BMC Surgery

RESEARCH Open Access

An elevated preoperative cholesterol-to-lymphocyte ratio predicts unfavourable outcomes in colorectal cancer liver metastasis patients receiving simultaneous resections: a retrospective study

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Abstract

Background To explore the clinical prognostic utility of the preoperative cholesterol-to-lymphocyte ratio (CLR) in outcomes for colorectal cancer liver metastasis (CRLM) patients receiving simultaneous resection of the primary lesion and liver metastases.

Methods A total of 444 CRLM patients receiving simultaneous resections were enrolled. The optimal cut-off value for CLR was determined using the highest Youden's index. Patients were divided into the CLR < 3.06 group and the CLR≥3.06 group. Propensity score matching analysis (PSM) and the inverse probability of treatment weighting (IPTW) method were conducted to eliminate bias between the two groups. The outcomes included short-term outcomes and long-term outcomes. Kaplan–Meier curves and log-rank tests were used to analyse progression-free survival (PFS) and overall survival (OS).

Results In the short-term outcome analysis, after 1:1 PSM, 137 patients were distributed to the CLR < 3.06 group and CLR≥3.06 group. No significant difference was noted between the two groups ($P > 0.1$). Compared with patients with CLR < 3.06, patients with CLR≥3.06 had comparable operation times (320.0 [272.5–421.0] vs. 360.0 [292.5-434.5], $P = 0.088$), blood loss (200.0 [100.0-400.0] vs. 200.0 [150.0-450.0], $P = 0.831$), postoperative complication rates (50.4% vs. 46.7%, $P = 0.546$) and postoperative ICU rates (5.8% vs. 11.7%, $P = 0.087$). In the long-term outcome analysis, Kaplan–Meier analysis showed

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that compared with patients with CLR < 3.06, patients with CLR≥3.06 had worse PFS (P = 0.005, median: 10.2 months vs. 13.0 months) and OS (P = 0.002, median: 41.0 months vs. 70.9 months). IPTW-adjusted Kaplan–Meier analysis showed that the CLR≥3.06 group had worse PFS (P = 0.027) and OS (P = 0.010) than the CLR < 3.06 group. In the IPTW-adjusted Cox proportional hazards regression analysis, CLR≥3.06 was an independent factor for PFS (HR = 1.376, 95% CI 1.097–1.726, P = 0.006) and OS (HR = 1.723, 95% CI 1.218–2.439, P = 0.002). IPTW-adjusted Cox proportional hazards regression analysis including postoperative complications, operation time, intraoperative blood loss, intraoperative blood transfusion and postoperative chemotherapy revealed that CLR≥3.06 was an independent factor for PFS (HR = 1.617, 95% CI 1.252–2.090, P < 0.001) and OS (HR = 1.823, 95% CI 1.258–2.643, P = 0.002).

Conclusions The preoperative CLR level predicts unfavourable outcomes in CRLM patients receiving simultaneous resection of the primary lesion and liver metastases and should be taken into consideration when developing treatment and monitoring strategies.

Keywords Colorectal cancer liver metastases, Simultaneous resection, Cholesterol-to-lymphocyte ratio, Outcomes, Inverse probability of treatment weighting

Introduction

Colorectal cancer (CRC) is a digestive tract tumour, and liver metastases represent its most common malignant progression [1]. The 5-year survival rate of patients with colorectal cancer liver metastases (CRLM) is less than 10% [2] without surgical resection and approaches 50% [3] after active multimodal treatment comprising chemotherapy and hepatic resection. Surgical treatment remains the dominant contributor to the long-term survival of CRLM patients [4]. At colorectal cancer diagnosis, synchronous liver metastases occur in approximately 15% [2, 5] of patients. Simultaneous resection of primary lesions and liver metastases, an emerging curative resection for synchronous CRLM, has been increasingly [6] performed by surgeons. Compared with traditional staged resection, simultaneous resection can yield comparable short-term outcomes [6–9] and has a tendency to improve long-term outcomes [9]. Simultaneous resection is often associated with a shorter hospital stay, reduced hospital costs and a better experience for CRLM patients [7–9].

Due to the heterogeneous nature of tumours, the precise and personalized preoperative classification of surgery for CRLM patients could bring many benefits. There is a consensus [10, 11] that chronic inflammatory status instigates the initiation and development of cancer. Based on this notion, preoperative inflammatory biomarkers, such as the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), were established, and the utility of their prognostic value in multiple cancers was validated [12–14]. Among them, lymphocytes, especially tumour-infiltrating lymphocytes (TILs), played an essential role in the process of progression in CRC [15, 16]. More interestingly, peripheral lymphocyte counts were demonstrated to be useful in predicting the survival of triple-negative breast cancer [17], oral cancer [18] and colon cancer patients [19], and the prognostic utility of lymphocyte counts was reported to be better than that of other circulating serum cells, such as platelets and neutrophils [18].

Alteration of lipid metabolism is a hallmark in cancer. Cancer cells increase the uptake and storage of fatty acids, phospholipids and cholesterol, which supports the survival of cancer cells in a nutrient-poor microenvironment. These substances could also act as signalling molecules that activate tumour-related signalling pathways to promote proliferation, invasion and metastases [20–22]. Additionally, dysregulated cholesterol metabolism substantially promoted the progression of multiple cancers [23–25], including CRC [25]. The prognostic role of blood lipid markers, such as total cholesterol and high-density lipoprotein cholesterol (HDL-C), was reported in patients with endometrial cancer, non-small-cell lung cancer and CRC [26–28]. Recently, Zhou et al. [29] found that in CRC, the cholesterol-to-lymphocyte ratio (CLR), a marker that combines inflammatory status and lipid metabolism, was associated with long-term prognosis in CRC and exhibited more sensitivity and specificity than the common inflammatory marker NLR. However, the prognostic role of preoperative CLR in CRLM remains unknown. Given the abovementioned evidence, we aimed to verify and examine the predictive value of preoperative CLR in distinguishing the short-term and long-term prognosis of patients with CRLM who received simultaneous resection of the primary lesion and liver metastases.

