Prognostic impact of the pre-treatment controlling nutritional status score in patients with non-small cell lung cancer
A meta-analysis

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Abstract
Background: The influence of pre-treatment controlling nutritional status (CONUT) score on the prognosis of non-small cell lung cancer (NSCLC) patients is inconclusive. We performed this meta-analysis to evaluate the prognostic significance of CONUT score in NSCLC patients.

Methods: A systematic literature review was conducted using PubMed, Embase, and the Cochrane Library databases. The hazard ratio (HR) and 95% confidence interval (CI) were extracted to assess the correlation between the CONUT score and the overall survival (OS), disease-free survival (DFS), recurrence-free survival (RFS), as well as the cancer-specific survival.

Results: A total of 11 studies with 3029 patients were included in the analysis. Pooled results indicated that a high CONUT score was positively correlated with poor OS (HR: 1.63, 95%CI: 1.40–1.88, P<.001) and shortened DFS/RFS (HR: 1.65, 95%CI: 1.35–2.01, P<.001), but no significant relationship with the cancer-specific survival (HR: 1.28, 95%CI: 0.60–2.73, P=.517) was identified. The negative effect of high CONUT score on the OS and DFS/RFS was detected in every subgroup with varying treatment methods, cancer stage, CONUT cut-off values, sample size, and analysis methods of HR. Additionally, preoperative high CONUT score was an independent predictor of postoperative complications (odds ratio: 1.58, 95%CI: 1.21–2.06, P=.001) in NSCLC. Last but not least, high CONUT score was not significantly correlated with the patients’ sex, smoking status, cancer stage, lymphatic invasion, vascular invasion, pleural invasion, and pathological cancer type.

Conclusion: These results demonstrate that high CONUT score is positively related to poor prognoses. The CONUT score may therefore be considered as an effective prognostic marker in NSCLC patients.

Abbreviations: CI = confidence interval, CONUT = controlling nutritional status, CSS = cancer-specific survival, DFS = disease-free survival, GPS = Glasgow prognostic score, HR = hazard ratio, NOS = Newcastle-Ottawa Quality Assessment Scale, NSCLC = non-small cell lung cancer, OS = overall survival, RFS = recurrence-free survival.

Keywords: controlling nutritional status score, meta-analysis, non-small cell lung cancer, prognosis

1. Introduction
Lung cancer, the most common type of cancer, represents the leading cause of death from cancer for men and the second leading cause of cancer mortality for women globally.[1,2] According to global cancer statistics, there are an estimated 1.8 million new cases of lung cancer annually, with lung cancer associated mortality expected to exceed 1 million on an annual basis.[3] Approximately 85% of all lung cancers are non-small cell lung cancer (NSCLC).[4] Despite the tremendous progress made in the diagnosis, staging, and treatment of NSCLC, the 5-year overall survival (OS) has not increased significantly over the past 2 decades, remaining below 15%.[5] Establishing a well elaborated treatment regimen based on the prognostic considerations of patients could tremendously improve the cure rate and quality of life of NSCLC patients. Currently, a series of traditional prognostic indicators for NSCLC patients have been identified including: age, sex, smoking status, performance status, and tumor-node-metastasis stage.[6] However, the inadequate specificity and sensitivity of these parameters render them somewhat cumbersome to integrate into clinical practice. Consequently, it is imperative to identify new effective prognostic biomarkers to predict the treatment response or long-term survival of NSCLC patients.
2. Materials and methods

This work was conducted according to the preferred reporting items for systemic reviews and meta-analysis. This meta-analysis was registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols (Registration Number: INPLASY2020120112).

2.1. Search strategy and selection criteria

The PubMed, Embase, and Cochrane Library databases were searched to identify relevant studies assessing the relationship between the CONUT score and the prognosis of NSCLC patients, published up to November 2020. The search terms used were “Controlling Nutritional Status,” “CONUT,” “lung cancer,” “non-small cell lung cancer,” “NSCLC,” “prognosis,” “prognostic,” and “survival.” References cited in selected publications were also retrieved to identify other relevant studies.

