

Original Article



Pre-treatment Nutritional Risk Assessment by NRS-2002 Predicts Prognosis in Patients With Advanced Biliary Tract Cancer: A Single Center Retrospective Study

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OPEN ACCESS

Received: Apr 22, 2022

Revised: Jul 20, 2022

Accepted: Jul 24, 2022

Published online: Jul 28, 2022

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Funding

This study was supported by a grant from the Health Fellowship Foundation (to Oh SE) and the grant from the National R&D Program for

ABSTRACT

We investigated the predictors of survival in patients with advanced BTC according to their baseline nutritional status estimated by the Nutritional Risk Screening (NRS)-2002. From September 2006 to July 2017, we reviewed the data of 601 inpatients with BTC. Data on demographic and clinical parameters was collected from electronic medical records, and overall survival (OS) and progression-free survival were analyzed using the Kaplan-Meier method and the stepwise Cox regression analysis. Patients with an NRS-2002 score of ≤ 2 , 3, and ≥ 4 were respectively classified as “no risk,” “moderate risk,” “high risk.” Following initial NRS-2002 score, 333 patients (55%) were classified as “no-risk,” 109 patients (18%) as “moderate-risk,” and 159 patients (27%) as “high-risk.” Survival analysis demonstrated significant differences in the median OS: “no-risk”: 12.6 months (95% confidence interval [CI], 11.5–13.7); “moderate-risk”: 6.1 months (95% CI, 4.3–8.0); and “high-risk”: 3.9 months (95% CI, 3.2–4.6) ($p < 0.001$). NRS-2002 score was an independent factor for OS (hazard ratio [HR], 1.616 for “moderate-risk”, 95% CI, 1.288–2.027, $p < 0.001$; HR, 2.121 for “high-risk”, 95% CI, 1.722–2.612, $p < 0.001$), along with liver metastasis, peritoneal seeding, white blood cell count, platelet count, neutrophil-to-lymphocyte ratio, cholesterol, carcinoembryonic antigen, and carbohydrate antigen 19-9. In conclusion, baseline NRS-2002 is an appropriate method for discriminating those who are already malnourished and who have poor prognosis in advanced BTC patient. Significance of these results merit further validation to be integrated in the routine practice to improve quality of care in BTC patients.

Keywords: Biliary tract cancer; Survival; Nutrition risk screening 2002 (NRS-2002); Prognosis

INTRODUCTION

Biliary tract cancer (BTC) represents an aggressive malignancy that arises from the biliary tree-lining epithelia. BTC can manifest at various anatomical locations of intra- and extrahepatic bile duct, gall bladder and ampulla of Vater [1]. BTC is the sixth most common

Cancer Control, Ministry of Health & Welfare, Republic of Korea (to Jeung HC, No. 1420060).

Conflict of Interest

The authors declare that they have no competing interests.

Author Contributions

Conceptualization: Jeung HC; Data curation: Jeung HC, Park JS, Oh SE; Funding acquisition: Oh SE, Jeung HC; Investigation: Park JS, Oh SE; Methodology: Park JS, Oh SE; Project administration: Park JS, Oh SE; Supervision: Jeung HC; Validation: Jeung HC; Visualization: Park JS, Oh SE; Writing - original draft: Oh SE; Writing - review & editing: Park JS, Jeung HC.

cause of cancer-related mortality in Korea, when 7,179 new cases and 4,871 deaths were reported in 2018 [2]. The only potentially curative treatment option is surgical resection. However, only about 30% of patients are resectable at the time of diagnosis. The high recurrence rate following surgery even after adjuvant therapy (about 50%) and the frequent presentation of advanced stage at initial diagnosis (approximately 70%) make palliative chemotherapy the mainstay of treatment. For many years, combination chemotherapy of cisplatin and gemcitabine (GemCis) have been the gold standard of treatment for advanced cancer [3]. However, the median overall survival (OS) was 11.7 months with the overall response rate of just 26% [3].

Prognostic predictors in advanced BTC have received relatively little attention to date [4,5]. Performance status, markers of immunocompetence (such as neutrophil-to-lymphocyte ratio [NLR], white blood cell [WBC] counts, or C-reactive protein levels [CRP]), the primary tumor location, and cancer load (such as metastatic site and number) are some of the suggested ones. However, malnutrition is a serious concern for BTC patients: Most patients are elderly at diagnosis, and they frequently accompany stricture or obstruction at the gastric outlet, duodenum, or pancreatic duct, which lead to early satiety, anorexia, and emesis that necessitate duodenal stent or bypass surgery [6]. Immune dysfunction brought on by malnutrition may manifest as aberrant neutrophil, macrophage, and lymphocyte numbers. All of these components can have an impact on cancer progression, treatment toxicity, and unfavorable impact on survival.

