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The Geriatric Nutritional Risk Index predicts postoperative complications and prognosis in elderly patients with colorectal cancer after curative surgery

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Malnutrition has been considered to be associated with the prognosis of cancer. The Geriatric Nutritional Risk Index (GNRI), based on serum albumin levels, present body weight, and ideal body weight, is a simple screening tool to predict the risk of nutrition-related morbidity and mortality in elderly patients. We aimed to evaluate whether preoperative GNRI was associated with postoperative complications and prognosis in elderly patients with colorectal cancer (CRC). We retrospectively enrolled 313 CRC patients aged ≥65 years after curative surgery and classified them into an all-risk GNRI (≤98) group and a no-risk GNRI (>98) group. Kaplan-Meier analysis showed overall survival was significantly worse in the all-risk GNRI group than in the no-risk GNRI group ($P = 0.009$). Multivariable analyses showed low GNRI (≤98) was an independent risk factor for postoperative complications ($P = 0.048$) and overall survival ($P = 0.001$) in the patients. Among the complications, the incidence of surgical site infection, in particular, was significantly higher in the all-risk GNRI group ($P = 0.008$). In conclusion, low preoperative GNRI (≤98) was associated with increased postoperative complications and poor prognosis. Preoperative GNRI can be used as an identifier for potential high-risk group of morbidity and mortality in elderly CRC patients.

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer-related mortality worldwide[1,2]. According to the World Health Organization GLOBOCAN database, there were an estimated 1,849,518 new CRC cases and 880,792 CRC-related deaths in 2018[3]. As life expectancy increases and the population ages, the number of elderly patients undergoing surgery also increases[4,5]. For instance, in the United States, 60.7% of all the incident CRC patients in 2018 were 65 years or older, and then 81% of the elderly patients and even 64% of the patients aged ≥85 years underwent surgery from 2011 to 2015[3,6].

Elderly patients often have some comorbidities, such as cardiovascular disease and respiratory dysfunction[7,8], and often become malnourished[9,10]. In elderly patients, disease-related malnutrition is associated with increased morbidity and mortality[9–12] and prolonged length of stay in hospital due to decrease in their life activity, performance status, and immune function[11–14].

The Geriatric Nutritional Risk Index (GNRI) is an elderly-specific index that has been proposed to assess the nutrition-related risk of morbidity and mortality for elderly patients in hospital[15,16]. This index was first reported by Bouillanne *et al.* They divided patients into four groups—a major-risk group (GNRI: <82), a moderate-risk group (GNRI: 82–<92), a low-risk group (GNRI: 92–98), and a no-risk group (GNRI: >98)—and suggested that the risk of infectious complications or mortality was significantly higher in the major-, moderate-, and low-risk groups than in the no-risk group[17]. The GNRI is also used for prognosis of chronic diseases[18–20], and in recent

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Variables	Total (n = 313)
Age (years)*	73 (65–94)
Sex (male/female)	201/112
BMI (kg/m^2)*	22.2 (8.7–33.6)
ALB (g/dL)*	3.8 (1.9–4.8)
WBC (/μL)*	5610 (2360–13700)
CRP (mg/dl)*	0.07 (0.04–9.07)
Preoperative CEA (ng/mL)*	3 (0.1–321)
Preoperative CA19–9 (U/mL)*	11 (0–2505)
Tumor location (colon/rectum)	239/74
Degree of differentiation (tub1/tub2/por/pap/muc)	132/156/14/1/10
Depth of tumor invasion (Tis/T1/T2/T3/T4)	29/73/58/136/17
Lymph node metastasis (N0/N1/N2)	225/65/23
Lymphatic vessel invasion (ly0/ly1/ly2/ly3)	117/163/29/4
Venous invasion (v0/v1/v2/v3)	238/62/12/1
Distant metastasis (none/HEP/PUL/LYM/PER)	304/6/0/1/2
TNM stage (0/I/II/III/IV)	29/115/77/83/9
Complication (CD grade) (none/I/II/III/IV/V)	249/23/23/16/2/0
GNRI	99.0 (62.2–122.6)