Methods

Study population and variables

Collection and analysis of data in the study was performed after ethical approval (No. 81,972,311) was approved from the Institutional Review Board of the Cancer Hospital, Chinese Academy of Medical Sciences. The inclusion criteria were as follows: (1) histologically proven liver metastases of colorectal adenocarcinoma and (2) curative simultaneous resection of primary

tumour and liver metastases. The exclusion criteria were as follows: (1) failure to follow-up or absence of clinical data; (2) other coexisting malignancies; and (3) presence of infectious disease before operation. In this study, we retrospectively collected the clinical information of 444 patients with CRLM who underwent simultaneous resection of primary lesions and liver metastases at the Cancer Hospital, Chinese Academy of Medical Sciences from January 2009 to November 2020.

Detailed information, including demographic characteristics (age, sex, body mass index (BMI), comorbidities, and American Society of Anaesthesiology (ASA) score), clinicopathological characteristics (preoperative cholesterol level, lymphocyte counts, neutrophil counts, and serum carcinoembryonic antigen (CEA)), tumour-related characteristics, treatment and oncological outcomes, was collected from every patient. In this study, comorbidity among CRLM patients was characterized as the presence of preoperative coexisting medical conditions or diseases, including but not limited to hypertension, diabetes, and dementia. All postoperative complications were evaluated using the Clavien-Dindo classification system. Complications were categorized as minor (Clavien-Dindo I-II) or major (Clavien-Dindo III-V) based on the severity of their impact on the patient's health and recovery.

Cholesterol-to-lymphocyte ratio (CLR)

Peripheral blood samples from each patient were collected within 1–3 weeks before the simultaneous resection. Preoperative CLR was defined by dividing total cholesterol by the lymphocyte count. The optimal cut-off value for CLR as a predictive tool for mortality in patients with CRLM undergoing simultaneous resection was determined using the highest Youden's index (sensitivity + 1-specificity), which was graphically exhibited as the distance between the 45° line and the ROC. Then, patients were divided into two groups: patients with CLR < 3.06 in one group and patients with CLR ≥ 3.06 in the other group.

Treatment

The optimal treatment management protocol for CRLM patients was discussed and confirmed by a multidisciplinary team (MDT) composed of surgeons, oncologists and radiologists. The surgical data mainly included surgical margin (R0 resection or not), extent of liver resection (major resection or not), intraoperative radiofrequency ablation (RFA) and hepatic portal occlusion. Major resection was defined as resections of ≥ three segments of liver metastases. A combination of 5-fluorouracil/capecitabine and oxaliplatin/irinotecan with or without bevacizumab and cetuximab comprised the pretreatment chemotherapy regimen.

Follow-up and outcomes

After surgery, patients were followed up with regular clinical examinations. The first postoperative follow-up was conducted one month from the date of surgery. Then, all follow-ups were regularly conducted every 3 months for 5 years and every 1 year thereafter.

The oncological outcomes were divided into short-term outcomes and long-term outcomes. The short-term outcomes included intraoperative operation time, intraoperative blood loss, postoperative hospital stay, incidence of postoperative complications and postoperative ICU rate. ICU rate is defined as the percentage of patients who required admission to the intensive care unit after surgery for any reason. The long-term outcomes included progression-free survival (PFS) and overall survival (OS). PFS was defined as the period of time from the date of surgical treatment to progression or the last follow-up date. OS was defined as the period of time from the date of surgical treatment to death or the last follow-up date.

Statistical analysis

Continuous variables were measured as the median and interquartile range, and *t test*s or Mann–Whitney U tests were performed for comparison. Categorical variables were calculated as percentages and compared using the chi-square test. The preoperative NLR was calculated as (neutrophil count/lymphocyte count). The association of CLR with PFS and OS was firstly evaluated using univariable and multivariable Cox regression analyses. Only variables with $P < 0.10$ in the univariable analysis were included in the subsequent multivariable analysis. And the additional clinical net-benefit of CLR ≥ 3.06 was assessed by employing decision curve analysis (DCA). To compare the short-term outcomes between the CLR < 3.06 group and CLR ≥ 3.06 group, the propensity score matching (PSM) method was performed to balance the imbalanced covariates between the two groups. The inverse probability of treatment weighting (IPTW) method was performed to eliminate selection bias between the CLR < 3.06 group and the CLR ≥ 3.06 group in the comparison of long-term outcomes.

The balance in covariates was evaluated using the standardized difference (SD) approach. A meaningful imbalance in the factors between the two groups was represented as an SD > 0.1. In the IPTW models, we retained all possible factors associated either with the CLR level or survival. We adopted adjusted Kaplan–Meier curves and log-rank tests to compare long-term outcomes (PFS and OS) between the CLR < 3.06 group and the CLR ≥ 3.06 group. The inverse probability weighted Cox proportional hazards model was used to estimate the IPTW-adjusted hazard ratio (HR) of the level of CLR. $P < 0.05$ (two-sided) was considered to be statistically significant. Statistical analyses were performed

Table 1 Clinicopathological characteristics and short-term outcomes in CRLM patients receiving simultaneous resection before PSM

