Journal of Clinical Ultrasound

WILEY

RESEARCH ARTICLE OPEN ACCESS

Use of Dynamic Contrast-Enhanced Magnetic Resonance Imaging Combined With Serum Carcinoembryonic Antigen and Carbohydrate Antigen 19-9 in Predicting Colorectal Cancer Liver Metastasis

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Received: 24 July 2024 | **Revised:** 23 September 2024 | **Accepted:** 9 December 2024

Funding: This work was supported by the Nanjing Medical Science and Technology Development Project (YKK16262) and the 13th Five-Year Nanjing Health Youth Talent Training Project (QRX17207).

Keywords: carbohydrate antigen 19-9 | carcinoembryonic antigen | colorectal cancer liver metastases | dynamic contrast-enhanced magnetic resonance imaging

ABSTRACT

Background: Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) combined with serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels to evaluate the efficacy of colorectal cancer liver metastasis (CRCLM) treatment is still rare.

Purpose: To investigate the predictive value of DCE-MRI combined with serum CEA and CA 19-9 concerning the efficacy of comprehensive treatment for CRCLM.

Materials and Methods: A total of 120 patients with CRC were retrospectively recruited using convenience sampling between May 2019 and March 2024. After treatment, they were divided into two groups according to the treatment efficacy: responders (86 cases) and non-responders (34 cases), and their clinical data were collected for comparison.

Results: Before treatment, there were statistically significant differences between the groups in terms of the proportion of positive CEA ($\chi^2 = 17.364$, $p < 0.001$), the proportion of positive CA 19-9 ($\chi^2 = 23.639$, $p < 0.001$), the rate constant of a contrast agent from the vascular to the interstitial compartment (K_{trans}) ($\chi^2 = 2.341$, $p = 0.023$), and the rate constant between the extravascular extracellular space (EES) (K_{ep}) ($\chi^2 = 2.556$, $p = 0.011$). The values of K_{trans}, K_{ep}, CEA, and CA 19-9 reflected a certain degree of predictive value for the efficacy of comprehensive treatment in patients with CRCLM ($p < 0.05$). The combination of the four measurements is better than any single value, with an area under the curve of 0.898 (95% CI: 0.833, 0.922).

Conclusion: Dynamic contrast-enhanced magnetic resonance imaging, CEA, and CA 19-9 have predictive value for the early efficacy of comprehensive treatment for CRCLM.

1 | Introduction

Colorectal cancer (CRC) is among the most common malignant tumors of the digestive tract, leading to approximately 500000 deaths worldwide each year, with the majority occurring in developing countries [1]. It is the foremost cause of cancer-related morbidity and mortality. Despite improvements in overall survival rates, distant metastasis, particularly hematogenous liver metastasis, remains the primary cause of death [2]. Hematogenous metastasis of CRC occurs mainly through the liver as a target organ [3, 4]. Approximately 15%–25% of patients with CRC have liver metastasis at the initial diagnosis. Without timely diagnosis and treatment, survival time is usually <7 months [5].

In recent years, advances in surgical and chemotherapy techniques have significantly improved the therapeutic outcomes for CRC liver metastases (CRCLM), rendering some previously unresectable cases resectable and significantly prolonging survival [6]. Therefore, studying new biological targets and imaging indicators to evaluate treatment efficacy and devise individualized treatment plans is crucial.

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) provides vital information on tumor vascularization by tracking the process of intravenous injection of contrast agents, making it an important tool for evaluating tumor microcirculation perfusion [7]. Quantitative parameters such as K_{trans} and K_{ep} have been shown to have predictive value for CRC treatment response [8, 9]. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) are commonly used serum tumor markers that play an important role in monitoring CRC recurrence and metastasis [10]. Patients with CRC and elevated CEA levels are often associated with a higher incidence of liver recurrence and metastasis [11]. Therefore, it is necessary to detect K_{trans}, K_{ep}, CEA, and CA 19-9 before admission and in the follow-up of patients after discharge every 2–3 months. The index should be detected in real-time to evaluate patients' treatment effects and recovery.