Two independent authors reviewed all the relevant articles. Studies were considered eligible after meeting all of the following criteria:

(a) Included patients with NSCLC diagnosed through histopathology;
(b) Reported the hazard ratio (HR) and 95% confidence intervals (CI) for the OS or disease-free survival (DFS) or recurrence-free survival (RFS) or cancer-specific survival (CSS); or included sufficient data to calculate the HR and 95% CI;
(c) Published in English.

The exclusion criteria were as follows:

(a) Letters, reviews, and case reports;
(b) HR and 95% CI were not reported or could not be calculated;
(c) The cut-off value was not given;
(d) Articles not published in English.

2.2. Data extraction and quality assessment

Two authors carefully reviewed the eligible studies to obtain the following information: first author’s surname, country of origin, year of publication, study design, number of patients enrolled, duration of follow-up, tumor stage, treatment methods, cut-off value, survival data, and clinicopathologic parameters. Assessment of study quality was independently performed for all the primary studies by 3 investigators using the Newcastle-Ottawa Quality Assessment Scale (NOS).[13] With a maximum score of 9 points, studies with NOS scores ≥ 6 were considered as high-quality studies.

2.3. Statistical analysis

The HR and 95% CI were retrieved directly from the included studies or calculated as described previously.[16] In order to establish an estimate of the overall HR with a 95% CI, the HR from the multivariate or univariate analysis was extracted from each study. Subsequently, the statistical heterogeneity of pooled results was assessed using the Cochran’s Q test and I² statistical methods.[17] Our results were reckoned to have been unaffected by heterogeneity if I² < 50% or P > .10. In this scenario, a fixed-effects model was utilized to obtain the pooled estimates; otherwise, a random-effects model was used. Subsequently, additional subgroup analysis was carried out based on the treatment methods, cancer stage, CONUT cut-off values, sample size, and analysis methods of HR. The relationship between the CONUT score and clinicopathologic features was presented in the form of odd ratios and their corresponding 95% CIs. The Begg’s test and a funnel plot were implemented for the detection of any potential publication bias. A P-value < .05 was considered statistically significant. Ultimately, a sensitivity analysis was performed by sequentially excluding each study to assess the impact of each included study on the final pooled results. The Stata software version 12.0 was used for all the analyses performed.

2.4. Ethical approval

Ethical approval or patient consent was not required since all analyses in this study were conducted with data from previously published articles.
3. Results

3.1. Characteristics of selected articles

A flow chart showing the selection procedure is illustrated in Figure 1. In total, 68 potentially relevant articles were identified through the database search, of which 56 were excluded after scanning titles and abstracts. Following deeper screening of the full texts of the remaining 12 studies, 1 article was excluded for a lack of necessary data.\(^{[18]}\) Finally, 11 studies encompassing a total of 3029 patients were selected for our meta-analysis.\(^{[11–14,19–25]}\) The characteristics of the 11 included studies are delineated in Table 2. A total of 9 enrolled studies were performed in Japan, 1 in Korea, and 1 in Turkey. The sample sizes ranged from 32 to 922 patients. Surgical resection was reported in 9 studies as the vital treatment modality and 2 studies stated that all the patients were receiving chemotherapy. All of the included studies evaluated the OS, whereas 7 evaluated either the DFS or RFS, and 2 evaluated the CSS. All the included studies were considered to be of high quality according to their NOS.

3.2. The CONUT score and OS in NSCLC patients

The pooled data revealed that patients with high CONUT score had worse OS than those with low CONUT score (HR: 1.63, 95%CI: 1.40–1.88, \(P < .001\)). No significant heterogeneity (\(I^2 = 31.9\%, P = .144\)) was observed, hence the fixed-effect model was used for analysis (Fig. 2). Subgroup analyses indicated that elevated CONUT score predicted poor OS in patients with NSCLC (Table 3), regardless of the treatment methods (surgery and non-surgery), cancer stage (I–III and III–IV), CONUT cut-off values (1 and 2), sample size (<200 and >200), and analysis methods of HR (multivariable and univariable).

3.3. The CONUT score and DFS/RFS in NSCLC patients

There were 7 studies with a total of 1391 patients investigating the correlation between the CONUT score and DFS/RFS. A combined analysis demonstrated that high CONUT score was significantly positively correlated with shortened DFS/RFS (HR: 1.65, 95% CI: 1.35–2.01, \(P < .001\)), with no significant
heterogeneity identified between studies ($P = .383$, $I^2 = 5.9\%$; Fig. 3). As shown in Table 3, high CONUT score was positively correlated with shortened DFS/RFS regardless of the cancer stage (I–III and I–IV), CONUT cut-off values (1 and 2), sample size (<200 and >200), and analysis methods of HR (multivariable and univariable).