Item	CLR < 3.06 (n = 285)	CLR ≥ 3.06 (n = 159)	*P*	All patients (n = 444)
Age ≥60 years, n (%)	126 (44.2%)	80 (50.3%)	0.216	206(46.4%)
Male, n (%)	185 (64.9%)	101 (63.5%)	0.769	286(64.4%)
BMI ≥ 24 kg/m^2, n (%)	134 (47.0%)	75 (47.2%)	0.975	209(47.1%)
NLR ≥ 1.86, n (%)	113 (39.6%)	107 (67.3%)	< 0.001	220(49.5%)
Comorbidity, n (%)	123 (43.2%)	65 (40.9%)	0.641	188(42.3%)
ASA score 3–4, n (%)	30 (10.5%)	24 (15.1%)	0.158	54(12.2%)
Preoperative CEA ≥ 200 ng/ml, n (%)	10 (3.5%)	9 (5.7%)	0.283	19(4.3%)
Primary site in colon, n (%)	167 (58.6%)	85 (53.5%)	0.295	252(56.8%)
Right hemicolon, n (%)	53 (18.6%)	36 (22.6%)	0.307	89(20.0%)
Diameter of liver metastases ≥ 5 cm, n (%)	34 (11.9%)	29 (18.2%)	0.068	63(14.2%)
Multiple liver metastases, n (%)	168 (58.9%)	92 (57.9%)	0.824	260(58.6%)
Bilobar liver distribution, n (%)	108 (37.9%)	69 (43.4%)	0.256	177(39.9%)
Poor differentiation, n (%)	88 (30.9%)	56 (35.2%)	0.349	144(32.4%)
T3-T4 stage, n (%)	263 (92.3%)	146 (91.8%)	0.864	409(92.1%)
Positive lymph node metastasis, n (%)	206 (72.3%)	115 (72.3%)	0.992	321(72.3%)
Extrahepatic metastases, n (%)	30 (10.5%)	14 (8.8%)	0.561	44(9.9%)
Concomitant RFA, n (%)	25 (8.8%)	18 (11.3%)	0.384	43(9.7%)
R0 resection, n (%)	214 (75.1%)	119 (74.8%)	0.954	333(75.0%)
Major liver resection, n (%)	138 (48.4%)	76 (47.8%)	0.900	214(48.2%)
Pretreatment chemotherapy, n (%)	160 (56.1%)	93 (58.5%)	0.632	253(57.0%)
Hepatic portal occlusion, n (%)	192 (67.4%)	117 (73.6%)	0.172	309(69.6%)
All laparoscopic operation, n (%)	57 (20.0%)	40 (25.2%)	0.207	97(21.8%)
Operation time, min (median, IQR)	340.0(260.0-420.0)	320.0(270.0-430.0)	0.971	335.0(265.0-420.0)
Blood loss, ml (median, IQR)	200.0(100.0-400.0)	200.0(150.0-400.0)	0.163	200.0(100.0-400.0)
Blood transfusion, n (%)	66(23.2%)	37(23.3%)	0.979	103(23.2%)
Complications, n (%)				
0, n (%)	149(52.3%)	77(48.4%)	0.335	226(50.9%)
1–2, n (%)	83(29.1%)	43(27.0%)		126(28.4%)
3–5, n (%)	53(18.6%)	39(24.5%)		92(20.7%)
Postoperative minor complications, n (%)	83(29.1%)	43(27.0%)	0.641	126(28.4%)
Postoperative major complications, n (%)	53(18.6%)	39(24.5%)	0.139	92(20.7%)
ICU, n (%)	22(7.7%)	13(8.2%)	0.864	35(7.9%)
Post-operative hospital stay, days (median, IQR)	10.0(9.0–13.0)	10.0(8.0–14.0)	0.453	10.0(9.0–13.0)

using SPSS version 25 software (Armonk NY, USA) and R software (http://www.r-project.org).

Results

Clinicopathological characteristics

There were 444 patients enrolled in the present study with a median age of 59.0 (IQR [52.0, 65.0]) years. Greater than half of the patients were male (286/444, 64.4%), and comorbidities were present in 188 (42.3%) patients. The median NLR of the patients was 1.86 (IQR [1.34, 2.55]). Fifty-four (12.2%) patients had an ASA score of 3–4, whereas 209 (47.1%) patients had a BMI ≥ 24 kg/m^2. Before simultaneous resection, 253 (57.0%) patients received pretreatment chemotherapy. For patients who had primary tumours located in the colon, the rate of patient population was 56.8%, and 89 (20.0%) among them had primary tumours located in the right hemicolon. For liver metastases, the median largest size was 2.5 cm (IQR [1.5, 4.0]), and the median number was 2 (IQR [1, 4]). Bilobular liver metastasis distribution was noted in 177 (39.9%) patients. Three hundred and twenty-one (72.3%) patients had positive lymph node metastasis. As depicted in the Figure S1, the optimal cutoff value of CLR for mortality was determined as 3.06. And two hundred eighty-five (64.2%) patients had CLR < 3.06, whereas 159 (35.8%) patients had CLR ≥ 3.06. For patients who received all laparoscopic surgeries, the rate of the patient population was 21.8%. Concomitant RFA was performed in 43 (9.7%) patients, and the rate of hepatic portal occlusion among the patients was 69.6%. Two hundred and fourteen (48.2%) patients underwent major liver resection. The detailed clinicopathological characteristics of the patients are listed in Table 1.

