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Lymphovascular invasion affects prognosis of colorectal cancer liver metastasis underwent primary resection: a propensity score matching analysis

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Abstract

Background Lymphovascular invasion (LVI) is associated with poor prognosis in a variety of malignancies; however, its prognostic value has not been fully defined in patients with colorectal cancer with liver metastases (CRCLM). The aim of this study was to investigate the impact of LVI on long-term postoperative recurrence and survival in patients with CRCLM.

Methods Clinicopathologic data were retrospectively collected from patients who underwent primary resection for CRCLM at Wuhan Union Hospital from 2013 to 2018. To reduce potential confounders and selection bias, we used propensity score matching (PSM) to compare the clinicopathologic characteristics and long-term prognostic outcomes of patients in the LVI (+) and LVI (-) groups. Cox unifactorial and multifactorial analyses were used to screen relevant factors affecting patient prognosis, and Kaplan-Meier curves were plotted to compare differences in patient overall survival (OS) and disease-free survival (DFS). The predictive power of independent factors on patients' long-term prognosis was assessed using receiver operating characteristic ROC) curves and area under the curve (AUC).

Results After PSM, 230 patients were enrolled in the study ($n=115$ per group). Multifactorial analysis revealed that LVI was an independent prognostic factor for OS and DFS (hazard ratio [HR], 1.424; 95% confidence interval [CI], 1.004–2.022; $P=0.048$ and HR, 1.452; 95% CI, 1.020–2.069; $p=0.039$, respectively). In the LVI (-) group, postoperative chemotherapy did not significantly improve OS or DFS; however, in the LVI (+) group, those who received chemotherapy had significantly improved OS (HR: 1.593, 95% CI: 1.187 – 2.571; $P=0.044$) and DFS (HR: 1.503, 95% CI. 1.033 – 2.422; $P=0.045$) compared with patients not treated with chemotherapy. In the LVI (+) group, the AUC for the OS AUROC curves was more favorable compared with after PSM (AUC at 3 years: 0.786 vs. 0.903; AUC at 5 years: 0.744 vs. 0.889). For DFS, the area under the AUROC curve was also better in the LVI (+) subgroup compared with after PSM (AUC at 3 years: 0.825 vs. 0.874; AUC at 5 years: 0.839 vs. 0.863).

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Conclusions LVI may significantly impact long-term survival and prognosis in patients with CRCLM undergoing primary resection, potentially serving as an independent prognostic factor for OS and DFS. Additionally, postoperative chemotherapy appears to significantly improve the long-term prognosis of patients with LVI (+).

Introduction

Colorectal cancer (CRC) is the third most common malignant tumor and a leading cause of tumor-related deaths [1]. In China, the incidence and mortality of colorectal cancer have increased significantly in recent years [2]. Early-stage colorectal cancer can be treated with surgery and medication to improve long-term survival prospects [3]; however, 25–50% of early-stage patients develop distant metastasis [4]. Colorectal venous drainage returns to the liver through the portal venous system, potentially facilitating the hepatic metastasis of colorectal cancer cells.Overall, 15–25% of patients with CRC develop synchronous liver metastases(CRCLM), and 18–25% of patients eventually develop heterochronous liver metastases within 5 years of initial diagnosis. Of these, around 35% eventually die as a result of colorectal cancer liver metastases [5–9]. Despite with the continuous development of surgery, immunotherapy and targeted therapy, the long-term prognosis for patients with CRCLM remains poor [10]. LVI is defined as the presence of cancer cells within the thin-walled lymphatic or vascular channels and is considered an early step in the process of lymph node metastasis or dissemination through the circulatory system to other organs.The overall incidence of LVI in CRC is 12.5–26.3%, and the LVI positivity rate varies depending on tumor stage [11–13]. Previous studies have shown that LVI is an important step in lymph node metastasis and distant metastasis of tumor cells, which is an important marker of poor prognosis and more aggressive tumor behavior. In addition, LVI predicts poorer survival outcomes in patients with CRC [12, 14–17]. Most prior studies have focused on investigating the prognostic role of LVI in stage I, II, and III CRC and concluded that the presence of LVI is as an indicator for adjuvant chemotherapy [14, 16, 18]. Previous studies have focused on the prognostic significance of LVI in patients with CRCLM and have identified LVI as a risk factor for prognosis in these patients [19, 20]. However, these studies did not adequately account for the potential confounding effects of factors such as peri/intraneural invasion, tumor deposits, T stage, N stage, age, and the number of liver metastases, leading to conclusions that are subject to scrutiny. In our study, we employed PSM to ensure that patients in the LVI (-) and LVI (+) groups did not differ significantly in their clinical and pathological characteristics or treatment regimens, thereby effectively eliminating the influence of confounding factors. Consequently, our conclusions are more reliable, and we further investigate whether patients in the LVI (+) group can benefit from chemotherapy.

Thus, we collected data from a large single-center database and utilized PSM and survival analysis to investigate whether LVI can be used for risk stratification and to evaluate its impact on the long-term prognosis of patients with CRCLM who underwent surgical intervention. Additionally, in LVI(+) patients, we explored factors affecting patient prognosis and developed predictive models. This study aims to provide scientific evidence to inform treatment strategies.

Patients and study design

To develop a reliable 5-year prediction tool and assess the long-term prognostic value of LVI in CRCLM patients, we retrospectively collected data on 1189 CRCLM patients from Wuhan Union Hospital between 2013 and 2018.The study focuses on the inclusion of 445 CRCLM patients who underwent surgical resection of the primary lesion.Inclusion criteria: (1) age > 18 years with CRCLM confirmed by imaging and pathology; (2) undergoing standard complete mesocolicexcision and regional lymphadenectomy; and (3) available and complete information, including clinical information, pathological information (including definite LVI status) and follow-up information. Exclusion criteria: (1) concomitant other tumour types; (2) incomplete information. LVI is defined as the presence of cancer cells within the thin-walled lymphatic or vascular channels.

Data collection

The collection of data comprised of the following variables: age, gender, body mass index (BMI), history of preoperative intestinal obstruction, preoperative chemotherapy, postoperative chemotherapy, surgical approach, resection of liver metastases, number of hepatic metastases, American Anaesthesiologist (ASA) score, tumour location, tumor size, degree of differentiation, T stage, N stage, No. of sampled lymph nodes, No. of positive lymph nodes, LVI, peri/intraneural invasion, tumour deposits, pre-operative tumour markers (carcinoembryonic antigen [CEA], carbohydrate antigen 19 – 9 [CA19 – 9], carbohydrate antigen12-5[CA12-5]).The ethics committee of Wuhan Union Hospital (No. 2018-S377) approved the study, which was conducted in line with the ethical standards of the World Medical Association Declaration of Helsinki. Patient data was kept confidential.

Follow-up

To obtain comprehensive information, according to the international consensus on CRC management, we established a complete and standardized follow-up protocol. From the time of discharge after surgery, patients were followed up every three months during the first two postoperative years via telephone, outpatient visits, and readmissions. From the third to the fifth postoperative year, follow-ups were conducted every six months using the same methods. During outpatient and hospital follow-ups, clinicians arranged for routine blood tests, liver and kidney function tests, and tumor markers such as CEA, CA12-5, and CA19-9, along with enhanced Computed Tomography (CT) scans of the chest, abdomen, and pelvis. Positron Emission Tomography – Computed Tomography (PET-CT) and electronic colonoscopies were performed when tumor recurrence or metastasis was suspected. Patients who could not be contacted within one year of their last follow-up were considered lost to follow-up. Throughout the follow-up process, we recorded the survival status of patients, the time and cause of death for deceased patients, and whether there was any recurrence or metastasis; if recurrence or metastasis occurred, the time and location were documented. We measured patient survival using OS and DFS. OS was defined as the time from the first day after surgery until death or the end of the last follow-up. DFS is defined as the time from the first day after surgery to the recurrence, metastasis, or death, whichever occurs first, or until the end of the last follow-up. This study adhered to the ethical standards of the World Medical Association Declaration of Helsinki and was approved by the Ethics Committee of Wuhan Union Medical College Hospital (Approval No.: 2018-S377). All patient data were recorded confidentially.

