CANCER DIAGNOSIS & PROGNOSIS
1: 479-484 (2021) doi: 10.21873/cdp.10064

Prognostic Utility of Geriatric Nutritional Risk Index After Curative Resection of Colorectal Cancer: A Propensity Score-matched Study

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Abstract. *Background/Aim: The geriatric nutrition risk index (GNRI) is a presumptive prognosticator in a variety of carcinomas. We investigated whether it similarly predicts outcomes of elderly patients with colorectal cancer (CRC). Patients and Methods: A total of 904 older adults (≥65 years) undergoing radical resections of CRC between April 2011 and December 2015 proved eligible for study. Each was grouped by preoperative status (cut-off point, 98) as low-level or normal GNRI, using propensity score matching to compare rates of complications, disease-free survival (DFS), and overall survival (OS). Results: After matching (n=127, each group), those with low-level (vs. normal) GNRI values experienced significantly more complications (p=0.001), and 5-year survival was significantly poorer (DFS: p=0.006; OS: p=0.002). Conclusion: In elderly patients with resected CRC, preoperative GNRI may have significant prognostic merit.*

Colorectal cancer (CRC) ranks third among all cancers and claims the second highest frequency of cancer-related deaths worldwide (1). Although surgical intervention is the core treatment (2), malnutrition may ostensibly delay wound healing and postoperative recovery and worsen postoperative mortality in elderly patients with CRC (3). Malnutrition is common in this demographic, due to tumor-related or non-tumor factors. Various studies of patients with CRC have shown that standard gauges of adverse nutritional status, namely neutrophil-to-lymphocyte ratio (NLR), prognostic nutritional index (PNI), and modified Glasgow prognostic score (mGPS), are predictive of a poorer prognosis (4-6).

The geriatric nutritional risk index (GNRI) is a metric adapted for the elderly by Bouillanne *et al*. (2005) (7), based on the nutritional risk index (NRI) that Buzby *et al*. devised (8). Its values are computed using serum albumin level, present weight, and ideal weight. The prognostic utility of GNRI has already been tested in older patients with heart failure, required hemodialysis, and chronic obstructive pulmonary disease (9-11). Recent studies have also linked the GNRI prognostically to assorted cancers of the kidney (renal cell), lung, esophagus, and liver (hepatocellular) (12-16). Some studies have also implicated the GNRI in CRC prognosis (17, 18), including one source exploring its prognostic implications in synchronous CRC liver metastasis (19). However, such analyses have been relatively small and have not truly confirmed an association between GNRI and postoperative CRC prognosis.

In the present investigation, we analyzed postoperative complication rates, recurrences, and prognosis after resection of CRC in older patients (≥65 years), using propensity score matching (PSM) on a larger scale than in previous studies.

Patients and Methods

Population selection and characteristics. We retrospectively reviewed clinical data from 984 patients of advanced age (≥65 years), each undergoing radical CRC resection between April 2011 and December 2015 at Saitama Medical University International Medical Center. Those with recurrent CRC, synchronous malignancy, or squamous cell carcinoma were excluded, leaving 904 cases for analysis. Written informed consent was granted by all suitable enrollees, and the Ethics Committee at the center approved our study protocol. Resected tumors were categorized using the

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Key Words: Geriatric nutritional risk index, colorectal cancer, elderly, prognosis.