The Nutritional Risk Screening (NRS)-2002 is a tool made to determine the severity of a disease as well as any present probable undernutrition [7]. It is recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN) for use in hospitals and for screening purposes within 48 hours of admission, with a final score of 3 indicating nutritional risk [8]. It has been proven effective in numerous controlled nutrition support trials, which looked at whether this tool could help separate patients who had positive clinical outcomes from those who did not. In addition, baseline nutritional status and nutritional therapies play a significant role in overall patient outcomes and even in outcomes for patients with advanced stage cancer [9-11]. However, to our knowledge, no similar research has been done involving patients with advanced BTC.

Since 2006, our institution has made the NRS-2002 the standard screening tool for all cancer patients upon admission. In this study, we examined the relationships between baseline NRS-2002 scores and prognosis in patients with advanced BTC. Finally, we make the recommendation that the initial NRS-2002 evaluation be used as a tool to enable patient categorization by nutritional risk and to optimize treatment.

MATERIALS AND METHODS

Patient eligibility

At the pancreato-biliary cancer center at Gangnam Severance Hospital, Seoul, Korea, from September 2006 to July 2017, 892 patients received a diagnosis of metastatic or recurrent BTC. Age over 18 years, a histologically confirmed BTC, the presence of systemic disease at the time of presentation or after curative resection, and the availability of electronic medical data were the inclusion criteria for this investigation (including treatment information).

The exclusion criteria were as follows: (1) widespread central nervous system or leptomeningeal metastasis, (2) localized disease for which definitive therapy is indicated, (3) synchronous metastatic malignancies other than BTC or (4) uncontrolled infection, active gastrointestinal bleeding, and severe concurrent medical conditions (e.g., advanced liver cirrhosis or chronic kidney disease), as well as (5) lack of follow-up (FU) or transfer to a different hospital before a decision had been made regarding treatment (including diagnosis only).

Of the 892 patients screened, 601 met the above criteria and were included in the study. The study protocol was approved by the Institutional Review Board (IRB) of the Gangnam Severance Hospital (IRB number: 3-2019-0159). The requirement for patient consent was waived considering the retrospective study design.

Clinical data collection

The following clinical details were collected; age, sex, anthropometric data (weight, height, body mass index [BMI]), disease status (recurrent/metastatic), primary tumor location (gallbladder, intrahepatic or extrahepatic bile duct, ampulla), metastasis sites, Eastern Cooperative Oncology Group-performance status (ECOG-PS), and the presence of diabetes mellitus (DM) or jaundice. The following blood and serum biochemistry data were collected at baseline: WBC, hemoglobin (Hb), platelet, CRP, serum protein, albumin, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase (ALP), and cholesterol. The tumor markers carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 were also collected. The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.

Nutritional risk assessment

In the case of metastatic cancer patients, NRS-2002 scoring and nutrition evaluation were performed at the time of first hospitalization after cancer diagnosis and just before chemotherapy. In the case of recurrent cancer patients, it was performed at the time of first hospitalization after recurrence was confirmed, right before chemotherapy.

The nutritional status data collection, NRS and nutritional counselling were performed by 2 investigators (JSP, SEO), who interviewed patients within 48 hours of hospitalization to prepare weight changes and meal records, and a dietary intake survey and food intake frequency were investigated according to the 24-hour recall method. All the implemented data was stored as separate records. Screening for the risk of malnutrition was conducted using the NRS-2002, in which patients are scored in each of the 2 components (1) undernutrition and (2) disease severity, according to whether they are absent, mild, moderate or severe, giving a total score 0–6, with an adjustment for age of ≥ 70 years [7]. The final scoring of NRS-2002 ranges from 0 to 7.

Moreover, we introduced 2 familiar nutritional indices, prognostic nutritional index (PNI) and nutrition risk index (NRI), for the purpose of correlating these with the NRS-2002 score. PNI [12] was defined as $10 \times \text{serum albumin value (g/dL)} + 0.005 \times \text{peripheral lymphocyte count (/mm}^3\text{)}$. A higher PNI indicates low risk of malnutrition. NRI [13] was calculated as $(1.519 \times \text{serum albumin, g/dL}) + [41.7 \times \text{weight (kg)/ideal body weight (IBW; kg)}]$. IBW was calculated using the Lorentz formulae; i.e., $\text{height (cm)} - 100 - \{[\text{height (cm)} - 150]/4\}$ for men and $\text{height (cm)} - 100 - \{[\text{height (cm)} - 150]/2.5\}$ for women.