Propensity score matching

The study analysed 445 patients who were PSM based on their LVI status using the nearest neighbour algorithm without replacement. A matching ratio of 1:1 was implemented with a tolerance of 0.01. Matching parameters included age, gender, BMI, preoperative intestinal obstruction, preoperative chemotherapy, postoperative chemotherapy, surgical approach, resection of liver metastases, as well as the number of hepatic metastases. preoperative intestinal obstruction, preoperative chemotherapy, post-operative chemotherapy, surgical approach, liver metastasis resection, number of hepatic metastases, American Society of Anaesthesiologists (ASA) score, tumour location, tumour size, No of sampled LNs, number of positive lymph nodes, degree of differentiation, T stage, N stage, peri/intraneural invasion, tumour deposits, CEA, CA12-5 and CA19-9 underwent propensity matching analysis to adjust for confounding indices and facilitate balanced comparisons between LVI (-) and LVI (+) groups. Ultimately, our database provided 230 patients who met the inclusion criteria, as depicted in Fig. 1.

Statistical methods

All statistical analyses were carried out using R 4.3.1 software provided by the Institute for Statistics and Mathematics in Vienna, Austria. Mean values ± standard deviation were used to express continuous data, while percentages were employed to express categorical variables. Comparison of groups was performed using the chi-square test or Fisher exact probability method. Kaplan-Meier curves were used to evaluate OS and DFS, and log-rank tests used to assess the OS and DFS differences among groups. Univariate analysis was employed to investigate survival ($P<0.05$), followed by multivariate Cox regression. This yielded HRs and 95% CIs. All statistical testing was two-sided and significance was established at $P<0.05$.

Patients' demographic characteristics and clinicopathological features

In the original cohort, 445 patients with CRCLM were enrolled. Compared with the LVI (-) group, the LVI (+) group included a smaller proportion of patients who underwent preoperative chemotherapy (23.7% vs. 14.2%; $P=0.019$) and a lower proportion of laparoscopic surgery (76.3% vs. 54.1%; $P<0.001$). Patients in the LVI(+) group had a higher number of positive lymph nodes (1.68 vs. 4.63; $P<0.001$), as well as a higher percentage of patients with N2 staging (18.3% vs. 47.0%; $P<0.001$), a lower degree of differentiation (13.4% vs. 33.3%; $P<0.001$), peri/intraneural invasion (28.2% vs. 56.3%; $P<0.001$) and tumor deposits (23.3% vs. 49.7%; $P<0.001$). Regarding tumor markers, preoperative CEA (62.4% vs. 76.5%; $P=0.003$) and CA12-5 (13.7% vs. 25.1%; $P=0.003$) were significantly and statistically elevated in patients in the LVI(+) group compared with the LVI(-) group. There were a total of 230 patients in the LVI(-) and LVI(+) groups after PSM matching, and there was no significant difference between the status of LVI and clinicopathologic features ($P>0.05$) (Table 1).

Comparison of patients long-term prognosis

In the original cohort, the mean follow-up time was 20.94 months. The OS in the LVI (+) group was significantly lower than the LVI (-) group (HR: 2.029; 95% CI: 1.581–2.604; $P<0.001$). The DFS for patients in the LVI (+) group was also significantly lower than the LVI (-) group (HR: 2.190; 95% CI: 1.705–2.813; $P<0.001$).

After PSM, the mean follow-up time was 19.90 months The OS in the LVI (+) group was significantly lower than the LVI (-) group (HR: 1.450; 95% CI: 1.031–2.040;

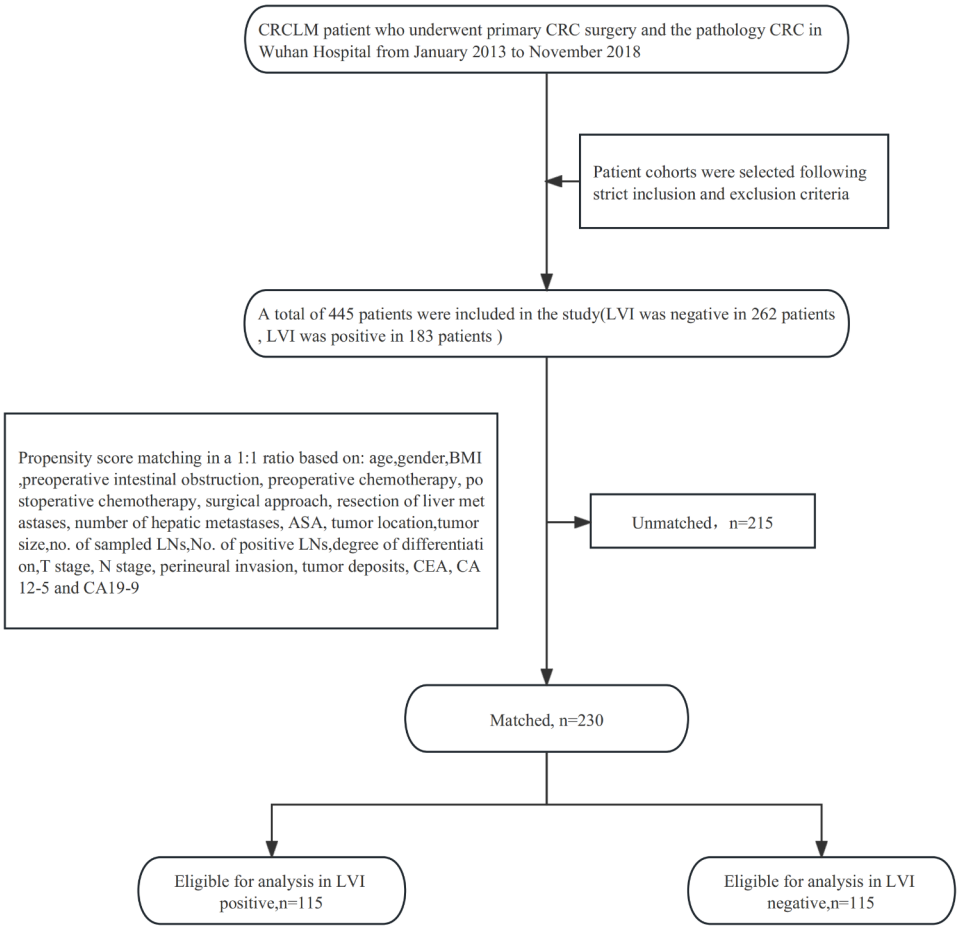

Fig. 1 Strategies for selecting patients to be included in the study

$P=0.032$). The DFS of patients in the LVI (+) group was also significantly lower than the LVI (-) group (HR: 1.479; 95% CI: 1.051–2.080; $P=0.025$).

Factors influencing patients' OS and DFS

Uni- and multivariate analyses of OS and DFS

In the initial analysis of our study, we identified seven factors from the original cohort that had independent prognostic significance for OS: Postoperative chemotherapy, number of liver metastases, N Stage, LVI, tumor deposits, and preoperative CA12-5 and CA19-9 (Supplementary Table 1). To further eliminate the influence of potential confounding factors and ensure the accuracy and reliability of the results, we employed PSM for an in-depth analysis. A Cox univariate analysis showed that postoperative chemotherapy, number of liver metastases, N stage, number of positive lymph nodes, LVI, preoperative CA12-5 level, and preoperative CA19-9 level were correlated with prognosis ($P<0.05$). The multivariate analysis showed that postoperative chemotherapy (HR: 0.670; 95% CI, 0.461–0.974; $P=0.038$), number of liver metastases (2 metastases, HR: 1.338; 95% CI, 0.864–2.070; $P=0.192$; ≥3 metastases, HR: 1.785; 95% CI, 1.020–3.123; $P=0.042$), LVI (HR: 1.424; 95% CI, 1.004–2.022; $P=0.048$), preoperative CA12-5 level (HR: 2.019; 95% CI, 1.276–3.197; $P=0.002$), and preoperative CA19-9 level (HR: 1.862; 95% CI, 1.149–3.018; $P=0.012$) were independent prognostic factors for OS (Table 2). After PSM processing, we confirmed that postoperative chemotherapy, number of liver metastases, LVI, and the preoperative CA12-5 and CA19-9 were independent prognostic factors for OS.