Table 1. The characteristics of 313 patients with CRC. CRC = colorectal cancer, BMI = body mass index, ALB = serum albumin, WBC = white blood cell, CRP = C-reactive protein, CEA = carcinoembryonic antigen, CA19–9 = carbohydrate antigen 19–9, tub1 = well differentiated adenocarcinoma, tub2 = moderately differentiated adenocarcinoma, por = poorly differentiated adenocarcinoma, pap = papillary adenocarcinoma, muc = mucinous adenocarcinoma, HEP = liver, PUL = pulmonary, LYM = extra-regional lymph node, PER = peritoneal, TNM = tumor-node-metastasis, CD = Clavien-Dindo, GNRI = geriatric nutritional risk index, Asterisk values indicate median (range).

years, it has been reported as a useful screening tool to predict prognosis for not only chronic diseases but also malignant tumors[21–24].

To date, there have been no reports on the relationship between GNRI and short- or long-term outcomes for elderly patients with CRC after surgery. Therefore, in this study, we investigated whether preoperative GNRI was associated with postoperative complications and prognosis for elderly patients with CRC who underwent curative surgery.

Methods

Patients and datasets. This study retrospectively enrolled 313 patients with CRC aged ≥65 years who underwent curative resection at Osaka University Hospital from August 2007 to December 2012. Patients who underwent curative resection for distant metastases were also included. Exclusion criteria for patients were as follows: (1) aged <65 years, (2) surgery for recurrence, (3) multiple primaries, (4) colitic cancer, (5) received neoadjuvant chemotherapy, (6) underwent transanal endoscopic microsurgery, (7) cases which lacked any of preoperative laboratory data or pathological findings described in Table 1. Two hundred and eighteen elderly CRC patients who underwent curative surgery at Osaka International Cancer Institute from January 2007 to December 2013 were enrolled according to the same criteria as described above, and analyzed as another dataset.

Clinicopathological factors such as age, sex, body mass index (BMI), serum albumin level (ALB), white blood cells, C-reactive protein (CRP), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), primary tumor location, distant metastases, pathological findings, and postoperative complications were collected from patients' medical records. Clinicopathological factors were classified according to the eighth edition of the Union for International Cancer Control (UICC) tumor-node-metastasis (TNM) classification[25]. Preoperative blood samples, height, and weight data were obtained within 7 days before surgery. Postoperative complications were classified according to the Clavien-Dindo (CD) grade[26]. In the present study, we examined those of CD grade ≥II[27].

After surgery, all patients were followed up according to the Japanese guidelines[28]. They were regularly examined using tumor markers, such as CEA and CA19-9, and screened using computed tomography every 3–6 months and colonoscopy every 1–2 years.

Nutritional assessment by GNRI. The GNRI is a simple and objective screening tool for elderly patients' nutrition-related risk calculated using ALB, present body weight (PBW), and ideal body weight (IBW). IBW in this study was calculated as follows: IBW = height^2 (m) × 22. The GNRI formula is: GNRI = 1.487 × ALB (g/L) + 41.7 × PBW/IBW (kg)[17].

Statistical analysis. Continuous variables were expressed as means ± standard deviation (SD) values. Differences between the classified GNRI groups and clinicopathological factors were analysed using chi-squared test or Fisher's exact test. The relationships between GNRI and each complication were also analysed by the same tests. Continuous variables with parametric distribution were analysed by Student's t-test or analysis of variance

