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*Retrospective Study*

**Prognostic** value of a nomogram model for postoperative liver metastasis of colon cancer

## INTRODUCTION

Colon cancer is a highly aggressive and migratory malignant tumor, which is most commonly characterized by intestinal obstruction, loss of body mass, abdominal pain, and blood in the stool[1]. The liver is the most common metastatic site in patients with colon cancer[2], with liver metastasis occurring in 25% of patients after surgery[3]. Therefore, designing a convenient and efficient predictive index for liver metastasis after colon cancer surgery would not only be beneficial for the early screening of colon cancer but also play an important role in knowing whether liver metastasis occurs after colon cancer surgery.

Several studies have shown that tumor-associated inflammatory cells can directly or indirectly act on tumors and are closely related to tumorigenesis and migration[4]. Systemic inflammation can occur within the tumor immune microenvironment and is closely related to tumor development[5,6]. The systemic inflammatory index (SII) is a test that assesses the impact of peripheral blood neutrophil, lymphocyte, and platelet counts on the biological behavior of cells. By detecting these relative values from these cell types, the SII measures whether their function is normal and subsequently assesses the patient's status[7]. Studies have demonstrated that SII is independently associated with postoperative liver metastasis in colon cancer, and its predictive ability is superior to that of other inflammatory factors[8]. Therefore, the SII may be a marker for the prediction of liver metastasis after colon cancer surgery.

C-reactive protein (CRP) levels are influenced by tumor necrosis factor-α, interleukin (IL)-1β, and IL-6, indicating a strong association with acute inflammation[9]. Conversely, albumin levels have been associated with chronic inflammation and can indicate nutritional status[10,11]. The CRP/albumin ratio (CAR) reflects the inflammatory status and nutritional level of the patient, is less susceptible to the influence of other factors, and has better stability. Therefore, studies have confirmed that CAR can be used as a prognostic marker for colon cancer in clinical practice[12]. CAR has also been shown to be a reliable marker for predicting survival in patients with metastatic colon cancer[13]. Therefore, we hypothesized that CAR could be used as a new parameter for predicting liver metastasis after colon cancer surgery.

Owing to the many advantages of blood sample analysis, including easy accessibility and low invasiveness, as well as its ability to allow long-term monitoring and assessment of systemic status, clinical blood tests are commonplace. Among these, red cell distribution width (RDW) is a standard blood test measurement item that reflects the homogeneity of red blood cells[14]. RDW has been used as a prognostic marker for various cancers, including lung, liver, esophagogastric, and breast cancers[15,16], and has also been used as a potential prognostic marker for colon cancer. However, the predictive value of RDW for the occurrence of postoperative liver metastasis in colon cancer remains unclear. Therefore, a more accurate and comprehensive assessment of the predictive value of postoperative liver metastasis in colon cancer through the continuous exploration of new blood indices would be crucial in guiding clinical work.

In recent years, relevant studies have reported the factors influencing the occurrence of liver metastasis following colon cancer surgery; however, a more accurate prediction model is still lacking. Columnar graphs can visualize the probability of patients presenting with corresponding diseases, meaning that they are commonly used for the rapid clinical screening of high-risk groups and the development of effective interventions. Therefore, this retrospective study aimed to investigate the predictive value of the column chart model based on SII, CAR, and RDW for postoperative liver

metastasis of colon cancer to aid in the clinical screening of postoperative liver metastasis of colon cancer.

## MATERIALS AND METHODS

### Clinical data

The general and clinical data of 242 patients with colon cancer admitted to the Zhejiang Provincial People's Hospital between December 2019 and December 2022 were retrospectively analyzed. Patients were divided into the transfer ($n$ = 52) and non-transfer ($n$ = 190) groups based on whether they developed liver metastasis after surgery or not. The analysis process is shown in Figure 1.

### Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) preoperative diagnosis of colon cancer by imaging and histopathology; (2) postoperative pathologic examination confirming colon cancer; (3) radical resection of colon cancer; (4) availability of complete clinicopathological data; and (5) complete follow-up data.

