Modified Geriatric Nutritional Risk Index in Patients with Pancreatic Cancer

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Abstract

Background: The geriatric nutritional risk index (GNRI) was recently reported not as a nutritional assessment tool but as a useful index for predicting prognosis in various diseases including malignancies. The modified nutritional geriatric risk index (mGNRI), incorporating C-reactive protein instead of albumin, was developed as a novel index and provides a more appropriate prognostic index than the original GNRI. This study aimed to establish the prognostic significance of the mGNRI compared with the GNRI in patients with pancreatic cancer.

Methods: This retrospective study included 137 patients who had undergone pancreatectomy for pancreatic cancer. The enrolled patients were grouped as high mGNRI (≥ 85.3) or low mGNRI (< 85.3), and high GNRI (≥ 92) or low GNRI (< 92) for prognostic analysis based on cutoff values.

Results: The 5-year overall survival and recurrence-free survival of patients in the high mGNRI group were significantly longer than those in the low mGNRI group. Similarly, the 5-year overall survival and recurrence-free survival of patients in the high GNRI group were significantly longer than those in the low GNRI group. The concordance index of the mGNRI to predict the 5-year overall survival was greater than that of the GNRI. Multivariate analysis revealed that the mGNRI was an independent prognostic factor for patients with pancreatic cancer ($P = 0.004$).

Conclusions: The mGNRI might be a useful prognostic factor for patients with pancreatic cancer and might predict prognostic outcomes more accurately than the GNRI.

Background

The nutritional status and systemic inflammatory response of patients have a striking influence on the development and progression of cancer, and a negative correlation exists between nutrition status and inflammation. Among various nutritional indicators, the geriatric nutritional risk index (GNRI) consisting of serum albumin level and patient height and body weight was originally developed to assess the risks of mortality and morbidity in older hospitalized patients [1]. However, in the last decade, the GNRI has gained attention as a simple nutritional indicator to predict the prognosis of patients with cancer and several studies with a cohort including not only older patients but also non-older patients reported that the GNRI was a useful prognostic factor in lung cancer, esophageal cancer, gastric cancer, and pancreatic cancer [2–5].

Recently, the modified geriatric nutritional risk index (mGNRI) incorporating C-reactive protein (CRP), a well-known acute-phase reactant in inflammatory responses, instead of serum albumin was reported to be useful for the prediction of early recurrence and prognosis in patients with esophageal cancer [6]. Additionally, they reported that the mGNRI was a more appropriate prognostic index than the GNRI or other nutritional or inflammatory markers in esophageal cancer. However, the prognostic influence of the mGNRI in patients with pancreatic cancer has not been reported.

Therefore, this study aimed to evaluate the prognostic significance of the mGNRI compared with GNRI in patients with pancreatic cancer.

Methods

Patients

This study included 137 patients with histologically confirmed pancreatic ductal adenocarcinoma who had undergone pancreatectomy at our hospital between July 2005 and December 2019. The resectability status of patients enrolled in this study was resectable pancreatic cancer in 135 patients and borderline resectable pancreatic cancer in 2 patients. No patient had distant metastasis in this study. The clinicopathological findings of the patients were collected from their medical records. Histopathological findings, including tumor size, lymph node involvement, and histological differentiation were classified in accordance with the 8th edition of the International Union Against Cancer Tumor-Node-Metastasis classification system [7]. All patients in this study were of Japanese ethnicity.

Modified Geriatric Nutritional Risk Index and Geriatric Nutritional Risk Index

In accordance with a previous report, the mGNRI was calculated using the following formula: $mGNRI = [14.89/CRP \text{ (mg/dL)}] + [41.7 \times \text{actual body weight/ideal body weight}]$. The serum CRP level was set as 0.3 mg/dL when the patients' serum CRP level was less than 0.3 mg/dL because the normal upper limit of serum CRP is 0.3 mg/dL [6].

The following formula reported by Bouillanne et al. was used to calculate the GNRI: $GNRI = [14.89 \times \text{serum albumin level (g/dL)}] + [41.7 \times \text{actual body weight/ideal body weight}]$. In accordance with their report, the cutoff value of GNRI in this study was set as 92 [1].

The values of preoperative serum CRP level, preoperative serum albumin level, and patient height and body weight obtained within 1 week prior to surgery were used in this study. The value of a patient's actual body weight divided by the ideal body weight was set as 1 when the patient's weight exceeded the ideal body weight [1].