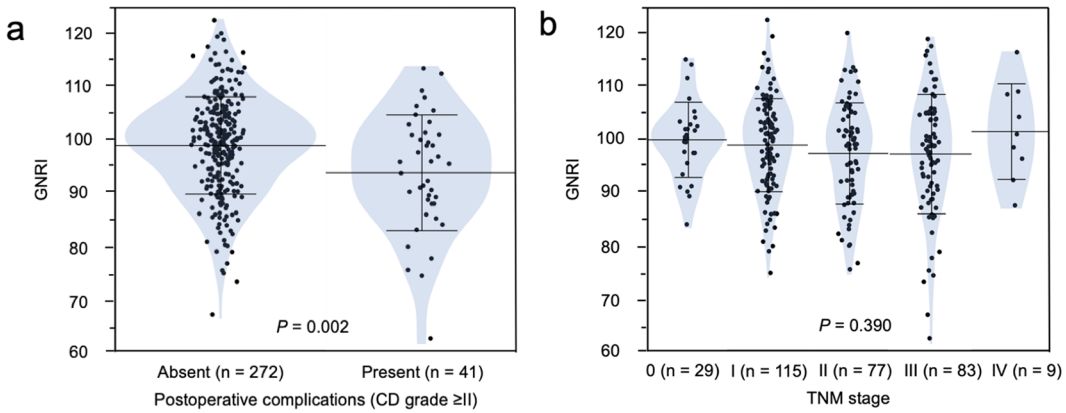

Figure 1. Distribution of GNRI according to (**a**) postoperative complications (Clavien-Dindo grade ≥II) and (**b**) TNM stages. (**a**) GNRI is significantly lower in patients with postoperative complications than in those without them ($P = 0.002$). (**b**) GNRI is not significantly different among TNM stages ($P = 0.390$).

(ANOVA). Overall survival (OS) curves were plotted using the Kaplan–Meier method and compared using the generalised log-rank test. Univariate and multivariate analyses were performed using a logistic regression model to identify independent risk factors for postoperative complications and using a Cox proportional hazards regression model for OS. Receiver operating characteristic (ROC) curve analysis was used to predict the optimal cut-off value of GNRI for OS[29]. In this study, we used the patients who were followed for at least one year as evaluable for the prognostic outcome to perform the ROC analysis. Then, the value was provided based on Youden's index[30]. Two-sided $P < 0.05$ was considered to denote statistical significance. All statistical analyses were performed using JMP software version 13 (SAS Institute Inc., Cary, NC, USA).

Compliance with ethical review. This study was performed in accordance with the principles of Declaration of Helsinki. This study was approved by the Institutional Review Boards of Osaka University and Osaka International Cancer Institute, and informed consent was obtained from all patients according to the guideline.

Results

Patient characteristics. Two hundred one (64.2%) males and 112 (35.8%) females were included in this study. Characteristics of all patients are listed in Table 1. The median age was 73 years (range, 65–94 years). There were 29 (9.3%) patients with stage 0, 115 (36.7%) patients with stage I, 77 (24.6%) patients with stage II, 83 (26.5%) patients with stage III, and 9 (2.9%) patients with stage IV. The stage IV cases included liver metastasis (6 cases), extra-regional lymph node metastasis (1 case), and peritoneal dissemination (2 cases). Sixty-four (20.4%) patients had postoperative complications and 41 (13.1%) patients had those of CD grade ≥II.

Distribution and classification of GNRI. The mean preoperative GNRI in 313 patients with CRC was 98.2 ± 9.6. Differences in the distribution of preoperative GNRI according to postoperative complications (CD grade ≥II) and TNM stages are shown in Fig. 1. The mean GNRI was 98.9 ± 9.2 in patients who had postoperative complications and 93.8 ± 11.0 in those without complications. There was a significant difference in preoperative GNRI between the two groups ($P = 0.002$) (Fig. 1a). The mean GNRI was 99.9 ± 7.1 in stage 0, 98.9 ± 8.8 in stage I, 97.3 ± 9.6 in stage II, 97.2 ± 11.3 in stage III, and 101.4 ± 9.1 in stage IV. There were no significant differences in preoperative GNRI among these stages ($P = 0.390$) (Fig. 1b).

A previous study showed that a good sensitivity for risk prediction was found only for a GNRI cut-off value of 98[31]. ROC curve analysis for OS also showed that the optimal cut-off value of GNRI was 98.082 (area under the curve = 0.574, sensitivity = 0.591, and specificity = 0.569) (Fig. 2).

According to previous studies[23,24,31] and the ROC analysis, we classified patients more simply into an all-risk GNRI (≤98) group (137 patients, 43.8%) and a no-risk GNRI (>98) group (176 patients, 56.2%), instead of the four classifications of Bouillanne *et al.*[17]. The relationship between GNRI status and clinicopathological factors in all patients is shown in Table 2. Between the all- and no-risk GNRI groups, there were no significant differences in age, white blood cells, preoperative CEA, preoperative CA19-9, tumor location, degree of differentiation, depth of tumor invasion, lymph node metastasis, lymphatic vessel invasion, venous invasion, distant metastasis, or TNM stage. However, there were significant differences in sex, BMI, ALB, CRP, and postoperative complications (CD grade ≥II) between the two groups.

