Prognostic Impact of the Controlling Nutrition Status Score in Patients With Peripheral T-cell Lymphoma

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Abstract

The controlling nutritional status (CONUT) is a simplified nutritional index calculated from serum albumin, total cholesterol, and the total lymphocyte count. Although the CONUT score is an independent prognostic factor in several hematological malignancies, the prognostic impact of the CONUT score in peripheral T-cell lymphoma (PTCL) is unclear. This study evaluated the prognostic impact of the CONUT score on overall survival (OS) in patients with PTCL. A multicentre, retrospective, cohort study including 99 patients with PTCL was conducted. The CONUT score was significantly higher in the non-survivor group (median 5, range 0-12) than in the survivor group (median 3, range 0-11) ($P = 0.026$). The CONUT score was an independent prognostic factor in a multivariable Cox proportional hazards model (hazard ratio 1.118, 95% confidence interval 1.020-1.225, $P = 0.017$). The Cox proportional hazards model with restricted cubic spline showed an S-shaped relationship between the CONUT score and OS. No significant effect-modification by the International Prognostic Index (IPI) was observed, and the CONUT score affected the prognosis of PTCL regardless of the IPI (P for interaction = 0.208). In conclusion, the CONUT score is an independent prognostic factor in patients with PTCL irrespective of IPI categories.

Introduction

Peripheral T cell lymphoma (PTCL) is a heterogeneous group arising from mature T-cells that account for less than 15% of all non-Hodgkin's lymphomas in adults ¹. Many patients with PTCL are treated with CHOP [cyclophosphamide (CPA), doxorubicin, vincristine (VCR), prednisolone (PSL)] or CHOP-like regimens, but the prognosis for patients with PTCL is inferior to that of patients with aggressive B-cell lymphoma ². Even though a new treatment strategy using CD30-directed antibody-drug conjugate (brentuximab vedotin) has recently been developed for CD30-positive PTCL ³, the current treatment strategies for PTCL remain unsatisfactory, and there is a need for better therapies based on accurate prediction of patients' prognosis. Prognostic risk stratification has been developed for PTCL, including the International Prognostic Index (IPI) ^{4,5} or the Prognostic Index for PTCL-U (PIT) ⁶, but patients' comorbidities have not been considered in these indices. Thus, there are modest discriminative abilities that are not sufficient for risk stratification to be clinically useful ⁷.

Poor nutrition is a frequent comorbidity in cancer patients and correlates with disease progression and survival ⁸. The controlling nutritional status (CONUT) score is a simplified nutritional index used to detect malnutrition and is calculated from serum albumin, total cholesterol, and the total lymphocyte count ⁹. Several cohort studies have reported that the CONUT score is an independent prognostic factor in solid cancer patients ¹⁰. In several haematological malignancies, including B-cell lymphoma, leukemia, and myeloma ¹¹⁻¹⁶, the CONUT score provided useful prognostic information. However, it remains unclear whether nutritional status has a clinical impact in patients with PTCL.

In this study, the aim was to evaluate the prognostic impact of the CONUT score on overall survival (OS) in patients with PTCL. The differential effects of IPI categories on survival in association with the CONUT

score were also explored using restricted cubic spline (RCS) to assess non-linear correlations with OS.

Results

Patients' characteristics.

A total of 132 patients newly diagnosed with PTCL at seven institutions of the Gifu Hematology Study Group were enrolled. Thirty patients with insufficient data and 3 patients with a treatment history of diffuse large B-cell lymphoma (DLBCL) were excluded, and the remaining 99 patients were included in this analysis (Fig. 1). Patient characteristics at diagnosis and comparing survivor ($n = 44$) and non-survivor groups ($n = 55$) are summarized in Table 1. The median age at diagnosis was 67 (range 16–87) years, and the most common pathological diagnosis was PTCL not otherwise specified (PTCL-NOS) ($n = 65$), followed by angioimmunoblastic T-cell lymphoma (AITL) ($n = 13$) and anaplastic large cell lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) ($n = 10$). The median CONUT score was 3 (0–12), and nutritional status was normal (0–1), mild (2–4), moderate (5–18), and severe (9–12) in 16 (16.2%), 45 (45.5%), 23 (23.3%), and 15 (15.2%) patients, respectively. Forty-four patients (44.4%) received CHOP, 43 patients (43.4%) received THP-COP (CPA, tetrahydropyranyl adriamycin, VCR, OSL), and 10 patients (10.1%) received best supportive care (BSC). There were more patients with high-intermediate or high IPI risk in the non-survivor group (72.2%) compared to the survivor group (38.7%) ($P < 0.001$). The CONUT score was significantly higher in the non-survivor group (median 5, range 0–12) than in the survivor group (median 3, range 0–11) ($P = 0.026$).

