Predicting Survival for Patients with Malignant Pleural Effusion: Development of the CONCH Prognostic Model

Xin Zhang*
Feng-Shuang Yi
Huan-Zhong Shi

Department of Respiratory and Critical Care Medicine, Beijing Institute of Respiratory Medicine and Beijing Chao-Yang Hospital, Capital Medical University, Beijing, 100020, People’s Republic of China

*These authors contributed equally to this work

Background: Malignant pleural effusion (MPE) is a frequent complication of advanced malignancies that leads to a poor quality of life and limits treatment options.

Objective: The objective of this study was to identify biomarkers of survival in patients with MPE, which will greatly facilitate the clinical management of this complication.

Methods: This retrospective study recruited patients who had been pathologically diagnosed with MPE, regardless of the type of primary cancer, at Beijing Chao-Yang Hospital over 158 months. Demographic, clinical, hematological, and pleural fluid data were collected and analyzed as potential predictors of survival, and a new predictive model was developed based on Cox and logistic regression analyses.

Results: In our alternative prognostic model (n = 281), four routinely detected variables, namely, carcinoembryonic antigen (CEA) level, monocyte count, N-terminal pro B-type natriuretic peptide (NT-pro-BNP) level, and pleural effusion chloride level on admission, were identified as predictors (the CONCH prognostic score). Patients were divided into three prognosis subgroups based on risk stratification, with median survival periods of 17, 11, and 5 months, respectively. In comparison with the low-risk group, patients in the medium- and high-risk groups showed significantly poorer survival (medium-risk group: hazard ratio [HR], 1.586; 95% confidence interval [CI], 1.047–2.402; P = 0.029; high-risk group: HR, 4.389; 95% CI, 2.432–7.921; P < 0.001).

Conclusion: Four routinely detected variables were used to develop the CONCH scoring system, which was confirmed to be an accurate prognostic score for patients with MPE. This system can guide the selection of interventions and management for MPE.

Keywords: malignant pleural effusion, prognosis, CEA, monocyte, NT-pro-BNP

Introduction

Malignant pleural effusion (MPE) is a frequently occurring complication associated with poor patient outcomes, high mortality rates, and increased healthcare costs. The most common complaint in patients with MPE is dyspnea, which is prior to chest distress and cough. Metallic disease is the leading cause of MPE, among which most commonly observed is lung cancer, followed by breast cancer. Mesothelioma, which accounts for the majority of primary pleural tumors leading to the formation of MPE, has attracted wide attention and is a challenging diagnosis. Cytological examination of pleural fluid and pleural biopsy are the two main diagnostic methods for mesotheliomas. More recently, immunohistochemistry (IHC) using soluble mesothelin-related peptide (SMRP) and the combination of MTAP and BAP1 have
been confirmed to be useful for diagnosis. In addition, based on the multiple chromosomal imbalances in a series of malignant peritoneal mesothelioma cases, Serio et al hypothesized that the loss of function of ubiquitination, as well as of the defensins, could play an important role in the initial development and subsequent progression of mesothelioma.

The treatment strategy for patients with MPE remains palliative, and mainly aims to relieve symptoms and improve patients’ quality of life. At present, pleurectomy is usually replaced by less invasive management procedures such as pleurodesis and indwelling pleural catheters, and trials for some novel technologies are underway. Determination of the most appropriate treatment is challenging when the precise survival of certain patients is unpredictable, since patients with longer life expectancy may adopt more positive treatment options.

Predictive indicators for many malignant diseases have been thoroughly studied over the past few decades. However, evaluation of the prognosis of patients with MPE remains challenging. Psallidas et al reported the pleurodesis response markers in MPE (PROMISE) for assessments of survival; however, these markers were largely associated with prior chemotherapy or radiotherapy and focused less on patients without any anticancer treatment. For newly diagnosed or recurrent MPE, the LENT prognostication score proposed by Clive et al was applied to predict patient survival based on tumor type, lactate dehydrogenase (LDH) level, Eastern Cooperative Oncology Group performance status (ECOG PS), and blood neutrophil-to-lymphocyte ratio (NLR). However, in comparison with patients showing MPE secondary to lung adenocarcinoma from a study in Singapore, the LENT score appears to predict a much shorter survival. To identify predictors suitable for patients with MPE in our center, we conducted the present study.

The present study was designed with the objective of taking as many clinical and biological variables as possible into consideration and to develop an alternative risk stratification tool to help guide clinical management decisions.