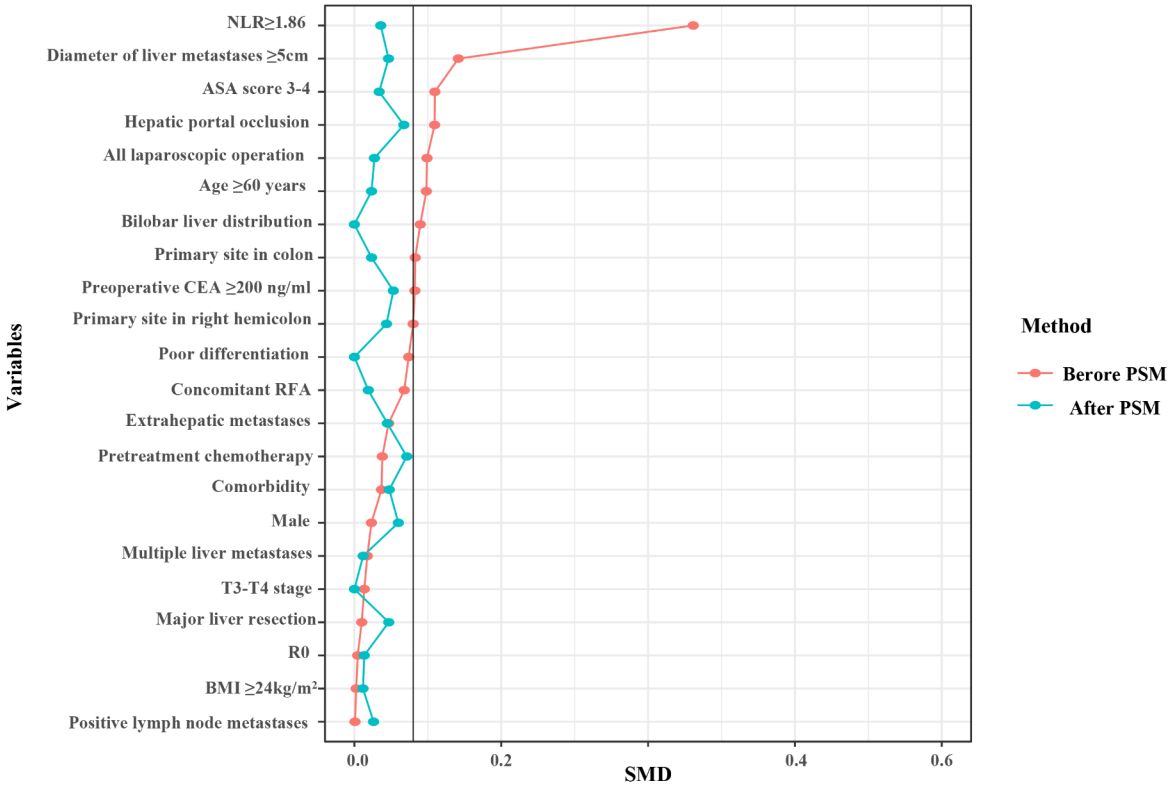

Fig. 1 Standardized mean difference (SMD) of CLR < 3.06 vs. CLR ≥ 3.06 before and after PSM

Short-term outcomes

The median operative time of patients was 335.0 min (IQR [265.0-420.0]). The median intraoperative blood loss volume was 200 ml (IQR [100, 400]), and 103 (23.2%) patients received an intraoperative blood transfusion. The median postoperative hospital stay duration was 10 days (IQR [9.0, 13.0]). Postoperative complications were observed in 218 (49.1%) patients, and 92 (20.7%) patients experienced major complications according to the Clavien-Dindo classification system. Thirty-five (7.9%) patients had postoperative ICU admission (Table 1).

Compared to CLR < 3.06, patients with CLR≥3.06 had comparable operation times (320.0 [270.0-430.0] vs. 340.0 [260.0-420.0], $P=0.971$), blood loss (200.0 [100.0-400.0] vs. 200.0 [150.0-400.0], $P=0.163$), postoperative complication rates (51.6% vs. 47.7%, $P=0.436$) and postoperative ICU rates (8.2% vs. 7.7%, $P=0.864$).

After 1:1 PSM, 137 patients were distributed to the CLR < 3.06 group and CLR≥3.06 group (Fig. 1). No significant difference was noted between the two groups ($P>0.1$). After PSM, compared with CLR < 3.06, patients with CLR≥3.06 had comparable operation times (320.0 [272.5–421.0] vs. 360.0 [292.5-434.5], $P=0.088$), blood loss (200.0 [100.0-400.0] vs. 200.0 [150.0-450.0], $P=0.831$), postoperative complication rates (50.4% vs. 46.7%, $P=0.546$), and comparable postoperative ICU rates (5.8% vs. 11.7%, $P=0.087$) (Table 2).

Association with survival outcomes of CLR before IPTW adjustment

At the time of analysis, three hundred fifteen patients experienced recurrence, and 160 patients had died. The median PFS was 10.1 (IQR 4.1–23.2) months. The 1-year and 3-year PFS rates were 48.6% and 24.5%, respectively. The median OS was 30.9 (IQR 20.0-44.5) months. The 1-year, 3-year, and 5-year OS rates were 95.3%, 64.8% and 47.6%, respectively.

According to the univariable Cox regression analyses, CLR≥3.06 was found to be linked with PFS (Hazard ratio (HR) = 1.380, 95% CI 1.100–1.730; $P=0.006$) and OS (HR = 1.630, 95% CI 1.190–2.230, $P=0.003$). Furthermore, after adjusting for preoperative features in the

Table 2 Clinicopathological characteristics and short-term outcomes in CRLM patients receiving simultaneous resection after PSM

