

GLIM Criteria as Prognostic Factor in Patients Undergoing Adjuvant S-1 Chemotherapy for Biliary Tract Cancer

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Abstract

Background/Aim: Biliary tract cancers (BTCs) have poor prognoses, with limited curative options beyond surgical resection. Adjuvant S-1 chemotherapy has shown survival benefits in Japanese patients undergoing resection for BTC. However, prognostic factors influencing survival in these patients remain uncertain. In this study, we aimed to investigate the efficacy of preoperative nutritional status using the Global Leadership Initiative on Malnutrition (GLIM) criteria as a prognostic factor in patients receiving adjuvant S-1 chemotherapy for BTC.

Patients and Methods: In this retrospective study, excluding intrahepatic cholangiocarcinoma, we evaluated 58 patients who underwent curative surgery for BTC at Kobe University from 2013 to 2022, followed by adjuvant S-1 chemotherapy. Nutritional status was classified by GLIM criteria into normal/moderate and severe malnutrition groups. Overall (OS) and recurrence-free (RFS) survival were analyzed using Kaplan-Meier and Cox proportional hazards models.

Results: Of the 58 patients, 3.4% had no malnutrition, 72.5% had moderate malnutrition, and 24.1% had severe malnutrition. Patients with severe malnutrition had significantly worse 5-year OS (24.7% vs. 52.5%, $p=0.0014$) and RFS (34.3% vs. 52.0%, $p=0.0066$). Severe malnutrition was an independent prognostic factor for poorer OS (hazard ratio=3.40, 95% confidence interval=1.46-7.94; $p=0.0047$) and RFS (hazard ratio=2.48, 95% confidence interval=1.07-5.76; $p=0.035$). No significant difference in S-1 completion rates was observed.

Conclusion: Severe malnutrition, as defined by GLIM criteria, is a poor prognostic factor in patients with BTCs undergoing adjuvant S-1 chemotherapy.

Keywords: Biliary tract cancer, GLIM criteria, adjuvant S-1 chemotherapy.



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Introduction

Biliary tract cancer (BTC) includes intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma, distal cholangiocarcinoma, gallbladder cancer, and ampullary cancer (1). In Japanese cancer staging, extrahepatic cancer, gallbladder cancer and ampullary cancer are classified as biliary tract cancers, while intrahepatic cholangiocarcinoma is often classified in accordance with hepatocellular carcinoma (2). Surgical resection is the only potentially curative treatment; however, the 5-year survival rate post-resection remains below 40% (3). Recently, the Japan Clinical Oncology Group 1202 (JCOG1202) study (UMIN000011688), a randomized phase III trial conducted on patients with BTC, demonstrated the superiority of adjuvant S-1 chemotherapy over surgery alone for overall survival (OS) [hazard ratio (HR)=0.694, $p=0.008$] (4). Adjuvant S-1 chemotherapy may become a standard treatment in patients undergoing resection of BTC.

In recent years, the association between nutritional status and prognosis in gastrointestinal cancers has gained significant attention (5, 6). Sarcopenia has emerged as a significant prognostic indicator in patients undergoing chemotherapy for colorectal and pancreatic cancer (6, 7). In 2018, the Global Leadership Initiative on Malnutrition (GLIM) introduced internationally recognized diagnostic criteria for malnutrition (8), which are now being used to predict outcomes of various diseases (9, 10). Prognostic factors for BTC include positive resection margins (11, 12), infiltration into other organs (13-15), lymph node metastasis (12), vascular invasion (12, 15), lymphatic invasion (16), perineural invasion (12, 15), preoperative cholangitis (17), type of histology such as poorly differentiated adenocarcinoma and mucinous carcinoma (11), and preoperative carbohydrate antigen 19-9 (CA19-9) level (18). Severe malnutrition diagnosed by GLIM criteria has been identified as a poor prognostic factor for postoperative outcomes, including in extrahepatic cholangiocarcinoma (19).

Based on the JCOG1202 study, the number of patients receiving adjuvant S-1 chemotherapy following surgery

for BTC is expected to rise. However, prognostic factors in patients with resected BTC undergoing S-1 adjuvant chemotherapy remain unclear, although an association between chemotherapy outcomes and preoperative malnutrition diagnosed by GLIM criteria has been reported in other cancer types (7, 20).