Postoperative complications (CD grade ≥ II). A total of 41 patients had postoperative complications defined CD grade ≥II. These were surgical site infection (11 cases), ileus (8 cases), anastomotic leakage (7 cases), intra-abdominal abscess (5 cases), colitis (4 cases), pneumonia (3 cases), and urinary infection (3 cases). More patients had postoperative complications in the all-risk GNRI group (18.2%) than in the no-risk GNRI group (9.1%) ($P = 0.018$). The relationship between GNRI status and each complication was examined, and surgical site infection occurrence was higher in the all-risk GNRI group than in the no-risk GNRI group ($P = 0.008$) (Table 3).

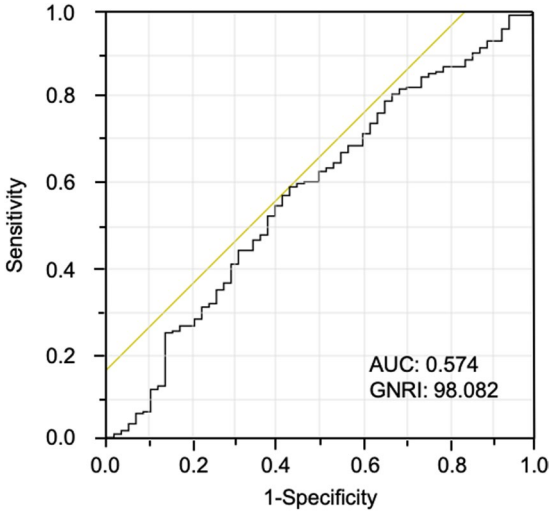

Figure 2. Receiver operating characteristic (ROC) curve analysis of GNRI for overall survival in elderly patients with colorectal cancer. The ROC curve shows that the optimal cut-off value of GNRI is 98.082. Area under the curve for GNRI is 0.574. The sensitivity is 0.591, and the specificity is 0.569.

Variables	GNRI		
	All-risk ≤ 98 (n = 137)	No-risk > 98 (n = 176)	*P*-value
Age (≥73/<73)	83/54	88/88	0.062
Sex (male/female)	77/60	124/52	0.009*
BMI (≥22/<22)	30/107	139/37	<0.001*
ALB (≥3.5/<3.5)	75/62	169/7	<0.001*
WBC (≥10000/<10000)	4/133	2/174	0.254
CRP (≥1/<1)	20/117	11/165	0.014*
Preoperative CEA (≥5/<5)	45/92	51/125	0.462
Preoperative CA19–9 (≥38/<38)	22/115	17/159	0.090
Tumor location (colon/rectum)	102/35	137/39	0.485
Degree of differentiation (tub1, tub2/por, pap, muc)	127/10	161/15	0.691
Depth of tumor invasion (Tis, T1, 2/T3, 4)	71/66	89/87	0.825
Lymph node metastasis (present/absent)	41/96	47/129	0.530
Lymphatic vessel invasion (present/absent)	90/47	106/70	0.321
Venous invasion (present/absent)	35/102	40/136	0.563
Distant metastasis (present/absent)	3/134	6/170	0.517
TNM stage (0-II/III, IV)	95/42	126/50	0.665
Complication (CD grade ≥II) (present/absent)	25/112	16/160	0.018*

Table 2. The relationship between GNRI status and clinicopathological factors in the elderly patients with CRC. GNRI = geriatric nutritional risk index, CRC = colorectal cancer, BMI = body mass index, ALB = serum albumin, WBC = white blood cell, CRP = C-reactive protein, CEA = carcinoembryonic antigen, CA19–9 = carbohydrate antigen 19–9, tub1 = well differentiated adenocarcinoma, tub2 = moderately differentiated adenocarcinoma, por = poorly differentiated adenocarcinoma, pap = papillary adenocarcinoma, muc = mucinous adenocarcinoma, TNM = tumor-node-metastasis, CD = Clavien-Dindo, Asterisk values indicate P-values < 0.05.