There are few studies evaluating the efficacy of DCE-MRI combined with serum CEA and CA 19-9 levels in treating CRCLM. Consequently, no relevant references have been found, indicating a need for further exploration. This study aims to investigate the predictive value of DCE-MRI combined with serum CEA and CA 19-9 levels for the early efficacy of comprehensive treatment of CRCLM, providing a new reference for individualized treatment.

2 | Materials and Methods

2.1 | Study Participants

A total of 120 patients with CRC admitted to the oncology department of our hospital between May 2019 and March 2024 were retrospectively recruited using convenience sampling. The patients comprised 55 men and 65 women, with an average age of 57.22 ± 9.57 years old. There were 66 patients with Child-Pugh A and 54 patients with Child-Pugh B. All patients received the same comprehensive treatment regimen, which included preoperative neoadjuvant chemotherapy, surgery, and radiotherapy. They are all using the same system. After treatment, the therapeutic efficacy of the two groups was evaluated according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [12]. The patients were divided into responders, a total of 86 cases (26 cases of CR and 60 cases of PR), and non-responders, a total of 34 cases (24 cases of SD and 10 cases of PD).

The inclusion criteria were as follows: (1) patients with histologically confirmed CRC; (2) patients with liver metastases confirmed by imaging or pathological examination before the end of follow-up; (3) patients with liver metastases within 6 months of a CRC diagnosis; (4) patients aged 18–80 years; (5) patients with Child-Pugh A or B liver function; (6) patients with normal blood coagulation function; (7) single tumor metastasis diameter ≤ 5.0 cm (or multiple metastatic tumors ≤ 3, each ≤ 5 cm); and (8) patients who received comprehensive treatment, including neoadjuvant radiotherapy before primary cancer resection, primary cancer resection, postoperative radiotherapy or chemotherapy, chemotherapy after liver metastasis, immunotherapy and targeted drug therapy.

The exclusion criteria were as follows: (1) patients with non-primary CRC; (2) patients with other malignant tumors metastasising to the liver; (3) patients with severe liver disease; (4) patients with rheumatic and immune-related diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, systemic sclerosis, dermatomyositis, T cell immunodeficiency disease, X-linked agammaglobulinemia, chronic granulomatous disease, AIDS); (5) patients whose liver lesions considered to be in situ carcinoma by imaging or pathology; (6) patients with Child-Pugh C liver function; (7) patients with more than three metastases; (8) pregnant or lactating women; and (9) patients with incomplete and irreparable data. This study was approved by the ethics committee of our hospital. All of the study participants provided informed written consent.

2.2 | Study Methods

2.2.1 | Dynamic Contrast-Enhanced Magnetic Resonance Imaging and Data Processing

Scan: All patients underwent MRI examination using the Siemens flux onTrio, Tim system 3T (Skyra) superconducting MRI scanner. The body-wrapped coil received more signals and improved image quality. The patient was in a supine position, with the head moving forward, and the median sagittal plane aligned with the XO plane. The respiratory compensation sensor was installed in the middle of the upper abdomen, with the midline aligned with the midpoint of the rib arch. First, the intravenous puncture needle was connected to the Solaris EP MR injection system for automatic injection. After positioning, conventional sequence scanning was performed. Enhanced scanning was carried out using the T1 WI 3D-VIBE sequence, and coronal dynamic enhanced scan data were collected. Upon completion of the third phase of the scan, the contrast agent gadolinium-diethylenetriaminepentaacetic acid (Consun Pharmaceutical, Guangzhou, China) was injected using a

high-pressure syringe (Medrad, United States). The dose was 0.2 mmol/kg, and the injection rate was 3–4 mL/s. Subsequently, 20 mL of normal saline was immediately injected at the same rate to rinse the residual contrast agent in the tube. Finally, a dynamic enhanced image was obtained.

