Nutritional indices are potentially important prognostic biomarkers before chemotherapy for non-specific subsets of cancer of unknown primary origin

SHOTARO YAMAGUCHI[1,2], TOSHIMITSU TANAKA[1,2], SACHIKO NAGASU[1,3], MASARU FUKAHORI[1,2], YASUTAKA SHIMOTSUURA[1,2], FUMIHIKO FUJITA[3], KENTA MUROTANI[4,5], TAKUMI KAWAGUCHI[2] and KEISUKE MIWA[1,3]

[1]Multidisciplinary Treatment Cancer Center, Kurume University Hospital, Kurume 830-0011, Japan; [2]Department of Medicine, Division of Gastroenterology, Kurume University School of Medicine, Kurume 830-0011, Japan; [3]Department of Surgery, Kurume University School of Medicine, Kurume 830-0011, Japan; [4]School of Medical Technology, Kurume University, Kurume 830-0011, Japan; [5]Biostatistics Center, Kurume University, Kurume 830-0011, Japan

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Abstract. Patients with cancer of unknown primary origin (CUP) account for 2-5% of all types of cancer worldwide and have a poor prognosis, with a reported 1-year survival rate of ~20%. Furthermore, global data indicate that in patients with unfavorable subsets, the median overall survival (OS) is ~12 months from the initiation of first-line therapy; however, reliable prognostic biomarkers in patients with the unfavorable subset are yet to be elucidated. As nutritional indices are used as prognostic factors in various malignancies, such as gastrointestinal cancer, the present retrospective study aimed to examine the impact of nutritional status on the prognosis of patients that underwent chemotherapy for CUP. The association between four indices of nutritional status and OS and progression-free survival (PFS) was investigated in 25 patients with CUP who received chemotherapy at Kurume University Hospital (Kurume, Japan) between July 2011 and June 2023. Nutritional status was evaluated using the prognostic nutritional index, neutrophil-to-lymphocyte ratio (NLR), modified Glasgow prognostic score (mGPS) and controlling nutritional status (CONUT) score. Low NLR (≤3), mGPS (0-1) and CONUT (0-3) scores indicated good nutritional status. The median PFS and OS for all patients were 6.3 and 17.2 months, respectively. Univariate analyses revealed that low mGPS [hazard ratio (HR), 0.27; 95% confidence interval (CI), 0.09-0.80; P=0.017) and CONUT (HR, 0.23; 95% CI, 0.07-0.75; P=0.015) scores were favorable prognostic factors for OS. Furthermore, a low mGPS (HR, 0.21; 95% CI, 0.08-0.61; P=0.004) score was predictive of favorable PFS. Multivariate analyses revealed that low mGPS (HR, 0.21; 95% CI, 0.05-0.94; P=0.041) and CONUT (HR, 0.20; 95% CI, 0.05-0.90; P=0.035) scores, and a low mGPS (HR, 0.20; 95% CI, 0.06-0.71; P=0.012) score, were independent prognostic factors for OS and PFS, respectively. In conclusion, a good nutritional status (as indicated by low mGPS and CONUT scores) independently predicted a potentially favorable prognosis in chemotherapy-treated patients with CUP. These results may be used in order to estimate prognosis before chemotherapy.

Introduction

A cancer of unknown primary origin (CUP) is a metastatic tumor for which a primary site cannot be identified despite examination using appropriate techniques, such as imaging with CT or MRI, endoscopic evaluations and investigating various tumor markers (1). CUP is a rare cancer, accounting for 2-5% of all types of cancer globally and patients with CUP have a poor prognosis, with a 1-year survival rate of ~20% (2-4). Furthermore, ~15% of patients with CUP respond to specific therapies and achieve long-term survival, with a prognostic analysis of 1,000 cases demonstrating a median survival of 11 months (2). Favorable histological entities of CUP represent a distinct minority of patients and include well-defined clinicopathological subsets such as isolated unilateral axillary lymph node metastases with breast cancer-like features, squamous-cell carcinoma involving cervical lymph nodes, poorly differentiated carcinoma with midline distribution, women with papillary serous adenocarcinoma of the peritoneum and men with osteoblastic bone metastases and elevated serum prostate-specific antigen (1). These favorable subsets have outcomes comparable with those of corresponding known primary tumors and are associated with improved prognoses. By contrast, unfavorable subsets of

Correspondence to: Dr Toshimitsu Tanaka, Multidisciplinary Treatment Cancer Center, Kurume University Hospital, 67 Asahi-machi, Kurume 830-0011, Japan
E-mail: tanaka_toshimitsu@med.kurume-u.ac.jp

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CUP are defined as patients with disseminated visceral disease such as adenocarcinoma metastatic to the liver, non-papillary malignant ascites, multiple lung or pleural metastases, multiple brain metastases, or lytic bone disease (1,2). Previous randomized global trials in patients with unfavorable subsets of CUP report a median overall survival (OS) of ~12 months from the initiation of first-line treatment, with the longest median OS being 13.6 months (5,6).