Statistical analysis

The hematological and blood chemistry values were transformed to categorical variables according to the upper normal ranges (WBC, Hb, platelet, serum protein, albumin, BUN, AST, ALT, total bilirubin, ALP, cholesterol) or the best cutoff point (CEA, CA19-9, and NLR). The latter were determined using the Contal and O'Quigley method, which calculates the maximum hazard ratio (HR) based on log-rank statistics and estimates the best cutoff value [14].

The OS was defined as the time from the date of diagnosis to death from any cause. Progression-free survival (PFS) was defined as the time from chemotherapy to disease progression or death from any cause. Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test.

Univariate analysis was performed to determine the association of the following prognostic factors with OS: age, sex, disease status, ECOG-PS, primary site, BMI, WBC and lymphocyte count, Hb, platelet count, serum protein, albumin, BUN, AST, ALT, ALP, cholesterol, CEA, CA19-9, NLR, and PLR. Subsequently, stepwise multivariate analysis based on Cox's proportional hazard model was performed, using the significant factors identified through univariate analysis. HRs, 95% confidence intervals (CIs), and chi-square scores were obtained for all regressions. All statistical analyses were performed using PASW Statistics ver. 18.0 (SPSS Inc., Chicago, IL, USA), SAS v. 9.4 (SAS Institute Inc., Cary, NC, USA), and R ver. 3.2.4 (Institute for Statistics and Mathematics, Vienna, Austria; <http://www.R-project.org>). A p value of < 0.05 was considered significant.

RESULTS

Baseline clinical parameters by NRS-2002 risk groups

The median age of the entire patient group (n = 601) was 67 years, and 346 patients (58%) were men. Patients' ages ranged from 30 to 91 years. Forty-three percent of cases were of intrahepatic and perihilar bile duct cancer, 30% were of gallbladder cancer, and the remainder were of distal bile duct and periampullary cancer (27%). Regarding disease state, 65% of patients had untreatable metastatic disease at the time of their diagnosis, whereas others had recurring metastatic disease following prior curative resection. More than half of the patients (57%) had metastases at multiple locations. Twenty-two percent of patients had underlying DM, and 22% of patients had jaundice.

At the time of diagnosis, 199 patients (33%) had experienced involuntary weight loss (amounting to more than 5%) over the past 3 months, and 195 patients (32%) had complained of inappetence persistent for more than 1 week. Upon dividing the patients into nutritional risk groups based on the NRS-2002 score, 333 patients (55%) were classified into "no-risk" (score ≤ 2), 109 patients (18%) were into "moderate-risk" (score = 3), and the remaining patients (27%) were included as "high-risk" (score ≥ 4). Demographic characteristics and clinical parameters were significantly different among the 3 risk groups (**Table 1**). The "high-risk" group included more elderly patients (median age, 73), peritoneal metastasis, and poor ECOG-PS compared with the "no-risk" and "moderate-risk" groups. Blood tests also showed differences between groups; the "high-risk" group showed higher levels of BUN, total bilirubin, ALT, CRP, and CA19-9. Conversely, albumin and total protein levels were significantly lower in the "high-risk" group, which also presented significantly lower Hb levels and lymphocyte counts.

Table 1. Comparison of baseline demographic and clinical parameters by NRS-2002 groups in the patients with advanced biliary tract cancer

