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RESEARCH

# Non-Alcoholic Fatty Liver Disease May Be a Risk Factor for Liver Metastasis After Radical Surgery for Colorectal Cancer: A Retrospective Study

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## Abstract

**Purpose** Distant metastasis develops in approximately one-third of patients with colorectal cancer (CRC) who undergo radical surgery, and colorectal liver metastasis (CRLM) is the most common form of distant metastasis in CRC. Hepatectomy is the only potentially curative treatment for CRLM, but few patients with metastatic CRC meet the criteria for this radical resection, and the 5-year survival rate is poor. Identifying risk factors for CRLM is critical. Non-alcoholic fatty liver disease (NAFLD) is an independent risk factor for CRC. However, the effect of NAFLD on CRC liver metastasis after radical surgery remains unclear. Therefore, we examined the impact of NAFLD-associated hepatic fibrosis on liver metastasis after radical surgery for CRC.

**Methods** We retrospectively analyzed data from 388 patients who underwent curative surgery for CRC at our hospital between April 2008 and March 2015. The patients' clinical results, surgical procedures, postoperative course, and pathological and survival data were collected from the hospital records. The NAFLD fibrosis score was calculated and used to divide the patients into two groups (NAFLD and non-NAFLD).

**Results** Recurrence was observed in 83/388 (21.4%) patients after a mean follow-up of $65.6 \pm 15.1$ months. Twenty-five patients had liver metastasis: 8 in the NAFLD group (8/45; 17.8%) and 17 in the non-NALFD group (17/343; 5.0%) ($p = 0.004$). Liver metastasis-free survival was significantly worse in the NAFLD than non-NAFLD group ($p < 0.001$). NAFLD and cancer stage were independent risk factors for liver metastasis recurrence.

**Conclusion** NAFLD may be a risk factor for liver metastasis in patients with CRC who undergo curative surgery.

**Keywords** Non-alcoholic fatty liver disease · Colorectal cancer · Liver metastasis · Non-alcoholic fatty liver disease fibrosis score

## Introduction

Colorectal cancer (CRC) is the third most common cancer and has the second highest cancer-related mortality rate worldwide [1]. Although radical surgery and postoperative adjuvant therapy have progressed, approximately 30% of patients with CRC develop metachronous metastases, most often to the liver [2]. Hepatectomy is the only potentially curative treatment for colorectal liver metastasis (CRLM), but few patients meet the requirements for surgery, and the 5-year survival rate for those not undergoing radical resection is low [3, 4]. Additionally, among patients who do undergo hepatectomy for CRLM, 60% experience recurrence [5]. Therefore, studying the risk factors for CRLM is important and will help to establish an effective strategy to improve the prognosis.

Because of changes in lifestyle and diet, the incidence of non-alcoholic fatty liver disease (NAFLD) in adults is increasing. The worldwide prevalence of NAFLD is 32.4% [6], making it a main cause of chronic liver disease [7]. Additionally, molecular and pathophysiological changes caused by NAFLD may influence the epidemiology of primary liver cancer [8–10].

NAFLD is an independent risk factor for CRC [11, 12]; however, the effect of NAFLD on CRC liver metastasis after radical surgery is poorly documented. Given the expected

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increase in the number of patients with CRC and NAFLD, as well as the medical costs associated with both diseases, identifying the link between CRLM and NAFLD is critical. Therefore, we retrospectively investigated the impact of NAFLD-associated hepatic fibrosis on liver metastasis after radical surgery for CRC.