Table 1

Patients' characteristics at diagnosis. AITL angioimmunoblastic T-cell lymphoma, ALCL anaplastic large cell lymphoma, ALK anaplastic lymphoma kinase, BM bone marrow, BSC best supportive care, CONUT Controlling Nutritional Status, EATL enteropathy-associated T-cell lymphoma, ECOG PS Eastern Cooperative Oncology Group performance status, HSTL hepatosplenic T-cell lymphoma, IPI International Prognostic Index, LDH Lactate dehydrogenase, PTCL-NOS peripheral T-cell lymphoma not otherwise specified, T-Chol Total cholesterol, TLC total lymphocyte count, ULN Upper limit of normal.

Characteristics	All patients (N = 99)	Non-survivor group (n = 55)	Survivor group (n = 44)	P value
Age, y, median, range	67 (16–87)	69 (34–87)	62.5 (16–84)	0.010
Male - <i>n</i> (%)	69 (69.7)	39 (70.9)	30 (68.2)	0.828
Diagnosis - <i>n</i> (%)				
PTCL-NOS	65 (65.7)	39 (70.9)	26 (59.1)	0.002
AITL	13 (13.1)	8 (14.5)	5 (11.4)	
ALK-positive ALCL	10 (10.1)	1 (1.8)	9 (20.5)	
ALK-negative ALCL	5 (5.1)	1 (1.8)	4 (9.1)	
EATL	5 (5.1)	5 (9.1)	0 (0.0)	
HSTL	1 (1.0)	1 (1.8)	0 (0.0)	
ECOG PS ≥ 2 - <i>n</i> (%)	33 (33.3)	26 (47.3)	7 (15.9)	0.001
Extranodal sites ≥ 2 - <i>n</i> (%)	24 (24.5)	16 (29.6)	8 (18.2)	0.240
Ann Arbor Stage III/IV - <i>n</i> (%)	78 (78.8)	49 (89.1)	29 (65.9)	0.007
Elevated LDH ($> \text{ULN}$) - <i>n</i> (%)	59 (59.8)	37 (67.3)	22 (50.0)	0.101
Bulky mass - <i>n</i> (%)	6 (6.1)	2 (5.6)	4 (13.3)	0.399
B symptoms - <i>n</i> (%)	49 (50.0)	29 (53.7)	20 (45.5)	0.543
BM involvement (%)	21 (21.2)	13 (23.6)	8 (18.2)	0.623
IPI - <i>n</i> (%)				
Low (0, 1)	22 (22.2)	5 (9.3)	17 (38.6)	0.001
Low intermediate (2)	20 (20.2)	10 (18.5)	10 (22.7)	
High intermediate (3)	32 (32.3)	20 (37.0)	12 (27.3)	
High (4, 5)	24 (24.2)	19 (35.2)	5 (11.4)	
Serum albumin (g/dl) - median, range	3.7 (1.9–4.7)	3.3 (2.0–4.7)	3.75 (1.9–4.7)	0.006

Characteristics	All patients (N = 99)	Non-survivor group (n = 55)	Survivor group (n = 44)	P- value
T-Chol (mg/dL) - median, range	147 (72–252)	144 (72–252)	162 (84–246)	0.097
TLC (/μL) - median, range	1,140 (8-15218)	1,112 (8–15,218)	1,143.5 (79 – 9,020)	0.709
CONUT - n (%)				
Score - median, range	3 (0–12)	5 (0–12)	3 (0–11)	0.026
Normal (0–1)	16 (16.2)	7 (12.7)	9 (20.5)	0.043
Mild (2–4)	45 (45.5)	20 (36.4)	25 (56.8)	
Moderate (5–8)	23 (23.3)	17 (30.9)	6 (13.6)	
Severe (9–12)	15 (15.2)	11 (20.0)	4 (9.1)	
First treatment - n (%)				
CHOP	44 (44.4)	23 (41.8)	21 (47.7)	0.419
THP-COP	43 (43.4)	23 (41.8)	20 (45.5)	
Hyper-CVAD	2 (2.0)	1 (1.8)	1 (2.3)	
BSC/Steroid	10 (10.1)	8 (14.5)	2 (4.5)	

Predictors of overall survival.