Materials and Methods

Patients and Data Collection

We carried out a retrospective study on patients pathologically diagnosed as malignant pleural effusion (MPE) at Beijing Chao-Yang Hospital during October 2005 to December 2018. Patients who had received anticancer therapy (surgery, chemotherapy, radiotherapy, targeted therapy) at the time of admission were excluded from this study.

We collected the clinical and laboratory data (Table 1) of all patients during the first hospital visit before they received any kind of anticancer therapy. Data for general indicators, including age, sex, smoking history, and Eastern Cooperative Oncology Group performance status were collected. Laboratory indexes, including leukocyte, neutrophil, lymphocyte, monocyte, eosinophil, and platelet (PLT) counts; mean platelet volume (MPV), NLR, lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), erythrocyte sedimentation rate (ESR); hemoglobin (HGB), C-reactive protein (CRP), albumin, LDH, alkaline phosphatase (ALP), serum Ca²⁺, fibrinogen, D-dimer, N-terminal pro B-type natriuretic peptide (NT-Pro-BNP), carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), squamous cell carcinoma antigen (SCC), and cytokeratin 19 fragment (CYRFA) levels; and pleural effusion variables, including total cell, leukocyte, mononuclear cell, and multinuclear cell counts and chloride, glucose, LDH, adenosine deaminase (ADA), CEA, and albumin levels were recorded and presented as median (range).

Overall survival (OS) was defined as the duration from diagnosis to death for any reason or the last date on which the patient was known to be alive. Clinical and laboratory data used in the survival analysis were recorded at the time of admission.

Statistical Analysis

SPSS software (version 20.0; Chicago, USA) was used for performing the analyses. We used proportions for categorical variables and medians with ranges for continuous variables. Descriptive statistical methods were used to describe the baseline characteristics. Survival curves were estimated using the Kaplan–Meier survival function. To describe the association between a certain factor and an increased or decreased OS, we reported hazard ratios (HRs) from univariate and multivariate Cox logistic regressions with their respective 95% confidence intervals (95% CIs). Patients were stratified by various factors including age, sex, smoking history, ECOG PS, pathological findings, and laboratory data, and the median values of continuous variables served as cutoff values. Univariate survival analyses were applied to detect potential independent factors associated with prognosis, and variables with P values no more than 0.05 were further
fitted into a multivariate Cox’s proportional hazard model. Differences with P values less than 0.05 were defined as statistically significant.

**Results**

**Baseline Patient Characteristics**

Between October 2005 and December 2018, 281 patients were diagnosed with malignant pleural effusion (MPE) by pleural biopsy or cytopathology before receiving any anticancer treatment. A total of hundred and ninety-five (69.4%) patients died during the follow-up period; 58 (20.6%) patients were alive until the end of our follow-up period; and 28 (10.0%) patients were lost to follow-up.

Baseline descriptive statistics are shown in **Table 1**.

The mean follow-up period was 8 months (range, 0–152 months), and the mean age of the patients was 65 years (range, 21–88 years). The numbers of male and female patients with MPE in our study were similar (144 vs 137).

One hundred and ten (39.1%) patients had been smoking, quitting or not. All patients were graded according to the ECOG PS; a slightly larger proportion of patients (153, 54.4%) scored 0–2 points. Metastasis of lung adenocarcinoma was the leading cause of MPE in our study (166, 59.1%), followed by squamous cell carcinoma (16, 5.7%), small cell carcinoma (15, 5.3%), mesothelioma (20, 7.1%), and other pathological types (10, 3.6%), including metastatic spindle cell carcinoma, lymphoma, colon cancer, breast cancer, Wilms tumor, neuroendocrine carcinoma, thyroid cancer, renal carcinoma, fibrosarcoma, and liver cancer. Available hematological indices, including