## Materials and Methods

### Patient Selection

Patients who underwent curative surgical resection for newly diagnosed histologically confirmed stage I, II, or III CRC at our hospital between April 2008 and March 2015 were considered for inclusion. The exclusion criteria were as follows: preoperative treatment such as surgery; interventional treatment, chemotherapy, or radiotherapy for CRC; emergency surgery; malignant tumors elsewhere in the body; < 5-year postoperative follow-up; appendiceal carcinoma; insufficient data to allow preoperative calculation of the NAFLD fibrosis score (NFS); cirrhosis or chronic viral hepatitis; and previous liver surgery, including surgery for recurrence within 6 months after surgery (i.e., "simultaneous metastasis"). After application of the exclusion criteria, the study population comprised 388 patients. The primary end point of this study was 5-year hepatic metastasis-free survival. Secondary end points were 5-year recurrence-free survival, and extrahepatic metastasis-free survival. We additionally investigated whether NAFLD is associated not only with postoperative recurrence but also with synchronous liver metastasis. To this end, we also investigated an additional 87 patients with CRC who had synchronous metastasis to only one organ at the initial diagnosis, 66 patients with CRC who had synchronous metastasis only to the liver at the initial diagnosis, and 21 patients with CRC who had synchronous metastasis to an organ other than the liver at the initial diagnosis.

### Clinical Data

We retrospectively collected the patients' clinical data, surgical procedure, postoperative course, and pathological and survival data from our hospital records. Clinical and laboratory data were collected preoperatively. Clinical data comprised age, sex, overweight status (body mass index [BMI] was calculated using the patient's height and weight), and the presence of diabetes mellitus (DM) (fasting glucose level of ≥ 126 mg/dL or taking anti-diabetic drugs). Laboratory evaluation included measurement of the following: NFS, hepatitis B surface antigen, neutrophil-to-lymphocyte ratio, and tumor markers (carcinoembryonic antigen and carbohydrate antigen 19-9 levels). The tumor site was classified as the right-sided colon (cecum to transverse colon), left-sided colon (descending to rectosigmoid colon), or rectum. The CRC classification was in accordance with the guidelines from the American Joint Committee on Cancer Stage, 7th edition [13], using the detailed description from each patient's pathology report. All metastasis diagnoses were independently confirmed using computed tomography, magnetic resonance imaging, and positron emission tomography-computed tomography by at least two radiologists.

### NFS

The NFS was used to confirm the presence of liver fibrosis. The score was calculated as follows:

$$\mathrm{NFS} = -1.675 + 0.037 \times \mathrm{age\ (years)} + 0.094 \times \mathrm{BMI\ (kg/m^2)} + 1.13 \times \mathrm{impaired\ fasting\ glucose\ or\ DM\ (yes = 1,\ no = 0)} + 0.99 \times \mathrm{AST/ALT} - 0.013 \times \mathrm{platelet\ count\ (10^9/L)} - 0.66 \times \mathrm{albumin\ level\ (g/dL)}$$

where AST is aspartate aminotransferase and ALT is alanine aminotransferase.

Patients with a high NFS (> 0.676) were assigned to the NAFLD group, and those with a low NFS (< 0.676) were assigned to the non-NAFLD group [14].

### Statistical Analysis

Continuous values are expressed as mean ± standard deviation, and categorical variables are presented as number and percentage. Statistical analyses were performed using the two-sided Student's *t*-test and the Mann-Whitney *U*-test for continuous data or Fisher's exact test. The log-rank test was used to identify significant differences between curves. Patterns of recurrence consist of several distinct recurrence events attributed exclusively to one event, which is defined as a "competing risks situation." Recurrences were therefore grouped as either liver-specific or extrahepatic. The cumulative incidence was estimated using each type of recurrence as a competing risk (liver-specific vs. extrahepatic). We included age, sex, BMI, and DM in the interaction analysis for all multivariate analyses. All statistical tests were two-sided. In all analyses, death before an event of interest was treated as a censoring event. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 28.0 (IBM Corp., Armonk, NY, USA). Significance was defined as $p < 0.05$.

## Results

### Patients' Characteristics and Intraoperative Findings After Curative Surgical Resection

We retrospectively analyzed data from 388 patients who underwent curative surgical resection for CRC during the study period. The mean NFS was − 1.52 ± 1.72. Among the 388 patients, 45 were diagnosed with

NAFLD (NAFLD group) and 343 patients did not have NAFLD (non-NAFLD group). Data from the two groups are summarized in Table 1. Age, BMI, and prevalence of DM were significantly higher in the NAFLD group than in the non-NAFLD group, while the white blood cell count, carbohydrate antigen 19-9 level, and adjuvant chemotherapy use were also significantly different between the groups.

