

## ORIGINAL ARTICLE

# Neuron specific enolase and prognosis of non-small cell lung cancer: A systematic review and meta-analysis

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### Summary

**Purpose:** The predictive and prognostic role of neuron-specific enolase (NSE) in non-small cell lung cancer (NSCLC) is still under debate. The present meta-analysis aimed to evaluate the relation between serum NSE levels and the prognosis of NSCLC.

**Methods:** We performed a meta-analysis of published studies assessing the association of NSE with the prognosis of NSCLC. Literature retrieval, trials' selection and assessment, data collection, and statistical analysis were performed according to the Revman 5.0 guidelines. A fixed-effect model was used to pool the hazard ratio (HR)

and 95% confidence intervals (95% CIs).

**Results:** A total of 8 eligible studies that included 2389 NSCLC patients were analyzed. We did not find prognostic value of NSE for NSCLC (HR=1.17, 95% CI: 0.95-1.44,  $p=0.14$ ).

**Conclusion:** The present study indicated that serum NSE level is of no prognostic significance in patients with NSCLC.

**Key words:** meta-analysis, non-small cell lung cancer, prognosis, serum neuron-specific enolase

### Introduction

Lung cancer is the most common cause of cancer-related deaths in recent years. NSCLC represents 75-80% of lung cancer cases and accounts for approximately 1.2 million new cases worldwide each year [1]. Despite extensive pre-clinical and clinical research, the prognosis for patients with NSCLC remains poor. The knowledge of prognostic determinants of NSCLC might be important not only in clinical trials but also in routine practice [2-5].

Recently, the prognostic significance of several biological factors, including NSE, has been investigated [6-8]. NSE is a well-established tumor marker for small-cell lung cancer (SCLC), whereas its role is still not clear in NSCLC [9-11]. Immunohistochemical staining demonstrated NSE over-expression in 70-100% of SCLC, while positive results for NSE were seen in 0-67% of NSCLC [12]. However, its prognostic value in patients with

NSCLC is still controversial since several studies did not find a prognostic value of NSE in NSCLC [13,14], while others reported that NSE is an important prognostic factor for NSCLC [15-20].

This article is a retrospective analysis of published studies to evaluate the prognostic value of NSE level before treatment in patients with NSCLC.

### Methods

#### Publication search

We searched PubMed, Medline, Embase, AACR (American Association for Cancer Research), Chinese Biomedical Literature Database, China National Knowledge Infrastructure (CNKI), and Wanfang databases using the search terms "neuron-specific enolase" or "NSE" and "non-small cell lung cancer" or "NSCLC" and "prognosis" updated until May 25, 2013. The online searching was accompanied by checking reference lists from the identified articles and reviews for poten-

tially eligible original reports.

#### *Inclusion and exclusion criteria*

*Inclusion criteria:* (1) clinical research with direct comparison of NSE levels in NSCLC before and after treatment, without any restriction on language or year of publication; (2) research subjects should be NSCLC patients without any restriction on age or race; (3) outcome indicators: overall survival.

*Exclusion criteria:* The major exclusion criteria were as follows: 1) duplicate data; 2) case reports, series, abstract, comment, review and editorial; and 3) insufficient data.

#### *Literature quality assessment and data extraction*

From each study, information like author, year of publication, country of origin, cancer type, ethnicity, number of cases, and NSE detection method was extracted. In some cases, identical data were described in more than one publication; in such cases the secondary studies were not included in the meta-analysis. In a few studies, part of the data had already been reported elsewhere, therefore, only the novel data was included.

#### *Data analysis*

Meta-analysis was performed by using RevMan 5.0 software [21] provided by the Cochrane Collaboration. We directly used Q-test and  $I^2$  test to examine the heterogeneity between each study. Hazard ratio (HR) value was used to evaluate the relation between serum NSE level and overall survival in NSCLC. With the heterogeneity test we selected the Fixed Effect Model to merge HR. Analysis of sensitivity included the difference of point estimation and confidence intervals (CI) of the combined effects value in a different model, to observe whether it changed the result; we excluded poor quality studies from the literature or reanalyzed the pool or value according to the quality evaluation criteria to observe whether they changed the result. To test the publication bias, we used the RevMan 5.0 statistical software to make the funnel plot. A p-value <0.05 was considered as statistically significant.