CUP is typically diagnosed at an advanced metastatic stage where the primary site remains undetermined despite extensive evaluation (7). Consequently, surgical intervention is generally limited to diagnostic or palliative purposes. Furthermore, curative surgery for CUP is rare, and systemic therapy, including chemotherapy, is the cornerstone of treatment (7).

The treatment approach for CUP involves identifying the most probable primary site based on its unique clinical presentation, histopathological findings and genetic profile (4). The European Society for Medical Oncology recommends that therapy is selected based on the provisional primary site identified through the gene expression profiling of collected cancer tissue (site-specific regimen) (4). For unfavorable subsets with no histological organ-specific findings, a platinum-doublet regimen (empirical regimen) (4,8) is recommended; carboplatin-paclitaxel is often used; however, there is not an established advantage compared with other regimens. Findings from recent studies suggest that CUP shares similar immunological characteristics with solid tumors that are responsive to immune checkpoint inhibitors, including higher levels of tumor-infiltrating lymphocytes and an increased expression of PD-L1 (9-11). Therefore, administering immune checkpoint inhibitors, such as nivolumab, to patients with CUP yields a certain degree of efficacy, which makes it a possible treatment option (11,12).

Previous studies report that the poor performance status (PS), high levels of lactate dehydrogenase, high number of organs with metastasis and the presence of liver metastases are predictive factors for a poor prognosis and reduced probability of survival in patients with CUP (13,14). However, useful prognostic biomarkers are yet to be elucidated. Furthermore, CUP is a rare cancer with a high level of heterogeneity and a poor prognosis.

In recent years, the nutritional status of patients with cancer has been recognized as a factor influencing treatment response and survival duration (15). The nutritional status of patients with advanced cancer is a useful prognostic factor. The most common nutritional marker is the albumin level. Other nutritional markers include the neutrophil-to-lymphocyte ratio (NLR), prognostic nutritional index (PNI), modified Glasgow prognostic score (GPS; mGPS) and controlling nutritional status (CONUT) score (12). Previous studies demonstrate the usefulness of the aforementioned nutritional markers in estimating the prognosis, especially in the perioperative period and during chemotherapy, of patients with gastrointestinal types of cancer (16,17). By contrast, the association between nutritional status and survival outcomes in patients with CUP is yet to be fully elucidated. Therefore, the present study aimed to investigate the effect of nutritional status on the prognosis of patients with CUP who were treated with chemotherapy.

Materials and methods

Study design and patient selection. In the present study, the data of 25 patients with CUP who received chemotherapy at Kurume University Hospital (Kurume, Japan) between July 2011 and December 2023 was retrospectively evaluated. All patients were diagnosed with CUP because of the difficulty in identifying the primary tumor site after close examination using imaging and histological techniques, including CT and MRI scans, endoscopic evaluations, tumor marker assessments, and tissue biopsies of metastatic lesions. Tissue samples collected from the patients were subjected to histological evaluation and immunohistochemical analysis to predict the primary site. Clinical data were collected from the medical records, including age, sex, PS, body mass index (BMI), type of pathology (adenocarcinoma, squamous cell carcinoma or undifferentiated carcinoma), number of organs with metastasis, laboratory results (blood count and chemistry profiles), NLR, PNI, mGPS and CONUT scores.

The present study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Committee of Kurume University (Kurume, Japan; approval no. 23229). An opt-out approach was used to obtain informed consent from the patients, and personal information was protected during data collection.