Statistical analysis

Chi-squared or Fisher's exact probability tests for categorical variables, and the Mann-Whitney *U*-test for continuous variables were used to evaluate differences between two groups. The 5-year overall survival (OS) curves and 5-year recurrence free survival (RFS) curves were constructed using the Kaplan–Meier method, and differences between survival curves were examined by the log-rank test. Receiver operating characteristic analysis was used to determine the cutoff value of mGNRI. The concordance index (C-index) was used to evaluate the mGNRI and GNRI to predict the 5-year OS. Univariate and multivariate analyses were performed using Cox proportional hazard regression models to determine factors with prognostic significance for OS. *P*-values of less than 0.05 were considered statistically significant. All

statistical analyses were performed using IBM SPSS Statistics for Windows (version 24; IBM, Armonk, NY, USA).

Results

The median follow-up period in this study was 27.9 months (range: 1.7–177.4 months). The mean mGNRI of the patients in this study was 82.6 ± 14.2 . The cutoff value of mGNRI was set at 85.3 using receiver operating characteristic curve analysis to predict the 5-year OS. Based on the cutoff value of mGNRI, the patients were divided into high mGNRI or low mGNRI groups.

Table 1 shows comparisons of the clinicopathological characteristics between the high mGNRI and low mGNRI groups. The body mass index, preoperative albumin level, and preoperative lymphocyte count in the high mGNRI group were significantly higher than those in the low mGNRI group, whereas the presence of lymph node involvement in the low mGNRI group was significantly more common than that in the high mGNRI group. The 5-year OS and RFS curves were stratified according to the mGNRI (Figure 1). The 5-year OS rate and median survival time (MST) were significantly higher in the high mGNRI group (38.7% and 41.1 months) compared with the low mGNRI group (16.1% and 16.4 months; $P < 0.001$, Figure 1a). The 5-year RFS and MST were significantly higher in the high mGNRI group (30.9% and 21.5 months) compared with the low mGNRI group (15.1% and 8.1 months; $P < 0.001$, Figure 1b). When the patients were grouped into high GNRI and low GNRI groups, the 5-year OS and 5-year RFS rates in the high GNRI group were significantly better than those in the low GNRI group (5-year OS rate: 35.9% vs 13.0%, $P < 0.001$; 5-year RFS rate: 30.7% vs 0.0%, $P < 0.001$, Figure 2a, b). Figure 3 shows the C-index for the prediction of the 5-year OS rate of mGNRI and GNRI using the area under the curve by ROC analysis. The C-index of mGNRI (0.631) was greater than that of GNRI (0.587).

Table 1

Comparison of clinicopathological characteristics between high and low mGNRI groups in patients with pancreatic cancer.

Characteristics	High mGNRI group (n = 91)	Low mGNRI group (n = 46)	P-value
Age (years), median (range)	72 (47–85)	72.5 (44–85)	0.616
Sex (male), n (%)	51 (56%)	30 (65.2%)	0.302
Body mass index (kg/m ²), median (range)	22.7 (18.8–32.5)	19.4 (13.7–29.4)	<0.001
Tumor size (mm), median (range)	27.0 (11.0–85.0)	28.0 (5.0–60.0)	0.791
Tumor location (pancreatic head), n (%)	40 (44.0%)	16 (34.8%)	0.302
Histological grading (G2 ^a or G3 ^b), n (%)	42 (46.2%)	25 (54.3%)	0.365
Lymph node involvement (present), n (%)	44 (48.4%)	36 (78.3%)	0.001
Residual tumor (present), n (%)	10 (11.0%)	3 (6.5%)	0.543
ASA-PS (1 or 2, %)	78 (85.7%)	33 (71.7%)	0.065
Preoperative albumin, g/dL, median (range)	4.1 (2.6–4.9)	3.8 (2.1–4.9)	0.001
Preoperative lymphocyte count, median (range)	1640 (140–3800)	1405 (400–6660)	0.004
Preoperative CA19-9, U/mL, median (range)	53.3 (0.7–3270.7)	106.7 (0.7–3435.0)	0.121
Neoadjuvant chemotherapy (present), n (%)	15 (16.5%)	4 (8.7%)	0.297
Adjuvant chemotherapy (present), n (%)	52 (59.1%)	28 (60.9%)	0.842
Continuous variables are expressed as the median and range.			
^a G2: moderately-differentiated.			
^b G3: poor-differentiated.			
mGNRI, modified geriatric nutritional risk index; ASA-PS, American Society of Anesthesiologists physical status; CA19-9, carbohydrate antigen 19-9.			