Characteristics	A: "No-risk" group (n = 374, 56.3%)	B: "Moderate-risk" group (n = 115, 17.3%)	C: "High-risk" group (n = 175, 26.4%)	p value	p value (post hoc)
Sex				0.391	
Male	224 (59.9)	66 (57.4)	94 (53.7)		
Female	150 (40.1)	49 (42.6)	81 (46.3)		
Age (median)	64 (32–88)	66 (31–91)	70 (30–91)	< 0.001	A = B < C
ECOG-PS				< 0.001	
0–1	281 (75.1)	52 (45.2)	51 (29.1)		
2–4	93 (24.8)	63 (55.8)	124 (70.9)		
Diabetes mellitus				0.499	
No	286 (76.5)	87 (75.7)	141 (80.6)		
Yes	88 (23.5)	28 (24.3)	34 (19.4)		
BMI (kg/m ²)	24.0 (17.3–34.3)	22.4 (17.2–30.1)	21.1 (12.0–35.6)	< 0.001	A > B > C
Disease status				< 0.001	
Recurrent	190 (50.8)	20 (17.4)	35 (20.0)		
Metastatic	184 (49.2)	95 (82.6)	140 (80.0)		
Biochemistry					
Albumin (g/dL)	4.0 (2.4–5.2)	3.7 (1.7–4.9)	3.4 (1.9–4.9)	< 0.001	A > B > C
Protein (g/dL)	7.0 (4.2–9.0)	6.9 (4.8–8.5)	6.7 (4.5–8.7)	< 0.001	A = B > C
CRP (mg/L)	25.5 (0.1–288.5)	34.6 (0.3–244.5)	61.9 (0.2–456.2)	< 0.001	A = B < C
Total cholesterol (mg/dL)	175 (67–580)	176 (85–762)	171 (32–748)	0.738	
BUN (mg/dL)	15.1 (3.0–39.7)	15.8 (3.6–61.9)	19.1 (5.6–82.6)	< 0.001	A = B < C
T.bil (mg/dL)	2.6 (0.1–38.5)	3.4 (0.2–28.5)	5.0 (0.2–40.1)	< 0.001	A = B < C
ALP (IU/L)	206 (45–1,132)	284 (36–1,125)	379 (50–2,212)	< 0.001	A < B < C
AST (IU/L)	56 (11–483)	78 (14–548)	89 (13–905)	< 0.001	A < B < C
ALT (IU/L)	61 (4–485)	78 (6–669)	78 (5–933)	0.077	
Tumor marker					
CEA (ng/mL)	61.7 (0.1–8,281)	59.6 (0.5–2,355)	89.1 (0.7–6,404)	0.782	
CA19-9 (IU/mL)	1,784 (0.6–25,160)	1,680 (0.7–20,210)	4,220 (0.8–20,460)	< 0.001	A = B < C
Complete blood count					
Hb (g/dL)	12.6 (6.5–18.4)	12.2 (5.1–16.2)	11.6 (5.0–15.3)	< 0.001	A = B > C
WBC (10 ³ /uL)	7.19 (2.54–23.66)	8.54 (1.99–21.14)	9.99 (2.61–44.24)	< 0.001	A < B < C
Neutrophil (10 ³ /uL)	4.75 (0.96–20.71)	6.12 (1.01–19.05)	7.66 (1.14–41.20)	< 0.001	A < B < C
Lymphocyte (10 ³ /uL)	1.66 (0.25–3.83)	1.58 (0.42–4.87)	1.39 (0.23–5.28)	< 0.001	A = B > C
Platelet (10 ³ /uL)	251 (67–612)	267 (63–604)	278 (18–630)	0.010	A = B < C
Primary location				< 0.001	
Gallbladder	103 (27.5)	30 (26.1)	62 (35.4)		
Intrahepatic CCC	87 (23.3)	42 (36.5)	50 (28.6)		
Extrahepatic CCC	133 (35.6)	38 (33.0)	56 (32.0)		
Periampullary	51 (13.6)	5 (4.3)	7 (4.0)		
Metastasis site					
Liver	63 (16.8)	27 (23.5)	66 (37.7)	< 0.001	
Lung	50 (13.4)	15 (13.0)	30 (17.1)	0.457	
Peritoneum (carcinomatosis)	50 (13.4)	15 (13.0)	30 (17.1)	0.457	

All data are present as mean (range) or number (%).

NRS, Nutritional Risk Screening; ECOG-PS, Eastern Cooperative Oncology Group-performance status; BMI, body mass index; CRP, C-reactive protein; BUN, blood urea nitrogen; T.bil, total bilirubin; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; Hb, hemoglobin; WBC, white blood cell; Hb, hemoglobin; CCC, cholangiocellular carcinoma.

Correlation between NRS-2002 risk groups and other nutritional parameters

We correlated the NRS-2002 scores with other nutritional indices. The median actual and lean body weight of the entire patient group was 60.0 kg (ranging from 34.0 to 97.0 kg) and 44.1 kg (ranging from 25.3 to 70.2 kg), respectively. The mean BMI of the whole patient group was 22.9 kg/m² (ranging from 12.0 to 35.6 kg/m²), which was negatively correlated with the NRS-2002 risk groups. The "no-risk" group had the highest BMI (24.0 kg/m²), while the mean BMI declined to 22.4 and 21.0 kg/m² in the "moderate-risk" and "high-risk" group, respectively (p < 0.001).