### 3.4. The CONUT score and CSS in NSCLC patients

There were only 2 studies reporting the relationship between the CONUT score and CSS. The pooled results suggested that there was no significant correlation between the CONUT score and CSS (HR: 1.28, 95% CI: 0.60–2.73, $P = .517$), with no significant heterogeneity detected between studies ($P = .169$, $I^2 = 47.2\%$; Fig. 4).

### 3.5. CONUT score and clinicopathological features

The relationship between CONUT score and postoperative complications was detected for investigating the effect of CONUT score on short-term outcomes in NSCLC. The results revealed that preoperative high CONUT score was an independent predictor of postoperative complications (odd ratios: 1.58, 95%CI: 1.21–2.06, $P = .001$). To further explore the impact of

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**Table 2**

Characteristics of studies included in this meta-analysis.

| Study, year | Country  | Duration | Study design | Sample size | Follow-up (mo) | Stage | Treatment | Cut-off | Survival analysis | HR estimate | Analysis | NOS |
|-------------|----------|----------|--------------|-------------|---------------|-------|-----------|---------|------------------|-------------|----------|-----|
| Akamine 2017 | Japan    | 2003–2012 | Retrospective | 109         | 60            | I–IV  | Surgery   | 1       | OS/DFS          | R/R         | M/M     | 8   |
| Shoji 2017  | Japan    | 2005–2010 | Retrospective | 138         | 94            | I     | Surgery   | 1       | OS/DFS/ CSS     | E/E/R       | U/U/M   | 7   |
| Toyokawa 2017 | Japan   | 2003–2012 | Retrospective | 108         | 60            | I–III | Surgery   | 2       | OS/DFS          | R/R         | M/M     | 8   |
| Shoji 2018  | Japan    | 2005–2012 | Retrospective | 272         | 132           | I–III | Surgery   | 1       | OS             | R           | M       | 8   |
| Ohba 2019   | Japan    | 2017–2018 | Retrospective | 32          | 12            | III–IV| Non-surgery| 2       | OS             | R           | M       | 7   |
| Takamori 2019 | Japan  | 2005–2010 | Retrospective | 189         | 80            | I–III | Surgery   | 2       | OS/DFS          | R/R         | U/U     | 8   |
| Toyokawa 2019 | Japan   | 2007–2010 | Retrospective | 273         | 60            | I     | Surgery   | 2       | OS/DFS/ CSS     | R/R         | M/M     | 7   |
| Gul 2020    | Turkey   | 2012–2015 | Retrospective | 412         | 80            | III–IV| Non-surgery| 2       | OS             | R           | M       | 8   |
| Lee 2020    | Korea    | 2016–2017 | Retrospective | 922         | 12            | I–III | Surgery   | 1       | OS             | R           | M       | 7   |
| Miura 2020  | Japan    | 2007–2010 | Retrospective | 99          | 117           | I–III | Surgery   | 1       | OS/DFS/ CSS     | R/E/E       | M/U/U   | 7   |
| Takahashi 2020 | Japan   | 2012–2016 | Retrospective | 475         | 60            | I–III | Surgery   | 2       | OS/DFS/ CSS     | R/R         | M/M     | 8   |

CSS = cancer-specific survival, DFS = disease-free survival, E = estimated, HR = hazard ratio, M = multivariable, NOS = Newcastle-Ottawa Scale, OS = overall survival, R = reported, RFS = recurrence-free survival, U = univariable.

