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Prognostic Impact of Geriatric Nutritional Risk Index in Patients With Synchronous Colorectal Liver Metastasis

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Abstract. *Background/Aim: The Geriatric Nutritional Risk Index (GNRI) is a prognostic indicator for several cancers; however, the association between the GNRI and colorectal liver metastasis (CRLM) remains unknown. Patients and Methods: Eighty patients who underwent hepatectomy for synchronous CRLM were divided into two groups based on the GNRI. Results: The preoperative CA19-9 levels were significantly higher in the low (GNRI ≤98; n=30) than the normal GNRI group (GNRI >98; n=50). Patients in the low GNRI group had poorer outcomes than those in the normal GNRI group. A low GNRI was an independent prognostic factor for recurrence-free survival and overall survival. Among 50 patients who experienced recurrence, only 16 of 22 patients (72.7%) in the low GNRI group could receive intensive treatment and 27 of 28 patients (96.4%) in the normal GNRI group. Conclusion: The GNRI is a simplified prognostic factor for patients with CRLM.*

Colorectal cancer is the third most common neoplasm worldwide and the second leading cause of cancer mortality (1). The liver is the most common site of colorectal cancer metastasis, and 15% to 25% of patients have colorectal liver metastasis (CRLM) at the time of diagnosis (2). Surgical resection of CRLM has been shown to significantly improve survival, with a reported 5-year survival rate of approximately 50% (3, 4); however, the incidence of postoperative recurrence remains high (5). Therefore, identification of relevant prognostic factors after hepatectomy for CRLM has become important.

Metastatic cancers are associated with poor nutrition, which occurs in 37% of patients with metastatic digestive cancer (6). Cancer-associated malnutrition, termed cachexia, is associated with an impaired immune response, performance status, muscle function, quality of life, and tolerance of and response to chemotherapy, leading to a poor prognosis (7). Implementation of nutritional treatment is therefore warranted to improve the clinical outcome (8, 9), and more attention has been given to the correlation between cancer and the nutritional status.

Several studies have shown a relationship between poor prognosis and several preoperative nutritional status markers, such as the neutrophil-to-lymphocyte ratio, modified Glasgow prognostic score, and prognostic nutritional index, in patients with CRLM (10-12). However, these nutritional status markers are directly affected by inflammatory markers. The Geriatric Nutritional Risk Index (GNRI) has been established to predict the risk of malnutrition-related morbidity and mortality in advanced age patients (13) and has been reportedly associated with a poor outcome in many diseases, including cancer (14-18). The GNRI is a well-established, simplified tool that is used to assess the nutritional status. This index combines only two nutritional indicators: the serum albumin level and the actual weight compared with the ideal weight. To date, however, the influence of the GNRI on outcomes after hepatectomy for CRLM has not been described. Thus, the present study was performed to evaluate the significance of the GNRI in patients with CRLM.

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Key Words: Geriatric nutritional risk index, colorectal liver metastasis, prognosis.

Table I. *Comparative analysis of clinicopathological findings between the two groups stratified by GNRI.*

Factors	Normal GNRI group (n=50)	Low GNRI group (n=30)	*p*-Value
Age (years)	62.4±10.7	65.5±8.9	0.506
Gender (male/female)	26/24	18/12	0.643
BMI (kg/m^2)	24.1±3.0	21.1±3.6	<0.001
CRC location (right/left)	8/42	5/25	0.999
CRC histology (well/mod/poor)	5/43/2	3/26/1	0.989
pT category* (≤T3/T4)	44/6	27/3	0.999
pN category* (0/1/2)	21/15/14	11/13/6	0.457
Maximum diameter of liver metastasis (cm)	3.2±3.0	4.2±3.6	0.148
Number of liver metastasis	2.9±2.3	3.5±3.2	0.401
Distribution (unilobar/bilobar)	24/26	11/19	0.360
Timing of resection (synchronous/metachronous)	26/24	9/21	0.066
Extent of liver resection (minor/major)	33/17	17/13	0.477
Operative time (min)	350.9±164.6	266.6±173.8	0.034
Blood loss (g)	596.5±712.8	540.8±603.8	0.722
Postoperative complication CD (0-1/≥2)	42/8	25/5	0.999
Perioperative chemotherapy			
Neoadjuvant	17 (34.0%)	13 (43.3%)	0.477
Adjuvant	37 (75.5%)	20 (69.0%)	0.601
Preoperative laboratory data			
Albumin (g/dl)	4.2±0.3	3.6±0.4	<0.001
CEA (ng/ml)	82.4±187.4	868.1±4134.1	0.182
CA19-9 (ng/ml)	79.1±204.1	285.0±683.8	0.049
GNRI	104.2±4.3	91.7±5.8	<0.001

Values are presented as number (%) or mean±standard deviation. GNRI: Geriatric nutritional risk index; BMI: body mass index, CRC: colorectal cancer; CD: Clavien-Dindo classification; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9. *According to UICC 8th TNM Classification.