Item	CLR < 3.06 (n = 137)	CLR ≥ 3.06 (n = 137)	*P*	All patients (n = 274)
Age ≥60 years, n (%)	65 (47.4%)	67 (48.9%)	0.809	132(48.2%)
Male, n (%)	81 (59.1%)	86 (62.8%)	0.536	167(60.9%)
BMI ≥ 24 kg/m^2, n (%)	65 (47.4%)	64 (46.7%)	0.904	129(47.1%)
NLR ≥ 1.86, n (%)	82 (59.9%)	85 (62.0%)	0.710	167(60.9%)
Comorbidity, n (%)	58 (42.3%)	54 (39.4%)	0.623	112(40.9%)
ASA score 3–4, n (%)	18 (13.1%)	20 (14.6%)	0.727	38(13.9%)
Preoperative CEA ≥ 200 ng/ml, n (%)	6 (4.4%)	8 (5.8%)	0.583	14(5.1%)
Primary site in colon, n (%)	71 (51.8%)	73 (53.3%)	0.809	144(52.6%)
Right hemicolon, n (%)	26 (19.0%)	29 (21.2%)	0.651	55(20.1%)
Diameter of liver metastases ≥ 5 cm, n (%)	22 (16.1%)	25 (18.2%)	0.631	47(17.2%)
Multiple liver metastases, n (%)	82 (59.9%)	81 (59.1%)	0.902	163(59.5%)
Bilobar liver distribution, n (%)	57 (41.6%)	57 (41.6%)	1	114(41.6%)
Poor differentiation, n (%)	43 (31.4%)	43 (31.4%)	1	86(31.4%)
T3-T4 stage, n (%)	126 (92.0%)	126 (92.0%)	1	252(92.0%)
Positive lymph node metastasis, n (%)	98 (71.5%)	100 (73.0%)	0.787	198(72.3%)
Extrahepatic metastases, n (%)	9 (6.6%)	11 (8.0%)	0.642	20(7.3%)
Concomitant RFA, n (%)	15 (10.9%)	14 (10.2%)	0.844	29(10.6%)
R0 resection, n (%)	103 (75.2%)	102 (74.5%)	0.889	205(74.8%)
Major liver resection, n (%)	63 (46.0%)	67 (48.9%)	0.628	130(47.4%)
Pretreatment chemotherapy, n (%)	84 (61.3%)	78 (56.9%)	0.461	162(59.1%)
Hepatic portal occlusion, n (%)	105 (76.6%)	100 (73.0%)	0.486	205(74.8%)
All laparoscopic operation, n (%)	34 (24.8%)	32 (23.4%)	0.778	66(24.1%)
Operation time, min (median, IQR)	360.0(292.5-434.5)	320.0(272.5–421.0)	0.088	345.0(280.0-431.5)
Blood loss, ml (median, IQR)	200.0(150.0-450.0)	200.0(100.0-400.0)	0.831	200.0(100.0-400.0)
Blood transfusion, n (%%)	35(25.5%)	31(22.6%)	0.572	66(24.1%)
Complications, n (%)				
0, n (%)	73(53.5%)	68(49.6%)	0.814	141(51.5%)
1–2, n (%)	35(25.5%)	39(28.5%)		74(27.0%)
3–5, n (%)	29(21.2%)	30(21.9%)		59(21.5%)
Postoperative minor complications, n (%)	35(25.5%)	39(28.5%)	0.586	74(27.0%)
Postoperative major complications, n (%)	29(21.2%)	30(21.9%)	0.883	59(21.5%)
ICU, n (%)	16(11.7%)	8(5.8%)	0.087	24(8.8%)
Post-operative hospital stay, days (median, IQR)	10.0(9.0–13.0)	10.0(8.0–14.0)	0.913	10.0(9.0–14.0)

multivariable Cox regression models, CLR≥3.06 continued to demonstrate a significant association with both PFS (HR = 1.400, 95% CI 1.110–1.780, *P* = 0.005) and OS (HR = 1.660, 95% CI 1.180–2.320, *P* = 0.003) (Table S2 & S3). Based on the DCA analysis results, CLR has the potential to produce more clinical net-benefit than several common clinical features in predicting both PFS and OS (Figure S2 & S3).

Association with survival outcomes of CLR after IPTW adjustment

IPTW was performed to avoid bias between the CLR < 3.06 group and the CLR≥3.06 group. After IPTW adjustment, the SD for all characteristics was less than 0.1 (Fig. 2), indicating that the weighted population was subsequently comparable.

Kaplan–Meier analysis showed that compared with patients with CLR < 3.06, patients with CLR≥3.06 had a worse PFS (*P* = 0.005, median: 10.2 months vs. 13.0 months) and a worse OS (*P* = 0.002, median: 41.0 months vs. 70.9 months). IPTW-adjusted Kaplan–Meier analysis showed that patients with CLR≥3.06 had an unfavourable PFS (*P* = 0.027, median: 10.4 months vs. 13.1 months) and an unfavourable OS (*P* = 0.010, median: 42.5 months vs. 75.9 months) compared with those with CLR < 3.06 (Figs. 3 and 4).

In the Cox proportional hazards regression analysis, CLR≥3.06 was significantly associated with worse PFS (HR = 1.376, 95% CI 1.097–1.726, *P* = 0.006) and OS (HR = 1.628, 95% CI 1.186–2.234, *P* = 0.003). In the IPTW-adjusted Cox proportional hazards regression analysis, CLR≥3.06 was an unfavourable risk factor for PFS (HR = 1.513, 95% CI 1.177–1.946, *P* = 0.001) and OS (HR = 1.723, 95% CI 1.218–2.439, *P* = 0.002).

When including postoperative complications, operation time, intraoperative blood loss and postoperative

