Original Article

Controlling nutritional status is a prognostic factor for patients with lung cancer: a systematic review and meta-analysis

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Background: Nowadays, controlling nutritional status (CONUT) has been used as a prognostic factor in variety of cancers. However, no consensus has been reached on the prognostic value of CONUT in lung cancer. In this study, we aim to investigate the role of CONUT in survival of patients with lung cancer.

Methods: EMBASE, web of science, and Medline were used to search articles in English-language journals. The association between CONUT score and survival of patients with lung cancer was evaluated by using pooled HRs and their 95% CIs. Chi-square test and I-Square was used to test heterogeneity among studies. Analyses were all performed using Stata 13.0 (Stata Corporation, College Station, TX).

Results: Eight studies with 1,836 patients were eventually included in this meta-analysis. The pooled results showed that high CONUT score had an unfavorable impact on OS (HR =1.63, 95% CI: 1.30–2.04), DFS (HR =1.75, 95% CI: 1.35–2.26), CSS (HR =1.45, 95% CI: 1.01–2.07) and PFS (HR =1.67, 95% CI: 0.99–2.35), compared with those with low-CONUT.

Conclusions: CONUT can be used as a predictor of prognosis in patients with lung cancer. High-CONUT score was significantly associated with poor OS, DFS, CSS and PFS.

Keywords: Controlling nutritional status (CONUT); lung cancer; prognostic factor

Submitted Nov 23, 2020. Accepted for publication Jan 15, 2021.
doi: 10.21037/apm-20-2328
View this article at: http://dx.doi.org/10.21037/apm-20-2328

Introduction

Lung cancer is a main cause of cancer death worldwide. Despite the development of a variety of treatments, including surgery, radiotherapy and chemotherapy, the prognosis of lung cancer patients is still very poor (1). Even with pathological stage I non-small cell lung cancer, 10–20% of patients will relapse and die after undergoing curative surgery (2).

Over the years, people have been studying the prognostic factors of lung cancer. More and more evidence showed that systemic inflammation and malnutrition are related to the poor prognosis of various malignant tumors. So far, many inflammatory and nutritional markers have

Table 1 The CONUT scoring system

Parameter	Degree			
	Normal	Light	Moderate	Severe
Serum albumin (g/dL)	≥3.5	3.0–3.49	2.50–2.99	<2.50
Score	0	2	4	6
TC (mg/dL)	≥180	140–179	100–139	<100
Score	0	1	2	3
TLC (/mm^3)	≥1,600	1,200–1,599	800–1,199	<800
Score	0	1	2	3

CONUT, controlling nutritional status; TC, total serum cholesterol; TLC, total lymphocyte count.

been advanced to predict the prognosis of lung cancer, including neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), C-reactive protein to albumin ratio (CAR), lymphocyte to monocyte ratio (LMR) and advanced lung cancer inflammation index (ALI) (3-6).

Controlling nutritional status (CONUT) was first proposed by Ignacio de Ulíbarri *et al.* based on three parameters, including serum albumin, total lymphocyte count and total cholesterol (7). The scoring system stratifies the CONUT into 4 levels (none/normal: 0; mild/light: 1; moderate: 2; severe: 3) (*Table 1*). Albumin is considered to be one of the indicators for evaluating human nutritional status, and it can also be used as an acute phase protein to mediate inflammation (8). At present, a large number of studies have confirmed that patients with low albumin level before anti-tumor treatment have poor prognosis. The change of albumin level is closely related to the stage of tumor, and albumin level can reflect the disease progression of patients with malignant carcinoma (9). Lymphocytes play a very important role in tumor immunity. The decrease in the number and the functional defects of lymphocytes indicate a weakened immune system (10). As one of the structural components of cell membrane, cholesterol participates in certain signal pathways being considered necessary for malignant transformation. Many studies have confirmed the relationship between cholesterol and cancer (11). According to recent reports, people with low-density lipoprotein cholesterol levels are more likely to develop tumors (12).

According to the report, CONUT can be used as a prognostic factor to evaluate the prognosis of esophageal cancer, colorectal cancer and other cancers (13-15). However, no consensus has been reached on the prognostic value of CONUT in patients with lung cancer. Thus, we conducted this study to investigate the role of the CONUT score in survival of lung cancer patients. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/apm-20-2328).