## Patient Outcomes and Their Association with NAFLD

The mean follow-up period was 65.6 ± 15.1 months. Recurrence was observed in 83/388 (21.4%) patients, among whom 3 were classified as having stage I, 16 as having stage II, and 64 as having stage III. Twenty-five patients had liver metastasis: 18 patients had recurrence of liver metastasis alone and 7 patients had multiple organ recurrences, including liver metastasis. Among the 25 patients with liver metastasis, 8 were in the NAFLD group (8/45, 17.8%) (Table 2) and 17 were in the non-NAFLD group (17/343, 5.0%) ($p = 0.004$). Among the 58 patients with recurrence in organs other than the liver, only 3/45 (6.7%) were in the NAFLD group, whereas 55/343 (16.0%) were in the non-NAFLD group, with no significant difference in extrahepatic recurrence between the groups ($p = 0.120$) (Table 3).

**Table 1** CRC patients' perioperative clinical variables

| | NAFLD ($n = 45$) | Non-NAFLD ($n = 343$) | $p$-value |
|---|---|---|---|
| Age (years) | 76.1 ± 12.1 | 70.5 ± 11.0 | < 0.001 |
| Sex (male) | 24 (53%) | 189 (55%) | 1.0 |
| BMI (kg/m$^2$) | 24.1 ± 4.0 | 22.5 ± 3.1 | 0.011 |
| ASA-PS<br>1 or 2<br>3 or 4 | 43 (95%)<br>2 (5%) | 333 (97%)<br>10 (3%) | 0.491 |
| Diabetes mellitus present | 29 (64%) | 61 (18%) | < 0.001 |
| Hepatitis B surface antigen present | 5 (11%) | 38 (11%) | 1.0 |
| Location<br>Right<br>Left<br>Rectum | 15 (33%)<br>22 (49%)<br>8 (18%) | 141 (41%)<br>141 (41%)<br>61 (18%) | 0.785 |
| CRP | 0.57 ± 1.0 | 0.90 ± 2.8 | 0.692 |
| WBC | 5568 ± 1973 | 6264 ± 2802 | 0.022 |
| NLR | 3.69 ± 3.88 | 3.30 ± 4.31 | 0.953 |
| LMR | 4.70 ± 2.27 | 4.89 ± 2.32 | 0.588 |
| CEA > 5.0 ng/mL | 20 (44%) | 109 (32%) | 0.095 |
| CA19-9 > 37 U/mL | 15 (33%) | 43 (13%) | 0.001 |
| Surgery time (mins) | 219 ± 80.4 | 213 ± 86 | 0.297 |
| Approach (laparotomy) | 37 (82%) | 274 (80%) | 0.843 |
| Complication<br>≤ CD-II | 8 (18%) | 48 (14%) | 0.558 |
| > CD-III | 5 (11%) | 19 (6%) | 0.180 |
| Pathological stage<br>Stage I<br>Stage II<br>Stage III | 7 (16%)<br>20 (44%)<br>18 (40%) | 62 (18%)<br>122 (36%)<br>159 (46%) | 0.634 |
| Differentiation<br>Well or moderate<br>Poor or other | 45 (100%)<br>0 (0%) | 320 (93%)<br>23 (7%) | 0.092 |
| Vascular invasion present | 24 (53%) | 211 (62%) | 0.331 |
| Nerve invasion present | 30 (67%) | 238 (69%) | 0.733 |
| Adjuvant chemotherapy yes | 18 (40%) | 199 (58%) | 0.026 |

*CRC* colorectal cancer, *NAFLD* non-alcoholic fatty liver disease, *BMI* body mass index, *ASA-PS* American Society of Anesthesiologists Physical Status, *CRP* C-reactive protein, *WBC* white blood cell, *NLR* neutrophil-to-lymphocyte ratio, *LMR* lymphocyte-to-monocyte ratio, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, *CD* Clavien-Dindo