Patients and Methods

Patients. Eighty patients who met the following inclusion criteria were enrolled in the present study: treatment with radical surgery for colorectal cancer and synchronous CRLM from May 2005 to December 2017, initial diagnosis of colorectal cancer with liver metastasis, and histological diagnosis of CRLM. The patients had no organ metastasis other than liver metastasis prior to surgery. This study was approved by the Ethics and Indications Committee of the National Hospital Organization Kyushu Cancer Center.

The selected patients' characteristics were as follows. The mean age of the patients was 63.6 years (range=30-86 years). The male:female ratio was 44:36. The mean (± standard deviation) body mass index and serum albumin levels before hepatectomy were 22.9±3.6 kg/m^2 and 4.0±0.5 mg/dl, respectively. The primary tumor was located in the right colon (proximal to the splenic flexure) in 13 (16.3%) patients and in the left colon (distal to the splenic flexure) in 67 (83.7%) patients, and 30 patients had rectal cancer. In 48 (60.0%) patients, the primary tumor involved regional lymph node metastasis. All patients had synchronous liver metastasis, with a mean size and number of 3.5±3.0 cm and 3.1±2.7, respectively. The mean preoperative serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels were 377.1±2538.2 ng/ml and 156.3±455.6 ng/ml, respectively. Thirty-five patients (43.8%) underwent synchronous surgery of the primary tumor and liver metastases. With respect to perioperative chemotherapy, 30 (37.5%) patients received preoperative chemotherapy before undergoing hepatectomy and 57 (73.1%) patients received postoperative chemotherapy. The mean number of follow-up days after the initial hepatectomy was 1545.5±963.4 days. Fifty-three of 80 patients developed disease recurrence after radical surgery for colorectal cancer and liver metastasis at a median of 0.69 years, and 35 patients died at a median of 3.46 years.

Nutritional assessment by GNRI. The GNRI was calculated as follows: (14.89× albumin in mg/dl) + [41.7× (present/ideal body weight in kg)]. The present/ideal body weight value was set to 1 when the patient's body weight exceeded the ideal body weight (13). The ideal body weight was defined as a body mass index of 22 kg/m^2 (19). The GNRI was evaluated before hepatectomy for synchronous CRLM.

Statistical analysis. The clinicopathological records of the 80 patients were collected and retrospectively reviewed. Comparisons between the two groups divided by the GNRI were performed using the χ^2 test and Student's *t*-test. The patient survival analysis was performed by the Kaplan–Meier method, and differences were evaluated by the log-rank test. A Cox proportional hazards regression model was used in the multivariate survival analysis. The results were analyzed using the JMP 13.0.0 software program (SAS Institute Inc., Cary, NC, USA). A *p*-value of <0.05 was considered statistically significant.

Results

GNRI. The GNRI of all 80 patients with CRLM undergoing hepatectomy exhibited a normal distribution, and the mean GNRI was 99.5±7.8 (range=77.5-116.2). According to a