Methods

Search strategy

EMBASE (OVID, 1990 to October 1, 2020), web of science (1990 to October 1, 2020), and Medline (PubMed, 1990 to October 1, 2020) were used. Medical subject heading (MeSH) was used: "Lung Cancer" [Mesh], "controlling nutritional status" [Mesh], "Pulmonary Neoplasms", "Neoplasms, Lung", "Lung Neoplasm", "Neoplasm, Lung", "Neoplasms, Pulmonary", "Neoplasm, Pulmonary", "Pulmonary Neoplasm", "Lung Cancer", "Cancer, Lung", "Cancers, Lung", "Lung Cancers", "Pulmonary Cancer", "Cancer, Pulmonary", "Cancers, Pulmonary", "Pulmonary Cancers", "Cancer of the Lung", "CONUT". Only articles published in English language were included.

Selection criteria

The eligibility of studies was assessed by two independent reviewers by reviewing titles, abstracts or full text identified by the search. The inclusion criteria were as follows: (I) the patients in the study were diagnosed as lung cancer histologically; (II) serum albumin, total lymphocyte count, and total cholesterol were detected; (III) hazard ratio (HR) and 95% confidence interval (CI) can be estimated by ample survival data; (IV) Only the newest, largest, or most informative article was included if there were multiple articles based on similar populations. The exclusion criteria were as follows: (I) in animal experiments or vitro studies; (II) review, meeting, comment, editorial, meta-analysis, expert opinion, basic research, and case report; (III) non-English.

Quality assessment and data extraction

Two reviewers (Chi Zhang and Xiao-Kun Li) assessed the eligible studies, and disagreements were resolved by a third reviewer (Zhuang-Zhuang Cong). Characteristics (first author, publication year, country, number of patients, cut-off values, etc.) were extracted from included studies into results table. The following data were extracted for

statistical analysis: gender, age, body mass index (BMI), T stage, N stage, TNM stage, differentiation, smoking, pleural invasion, lymphatic invasion, vascular invasion, surgical procedure, histology, serum carcinoembryonic antigen (CEA), neutrophil–lymphocyte ratio (NLR), performance status and prognostic outcomes (OS, DFS, CSS, PFS). Survival data, including HR, CI, and P value, were extracted from text or tables of the included articles. Only the data of multivariate analysis were extracted when both univariate and multivariate analysis for survival outcome were provided, since the multivariate analysis is more precise compared with univariate analysis. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the included studies, consisting of three factors: patient selection, comparability of the study groups, and assessment of outcome (16). Studies were assigned using a score of 0–9, and the high-quality study was defined as a study with quality scores ≥ 6.

Statistical analysis

Pooled hazard ratios (HR) and their 95% confidence intervals (95% CI) were used to evaluate the association between CONUT score and survival of lung cancer patients, and pooled odds ratios (OR) and their 95% CIs were used to evaluate the association between CONUT score and clinicopathological parameters. Statistical parameters were calculated from available numerical data by methods of Parmar *et al.* (17) when not given directly in a study. Chi-square test and I^2 was used to test heterogeneity among studies. When I^2>50% or P value <0.1 indicated significant heterogeneity among studies. If heterogeneity was identified among studies, a random effects model was selected to pool the ORs or HRs, otherwise a fixed effects model was performed. By convention, HR >1 implied a worse survival outcome in high-CONUT group. Effect of high-CONUT on survival was considered to be statistically significant when 95% CI for the HR did not overlap 1. The funnel plot with Egger's weighted regression method and Begg's rank correlation method (18,19) was used to evaluate the publication bias. P values <0.05 were considered as statistical significance. A trim and fill analysis (20) were performed when publication bias was indicated, estimating the number of missing studies (comparisons) in the original dataset and providing a true effect size which has no publication bias. Analyses were all performed using Stata 13.0 (Stata Corporation, College Station, TX).