Multivariate analysis revealed that mGNRI was an independent prognostic factor (hazard ratio [HR]: 2.137; 95% confidence interval [CI]: 1.283–3.560; $P = 0.004$), as well as sex (HR: 1.797; CI: 1.082–2.983; $P = 0.023$), histological grading (HR: 1.965; CI: 1.205–3.203; $P = 0.007$), lymph node metastasis (HR: 2.870; CI: 1.661–4.957; $P < 0.001$), residual tumor (HR: 2.637; CI: 1.239–5.612; $P = 0.012$), preoperative CA19-9

(HR: 1.823; CI: 1.043–3.184; $P = 0.035$), and adjuvant chemotherapy (HR: 0.457; CI: 0.278–0.751; $P = 0.002$) in patients with resected pancreatic cancer (Table 2).

Table 2
Univariate and multivariate analyses of prognostic factors for overall survival in patients with pancreatic cancer.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>P</i>	HR	95% CI	<i>P</i>
Age (≥ 70 vs <70), years	1.120	0.721–1.738	0.614			
Sex (male vs. female)	1.684	1.070–2.649	0.024	1.797	1.082–2.983	0.023
BMI (<22 kg/m ² vs ≥ 22 kg/m ²)	1.636	1.061–2.522	0.026	1.303	0.792–2.144	0.297
Tumor size (≥ 20.0 mm vs <20.0 mm)	2.036	1.100–3.767	0.024	1.547	0.795–3.012	1.547
Histological grading for tumor (G2 ^a or G3 ^b vs G1 ^c)	1.568	1.023–2.402	0.039	1.965	1.205–3.203	0.007
Lymph node metastasis (present vs absent)	2.904	1.809–4.663	<0.001	2.870	1.661–4.957	<0.001
Residual tumor (present vs absent)	2.596	1.404–4.798	0.002	2.637	1.239–5.612	0.012
ASA-PS (3 vs 1 or 2)	1.909	1.153–3.160	0.012	1.439	0.819–2.530	0.206
Preoperative CA19-9 (≥ 274.9 U/mL vs <274.9 U/mL)	2.393	1.470–3.896	<0.001	1.823	1.043–3.184	0.035
Neoadjuvant chemotherapy (present vs. absent)	0.787	0.407–1.524	0.478			
Adjuvant chemotherapy (present vs. absent)	0.688	0.447–1.061	0.090	0.457	0.278–0.751	0.002
PNI (high: ≥ 47.7 vs low: <47.7)	1.373	0.892–2.114	0.147			
GNRI (high: ≥ 92 vs low: <92)	2.607	1.609–4.225	<0.001	1.818	0.985–3.357	0.056

^aG2: moderately-differentiated.

^bG3: poor-differentiated.

^cG1: well-differentiated.

HR, hazard ratio; CI, confidence interval; BMI, body mass index; ASA-PS, American Society of Anesthesiologists physical status; CA19-9, carbohydrate antigen 19-9; GNRI, geriatric nutritional risk index; mGNRI, modified geriatric nutritional risk index.

	Univariate analysis			Multivariate analysis		
mGNRI (high: ≥ 85.3 vs low: < 85.3)	2.491	1.617– 3.837	< 0.001	2.137	1.283– 3.560	0.004
^a G2: moderately-differentiated.						
^b G3: poor-differentiated.						
^c G1: well-differentiated.						
HR, hazard ratio; CI, confidence interval; BMI, body mass index; ASA-PS, American Society of Anesthesiologists physical status; CA19-9, carbohydrate antigen 19-9; GNRI, geriatric nutritional risk index; mGNRI, modified geriatric nutritional risk index.						

Discussion

Nutritional status greatly affects the outcomes of cancer patients, and thus several nutritional markers have been reported as prognostic factors for various malignancies. The GNRI was reported to be a significantly useful and simple nutritional-related prognostic index that consisted of serum albumin level and patient height and body weight to predict survival outcomes in patients with gastrointestinal tract cancers, including esophageal cancer, gastric cancer, and colorectal cancer [3, 5] [8] [9]. Furthermore, pancreatic cancer patients with a low GNRI had significantly poorer prognostic outcomes than patients with high GNRI [2] [10]. Serum albumin, a protein used in clinical tests to assess nutritional condition, has been used to evaluate the morbidity and mortality of patients indicated for surgical treatment or as a prognostic predictive factor of various diseases including malignancies [11, 12] [13]. However, the American Society for Parenteral and Enteral Nutrition recently reported that serum albumin is an inflammatory marker associated with nutritional risk during nutritional assessments, and therefore, should not be used as a nutritional marker [14]. As an alternative, the GNRI is an inflammatory index, which was reported originally as a nutritional assessment tool. CRP is an acute protein involved in systemic inflammation, which can be also used as an indicator to predict survival in patients with cancer [15, 16]. A negative correlation was reported between the production of CRP and albumin, although both proteins are synthesized by hepatocytes [17, 18]. The mGNRI developed by Kouzu et al. is a novel prognostic index that uses inverse CRP instead of albumin, which is based on the reported negative correlation [6]. Furthermore, they suggested that the mGNRI was an independent prognostic factor for patients with esophageal cancer. However, the relationship between the mGNRI and prognostic outcomes in pancreatic cancer patients remains unclear. Therefore, the present study was conducted to evaluate the prognostic usefulness of the mGNRI compared with the GNRI in patients with pancreatic cancer. We found that patients with a high mGNRI had a significantly better prognosis than those with a low mGNRI and that the mGNRI was a predictive prognostic factor for patients with resected pancreatic cancer. Furthermore, the mGNRI was indicated to be more appropriate than the original GNRI when predicting the prognosis of patients with resected pancreatic cancer.