Calculations of the nutritional scores and definitions of the cut-off values. Various nutritional scores were calculated before chemotherapy and their relevance to prognosis was assessed. NLR was calculated by dividing the total neutrophil count by the total lymphocyte count. PNI was calculated as [10 x serum albumin (g/dl)] + [0.005 x total lymphocyte count (ml)]. mGPS was calculated based on the levels of serum C-reactive protein and albumin [C-reactive protein, <0.5 mg/dl and albumin, ≥3.5 g/dl (0 points); C-reactive protein, <0.5 mg/dl or albumin, ≥3.5 g/dl (1 point); or C-reactive protein, ≥0.5 mg/dl and albumin, <3.5 g/dl (2 points)]. The CONUT score was calculated based on the serum albumin content [≥3.5 g/dl (0 points); 3.0-3.4 g/dl (2 points); 2.5-2.9 g/dl (4 points); or <2.5 g/dl (6 points)], total lymphocyte count [≥1,600 cells/μl (0 points); 1,200-1,599 cells/μl (1 point); 800-1,199 cells/μl (2 points); or <800 cells/μl (3 points)] and serum levels of total cholesterol [≥180 mg/dl (0 points); 140-179 mg/dl (1 point); 100-139 mg/dl (2 points); or <100 mg/dl (3 points)]. The nutritional scores defined in the present study were based on the cut-off values used in previous studies (low NLR, <3; high PNI, >40; low mGPS, ≤1 point; and low CONUT score, ≤3 points) (18-20).

Regimen selection. All patients underwent a biopsy of the tumor tissue for histological and immunological diagnoses. To estimate the location of the primary tumor immunohistochemistry was used. Tissue preparation and staining were carried out as follows: Paraffin-embedded tissue samples (samples treated with 10% neutral buffered formalin at room temperature for 6-72 h) were cut 5 μm thick and examined on a coated glass slide (cat. no. SCRE-13; Matsunami Glass Ind., Ltd.). Each slide was heat-treated at 99˚C using Ventana CC1 retrieval solution (Roche Tissue Diagnostics) for 64 min. Subsequently, samples were labeled with primary antibodies

using the BenchMark ULTRA (Roche Tissue Diagnostics) and Bond-III autostainer (Leica Microsystems, Ltd.). This automated system used a biotin-free polymer detection method. Specifically, positive immunoreactive signals were visualized using the UltraView Universal DAB Detection kit (cat. no. 760-500; Roche Diagnostics KK), which used the UltraView Universal HRP Multimer containing a cocktail of HRP-labeled secondary antibodies. Blocking reagents were not used with the antibodies in the present study. Although exogenous blocking reagents were not applied separately, the automated staining system used in the present study used optimized buffer formulations and detection kits designed to minimize non-specific background. In the present study, no notable non-specific binding or background interference was observed that would confound the interpretation of the biopsies. The primary antibodies used were: Cytokeratin (CK)7 (undiluted; cat. no. 05986818001; Roche Diagnostics, Ltd.) and CK20 (undiluted; cat. no. 05587760001; Roche Diagnostics, Ltd.), at room temperature for 16 min; synaptophysin (undiluted; cat. no. 413831; Nichirei Biosciences, Inc.) and chromogranin (undiluted; cat. no. M0869; Dako; Agilent Technologies, Inc.) at room temperature for 16 min, with heat-induced antigen retrieval at 95˚C with epitope retrieval solution 2 (pH 9.0) for 20 min and a Refine polymer detection system (Leica Microsystems, Ltd.); and S100 protein (undiluted; cat. no. IR504; Dako; Agilent Technologies, Inc.) and HMB-45 (1:100; cat. no. M0634; Dako; Agilent Technologies, Inc.) at room temperature for 16 min using the Refine polymer detection system without the heat-induced antigen retrieval and epitope retrieval solution. Positive immunoreactive signals [UltraView Universal HRP Multimer containing a cocktail of HRP-labeled antibodies (goat anti-mouse IgG, goat anti-mouse IgM and goat anti-rabbit; undiluted) in a buffer containing protein with ProClin 300, a preservative, at 36˚C for 8 min] and chromogen detection [UltraView Universal DAB H_2O_2 was used containing 0.04% hydrogen peroxide in phosphate buffer solution, then UltraView Universal DAB Copper was used in an acetic acid buffer solution containing copper sulfate (5 g/l) with a proprietary preservative formulation] were visualized using the UltraView Universal DAB Detection kit (cat. no. 760-500; Roche Diagnostics KK). All images of the stained sections were obtained with an all-in-one fluorescence microscope (model, BZ-X700; Keyence Corporation).

If the location of a primary tumor site could be estimated based on only the histological findings (without using next-generation sequencing), a site-estimated treatment regimen was used (Table SI). Patients were divided into groups according to whether the location of the primary tumor could be estimated or not; this was carried out based on the differences in the treatment regimens of the patients. The group with an estimated location of the primary tumor (but without a tumor found at the estimated location) underwent site-specific treatment. If no clear histological features were present, the patients were diagnosed with undifferentiated carcinoma, and carboplatin-paclitaxel was used as the empirical regimen (21). The patients underwent treatment in 21-day cycles, with up to six cycles administered. The dose of carboplatin was 6 mg/ml per min on day 1 based on an area under the concentration-time curve, while paclitaxel was administered at 200 mg/m^2 on day 1, with dosage adjustments made at the discretion of the attending physician.