Results

Search results

The search results have been shown in *Figure 1*. In our study, 318 studies were initially identified from three electronic databases. After screening the title of citations, 173 studies were excluded since they were duplicate studies. After reading the abstracts and full text, 116 of which were excluded for not fulfil the inclusion criteria. After reviewing 29 potentially eligible articles in detail, 8 studies were eventually included in this meta-analysis (21-28).

Study characteristics

The characteristics of eligible studies are summarized in *Table 2*. A total of 8 studies published from 2017 to 2020 met the criteria for this meta-analysis. Six studies (21,23-26,28) were conducted in Japan and the remaining two originated from Korea (27) and Turkey (22). All of studies were based on retrospective analysis of the data. The sample sizes of these studies ranged from 32 to 922 patients, with a total of 1,836 patients. Five studies (23,25-28) investigated squamous cell carcinoma and adenocarcinoma, while the remaining three studies investigated only squamous cell carcinoma (24), adenocarcinoma (21) or small cell lung cancer (22). According to cut-off values defined by each study's author for high-CONUT score, 796 patients (43.4%) in this meta-analysis had high-CONUT score, ranging from 29.6% to 67.8%. HRs on overall survival (OS), disease-free survival (DFS), cancer-specific survival (CSS) and progression-free survival (PFS) could be extracted from 7, 4, 2 and 2 of studies, respectively. Since the study by Lee *et al.* (27) did not provide the original data and only twelve months of Kaplan–Meier survival curves was provided, HR and 95% CI was not calculated for the accuracy of the conclusion. The Newcastle-Ottawa quality assessment scale (NOS) score for study quality ranged from 6 to 8.

Association between CONUT score and prognosis

The association between CONUT score and OS was provided in 7 studies (21-26,28), including 914 patients (*Figure 2A*). Heterogeneity was nonsignificant (χ^2=2.98, P=0.812, I^2<0.1%), thus, a fixed effects model was conducted. The pooled analysis (HR =1.63, 95% CI: 1.30–2.04; P<0.001), suggesting that patients with high-CONUT score had shorter OS than those with low-CONUT score.

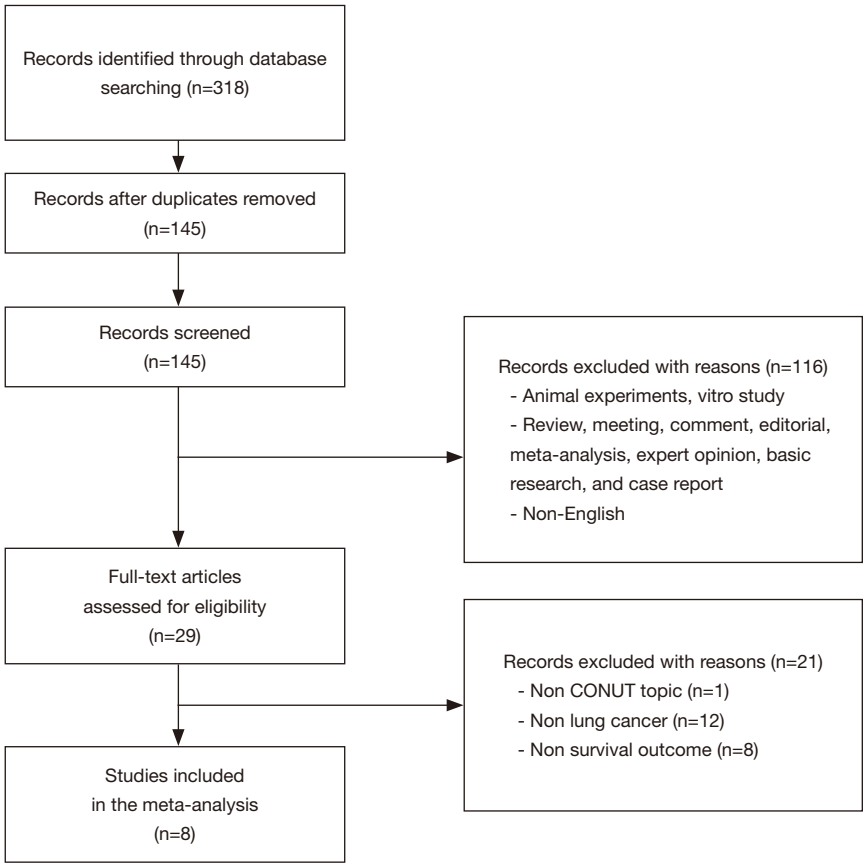

Figure 1 Flow chart.