The exclusion criteria were as follows: (1) preoperative colon cancer with distant metastasis; (2) colon cancer with perforation or hemorrhage; (3) previous history of malignancy; and (4) underlying severe cardiac, hepatic, renal, pulmonary, or hematological diseases.

### Observation indexes

General and clinicopathological data were collected for all patients, including age, sex, body mass index (BMI), history of alcohol consumption, smoking, and history of diseases (cardiac disease, diabetes mellitus, and hypertension). Clinicopathological data included SII, CAR, RDW, total bilirubin, albumin, platelet count, white blood cell (WBC) count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), surgical modality, vascular invasion, tumor site, type of pathology, postoperative

chemotherapy, preoperative carcinoembryonic antigen (CEA) levels, and lymph node metastasis status.

*Statistical analysis*

The Statistical Package for Social Science (SPSS, version 26.0) was used to analyze all data. For normally distributed data points, comparisons between two groups were performed using *t*-test, and results are expressed as mean ± SD. Non-normally distributed data were analyzed by the Mann-Whitney *U*-test and expressed as M (P25-P75). Comparisons of counting data between the two groups were performed using the $\chi^2$ test, expressed as n (%). Binary logistic regression was applied to analyze the relevant influencing factors of liver metastasis after surgery for colon cancer.

A predictive model was constructed using *R* software based on multifactorial logistic regression analysis, and the model was internally validated using the bootstrap method with 1000 repetitive samples. The accuracy of the model was assessed by the area under the curve (AUC) of the receiver operating characteristic (ROC) curve, the calibration curve, and the decision curve analysis (DCA).

## RESULTS

*Comparison of general data between the liver transfer and non-transfer groups after colon cancer surgery*

General information such as age, BMI, sex, drinking history, smoking history, and medical history of the patients in the two groups were analyzed separately. There was no significant difference between the two groups ($P > 0.05$) (Table 1).

*Clinical data comparison between the two patient groups*

To investigate the predictive value of the SII, CAR, and RDW for the development of liver metastases after surgery in patients with colon cancer, a one-way analysis of all case information collected was performed. The results revealed no significant difference between the two groups in terms of total bilirubin, albumin, platelet count, WBC count,

AST level, surgical method, vascular invasion, tumor site, pathology type, or postoperative chemotherapy ($P > 0.05$). However, there was a significant difference between the metastatic and non-metastatic groups in the comparison of SII, CAR, RDW, ALT, preoperative CEA, and lymphatic metastasis ($P < 0.05$) (Table 2).

*Multifactorial analysis of liver metastasis after colon cancer surgery*

Binary logistic regression analysis was performed with the occurrence of liver transfer as the dependent variable and SII, CAR, RDW, ALT, preoperative CEA, and lymphatic metastasis as the independent variables. The variable assignments are shown in Table 3. Factors affecting the univariate analysis ($P < 0.05$) (SII, CAR, RDW, ALT, preoperative CEA, and lymphatic metastasis) in the transfer and non-transfer groups were included in the binary logistic regression analysis, which showed that SII, CAR, and RDW were independent risk factors for liver transfer in the postoperative period, and the model excluded the three factors of ALT, preoperative CEA, and lymphatic metastasis ($P > 0.05$) (Table 4).

*Predictive value of SII, CAR, and RDW for postoperative liver metastasis in patients*

The ROC curves showed that the predicted AUCs of SII, CAR, and RDW were 0.88, 0.68, and 0.67, respectively, with sensitivities of 96.20%, 65.40%, and 50.00% and specificities of 71.60%, 67.40%, and 87.40%, respectively (Table 5 and Figure 2).

*Construction and validation of the column-line diagram model*

Based on the results of the multifactorial logistic regression analysis, three factors, namely SII, CAR, and RDW, were used in a columnar graphical prediction model constructed using the R software for the occurrence of liver metastasis after radical resection of colon cancer (Figure 3). The ROC curve (Figure 4A) assessed that the AUC (95%CI) of the column chart for distinguishing the occurrence of liver metastasis after radical resection of colon cancer was 0.93 (0.89–0.96), and the optimal cut-off value of the column chart was 0.16, with a sensitivity of 91.30% and a specificity of 81.10%.