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**Figure 2.** Forest plot of the relationship between high CONUT score and OS. CONUT = controlling nutritional status; OS = overall survival.
Disease/recurrence-free survival evaluate the correlation between the CONUT score and CSS. Publication bias and sensitivity analyses were not performed to study was removed. Given the limited number of eligible studies, Overall survival and disease/recurrence-free survival. Subgroup No. of studies HR (95% CI) P H (%) Ph Model

| Overall survival | Treatment |
|-----------------|-----------|
| Surgery         | 9         | 1.81 (1.49–2.20) <.001 20.1 .256 Fixed |
| Non-surgery     | 2         | 1.41 (1.13–1.76) .002 48.0 .166 Fixed |
| Cancer stage    |           |                       |                       |
| I–II            | 8         | 1.79 (1.46–2.18) <.001 25.9 .222 Fixed |
| III–IV          | 2         | 1.41 (1.13–1.76) .002 48.0 .166 Fixed |
| I–IV            | 1         | 2.64 (0.97–7.16) .057 – – – |
| Cut-off value   |           |                       |                       |
| 1               | 5         | 2.14 (1.32–3.47) .002 53.7 .071 Random |
| 2               | 6         | 1.58 (1.33–1.87) <.001 11.2 .344 Fixed |
| Sample size     |           |                       |                       |
| <200            | 6         | 2.13 (1.58–2.88) <.001 0.0 .809 Fixed |
| >200            | 5         | 1.61 (1.21–2.15) .001 52.2 .079 Random |
| Analysis of HR  | Multivariable | 1.59 (1.36–1.85) <.001 36.2 .129 Fixed |
| Univariable     | 2         | 2.02 (1.25–3.26) .004 21.8 .258 Fixed |
| Disease/Recurrence-free survival | Treatment |
| Surgery         | 7         | 1.65 (1.35–2.01) <.001 5.9 .383 Fixed |
| Cancer stage    |           |                       |                       |
| I–II            | 6         | 1.59 (1.29–1.95) <.001 0.0 .460 Fixed |
| III–IV          | 1         | 2.63 (1.28–5.43) .009 – – – |
| Cut-off value   |           |                       |                       |
| 1               | 3         | 1.74 (1.14–2.65) .010 52.5 .122 Random |
| 2               | 4         | 1.63 (1.30–2.04) <.001 0.0 .555 Fixed |
| Sample size     |           |                       |                       |
| <200            | 5         | 1.80 (1.35–2.39) <.001 6.4 .370 Fixed |
| >200            | 2         | 1.52 (1.15–2.01) .003 29.1 .235 Random |
| Analysis of HR  | Multivariable | 1.67 (1.32–2.12) <.001 15.7 .313 Fixed |
| Univariable     | 3         | 1.60 (1.11–2.30) .011 27.9 .250 Fixed |

Cl = confidence interval, HR = hazard ratio, Ph = P values of Q test for heterogeneity test.

the clinical features on the CONUT score in NSCLC patients, we identified 7 clinical factors in NSCLC. As portrayed in Table 4, the pooled analysis demonstrated that no significant association was found with respect to the patients’ sex, smoking status, cancer stage, lymphatic invasion, vascular invasion, pleural invasion, and pathological cancer type. These results indicated that the CONUT score was a powerful prognostic indicator independent of the clinical factors.

3.6. Publication bias and sensitivity analyses

Publication bias in studies on the CONUT score and pooled OS (P = .008) or DFS/RFS (P = .368), based on the Begg’s test and funnel plots, was shown in Figure 5. We also carried out a sensitivity analysis mainly through estimation of the probable influence of selected studies on the pooled data. It can be depicted from Figure 6 that the pooled HR was not considerably modified as each single study was removed. Given the limited number of eligible studies, publication bias and sensitivity analyses were not performed to evaluate the correlation between the CONUT score and CSS.

4. Discussion

NSCLC is the most common cause of cancer related death worldwide, accounting for over 1 million deaths annually.[26] Accumulating studies demonstrate that host nutritional status plays an important role in progression of NSCLC and survival of NSCLC patients.[27] Recently, several nutrition-based biomarkers such as prognostic nutritional index,[28,29] Glasgow prognostic score (GPS),[30] modified GPS (mGPS),[31] C-reactive protein-to-albumin ratio,[32] and albumin-to-globulin ratio[33] have been identified as prognostic index in NSCLC. Compared to these mentioned biomarkers which were determined from only 2 types of serum inflammatory markers, the CONUT score may be able to provide a more comprehensive clinical picture of the patient’s nutritional and immune status since it is derived from up to 3 blood parameters. The CONUT score was previously reported to be an independent predictor of OS and RFS in patients with esophageal cancer[34] and in those who undergo curative hepatectomy for hepatocellular carcinoma.[19] Moreover, a study reported that preoperative CONUT scores predicted survival and postoperative severe complications in gastric cancer patients.[8] Previous articles have also showed the prognostic role of CONUT score for patients with urological cancers.[35] Therefore, CONUT score can be considered as an available prognostic biomarker. This is the first meta-analysis to investigate the relationship between the CONUT score and the prognosis of NSCLC patients. The pooled outcomes from 11 studies with a total of 3029 patients demonstrated that high CONUT score predicted poor OS and poor DFS/RFS in NSCLC. A stratified analysis
Figure 3. Forest plot of the relationship between high CONUT score and DFS/RFS. CONUT = controlling nutritional status; DFS = disease-free survival; RFS = recurrence-free survival.