**Table 2** The patients with NAFLD who developed liver metastasis after curative surgical resection

| | Age | Sex | NFS | Location | CEA ng/mL | CA19-9 U/mL | T | N | Stage | Adjuvant chemotherapy | Adjuvant chemotherapy cylces | RFS months | OS months | Cause of death |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 81 | F | 1.269 | Right | 2.2 | 17.4 | SE | N1a | IIIb | Xeloda | 8 | 8.6 | 32.4 | CRC |
| 2 | 79 | F | 1.478 | Left | 5.5 | 28.6 | SS | N1a | IIIb | - | - | 6.5 | 62.6 | Other |
| 3 | 65 | M | 1.195 | Left | 14.9 | 96.1 | SS | N1a | IIIb | Xeloda | 7 | 48.0 | 58.5 | CRC |
| 4 | 87 | F | 1.793 | Right | 27.4 | 44.7 | SE | N1b | IIIb | - | - | 14.3 | 42.4 | Other |
| 5 | 84 | M | 0.960 | Right | 10.0 | 40.2 | SS | N1b | IIIb | - | - | 21.6 | 30.2 | CRC |
| 6 | 88 | M | 1.516 | Right | 29.1 | 588.0 | SI | N1a | IIIc | Capox | 6 | 6.2 | 11.0 | CRC |
| 7 | 60 | M | 1.475 | Left | 8.7 | 15.9 | SS | N1a | IIIb | Capox | 8 | 7.9 | 17.8 | CRC |
| 8 | 78 | M | 0.759 | rectum | 1.4 | 3.9 | SS | 0 | IIa | - | - | 9.5 | 20.5 | CRC |

*NFS* non-alcoholic fatty liver disease fibrosis score, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, *CRC* colorectal cancer

**Table 3** CRC patients' postoperative recurrence

| | NAFLD ($n=45$) | non-NAFLD ($n=343$) | $p$-value |
|---|---|---|---|
| Overall recurrence | 11 (24%) | 72 (21%) | 0.567 |
| All liver metastasis | 8 (18%) | 17 (5%) | 0.004 |
| All metastasis other than liver | 3 (7%) | 55 (16%) | 0.120 |

*CRC* colorectal cancer, *NAFLD* non-alcoholic fatty liver disease

Liver metastasis recurrence was investigated in both groups. A Kaplan-Meier curve of hepatic metastasis-free survival showed the 5-year cumulative incidence of liver metastasis recurrence. Hepatic metastasis-free survival was significantly worse in the NAFLD group than in the non-NAFLD group (NAFLD 79.4%, 95% confidence interval [CI] 62.4–89.4 vs. non-NAFLD 95.2%, 95% CI 92.2–97.1; $p<0.001$). However, there was no significant difference in the 5-year cumulative incidence of recurrence-free survival (NAFLD 72.6%, 95% CI 55.3–84.1 vs. non-NAFLD 79.7%, 95% CI 74.9–83.8; $p=0.427$) and extrahepatic metastasis-free survival (NAFLD 93.0%, 95% CI 79.8–97.7 vs. non-NAFLD 84.5%, 95% CI 79.9–88.0; $p=0.160$) between the two groups (Fig. 1a–c).

## Univariate and Multivariate Analyses

We performed univariate and multivariate analyses to evaluate the significance of NAFLD as an independent prognostic marker of liver metastasis (Table 4). Logistic regression analysis showed that NAFLD ($p=0.013$, hazard ratio 3.239, 95% CI 1.282–8.187) and the cancer stage ($p=0.009$, hazard ratio 3.059, 95% CI 1.330–7.035) were independent risk factors for liver metastasis recurrence.

## Outcomes in Patients with Synchronous Distant Metastasis at Initial Diagnosis

In 66 patients with synchronous liver metastasis only (15 with NAFLD, 51 without NAFLD), the mean NFS was $-1.68\pm2.04$. In 21 patients with CRC who had synchronous metastasis to organs other than the liver (all 21 without NAFLD), the mean NFS was $-2.03\pm1.75$. Evaluation of the 87 patients with synchronous metastasis showed that the prevalence of synchronous liver metastases was significantly higher in the NAFLD group than in the non-NAFLD group (100 vs. 70.8%, respectively; $p=0.017$) (Table 5a). Additionally, among all 475 patients examined in this study, the prevalence of synchronous liver metastases was significantly higher in the NAFLD than non-NAFLD group (25.0 vs. 12.3%, respectively; $p=0.015$) (Table 5b).