Similarly, the PNI value was negatively correlated with NRS-2002 values. The average PNI values were 48.1 in the “no-risk” group, 45.7 in the “moderate-risk” group, and 40.6 in the “high-risk” group ($p < 0.001$). This trend was also observed with regard to NRI; the average scores for the “no-risk,” “moderate-risk” and “high-risk” were 106.6, 100.0, and 91.8, respectively ($p < 0.001$). These findings suggest that baseline nutritional assessment according to the NRS-2002 is well correlated with laboratory parameters in patients with advanced BTC.

When we selected a cutoff of ≥ 3 as indicative of malnutrition, logistic regression analysis revealed the following independent predictors of malnutrition: old age (> 67) (odds ratio [OR], 1.867, 95% CI, 1.266–2.752, $p = 0.002$), metastatic disease (OR, 2.459, 95% CI, 1.572–3.846, $p = 0.001$), low albumin (< 3.4 g/dL) (OR, 2.402, 95% CI, 1.456–3.963, $p = 0.001$), and ECOG-PS (OR, 2.357, 95% CI, 1.815–3.062, $p < 0.001$).

Prediction of chemotherapy outcome by baseline nutritional assessment

Of all patients, 353 (59%) were treated with a first-line standard GemCis chemotherapy, and 90 patients (19%) received monotherapy with gemcitabine or 5-FU alone. The remaining 158 patients (22%) did not receive any chemotherapy. There was a difference in treatment pattern according to the NRS-2002 risk groups. In the “no-risk” group, 71% of patients received GemCis treatment, while only 35% of the “high-risk” group received the ‘doublet.’

Of the patients who received GemCis chemotherapy, 301 patients progressed after chemotherapy, with a median PFS of 6.3 months (95% CI, 5.4–7.2). Analyzing the PFS according to the NRS-2002 groups, we found that PFS was higher in the “no-risk” group (7.0 months, 95% CI, 5.9–8.1) than in the less favorable groups (“moderate to high-risk” groups, 4.5 months, 95% CI, 3.0–5.7) ($p = 0.013$) (Figure 1A). Median OS was also longer according to the risk groups (“no-risk” group [12.8 months, 95% CI, 11.2–14.3] vs. the other 2 groups [8.6 months, 95% CI, 6.2–12.5]) ($p < 0.001$).

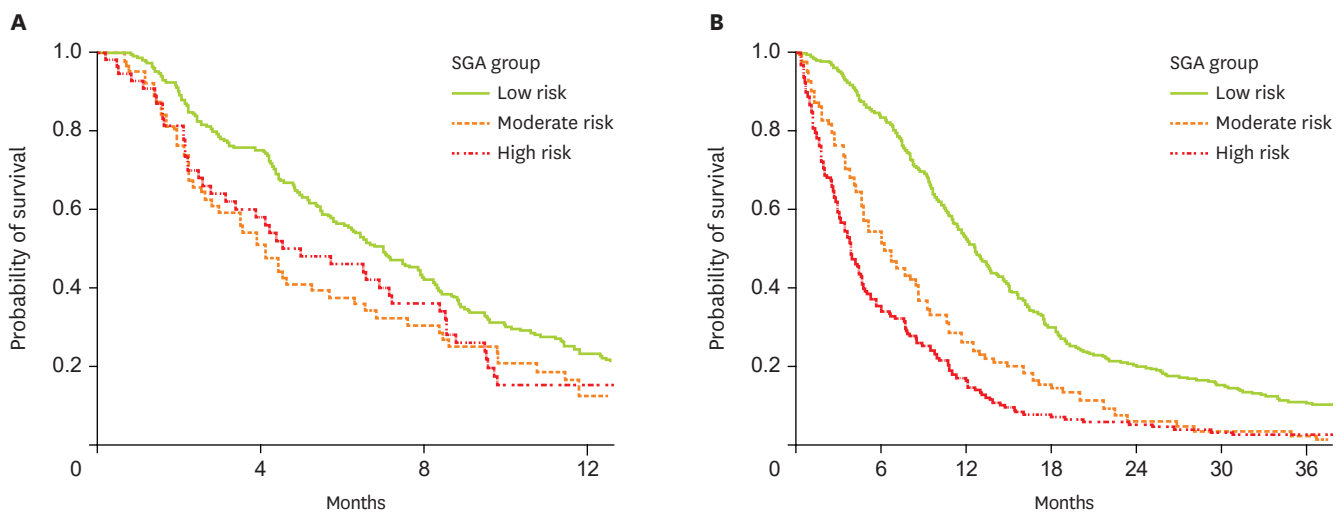


Figure 1. Comparison of survival of patients according to the NRS-2002 risk groups; (A) progression-free survival of the patients who received first-line chemotherapy of GemCis ($n = 353$), (B) overall survival of the whole patients ($n = 601$).