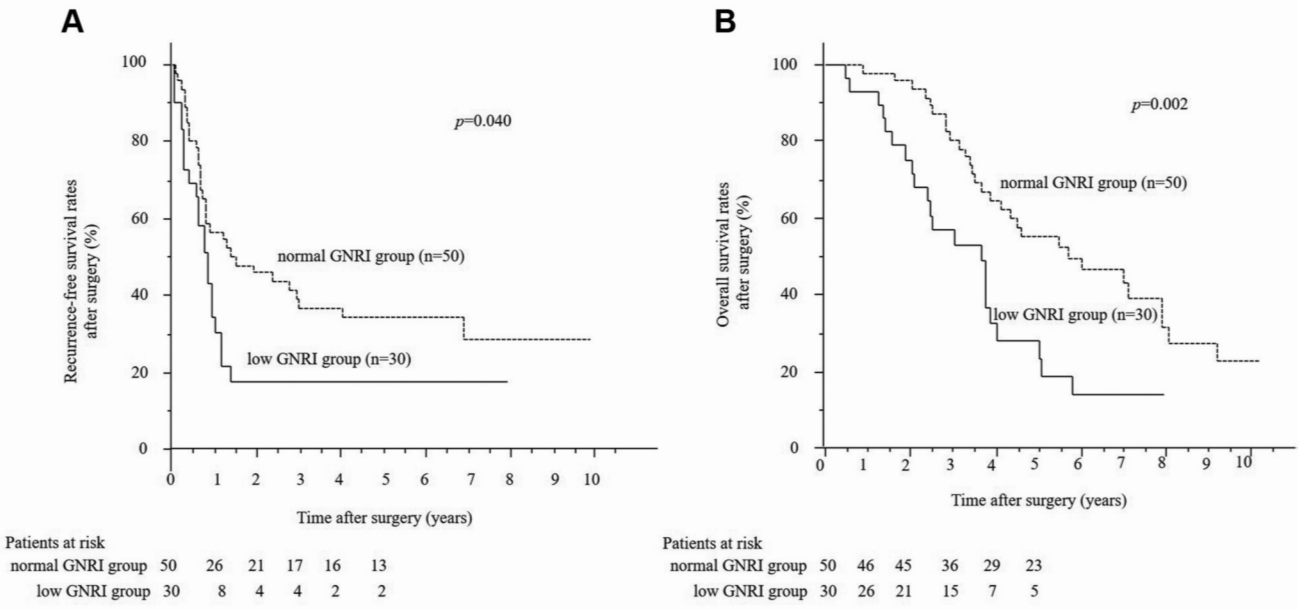

Figure 1. *Kaplan–Meier curves of recurrence-free survival and overall survival. (A) Recurrence-free survival and (B) overall survival curves of 80 patients with CRLM divided into the low Geriatric Nutritional Risk Index (GNRI group) and the normal GNRI group (p=0.040 and p=0.002, respectively, log-rank test). Solid line: Low GNRI group; dotted line: normal GNRI group.*

previous meta-analysis (20), the 80 patients were divided into the normal GNRI group [GNRI of >98 (n=50, 62.5%)] and the low GNRI group [GNRI of ≤98 (n=30, 37.5%)].

Clinicopathological comparisons between normal and low GNRI groups. We compared the clinicopathological findings between the normal and low GNRI groups (shown in Table I). No significant differences were found in any clinicopathological parameters, including age, sex, the characteristics of the primary tumor, regional lymph node metastasis, the maximum size and number of CRLMs, and perioperative chemotherapy. The preoperative CA19-9 levels were significantly higher in the low than in the normal GNRI group (p=0.049). Although no difference in the operative procedure was found, more patients in the low than normal GNRI group underwent metachronous surgery for the primary tumor and liver metastases, and the operative time was shorter in the low than in the normal GNRI group.

Comparison of clinical outcomes between normal and low GNRI groups. The analysis of recurrence-free survival (RFS) revealed significantly poorer outcomes in the low than in the normal GNRI group (p=0.040) (Figure 1A). The analysis of overall survival (OS) also revealed significantly poorer outcomes in the low than in the normal GNRI group (p=0.002) (Figure 1B).

In the univariate analysis of patients with CRLM undergoing hepatectomy, the following factors were associated with lower RFS: worse histological grade of the primary tumor, the presence of lymph node metastasis, a >5 cm maximum diameter of liver metastasis, the induction of neoadjuvant chemotherapy, no adjuvant chemotherapy after hepatectomy, higher preoperative CEA and CA19-9 levels (>200 and >100 ng/ml, respectively), and a low GNRI. The multivariate analysis revealed that a low GNRI was an independent prognostic factor for RFS (p=0.030) (Table II).

In the univariate analysis of patients with CRLM undergoing hepatectomy, the following factors were associated with lower OS: the presence of lymph node metastasis, a >5 cm maximum diameter of liver metastasis, no adjuvant chemotherapy after hepatectomy, higher preoperative CEA and CA19-9 levels (>200 and >100 ng/ml, respectively), and a low GNRI. The multivariate analysis revealed that a low GNRI (p=0.008), the presence of lymph node metastasis (p=0.041), and no adjuvant chemotherapy after hepatic resection (p<0.001) were independent prognostic factors for OS (Table III).