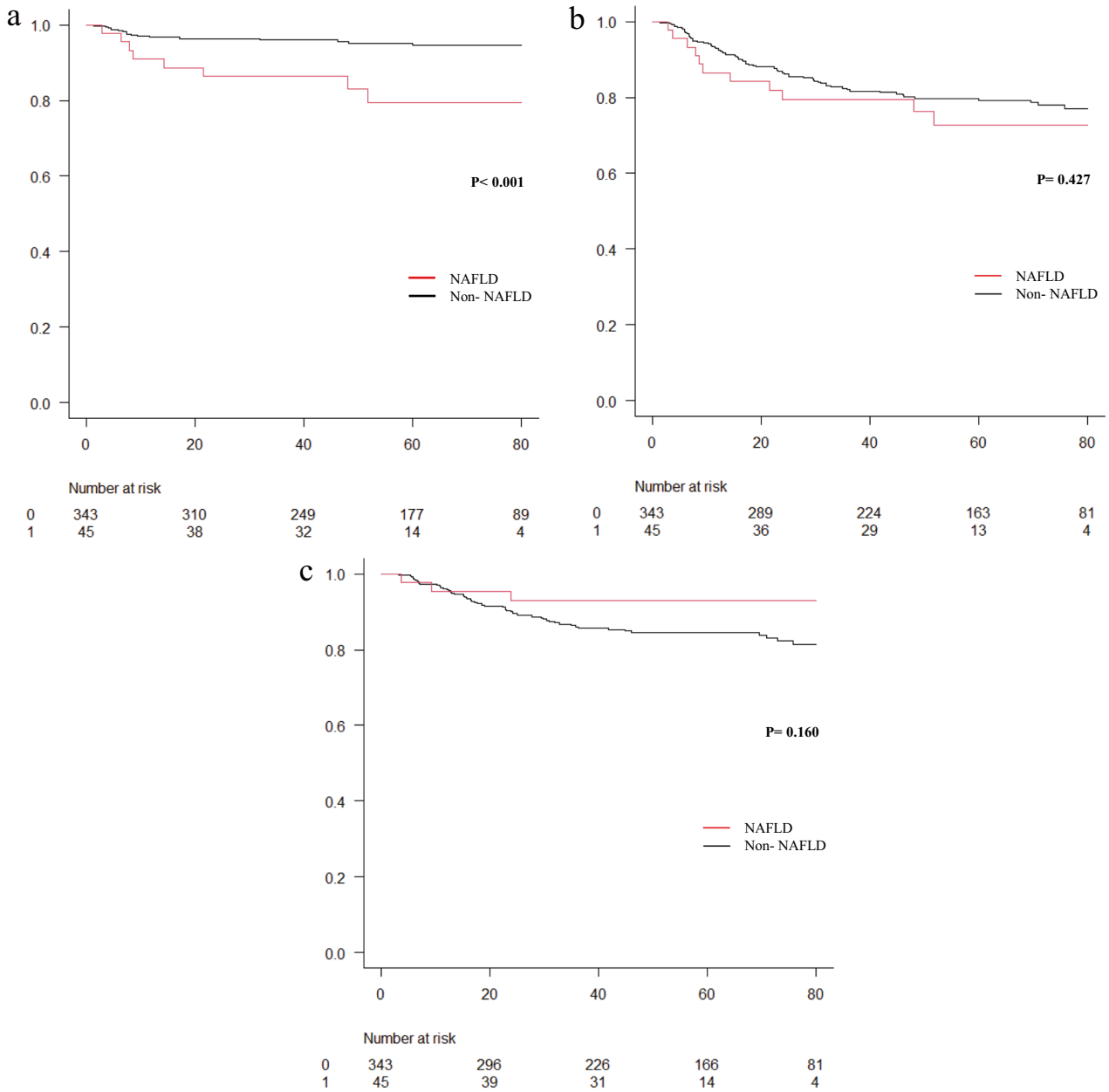


**Fig. 1** Kaplan-Meier curves of RFS of the NAFLD and non-NAFLD groups by recurrence site. **a** Hepatic metastasis-free survival curve. Patients in the NAFLD group had a significantly worse hepatic metastasis survival rate than patients in the non-NAFLD group ($p < 0.001$). **b** RFS curve. **c** Extrahepatic metastasis-free survival curve. The 5-year RFS rate and extrahepatic RFS rate in the NAFLD group were not significantly worse than those in the non-NAFLD group. NAFLD, non-alcoholic fatty liver disease; RFS, recurrence-free survival

**Table 4** Analysis of risk factors for liver metastasis

| | Univariate analysis | Multivariate analysis | | |
|---|---|---|---|---|
| | *p*-value | HR | 95% CI | *p*-value |
| CRP | 0.492 | | | |
| WBC | 0.718 | | | |
| NLR | 0.093 | | | |
| LMR | 0.016 | 0.796 | 0.613–1.034 | 0.088 |
| T-cho | 0.079 | | | |
| CHE | 0.021 | 0.998 | 0.992–1.004 | 0.453 |
| CEA > 5.0 | 0.125 | | | |
| CA19-9 > 37.0 | 0.081 | | | |
| NAFLD | 0.004 | 3.239 | 1.282–8.187 | 0.013 |
| Location | 0.734 | | | |
| Stage | 0.002 | 3.059 | 1.330–7.035 | 0.009 |
| Complication | 0.440 | | | |
| Differentiation | 1.000 | | | |
| Vascular invasion | 0.202 | | | |
| Nerve invasion | 0.106 | | | |
| Adjuvant chemotherapy | 0.659 | | | |

*CRP* C-reactive protein, *WBC* white blood cell, *NLR* neutrophil-to-lymphocyte ratio, *LMR* lymphocyte-to-monocyte ratio, *T-cho* total cholesterol, *CHE* cholinesterase, *CEA* carcinoembryonic antigen carbohydrate antigen, *CA19-9* carbohydrate antigen 19-9, *NAFLD* non-alcoholic fatty liver disease, *HR* hazard ratio, *CI* confidence interval

**Table 5** Prevalence of NAFLD in patients with only synchronous liver metastasis of CRC at the initial diagnosis

| a | NAFLD ($n=15$) | Non-NAFLD ($n=72$) | *p*-value |
|---|---|---|---|
| Synchronous liver metastases | 15 (100%) | 51 (70.8%) | 0.017 |
| b | NAFLD ($n=60$) | Non-NAFLD (n = 415) | |