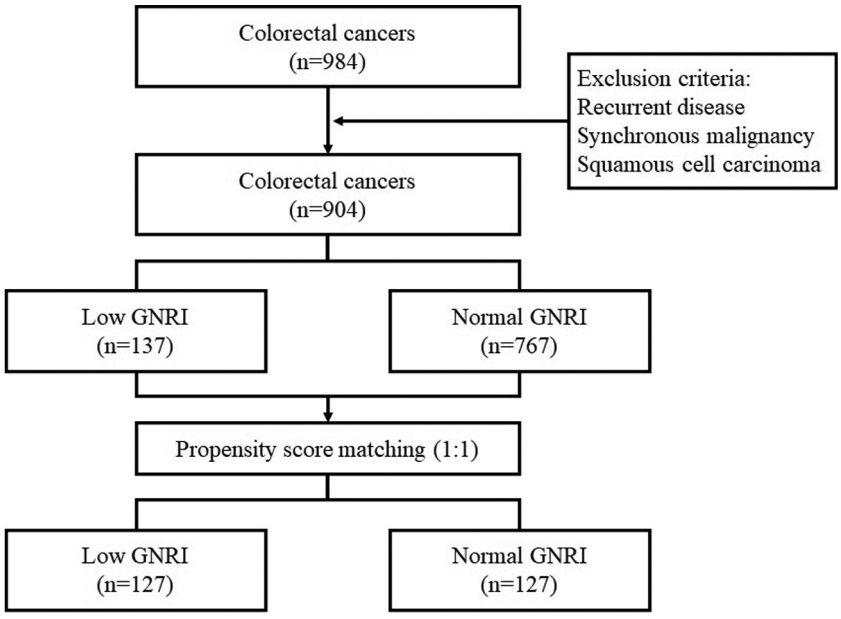

Figure 1. *Schematic of study design.*

Union for International Cancer Control (UICC), 8th edition tumor-node-metastasis (TNM) classification system. Postoperative complications were graded according to Clavien-Dindo criteria (20).

GNRI calculation. The specific formula for GNRI was as follows: 14.89 × serum albumin (g/dl) + 41.7 × [preoperative body weight (kg)/ideal body weight (kg)]. Ideal body weight was determined using a body mass index of 22 kg/m^2. If preoperative body weight exceeded ideal body weight, this ratio was set to 1 (7). A value ≤98 separated low-level from normal GNRI.

Statistical analysis. All computations relied on open-source software (EZR; R Foundation for Statistical Computing, Vienna, Austria), invoking PSM to minimize group bias. A 1:1 match without replacement was performed through nearest available matching, with caliper set at 0.2. Each patient was propensity scored in a logistic regression model centered on 10 covariates, including sex, age, American Society of Anesthesiologists physical status (ASA-PS), serum CEA level, tumor attributes (location, size, histotype), lymphatic invasion, venous invasion, and TNM stage. After matching, logistic regression analysis was performed to determine group differences in complication rates and survival. Differences in categorical variables were assessed by Chi-square or Fisher's exact test, and survival rates (DFS, OS) were estimated *via* the Kaplan–Meier method. Significance was set at $p<0.05$.

Results

A total of 904 older patients (≥65 years) were selected for study, each undergoing radical resection of CRC. Only 137 patients (15.2%) of low-level status emerged, the vast majority (767/904, 84.8%) showing normal GNRI values (>98).

We first conducted a single-factor analysis, comparing patients in low-level (n=137) and normal (n=767) GNRI groups. Multiple group-wise background differences were subsequently identified. At low-level (vs. normal) GNRI, the proportion of men was significantly reduced (48.9% *vs*. 61.6%; $p=0.008$), and subjects were significantly older (75.44±6.55 *vs*. 73.29±5.93; $p<0.001$). Likewise, there were significant group differences in ASA-PS ($p=0.001$), CEA elevation (CEA ≥5: 50.4% *vs*. 32.3%; $p<0.001$), tumor size (≥50 mm: 63.5% *vs*. 34.6%; $p<0.001$), and tumor histotype (combined rates of mucinous or poorly differentiated adenocarcinoma and signet-ring cell carcinoma: 13.1% *vs*. 4.3%; $p<0.001$). However, tumor location (colon: 68.6% *vs*. 63.5%; $p=0.287$), lymphatic invasion (27.7% *vs*. 23.6%; $p=0.330$), venous invasion (59.9% *vs*. 55.9%; $p=0.402$), and pathologic stage ($p=0.062$) did not differ significantly.

The two groups were then propensity score matched at 1:1 ratio, each accruing 127 members (Figure 1). The significant group-wise differences observed in the above parameters (sex, age, ASA-PS, CEA value, tumor size, and tumor histotype) were no longer manifested thereafter (Table I).

When comparing postoperative complication rates (Clavien-Dindo grade ≥II) prior to matching, the low-level (*vs*. normal) GNRI group showed a significantly higher percentage (22.6% *vs*. 11.1%; $p<0.001$). After PSM, respective complication rates were at 24.2% and 7.8%, indicating that a significant difference was sustained ($p=0.001$) (Table I).