We initially conducted an analysis of the original cohort to identify independent prognostic factors for DFS. The preliminary analysis revealed that postoperative chemotherapy, number of liver metastases, N Stage, No of sampled LNs, LVI, and preoperative CA12-5 and CA19-9 were all significant prognostic factors for DFS (Supplementary Table 2).

After PSM, a Cox univariate analysis showed that the number of liver metastases, No of sampled LNs, N stage, LVI, preoperative CA12-5 level, and preoperative CA19-9 level were significantly correlated with DFS ($P<0.05$). The multivariate analysis showed that N stage (N1, HR: 1.081; 95% CI, 0.661–1.769; $P=0.766$; N2, HR: 1.903; 95% CI, 1.135–3.190; $P=0.015$), and No of sampled LNs (HR: 0.970; 95% CI, 0.947–0.995; $P=0.017$), LVI (HR: 1.452;

Table 1 Characteristics of patients in the original cohort and post-matching cohort

Characteristics	Original cohort			Matched cohort		
	LVI(-)	LVI(+)	*P*	LVI(-)	LVI(+)	*P*
N	262	183		115	115	
Age, year			0.333			0.596
< 60	142(54.2%)	90(49.9%)		65 (56.5%)	60 (52.2%)	
>=60	120(45.8%)	93(50.1%)		50 (43.5%)	55 (47.8%)	
Gender			0.982			0.665
Female	93(35.5%)	66(36.1%)		32 (27.8%)	36 (31.3%)	
Male	169 (64.5%)	117 (63.9%)		83 (72.2%)	79 (68.7%)	
BMI	22.40 (3.31)	22.66 (3.62)	0.568	22.98 (3.91)	22.40 (3.95)	0.128
Preoperative intestinal obstruction			0.222			0.410
No	218(83.2%)	143(78.1%)		89 (77.4%)	95 (82.6%)	
Yes	44 (16.8%)	40 (21.9%)		26 (22.6%)	20 (17.4%)	
Preoperative Chemotherapy			0.019			1.000
No	200(76.3%)	157(85.8%)		95 (82.6%)	94 (81.7%)	
Yes	62 (23.7%)	26 (14.2%)		20 (17.4%)	21 (18.3%)	
Postoperative Chemotherapy			0.127			0.890
No	89(44.0%)	76(41.5%)		39 (33.9%)	41 (35.7%)	
Yes	173(66.0%)	107(58.5%)		76 (66.1%)	74 (64.3%)	
Surgical approach			< 0.001			
Laparoscopy	200(76.3%)	99(54.1%)		71 (61.7%	69 (60.0%)	0.893
Open	62 (23.7%)	84 (45.9%)		44 (38.3%)	46 (40.0%)	
Resection of liver metastases			0.054			1.000
No	198(75.6%)	153(83.6%)		93 (80.9%)	92 (80.0%)	
Yes	64 (24.4%)	30 (16.4%)		22 (19.1%)	23 (20.0%)	
Number of hepatic metastases			0.283			0.736
1	73 (27.9%)	40 (21.9%)		29 (25.2%)	30 (26.1%)	
2	155(59.2%)	113(61.7%)		69 (60.0%)	72 (62.6%)	
≥ 3	34 (13.0%)	30 (16.4%)		17 (14.8%)	13 (11.3%)	
ASA			0.295			0.617
1	7 (2.7%)	7 (3.8%)		5 (4.3%)	6 (5.2%)	
2	204(77.9%)	137(74.9%)		94 (81.7%)	88 (76.5%)	
≥ 3	51 (19.5%)	39 (21.3%)		16 (13.9%)	21 (18.3%)	
Tumor location			0.088			0.944
Left colon	74 (28.2%)	36 (19.7%)		29 (25.2%)	27 (23.5%)	
Right colon	86 (32.8%)	61 (33.3%)		42 (36.5%)	42 (36.5%)	
Rectum	102(38.9%)	86 (47.0%)		44 (38.3%)	46 (40.0%)	
Tumor size, cm			0.068			0.943
< 2	23 (8.8%)	6 (3.3%)		4 (3.5%)	5 (4.3%)	
2—5	194(74.0%)	145 (79.2%)		95 (82.6%)	94 (81.7%)	
> 5	45 (17.2%)	32 (17.5%)		16 (13.9%)	16 (13.9%)	
Differentiation			< 0.001			0.543
Well	19 (7.3%)	8 (4.4%)		7 (6.1%)	6 (5.2%)	
Moderately	208(79.4%)	114(62.3%)		85 (73.9%)	79 (68.7%)	
Poorly	35 (13.4%)	61 (33.3%)		23 (73.9%)	30 (26.1%)	
T stage			0.154			0.332
T1/T2	16 (6.1%)	5 (2.7%)		7 (6.1%)	3 (2.6%)	
T3/T4	246(93.9%)	178(97.3%)		108(93.9%)	112(97.4%)	
N stage			< 0.001			0.865
N0	117(44.7%)	21 (11.5%)		19 (16.5%)	21 (18.3%)	
N1	97 (37.0)	76 (41.5%)		61 (53.0%)	57 (49.6%)	
N2	48 (18.3%)	86 (47.0%)		35 (30.4%)	37 (32.2%)	
No of sampled LNs	17.2(7.78)	17.0 (7.85)	0.785	17.6 (7.96)	17.3 (7.96)	0.865
No of positive LNs	1.68 (2.28)	4.63 (5.37)	< 0.001	1.73 (2.34)	4.66 (5.18)	0.848

Characteristics	Original cohort			Matched cohort		
	LVI(-)	LVI(+)	*P*	LVI(-)	LVI(+)	*P*
Peri/intraneural invasion			< 0.001			0.790
PNI(-)	188(71.8%)	80 (43.7%)		67 (58.3%)	64 (55.7%)	
PNI(+)	74 (28.2%)	103(56.3%)		48 (41.7%)	51 (44.3%)	
Tumor deposits			< 0.001			0.891
Absent	201(76.7%)	92(50.3%)		73 (63.5%)	75 (65.2%)	
Present	61 (23.3%)	91 (49.7%)		42 (36.5%)	40 (34.8%)	
CEA level			0.003			0.546
Normal	98 (37.4%)	43 (23.5%)		32 (27.8%)	27 (23.5%)	
Elevated	164(62.4%)	140(76.5%)		83 (72.2%)	88 (76.5%)	
CA12–5 level			0.003			1.000
Normal	226(86.3%)	137(74.9%)		93 (80.9%)	93 (80.9%)	
Elevated	36 (13.7%)	46 (25.1%)		22 (19.1%)	22 (19.1%)	
CA19–9 level			0.132			0.787
Normal	181(69.1%)	113(61.7%)		72 (62.6%)	69 (60.0%)	
Elevated	81 (30.9%)	70 (38.3%)		43 (37.4%)	46 (40.0%)	

95% CI, 1.020–2.069; $P = 0.039$), preoperative CA12-5 level (HR: 1.830; 95% CI, 1.155–2.901; $P = 0.010$), and preoperative CA19-9 level (HR: 2.113; 95% CI, 1.317–3.390; $P = 0.002$) were independent prognostic factors for DFS (Table 3). In the cohort after PSM adjustment, we confirmed that N stage, No of sampled LNs, LVI, and preoperative CA125 and CA19-9 were independent prognostic factors for DFS.

Subgroup analysis of long-term prognostic factors in LVI (+) patients

In the original cohort of LVI(+) patients, we identified CEA, CA12-5, and CA19-9 as independent prognostic factors for OS (Supplementary Table 3). The results of the univariate Cox analysis for LVI (+) patients showed that the number of liver metastases, preoperative CEA level, preoperative CA12-5 level, and preoperative CA19-9 level were prognostic factors for OS ($P < 0.05$). The multivariate analysis showed that preoperative CEA level (HR: 2.324; 95% CI, 1.162–4.650; $P = 0.017$), preoperative CA12-5 level (HR: 1.982; 95% CI, 1.088–3.608; $P = 0.025$), preoperative CA19-9 level (HR: 1.843; 95% CI, 1.096–3.098; $P = 0.021$) were independent prognostic factors for OS (Supplementary Table 4). After adjustment using PSM, which eliminated the influence of potential confounding factors, we further confirmed that in LVI(+) patients, CEA, CA12-5, and CA19-9 are indeed independent prognostic factors for OS.