NRS, Nutritional Risk Screening; GemCis, gemcitabine plus cisplatin; SGA, subjective global assessment.

Assessment of prognostic factors of the whole patients

The median FU period of the entire study population was 9.4 months (ranging from 0.1 to 120 months), and the median OS was 9.4 months (95% CI, 8.5–10.3 months). When we compared OS between the NRS-2002 groups, we observed significant differences in cumulative OS. The “no-risk” group had a median OS of 12.6 months (95% CI, 11.5–13.7 months) compared with the “moderate-risk” group (6.1 months, 95% CI, 4.3–8.0) and the “high-risk” group (3.9 months, 95% CI, 3.2–4.6) ($p < 0.001$) (**Figure 1B**).

In the univariate analysis, hematological and blood chemistry values were transformed into categorical variables according to the upper normal values. The cutoff value for CEA, CA19-9, and NLR, which were derived from the Contal and O’Quigley method, were 9 ng/mL, 120 U/mL, and 3.0, respectively. Univariate analysis showed that many factors, including NRS-2002 groups, were associated with OS. These included disease status, metastatic sites, tumor location, ECOG-PS, BMI, and numerous tumor markers and hematologic/blood chemistry parameters

Finally, in the multivariate analysis, NRS-2002 groups were identified as the most significant determinants for OS (HR, 1.611 for “moderate-risk,” 95% CI, 1.285–2.022, $p < 0.001$; HR, 2.129 for “high-risk,” 95% CI, 1.728–2.624, $p < 0.001$). Other independent factors included the presence of liver metastasis and peritoneal metastasis, low WBC, platelet, and cholesterol values, high NLR, and tumor markers (CEA and CA19-9) (**Table 2**).

DISCUSSION

To our knowledge, this study is the first to use the NRS-2002 as a fundamental nutritional evaluation tool for patients with advanced BTC. Prognosis of malignant disease is influenced not only by tumor-specific markers (reflecting cancer burden), but also by more constitutional markers that present the patients’ condition. These markers include performance, weight loss, and immune-competence-reflecting parameters. Among these, ECOG-PS is a well-known, robust prognostic factor in wide variety of cancer types. Weight loss indicates malnutrition and tumor-related inflammation induced by cytokines. High neutrophil and/or low lymphocyte counts can contribute to a tumor-promoting microenvironment characterized by suppressed immune-competence [15]. Therefore, as patients’ nutritional status reflects the constitution of all these parameters, nutritional assessment at the time of diagnosis may stratify patients according to the prognosis.

There is no consensus on the best way of screening the nutritional status of cancer patients, although several nutritional screening tools are available. A large comparative study has shown that the NRS-2002 has better sensitivity or specificity than malnutrition universal screening tool and NRI, compared to subjective global assessment (SGA) [16]. In this regard, we found that NRS-2002 was fully suitable for advanced BTC patients, since many recognized prognostic factors (such as the type of the primary tumor, performance status, and symptoms) are well correlated with NRS-2002 score. The first highlight of our study is that 45% of the patients were at risk of malnutrition (NRS-2002 score ≥ 3). Although we had not compared the NRS-2002 score with PG-SGA, we introduced this cutoff point according to the study of Orell-Kotikangas et al. [17], which showed that a cutoff of ≥ 3 was highly sensitive and specific in indicating malnutrition in head and neck cancer patients. The prevalence of malnutrition in BTC patients has not been previously determined. The PreMio study, which evaluated the prevalence of malnutrition in patients at their first medical oncology visit,