## **Results**

#### *Literature screening*

Two hundred and seventy-five studies were initially identified and 267 were excluded because of duplicate publication and nonclinically-based research. A total of 8 studies were included, all of them were clinical studies, 2 were Chinese [11,16], 5 English [13-15,17,18] and one Serbian [19]. These 8 studies with 2389 patients were included in this research.

#### *Treatments used in these 8 studies*

Of these 8 studies 6 reported usage of chemotherapy, and 2 reported that the majority of the patients were treated with chemotherapy, and some patients with radiotherapy and chemotherapy.

#### *Methodology assessment of serum NSE level detection*

NSE detection methods included enzyme-linked immunoassay (ELISA), electrochemiluminescence (ECL), and radioimmunoassay (RIA) methods. There were 3 studies using the RIA method, 2 studies using the ELISA method, 2 studies using ECL detection method and the remaining one study did not describe the detection method.

#### *NSE level and prognosis*

Six of the 8 studies provided HR values and their 95% CI used for the evaluation of serum NSE levels and prognosis. The other 2 studies did not provide HR values and their 95% CI, but they both could be calculated based on the data provided by the authors. There was better homogeneity between each study ( $p=1.00$ ,  $I^2=0\%$ ). We did not find a prognostic value of NSE for NSCLC (HR=1.17, 95% CI: 0.95 to 1.44,  $p=0.14$ ; Figure 1).

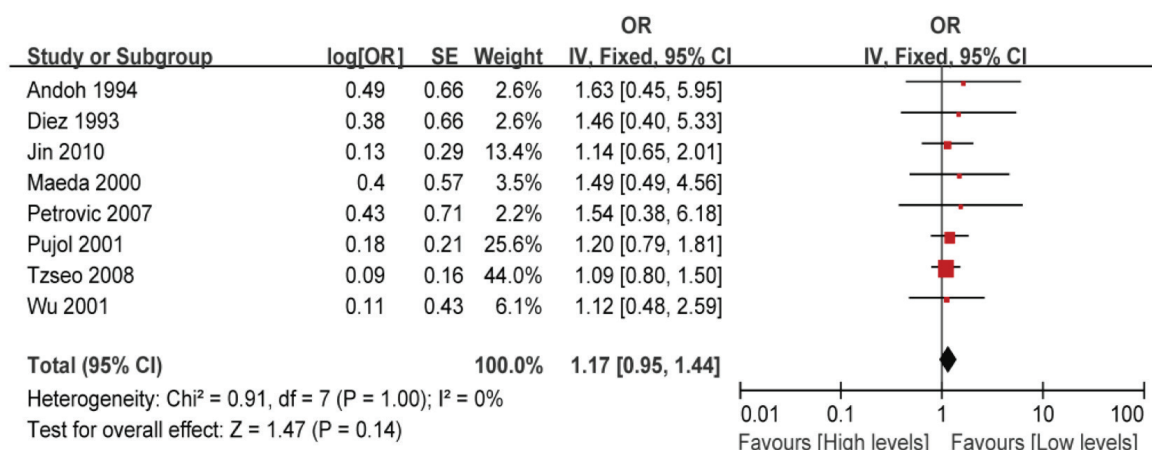
#### *Publication bias analysis*

We analyzed publication bias by using Revman 5.0 software. The funnel plot showed that the points were evenly distributed, symmetrical, and most of the points were within the 95% CI (Figure 2), indicating no publication bias.