Assessment of the calibration curve (Figure 4B) showed that the column chart could predict the occurrence of liver metastasis after radical resection of colon cancer (Figure 4B). Further assessment of the curves showing the predicted risk of occurrence of postoperative liver metastases from colon cancer in the column-line diagram and the actual risk of occurrence of postoperative liver metastases from colon cancer showed high homology. This result indicates that the predicted risk of occurrence of postoperative liver metastases from colon cancer by the column-line diagram matched well with the risk of occurrence of liver metastases from actual postoperative liver metastases from colon cancer. Based on the predicted model curve in the DCA curve compared to that in the extreme case, the net benefit of the model is superior in the larger threshold range (above 15%), indicating that the model is safer (Figure 4C).

## DISCUSSION

Colon cancer is a highly aggressive and migratory malignant tumor, and the liver is the most common organ site for postoperative metastasis[17]. Liver metastasis occurs in approximately 50% of patients with colon cancer, with metastases found at diagnosis in 25% of patients[18]. Further, metastasis is the primary cause of death in patients with colon cancer[19]. Therefore, assessing the predictive value of liver metastases after surgery in patients with colon cancer is clinically important. Overall, we found that SII, CAR, and RDW alone had some assessment value for the postoperative prognosis of patients with colon cancer[12,20,21], and the SII had a high predictive ability for the occurrence of liver metastasis after surgery in these patients[8]. Therefore, we constructed a column-line graph prediction model for the occurrence of liver metastasis after radical resection of colon cancer using SII, CAR, and RDW to help clinicians identify patients at high risk of liver metastasis. Such predictions would allow timely intervention, which could help promote optimal treatment timing.

An impaired immune function, systemic inflammatory state, and chronic inflammatory response promote the development and progression of malignant tumors and are closely associated with patient prognosis. SII is a novel inflammatory index

closely related to inflammatory and immune pathways. This relationship can be expressed by the formula SII = platelets × neutrophils/Lymphocyte ($\times 10^9$/L)[19]. Studies have shown that the SII has a high value in predicting the prognosis of malignant tumors[22]. In the present study, we reviewed related studies on postoperative liver transfer for colorectal cancer, which showed that the preoperative SII level of patients in the transfer group was higher than that of both the transfer and non-transfer groups, indicating that the preoperative SII level has some predictive value for liver metastasis of colorectal cancer after surgery. The results of the ROC curve analysis revealed an AUC of 0.88, which suggests that the efficacy of the SII in predicting liver metastasis of colon cancer after surgery improved, with a sensitivity of 96.20%. This result is consistent with the findings of Lu *et al*[8] (AUC = 0.882).

Related studies have shown that the prognoses of patients with malignant tumors such as colorectal cancer[23] and hepatocellular carcinoma[24] are closely related. Preoperative CAR (a systemic inflammatory marker) has further been found to serve as a prognostic marker for liver metastases of colorectal cancer treated with potential radical resection[25]. Meanwhile, other studies have shown that CAR reflects the inflammatory status and nutritional level of the patient, with low susceptibility and high stability[26]. In the present study, we showed that CAR levels were higher in the group with liver metastases than in those without liver metastases after colon cancer surgery; this is consistent with the findings of Liao *et al*[12]. These results suggest that the preoperative CAR level has some predictive value for postoperative liver metastasis of colon cancer. In our study, the ROC results showed that the efficacy of CAR in predicting postoperative hepatic metastasis of colon cancer was average (AUC = 0.68), indicating that there is a limitation to the value of CAR alone for predicting postoperative hepatic metastasis of colon cancer.

Platelet secretion, migration, and endothelial cell proliferation of vascular endothelial growth factor have an inducing effect and increase vascular permeability, while tumor cells penetrate the machinery of blood vessels to metastasize and invade. RDW reflects the heterogeneous parameters of erythrocyte size and peripheral blood volume[27].