Table 2. Univariate and multivariate analysis of overall survival

Category	Characteristics	Variables	Univariate analysis			Multivariate analysis		
			HR	95% CI	p value	HR	95% CI	p value
Demographic	Age	≥ 67/< 67	1.176	0.997–1.386	0.054			
	Sex	Female/Male	0.966	0.818–1.141	0.684			
	Disease status	Metastatic/Recurrent	1.686	1.414–2.010	< 0.001			
	ECOG-PS	2–4/0–1	2.249	1.902–2.659	< 0.001			
	Primary site	Intrahepatic CCC/Periampullary	1.771	1.309–2.395	< 0.001			
		Extrahepatic CCC/Periampullary	1.441	1.029–2.018	0.034			
		Gallbladder/Periampullary	1.620	1.182–2.221	0.003			
	Liver metastasis	Yes/No	1.732	1.460–2.055	< 0.001	1.701	1.421–2.033	< 0.001
	Lung metastasis	Yes/No	1.380	1.097–1.737	0.006			
	Peritoneal metastasis	Yes/No	1.925	1.584–2.339	< 0.001	1.735	1.416–2.126	< 0.001
DM	Yes/No	0.940	0.771–1.146	0.539				
Hematologic	Hb (g/dL)	< 12.0/≥ 12.0	1.420	1.202–1.667	< 0.001			
	WBC (μL)	< 10,800/≥ 10,800	1.929	1.550–2.400	< 0.001	0.759	0.599–0.961	0.022
	Platelet (μL)	≥ 150K/< 150K	1.358	1.036–1.780	0.027	0.658	0.496–0.874	0.004
	NLR	≥ 3/< 3	1.998	1.691–2.361	< 0.001	1.373	1.138–1.657	0.001
Biochemical	CRP (mg/L)	≥ 6.0/< 6.0	1.920	1.613–2.285	< 0.001			
	Cholesterol (mg/dL)	≥ 139/< 139	0.701	0.582–0.843	< 0.001	0.763	0.630–0.925	0.006
	Protein (g/dL)	< 6.9/≥ 6.9	1.317	1.116–1.555	< 0.001			
	Albumin (g/dL)	< 3.4/≥ 3.4	1.635	1.342–1.992	< 0.001			
	BUN (mg/dL)	≥ 23/< 23	1.397	1.080–1.807	0.011			
	ALP (IU/L)	≥ 123/< 123	1.485	1.254–1.759	< 0.001			
	AST (IU/L)	≥ 30/< 30	1.275	1.076–1.509	0.005			
	ALT (IU/L)	≥ 33/< 33	1.106	0.938–1.303	0.231			
	Bilirubin (mg/dL)	≥ 1.2/< 1.2	1.169	0.986–1.387	0.073			
	CEA (ng/mL)	≥ 9/< 9	1.826	1.524–2.188	< 0.001	1.377	1.136–1.670	0.001
CA19-9 (U/mL)	≥ 120/< 120	1.529	1.294–1.806	< 0.001	1.248	1.045–1.489	0.014	
Nutritional	NRS-2002 risk groups	Moderate/Low	1.895	1.516–2.368	< 0.001	1.616	1.288–2.027	< 0.001
		High/Low	2.615	2.150–3.181	< 0.001	2.121	1.722–2.612	< 0.001
	BMI (kg/m ²)*	< 18.5/18.5–25.0	1.513	1.092–2.097	0.013			
		> 25.0/18.5–25.0	0.901	0.744–1.092	0.290			
Treatment	Chemotherapy	Monotherapy/No treatment	0.543	0.417–0.709	< 0.001			
		Gemcitabine doublet/No treatment	0.438	0.361–0.531	< 0.001			

HR, hazard ratio; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group-performance status; CCC, cholangiocellular carcinoma; DM, diabetes mellitus; Hb, hemoglobin; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; BUN, blood urea nitrogen; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; NRS, Nutritional Risk Screening; BMI, body mass index.

*It is in accordance with the cutoff point by Korean Society for the Study of Obesity, which classified BMI below 18.5 kg/m² as low weight, and ≥ 25 kg/m² as obesity.

reported that 65% of patients with stage M1 liver and bile duct cancer met the criteria of cachexia (characterized by weight loss > 5% or by the dual criteria of BMI < 20 with weight loss of 2%–5%) [18]. However, there are no reports on the incidence of malnutrition in Asian populations, especially in patients with advanced disease. Our data are intermediate between the values extrapolated for hospitalized cancer patients in large surveys of populations with mixed pathologies, which range from 27% to 43% [19].