Assessment of outcomes. Response to treatment was evaluated at 8-week intervals using dynamic computed tomography according to the Response Evaluation Criteria in Solid Tumors version 1.1 (22). Progression-free survival (PFS) was defined as the duration between the enrollment date and the occurrence of progressive disease or mortality due to any cause. OS was defined as the duration between the date of enrollment and mortality due to any cause.

Statistical analysis. Univariate analyses were conducted using the Cox regression model to identify risk factors associated with OS or PFS. Multivariate analyses were used to assess the impact of independent variables on survival. For variable selection, all factors were evaluated using $P<0.10$ in univariate analyses. OS and PFS were calculated using the Kaplan-Meier method and assessed using the log-rank test. Data analysis was carried out using JMP Pro version 17.0 (SAS Institute, Inc.). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. Table I presents the characteristics of the patients with CUP that were included in the present study. In total, 25 patients were diagnosed with CUP and treated with chemotherapy at Kurume University Hospital (Kurume, Japan) between July 2011 and December 2023. Overall, 9 patients (36%) were aged <65 years, and 16 patients (64%) were women. The PS score was 0 or 1 in 20 patients (80%). The pathological types of tumor diagnosed in the present cohort were adenocarcinoma [12 patients (48%)], squamous cell carcinoma [6 patients (24%)] and undifferentiated carcinoma [7 patients (28%)]. Metastasis to <3 organs was identified in 16 patients (64%). In total, 14 patients (56%) were treated with organ-specific regimens. Regarding the nutritional scores, 11 patients (44%) had low NLR, 12 patients (48%) had high PNI, 16 patients (64%) had low mGPS and 14 patients (56%) had low CONUT scores.

OS and PFS in patients with CUP. To evaluate the prognosis of patients with CUP in the present study, the OS and PFS was assessed in all cases. The Kaplan-Meier survival curves for OS and PFS in patients receiving chemotherapy for CUP are shown in Fig. 1. The median OS was 17.2 months [95% confidence interval (CI), 12.5-26.9 months) (Fig. 1A), and the median PFS was 6.3 months (95% CI, 2.9-8.2 months) (Fig. 1B).

Prognostic factors for OS and PFS in patients with CUP. Univariate and multivariate analyses were carried out to evaluate factors affecting the prognosis of patients with CUP. The results of the univariate analyses of the prognostic factors for OS and PFS are presented in Tables II and III, respectively. The univariate analysis demonstrated that the site-estimated regimen was significantly associated with poor OS, while metastasis in three or fewer organs, a low mGPS and a low CONUT score were significantly associated with good prognoses. There were no significant differences in OS based on

Table I. Patient characteristics.

Characteristic	Number of patients, N (%)
Age, years	
<65	9 (36)
≥65	16 (64)
Sex	
Male	9 (36)
Female	16 (64)
Performance status score	
0 or 1	20 (80)
≥2	5 (20)
BMI, kg/m^2	
<22	11 (44)
≥22	14 (56)
Type of pathology	
Adenocarcinoma	12 (48)
Squamous cell carcinoma	6 (24)
Undifferentiated carcinoma	7 (28)
Number of organs with metastasis	
<3	16 (64)
≥3	9 (36)
Regimen	
Site-estimated	14 (56)
Empirical	11 (44)
NLR	
Low (<3)	11 (44)
High (≥3)	14 (56)
PNI	
Low (≤40)	13 (52)
High (>40)	12 (48)
mGPS	
Low (0 or 1)	16 (64)
High (2)	9 (36)
CONUT score	
Low (≤3)	14 (56)
High (>3)	11 (44)

BMI, body mass index; CONUT, controlled nutritional status; mGPS, modified Glasgow prognostic score; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index.

age, sex, PS, BMI, type of pathology, albumin levels, low NLR or high PNI scores.

Univariate analysis of the prognostic factors for PFS demonstrated that low mGPS and low NLR were significantly associated with a good prognosis. There were no significant differences in PFS based on age, sex, PS, BMI, pathology type, number of organs with metastases, use of a site-specific regimen, albumin level, high PNI or low CONUT score.

Furthermore, patients were divided into two groups based on whether the location of the primary tumor could be estimated. The univariate analysis results for the OS and PFS are presented in Tables SII and SIII, respectively. In the group with an estimated location of the primary tumor (but without a tumor found at the presumed primary site), the PS, a high PNI, low mGPS and a low CONUT score were associated with a significant increase in the OS. There were no significant differences in the OS in the group in which the location of the primary tumor could not be estimated.