The median follow-up was 5.46 (range 0.02–14.09) years, 55 patients (55.6%) died, and 37 of 55 (67.3%) patients died from lymphoma. The median OS was 3.72 years [95% confidence interval (CI) 1.60–6.79], and 5-year estimated OS was 47.5% (95% CI 36.7–57.5) (Fig. 2). A multivariable Cox proportional hazards model for OS was evaluated (Table 2). The IPI categories [hazard ratio (HR) 1.523, 95% CI 1.085–2.138, $P = 0.015$], the CONUT score (HR 1.118, 95% CI 1.020–1.225, $P = 0.017$), and BSC (HR 6.196, 95% CI 2.368–16.210, $P < 0.001$) were the independent prognostic factors for OS. The correlation between the CONUT score and OS was also examined in the covariate-adjusted Cox proportional hazards model with RCS. The Cox proportional hazards model with RCS showed the significant effect of the CONUT score on mortality risk, as did the Cox proportional hazards model (Fig. 3, P for effect of CONUT = 0.019). The relationship between the CONUT score and OS did not appear to be linear, but it was almost S-shaped. In those with a CONUT score < 5 , the log hazard ratio of the mortality risk was lower than 0, but plateaued. With CONUT scores 5–8, the log hazard ratio of the mortality risk was over 0 and rose steadily as the CONUT score increased. For CONUT scores > 8 , the curve of mortality risk was continually higher than 0, but approached a plateau.

Table 2

Univariable and multivariable Cox proportional hazards model of clinical factors significantly associated with overall survival. ALCL, anaplastic large cell lymphoma, ALK, anaplastic lymphoma kinase, BM, bone marrow, BSC, best supportive care, CI, confidence interval, CONUT, Controlling Nutritional Status, HR, Hazard ratio, IPI, International Prognostic Index.

Factor	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Female	1.097 (0.612–1.965)	0.755	0.991 (0.512–1.880)	0.977
ALK-positive ALCL	0.125 (0.017–0.906)	0.040	0.251 (0.033–1.904)	0.181
BM involvement	1.160 (0.623–2.163)	0.640	0.684 (0.321–1.457)	0.325
IPI, categories	1.985 (1.487–2.651)	< 0.001	1.523 (1.085–2.138)	0.015
CONUT, score	1.150 (1.064–1.244)	< 0.001	1.118 (1.020–1.225)	0.017
BSC	11.03 (4.810–25.290)	< 0.001	6.196 (2.368–16.210)	< 0.001

Prognostic impact of the CONUT score on overall survival.

According to the receiver operating characteristic (ROC) curves using Youden's index, the optimal cut-off value for the CONUT score was 5 (sensitivity 50.9%, specificity 77.3%), and the area under the curve (AUC) was 0.629 (95% CI 0.519–0.740) (Fig. 4). The Kaplan-Meier curves for the four groups of CONUT scores showed a worse prognosis for moderate (5–8) and severe (9–12) patients compared to normal (0–1) and mild (2–4) patients (Fig. 5a). When analyzed in two groups according to the CONUT score, the moderate and severe group with CONUT scores ≥ 5 had a worse prognosis compared to the normal and mild group with CONUT scores < 5 [median OS: 0.85 years (95% CI 0.35–1.97) vs. 6.79 years (95% CI 3.46 - not available), $P < 0.001$] (Fig. 5b).

Analysis of effect modification by IPI.

To assess whether IPI had an interaction effect with the impact of the CONUT score on OS, a multivariable Cox proportional hazards model was created with RCS in the binary group according to the IPI (low/low-intermediate risk: < 3 vs. high-intermediate/high risk: ≥ 3) (Fig. 6). No significant effect-modification by the IPI was observed, and the CONUT score affected the prognosis of PTCL regardless of the IPI (P for interaction = 0.208).

Discussion

This retrospective cohort study showed the prognostic utility of the CONUT score in patients with PTCL. The main findings of the study were as follows: first, the CONUT score was an independent prognostic factor for OS in PTCL; second, the Cox proportional hazards model with RCS showed an S-shaped

relationship between the CONUT score and OS; and third, no significant interaction was found between the IPI and the CONUT score.