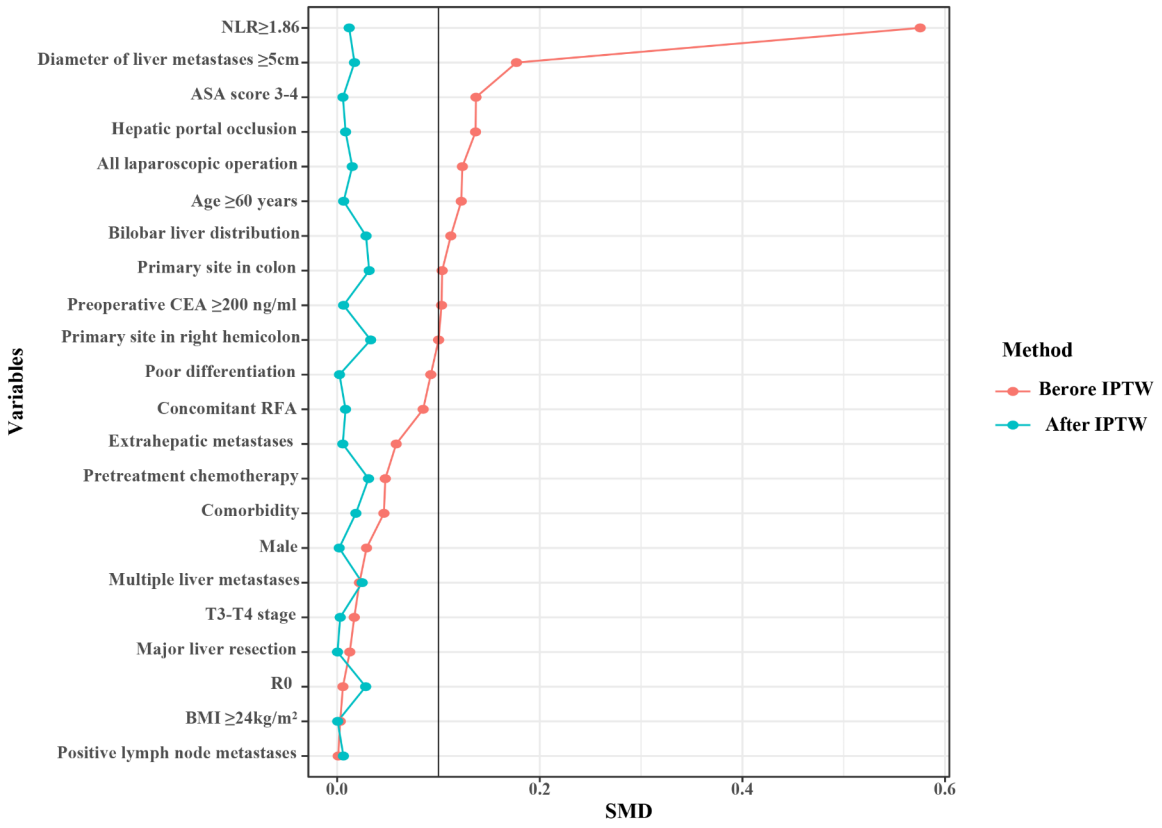

Fig. 2 Standardized mean difference (SMD) of CLR < 3.06 vs. CLR ≥ 3.06 before and after IPTW

chemotherapy in the Cox proportional hazards regression analysis, CLR≥3.06 was still significantly associated with a worse PFS (HR=1.415, 95% CI 1.123–1.782, *P*=0.003) and a poor OS (HR=1.611, 95% CI 1.166–2.226, *P*=0.004). In the IPTW-adjusted Cox proportional hazards regression analysis, CLR≥3.06 was an unfavourable risk factor for PFS (HR=1.617, 95% CI 1.252–2.090, *P*<0.001) and OS (HR=1.823, 95% CI 1.258–2.643, *P*=0.002).

Discussion

In this study, we first verified and rationalized the predictive effect of preoperative CLR on short-term and long-term prognosis in 444 patients with CRLM who received simultaneous resection of the primary lesion and liver metastases. PSM and IPTW were applied to eradicate the interfering bias between patients with CLR<3.06 and patients with CLR≥3.06. The main findings were as follows: (1) The preoperative CLR level could distinguish the long-term prognosis of patients with CRLM undergoing simultaneous resection of the primary lesion and liver metastases. Patients with CLR<3.06 were associated with prolonged PFS and OS. (2) The preoperative CLR level could not distinguish the short-term prognosis of patients with CRLM undergoing simultaneous resection of the primary lesion and liver metastases. No differences in intraoperative operation time, intraoperative blood loss, postoperative hospital stay, incidence of postoperative complications or postoperative ICU rate were noted between the two groups.

Patients would benefit from convenient and reliable markers that could precisely identify their prognosis before receiving surgical resection or other treatment. In addition, this information would allow the surgeons perform more personalized management for patients since the allocation of medical resources would be more appropriate and satisfactory. To date, previous studies have mainly focused on patients with CRLM who receive staged resection, especially hepatic resection [30–32], and the subgroup of CRLM patients who receive simultaneous resection, as well as the specific surgical strategies employed (e.g., laparoscopic or open surgery)