The processing method of DCE-MRI data was as follows. First, the temporal image was transferred to the image post-processing workstation. After eliminating the influence of minor breathing motion with 3D correction, the region of interest (ROI) was manually stratified, and its signal intensity was measured. Subsequently, quantitative dynamic pseudo-color functional imaging was performed, adjusting the display threshold and pseudo-color coding range. The phase image showing the most obvious enhancement of the tumor parenchyma was selected, and the ROI was manually layered to avoid cystic degeneration, necrosis, and blood vessels. The ROI included the entire tumor area. Finally, the rate constant (K_{trans}) of the contrast agent from the blood vessel to the interstitial chamber, the rate constant between the EES (K_{ep}) and the unit volume EES volume tumor (V_e) were automatically generated. All data were measured 4 times and averaged.

2.2.2 | Detection of Tumor Markers Carcinoembryonic Antigen and Carbohydrate Antigen 19-9

In the early morning, 5 mL of peripheral venous blood was extracted from the patient after 12 h of fasting and centrifuged for 5 min at 4000 r/min. After centrifugation, the upper layer of serum was taken and placed on the sample rack of the Cobas E immunoassay analyzer (Roche, Germany, 8000e801). The samples were tested in strict accordance with the reagent instructions and instrument requirements. Finally, the test results of CEA and CA 19-9 were obtained directly from the instrument. The reference intervals for CEA and CA 19-9 were 0–4.7 ng/mL and 0–27 U/mL, respectively.

2.3 | Data Collection

The general clinical data of the patients were collected, including gender, age, primary tumor location, maximum diameter of metastatic lesions, tumor markers (CEA, CA 19-9), and the number of metastatic lesions. (We selected the region of interest at the maximum level of the lesion (to avoid liquefaction, necrosis, and bleeding). If the case is multiple lesions, the corresponding lesions are selected according to the pathological results, and the average value of multiple regions of interest is taken.)

All 120 patients were followed up through outpatient examinations or telephone interviews starting from the day of blood collection. Medical history was monitored post-operation, with physical and laboratory examinations conducted every 2–3 months. Abdominal ultrasound or computed tomography was performed every 6 months, chest X-ray and colonoscopy annually, and telephone interviews monthly. The follow-up endpoint was progression-free survival (PFS), defined as the time from the start of treatment to disease progression or death from any cause. The entire follow-up period concluded in March 2024.

All the patients were evaluated for short-term efficacy using mRECIST after treatment, categorized as follows: CR, complete disappearance of the tumor with no recurrence for > 1 month; PR, tumor shrinkage > 50% with no enlargement for > 1 month; SD, tumor shrinkage < 50% with < 25% enlargement within 1 month; PD, tumor enlargement > 25% or new lesions appeared.

2.4 | Statistical Processing

All data in this study were statistically analyzed using SPSS 26.0 software. Normality was assessed using the K–S test. Normally distributed measurement data were expressed as ($x \pm s$), and inter-group comparisons were conducted using independent samples *t*-test. Non-normally distributed measurement data were expressed as M [Q1, Q3], and inter-group comparisons were performed using the rank sum test. Count data were expressed as frequency (*n*) or percentage (%), and the χ^2 test was used for inter-group comparisons. Additionally, receiver operating characteristic (ROC) curves were constructed to evaluate the predictive value of DCE-MRI, CEA, and CA 19-9 for treatment efficacy in patients with liver cancer metastasis. Survival curves were generated using the Kaplan–Meier method. When $p < 0.05$, the difference was statistically significant.

3 | Results

The predictors we are studying are all detected before treatment. The efficacy was evaluated by indicators during and after treatment.