Univariate and multivariate analyses of clinicopathological factors for postoperative complications (CD grade ≥II) are shown in Table 4. According to the univariate analysis, high CRP ($P = 0.032$), tumor location (rectum) ($P = 0.005$), and low GNRI ($P = 0.019$) were significantly correlated with the complications. The multivariate analysis showed that tumor location (rectum) ($P = 0.005$) and low GNRI ($P = 0.048$) were independent risk factors for postoperative complications.

Survival analysis and risk factors for mortality. The median follow-up was 60.5 months (range, 1–137 months). Thirty-two death events and 105 censoring cases were recorded in the all-risk GNRI group, and 26 death events and 150 censoring cases were recorded in the no-risk GNRI group. OS rate was significantly worse in the

Variables	Total (n = 313) (%)	GNRI		
		All-risk ≤ 98 (n = 137)	No-risk > 98 (n = 176)	*P*-value
All	41 (13.1)	25	16	0.018*
Surgical site infection	11 (3.5)	9	2	0.008*
Ileus	8 (2.6)	4	4	0.720
Leakage	7 (2.2)	3	4	0.961
Intra-abdominal abscess	5 (1.6)	3	2	0.463
Colitis	4 (1.3)	3	1	0.202
Pneumonia	3 (1.0)	1	2	0.711
Urinary infection	3 (1.0)	2	1	0.423

Table 3. The relationship between GNRI status and postoperative complications (CD grade ≥II) in the elderly patients with CRC. GNRI = geriatric nutritional risk index, CD = Clavien-Dindo, CRC = colorectal cancer, Asterisk values indicate P-values < 0.05.

Variables	Univariate			Multivariate		
	RR	95%CI	*P*-value	RR	95%CI	*P*-value
Age (≥73/<73)	1.518	0.770–2.993	0.228			
Sex (male/female)	1.233	0.610–2.489	0.560			
BMI (≥22/<22)	0.880	0.456–1.697	0.702			
WBC (≥10000/<10000)	3.436	0.609–19.386	0.162			
CRP (≥1/<1)	2.625	1.086–6.344	0.032*	2.471	0.980–6.231	0.055
Preoperative CEA (≥5/<5)	1.730	0.882–3.396	0.111			
Preoperative CA19–9 (≥38/<38)	1.544	0.632–3.772	0.340			
Tumor location (rectum/colon)	2.672	1.345–5.308	0.005*	2.741	1.356–5.539	0.005*
Degree of differentiation (por, pap, muc/tub1, tub2)	1.292	0.420–3.974	0.655			
Depth of tumor invasion (T3, 4/Tis, T1, 2)	1.758	0.898–3.439	0.100			
Lymph node metastasis (present/absent)	1.067	0.518–2.199	0.860			
Lymphatic vessel invasion (present/absent)	1.333	0.661–2.690	0.422			
Venous invasion (present/absent)	1.794	0.886–3.632	0.105			
Distant metastasis (present/absent)	0.825	0.100–6.773	0.858			
GNRI (≤98/>98)	2.232	1.140–4.372	0.019*	2.001	1.002–3.999	0.048*

Table 4. The univariate and multivariate analyses of predictors for postoperative complications (CD grade ≥II). CD = Clavien-Dindo, RR = risk ratio, CI = confidence interval, BMI = body mass index, WBC = white blood cell, CRP = C-reactive protein, CEA = carcinoembryonic antigen, CA19–9 = carbohydrate antigen 19-9, por = poorly differentiated adenocarcinoma, pap = papillary adenocarcinoma, muc = mucinous adenocarcinoma, tub1 = well differentiated adenocarcinoma, tub2 = moderately differentiated adenocarcinoma, GNRI = geriatric nutritional risk index, Asterisk values indicate P-values < 0.05.

all-risk GNRI group than in the no-risk GNRI group ($P = 0.009$) (Fig. 3). The 3- and 5-year OS rates in the all-risk GNRI group were 89.0% and 79.6%, and those in the no-risk GNRI group were 92.2% and 86.0%, respectively.