Interleukin (IL)-6 and other proinflammatory cytokines, including tumor necrosis factor, are released by inflammatory cells in the tumor microenvironment in response to tissue necrosis and the presence of tumor cells [19]. These cytokines, especially IL-6, were also shown to promote tumorigenesis by regulating multiple signaling pathways related to apoptosis, proliferation, angiogenesis, invasiveness, and metastasis [20]. Moreover, the synthesis of CRP is promoted in hepatocytes via activation by IL-6. Subsequently, CRP returns to the tumor microenvironment and promotes the autocrine growth of malignant tumors as an opsonin [19]. Therefore, serum CRP levels in patients with cancer might represent the biological behavior of cancer tissues because of the close relationship between IL-6 and CRP. In contrast, the reduced synthesis of albumin in the liver of patients with cancer is caused by the combined effects of inflammation and non-inflammatory factors such as inadequate protein and caloric intake; therefore, albumin may not reflect cancer progression as accurately as CRP in patients with cancer. Indeed, in renal cell carcinoma, CRP had a higher area under the curve for predicting OS compared with albumin [21]. These findings support the results observed in the current study.

There were several limitations in this study. It was a retrospective study with a small population of patients of East Asian ethnicity, and therefore, the findings might have led to bias and limited their generalizability. The cutoff value of the mGNRI in this study was set at 85.3 by ROC analysis. However, the optimal cutoff value in patients with pancreatic cancer remains unclear. A large prospective study involving individuals with various ethnicities is necessary to confirm our findings.

Conclusions

The mGNRI might be a useful prognostic factor that predicts the prognosis of patients with pancreatic cancer more accurately than the original GNRI.

Abbreviations

GNRI, geriatric nutritional risk index; mGNRI, modified geriatric nutritional risk index; C-reactive protein, CRP; OS, overall survival; RFS, recurrence-free survival; Concordance index, C-index; median survival time, MST; interleukin-6, IL-6.

Declarations

Ethics approval and consent to participate

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional review board of ethics committee and national research committee with the 1964 Helsinki declaration and its later amendments. The Tottori University Hospital Ethics Committee approved this study (No. 21A125) and informed consent was waived by the Tottori University Hospital Ethics Committee.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated during and analysed during the current study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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There was no funding source.

Authors' contributions

Study conception: T. Sakamoto; study design: T. Sakamoto; data acquisition: T. Sunaguchi, K. Goto; quality control of data and algorithms: T. Hanaki and K. Kihara; data analysis and interpretation: T. Sakamoto and K. Miyatani; statistical analysis: M. Morimoto, Y. Murakami and Y. Shishido; manuscript preparation: T. Sakamoto; manuscript editing: T. Matsunaga, M. Yamamoto and N. Tokuyasu; manuscript review: Y. Fujiwara; final approval of the article: all authors.

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Figures

Figure 1

Figure 1

Overall survival and recurrence free survival curves in patients with pancreatic cancer based on mGNRI.

Overall survival (a), recurrence free survival (b). One patient lacked data related to recurrence free survival curves.

Abbreviations: mGNRI, modified geriatric nutritional risk index.

Figure 2

Figure 2

Overall survival and recurrence free survival curves in patients with pancreatic cancer based on mGNRI.

Overall survival (a), recurrence free survival (b). One patient lacked data related to recurrence free survival curves.

Abbreviations: GNRI, geriatric nutritional risk index.

Figure 3

Figure 3

Prediction of 5-year overall survival in patients with pancreatic cancer. C-indices of mGNRI and GNRI.

Abbreviations: mGNRI, modified geriatric nutritional risk index; GNRI, geriatric nutritional risk index.