Studies have shown that the prognosis of patients with solid tumors is closely related to RDW[16]. In the present study, we showed that the RDW level was higher in the group with liver metastasis than in the group without liver metastasis after colon cancer surgery. This result is consistent with the findings of Lu *et al*[28]. These results suggest that preoperative RDW has a certain predictive value for postoperative liver metastasis in colon cancer. The ROC results showed that the efficacy of RDW in predicting the postoperative incidence of liver metastasis in colon cancer was average (AUC = 0.67), suggesting that the use of RDW alone does not have a good predictive value for liver metastasis in postoperative colon cancer.

Pang *et al*[29] showed that column-line diagrams performed better in risk stratification of prognosis for patients undergoing radical colon cancer surgery. Therefore, in the present study, we further constructed a column-line diagram prediction model of the occurrence of liver metastasis after radical resection of colon cancer by SII, CAR, and RDW. The ROC results showed an AUC (95%CI) of 0.93 (0.89-0.96). In a prior study, Nagata *et al*[30] developed a prediction model for liver metastasis involving tumor differentiation, pathological staging, and preoperative CEA level. The AUC (95%CI) of this model was 0.78 (0.71-0.84), which was less effective than the model we constructed, suggesting that the models constructed by SII, CAR, and RDW can improve the prediction of liver metastasis after colon cancer surgery accuracy. In addition, we plotted calibration curves and DCA curves to further evaluate the efficacy of the model. The results of the calibration curve analysis showed that the actual curves of the column-line graph model for predicting the occurrence of postoperative liver metastasis in colon cancer largely agreed with the ideal curves, which indicated that the model had good consistency. In addition, the DCA curve suggested that the net benefit of the model was superior to the threshold value of 15%, indicating that the model was safer and had a higher clinical utility.

Overall, the results of the present study show that poor SII, CAR, and RDW results are risk factors for liver metastasis after colon cancer surgery. The prediction model established in this study based on these risk factors has good discriminatory power and

a high calibrating ability for the occurrence of liver metastasis after radical resection of colon cancer. Thus, this model could help clinicians more intuitively identify high-risk patients prone to liver metastasis after surgery, take targeted screening measures, and formulate individualized medical treatment strategies. However, this study had certain limitations. First, only the data of patients who underwent radical resection for colon cancer in our hospital at a fixed time period were selected, meaning that selection bias may have been an issue. Second, as this study was a retrospective study, there is a possibility of retrospective bias. Third, the single-center design limits the generalizability of the results. Finally, only the bootstrap method was used for the internal validation of the predictive model of the risk of liver metastasis after surgery for colon cancer, and no other validation method was used. Therefore, external validation with large samples and multicenter data is needed in the future to assess the generalizability of the model and further validate and improve its prediction ability.

## CONCLUSION

We identified SII, CAR, and RDW as risk factors affecting the occurrence of liver metastasis after colon cancer surgery. Further, we showed that the combination of these three factors could effectively predict the risk of liver metastasis, and our prediction model based on these three risk factors had good predictive efficacy. Therefore, in clinical practice, SII, CAR, and RDW can be beneficial for the early screening of colon cancer and predict the occurrence of liver metastasis after surgery in advance, which can help determine the best time for treatment.

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## Figure Legends

**Figure 1 Flow chart of the study.** SII: Systemic inflammatory index; CAR: C-reactive protein/albumin ratio; RDW: Red blood cell distribution width.

**Figure 2 Receiver operating characteristic curves showing the prediction sensitivity of systemic inflammatory index, C-reactive protein/albumin ratio, and red blood cell distribution width in patients with postoperative liver metastases.** SII: Systemic inflammatory index; CAR: C-reactive protein/albumin ratio; RDW: Red blood cell distribution width.

**Figure 3 Nomogram prediction model of the risk of postoperative liver metastases in patients with colon cancer.** SII: Systemic inflammatory index; CAR: C-reactive protein/albumin ratio; RDW: Red blood cell distribution width.