In the original cohort of LVI(+) patients, we identified postoperative chemotherapy, resection of liver metastases, CEA, CA12-5, and CA19-9 as independent prognostic factors for DFS (Supplementary Table 5). For DFS, we found that the number of liver metastases, resection of liver metastases, preoperative CEA level, preoperative CA12-5 level, preoperative CA19-9 level, and BMI were associated with prognosis for DFS ($P < 0.05$). Multifactorial analysis showed that resection of liver metastases (HR: 0.640; 95% CI, 0.344–0.985; $P = 0.017$), preoperative CEA level (HR: 2.085; 95% CI, 1.027–4.235; $P = 0.042$), preoperative CA12-5 level (HR: 2.692; 95% CI, 1.467–4.940; $P = 0.001$) were independent prognostic factors for DFS (Supplementary Table 6). After adjustment using PSM, we further confirmed that resection of liver metastases, CEA, and CA12-5 are independent prognostic factors for DFS.

Subgroup analysis of factors associated with postoperative chemotherapy

We analyzed the clinical characteristics of patients who received postoperative chemotherapy versus those who did not receive postoperative chemotherapy in both the original cohort and the propensity score-matched cohort (Supplementary Table 7). The following characteristics were associated with significantly higher rates of postoperative chemotherapy: patients aged ≥ 60 years old; those with no neoadjuvant chemotherapy; those who did undergo open surgery; those with presence of Tumor deposits and significant preoperative CA12-5 elevation (Supplementary Table 8). We found that postoperative chemotherapy had no significant effect on the prognosis of patients with LVI (-) (all $P > 0.05$) (Fig. 2A-B); however, among patients in the LVI (+) group, patients who received postoperative adjuvant chemotherapy had better OS and DFS than those who did not (HR: 1.593, 95% CI: 1.187 – 2.571; $P = 0.044$ and HR: 1.503, 95% CI. 1.033 – 2.422; $P = 0.045$ for OS and DFS, respectively) (Fig. 2C-D). These results suggest that postoperative chemotherapy improved OS and DFS in patients with LVI (+).

Table 2 Univariate and multivariate analyses of the prognostic factors for overall survival in the post-matching cohort

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Age, year		0.444		
< 60	1			
≥ 60	1.142(0.813,1.603)			
Gender		0.744		
Female	1			
Male	0.940(0.651,1.359)			
BMI	0.972(0.926,1.020)	0.253		
Preoperative intestinal obstruction		0.674		
No	1			
Yes	1.092(0.724,1.649)			
Preoperative Chemotherapy		0.715		
No	1			
Yes	0.915(0.568,1.475)			
Postpostoperative Chemotherapy		0.0467		0.038
No	1		1	
Yes	0.703(0.497,0.995)		0.670(0.461,0.974)	
Surgical approach		0.483		
Laparoscopy	1			
Open	1.131(0.802,1.595)			
Resection of liver metastases		0.927		
No	1			
Yes	0.980(0.642,1.496)			
Number of hepatic metastases				
1	1		1	
2	1.470(0.971,2.225)	0.069	1.338(0.864,2.070)	0.192
≥ 3	1.854(1.091,3.150)	0.022	1.785(1.020,3.123)	0.042
ASA				
1	1			
2	1.632(0.714,3.728)	0.245		
≥ 3	1.791(0.729,4.401)	0.204		
Tumor location				
Left colon	1			
Right colon	1.227(0.798,1.887)	0.352		
Rectum	0.746(0.467,1.170)	0.202		
Tumor size, cm				
< 2	1			
2—5	1.273(0.469,3.454)	0.636		
> 5	1.166(0.394,3.452)	0.782		
Differentiation				
Well	1			
Moderately	0.601(0.302,1.198)	0.148		
Poorly	1.447(0.703,2.980)	0.315		
T stage		0.250		
T1/T2	1			
T3/T4	1.796(0.662,4.876)			
N stage				
N0	1		1	
N1	0.972(0.6002,1.575)	0.909	1.096(0.645,1.862)	0.735
N2	1.696(1.034,2.781)	0.036	1.861(0.898,3.858)	0.095
No of sampled LNs	0.987(0.9654,1.010)	0.257		
No of positive LNs	1.062(1.005,1.122)	0.032	0.994(0.912,1.083)	0.886
Lymphovascular invasion		0.032		0.048

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P*	HR (95%CI)	*P*
LVI(-)	1		1	
LVI(+)	1.450(1.031,2.040)		1.424(1.004,2.022)	
Peri/intraneural invasion		0.108		
PNI(-)	1			
PNI(+)	0.752(0.530,1.065)			
Tumor deposits		0.328		
Absent	1			
Present	1.458(0.882,2.032)			
CEA level		0.929		
Normal	1			
Elevated	0.984(0.692,1.397)			
CA12–5 level		< 0.001		0.002
Normal	1		1	
Elevated	2.167(1.395,3.367)		2.019(1.276,3.197)	
CA19–9 level		< 0.001		0.012
Normal	1		1	
Elevated	2.483(1.656,3.723)		1.862(1.149,3.018)	

In addition, we found that among patients in the preoperative CEA-elevation group, LVI (+) patients had significantly worse OS and DFS than LVI (-) patients (OS HR: 1.594, 95% CI: 1.086–2.339; $P = 0.016$; DFS HR: 1.694, 95% CI: 1.153 – 2.489; $P = 0.0071$) (Fig. 3. C-D). In patients with normal levels of preoperative CEA, LVI status had no significant effect on OS or DFS (Fig. 3. A-B). For preoperative CA19-9-elevation, LVI status was significantly associated with OS (HR: 2.085, 95% CI: 1.226–3.545; $P = 0.005$) but showed no significiant correlation with DFS. In patients with normal levels of preoperative CA19-9, LVI status had no significant effect on OS or DFS (Fig. 4A–D).

Prediction model analysis of long-term patient prognosis

Significance indicators based on multifactorial Cox analysis of OS included postoperative chemotherapy(HR: 0.670, 95% CI: 0.461 – 0.974; $P = 0.038$), number of hepatic metastases (2 metastases, HR: 1.338; 95% CI, 0.864–2.070; $P = 0.192$; ≥3 metastases, HR: 1.785; 95% CI, 1.020–3.123; $P = 0.042$), LVI (HR: 1.424; 95% CI, 1.004–2.022; $P = 0.048$), preoperative CA12-5 level (HR: 2.019; 95% CI, 1.276–3.197; $P = 0.002$), and preoperative CA19-9 level (HR: 1.862; 95% CI, 1.149–3.018; $P = 0.012$) (Supplementary Table 9). Based on this, we established a prediction model for OS in patients with CRCLM. The AUROC for 1-year, 3-year and 5-year OS was 0.711, 0.786 and 0.744, respectively (Fig. 5A). N stage(N1, HR: 1.081; 95% CI, 0.661–1.769; $P = 0.766$; N2, HR: 1.903; 95% CI, 1.135–3.190; $P = 0.015$), No of sampled LNs (HR: 0.970; 95% CI, 0.947–0.995; $P = 0.017$), LVI (HR: 1.452; 95% CI, 1.020–2.069; $P = 0.039$), preoperative CA12-5 level (HR: 1.830; 95% CI, 1.155–2.901; $P = 0.010$), and preoperative CA19-9 level (HR: 2.113; 95% CI, 1.317–3.390; $P = 0.002$) were significantly associated with DFS (Supplementary Table 9). The AUROC for 1-year, 3-year and 5-year DFS was 0.725, 0.825 and 0.839, respectively (Fig. 5B), indicating that our model could accurately predict OS and DFS in patients with CRCLM.

In a subgroup analysis of LVI (+) patients, based on preoperative CEA(HR: 2.324, 95% CI: 1.162 – 4.650; $P = 0.017$), CA12-5(HR: 1.982 95% CI: 1.088 – 3.608; $P = 0.025$) and CA19-9(HR: 1.843, 95% CI: 1.096 – 3.098; $P = 0.021$) levels (Supplementary Table 10), we developed a predictive model for OS, with AUROCs of 0.662, 0.903 and 0.889 for 1-year, 3-year and 5-year OS, respectively (Fig. 6A). We also developed a predictive model for DFS in LVI (+) patients including the following variables: resection of liver metastases(HR: 0.640, 95% CI: 0.344 – 0.985; $P = 0.017$), preoperative CEA(HR: 2.085, 95% CI: 1.027 – 4.235; $P = 0.042$) levels, and CA12-5(HR: 2.692, 95% CI: 1.467 – 4.940; $P = 0.001$) levels (Supplementary Table 10). The AUROC for 1-year, 3-year and 5-year DFS was 0.701, 0.874 and 0.863, respectively (Fig. 6B).