To investigate the association between CONUT score and DFS, 4 studies (21,24,25,28) with a total of 528 patients were included (*Figure 2B*). Heterogeneity was not observed in the analysis (χ^2=2.41, P=0.544, I^2<0.1%). A fixed effects model was used, and the pooled results showed that patients with low-CONUT score have a better DFS compared with patients with high-CONUT score (HR =1.75, 95% CI: 1.35–2.26; P<0.001).

Two studies (25,26) investigated the association between CONUT score and CSS, including 260 patients (*Figure 2C*). A fixed effects model was chosen due to heterogeneity was not observed in the analysis (χ^2<0.01, P=0.961, I^2<0.1%). The pooled HR was 1.45 (95% CI: 1.01–2.07; P=0.045), suggesting that high-CONUT score was significantly associated with worse CSS.

A total of 248 patients in 2 studies (22,23) were evaluated to analyze the correlation between CONUT score and the PFS (*Figure 2D*). Pooled results indicated an association between a high CONUT score and poor PFS (HR =1.67, 95% CI: 0.99–2.35; P<0.001). For no heterogeneity was observed (χ^2=5.15, P=0.254, I^2=23%), a fixed effects model was used for the analysis.

Association between CONUT score and clinicopathological characteristics

We investigated the association between CONUT score and the clinicopathological characteristics of patients with lung cancer. Pooled results showed that CONUT score was high in elderly patients [odds ratio (OR) =1.47, 95% CI: 1.18–1.82; P<0.001], male patients (OR =1.47, 95% CI: 1.18–1.82; P=0.001), high-stage (OR =0.51, 95% CI: 0.40–0.65; P=0.001), smoking (OR =1.61, 95% CI: 1.31–1.97; P<0.001), abnormal level of preoperative CEA (OR =0.43, 95% CI: 0.25–0.73; P=0.002) and NLR (OR =3.91, 95% CI: 2.28–6.72; P<0.001). However, we detected no significant associations between CONUT score and BMI (OR =0.32, 95% CI: 0.09–1.16; P=0.084), T stage (OR =0.63, 95% CI: 0.40–1.01; P=0.055), N stage (OR =0.65, 95% CI: 0.33–1.30; P=0.222), differentiation (OR

Table 2 Characteristics of the selected studies included in the meta-analysis

Author	Year	Country	Study type	Number (male/female)	Mean age (range)	Tumor stage	Cut-off	CONUT score	Outcome	Quality[a]
Akamine *et al*. (21)	2017	Japan	Retrospective, single center	109 [76/33]	72 [45–85]	I: 74; II: 24; III: 9; IV: 2	≥1	0:35 (32.1%); ≥1:74 (67.8%)	OS; DFS	8
Shoji *et al*. (26)	2017	Japan	Retrospective, single center	138 [79/59]	68 [37–86]	I: 138	≥1	0:59 (42.8%); ≥1:79 (57.2%)	CSS; OS; RFS	7
Toyokawa *et al*. (24)	2017	Japan	Retrospective, single center	108 [96/12]	71 [45–89]	I: 61; II: 30; III: 17	≥2	≤1:76 (70.4%); ≥2:32 (29.6%)	OS; DFS	8
Ohba *et al*. (23)	2019	Japan	Retrospective, single center	32 [29/3]	65 [44–85]	III; IV	≥3	≤2:22 (68.8%); ≥3:10 (31.2%)	OS; PFS	7
Takamori *et al*. (28)	2019	Japan	Retrospective, single center	189 [113/76]	68 [29–93]	I [145]; ≥II [44]	≥2	≤1:127 (67.2%); ≥2:62 (32.8%)	OS; DFS	8
Lee *et al*. (27)	2020	Korea	Retrospective, single center	922 [522/400]	64.2	I [665]; II/III [257]	≥2	≤1:552 (59.9%); ≥2:370 (40.1%)	1-year mortality	7
Miura *et al*. (25)	2020	Japan	Retrospective, single center	122 [69/53]	79 [75–91]	I [96]; II/III [26]	≥1	0:57 (57.6%); ≥1:42 (42.4%)	OS; DFS; CSS	7
Yılmaz *et al*. (22)	2020	Turkey	Retrospective, single center	216 [184/32]	61 [36–83]	I–III [59]; IV [157]	≥2	≤1:89 (41.3%); ≥2:127 (58.7%)	OS; PFS	7