Multidisciplinary treatment for recurrence after initial hepatectomy. During the follow-up of this study, disease recurrence occurred in 31 (62.0%) and 22 (73.3%) patients in the normal and in the low GNRI groups, respectively. Of 50 patients for which there was information about multidisciplinary treatment for the initial recurrence, 43 patients underwent repeat hepatectomy (n=23), locoregional therapy such as radiofrequency ablation or microwave

Table II. *Univariate and multivariate Cox regression analyses for recurrence-free survival.*

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Age (≥65 *vs.* <65 years)	0.82 (0.477-1.412)	0.474		
Gender (male *vs.* female)	1.344 (0.775-2.332)	0.293		
CRC location (right *vs.* left)	0.899 (0.363-1.999)	0.808		
CRC histology				
(mod *vs.* well)	4.664 (1.133-19.204)	0.033	6.411 (1.303-31.547)	0.022
(poor *vs.* well)	4.874 (0.685-34.673)	0.114	14.571 (1.341-158.273)	0.028
pT category* (T4 *vs.* ≤T3)	0.942 (0.374-2.371)	0.899		
Lymph node metastsis (presence *vs.* absence)	2.314 (1.265-4.232)	0.007	2.568 (1.207-5.461)	0.014
Maximum diameter of liver metastasis (≥5 *vs.* <5 cm)	2.166 (1.143-4.104)	0.018		
Number of liver metastasis (>3 *vs.* ≤3)	1.237 (0.701-2.185)	0.463		
Distribution (bilobar *vs.* unilobar)	1.502 (0.868-2.600)	0.146		
Timing of resection (synchronous *vs.* metachronous)	1.214 (0.708-2.081)	0.480	7.257 (1.971-26.720)	0.003
Extent of liver resection (major *vs.* minor)	1.697 (0.980-2.938)	0.059		
Operative time (≥300 *vs.* <300 min)	1.087 (0.630-1.874)	0.764		
Blood loss (≥280 *vs.* <280 g)	1.652 (0.949-2.877)	0.077		
Postoperative complication CD (≥2 *vs.* <2)	1.095 (0.533-2.249)	0.803		
Perioperative chemotherapy				
Neoadjuvant (yes *vs.* no)	1.958 (1.136-3.377)	0.016	5.646 (1.895-16.823)	0.002
Adjuvant (yes *vs.* no)	0.514 (0.277-0.953)	0.034	0.302 (0.131-0.699)	0.005
CEA (≥200 *vs.* <200 ng/ml)	2.482 (1.153-5.341)	0.020		
CA19-9 (≥100 *vs.* <100 ng/ml)	2.289 (1.230-4.260)	0.009		
GNRI (low GNRI group *vs.* normal GNRI group)	1.779 (1.020-3.104)	0.043	2.401 (1.090-5.290)	0.030

HR: Hazard ratio; CI: confidence interval; CRC: colorectal cancer; CD: Clavien-Dindo classification; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; GNRI: geriatric nutritional risk index. *According to UICC 8th TNM Classification.

coagulation therapy (n=3), and/or standard systemic chemotherapy such as FOLFOX, CAPOX, or FOLFIRI± molecular targeted agents (n=21). The remaining seven patients were unable to receive intensive treatment; of these patients, four were treated with monochemotherapy± molecular targeted agents and three were treated with best supportive care. Among 22 patients in the low GNRI group, only 16 (72.7%) were able to receive intensive treatment; however, among the 28 patients in the normal GNRI group, 27 (96.4%) were able to receive intensive treatment (p=0.035).

Discussion

The nutritional status has been given increasingly more attention as a prognostic factor for patients with cancer including CRLM. However, an easy tool to assess the nutritional status is still needed. The GNRI, a simplified nutritional assessment tool, has been recognized to have prognostic value for several types of cancer, including colorectal cancer (14-17). This report provides the first evidence of a correlation between the GNRI and the prognosis of patients with CRLM.

The underlying mechanism resulting in a poor prognosis in patients with CRLM and a low GNRI is unclear. In one study, cancer-related cachexia was found in 30% of patients with CRLM and was associated with hypoalbuminemia and loss of muscle volume (21). Hypoalbuminemia reflects a systemic inflammatory condition in which inflammatory cytokines, such as interleukin-1 and -6 and tumor necrosis factor-alpha, are released from circulating neutrophils (22, 23). These cytokines also contribute to tumor progression, and an association between systemic inflammation, malnutrition, and tumor progression has been noted (24, 25). Malnutrition also impairs the immune response, compromising the host defenses against cancer (26, 27). In the current study, the preoperative CA19-9 levels were higher in the low than in the normal GNRI group. In addition, the liver metastases were larger and more numerous in the low than in the normal GNRI group, although the difference did not reach statistical significance. This suggests that the GNRI reflects tumor progression and cancer cachexia, resulting in unfavorable outcomes. Therefore, the GNRI may be an independent prognostic factor in patients with CRLM.