In this study, we aimed to investigate the efficacy of preoperative nutritional status, as diagnosed by the GLIM criteria, as a prognostic factor in patients receiving adjuvant S-1 chemotherapy for BTC.

Patients and Methods

Patients. This retrospective study included 276 patients who underwent radical surgery for BTC, excluding intrahepatic cholangiocarcinoma, at the Department of Hepato-Biliary-Pancreatic Surgery, Kobe University between January 2013 and December 2022. Patients with pathological tumor stage Tis (carcinoma *in situ*) or T1 (early-stage tumors), distant metastasis, macroscopic residual cancer after resection (R2 resection), and multiple simultaneous primary cancer were excluded. A total of 58 patients who received adjuvant chemotherapy were included in the final analysis. We collected clinical and laboratory data from medical records. The study was approved by the Ethics Committee of Kobe University and conducted following the Helsinki Declaration (approval ID number: B240153). Informed consent was obtained from all patients through an opt-out approach.

Surgical treatment and follow-up. Hemi-hepatectomy or tri-sectionectomy extending to the caudate lobe with extrahepatic bile duct resection was performed for perihilar cholangiocarcinoma and gallbladder cancer. Pancreatoduodenectomy was performed for distal cholangiocarcinoma, gallbladder cancer, and ampullary cancer. A liver bed resection was performed for gallbladder cancer. Extrahepatic bile duct resection was carried out only for patients with middle bile duct cancer and poor performance status. Since 2013, when the JCOG1202 trial began, S-1 adjuvant chemotherapy has

been administered at our Institution to patients with tumors classified as T2 or higher or those with lymph node metastasis.

Following the JCOG1202 protocol, patients received an oral dose of S-1 twice daily for 4 weeks, followed by a 2-week rest period. Three dosage levels of S-1 were used based on body surface area: $<1.25 \text{ m}^2$: 40 mg; 1.25 m^2 to $<1.50 \text{ m}^2$: 50 mg; and $\geq 1.50 \text{ m}^2$: 60 mg, twice daily. Patients with creatinine clearance levels of 50-60 ml/min received a 10 mg reduction of each dose. Treatment was continued for up to four cycles or 24 weeks (4). Patients were followed up for 5 years with serum tumor marker levels and enhanced computed tomography or magnetic resonance imaging at least every 3-6 months after surgery.

Definition of malnutrition diagnosis by the GLIM criteria in this study. For preoperative malnutrition diagnosis, the GLIM criteria recommend combining at least one phenotypic criterion (nonvolitional weight loss, low body mass index, or reduced muscle mass) and one etiological criterion (reduced food intake/assimilation or disease burden/inflammatory status) (8). In this study, malnutrition diagnosis was based on the phenotypic criterion, as patients with cancer already meet the etiological criterion of disease burden. Patients diagnosed with malnutrition were classified as having moderate or severe malnutrition based on the phenotypic criterion. The body mass index and L3- Skeletal Muscle Index (SMI) cutoff values used to distinguish moderate from severe malnutrition were based on previous reports (19).

Statistical analysis. Continuous and categorical variables are expressed as medians, ranges, and ratios. Continuous variables were compared using the Kruskal-Wallis test, while categorical variables were compared using the chi-squared or Fisher's exact test, as appropriate. OS was defined as the time from surgery to death from any cause or the most recent follow-up. Recurrence-free survival (RFS) was defined as the time from surgery, BTC relapse, death, or the most recent follow-up. Univariable and multivariable Cox proportional hazards regression models

were used to estimate HRs and 95% confidence intervals (CIs) for RFS and OS. Multivariate analysis was performed for factors with $p < 0.05$ in the univariate analysis. OS and RFS were calculated using the Kaplan-Meier method, and differences between curves were assessed using the log-rank test. A two-tailed $p < 0.05$ was considered statistically significant. All statistical analyses were performed using the JMP statistical program (version 16; SAS Institute Inc., Cary, NC, USA).