3.1 | Comparison of Clinical Characteristics Before Treatment Between the Responders and Non-Responders

The DCE-MRI imaging of CRCLM before and after comprehensive treatment was shown in Figure 1. After comprehensive treatment, the efficacy of the two groups was evaluated according to mRECIST criteria, including 26 cases of CR, 60 cases of PR, 24 cases of SD, and 10 cases of PD. A total of 86 patients were included in the responders group (CR + PR), whereas a total of 34 patients were included in the non-responders group (SD + PD). Before treatment, there were statistically significant differences between the two groups in terms of the proportion of positive CEA ($\chi^2 = 17.364$, $p < 0.001$), the proportion of positive CA 19-9 ($\chi^2 = 23.639$, $p < 0.001$), K_{trans} ($\chi^2 = 2.341$, $p = 0.023$), and K_{ep} ($\chi^2 = 2.556$, $p = 0.011$) (all $p < 0.05$). No statistically significant differences were observed between the two groups concerning gender, age, primary lesion site, and maximum diameter of metastases ($p > 0.05$), as shown in Table 1.

3.2 | Predictive Value of K_{trans}, K_{ep}, Carcinoembryonic Antigen, and Carbohydrate Antigen 19-9 on the Efficacy of Comprehensive Treatment

The area under the curve (AUC) of K_{trans} in predicting the efficacy of comprehensive treatment for CRCLM was 0.612 (95%