First, the present data showed that the CONUT score was associated with predicting OS across the entire spectrum of PTCL. The CONUT score is an efficient nutritional screening tool for assessing the nutritional status of patients and is useful for early detection of undernutrition⁹. Malnutrition is prevalent in cancer patients, and nutritional status has a prognostic impact on disease progression and survival outcome⁸. The frequent malnutrition in cancer patients may be due to decreased activity, inadequate intake of food, and abnormal catabolic metabolism. Poor nutritional status is correlated with the toxicity of chemotherapy, resulting in treatment reduction or interruption¹⁷. The present findings were consistent with previous reports in other hematological malignancies, which showed the significant prognostic utility of the CONUT score in adult T-cell leukemia/lymphoma (ATLL)¹¹, DLBCL^{12,13}, multiple myeloma^{14,15}, myelodysplastic syndrome (MDS), and acute myeloid leukemia (AML)¹⁶. This study is the first to confirm the prognostic impact of the CONUT score in patients with PTCL.

Second, the Cox proportional hazards model with RCS showed an S-shaped relationship between the CONUT score and OS. This relationship indicated that patients with a CONUT score ≥ 5 had a log hazard ratio of mortality risk over 0. Similarly, the optimal cut-off value of the CONUT score using the ROC curve for predicting the OS of PTCL was 5, the AUC was 0.629 (95% CI 0.519–0.740), sensitivity was 50.9%, and specificity was 77.3%. Nagata et al. reported the usefulness of the CONUT score in DLBCL; using an ROC curve with a cut-off value of 4, the AUC was 0.71 (95% CI 0.59–0.78), sensitivity was 59.3%, and specificity was 77.8%¹². Sakurai et al. also reported the utility of the CONUT score in MDS and AML; using an ROC curve with a cut-off value of 5, the AUC was 0.71 (95% CI 0.59–0.83), sensitivity was 84.4%, and specificity was 60.9%. The present finding was also supported by previous studies and involved only PTCL patients.

Third, no significant effect modification was found between the IPI and the CONUT score. The IPI was developed to predict outcomes in patients with aggressive non-Hodgkin lymphoma¹⁸, and the usefulness of the IPI for PTCL was assessed in several studies^{4,5}. PTCL is not a homogeneous disease¹⁹; thus, the modification by the IPI of the impact of the CONUT score on OS was evaluated. Although various prognostic factors for PTCL have been proposed, none has been reported to be superior to the IPI⁷. Even patients with a low risk on the IPI have a poor prognosis. Recently, the prognostic importance of malnutrition assessment tools that directly reflect patient frailty independent of the IPI has been recognized¹². The CONUT score was an IPI-independent predictor for PTCL in the present study. Thus, the combination of the IPI with the CONUT score can serve to refine risk stratification further to dictate treatment strategy. Unfortunately, the present results could not provide the optimal treatment, and future study is required to improve the prognosis of patients with PTCL.

PTCL is heterogeneous, and the prediction of chemosensitivity is important to select optimal treatment. Various prognostic factors, such as the IPI and PIT, have been developed and validated for PTCL, but they

have not led to stratified treatment ⁷. For patients with a high CONUT score may not be able to achieve long-term survival with conventional treatment, and it is necessary to establish new treatment methods or consider individualized treatment options in the future.

The present study was a multicentre, cohort study that was able to collect a relatively large number of patients with PTCL and to follow their long-term course. However, there were several limitations to this study. First, the current study was retrospective and could have had selection bias. Second, the study did not provide detailed information on treatment dose intensity or treatment toxicity. Third, the present study could not validate comparisons or combinations with other nutritional indicators or frailty scales. Finally, there is an absence of validation for the cut-off of the CONUT score, and these data warrant external validation in a future study.

In conclusion, the nutritional status evaluated by the CONUT score appears to be a prognostic factor in patients with PTCL, irrespective of IPI categories.

Methods

Patient cohort.