In the group with an estimated location of the primary tumor, the PS, albumin level, a high PNI and a low mGPS were associated with a significant increase in the PFS. There were no significant differences in the PFS across all factors in the group without an estimated location of the primary tumor.

The results of the multivariate analyses of the prognostic factors for OS and PFS are presented in Tables II and III, respectively. Low mGPS and CONUT scores were independent good prognostic factors for OS. No significant differences in OS were observed for the number of organs with metastasis or administration of site-specific regimens. A low mGPS was an independent good prognostic factor for PFS. No significant differences in PFS were observed for the low NLR nor the low CONUT score. These results indicated that low mGPS and low CONUT scores may be associated with prolonged survival.

Clinical outcomes based on the nutrition score. Univariate and multivariate analyses suggested that low mGPS and low CONUT nutritional scores may contribute to an improved prognosis. Therefore, these factors were further investigated using survival curves. The Kaplan-Meier survival curves for OS and PFS stratified by mGPS and CONUT scores are shown in Fig. 2. The median OS was significantly longer in the low-mGPS group [25.7 months (95% CI, 12.5-80.5 months)] compared with the high-mGPS group [7.2 months (95% CI, 0.4-17.2 months)] (Fig. 2A). In addition, the median PFS was significantly longer in the low-mGPS group [8.2 months (95% CI, 4.0-11.3 months)] compared with the high-mGPS group [1.9 months (95% CI, 0.4-7.0 months)] (Fig. 2B).

Additionally, the median OS was significantly longer in the low-CONUT group [26.1 months (95% CI, 12.5-80.5 months)] compared with the high-CONUT group [14.3 months (95% CI, 1.0-22.1 months)] (Fig. 2C). The median PFS tended to be longer in the low-CONUT group [7.5 months (95% CI, 4.7-11.3 months)] compared with the high-CONUT group [2.4 months (95% CI, 0.6-7.0 months)]; however, the difference was not statistically significant (Fig. 2D). By contrast, the median OS was significantly shorter in the high-mGPS and high-CONUT group [5.4 months (95% CI, 0.4-14.3 months)] compared with the low-mGPS and/or low-CONUT group [25.7 months (95% CI, 16.0-80.5 months)] (Fig. S1A). Furthermore, the median PFS was significantly shorter in the high-mGPS and high-CONUT group [1.3 months (95% CI, 0.4-5.4 months)] compared with the low-mGPS and/or low-CONUT group [7.5 months (95% CI, 4.6-10.2 months)] (Fig. S1B). These results indicated that patients with low-mGPS and/or low-CONUT scores may have a prolonged survival duration.

Discussion

To the best of our knowledge, the present study was the first to indicate that nutritional scores, such as the mGPS and CONUT

Table II. Univariate and multivariate analyses of prognostic factors for overall survival.

	Univariate analysis			Multivariate analysis		
Characteristic	HR	95% CI	P-value	HR	95% CI	P-value
Age, ≤65 years	1.13	0.39-3.28	0.823			
Sex, male	2.17	0.75-6.34	0.155			
Performance status score, 0-1	0.67	0.18-2.41	0.535			
BMI, >22 kg/m^2	1.25	0.43-3.65	0.693			
Type of pathology, adenocarcinoma	0.75	0.26-2.18	0.601			
Number of organs with metastasis, ≤3	0.20	0.06-0.66	0.008	0.28	0.06-1.43	0.127
Regimen, site-estimated	3.91	1.19-12.84	0.024	4.06	0.77-21.49	0.100
Albumin level, >3.5 g/dl	0.52	0.17-1.58	0.247			
Low NLR, ≤3	0.52	0.17-1.58	0.245			
High PNI, >40	0.61	0.20-1.82	0.370			
Low mGPS, 0 or 1	0.27	0.09-0.80	0.017	0.21	0.05-0.94	0.041
Low CONUT score, ≤3	0.23	0.07-0.75	0.015	0.20	0.05-0.90	0.035

BMI, body mass index; CI, confidence interval; CONUT, controlling nutritional status; HR, hazard ratio; mGPS, modified Glasgow prognostic score; NLR, neutrophil-lymphocyte ratio; PNI, prognostic nutritional index.