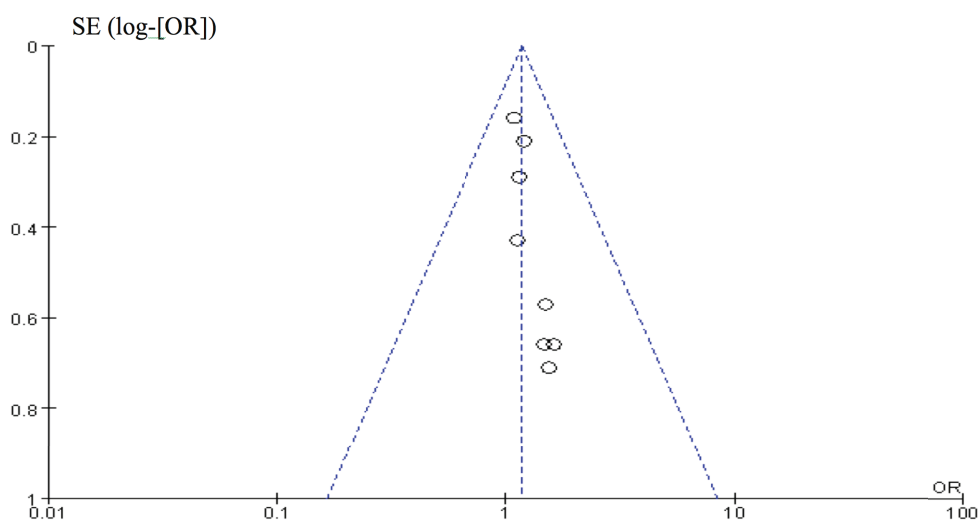
## **Discussion**

NSCLC is generally resistant to chemotherapy or radiotherapy. The International Association for the Study of Lung Cancer (IASLC) presented a Consensus Report for prognostic factors of NSCLC in 1991 [22]. In this report, clinical stage and performance status were definite prognostic factors and weight loss, gender, LDH and histology (squamous vs others) were possible prognostic factors. In addition to these factors, the updated consensus report by IASLC in 1994 included laboratory values (hemoglobin, platelets and white blood cells) and biological factors (dominant oncogenes, tumor suppressor genes, cell adhesion molecules, neuroendocrine markers and so on) [23].

Serum NSE is a glycolytic enzyme present in neurons, peripheral neuroendocrine tissues, and



**Figure 1.** Forest plot of prognosis of NSCLC and NSE levels. The horizontal lines correspond to the study-specific odds ratios (OR) and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI. In this analysis, The fixed-effects model was used.



**Figure 2.** Begg's funnel plot for publication bias test. Each point represents a separate study for the indicated association. Log odds ratio (OR) represents the natural logarithm of OR. The vertical line represents the mean effects size.

in some tumors, mainly in lung cancer and particularly in SCLC [7-9].

Petrovic et al. [24] performed a study to determine the frequency of NSE tissue expression and its possible influence on survival of patients treated for advanced NSCLC. The authors found a total of 28.5% of advanced NSCLC patients had positive NSE expression. Median 1- and 2-year survival time was significantly longer in patients with positive NSE expression. However, the association of NSE with NSCLC remains controversial. In the present study, we performed a meta-analysis which included 2389 patients with NSCLC and did not find any association of serum NSE concentration with prognosis for NSCLC. The 8 studies in

our meta-analysis had clear diagnostic, inclusion and exclusion criteria. The patients were grouped according to NSE levels, and overall survival was the main outcome. HR value was a statistical indicator to assess the impact of different levels of NSE for overall survival of patients with NSCLC. In addition, the present study included not only English articles, but also Chinese and Serbian articles for which the full texts were available, while studies in which only their summaries were available were excluded. However, this approach may cause selection bias. In these 8 included studies, only 6 provided the patient's pretreatment status. Because in the remaining 2 studies [11,16] baseline data and the detailed therapy were not avail-

able, the results might be distorted by selection bias. In addition, the main confounder of the present study was the different detection technologies used. In these 8 studies, the RIA method was used in the majority of them for detecting NSE levels, and the reagents used in each study were from different companies. Although the same kind of

detection technology was used, it is difficult to ensure that the detection result was homogeneous. This fact may be another confounder.

In summary, the present study indicated that serum NSE level has no prognostic significance in patients with NSCLC.

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