Five-year DFS rates were also compared by group, prior to PSM [low-level GNRI, 57.2% (95%CI=0.469-0.662); normal

Table I. *Analysis of CRC parameters in elderly patients (>65 years) relative to GNRI.*

Variable	Before PSM			After PSM		
	Low-level GNRI (<98)	Normal GNRI (>98)	*p*-Value	Low-level GNRI (<98)	Normal GNRI (>98)	*p*-Value
Gender, n	137	767		127	127	
Male	67 (48.9%)	469 (61.1%)		67 (52.8%)	65 (51.2%)	
Female	70 (51.1%)	298 (38.9%)	0.008	60 (47.2%)	62 (48.8%)	0.900
Age, yr	75.44±6.55	73.29±5.93	<0.001	74.90±6.09	75.33±6.14	0.573
ASA-PS						
1	20 (14.6%)	180 (23.5%)		20 (15.7%)	16 (12.6%)	
2	92 (67.2%)	524 (68.3%)		83 (65.4%)	98 (77.2%)	
3	25 (18.2%)	63 (8.2%)	0.001	24 (18.9%)	13 (10.2%)	0.084
CEA						
<5	68 (49.6%)	520 (67.8%)		66 (52.0%)	65 (51.2%)	
>5	69 (50.4%)	247 (32.2%)	<0.001	61 (48.0%)	62 (48.8%)	1.000
Tumor location						
Colon	94 (68.6%)	487 (63.5%)		84 (66.1%)	83 (65.4%)	
Rectum	43 (31.4%)	280 (36.5%)	0.287	43 (33.9%)	44 (34.6%)	1.000
Tumor size						
<50 mm	50 (36.5%)	502 (65.4%)		50 (39.4%)	50 (39.4%)	
>50 mm	87 (63.5%)	265 (34.6%)	<0.001	77 (60.6%)	77 (60.6%)	1.000
Tumor histotype						
pap/tub	119 (86.9%)	734 (95.7%)		116 (91.3%)	114 (89.8%)	
muc/por/sig	18 (13.1%)	33 (4.3%)	<0.001	11 (8.7%)	13 (10.2%)	0.831
Lymphatic invasion						
No	99 (72.3%)	586 (76.4%)		95 (74.8%)	103 (81.1%)	
Yes	38 (27.7%)	181 (23.6%)	0.330	32 (25.2%)	24 (18.9%)	0.289
Venous invasion						
No	55 (40.1%)	338 (44.1%)		52 (40.9%)	55 (43.3%)	
Yes	82 (59.9%)	429 (55.9%)	0.402	75 (59.1%)	72 (56.7%)	0.799
Pathological stage						
0	2 (1.5%)	22 (2.9%)		2 (1.6%)	4 (3.1%)	
I	25 (18.2%)	223 (29.1%)		25 (19.7%)	20 (15.7%)	
II	53 (38.7%)	237 (30.9%)		48 (37.8%)	55 (43.3%)	
III	53 (38.7%)	262 (34.2%)		49 (38.6%)	46 (36.2%)	
IV	4 (2.9%)	23 (3.0%)	0.062	3 (2.4%)	2 (1.6%)	0.746
Postoperative complication						
Clavien-Dindo >garde II	31 (22.6%)	85 (11.1%)	<0.001	31 (24.2%)	10 (7.8%)	0.001

CRC: Colorectal cancer; GNRI: geriatric nutritional risk index; PSM: propensity score matching; ASA-PS: American Society of Anesthesiologists physical status; CEA: carcinoembryonic antigen; Pap: papillary adenocarcinoma; Tub: tubular adenocarcinoma; Muc: mucinous adenocarcinoma; Por: poorly differentiated adenocarcinoma; Sig: signet-ring cell carcinoma.

GNRI, 76.5% (95%CI=0.730-0.797); $p<0.001$) (Figure 2) and after PSM [low-level GNRI, 58.5% (95%CI=0.478-0.678); normal GNRI, 72.3% (95%CI=0.622-0.801); $p=0.006$] (Figure 3), based on 127 paired cases. Significant differences were observed in both instances. The same was true regarding 5-year OS rates assessed before PSM [low-level GNRI, 68.0% [95% CI: 0.578-0.762]; normal GNRI, 85.4% (95%CI=0.821-0.882); $p<0.001$] (Figure 4) and after PSM [low-level GNRI, 68.1% (95%CI=0.574-0.766); normal GNRI, 81.1% (95% CI=0.710-0.880); $p=0.002$] (Figure 5).