Results

Between 2000 and 2022, 483 patients underwent curative resection for BTC. Patients with tumor invasion depths of Tis to T1, distant metastasis, macroscopic residual cancer after resection, and double cancer were excluded from this group. A total of 58 patients who received postoperative adjuvant S-1 chemotherapy were included in the study (Figure 1). According to the GLIM criteria, two patients (3.4%) had no malnutrition, 42 patients (72.5%) were classified as having moderate malnutrition, and 14 patients (24.1%) were classified as having severe malnutrition. Due to the small number of patients without malnutrition, the normal and moderate malnutrition groups were combined for comparison with the severe malnutrition group. Severe malnutrition was significantly more common in males; however, no statistically significant differences were found in other factors, including age, preoperative cholangitis, CA19-9 level, tumor location, histology, tumor invasion depth, lymph node metastasis, lymphatic invasion, vascular invasion, perineural invasion, or microscopic residual cancer (Table I).

Figure 2 shows the Kaplan-Meier analysis for OS and RFS based on preoperative nutritional status diagnosed using the GLIM criteria. In the normal and moderate malnutrition group, the 1-, 3-, and 5-year OS rates were 100%, 70.9% and 52.5%, respectively. In the severe malnutrition group, the corresponding rates were 85.7%, 37.0% and 24.7%, respectively. OS rates were significantly worse in the severe malnutrition group compared to the normal and moderate groups ($p = 0.0014$). For RFS, the 1-,

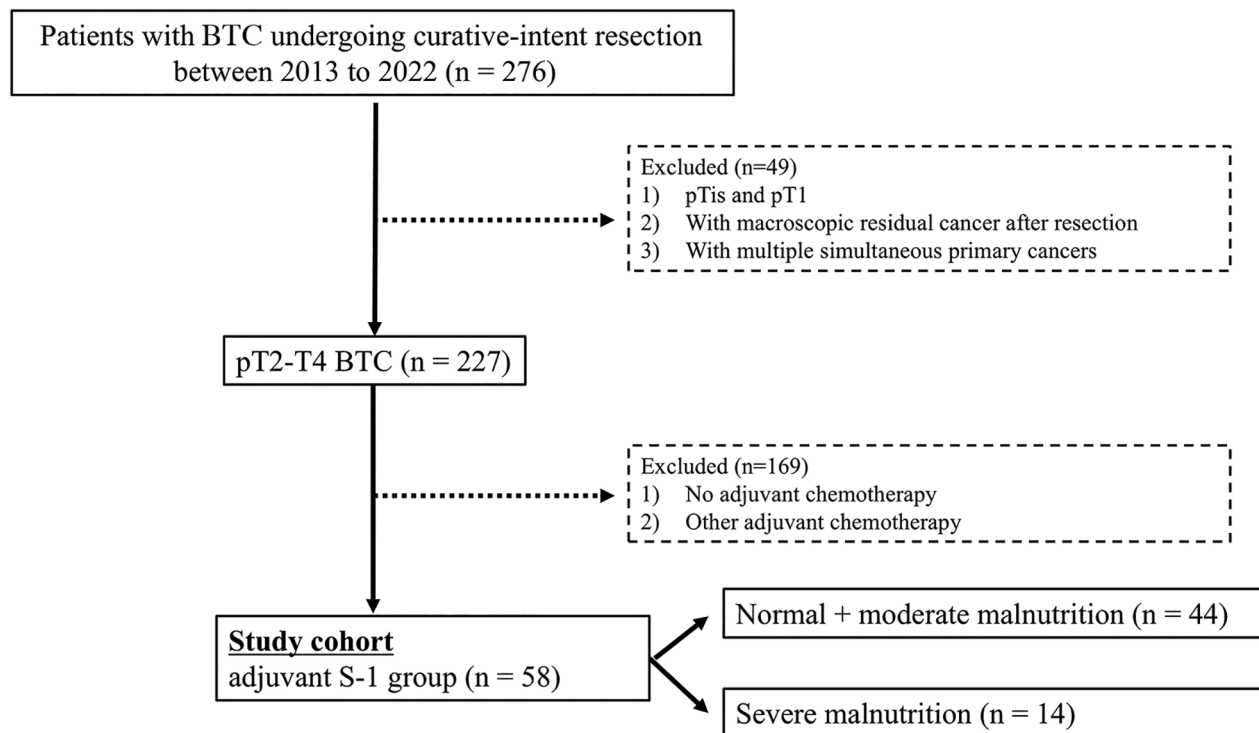


Figure 1. The flow diagram of this study on patients with biliary tract cancer (BTC).