The univariate and multivariate analyses of clinicopathological factors for OS are shown in Table 5. According to the univariate analysis, sex (male) ($P < 0.001$), high preoperative CEA ($P < 0.001$), high preoperative CA19-9 ($P < 0.001$), depth of tumor invasion (T3, 4) ($P < 0.001$), lymph node metastasis ($P < 0.001$), lymphatic vessel invasion ($P < 0.001$), venous invasion ($P < 0.001$), distant metastasis ($P < 0.001$), and low GNRI ($P = 0.010$) were significantly correlated with OS. The multivariate analysis showed that sex (male) ($P < 0.001$), high preoperative CEA ($P = 0.044$), lymph node metastasis ($P = 0.025$), distant metastasis ($P = 0.030$), and low GNRI ($P = 0.001$) were independent prognostic risk factors for OS.

Analyses of the complications and prognosis in the other dataset based on GNRI. To verify whether GNRI could be used for the prediction, we performed the other center study using the patient data in Osaka International Cancer Institute. Characteristics of all the patients in the other dataset are listed in Supplementary Table 1. The median age was 72 years (range, 65–88 years). Fifty-three (24.3%) patients had postoperative complications of CD grade ≥II. The mean preoperative GNRI in the patients was 101.9 ± 9.2.

The univariate and multivariate analyses for the complications in the other center study are shown in Supplementary Table 2. According to the univariate analysis, tumor location (rectum) ($P = 0.001$), venous invasion ($P = 0.047$), and low GNRI ($P < 0.0001$) were significantly related to the complications. The multivariate analysis showed that tumor location (rectum) ($P = 0.001$) and low GNRI ($P < 0.001$) were independent risk factors for the complications.

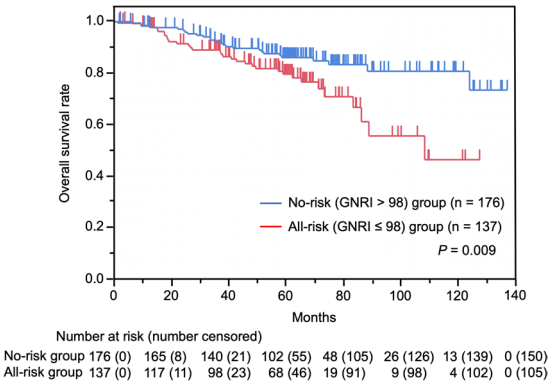

Figure 3. Kaplan-Meier analysis of overall survival according to GNRI. Overall survival rate is significantly worse in the all-risk GNRI (≤98) group than in the no-risk GNRI (>98) group ($P = 0.009$).

Variables	Univariate			Multivariate		
	HR	95%CI	*P*-value	HR	95%CI	*P*-value
Age (≥73/<73)	1.627	0.957–2.851	0.073			
Sex (male/female)	2.992	1.545–6.519	<0.001*	3.668	1.850–8.137	<0.001*
BMI (≥22/<22)	1.224	0.727–2.100	0.451			
Preoperative CEA (≥5/<5)	2.446	1.454–4.102	<0.001*	1.875	1.018–3.416	0.044*
Preoperative CA19–9 (≥38/<38)	3.387	1.817–5.974	<0.001*	1.963	0.953–3.806	0.067
Tumor location (rectum/colon)	1.217	0.654–2.140	0.520			
Degree of differentiation (por, pap, muc/tub1, tub2)	1.581	0.607–3.404	0.318			
Depth of tumor invasion (T3, 4/Tis, T1, 2)	3.112	1.786–5.700	<0.001*	1.282	0.624–2.749	0.506
Lymph node metastasis (present/absent)	3.036	1.808–5.097	<0.001*	1.976	1.089–3.624	0.025*
Lymphatic vessel invasion (present/absent)	2.963	1.564–6.217	<0.001*	1.062	0.463–2.552	0.890
Venous invasion (present/absent)	3.371	1.983–5.658	<0.001*	1.844	0.997–3.385	0.051
Distant metastasis (present/absent)	8.131	3.303–17.262	<0.001*	3.055	1.122–7.507	0.030*
GNRI (≤98/>98)	1.988	1.179–3.384	0.010*	2.429	1.414–4.230	0.001*