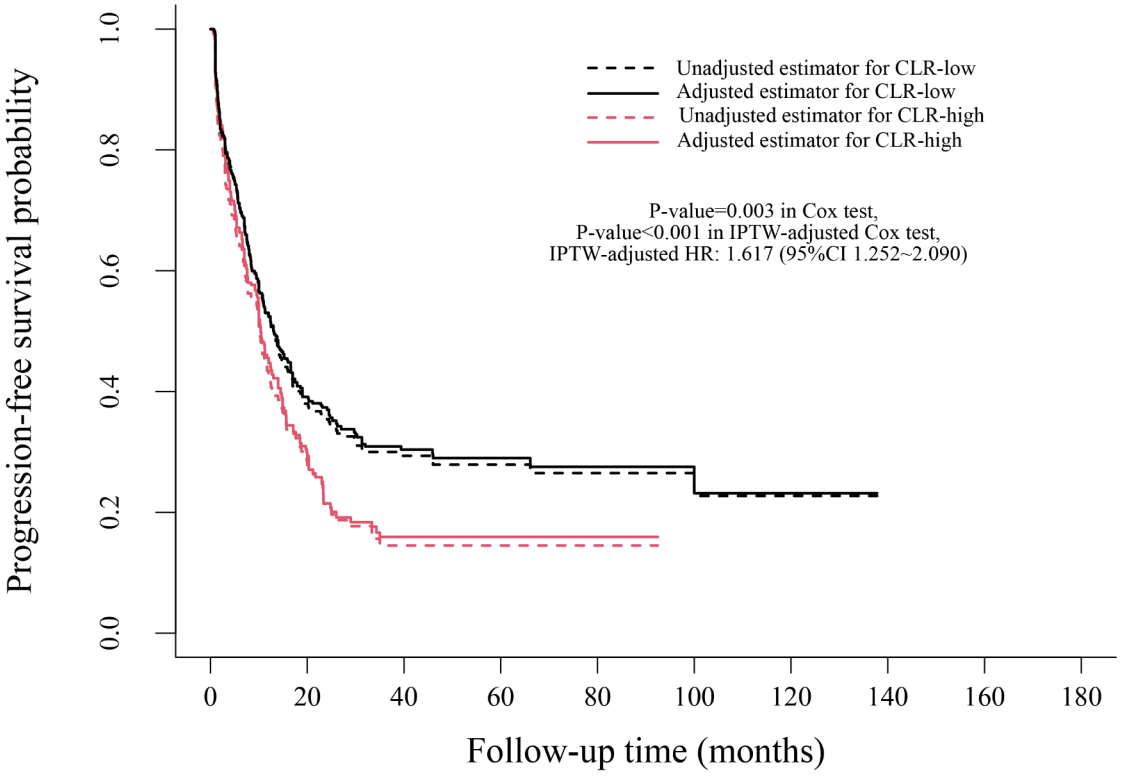

Fig. 3 Progression-free survival analysis of CLR levels before and after IPTW

[33], have been overlooked. Interestingly, the prognostic effect of CLR in CRC was demonstrated in a recent study [29]; however, researchers only investigated the relationship between CLR and survival in these patients but ignored the possible association between CLR and short-term outcomes or recurrence. Nevertheless, the relatively smaller scale and lower disease stage of the 223 CRC patients compared to the 444 CRLM patients in our study also confined their efforts. This study is the first to holistically estimate the prognostic value of CLR on short- and long-term outcomes in CRLM patients who receive simultaneous resection of the primary lesion and liver metastases, contribute to accumulating evidence on the patient's experience and provide new knowledge for the clinical guidance of this simultaneous resection procedure recommended by the NCCN guidelines [34] for surgeons. Given that the CLR level could be identified precisely and conveniently prior to surgery, this index would provide novel insight to optimize the risk stratification of CRLM patients.

In this study, we found that elevated CLR was associated with poor prognostic outcomes. Elevated CLR reflected elevated serum total cholesterol and/or decreased circulating lymphocyte counts. Inflammation plays a vital role in instigating the progression of multiple cancers, and a chronic inflammatory status could create a favourable tumour microenvironment (TME) to enable cancer cells to survive and proliferate, of which lymphocytes usually comprise an indispensable component. In general, lymphocytes include T cells, B cells and NK cells. These cells not only participate in host adaptive immunity but also reinforce innate immunity, thus being crucial to the antiviral and antitumour functions of cancer patients. The possible mechanisms explaining the finding that decreased lymphocyte counts were associated with poor prognosis are as follows. (1) Lymphocytes could regulate the secretion of potent cytotoxins, such as perforin [35], which contributed to both CD8+and CD4+CAR T-cell cytotoxicity and exerted the antitumour effect directly or indirectly. The depletion of lymphocyte count means weakened immune surveillance

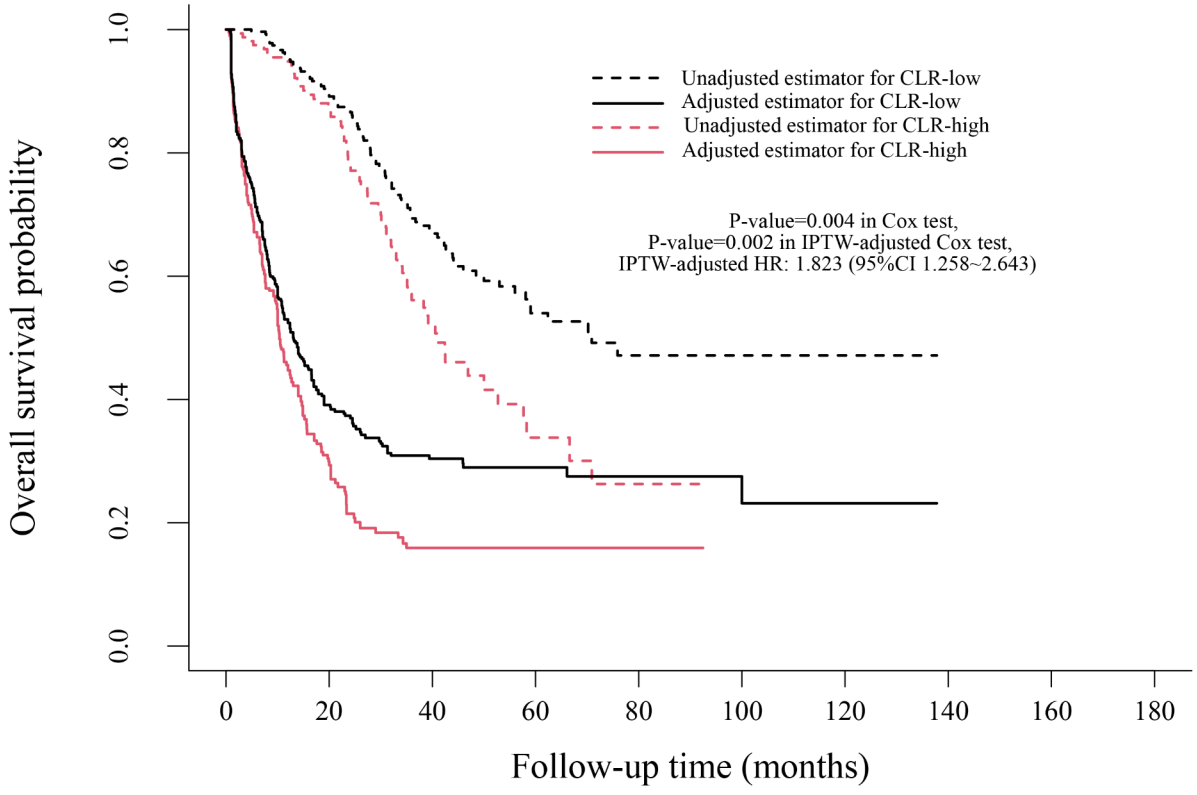

Fig. 4 Overall survival analysis of CLR levels before and after IPTW

and antitumour immunity. (2) Decreased lymphocyte counts could be ascribed to the inflammation generated by tumours, and the inflammatory environment is always accompanied by DNA damage, impaired DNA repair function, degeneration of extracellular matrix, and a disrupted vascular barrier, all of which facilitate tumour progression [11, 36, 37].