Figure 4. Forest plot of the relationship between high CONUT score and CSS. CONUT = controlling nutritional status.
demonstrated that high CONUT score was significantly correlated with decreased OS and DFS/RFS in patients with NSCLC, irrespective of the treatment methods, cancer stage, CONUT cut-off values, sample size, and analysis methods of HR. Additionally, preoperative high CONUT score was an independent predictor of postoperative complications in NSCLC. Furthermore, we assessed the correlation between pre-treatment CONUT score and clinicopathological features. The results highlighted the fact that the CONUT score was a reliable prognostic indicator independent of clinical factors since it was not significantly associated with patients’ demographic and clinical characteristics such as sex, smoking status, cancer stage, lymphatic invasion, vascular invasion, pleural invasion, and pathological cancer type. Thence, pre-treatment CONUT score represents a promising prognostic factor for NSCLC patients.

The mechanism of prognostic roles of CONUT scores in NSCLC was still unclear, but this can be clarified by the function of the 3 components. The CONUT score, which adequately reflects the nutritional and immune status of patients, is calculated from the serum albumin concentration, total cholesterol level, and peripheral blood lymphocyte count. Serum albumin constitutes the highest component of plasma proteins, and its level can determine the patient’s nutritional status. Poor nutritional status may lead to a worse prognosis. Moreover, hypoalbuminemia is associated with an impaired immune response through macrophage activation. Cholesterol is an indispensable component of cellular membranes which is crucial for cellular signalling. Thus, it is potentially correlated with carcinogenesis and the corresponding immune response. Thence, hypocholesterolemia may contribute to a worse cancer prognosis. Furthermore, lymphocytes play a crucial anti-neoplastic role by activating the p53 signalling pathway and secreting IL-17 which induces tumor cell death and inhibits tumor cell proliferation. The tumor immune response is lymphocyte-dependent and lymphocytopenia is also related with malnutrition and suppression of cellular immunity. Regarding the role of serum cholesterol levels in the CONUT score, hypocholesterolemia is more significantly associated with fewer circulating lymphocytes, total T cells, and CD8+ cells than is hypercholesterolemia. Additionally, cholesterol increases the antigen-presenting function of monocytes. Therefore, high CONUT score is closely related to low levels of serum albumin, cholesterol, and lymphocytes, which are associated with poor survival.

This meta-analysis had several limitations. First, there were an insufficient number of studies evaluating the relationship between the CONUT score and CSS. As a result, the reliability of the pooled data might have been diminished by low statistical power. Second, all the included studies were performed in Asia, so it was unclear whether our findings could be generalized to other regions of the world. Third, the cut-off values were inconsistent between the studies. Even though we pooled the results according to CONUT score = 1 or 2 in the subgroup analysis, some degree

![Begg’s funnel plot pseudo 95% confidence limits](image)

**Figure 5.** Begg’s publication bias funnel plots. (A) Correlation between high CONUT score with OS; (B) correlation between CONUT score and DFS/RFS. CONUT = controlling nutritional status; DFS = disease-free survival; OS = overall survival; RFS = recurrence-free survival.
of bias may exist in the different original studies. Fourth, publication bias was detected in the analysis of OS. Finally, all enrolled studies were retrospective design, which might contain a potential selection bias.

5. Conclusion

In a nutshell, our results prove that pre-treatment CONUT score can be implemented as an independent predictive factor for OS and DFS/RFS in patients with NSCLC.

Author contributions

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