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Table 1: Demographics and Baseline Patient Characteristics

| Variable                | No. of Patients (%) or Median (Range) |
|-------------------------|--------------------------------------|
| OS month                | 8 (0–152)                            |
| Age year                | 65 (21–88)                           |
| Gender                  | 144 (51.2)                           |
| Female                  | 137 (48.8)                           |
| Smoking history         | 110 (39.1)                           |
| Yes                     | 171 (60.9)                           |
| ECOG PS                 | 153 (54.4)                           |
| 0 – 2                   | 123 (43.8)                           |
| Pathology               | 166 (59.1)                           |
| Adenocarcinoma          | 16 (5.7)                             |
| SQC                     | 15 (5.3)                             |
| SCLC                    | 20 (7.1)                             |
| Mesothelioma            | 10 (3.6)                             |
| Hematological index     | 6.8 (2.9–16.46)                      |
| Leukocyte ×10^9/L       | 4.6 (1.58–13.36)                     |
| Neutrophil ×10^9/L      | 1.5 (0.34–5.69)                      |
| Lymphocyte ×10^9/L      | 0.5 (0.01–8.90)                      |
| Monocyte ×10^9/L        | 0.2 (0–26.9)                         |
| HGB g/L                 | 129 (14.7–180)                       |
| PLT ×10^9/L             | 255 (47–832)                         |
| Eosinophil ×10^9/L      | 10 (7.5–13.6)                        |
| HGB g/L                 | 3.2 (0.63–13.81)                     |
| MPV fl                  | 3.1 (0.11–61.33)                     |
| PLR                     | 175.7 (28.66–855.88)                 |
| CRP mg/dL               | 1.1 (0.11–85.68)                     |
| ESR mm/h                | 18 (2–100)                           |
| Albumin g/L             | 34.2 (17.5–48.6)                     |
| LDH U/L                 | 190.5 (93–1166)                      |
| ALP U/L                 | 85 (9–579)                           |
| Ca^2+ mmol/L            | 2.2 (1.06–3.43)                      |
| Fibrinogen mg/dL        | 396 (17.8–720.1)                     |
| D dimer µg/L            | 1472.6 (0–10,000)                    |
| NT-pro-BNP pg/mL        | 72.7 (2–2499)                        |
| CEA ng/mL               | 4.6 (0–1884.72)                      |
| NSE ng/mL               | 15.8 (1.67–580.58)                   |
| SCC ng/mL               | 0.7 (0–60.3)                         |
| CYFRA ng/mL             | 4.0 (0.76–219.99)                    |
| Pleural effusion index  | 10.714 (25–1,880,101)                |
| Total cell/μL           | 964 (25–192,460)                     |
| Leukocyte/μL            | 89 (7–100)                           |
| Mononuclear cell %      | 11.5 (1–94)                          |
| Multinuclear cell %     | 11.5 (1–94)                          |

(Continued)
leukocyte, neutrophil, lymphocyte, monocyte, eosinophil, and PLT counts; MPV, NLR, LMR, ESR, and PLR; HGB, CRP, albumin, LDH, ALP, serum Ca\(^{2+}\), fibrinogen, D dimer, NT-Pro-BNP, CEA, NSE, SCC, and CYRFA levels; as well as pleural effusion variables, including total cell, leukocyte, mononuclear cell, and multinuclear cell counts and chloride, glucose, LDH, ADA, CEA, and albumin levels are presented as median (range).

Survival Analysis
The median overall survival (OS) was 9 (95% CI 10.2–14.3) months, with 1-, 2-, and 3-year OS rates of 42.4%, 18.4%, and 7.4%, respectively. As shown in Table 2, univariate survival analyses (UVA) indicated that other pathological patterns rather than mesothelioma, ECOG PS > 2, CEA level > 4.6 ng/mL, NT-pro-BNP level > 72.7 pg/mL, chloride level in pleural effusion ≤ 105.9 mmol/L, leukocyte count > 6.8 × 10\(^7\)/L, neutrophil count > 4.6 × 10\(^7\)/L, monocyte count > 0.5 × 10\(^7\)/L, CRP level > 1.12 mg/dL, ESR > 18 mm/h, and LMR ≤ 3.1 may be significantly associated with a shorter OS (shown in Supplementary Figure 1, 2). No significant differences were found in age, sex, smoking history; lymphocyte, eosinophil, and PLT counts; MPV, NLR, LMR, PLR; HGB, albumin, LDH, ALP, Ca\(^{2+}\), fibrinogen, D dimer, NSE, SCC, and CYRFA levels; and pleural effusion-derived total cell, leukocyte, mononuclear cell, and multinuclear cell counts and glucose, LDH, ADA, CEA, and albumin levels. As shown in Table 3, variables with P values < 0.05, along with NSE level, the P value of which was 0.05, were further fitted into a multivariate Cox’s proportional hazard model, and CEA level (HR, 1.966; 95% CI 1.365–2.851; P < 0.001), monocyte count (HR, 1.534; 95% CI, 1.058–2.225; P = 0.024), NT-pro-BNP level (HR, 1.470; 95% CI, 1.021–2.116; P = 0.038), and pleural effusion chloride level (HR, 0.623; 95% CI, 0.433–0.895; P = 0.011) were identified as independent indicators of OS in patients with MPE.