A multicentre, retrospective, cohort study was conducted by the Gifu Hematology Study Group in Japan. The Gifu Prefecture of Japan has a population of 2.03 million (2015 census). Data on PTCL admissions from June 2004 to December 2019 were retrospectively collected. All histologically proven PTCL cases according to the World Health Organization classification ¹⁹ with patients aged 18 years and older were eligible for inclusion. PTCL subtypes included PTCL-NOS, AITL, ALCL with or without ALK, enteropathy-associated T-cell lymphoma, and hepatosplenic T-cell lymphoma. Exclusion criteria were any previous other chemotherapy for lymphoma or diagnosed with ATLL or extranodal NK/T-cell lymphoma, nasal type. Patients with central nervous system involvement or human immunodeficiency virus were also excluded. Variables included age, Eastern Cooperative Oncology Group Performance Status, number of extranodal sites, Ann Arbor stage, serum lactate dehydrogenase (LDH) levels, bulky mass (> 7.5 cm), B symptoms, bone marrow (BM) involvement, and all-cause death. The IPI was calculated using these data, and four risk categories were created ¹⁸. The treatment strategy was determined by the attending physician. If the patient received treatment with the intent to maximize the quality of life without a specific antineoplastic regimen, it was classified as BSC. BSC included steroids, antibiotics, analgesics, antiemetics, blood transfusions, or palliative radiation to control pain. This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the ethics committee of Gifu University Graduate School of Medicine (number: 2019 – 255). The Institutional Review Board of each participating center approved the protocol with a waiver of informed consent prior to data collection.

Controlling Nutrition Status Score.

As previously reported, the CONUT score was calculated from the serum albumin, total cholesterol, and total lymphocyte count ⁹. The data from the blood tests at the time of diagnosis were used. If abnormal

lymphocytes were present, they were excluded from the total lymphocyte count. Patients were divided into four categories according to the degree of undernutrition as follows: normal (0–1), mild (2–4), moderate (5–8), and severe (9–12) (Supplementary Table S1).

Statistical analysis.

The primary endpoint was OS, which was calculated from diagnosis to the last follow-up or death from any cause. Patients who became untraceable were censored at the last observation. Continuous variables are expressed as median values and range, and the groups were compared using the Mann-Whitney U test. Categorical variables are expressed as numbers and percentages, and the groups were compared using the chi-squared test or Fisher's exact test, as appropriate. Multivariable Cox proportional hazards model was fit to assess associations between prior specified traditional predictors of PTCL and OS. Sex, ALK-positive ALCL, BM involvement, IPI, CONUT score, and BSC were selected as predictors and used as covariates in a multivariable analysis. Non-linear regression with an RCS with 4 knots was used to examine the presence of a non-linear relationship between the CONUT score and mortality risk. The number of knots was determined using Akaike's information criterion. The optimal cut-off value of the CONUT score was determined by ROC curve analysis using Youden's index. Survival curves for each group were estimated using Kaplan-Meier's method and compared using the log-rank test. We planned a priori to examine the effect modification on the association between the CONUT score and IPI categories. A two-sided $P < 0.05$ and P for interaction < 0.15 were considered significant. Statistical analyses were performed with R (version 3.6.2), with the package rms for non-linear regression modeling, or EZR (version 1.37), which is a graphical user interface for R ²⁰.

Declarations

Acknowledgments

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Author contributions

N.N. and N.K. contributed to the study design, data collection, analysis, interpretation of the data, and manuscript writing. S.L., K.F., and T.M. helped to analyze the data and contributed to the study design, interpretation of the data, and manuscript writing. E.T., Y.S., H.G., K.F., T.Y., and M.S. provided study materials. All authors reviewed and approved the final version of the document.

Competing Interest

The authors declare no competing interests.

Data availability

The datasets generated during the current study are available from the corresponding author on reasonable request.

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Figures

Figure 1.

Figure 1

Flow chart of patient selection. CONUT, controlling nutritional status. DLBCL, diffuse large B-cell lymphoma. PTCL, peripheral T-cell lymphoma.

Figure 2.

Figure 2
Kaplan-Meier curves of overall survival in 99 patients.

Figure 3.

Figure 3

Association between the CONUT score and overall survival using the Cox proportional hazards model with restricted cubic spline with 4 knots. The solid line represents the log hazard ratio, and the shaded area is the 95% confidence interval. CONUT, controlling nutritional status.

Figure 4.

Figure 4

Receiver operating characteristic curves of the CONUT score for predicting mortality. AUC. area under the curve. CONUT, controlling nutritional status.

Figure 5.

Figure 5

Kaplan-Meier curves of overall survival among 4 groups (a) and 2 groups (b) of the CONUT score. CONUT, controlling nutritional status.

Figure 6.

Figure 6

Association between the CONUT score and overall survival of four groups divided by the International Prognostic Index using a covariate-adjusted restricted cubic splined hazard model. The solid line represents the log hazard ratio, and the shaded area is the 95% confidence interval. IPI, International Prognostic Index. CONUT, controlling nutritional status.

Supplementary Files

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- [PTCLCONUTTableS120210417.pdf](#)