Outcomes were thus significantly worse for the low-level (*vs*. normal) GNRI group in terms of both DFS and OS at 5 years, with or without PSM.

Discussion

Elderly patients with CRC are often at risk of malnutrition, owing to transit-impaired poor oral intake or tumor-related muscle and weight loss. Another reported impact of malnutrition is the heightening of postoperative complications through diminished immunity, delayed wound healing, and prolonged postoperative recovery (21).

There are a number of nutritional indices (NLR, NPI, mGPS) (4-6) available for clinical use. The NRI forged by Buzby *et al*. is a calculated figure reliant on serum albumin level, present body weight, and usual body weight (8). Because it is often difficult to decipher usual body weight in

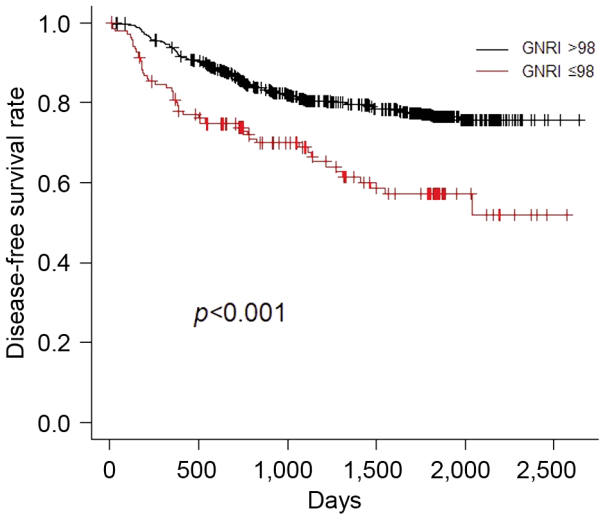

Figure 2. *Disease-free survival plotted by group (prior to propensity score matching).*

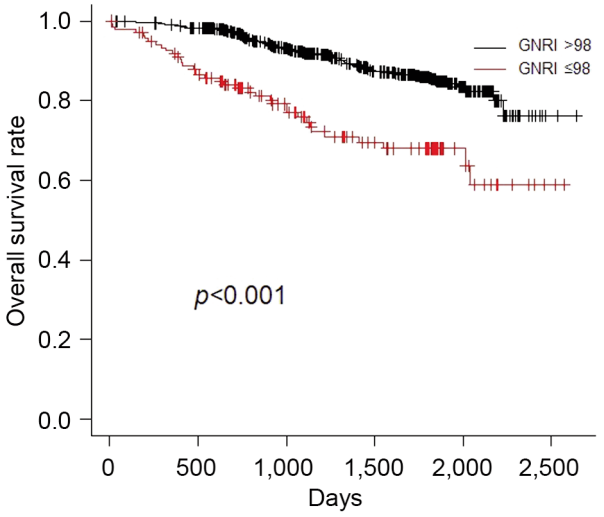

Figure 4. *Overall survival plotted by group (prior to propensity score matching).*

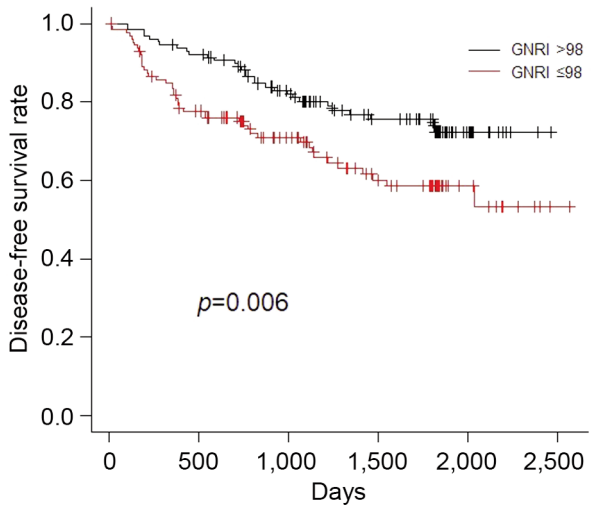

Figure 3. *Disease-free survival plotted by group (after propensity score matching).*