| Synchronous liver metastases | 15 (25%) | 51 (12.3%) | 0.01 |

*CRC* colorectal cancer, *NAFLD* non-alcoholic fatty liver disease

## Discussion and Conclusion

This retrospective analysis revealed that NAFLD significantly increased the risk of liver metastasis after curative CRC resection, whereas NAFLD had no influence on the development of extrahepatic recurrence. Compared with non-NAFLD, NAFLD was associated with more synchronous liver metastases. These results suggest that changes in the liver microenvironment caused by a host-associated factor such as NAFLD may affect the development of liver metastases. We deemed this to be a significant finding considering the increasing number of patients with CRC and NAFLD.

Autopsy studies conducted in the USA in the 1940s showed that among patients with cancer, liver metastasis was less likely to develop in those with than without cirrhosis [15]. This finding suggests the "seed–soil" hypothesis, which states that metastatic tumor cells migrate to an area where the local microenvironment is favorable [16]. However, most CRC research has since focused on revealing how cancer cells promote metastasis, not on the status of metastatic target organs. Additionally, a mouse CRC model established by injection of colon cancer cells showed that reducing hepatic fibrosis also reduced hepatic metastasis development. This finding implies that the microenvironment in a fatty liver may increase invasion and metastasis proliferation [17]. Subsequent reports focused on the relationship between NAFLD and CRC liver metastasis; recently, an experimental report has been published demonstrating that extracellular vesicles derived from hepatocytes in fatty liver promote the progression of CRC liver metastasis by promoting an immunosuppressive microenvironment, and the relationship between the mechanism of CRC liver metastasis and fatty liver is attracting attention [18].