[a], score from a maximum of 9 evaluated by the Newcastle-Ottawa quality assessment scale for cohort studies. CONUT, controlling nutritional status; OS, overall survival; DFS, disease-free survival; CSS, cancer-specific survival; PFS, progression-free survival; RFS, recurrence-free survival.

=0.92, 95% CI: 0.47–1.79; P=0.81), pleural invasion (OR =0.92, 95% CI: 0.47–1.79; P=0.81), lymphatic invasion (OR =1.25, 95% CI: 0.74–2.11; P=0.398), lymphatic invasion (OR =1.11, 95% CI: 0.54–2.29; P=0.783), vascular invasion (OR =1.45, 95% CI: 0.90–2.36; P=0.13), surgical procedure (OR =1.02, 95% CI: 0.74–1.39; P=0.926), Histology (OR =0.78, 95% CI: 0.37–1.66; P=0.52), and performance status (OR =0.90, 95% CI: 0.36–2.27; P=0.826). Heterogeneity was observed in the analysis of the relationships between CONUT score and BMI (P<0.001, I^2=87.6%) and histology (P=0.007, I^2=75.5%), therefore, a random effects model was used. The other assessments were performed using a fixed effects model (*Table 3*).

Cut-off values of CONUT score

Three studies (21,25,26) used 1 as cut-off, including 369 patients. The pooled HR was 1.55 (95% CI: 1.10–2.18, P=0.012). Three studies (22,24,28) used 2 as cut-off including 513 patients (HR =1.63, 95% CI: 1.21–2.21, P=0.002). These two subgroup analyses both observed that high-CONUT score was associated with unfavorable prognostic outcomes regardless of cut-off value.

Publication bias

There was publication bias for OS (Egger test, P=0.023) and DFS (Egger test, P=0.013). The trim and fill analysis suggested that 2 studies (comparisons) were missing from our datasets respectively (marked with a square border in Fig.3a and Fig.3b). Nevertheless, reported significant effects of CONUT on the survival outcomes were complete (OS: HR =1.553, 95% CI: 1.251–1.929; DFS: HR =1.581, 95% CI: 1.265–1.976) after adding those missing data to the original datasets, suggesting that the impact of publication bias on the overall results was negligible.

Discussion

In recent years, many researchers have focused on inflammation and nutritional status in various solid tumor for growing evidence has proven it a key role in the carcinogenesis, progression, and metastasis of cancer (29-32). It has been reported that CONUT can be used as an index to evaluate the prognosis of many solid cancers. Takagi *et al.* (33) conducted a meta-analysis investigating the prognostic value of CONUT in hepatocellular