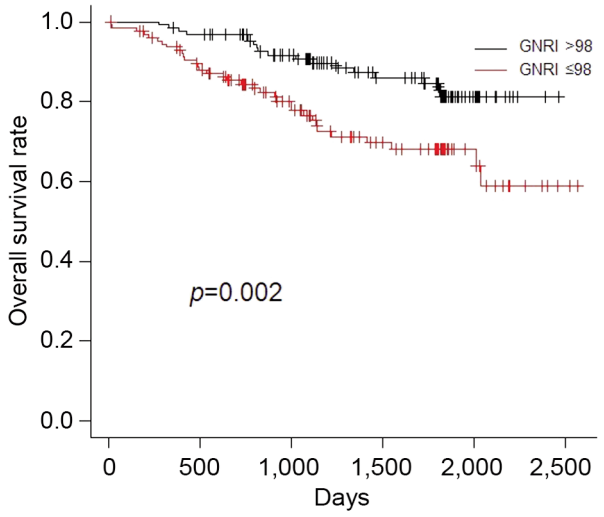

Figure 5. *Overall survival plotted by group (after propensity score matching).*

older adults, Bouillanne *et al*. created the GNRI, which instead substitutes ideal body weight for usual body weight (7). The GNRI has since been amply examined, establishing its prognostic utility in elderly patients with heart failure, required hemodialysis, and chronic obstructive pulmonary disease (9-11). Recent studies have additionally linked GNRI values to many malignant tumors. Low-level GNRI has been found to correlate with outcomes of kidney (renal cell), lung, esophageal, and liver (hepatocellular) carcinomas (12-16). Although not fully clarified, a relation between GNRI and CRC prognosis has also been cited in some reports (17, 18). Herein, we have recruited a relatively large study population, using PSM to compare patient outcomes.

Ultimately, our data indicate that at or below a set threshold (≥98), GNRI values in elderly patients with CRC are predictive of increased postoperative complications, greater recurrence risk, and poorer prognosis. As a factor in GNRI calculation, serum albumin is actually the most widely used measure of nutritional status (21). Low albumin itself is considered a poor sign in the context of cancer (22). In

addition to albumin, low levels of prealbumin, a rapid turnover protein that reflects nutritional status, has been reported to be a prognostic factor in postoperative patients with colorectal cancer (23). Fueled by malnutrition (*i.e.*, low albumin), postoperative complications in patients with CRC reportedly lead to increased recurrence rates and poorer prognosis (24). The immune suppression that malnutrition promotes may blunt tumor immunoreactivity as well. Immunity and malignant tumor progression are closely related; and impaired immunocompetence is a known prognostic factor in patients with malignant tumors (25, 26), perhaps affecting the present study outcomes.

Serum albumin is not only a direct measure of nutritional adequacy, it may also reflect states of systemic inflammation. Albumin is synthesized in the liver and thus declines under conditions of active inflammation (27). Malignant tumors are known to produce cytokines that trigger inflammation (28). In the presence of cancer, systemic inflammation appears to correlate with poor prognosis (29).

The GNRI component of body weight (present weight/ideal weight) may also signal loss of muscle mass, typical of elderly patients. Once muscle mass declines to the point of sarcopenia, marked by diminished strength and physical function, the likelihood of postoperative complications and worsened prognosis is greater in the context of CRC (30). Overall, the GNRI seems to precisely parallel the above prognostic factors.

There are certain study limitations to acknowledge, one being the retrospective, single-center design. Despite the use of PSM, the potential for selection/information bias and confounding remained, requiring a multicenter prospective approach to overcome. Another drawback was our inability to compare the GNRI with other nutritional indices mentioned earlier. This was imposed by the lack of research data, which we hope to rectify in future studies. Finally, we have yet to examine ways of improving patient prognosis in a low-level GNRI scenario. More research is clearly needed going forward.

Conclusion

Our findings show that low-level GNRI values correlate with postoperative complications, tumor recurrence, and prognostic status in elderly patients with CRC. The GNRI is a simple and useful metric for preoperative nutritional assessment. Improved preoperative nutrition and careful postoperative management are important goals in this particular setting.

Conflicts of Interest

The Authors have no competing interests to declare with regard to this study.

Authors' Contributions

MK drafted the manuscript. YH supervised and reviewed its content. TI, SI, AK, TF and SS reviewed the content as well. All Authors have read and approved the final deliverable.

Acknowledgements

The Authors wish to thank BioMed Proofreading LLC for English copyediting.

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Received September 13, 2021
Revised October 11, 2021
Accepted October 12, 2021