Reprogrammed cholesterol metabolism was detected in renal carcinoma, breast cancer and CRC cells [23–25]. In this study, we found that when total cholesterol levels in serum increased, the increased CLR was also related to the poor prognosis of patients. It was reasonable to postulate the following possible mechanisms: (1) Elevated serum total cholesterol may reflect the overexpression of its rate-limiting enzyme squalene epoxidase (SQLE), which was demonstrated to be associated with the progression of CRC by activating CYP24A1-mediated MAPK signalling pathway [38]. In addition, it has also been reported that SQLE could promote CRC cells to resist apoptosis and proliferate by triggering gut microbiota dysbiosis and impairing gut barrier function [39]. It is worth mentioning that the accumulation of cholesterol was found to be able to conversely reduce SQLE, which triggered the chain reaction, including activation of β-catenin and inactivation of the p53 tumour-suppressive pathway, thereby aggravating CRC progression [40]. (2) In addition, previous research also reported that the SREBP2-dependent cholesterol biosynthesis pathway was exclusively activated in the liver metastases of CRC [41] but not metastases to the brain or lung. SREBP2 could help circulating tumour cells to resist ferroptosis and acquire drug resistance by upregulating transcription of the iron carrier Transferrin (TF) [42]. The interaction between cholesterol and lymphocytes may also have an important impact on cancer progression. Cholesterol could cause alterations in intestinal immunity and impair intestinal innate immunity by restraining the differentiation of IgA plasma cells [43]. In addition, it has been suggested that cholesterol might disturb the normal function of activated T cells, such as $CD8^+$ T cells, which play an important role in antitumor immunity by regulating immune checkpoint expression levels [44] or specifically

combining with the TCR-CD3 complex and directly stopping TCR signalling in T cells [45]. It was also important to emphasize the fact that long-term dietary and behavioural habits are the main reasons explaining changes in the serum cholesterol level [46]. Acute aberrations in serum cholesterol levels before surgery were rarely observed based on our clinical experience. Therefore, the stability and reliability of the index were assured.

Although statistical methods, such as PSM and IPTW, were both applied to eliminate confounding interference between patients in the CLR < 3.06 group and patients in the CLR ≥ 3.06 group, inevitable innate bias could not be completely avoided due to the retrospective nature of the study. In addition, although up to 444 CRLM patients were enrolled in this study, the study size was still relatively small. The single-centre design also constrained our efforts and potentially affected the representativeness of our research. And lack of gene mutation data is also a constraint of our study, we will perform large-scale, multicentre and prospective studies to further verify our findings in the future.

Conclusions

In conclusion, we combined the influence of inflammation and lipid metabolism to validate the predictive value of preoperative CLR on the short- and long-term prognosis of 444 CRLM patients who received simultaneous resection. These findings provide novel insights into the characteristics of CRLM patients and conferred new knowledge to surgeons to guide the management of CRLM patients.

Abbreviations

CLR	Cholesterol-to-lymphocyte ratio
CRLM	Colorectal cancer liver metastasis
IPTW	Inverse probability of treatment weighting
PFS	Progression-free survival
OS	Overall survival
CRC	Colorectal cancer
TILs	Tumour-infiltrating lymphocytes
HDL-C	High-density lipoprotein cholesterol
BMI	Body mass index
ASA	American Society of Anaesthesiology
CEA	Carcinoembryonic antigen
MDT	Multidisciplinary team
RFA	Radiofrequency ablation
DCA	Decision curve analysis
NLR	Neutrophil-to-lymphocyte ratio
SD	Standardized difference
HR	Hazard ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12893-023-01988-7.

Additional File 1: STARD-Checklist

Additional File 2: Supplementary Tables

Additional File 3: Supplementary Figures

Acknowledgements

None.

Author contributions

Study conception and design: Z.H., J.C., H.Z. Drafting and revising the article: Y.D., Q.C., J.C., Z.H., J.C., H.Z. Analysis and interpretation of data: Y.D., Q.C., J.C. Final approval: All authors. All authors read and approved the final manuscript.

Funding

This study was supported by the National Natural Science Foundation of China (No. 81972311, 82141127), the CAMS Innovation Fund for Medical Sciences (CIFMS) (No. 2021-I2M-1-066), the Non-profit Central Research Institution Fund of Chinese Academy of Medical Sciences (No. 2019PT310026) and Sanming Project of Medicine in Shenzhen (No. SZSM202011010).

Data Availability

The datasets analysed during the current study are available from the corresponding author (H. Z., Email: pumc95zhao@126.com) on reasonable request.

Declarations

Ethics approval and consent to participate

This research was performed in accordance with Declaration of Helsinki and was approved by the Ethics Committee of the Cancer Hospital, Chinese Academy of Medical Sciences and Sun Yat-sen University Cancer Center (No. 81972311). Written informed consent for participation was obtained from the patients and/or their legal guardians. The patients' clinical and imaging information are the patient's private data, which are protected by Chinese laws. Therefore, the data and materials cannot be uploaded and shared with the public.

Consent for publication

Not applicable.

Ethical Guidelines

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 28 November 2022 / Accepted: 4 April 2023
Published online: 16 May 2023

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