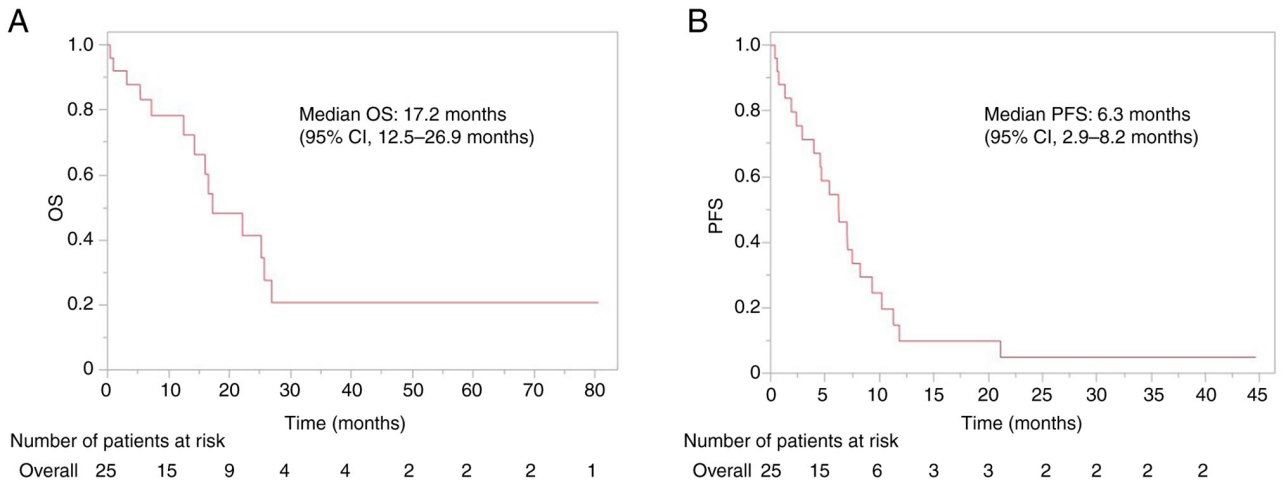

Figure 1. Kaplan-Meier survival analysis of OS and PFS. (A) OS and (B) PFS were estimated from the pooled data from patients with cancer of unknown primary origin (n=25). OS, overall survival; PFS, progression-free survival; CI, confidence interval.

scores, may be independent prognostic factors in patients undergoing chemotherapy for CUP. The results of the present study demonstrated that OS and PFS were significantly longer in the low-mGPS and/or low-CONUT groups compared with the respective high-mGPS and high-CONUT groups. The multivariate analysis of prognostic factors for OS indicated that low mGPS and low CONUT scores were independent good prognostic factors. Taken together, the results of these analyses suggested that good pretreatment nutritional status may be associated with increased treatment efficacy.

In previous clinical studies investigating CUP, the median patient age is 60-65 years (23-26), and the percentage of PS scores of 0 and 1 is >90% (25,27). In addition, adenocarcinoma accounts for ~50% of tumor histology, whereas undifferentiated carcinoma, which is difficult to classify, accounts for ~20% (23,25). Furthermore, the number of metastatic organs is <3 in 60% of the previous cases (23,27). In the present study, 64% of the patients with CUP were aged ≥65 years, which was higher compared with previously reported proportions in which 40-50% of patients were aged ≥60 years (3,26). However, the PS score, tumor histology and number of metastatic organs were similar to those reported previously. Therefore, the data of the present study suggested that advanced age may be a characteristic finding in Japanese patients with CUP.

There are various indicators of nutritional status. In the present study, the mGPS and CONUT scores were identified as prognostic factors, while the PNI and NLR did not affect prognosis. An ancillary study of the EXPAND trial (a phase III clinical trial), which investigates the efficacy of first-line chemotherapy for unresectable advanced gastric cancer, demonstrates that the low-mGPS group has a notably prolonged OS compared with the high-mGPS group (17,28).

Table III. Univariate and multivariate analyses of prognostic factors for progression-free survival.

	Univariate analysis			Multivariate analysis		
Characteristic	HR	95% CI	P-value	HR	95% CI	P-value
Age, ≤65 years	0.90	0.37-2.14	0.803			
Sex, male	1.85	0.78-4.41	0.165			
Performance status score, 0-1	1.04	0.34-3.14	0.951			
BMI, >22 kg/m^2	1.21	0.49-2.99	0.673			
Type of pathology, adenocarcinoma	0.67	0.29-1.59	0.365			
Number of organs with metastasis, ≤2	0.50	0.21-1.20	0.119			
Regimen, site-estimated	1.02	0.44-2.38	0.963			
Albumin level, >3.5 g/dl	0.55	0.23-1.29	0.168			
Low NLR, ≤3	0.48	0.20-1.14	0.095	1.65	0.41-6.72	0.483
High PNI, >40	0.53	0.23-1.25	0.146			
Low mGPS, 0 or 1	0.21	0.08-0.61	0.004	0.20	0.06-0.71	0.012
Low CONUT score, ≤3	0.45	0.19-1.06	0.067	0.44	0.13-1.53	0.197

BMI, body mass index; CONUT, controlling nutritional status; CI, confidence interval; HR, hazard ratio; mGPS, modified Glasgow prognostic score; NLR, neutrophil-lymphocyte ratio; PNI, prognostic nutritional index.