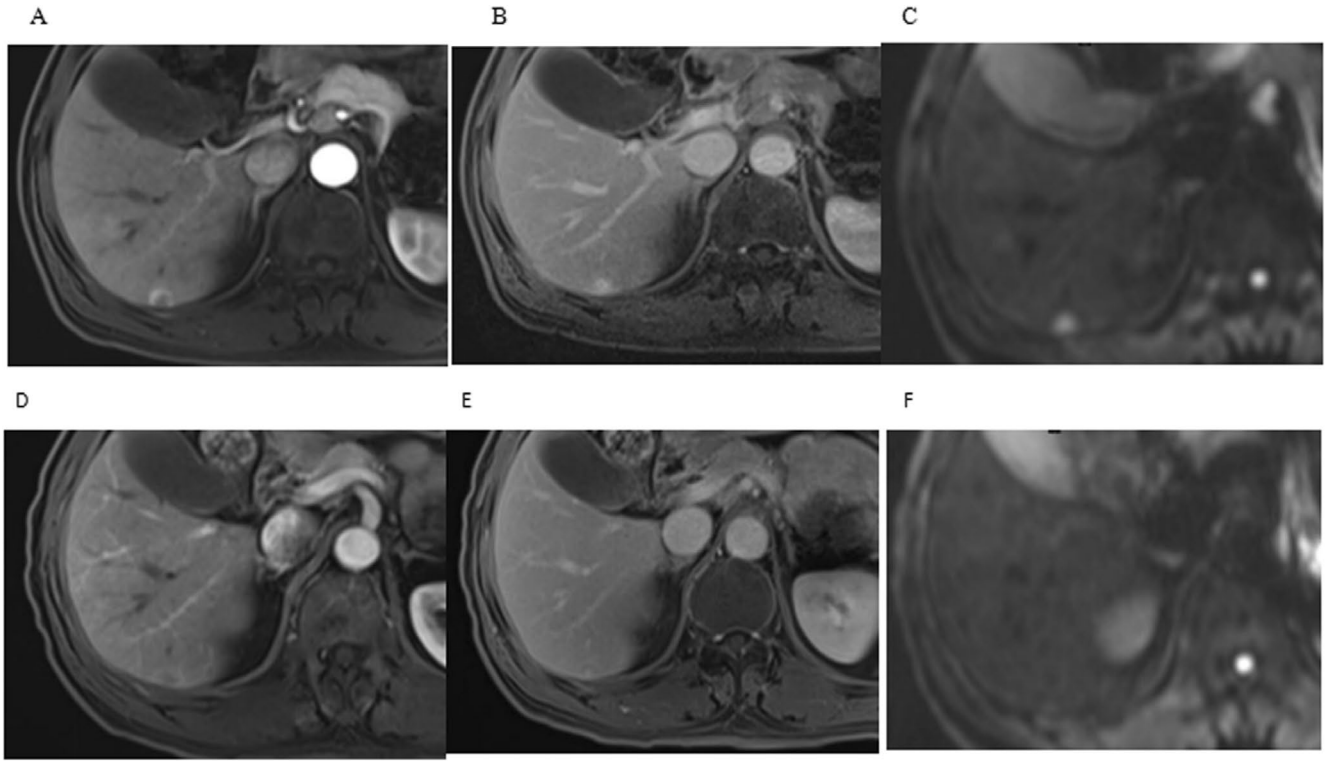

FIGURE 1 | DCE-MRI manifestations of colorectal cancer liver metastasis before and after comprehensive treatment. A–C shows early dynamic contrast enhancement, late contrast enhancement, and DWI images before treatment, from which it can be seen that the early arterial lesions are ring-enhanced, the late arterial lesions are nodularly enhanced, and DWI shows a significant signal. D–F shows early dynamic contrast enhancement, late contrast enhancement, and DWI images after treatment, from which it can be seen that the annular enhancement of the early arterial lesions is significantly reduced, the nodule enhancement of the late arterial lesions is significantly reduced, and the DWI signal remains unchanged.

CI: 0.580, 0.741); for K_{ep}, the same measurement was 0.718 (95% CI: 0.691, 0.754); for CEA, the measurement was 0.716 (95% CI: 0.689, 0.765); and for CA 19-9, it was 0.723 (95% CI: 0.682, 0.753), as shown in Table 2.

The combination of all measured values had a better predictive value than any single value on its own, with an AUC of 0.898 (95% CI: 0.833, 0.922), as shown in Table 2.

3.3 | Correlation Between K_{trans}, K_{ep}, Carcinoembryonic Antigen, and Carbohydrate Antigen 19-9, and Progression-Free Survival Rate of Patients

A total of 120 patients were followed up in this study, and no cases were lost to this process. The follow-up time lasted from 5 to 27 months, with a median follow-up time of 16.0 ± 5.3 months. Taking recurrence as the outcome index, the Kaplan–Meier method was used to draw the survival curve, and a log-rank test was used to analyze differences in the recurrence rates of different index categories. In terms of K_{trans}, 56 cases relapsed in the $K_{trans} < 0.430$ group and 16 in the $K_{trans} > 0.430$ group, with a statistically significant difference in the PFS rate between the groups ($\chi^2 = 10.204$, $p < 0.001$) (Figure 2A). In terms of K_{ep}, 56 cases relapsed in the $K_{trans} < 0.430$ group and 16 in the $K_{trans} > 0.430$ group, with a statistically significant difference in the PFS rate between the groups ($\chi^2 = 10.892$, $p = 0.001$) (Figure 2B). In terms of CEA, 56 cases relapsed in the positive group and 16 in the negative group, with a statistically significant difference in the PFS rate between the groups ($\chi^2 = 28.000$, $p < 0.001$) (Figure 2C). In terms of CA 19-9, 50 cases relapsed in the positive group and 13 in the negative group, with a statistically significant difference in the PFS rate between the groups ($\chi^2 = 11.819$, $p < 0.001$) (Figure 2D).

4 | Discussion

Tumor blood vessels have high permeability, which can support the high metabolic demand for oxygen and nutrients; they are the key markers of tumor development and metastasis [13]. In the study of 36 non-small cell lung cancer patients, Tao et al. [14] found that the K_{trans} and K_{ep} values of responders before treatment were higher than those of non-responders, whereas the V_e value of responders before treatment was lower than that of non-responders. The differences were statistically significant;this is consistent with the results of this study. The study of Ota et al. [15] also showed that K_{trans} and K_{ep} values were significantly lower post-treatment than before treatment. The correlation coefficients between tumor volume ratio and pre-treatment K_{trans}, as well as between tumor volume ratio and post-treatment K_{trans} and K_{ep}, were statistically significant. These results demonstrate the correlation between high K_{trans} and K_{ep} values before tumor treatment and better response to

TABLE 1 | Comparison of clinical characteristics before treatment between the responders group and the not-responders group.