**Figure 4 Predictive performance of the column graph model on the training set.** A: receiver operating characteristic curve of the training set; B: Calibration curve of the training set; C: The DCA curve of the training set. SII: Systemic inflammatory index; CAR: C-reactive protein/albumin ratio; RDW: Red blood cell distribution width.

**Table 1 Comparison of the general data in patients in the transfer and non-transfer groups, $n$ (%)**

| Considerations | Transfer group ($n$ = 52) | Non-transfer group ($n$ = 190) | $t/z/\chi^2$ | $P$ value |
| --- | --- | --- | --- | --- |
| Age (yr) | 58.96 ± 16.59 | 61.31 ± 14.00 | 0.93 | 0.35 |
| BMI (kg/m$^2$) | 22.16 ± 3.84 | 22.56 ± 2.92 | 0.69 | 0.50 |

| | | | | |
|---|---|---|---|---|
| Sex | | | 1.01 | 0.32 |
| Male | 30 (57.70) | 124 (65.30) | | |
| Female | 22 (42.30) | 66 (34.70) | | |
| Drinking history | | | 1.41 | 0.24 |
| Yes | 40 (76.90) | 130 (68.40) | | |
| No | 12 (23.10) | 60 (31.60) | | |
| Smoking history | | | 1.13 | 0.29 |
| Yes | 44 (84.60) | 148 (77.90) | | |
| No | 8 (15.40) | 42 (22.10) | | |
| Heart disease | | | 0.01 | 0.93 |
| Yes | 14 (26.90) | 50 (26.30) | | |
| No | 38 (73.10) | 140 (73.70) | | |
| Diabetes | | | 1.58 | 0.21 |
| Yes | 14 (26.90) | 36 (18.90) | | |
| No | 38 (73.10) | 154 (81.10) | | |
| Hypertension | | | 1.84 | 0.18 |
| Yes | 8 (15.40) | 46 (24.20) | | |
| No | 44 (84.60) | 144 (75.80) | | |

BMI: Body mass index.

Table 2 Comparison of the clinical data in the transfer and non-transfer groups

| Considerations | Transfer group ($n$ = 52) | Non-transfer group ($n$ = 190) | $t/z/\chi^2$ | $P$ value |
|---|---|---|---|---|
| SII | 385.21 ± 78.63 | 264.29 ± 64.43 | -10.19 | < 0.01 |
| CAR | 1.02 ± 0.40 | 0.79 ± 0.38 | -3.88 | < 0.01 |
| RDW (FL) | 17.64 ± 1.98 | 16.28 ± 1.26 | -4.72 | < 0.01 |
| Total bilirubin (μmol/L) | 13.45 ± 2.51 | 13.75 ± 3.28 | 0.71 | 0.48 |

| | | | | |
|---|---|---|---|---|
| Albumin (g/L) | 42.08 ± 3.81 | 42.22 ± 2.71 | 0.25 | 0.80 |
| Blood platelet count (10⁹/L) | 167.13 ± 65.02 | 157.29 ± 40.59 | -1.04 | 0.30 |
| WBC (10⁹/L) | 7.48 ± 2.58 | 7.52 ± 3.12 | 0.08 | 0.93 |
| ALT (U/L) | 47.88 ± 1.84 | 48.50 ± 1.59 | 2.40 | 0.017 |
| AST (U/L) | 47.29 ± 1.25 | 47.14 ± 1.76 | -0.61 | 0.54 |
| Surgical procedures | | | 0.01 | 0.94 |
| Laparoscopy | 32 (61.50) | 118 (62.10) | | |
| Open the abdomen | 20 (38.50) | 72 (37.90) | 0.01 | 0.93 |
| Vascular invasion | | | 3.26 | 0.07 |
| Yes | 24 (46.20) | 62 (32.60) | | |
| No | 28 (53.80) | 128 (67.40) | 1.58 | 0.21 |
| Tumor site | | | 1.01 | 0.32 |
| Left | 30 (57.70) | 124 (65.30) | | |
| Right | 22 (42.30) | 66 (34.70) | | |
| Pathological type | | | 1.05 | 0.31 |
| Adenocarcinoma | 48 (92.30) | 182 (95.80) | | |
| Other | 4 (7.70) | 8 (4.20) | | |
| Postoperative chemotherapy | | | 3.26 | 0.07 |
| Yes | 24 (46.20) | 62 (32.60) | | |
| No | 28 (53.80) | 128 (67.40) | | |
| Preoperative CEA (μg/L) | | | 9.59 | <0.01 |
| < 5 | 21 (40.40) | 122 (64.20) | | |
| ≥ 5 | 31 (59.60) | 68 (35.80) | | |
| Lymphatic node transfer | | | 4.90 | 0.03 |