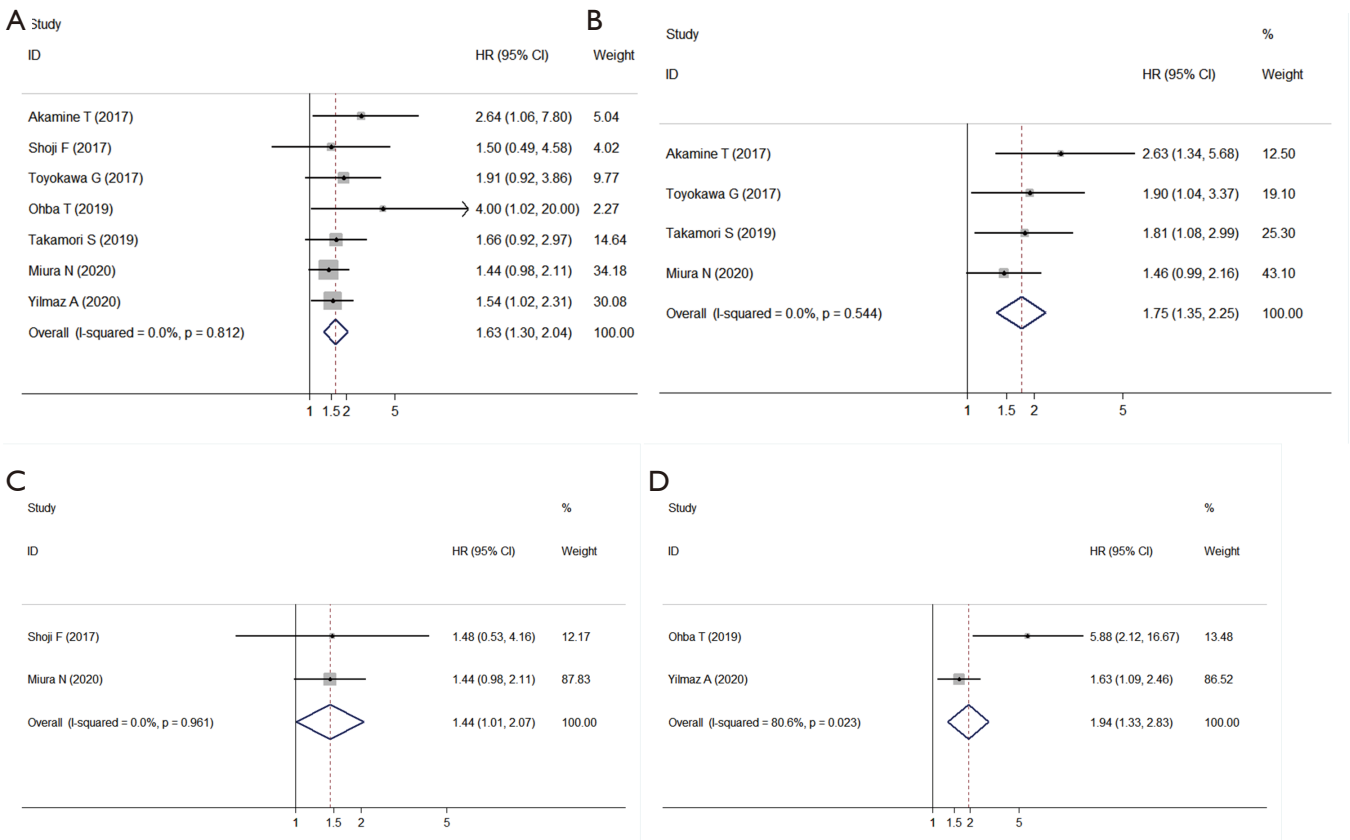

Figure 2 Forest plots demonstrating primary endpoint in terms of high controlling nutritional status (CONUT) group versus low CONUT group. (A) Overall survival; (B) disease-free survival; (C) cancer-specific survival; (D) progression-free survival.

carcinoma (HCC) patients undergoing hepatectomy. The results demonstrated that high-CONUT has a poor impact on OS and RFS in HCC patients. Takagi *et al.* (34,35) also conducted another two meta-analyses exploring the prognostic value of CONUT in gastric and colorectal cancer. The results revealed that both gastric and colorectal cancer patients with a high-COUNT score had reduced OS, CSS and RFS. Toyokawa *et al.* (36) introduced the CONUT as a prognostic factor in patients undergoing curative thoracoscopic esophagectomy. They found that the patients with low-CONUT yielded significantly longer OS and RFS compared with high-COUNT group. Huang *et al.* (37) confirmed that CONUT score was a prognostic factor for breast cancer patients. The results showed that low-CONUT yielded significantly longer OS and RFS compared with high-COUNT group. However, the relationship between CONUT score and the prognosis of patients with lung cancer remains controversial. As we know, this systematic review and meta-analysis is the first study of the prognostic significance of the CONUT score in lung cancer patients. And the results showed that high-CONUT score has unfavorable prognostic outcomes in patients with lung cancer.