In this study, OS was shorter in the low than in the normal GNRI group. As mentioned above, this may be explained by the fact that the GNRI reflects tumor progression and cancer cachexia through systemic inflammation and an impaired immune response. Interestingly, only 16 (72.7%) of 22 patients in the low GNRI group who developed recurrence after hepatectomy were able to receive intensive treatment. Previous studies have demonstrated that cancer cachexia is

Table III. *Univariate and multivariate Cox regression analyses for overall survival.*

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Age (≥65 *vs*. <65 years)	1.074 (0.540-2.136)	0.840		
Gender (male *vs*. female)	0.94 (0.475-1.859)	0.858		
CRC location (right *vs*. left)	0.872 (0.307-2.479	0.798		
CRC histology				
(mod *vs*. well)	5.063 (0.690-37.163)	0.111		
(poor *vs*. well)	5.447 (0.336-88.422)	0.233		
pT category* (T4 *vs*. ≤T3)	1.390 (0.418-4.620)	0.592		
Lymph node metastasis (presence *vs*. absence)	2.487 (1.111-5.565)	0.027	3.171 (1.050-9.578)	0.041
Maximum diameter of liver metastasis (≥5 *vs*. <5 cm)	2.123 (1.002-4.498)	0.049		
Number of liver metastasis (>3 *vs*. ≤3)	1.108 (0.518-2.371)	0.791		
Distribution (bilobar *vs*. unilobar)	1.818 (0.919-3.597)	0.086		
Timing of resection (synchronous *vs*. metachronous)	1.121 (0.576-2.182)	0.738		
Extent of liver resection (major *vs*. minor)	1.303 (0.665-2.553)	0.440		
Operative time (≥300 *vs*. <300 min)	1.002 (1.000-1.004)	0.146		
Blood loss (≥280 *vs*. <280 g)	1.000 (1.000-1.001)	0.118		
Postoperative complication CD (≥2 *vs*. <2)	0.96 (0.395-2.332)	0.927		
Perioperative chemotherapy				
Neoadjuvant (yes *vs*. no)	1.831 (0.933-3.594)	0.079		
Adjuvant (yes *vs*. no)	0.315 (0.159-0.625)	0.001	0.111 (0.040-0.308)	<0.001
CEA (≥200 *vs*. <200 ng/ml)	2.732 (1.176-6.346)	0.020		
CA19-9 (≥100 *vs*. <100 ng/ml)	2.210 (1.060-4.609)	0.034		
GNRI (low GNRI group *vs*. normal GNRI group)	2.492 (1.226-5.066)	0.012	3.725 (1.409-9.847)	0.008

HR: Hazard ratio; CI: confidence interval; CRC: colorectal cancer; CD: Clavien-Dindo classification; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; GNRI: geriatric nutritional risk index. *According to UICC 8th TNM Classification.

associated with increased toxicity and intolerance to cancer therapy (28, 29). Several studies have also shown that appropriate nutritional intervention for patients with cancer can improve the patients' outcomes (30). Additional prospective studies are needed to determine whether nutritional supplementation can improve patients' tolerance of intensive treatment for recurrence and improve the prognosis in patients with CRLM who have a low GNRI.

Our study has several limitations. First, this was a retrospective study that was not powered to determine the prognostic role of the GNRI. Second, the only nutritional screening tool used in this study was the GNRI, and the GNRI was not compared with other commonly utilized tools to assess the nutritional status. A larger prospective multicenter study performed according to appropriate protocols is needed to validate our results.

In conclusion, this prospective study suggests that the GNRI is a simplified prognostic factor for patients with CRLM. Standard treatment for recurrence after resection of CRLM is sometimes difficult in patients with a low GNRI before hepatectomy.

Conflicts of Interest

The Authors have no conflicts of interest related to this work.

Authors' Contributions

Tomohiro Iguchi: study concept and design, drafting of manuscript, Keishi Sugimachi: study concept and critical revision of the manuscript, Yohei Mano: data collection, Takashi Motomura: statistical analysis, Masahiko Sugiyama: data collection, Mitsuhiko Ota: data collection, Masahiko Ikebe: statistical analysis, Taito Esaki: data collection, Tomoharu Yoshizumi: statistical analysis, Masaru Morita: data collection, Masaki Mori: critical revision of the manuscript, Yasushi Toh: final approval of the manuscript.

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