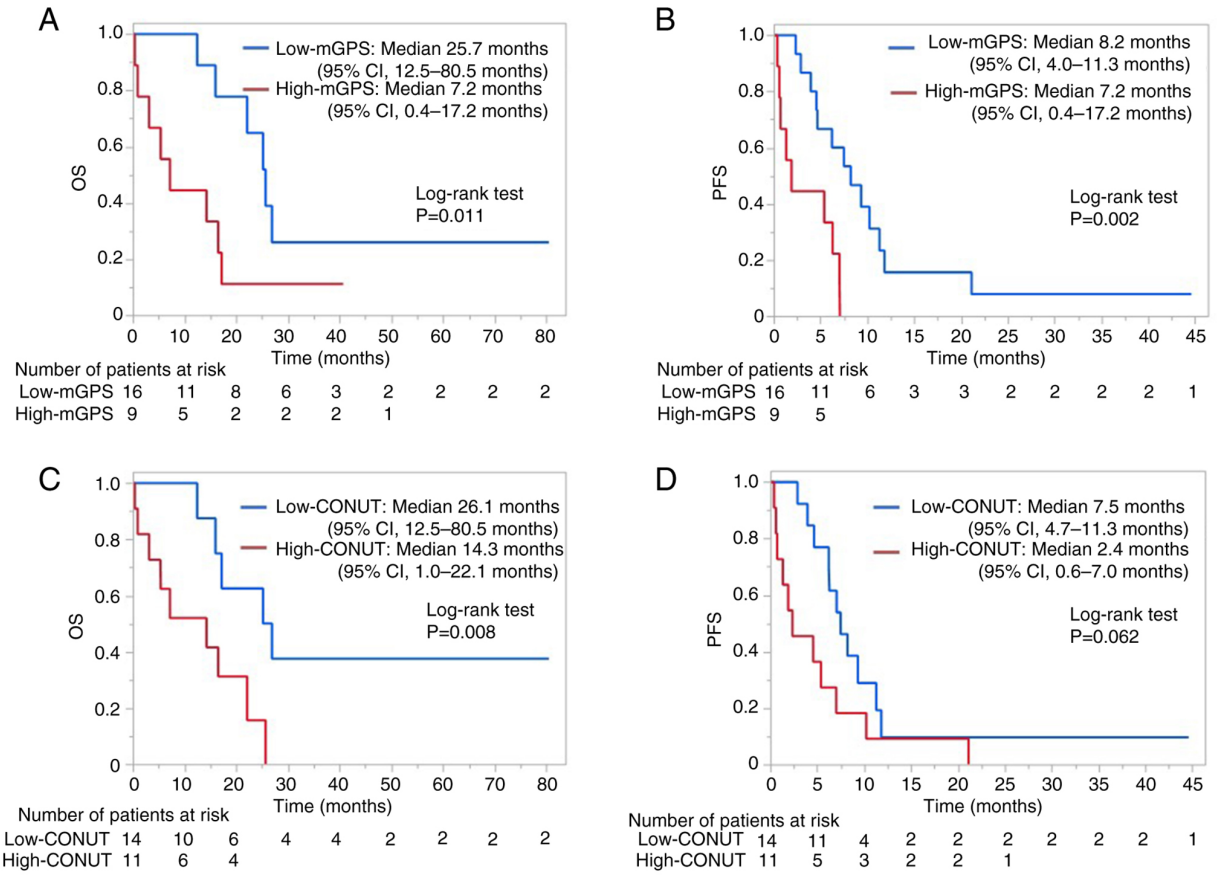

Figure 2. Kaplan-Meier survival analysis of the OS and PFS stratified by the nutrition score. (A) OS and (B) PFS of patients with CUP and a low-mGPS (n=16; blue line) or a high-mGPS (n=9; red line). (C) OS and (D) PFS of patients with CUP and a low-CONUT (n=14; blue line) or a high-CONUT (n=11; red line) score. OS, overall survival; PFS, progression-free survival; CI, confidence interval; CUP, cancer of unknown primary origin; mGPS, modified Glasgow prognostic score; CONUT, controlling nutritional status.