Discussion

The focus of this large-scale, single-center, retrospective clinical study was patients with LVI (+) CRCLM. We used PSM to compare clinical, pathologic, laboratory, and other indicators of survival in patients with LVI (+) and LVI (-) CRCLM to assess their prognostic significance. Our findings suggest that patients in the LVI (+) group have worse prognosis compared with patients in the LVI (-) group, which is influenced by different clinicopathologic factors.

Table 3 Univariate and multivariate analyses of the prognostic factors for disease-free survival in the post-matching cohort

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Age, year		0.682		
< 60	1			
>=60	1.074(0.765,1.507)			
Gender		0.590		
Female	1			
Male	0.904(0.625,1.306)			
BMI	0.960(0.915,1.007)	0.096		
Preoperative intestinal obstruction		0.890		
No	1			
Yes	1.030(0.682,1.554)			
Preoperative Chemotherapy		0.859		
No	1			
Yes	0.956(0.595,1.542)			
Postoperative Chemotherapy		0.155		
No	1			
Yes	0.777(0.549,1.100)			
Surgical approach		0.885		
Laparoscopy	1			
Open	0.975(0.691,1.376)			
Resection of liver metastases		0.676		
No	1			
Yes	0.914(0.599,1.395)			
Number of hepatic metastases				
1	1			
2	1.250(0.826,1.891)	0.291	1.315(0.852,2.030)	0.217
≥ 3	1.800(1.059,3.057)	0.030	1.515(0.853,2.670)	0.156
ASA				
1	1			
2	1.278(0.560,2.920)	0.560		
≥ 3	1.258(0.524,3.151)	0.583		
Tumor location				
Left colon	1			
Right colon	1.197(0.778,1.841)	0.413		
Rectum	0.772(0.493,1.210)	0.259		
Tumor size, cm				
< 2	1			
2—5	0.643(0.235,1.758)	0.389		
> 5	0.592(0.199,1.760)	0.345		
Differentiation				
Well	1			
Moderately	0.642(0.323,1.280)	0.209		
Poorly	1.220(0.593,2.509)	0.589		
T stage		0.133		
T1/T2	1			
T3/T4	2.150(0.793,5.828)			
N stage				
N0	1		1	
N1	1.091(0.673,1.768)	0.725	1.081(0.661,1.769)	0.766
N2	1.823(1.113,2.986)	0.017	1.903(1.135,3.190)	0.015
No of sampled LNs	0.977(0.954,1)	0.049	0.970(0.947,0.995)	0.017
No of positive LNs	1.051(0.997,1.109)	0.065		
Lymphovascular invasion		0.025		0.039

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P*	HR (95%CI)	*P*
LVI(-)	1		1	
LVI(+)	1.479(1.051,2.080)		1.452(1.020,2.069)	
Peri/intraneural invasion		0.116		
PNI(-)	1			
PNI(+)	0.756(0.534,1.071)			
Tumor deposits		0.116		
Absent	1			
Present	0.756(0.534,1.071)			
CEA level		0.592		
Normal	1			
Elevated	1.100(0.776,1.561)			
CA12–5 level		0.001		0.010
Normal	1		1	
Elevated	2.055(1.325,3.186)		1.830(1.155,2.901)	
CA19–9 level		< 0.001		0.002
Normal	1		1	
Elevated	2.619(1.754,3.911)		2.113(1.317,3.390)	

Previous studies have shown that LVI has a significant impact on postoperative survival in stage I–III CRC [16, 21, 22]. However, there have been few studies focused on the prognostic value of LVI in stage IV CRC, especially in patients with CRCLM. Here, we compared the prognosis of two groups of patients with CRCLM with or without LVI. We found that OS and DFS were significantly lower in LVI (+) patients compared with LVI (-) patients. In the original cohort, we also found that LVI (+) was associated with worse OS and DFS compared with LVI (-) patients.

Previous studies have shown that elevated preoperative CEA, CA19-9, and CA12-5 are associated with increased mortality and recurrence rates and shorter survival time in patients with CRC [23, 24]. In recent years, there have been multiple studies of clinical prediction models to identify prognostic factors for survival in CRC. One study found that the inclusion of CEA, CA19-9, and CA12-5 significantly improved the performance of a prediction model compared with a model that included only preoperative CEA [25]. Elevated preoperative CEA is an independent prognostic factor for OS and DFS in patients with CRC and is significantly associated with higher mortality [23]. Serum CEA is recommended in NCCN guidelines as a predictor of prognosis and monitoring of recurrence in patients with CRC [26]. CEA levels are also beneficial for defining long-term prognosis, especially for postoperative monitoring in CRC and assessing whether patients are likely to experience recurrence or metastasis after surgery [27–29]. In the present study, preoperative CEA levels were significantly associated with long-term prognosis of CRCLM, and elevated preoperative CEA significantly decreased OS and DFS, similar to previous studies [30]. We also found that elevated preoperative CA12-5 was associated with poor prognosis. This is in keeping with a study by Huang, J.H., et al. [31] who also found that elevated preoperative CA12-5 was associated with poor prognosis in patients with metastatic CRC, and that a prediction model incorporating tumor markers, including CA12-5, was able to improve the accuracy of the CRC prediction model [27]. On the contrary, one study concluded that CA12-5 was not significantly associated with outcomes in patients with CRC [32]. To date, most studies have focused on patients with Stage I-III CRC and elevated CA12-5; few studies have focused on the prognostic value of CA12-5 in patients with CRCLM. Therefore, the effect of preoperative CA12-5 levels on prognosis in patients with CRCLM remains largely unknown. In the present study, we found that preoperative CA12-5 level was an independent and significant prognostic factor for OS and DFS whereby patients with elevated preoperative CA12-5 had significantly lower OS and DFS than patients with normal preoperative CA12-5 (both $P < 0.05$). This suggests that CA12-5 may be combined with CEA to jointly predict prognosis in patients with CRCLM. In patients with LVI (+) CRCLM, preoperative CEA, CA12-5 and CA19-9 levels were independent prognostic factors for OS, while CEA and CA12-5 levels were associated with DFS and recurrence after surgery.

In CRC, N stage and No of sampled LNs are important to define patient prognosis, and intraoperative resection of a sufficient number of lymph nodes is essential for determining N stage. Current guidelines recommend intraoperative resection of at least 12 lymph nodes in patients with CRC to accurately assess N stage [26, 33]. Inadequate lymph node harvesting may lead to false-negative results, which may affect the accurate determination