| | | |
|---|---|---|
| Yes | 28 (53.80) | 70 (36.80) |
| No | 24 (46.20) | 120 (63.20) |

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CAR: C-reactive protein/albumin ratio; CEA: Carcinoembryonic antigen; RDW: Red blood cell distribution width; SII: Systemic inflammatory index; WBC: White blood cell.

Table 3 Variable assignment table

| Project | Assignment description |
|---|---|
| Dependent variable | Transfer group '1', Non-transfer group '0' |
| SII | Continuous variable |
| CAR | Continuous variable |
| RDW | Continuous variable |
| ALT | Continuous variable |
| Preoperative CEA | ≥ 5 μg/L '1', < 5 μg/L '0' |
| Lymphatic node transfer | Yes '1', No '0' |

ALT: Alanine aminotransferase; CAR: C-reactive protein/albumin ratio; CEA: Carcinoembryonic antigen; RDW: Red blood cell distribution width; SII: Systemic inflammatory index.

Table 4 Multifactorial analysis of liver metastases after surgery for colon cancer

| Considerations | $\beta$ | SE | Wald$\chi^2$ | $P$ value | OR | 95%CI |
|---|---|---|---|---|---|---|
| SII | 0.26 | < 0.01 | 36.78 | < 0.01 | 1.03 | 1.02–1.03 |
| CAR | 1.57 | 0.56 | 7.74 | 0.01 | 4.79 | 1.59–14.44 |
| RDW | 0.57 | 0.15 | 13.77 | < 0.01 | 1.76 | 1.31–2.38 |
| ALT | -0.25 | 0.15 | 2.87 | 0.09 | 0.78 | 0.58–1.04 |
| Preoperative CEA | 0.85 | 0.48 | 3.09 | 0.08 | 2.34 | 0.91–6.04 |
| Lymphatic node transfer | 0.7 | 0.49 | 2.04 | 0.15 | 2.01 | 0.77–5.23 |

| Constant | -9.17 | 7.71 | 1.41 | 0.24 | < 0.01 | - |

ALT: Alanine aminotransferase; CAR: C-reactive protein/albumin ratio; Carcinoembryonic antigen; RDW: Red blood cell distribution width; SII: Systemic inflammatory index.

Table 5 Predictive value of systemic inflammatory index, lymphatic metastasis, C-reactive protein/albumin ratio, and red blood cell distribution width in patients with postoperative liver metastasis

| Considerations | Truncation value | AUC | SE | $P$ value | 95%CI | Sensitivity (%) | Idiosyncrasy (%) |
|---|---|---|---|---|---|---|---|
| SII | 290.52 | 0.88 | 0.03 | < 0.01 | 0.83–0.94 | 96.2 | 71.6 |
| CAR | 0.86 | 0.68 | 0.04 | < 0.01 | 0.60–0.76 | 65.4 | 67.2 |
| RDW | 16.76 | 0.67 | 0.04 | < 0.01 | 0.59–0.76 | 50 | 87.4 |

CAR: C-reactive protein/albumin ratio; RDW: Red blood cell distribution width; SII: Systemic inflammatory index; AUC: Area under the curve.

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