Clinical data	Respondersgroup (CR + PR, $n = 86$)	Not responders group (SD + PD, $n = 34$)	$\chi^2/t/Z$ value	p
Age (years old)	57.92 ± 10.33	56.52 ± 8.81	0.356	0.721
Gender (male/female)	40/46	15/19	0.056	0.813
Child-Pugh classification (A/B)	47/39	19/15	0.015	0.903
CEA positive (cases)	32	27	17.364	< 0.001
CA19-9 positive (cases)	31	29	23.639	< 0.001
Primary tumor location (cases)			0.295	0.587
Rectum	33	11		
Colon	53	23		
Maximum diameter of metastatic lesions (cm)			0.185	0.667
≤ 3	34	12		
3–5	52	22		
Lymphatic metastasis			0.010	0.919
Yes	69	27		
No	17	7		
TNM			1.829	0.401
I	19	7		
II	35	10		
III ~ IV	32	17		
K-ras mutation			0.021	0.886
Positive	29	11		
Negative	57	23		
Number of metastatic lesions			0.001	0.976
1	63	25		
Above 1	23	9		
Degree of differentiation			1.502	0.472
Highly differentiated	10	6		
Mosderately differentiated	58	19		
Poorly differentiated	18	9		
Time of appearance of liver metastases			1.937	0.164
Simultaneous	45	13		
Non-simultaneous	41	21		
K_{trans} (min)	0.42 ± 0.25	0.31 ± 0.11	2.341	0.023
K_{ep} (min)	0.86 ± 0.62	0.44 ± 0.35	2.556	0.011
V_e	0.41 (0.27–0.48)	0.42 (0.20–0.50)	−0.139	0.883*

Abbreviations: CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; K_{trans}, rate constant of a contrast agent from vascular to the interstitial compartment; K_{ep}, rate constant between extravascular-extracellular space (EES); TNM, Tumor-Node-Metastasis; V_e, EES fractional volume per unit volume tumor.
*Rank sum test.

TABLE 2 | Predictive value of K_{trans}, K_{ep}, CEA, and CA19-9 on the efficacy of comprehensive treatment.

Variable	AUC	95%CI	Cutoff value	Sensitivity (%)	Specificity (%)
K_{trans}	0.612	(0.580, 0.741)	0.430	63.41	64.21
K_{ep}	0.718	(0.691, 0.754)	0.672	82.44	69.43
CEA	0.716	(0.689, 0.765)	0.5	74.67	73.62
CA19-9	0.723	(0.682, 0.753)	0.5	71.55	82.48
Combination of the four	0.898	(0.833, 0.922)	—	86.48	89.75

Abbreviations: CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; K_{trans}, rate constant of a contrast agent from vascular to the interstitial compartment; K_{ep}, rate constant between extravascular-extracellular space (EES).