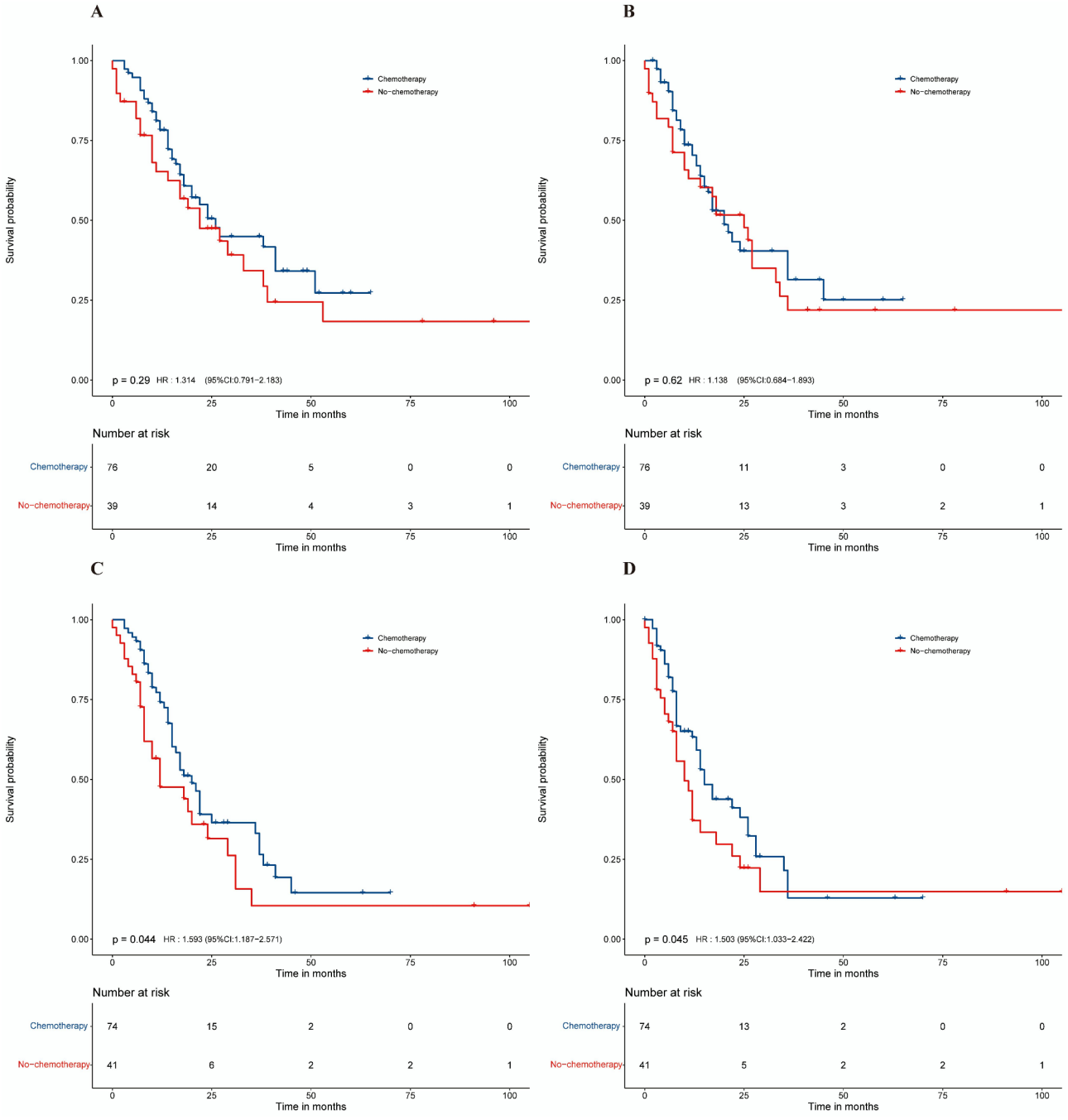

Fig. 2 The Kaplan-Meier survival curves of patients grouped according to with or without postoperative adjuvant chemotherapy. The Kaplan-Meier survival curves of OS and DFS for patients with LVI (-) (**A/B**) or LVI (+) (**C/D**) in the matched cohorts

of N stage and lead to selection of an inappropriate therapy. N stage depends on the number of lymph node metastases, and in turn the number of lymph node metastases determine tumor stage, risk of recurrence, long-term prognosis and distant metastasis. It has been shown that in stage IV tumors, the status and number of lymph nodes are important factors independent of chemotherapy and radical tumor surgery [34]. In our study, we found that higher N stage and fewer sampled lymph nodes was associated with an increased recurrence rate in patients with CRCLM and poorer DFS.

Surgical treatment in patients with CRCLM may be curative and can increase 5-year OS up to 71% [34, 35]. The number of liver metastases determines both whether a patient can undergo surgical resection and the likelihood of postoperative recurrence. Surgically resectable CRCLM was defined as fewer than three liver metastatic lesions, less than 5 cm in diameter, and the

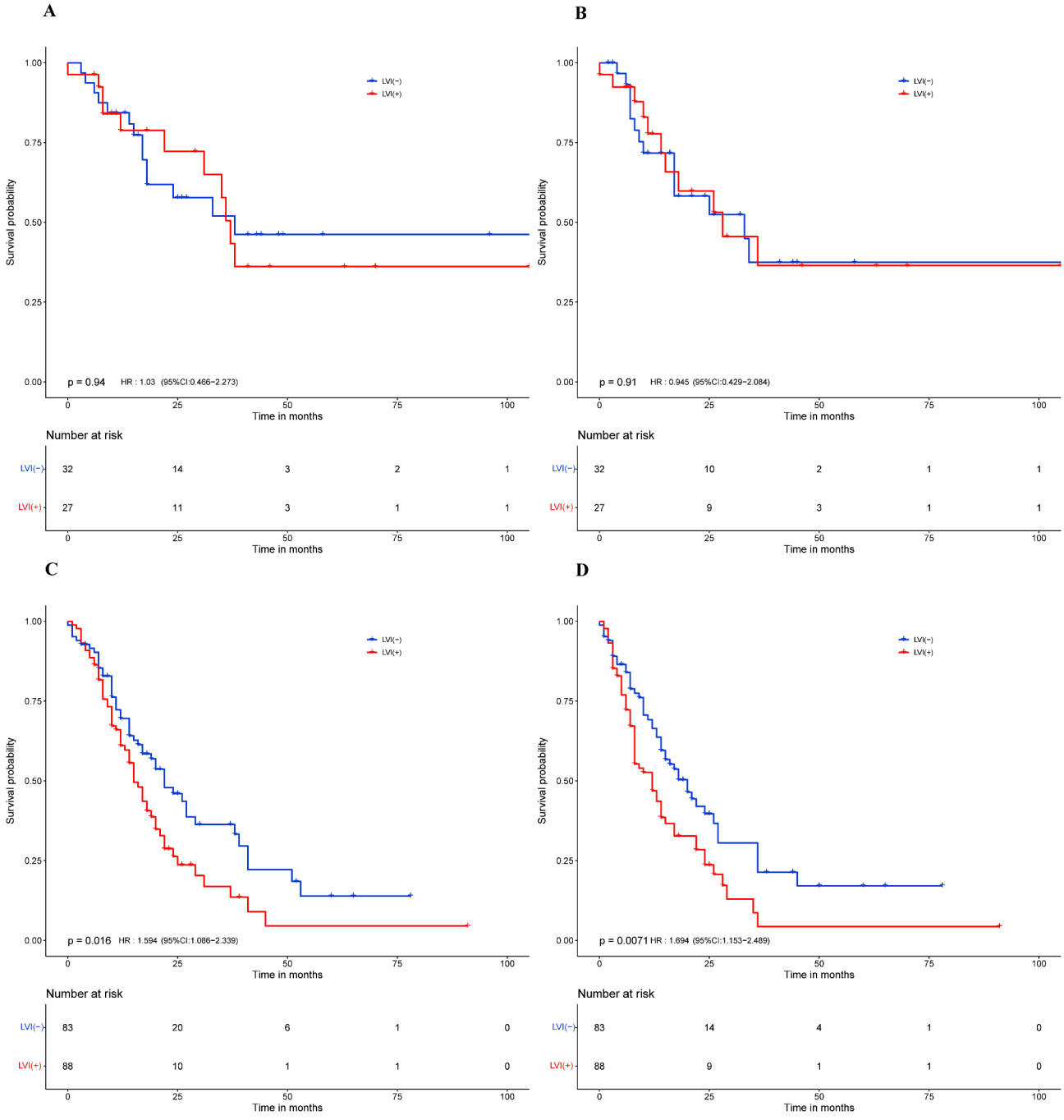

Fig. 3 Kaplan-Meier survival curves of patients with different level of CEA in the matched cohort. The Kaplan-Meier survival curves of the effect of LVI status on OS and DFS in the CEA-Normal group (**A/B**) and CEA-Elevated group (**C/D**)

absence of extrahepatic metastases [36]. Previous studies have shown that patients with ≥3 liver metastases have increased probability of early recurrence of liver metastasis, which is likely to require repeat surgical resection and may compromise OS [37]. Our results showed that in patients with ≥3 liver metastases, OS was significantly reduced compared with patients with fewer liver metastases; however, we did not identify a significant effect on DFS.