3-, and 5-year rates in the normal and moderate malnutrition groups were 90.9%, 57.2%, and 52.0%, respectively. In the severe malnutrition group, the corresponding rates were 71.4%, 34.3% and 34.3%, respectively. RFS rates were significantly lower in the severe malnutrition group compared to the normal and moderate groups ($p=0.0066$).

Table II shows the risk factors associated with OS. In the univariate analysis, a high CA19-9 level, lymph node metastasis, microscopic residual cancer, and severe malnutrition were identified as prognostic factors for poorer OS. In the multivariate analysis, microscopic residual cancer (HR=2.97, 95% CI=1.25-7.04; $p=0.014$) and severe malnutrition (HR=3.40, 95% CI=1.46-7.94; $p=0.0047$) were independent prognostic factors.

The factors associated with RFS are shown in Table III. Lymph node metastasis, lymphatic invasion, perineural invasion, microscopic residual cancer, and severe malnutrition were identified as prognostic factors in the

univariate analysis. In the multivariate analysis, severe malnutrition (HR=2.48, 95% CI=1.07-5.76; $p=0.035$) was the only independent prognostic factor.

Discussion

BTCs have a poor prognosis, with surgical resection recognized as the only potentially curative treatment. The JCOG study recently demonstrated that adjuvant S-1 chemotherapy prolongs overall survival in Japanese patients with resected BTCs. Postoperative adjuvant S-1 chemotherapy is now the standard of care in Japan and is expected to become the standard in Asia. However, prognostic factors in these patients remain unclear. The GLIM criteria, proposed in 2018, are used to diagnose nutritional status, and malnutrition diagnosed using the GLIM criteria has been reported as a prognostic factor in various cancer types (21, 22). To our knowledge, this study is the first to demonstrate the prognostic impact of

Table I. Baseline characteristics of patients undergoing adjuvant S-1 chemotherapy for biliary tract cancer according to nutritional status classified by the Global Leadership Initiative on Malnutrition (GLIM) criteria.

Variable	Subgroup	GLIM malnutrition class		p-Value
		Normal + Moderate (n=44)	Severe (n=14)	
Age, years	Median (range)	70 (48-82)	71.5 (52-79)	0.59
Sex, n	Male	24 (54.5)	12 (85.7)	0.04
	Female	20 (45.5)	2 (14.3)	
Preoperative cholangitis, n (%)	Yes	21 (47.7)	7 (50)	0.88
CA19-9, U/ml	Median (range)	42.5 (1-3757)	79.5 (10-6871)	0.12
Tumor location, n (%)	Gallbladder	9 (20.5)	2 (14.3)	0.41
	Extrahepatic	29 (65.9)	10 (71.4)	
	Ampulla of Vater	6 (13.6)	2 (14.3)	
Histological differentiation, n (%)	Well, pap	27 (61.4)	5 (35.7)	0.09
	Other	17 (38.6)	9 (64.3)	
UICC pT stage, n (%)	2	23 (52.3)	9 (64.3)	0.43
	3, 4	21 (47.7)	5 (35.7)	
Lymph node metastasis, n (%)	Yes	17 (38.6)	8 (57.1)	0.22
Invasion, n (%)	Lymphatic	21 (47.7)	10 (71.4)	0.12
	Venous	28 (63.6)	10 (71.4)	0.59
	Perineural	35 (79.6)	13 (92.9)	0.25
Residual cancer, n (%)	R0	30 (68.2)	10 (71.4)	0.82
	R1	14 (31.8)	4 (28.6)	

CA19-9: carbohydrate antigen 19-9; pap: papillary adenocarcinoma; UICC: Union for International Cancer Control, classification seventh edition; Well: tubular adenocarcinoma, well-differentiated. Statistically significant p-values are shown in bold.

