		
Maximum tumor size (cm) (≥5 vs. <5)	2.145 (1.323–3.479)	**0.002**	1.911 (1.172–3.114)	**0.009**
No. of liver metastases (>1 vs. 1)	1.365 (0.872–2.138)	0.173		
Distribution (bilobar vs. unilobar)	2.029 (1.257–3.275)	**0.004**	1.776 (1.097–2.873)	**0.019**
Timing of resection (metachronous vs. synchronous)	0.820 (0.526–1.279)	0.382		
Extent of liver resection (major vs. minor)	1.229 (0.767–1.968)	0.392		
Perioperative chemotherapy				
Neoadjuvant (yes vs. no)	1.367 (0.870–2.149)	0.175		
Adjuvant (yes vs. no)	0.793 (0.490–1.284)	0.346		
CEA (ng/ml) (≥5 vs. <5)	1.343 (0.834–2.163)	0.225		
CA19-9 (U/ml) (≥100 vs. <100)	2.162 (1.308–3.575)	**0.002**	1.954 (1.177–3.242)	**0.010**

Statistically significant values are given in bold

with good outcome treated by hepatic resection [4–6, 21–23]. However, few studies focused on the potential factors affecting prognosis of this group of patients. The present retrospective study analyzed the data of a pure cohort of 141 patients with CLOM who underwent hepatic resection. Our results demonstrate the prognostic value of the preoperative CA19-9 levels for CLOM. In addition, tumor size and tumor distribution of liver metastases are another two important prognostic factors for these patients. Because tumor size reflects tumor burden and tumor distribution reflects the extent of disease in liver, it is reasonable to explain why these factors are important in patients with CLOM. Thus, our study offers potential markers for evaluation of prognosis of patients with CLOM undergoing resection.

In clinical practice, CA19-9 is often used in combination with CEA to manage CRC patients, even though the American Society of Clinical Oncology guidelines suggest that there is insufficient evidence for using CA19-9 in the management of CRC patients [24]. The utility of CA19-9 in predicting prognosis with CLM is controversial. Many studies have described the prognostic significance of CA19-9 and the possible usefulness of CA19-9 in monitoring recurrence [16, 25–28]. In contrast, there are also a few studies which have shown contradictory results [29, 30]. Therefore, CA19-9 has not been gained widespread use in the assessment of prognosis.

In the present study, whether preoperative tumor markers had a role in predicting prognosis for patients with CLOM was evaluated in detail. Survival analysis revealed a significant association between OS and preoperative CA19-9 levels. In spite of different cutoff values, patients with a higher preoperative CA19-9 level were more likely to have a reduced chance of survival. By contrast, preoperative CEA was not significantly associated with survival. Moreover, preoperative CA19-9 was an independent prognostic factor for OS in patients with CLOM, while preoperative CEA was not. Our results were different from those described in other studies [29, 30], and this discrepancy was most likely to be attributable to the differences in study patients. Only CRC patients with liver oligometastases were included in our study. In addition, the differences in sample size and distribution of tumor stage might also have influence on outcome.

Our study highlights the prognostic usefulness of preoperative CA19-9 in patients with CLOM. In the current study, significant differences in OS between groups were shown at all preoperative CA19-9 cutoff values. The cutoff value with the highest HR was defined as the optimal point in this study, and it was adopted for further analysis. This method has been used in some previous studies [31, 32]. Our adopted preoperative CA19-9 cutoff point 100 U/ml was also consistent with a previous study on predictive value of CA19-9 in patients with CLM [33].

In analyzing the relationships between CA19-9 levels and clinicopathological factors, preoperative CA19-9 levels were higher in patients with larger tumor size of liver metastases. Larger tumors in liver reflect a heavier or more extensive tumor burden. This result indicated that higher preoperative CA19-9 levels may raise the suspicion of a more extensive tumor burden. Similar results have been demonstrated in previous studies [15, 34]. Also, our results showed that high CA19-9 values correlated with high CEA values, which indicated the clinical usefulness of simultaneous evaluations of CEA and CA19-9, even though CEA has not shown prognostic significance in this study.

Our study had several limitations. First, it was retrospective in design. The timing of CA19-9 and CEA measurement was not always the same, which could introduce bias or bias the results. However, we attempted to measure preoperative tumor markers within a 2-week timeframe. Second, a more comprehensive analysis in patients beyond CLOM (>5 liver metastases) will be potentially valuable. Third, this study cohort comes from a single institution, and the sample sizes of the entire cohort and high CA19-9 cohort are relatively small. Fourth, it would be better to include evaluation of molecular factors such as KRAS, NRAS, BRAF mutation, microsatellite instability (MSI) in the study. Further large-scale prospective studies are needed to confirm our results.

In conclusion, our study demonstrated that preoperative serum CA19-9 level, tumor size, and tumor distribution of liver metastases were independent prognostic factors for OS of patients with CLOM undergoing hepatic resection. In particular, measurement of preoperative CA19-9 levels offers an easy tool for stratification of patients with CLOM into subgroups with better and worse likelihood of survival, and may aid in improving the management of patients with CLOM.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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