In patients with CRCLM, chemotherapy is an important treatment option that can improve long-term prognosis and reduce the tumor stage in patients with unresectable CRCLM, which in turn may open up the possibility of surgical resection [38]. In stage II colon adenocarcinoma, patients with positive LVI have a lower

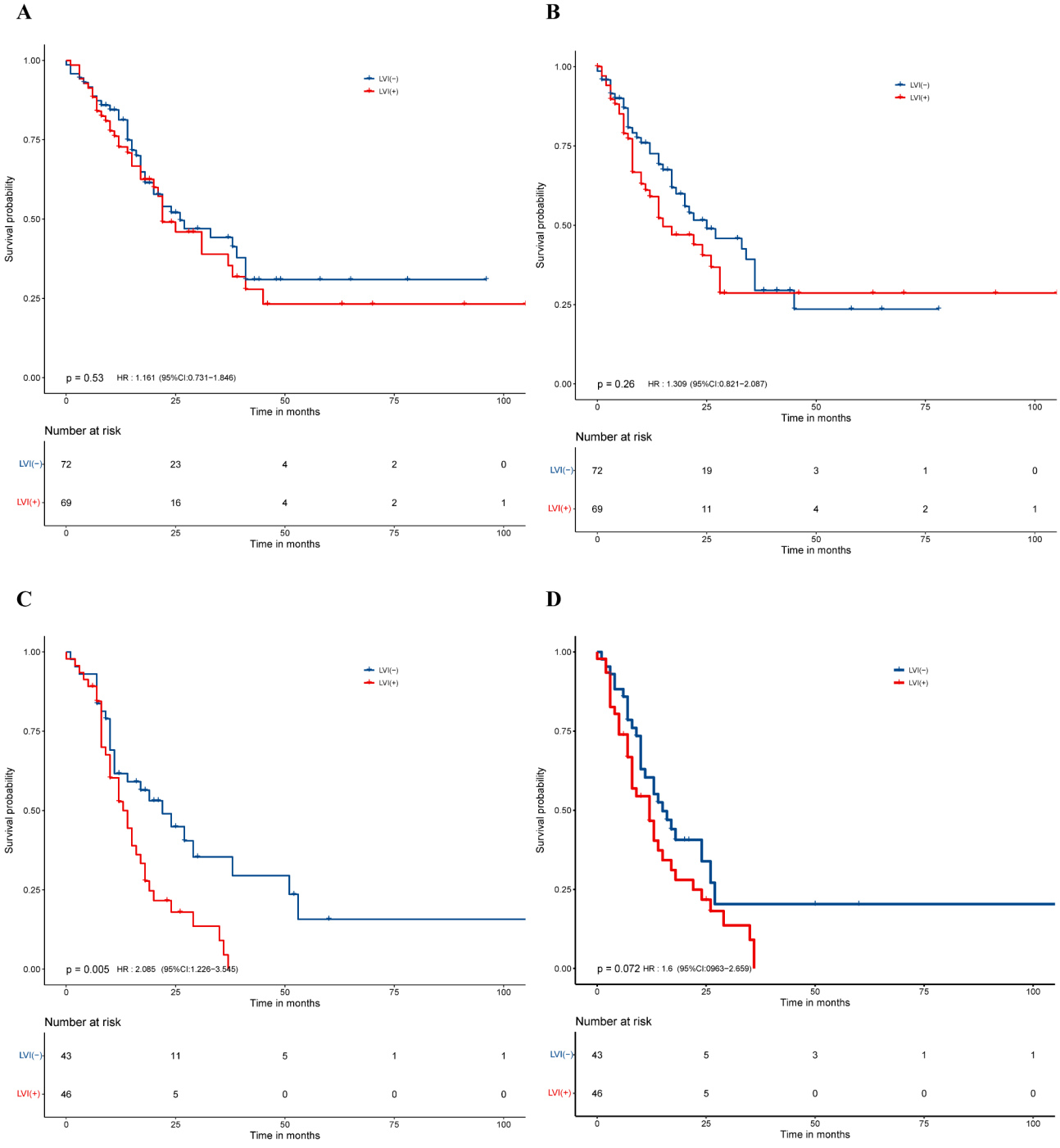

Fig. 4 Kaplan-Meier survival curves of patients with different level of CA19-9 in the matched cohort. The Kaplan-Meier survival curves of the effect of LVI status on OS and DFS in the CA19-9-Normal group (**A/B**) and CA19-9-Elevated group (**C/D**)

5-year overall survival rate, and adjuvant chemotherapy can improve the 5-year survival rate and reduce the risk of death in LVI (+) patients [39]. Gao et al. demonstrated that in LVI(+) stage II patients, the 5-year OS and 5-year DFS rates were significantly higher in the adjuvant chemotherapy (ACT) group compared to the surgery-alone (SA) group (5-year OS: 66.7% vs. 40.9%, $P = 0.004$; 5-year DFS: 64.1% vs. 36.3%, $P = 0.002$) [40]. In stage III patients with positive LVI, those who completed 6–8 cycles of adjuvant chemotherapy had significantly better 3-year DFS and OS rates compared to those who completed fewer than six cycles (DFS: 80.0% vs. 64.9%, $P = 0.019$; OS: 93.2% vs. 76.3%, $P = 0.002$) [41]. In contrast, no significant difference was observed in the LVI (-) stage III

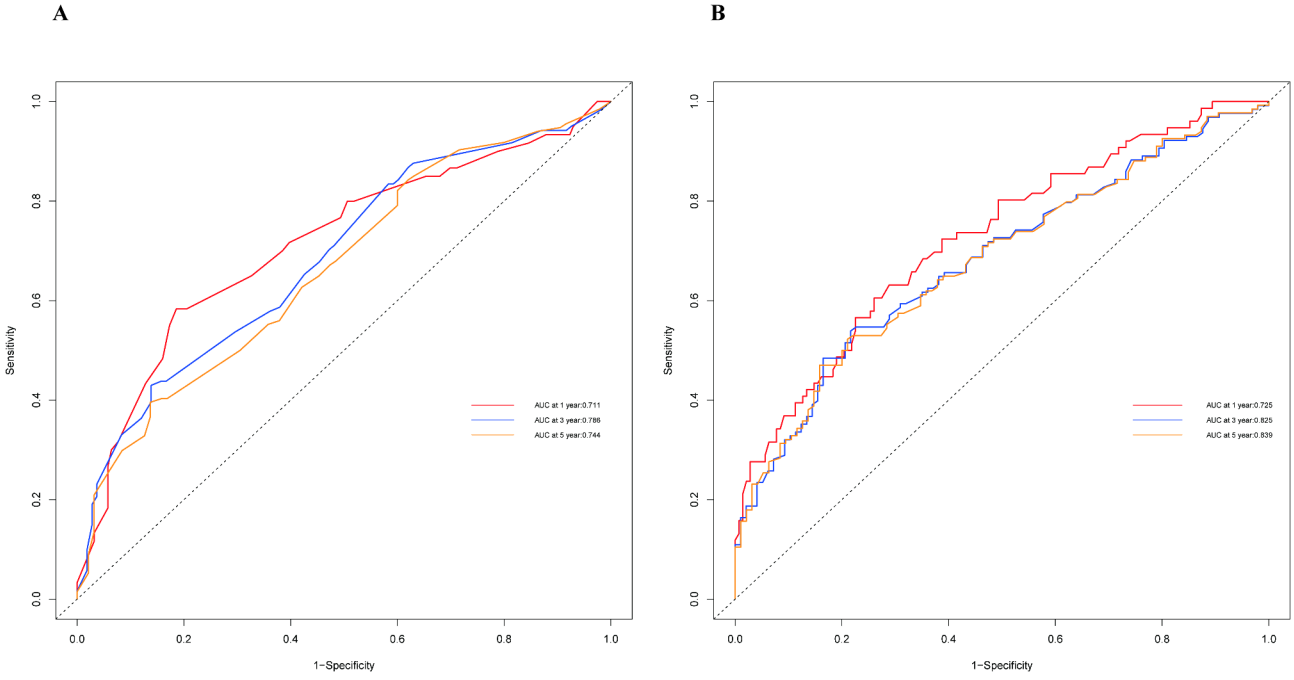

Fig. 5 The receiver operating characteristic (ROC) curve of independent prognostic factors. The Area under the curve (AUC) of OS (**A**) and DFS (**B**) of independent prognostic factors in patients grouped by LVI in the matched cohort