Several studies demonstrated a connection between NAFLD and CRC [19, 20]. Patients with inflammatory bowel disease are thought to have a higher risk of developing

CRC than those without inflammatory bowel disease, indicating that inflammation also facilitates CRC initiation [21]. Similarly, NAFLD is often associated with a high degree of inflammation. A significant positive correlation was recently shown between high C-reactive protein levels and increased mortality in patients with CRC, and high C-reactive protein levels may be an indicator of metastasis [22]. This result is interesting because it suggests that NAFLD may promote CRC cell migration and colonization of the liver in patients with highly inflamed NAFLD.

A meta-analysis estimated that the overall global prevalence of NAFLD increased significantly over time from 25.5 before 2005 to 32.4% in 2022. NAFLD is a major cause of liver-related morbidity and mortality and represents a current major medical problem [6]. Additionally, the NFS is easily calculated using the patient's age, BMI, hyperglycemia status, platelet count, albumin level, and AST/ALT ratio. The NFS classifications are as follows: liver fibrosis low-risk group ($< -1.455$), intermediate-risk group ($-1.455$ to 0.675), and high-risk group ($> 0.676$) [23]. In the present study, the prevalence of NAFLD was slightly lower than the current global prevalence (12.6 vs. 32.4%, respectively), but we consider this to be within the acceptable range because the cut-off NFS selected in our study was $> 0.676$, indicating the high-risk group. Easily obtainable NFS results are important because the incidence of CRC and NAFLD is increasing. In contrast to the results of our study, some reports indicated that CRC-derived liver metastases occur less frequently in patients with NAFLD than in those without NAFLD or chronic viral hepatitis [24]. However, the relationship between NAFLD and CRC liver metastasis requires further investigation.

Our study has several limitations. First, the sample size was small, there were inaccuracies in the serology-based scoring systems, and the recurrence of liver metastases in this study, 21%, were lower than current global recurrence rates [2]; this was a retrospective study performed at a single institution. And, in this study, the presence or absence of adjuvant chemotherapy was not a risk factor for liver metastasis in multivariate analysis. However, significantly fewer patients in the NAFLD group received adjuvant chemotherapy, which may be a result of the study being conducted at a single institution with a small sample size.

Second, the correlation between the results of the pathological examination of the liver environment upon liver metastasis occurrence and NAFLD remains to be fully clarified in the present study. This is because the NFS is a surrogate parameter, including such as age, BMI, or diabetes, for preoperative examination of CRC and is not equivalent to a more definitive histopathological tissue test such as liver biopsy. Furthermore, NAFLD is said to be related to alcohol intake and smoking in addition to BMI, but this study did not investigate the relationship between NFS and alcohol or smoking. The relationship between NFS and NAFLD, alcohol or smoking further investigation is required.

A larger-cohort study is required to confirm our findings using a different dataset that does not contain the original population involved in our study.

Our results suggest that not only the pathological stage at first operation but also NAFLD may be a risk factor for liver metastasis in patients treated surgically for CRC. Further research is needed to identify new therapeutic strategies to treat CRC, as well as to address NAFLD treatment.

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**Author Contributions** Takashi M and Hiroyuki T designed the study. Takashi M, Yuki S, SM, Yuta S, Hozumi T, TN, HN, AH, DK, HF, and NU collected and analyzed the data. Takashi M wrote the paper. Hiroyuki T revised the paper critically. All authors read and approved the final manuscript.

**Data Availability** All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

## Declarations

**Ethics Approval** The study protocol was approved by the Institutional Review Committee for the Department of General and Digestive Surgery, Kanazawa Medical University Hospital, Ishikawa, Japan (No. I457), and the study was conducted in accordance with the ethical criteria outlined in the World Medical Association Declaration of Helsinki.

**Consent to Participate** Written informed consent to participate in this study was obtained from all patients.

**Consent for Publication** Written informed consent for the publication of this study was obtained from all patients.

**Competing Interests** The authors declare no competing interests.

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