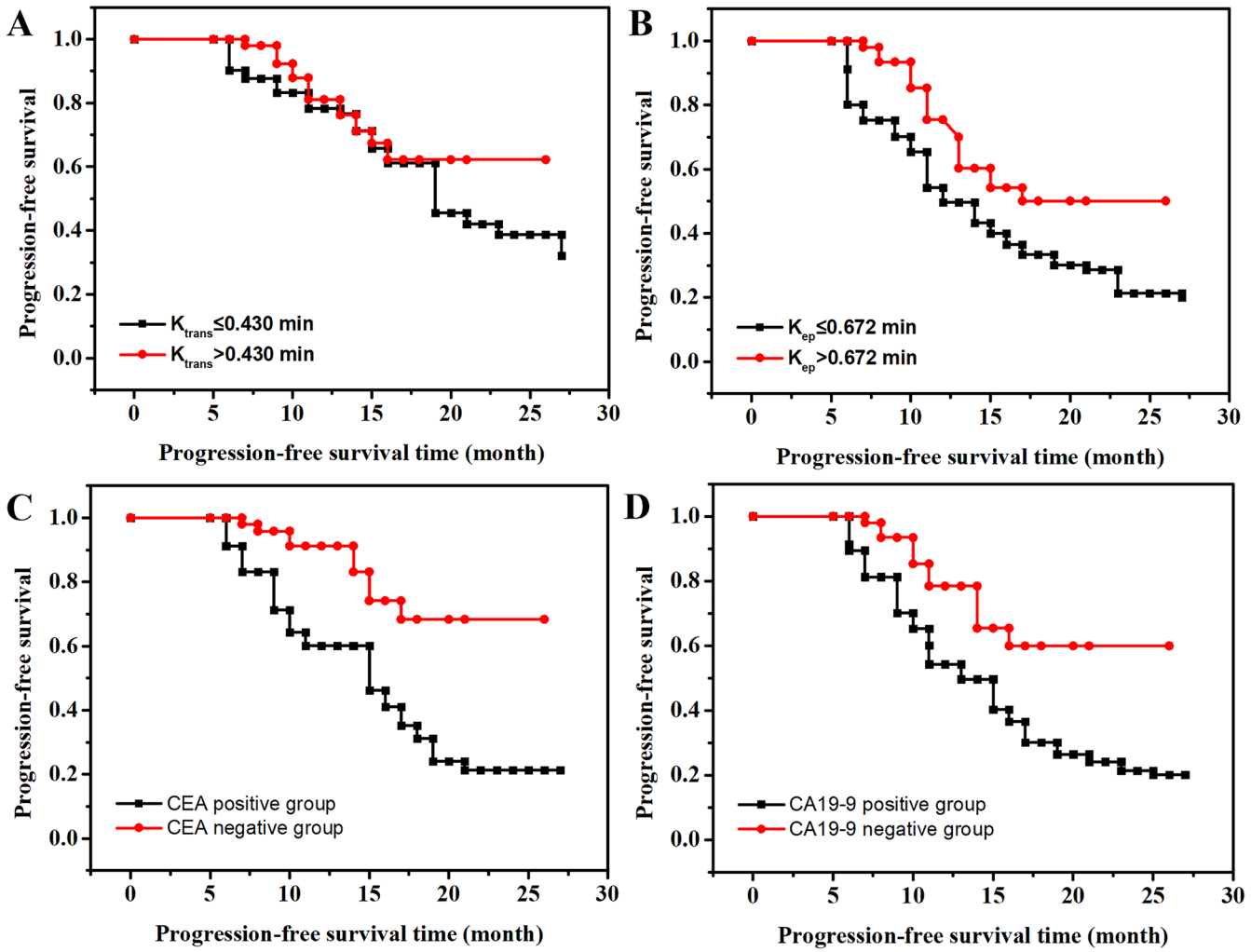

FIGURE 2 | (A) Progression-free survival curve of patients grouped by K_{trans}; (B) Progression-free survival curve of patients grouped by K_{ep}; (C) Progression-free survival curve of patients grouped by CEA; (D) Progression-free survival curve of patients grouped by CA19-9.

chemoradiotherapy. In our study, ROC analysis showed that the change rate of K_{trans} was the best parameter to evaluate efficacy. Although the V_e value increased after treatment, the difference was not statistically significant. This may be because patients who respond well to treatment develop a larger area of tissue fibrosis, resulting in tumor capillary compression after treatment, increased blood flow resistance, and reduced blood perfusion. Therefore, the Ve value increases as K_{trans} and K_{ep} values decrease. This study showed that the K_{trans} and K_{ep} values of responders were significantly higher than those of non-responders, which was consistent with previous studies [15]. These results indicate that higher K_{trans} and K_{ep} values reflect a more abundant blood circulation supply. Consequently, higher oxygenation levels lead to increased sensitivity to comprehensive treatment. Lei et al. [16] suggested that the K_{trans} value before treatment could distinguish the treatment response of radiotherapy and chemotherapy. The higher the K_{trans} value is, the better the response to radiotherapy and

chemotherapy, whereas the K_{ep} value does not correlate with the response to treatment. This may be due to a variety of confounding factors, such as small sample size, different clinical treatment options, and different clinical stages. These results demonstrate the correlation between high K_{trans} and K_{ep} values before tumor treatment and better treatment response to chemoradiotherapy.