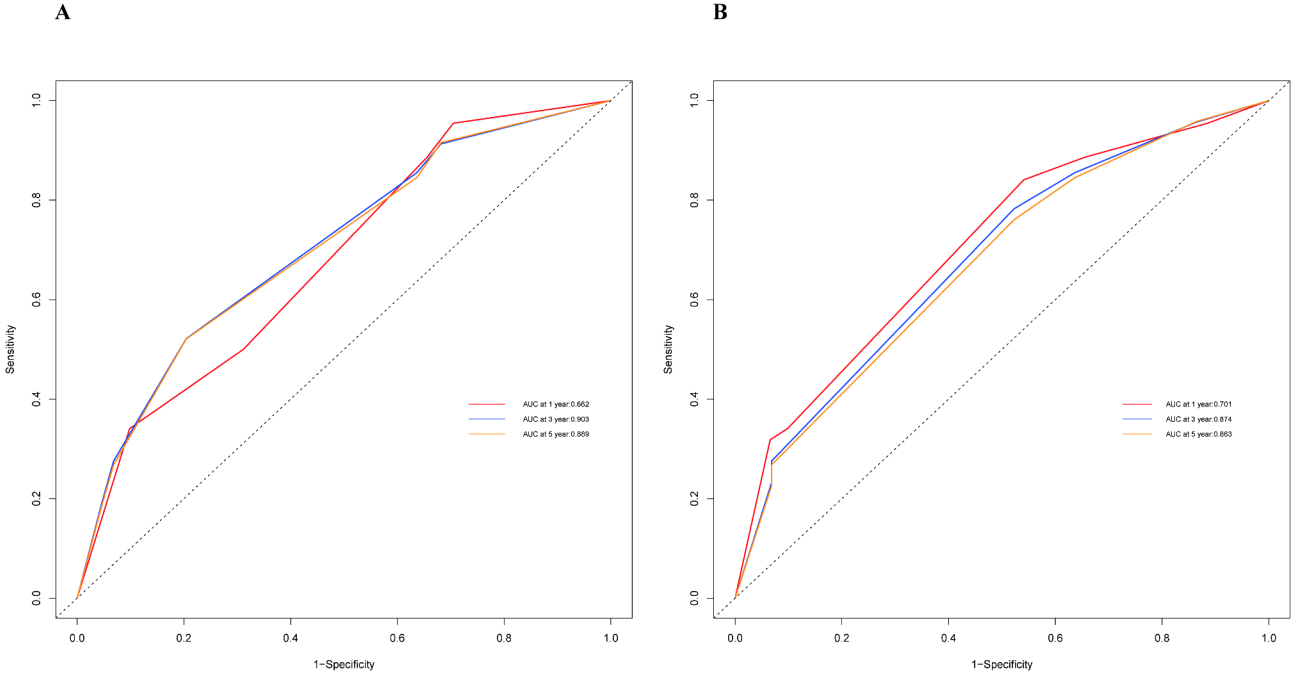

Fig. 6 The receiver operating characteristic (ROC) curve of independent prognostic factors. The Area under the curve (AUC) of OS (**A**) and DFS (**B**) of independent prognostic factors in LVI (+) subgroup after matching

patient group [41]. This indicates that completing the recommended number of adjuvant chemotherapy cycles (typically 6–8 cycles) effectively improves the 3-year DFS and OS in LVI (+) patients. In comparison, completing the recommended chemotherapy cycles did not show a significant difference in survival rates in LVI (-) patients. However, many patients with CRCLM cannot benefit from adjuvant chemotherapy. In our study 37.2% of patients in the LVI (+) group underwent postoperative chemotherapy, and OS and DFS were significantly

prolonged in patients who received chemotherapy compared with those who did not ($P < 0.05$). In contrast, postoperative chemotherapy status has no significant effect on long-term prognosis in patients with LVI (-) CRCLM ($P > 0.05$). Our study reached a similar conclusion, showing that chemotherapy can significantly improve the prognosis in LVI (+) CRCLM patients, while no significant improvement was observed in LVI (-) patients. In this study, patients with CRCLM who have LVI (+) received fewer postoperative chemotherapy compared to those who are LVI (-). This phenomenon may be due to the following reasons. LVI reflects an increased aggressiveness and worse biological behavior of the tumor, potentially leading to a broader range of tumor-related symptoms such as anemia, malnutrition, and cachexia. These symptoms can affect patients' overall health status, thereby reducing their tolerance and safety of chemotherapy. Additionally, patients with more aggressive tumors and worse biological behavior have a higher risk of postoperative complications such as bowel obstruction, bleeding, and infection. These complications not only affect the implementation of chemotherapy but can also lead to interruptions or delays in treatment, impacting overall treatment outcomes. LVI (+) indicates a poorer prognosis, often requiring more complex treatment regimens, and patients may experience greater psychological stress and anxiety, increasing the complexity of treatment and the difficulty of adherence.

We referenced previous studies on the role of the TNM staging system in predicting the prognosis of CRCLM patients. In the training set, the AUC values for 1-year, 3-year, and 5-year OS were 0.584, 0.608, and 0.627, respectively, while the corresponding AUC values in the validation set were 0.594, 0.597, and 0.621 [42]. This suggests that the TNM staging system has certain limitations in accurately predicting the prognosis of CRCLM patients, falling short of clinical needs. Subsequently, Cao et al. [42] developed a model to predict the overall survival rate of CRCLM patients using factors such as age, tumor location, differentiation, gender, TNM stage, chemotherapy, No of sampled LNs, number of positive lymph nodes, tumor size, and metastatic surgery. The model achieved AUC values of 0.816, 0.782, and 0.767 for 1-year, 3-year, and 5-year OS in the training cohort, respectively, and 0.827, 0.769, and 0.744 in the internal validation cohort, and 0.822, 0.756, and 0.785 in the external validation cohort [42]. Although this model demonstrates high accuracy, it includes many variables, making the prediction process complex and does not adequately account for the impact of confounding factors.In this study, we established a clinical predictive model for CRCLM patients based on the results of multivariate Cox regression analysis and plotted ROC curves. After PSM, we eliminated the confounding effects of LVI (–) and LVI (+). Based on the results of multivariate Cox regression analysis, we constructed predictive models for OS and DFS, which exhibited good performance and clinical applicability. Additionally, we focused on the specific subgroup of LVI (+) patients, identified independent prognostic factors for OS and DFS, and assessed the significance of adjuvant chemotherapy in this population. Our results indicate that the predictive model developed in this study has significant advantages in predicting the long-term prognosis of CRCLM patients and can serve as an important basis for postoperative treatment decisions by patients and clinicians. In our study, we particularly focused on the significance of LVI in the prognosis of CRCLM patients, accounted for the influence of confounding factors, and conducted subgroup analysis in LVI (+) patients, thereby constructing a prognostic model for this specific population.

There are some limitations in the present study. First, this was a single-center, retrospective study, and a multicenter study should be conducted for further validation. Second, this study only included clinicopathological features with imperfect detection indexes, and it will be necessary to include molecular or genetic indexes such as microsatellite phenotype, tumor budding, and mismatch repair (MMR) status, as well as extramural vascular invasion (EMVI), in future validation studies. Despite these limitations, we can conclude that LVI status is an important factor affecting the long-term prognosis of patients with CRCLM.

Conclusions

LVI may significantly impact long-term survival and prognosis in patients with CRCLM undergoing primary resection, potentially serving as an independent prognostic factor for OS and DFS. Additionally, postoperative chemotherapy appears to significantly improve the long-term prognosis of patients with LVI (+).

Figure Lengend.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14083-2.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Supplementary Material 8

Supplementary Material 9

Supplementary Material 10

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Not applicable.

Author contributions
WL, BL and XXX are the research leaders whilst QZ and QLY performed data collection. Furthermore, WL conducted data analysis and implemented the methodology. Moreover, WL authored the initial draft. BLand XXX improved the figures. QZ and BL reviewed the manuscript. XXX and QLY reviewed and edited it. All authors read and approved.

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Data availability
The datasets generated and analyzed during the current study are available from the corresponding author.

Declarations

Ethics approval and consent to participate
Our study was initiated after receiving approval from the Ethics Committee and Institutional Review Committee of Wuhan Union Hospital (No. 2018-S377). All methods were conducted in accordance with applicable regulations and guidelines. Informed consent was obtained from all individual participants included in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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