The second highlight of our study is NRS-2002 score was another factor for prognosis, along with already-known parameters of tumor marker and some hemato-serological factors. Moreover, in the patients who received standard GemCis chemotherapy, NRS-2002 score could effectively discriminate PFS. It is crucial that patients at risk are identified as early as possible to prevent malnutrition and its consequences—treatment failure and poor survival. Accordingly, nutritional intervention should be started as early as possible before any significant weight loss, which could compromise the overall efficacy of nutritional intervention occurred. The ESPEN guidelines on nutrition in cancer patients outline the need for the early detection and treatment of malnutrition [20,21]. In subgroup analysis, OS is 13.4

vs 12.0 months between patients with an NRS-2002 score of 1 and 2, respectively. Although this difference was not statistically significant ($p = 0.301$), we suggest that preventive nutrition intervention be applied even to the patients with an NRS-2002 score of 2. This will be even more important for patients who will evidently face nutritional deterioration during chemotherapy or radiotherapy. The time between initial diagnosis and the start of first-line chemotherapy is typically a few weeks, and it is possible to sufficiently improve nutritional intake during these weeks.

Our data also demonstrated that the NRS-2002 score was practicable to stratify patients for standard chemotherapy. However, the retrospective study design has some limitations with regard to interpreting the effects of the GemCis regimens used here. GemCis is accepted widely in Korea since 2011, before which various monotherapies and doublet regimens containing 5-FU, gemcitabine, and platinum agents were used. In the “no-risk” group, 70% of the patients received GemCis and 13% of patients refused or were excluded from chemotherapy due to old age, poor nutrition, and combined inflammation. By contrast, only 35% of patients in the “high-risk” group received GemCis and 53% did not have any systemic treatment. Our PFS data demonstrated that “no-risk” patients had a prolonged PFS of 12.7 months, which were superior to the results of ABC-02 trial (PFS of 8.0 months). However, even the “moderate-risk” and “high-risk” groups had PFS of around 8.6 months [3]. Therefore, it would be imprudent to conclude that chemotherapy is contraindicated for “moderate-to-high risk groups,” where survival curves are still separated between GemCis and supportive care-only group. Therefore, this should be interpreted with caution as the data in question is from retrospective analysis and highly-selective patients had been included for GemCis chemotherapy. Nevertheless, we suggest here that nutritional assessment be integrated into a more sophisticated scoring system for treatment decision-making. The ideal system can be utilized as follows: for “no-risk” patients, we speculate that their survival may be extended more by active chemotherapy (GemCis) or even more aggressive ‘triplet’ therapy or clinical trials of novel agent. Conversely, “high-risk” group patients would not be expected to show significant benefits from active treatment.

A limitation of this study is the fact that body composition measurements were not included during the data collection. The phase angle, which can be determined by bioelectrical impedance analysis, has been found to be a prognostic indicator in several diseases, including cancer. The phase angle can also be a sensitive indicator of malnutrition [22]. In addition, sarcopenia, characterized by a decline of skeletal muscle, low muscle strength, and/or physical performance, has also emerged to be an important prognostic factor. This is associated with poor performance status, toxicity from chemotherapy, and shorter time of tumor control. There is limited data about sarcopenia and associated factors in cancer patients. Future studies on the baseline nutritional status of patients with advanced BTC should include more meticulous measurement of body composition and sarcopenia. A large-scale multicenter study is necessary to confirm our findings.

Although including many patients, this is a single center study, and there is a limitation in that it is a cross-sectional research in which the test set and the validation set are not separated. As researchers have a convenient clinical application in mind at the beginning of the study, continuous variables such as blood tests were dichotomized according to normal and abnormal ranges, and cutoff points were set for other variables as much as possible from a statistical point of view. However, these results may vary depending on the selection of statistical tools and data extraction method. Therefore, for a more general application,

external validation performed with an independent data set from another hospital is required. It is preferable to interpret this study as follows rather than generalizability of the results: as the nutritional status at the time of diagnosis has prognostic significance to the patient, objective and credible nutritional evaluation should be implemented as a routine practice from the time cancer patients visit the hospital.

In conclusion, we showed that the NRS-2002's assessment of nutritional status at baseline correlates with the prognosis of patients with advanced BTC. As a result, we recommend that NRS-2002 be used as a suitable and trustworthy indication of malnutrition to help with patient prediction. Following that, baseline nutritional status can be further integrated into the implementation of a prognostic score system, which can give BTC patients with more complex risk stratification in daily clinical practice. This system may aid physicians in making treatment decisions.

ACKNOWLEDGEMENTS

We would like to thank all the patients with advanced biliary cancer whose data were included in this study.

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