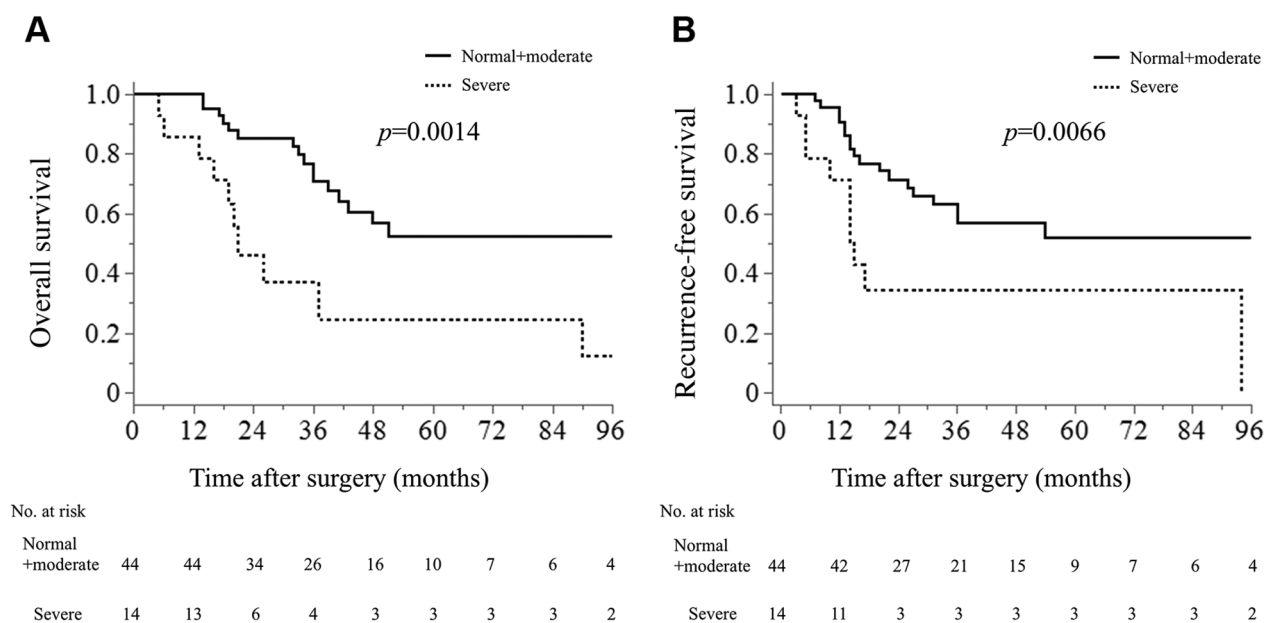


Figure 2. Kaplan-Meier curve of overall (OS) (A) and recurrence-free (RFS) (B) survival according to the status by the Global Leadership Initiative on Malnutrition criteria after resection of biliary tract cancer. The patients of the severe malnutrition group had poorer OS ($p=0.0014$) and RFS ($p=0.0066$) than those of the normal and moderate malnutrition groups, with 1-, 3- and 5-year OS rates of 100% vs. 85.7%, 70.9% vs. 37.0%, and 52.5% vs. 24.7%; and RFS rates of 90.9% vs. 71.4%, 57.2% vs. 34.3% and 52.0% vs. 34.3%, respectively.

Table II. Univariate and multivariate analysis for overall survival of patients undergoing adjuvant S-1 chemotherapy for biliary tract cancer.