Table 5. The univariate and multivariate analyses of prognostic factors for overall survival. HR = hazard ratio, CI = confidence interval, BMI = body mass index, CEA = carcinoembryonic antigen, CA19–9 = carbohydrate antigen 19–9, por = poorly differentiated adenocarcinoma, pap = papillary adenocarcinoma, muc = mucinous adenocarcinoma, tub1 = well differentiated adenocarcinoma, tub2 = moderately differentiated adenocarcinoma, GNRI = geriatric nutritional risk index, Asterisk values indicate *P*-values < 0.05.

Furthermore, Kaplan-Meyer curve analysis in the other center study also showed that OS rate was significantly worse in the all-risk GNRI group than in the no-risk GNRI group ($P = 0.002$) (Supplementary Fig. 1). The 3- and 5-year OS rates in the all-risk GNRI group were 83.7% and 77.6%, and those in the no-risk GNRI group were 96.7% and 91.1%, respectively. The univariate and multivariate analyses for OS are shown in Supplementary Table 3. According to the univariate analysis, lymph node metastasis ($P = 0.004$), distant metastasis ($P = 0.001$), and low GNRI ($P = 0.005$) were significantly related to OS. The multivariate analysis also showed that lymph node metastasis ($P = 0.035$), distant metastasis ($P = 0.042$), and low GNRI ($P = 0.048$) were independent prognostic risk factors for OS.

Discussion

Our results showed that GNRI was associated with increased postoperative complications and poor prognosis of CRC in elderly patients. Malnutrition has been found to be an important risk factor for postoperative morbidity and mortality in malignant tumors[32,33]. The Nutritional Risk Index (NRI), calculated by ALB, PBW, and usual body weight, was proposed by Buzby *et al.* to evaluate the association between nutrition and postoperative complications[34,35]. However, the NRI is often difficult to use in elderly patients[36] because half of them do not remember their own usual body weight[37]. Thus, Bouillanne *et al.* replaced usual body weight with IBW in the formula of NRI and developed a simple screening tool specific for elderly patients to predict nutrition-related risk of morbidity and mortality[17]. GNRI was developed in the population of which elderly patients aged ≥65 years were admitted into a geriatric rehabilitation care hospital due to rehabilitation after fractures, neurologic diseases, cardiovascular diseases, and postinfectious diseases and also reported to be significantly correlated with ALB, prealbumin, weight, and BMI[17].

There are several methods for assessing nutritional status, such as BMI, prognostic nutritional index, skeletal muscle mass index, and subjective global assessment. While these measures are relevant for the prognosis of

cancer[38–41], optimal cut-off values remain to be elucidated. Additionally, subjective global assessment is based on many subjective factors, and expert knowledge is required to use it[41].

In contrast, the advantage of GNRI is that it is an objective and easily available predicting tool. The classification value of GNRI has already been proposed[17]. Moreover, this index is calculated using ALB, height, and body weight, which are usually measured on admission.

Previously, GNRI was considered as a prognostic predictor for length of stay in hospital[31] and chronic diseases in elderly patients, such as those with heart failure[18] or chronic obstructive pulmonary disease[19], or those undergoing haemodialysis[20]. Recently, GNRI has been reported to be useful as a predictor for morbidity and mortality in patients with cancer. Li *et al*. reported that lower GNRI value was associated with severe postoperative complications, including liver failure, and poor OS in elderly patients with hepatocellular carcinoma[21]. Kushiyama *et al*. suggested that GNRI < 92 was a risk factor for postoperative complications in elderly patients with gastric cancer[22]. Bo *et al*. indicated that GNRI ≤ 98 could be an indicator of poor survival in elderly patients with oesophageal cancer treated with radiotherapy[23]. Miyake *et al*. also reported that GNRI could be a prognostic predictor in elderly patients with non-metastatic renal cell carcinoma, and those with GNRI ≤ 98 had significantly worse cancer-specific survival (CSS) than those with GNRI > 98[24].