Carcinoembryonic antigen and CA 19-9 are currently widely recognized as tumor markers in the diagnosis of CRC worldwide [17]. Studies have shown that serum CEA and CA 19-9 can be used as follow-up indicators of CRC, playing a role in predicting the recurrence or metastasis of CRC [18]. However, the mechanism of elevated serum CEA and CA 19-9 levels in patients with CRCLM is unclear. It may be related to the binding of CEA and CA 19-9 to tumor metastatic cells during liver circulation [19]. This study showed that the PFS time of patients with positive CEA and CA 19-9 results was shorter and that the sensitivity of serum CEA in predicting CRCLM was lower than that of K_{ep}, lacking specificity. However, the specificity of CA 19-9 was better than that of CEA, but the sensitivity was poor. Therefore, both of them are not completely reliable. Therefore, CEA, K_{trans}, K_{ep} and CA 19-9 can be used in combination to obtain a higher detection rate, which has a certain value for screening and auxiliary diagnosis of CRCLM.

This study has limitations:

1. Small sample size: This study only retrospectively recruited 120 patients with CRC, and the sample size was relatively small, which may affect the universality and statistical significance of the results.
2. Single-center study: This study was conducted in a single medical center and lacked multicenter data support, which may influence the external validity of the results due to a central effect.
3. The influence of confounding factors: The treatment plan, tumor stage, and patient status may have confounding effects on the results of this study, and these confounding factors cannot be completely controlled.
4. Differences in patient treatment options: Although all patients received comprehensive treatment, there may be differences in specific treatment options, which could impact efficacy evaluation.
5. Single evaluation criteria: This study mainly relies on the mRECIST for efficacy evaluation. However, it is designed for HCC and is based on the loss of hyperenhancement in the arterial phase after treatment. Therefore, other potential evaluation indicators and methods may be overlooked.
6. Short-term follow-up: This study only conducted a short-term follow-up examination, and did not carry out long-term monitoring; there may be some bias.

These limitations suggest the need for further research to verify and expand the results by increasing the sample size, adopting a multicenter design, conducting long-term follow-up, and controlling for confounding factors.

In conclusion, DCE-MRI, CEA, and CA 19-9 present a degree of value in predicting the early efficacy of comprehensive treatment for CRCLM. The values of K_{ep}, CEA, and CA 19-9 can be used as major predictive parameters to assist in the screening of patients who may benefit from comprehensive treatment. This will facilitate early prediction of clinical efficacy and precise individualized treatment. Combining these indicators can enhance efficacy prediction accuracy, aid in identifying patients likely to benefit from comprehensive treatment, and guide the formulation of individualized treatment plans. Therefore, the findings of this study can assist doctors in evaluating treatment efficacy in patients with colorectal liver metastases, guiding treatment decisions to improve outcomes and patient survival in clinical practice.

Author Contributions

H.-B.J.: conception and design. B.Q., J.-J.H.: administrative support. W.Q., Z.-G.C.: provision of study materials or patients. H.-B.J., Z.-G.C.: collection and assembly of data. B.Q., J.-J.H., W.Q.: data analysis and interpretation. All authors: manuscript writing. All authors: final approval of manuscript.

Acknowledgments

No funding or sponsorship was received for this study or publication of this article.

Ethics Statement

This study was conducted in accordance with the Declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Nanjing Tongren Hospital, School of Medicine, Southeast University.

Consent

Written informed consent was obtained from all participants. The manuscript is not submitted for publication or consideration elsewhere.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data generated or analyzed during this study are included in this published article.

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