In another study, the low-CONUT group showed a markedly higher 5-year OS and 5-year recurrence-free survival compared with the high-CONUT group when assessing preoperative nutritional status for resectable gastric

cancer (16). This indicates that a low CONUT score may be a useful indicator during the perioperative period. In the aforementioned study, the cut-off value of the CONUT score is set at ≤3, which was also used in the present study. However, the aforementioned study indicates that NLR and mGPS do not affect OS (16). Therefore, in gastric cancer, mGPS and CONUT scores may be useful prognostic indicators in unresectable cases treated with chemotherapy and resectable cases treated with surgery, respectively. Moreover, the association between mGPS/GPS and OS is highlighted as a strong prognostic factor in meta-analyses of multiple carcinomas (29). In the present study, multivariate analyses highlighted that a low mGPS was a possible independent favorable prognostic factor for PFS. Additionally, a low mGPS and low CONUT score were highlighted to be possible independent favorable prognostic factors for OS in multivariate analyses. These results supported the findings of previous reports (16,17,29). Furthermore, when patients were stratified according to whether the location of the primary tumor could be estimated or not, univariate analysis demonstrated that in cases where the location of the primary tumor could be estimated, low-mGPS was an independent favorable prognostic factor for PFS. In addition, a low mGPS and a low CONUT score were independent favorable prognostic factors for OS in cases where the location of the primary tumor could be estimated. However, in cases where the location of the primary tumor could not be estimated, a low mGPS and a low CONUT scores did not affect prognosis in terms of PFS and OS. This may be because, in the present study, the number of cases without an estimated location of the primary tumor was small, and the high clinical heterogeneity may have prevented an impact on prognosis. Therefore, future investigations should include a larger sample size. These results suggest that nutritional scores (low-mGPS and low-CONUT score) may serve as prognostic predictors for CUP before chemotherapy.

The present study suggested that the empirical regimen may be an improved prognostic factor compared with a site-estimated regimen in the univariate analysis of OS, excluding nutritional indices. In a previous report that estimates the primary tumor using DNA methylation profiles and reverse transcription PCR, treatment with a site-specific regimen notably prolonged OS compared with treatment with an empirical regimen (30,31). By contrast, a prospective randomized phase II clinical trial reports no notable difference in efficacy between empirical and site-estimated regimens (25). In general, site-specific regimens are based on gene expression profiles (25). However, in the present study, a site-estimated regimen was selected based exclusively on histological and immunological diagnoses; therefore, the regimens did not overlap. Despite this difference, the results of the present study did not support the efficacy of the site-estimated regimen, as the site-estimated regimen was not retained as an independent prognostic factor for OS in the multivariate analysis. However, the number of patients in the present study was small, which may have caused bias due to their high nutritional status. Therefore, additional studies should be conducted in the future.

The present study had a number of limitations. Firstly, the small sample size was a limitation, which may have potentially led to bias. Secondly, the present study was retrospective and was conducted at a single institution in Japan. Thirdly, although nutritional scores (such as the low-mGPS and low-CONUT score) were highlighted as potentially favorable prognostic factors in the present study, the cut-off values were determined based on prior research and standard cut-off values are yet to be established. Finally, a period of ~12 years was used to include patients into the present study, which is longer compared with the period of time used in the majority of cohort studies. During the long period of time used to include patients in the present study, the recommendations may have changed, especially in terms of site-estimated regimens, which may have affected survival outcomes.

In conclusion, the present study, to the best of our knowledge, indicated for the first time that nutritional scores, such as the mGPS and CONUT scores, are independent prognostic factors in patients undergoing chemotherapy for CUP. These nutritional scores may be useful biomarkers for estimating prognosis before chemotherapy.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

SY and TT conceived of the present study and drafted the manuscript. SN and YS collected clinical data and made substantial contributions to the conception and design of the present study. KMu, FF and KMi were involved in raw data analysis. MF and TK contributed to the analysis and interpretation of data and critically revised the manuscript for important intellectual content. TK supervised, wrote, reviewed and edited the manuscript. SY and TT confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was conducted in accordance with the principles in the Declaration of Helsinki and reviewed and approved by the Ethics Committee of Kurume University School of Medicine (approval no. 23229; Kurume, Japan). An opt-out approach was used to obtain informed consent from patients, and personal information was protected during data collection.

Patient consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

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