Some reports used the modified GNRI classification according to the complications[22,42], OS[23], CSS[24] and length of hospital stay[31], and some reports used the four-group classification proposed by Bouillanne *et al*.[21,43]. In this study, we divided the patients more simply into two groups by the GNRI value 98 based on the ROC analysis and these previous studies[23,24]. Cereda *et al*. also suggested that only a GNRI cut-off value of 98 had good sensitivity for risk prediction[31]. Our results showed that GNRI was related to the complications and prognosis of CRC, and it was considered that our classification was appropriate.

Postoperative complications after CRC resection have been reported to be associated with poor oncologic outcomes, even if they are mild or moderate (CD grade II)[27]. For this reason, we considered not only severe complications (CD grade $\geq$III) but all complications of CD grade $\geq$II in the present study.

To the best of our knowledge, this is the first study to investigate the relationship between GNRI and outcomes in elderly patients with CRC. Our study demonstrated that low preoperative GNRI ($\leq$98) was correlated with increased postoperative complications (CD grade $\geq$II) and worse OS compared with high GNRI ($>$98) and that low GNRI was an independent risk factor for morbidity and mortality. In addition, although we examined the relationship between GNRI and TNM stages, no significant correlation between them was found. Therefore, we considered that GNRI was also an independent prognostic factor that did not depend on TNM stage.

Several studies have suggested that preoperative nutritional status is an independent risk factor for anastomotic leakage and wound infection in patients with CRC[44,45]. Our study also showed that GNRI was a significant risk factor for wound infection, but it was not a risk factor for anastomotic leakage. Our result obtained for anastomotic leakage might be due to the small number of cases, and these may have been more influenced by tumor location and surgical procedure. Some studies also showed that enhanced recovery after surgery protocol was associated with decreased postoperative complications[46] and improved survival in CRC[47]. Appropriate management of nutritional status before and after surgery may be important to improve surgical risk and prognosis.

Low ALB is correlated with poor prognosis of cancer[48]. ALB is a known indicator of nutritional status[49], and malnutrition impairs various functions, such as immunity, digestive tract function, and wound healing[50]. Deficiency of these functions increases the risk of infection and postoperative complications[51,52], and an immunosuppressed condition leads to inadequate anti-tumor immunological reaction[53,54]. Furthermore, ALB is also influenced by inflammation[49], and systemic inflammation is associated with poor prognosis of cancer[55]. On the other hand, the PBW/IBW ratio used in GNRI, which replaces the PBW/usual body weight ratio indicating weight loss, might be interpreted as reflecting the degree of frailty and cachexia associated with poor prognosis in elderly patients[56]. Thus, the GNRI, which combines factors of ALB and body weight, may predict nutrition-related risk better than ALB alone.

There are some limitations to our study. First, this study was a retrospective study evaluated only a small number of patients and institutes, and also affected by some selection and information bias. Prospective multicenter studies should be performed. Second, there is no single definition of elderly patients. While we defined elderly patients as those aged $\geq$ 65 years in the present study, the life span has extended and the number of patients aged$>$80 years has been increasing. Similar analyses may also have to be performed in patients aged $>$80 years. Third, our study did not assess the influence of smoking behavior because of lack of the information. Smoking is well known as a risk factor of malnutrition, postoperative complications, and poor cancer prognosis[57–59]. In contrast, there is no consensus on the association between smoking and BMI or body weight[59,60]. How smoking actually influences on GNRI status and our findings is not clear, and further research including smoking status is necessary to make it more meaningful and accurate.

In conclusion, our study demonstrated that low preoperative GNRI value ($\leq$98) was associated with increased postoperative complications and poor prognosis in patients with CRC aged $\geq$65 years after curative surgery. Preoperative GNRI can be a useful tool to identify high-risk population of morbidity and mortality in elderly patients with CRC.

Data availability

The dataset used and analysed in the present study is available from the corresponding author on reasonable request.

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Author contributions

M.S., N.M., M.M. and Y.D. contributed to the conception and design of this study. M.S., T.O., H.T. and H.Y. collected the data. M.S., M.U., C.M. and T.M. analysed and interpreted the data. M.S., N.M. and S.F. wrote the manuscript. All authors discussed the results and approved the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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