Our meta-analysis included 8 studies with 1,836 patients and illustrated that high CONUT score has an unfavorable impact on OS (HR =1.63, 95% CI: 1.30–2.04), DFS (HR =1.75, 95% CI: 1.35–2.26), CSS (HR =1.45, 95% CI: 1.01–2.07) and PFS (HR =1.67, 95% CI: 0.99–2.35). However, Miura *et al.* (25) proved no statistical differences both in DFS (P=0.9238) and CSS (P=0.8661) in Kaplan–Meier analysis. Takamori *et al.* (28) found that CONUT score was not an independent prognostic factor for DFS (HR =1.66, 95% CI: 0.92–2.97; P=0.088). Several probable reasons for these inconsistent results have been speculated. One reason may be that the cut-off values adopted were different though all the investigators used Receiver operating characteristics curve (ROC) to determine the optimal cut-off value of CONUT. A study by Akamine

Table 3 Relationships between CONUT score and clinicopathological features

Clinicopathological feature	Studies	Heterogeneity		OR (95% CI)	P value
		P value	I^2 (%)		
Gender	7	0.860	0	1.47 (1.18–1.82)	0.001
Age	7	0.188	31.4	1.73 (1.41–2.13)	0.000
BMI	5	0.000	87.6	0.32 (0.09–1.16)	0.084
T	3	0.913	0	0.63 (0.40–1.01)	0.055
N	2	0.321	0	0.65 (0.33–1.30)	0.222
Stage	4	0.240	28.7	0.51 (0.40–0.65)	0.000
Differentiation	2	0.565	0	0.92 (0.47–1.79)	0.810
Smoking	7	0.322	14.2	1.61 (1.31–1.97)	0.000
Pleural invasion	3	0.853	0	1.25 (0.74–2.11)	0.398
Lymphatic invasion	3	0.559	0	1.11 (0.54–2.29)	0.783
Vascular invasion	3	0.950	0	1.45 (0.90–2.36)	0.130
Surgical procedure	3	0.401	0	1.02 (0.74–1.39)	0.926
Histology	4	0.007	75.5	0.78 (0.37–1.66)	0.520
CEA	2	0.736	0	0.43 (0.25–0.73)	0.002
NLR	2	0.558	0	3.91 (2.28–6.72)	0.000
Performance status	2	0.595	0	0.90 (0.36–2.27)	0.826

CONUT, controlling nutritional status; OR, odds ratio; BMI, body mass index; T, pathological T status; N, pathological N status; CEA, carcinoembryonic antigen; NLR, neutrophil-to-lymphocyte ratio.

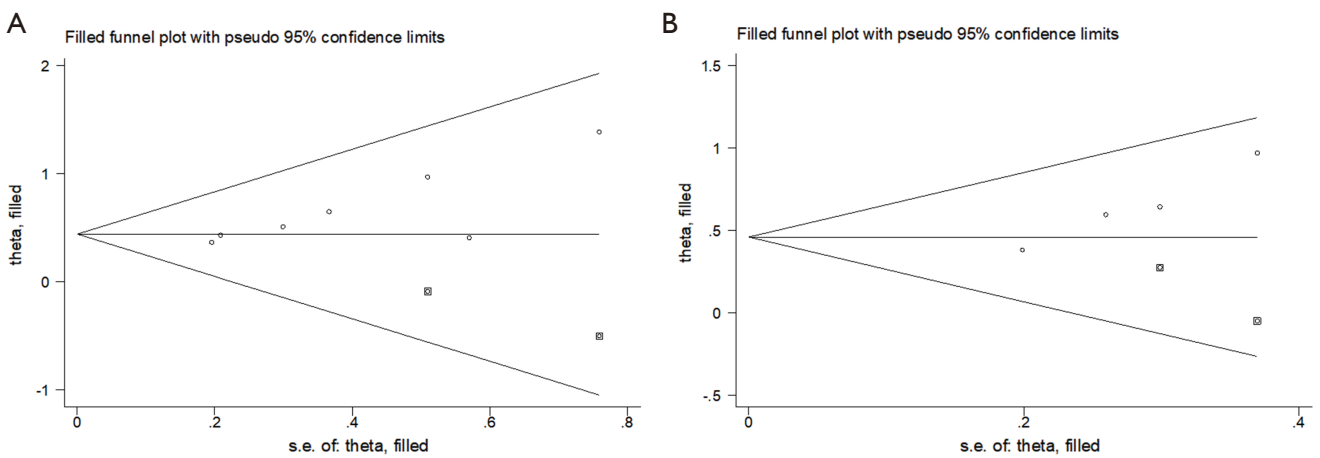

Figure 3 A funnel plot to assess potential publication bias. The circles and squares represent observed data and data added by the trim-and-fill analysis (see the main text). (A) Funnel plot of overall survival; (B) funnel plot of disease-free survival.