Variable	Subgroup	Univariate		Multivariate	
		HR (95% CI)	p-Value	HR (95% CI)	p-Value
Age	≥75 Years	0.71 (0.24-2.08)	0.530		
Sex	Male	2.37 (0.99-5.70)	0.053		
Preoperative cholangitis	Yes	1.53 (0.70-3.33)	0.280		
CA19-9	≥37 U/ml	2.33 (1.00-5.40)	0.049	1.69 (0.69-4.17)	0.250
Tumor location	Perihilar/distal	0.82 (0.47-1.32)	0.460		
Histological differentiation	Other/well, pap	1.86 (0.86-4.03)	0.120		
UICC pT stage	Increasing	1.26 (0.58-2.74)	0.560		
Metastasis	LN	2.77 (1.25-6.16)	0.012	1.73 (0.73-4.09)	0.210
Invasion	Lymphatic	1.96 (0.87-4.41)	0.100		
	Venous	1.82 (0.76-4.36)	0.180		
	Perineural	3.13 (0.74-13.3)	0.120		
Curability	R1	3.42 (1.58-7.41)	0.002	2.97 (1.25-7.04)	0.014
GLIM class	Severe malnutrition	3.27 (1.46-7.34)	0.041	3.40 (1.46-7.94)	0.005

CA19-9: Carbohydrate antigen 19-9; GLIM: Global Leadership Initiative on Malnutrition; HR: hazard ratio; LN: lymph node; pap: papillary adenocarcinoma; UICC: Union for International Cancer Control classification seventh edition; well: tubular adenocarcinoma, well-differentiated. Statistically significant *p*-values are shown in bold.

Table III. Univariate and multivariate analysis for recurrence-free survival of patients undergoing adjuvant S-1 chemotherapy for biliary tract cancer.

Variable	Subgroup	Univariate		Multivariate	
		HR (95% CI)	p-Value	HR (95% CI)	p-Value
Age	≥75 Years	0.90 (0.36-2.24)	0.830		
Sex	Male	1.41 (0.64-3.09)	0.390		
Preoperative cholangitis	Yes	1.39 (0.66-2.94)	0.390		
CA19-9	≥37 U/ml	2.08 (0.96-4.54)	0.064		
Tumor location	Perihilar/distal	0.95 (0.57-1.49)	0.690		
Histological differentiation	Other/well, pap	1.86 (0.88-3.92)	0.100		
UICC pT stage	Increasing	1.09 (0.82-2.30)	0.820		
Metastasis	LN	2.33 (1.08-5.05)	0.031	1.52 (0.65-3.55)	0.330
Invasion	Lymphatic	2.43 (1.09-5.40)	0.029	1.83 (0.76-4.38)	0.180
	Venous	2.45 (0.99-6.06)	0.053		
	Perineural	7.76 (1.05-17.2)	0.044	4.73 (0.61-3.66)	0.140
Curability	R1	2.61 (1.23-5.58)	0.013	2.26 (0.99-5.12)	0.051
GLIM class	Severe malnutrition	2.71 (1.24-5.95)	0.013	2.48 (1.07-5.76)	0.035

CA19-9: Carbohydrate antigen 19-9; GLIM: Global Leadership Initiative on Malnutrition; HR: hazard ratio; LN: lymph node; pap: papillary adenocarcinoma; UICC: Union for International Cancer Control classification seventh edition; well: tubular adenocarcinoma, well-differentiated. Statistically significant *p*-values are shown in bold.

preoperative nutritional status diagnosed using the GLIM criteria in patients after BTC resection who received postoperative adjuvant S-1 chemotherapy.

Microscopic residual cancer and preoperative severe malnutrition, as diagnosed by the GLIM criteria, were independent prognostic factors in patients undergoing adjuvant S-1 chemotherapy. Severe malnutrition emerged

as the only significant prognostic factor, suggesting that assessing preoperative nutritional status using the GLIM criteria is valuable for prognostic stratification.

Adjuvant S-1 chemotherapy can cause adverse events due to its toxicity, including gastrointestinal symptoms (nausea, vomiting, and diarrhea), neutropenia, hand-foot syndrome, and general fatigue (4, 23, 24). In this study, adverse events

were evaluated using the Common Terminology Criteria for Adverse Events version 5.0 (25). Grade 3 or higher adverse events included anemia, thrombocytopenia, neutropenia, diarrhea, drug rash, and fatigue (Table IV). The normal and moderate malnutrition groups had 10 cases (25.6%) of adverse events, while the severe malnutrition group had three (25%), with no significant difference between the groups ($p=0.96$). The proportion of S-1 treatment completion was 75% in the normal and moderate malnutrition groups and 78.6% in the severe malnutrition group ($p=0.53$). Since S-1 treatment completion rates were similar between groups, the preoperative nutritional status may be a potential prognostic factor.