et al. (21) demonstrated no significant association between the CONUT and the DFS and OS when the cut-off score was set at 2. Contrary to Akamine's conclusion, other studies (22,24,28) using 2 as the cut-off score confirmed the consistent prognostic value of CONUT. Moreover, the clinicopathological characteristics of each study were also different. Akamine's study only assessed patients with lung adenocarcinoma with obstructive lung disease, Shoji's study (26) only analyzed clinicopathological features of pathological stage I non-small cell lung cancer (NSCLC) patients, Ohba's (23) study only included patients with advanced NSCLC who received pembrolizumab monotherapy, Miura's (25) study only contained Elderly NSCLC patients.

Analysis in subgroup of different cut-off values was also performed. Both of the subgroup analysis showed significant differences [1 (HR =1.55, 95% CI: 1.10–2.18; P=0.012); 2 (HR: 1.63, 95% CI: 1.21–2.21; P=0.002)]. Besides, the study by Ohba *et al.* (23) used 3 as cut off value (HR =4.00, 95% CI: 1.02–20; P=0.048) also indicated significant differences. There is not much variation between the results produced using different cut-off values, and more research is needed to get uniform standards.

The biological mechanism explaining the correlation between the CONUT score and outcomes has not been adequately researched. Each component of the CONUT score is related to the prognosis of patients with lung cancer. The level of total lymphocyte count reflects the body's immune level and the development of tumorigenesis (38). Serum albumin itself is the main indicator of nutritional status, and is also the acute phase protein mediating inflammatory response (8). The production of albumin can also be regulated by inflammatory factors such as IL-6 or hormones (39). The change of albumin level is closely related to tumor stage, that is, albumin levels can reflect the progression of disease in lung cancer patients (40). Cholesterol is essential for maintaining the integrity, fluidity, and function of cell membranes and safeguarding signal transduction. Serum cholesterol levels have been reported to correlate with lung cancer progression and survival (41). In our analysis, we also noted that high CONUT score was significantly associated with elderly patients, male patients, advanced TNM stages, smoking and abnormal preoperative serum CEA, NLR level. These clinicopathological features are recognized as significant factors in the poor prognosis of cancer patients, providing evidence for the scientific validity of CONUT on the other hand.

Limitation

All the studies included were from Asia. Moreover, the cut-off value used to evaluate CONUT score may lack sensitivity and yield false-negative results, and there is no unified standard up to now. Although we used the trim and fill analysis when there is publication bias, the method failed to consider the other causes of funnel plot asymmetry except publication bias. The reason may be related to the number of included articles, the source of the studies, the clinical features of the patients included, types of research and so on. The existence of these defects indicates the necessity for more high-quality studies exploring the correlation of CONUT with survival outcomes in patients with lung cancer.

Conclusions

CONUT can be used as a predictor of prognosis in patients with lung cancer. High-CONUT score was significantly associated with poor OS, DFS, CSS and PFS.

Acknowledgments

The authors would like to acknowledge the support of all colleagues in Department of Cardiothoracic Surgery in Jinling Hospital.
Funding: This work was supported by the National Natural Science Foundation of China (81172032) and the Natural Science Foundation of Jiangsu Province (BK20181239).

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at http://dx.doi.org/10.21037/apm-20-2328

Peer Review File: Available at http://dx.doi.org/10.21037/apm-20-2328

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-2328). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Zhang C, Li XK, Cong ZZ, Zheng C, Luo C, Xie K, Xu Y, Gu WF, Qiang Y, Shen Y. Controlling nutritional status is a prognostic factor for patients with lung cancer: a systematic review and meta-analysis. Ann Palliat Med 2021;10(4):3896-3905. doi: 10.21037/apm-20-2328