As adjuvant S-1 chemotherapy following surgery for BTCs becomes more widespread, evaluating preoperative nutritional status and addressing malnutrition is crucial. Reports emphasize the importance of preoperative nutritional interventions, recommending routine high-protein oral nutritional supplements, immuno-nutrition, carbohydrate loading, and structured nutritional prehabilitation to optimize surgical outcomes and promote recovery (26, 27). These interventions aim to boost metabolic reserves, reduce complication risks, and improve overall survival, particularly in vulnerable patients undergoing cancer treatment (26, 27). Furthermore, future research should examine whether these interventions improve nutritional status as determined by the GLIM criteria and whether these improvements correlate with patient prognosis.

Malnutrition has been reported as a risk factor for poor compliance with adjuvant S-1 chemotherapy following gastric cancer surgery (20); however, we found no difference in the completion rate of adjuvant S-1 chemotherapy between the normal/moderate malnutrition group and the severe malnutrition group.

The relationship between chronic inflammation caused by tumors and malnutrition has been well documented. Tumor-related inflammatory mediators, such as tumor necrosis factor α , interleukin-6, and interleukin-1 β , suppress appetite, delay gastric emptying, and promote skeletal muscle catabolism, contributing to the multiple

Table IV. Adverse events ($>grade\ 3$) experienced by patients undergoing adjuvant S-1 chemotherapy for biliary tract cancer according to nutritional status as defined by Global Leadership Initiative on Malnutrition (GLIM) criteria.

Adverse event	GLIM criteria, n (%)	
	Normal + moderate malnutrition (n=44)	Severe malnutrition (n=14)
Anemia	1 (2%)	1 (2%)
Thrombocytopenia	2 (4%)	0
Neutropenia	6 (11%)	1 (2%)
Diarrhea	1 (2%)	0
Drug-related rash	1 (2%)	0
Fatigue	1 (2%)	1 (2%)

mechanisms that cause malnutrition (28). This suggests that malnutrition diagnosed using the GLIM criteria may reflect the degree of cachexia (29). Furthermore, cachexia has been reported to reduce chemotherapy efficacy. Therefore, patients diagnosed with severe malnutrition according to the GLIM criteria may experience reduced effectiveness of adjuvant S-1 chemotherapy.

Study limitations. Firstly, this retrospective study was conducted at a single institution with a small sample size. Secondly, due to the long study period, there was inconsistency in perioperative management, surgical techniques, and chemotherapy regimens. Thirdly, there were limitations in defining muscle mass loss. One of the phenotypic criteria in the GLIM criteria is reduced muscle mass; however, various methods exist for its assessment. In this study, the SMI was measured at the L3 level using computed tomographic scans, and cutoff values from previous studies were used (19). Generally, patients with BTC have reduced muscle mass compared to the general adult population, and further research is needed to establish disease-specific SMI values.

Conclusion

In cases where adjuvant S-1 chemotherapy is administered after surgery for BTC, severe preoperative malnutrition as diagnosed by the GLIM criteria has been identified as a

poor prognostic factor. Evaluating preoperative nutritional status with the GLIM criteria is valuable for prognostic stratification for patients receiving postoperative adjuvant S-1 chemotherapy for advanced BTC.

Conflicts of Interest

The Authors declare no conflicts of interest for this article.

Authors' Contributions

Hiroaki Yanagimoto and Ryunosuke Konaka designed the study. Masayuki Akita, Takuya Mizumoto, Toshihiko Yoshida, Shinichi Sou, Jun Ishida, Yoshihide Nanno, Takeshi Urade, Kenji Fukushima, Hidetoshi Gon, Daisuke Tsugawa, Shohei Komatsu, Sadaki Asari, Masahiro Kido, Hirochika Toyama and Takumi Fukumoto contributed to data collection, interpretation of data, and critical revision of manuscript. Ryunosuke Konaka drafted the manuscript. All Authors have read and agreed to the published version of the manuscript.

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