Development and Assessment of CONCH Prognostic Score Model
To precisely distinguish patients with different risk stratifications, CEA level, monocyte count, NT-pro-BNP level, and pleural effusion chloride level were employed to develop the CONCH prognostic score model. Patients would receive 1 point when they met any of the following conditions: CEA level > 4.6 ng/mL, monocyte count > 0.5 × 10\(^7\)/L, NT-pro-BNP level > 72.7 pg/mL, or pleural effusion chloride level ≤ 105.9 mmol/L. On the basis of this prognostic score, the patients were divided into low-risk (score 0–1), medium-risk (score 2–3), and high-risk (score 4) subgroups, with median survival periods of 17, 11, and 5 months, respectively (Table 4). The survival curves of the subgroups are shown in Figure 1. In comparison with the low-risk group, the medium- and high-risk groups showed significantly poorer survival (medium-risk group: HR, 1.586; 95% CI, 1.047–2.402, P = 0.029; high-risk group: HR, 4.389; 95% CI, 2.432–7.921, P < 0.001).

The Prognostic Model for Only Metastatic Cases
When focusing on metastatic MPE, we excluded 20 cases diagnosed with mesothelioma and performed UVA in 261 cases. Ten indicators (ECOG PS; NSE, CRP, CEA, and NT-pro-BNP levels; ESR and LMR; and monocyte and neutrophil counts and chloride level in pleural effusion) were then fitted into multivariate Cox’s proportional hazard model, showing that CEA level > 4.5 ng/mL, monocyte count > 0.5 × 10\(^7\)/L, and pleural effusion Cl\(^-\) level ≤ 105.9 mmol/L were significantly associated with a shorter OS (Supplementary Table 1). On the basis of these three indicators, patients were divided into two prognosis subgroups: low-risk group (score 0–1) and high-risk group (score 2–3), with median survival periods of 19 and 9 months, respectively (Supplementary Table 2). The survival curves are shown in Supplementary Figure 3. In comparison with the low-risk group, the high-risk group showed significantly poorer survival (HR, 1.791; 95% CI, 5.563–12.437; P = 0.001).

Discussion
In our study, lung cancer accounted for the majority (70.1%) of the primary diseases causing MPE, and mesothelioma (20%) was the only primary tumor of the pleura, the distribution of which is consistent with previous studies. The median survival of patients with mesothelioma is 13 months, and the corresponding value for patients with lung cancer is 10 months. The LENT score study showed a median survival of 3 months in patients with lung cancer.\(^{12}\) Similar to our results, John Abisheganaden et al in Singapore\(^{13}\) reported a median survival period of 8 months in MPE patients secondary to lung adenocarcinoma, which prompted us to wonder whether race has an underlying influence on the
differences. Pleural fluid LDH level, ECOG PS, NLR, and tumor type were the four factors employed in the LENT prognostic score system, none of which showed statistical significance in our multivariate survival analysis. These differences imply that outcomes vary with the diversity of the study population, and differences in races may play a role.

The CONCH score model we developed involves four key factors, among which CEA, a routinely tested indicator for detecting lung cancer, seems to be the least surprising. The term CEA is used to refer to a group of glycoprotein antigens associated with cell adhesion, which have been generally considered to be prognostic indicators of colorectal cancer and a sensitive index for its recurrence. Several studies have identified the role of CEA in the prevention, screening, treatment, and surveillance of breast cancer. Additionally, serum CEA level has also been shown to be associated with the prognosis in patients with intrahepatic cholangiocarcinoma after partial hepatectomy, and in postoperative patients with medullary thyroid cancer.

As for respiratory tumors, several studies have shown that in addition to carbohydrate antigen 125 (CA125) and cytokeratin-19 fragment (CYFRA21-1), CEA can facilitate the diagnosis and surveillance of lung cancer.

### Table 2 Univariate Analysis of Variables in MPE Patients with Statistic Difference

| Variable                  | HR   | 95% CI     | P value |
|---------------------------|------|------------|---------|
| General index             |      |            |         |
| Histology types           |      |            |         |
| ADC                       | 1.037| 0.708–1.520| 0.851   |
| SQC                       | 0.916| 0.471–1.780| 0.795   |
| SCLC                      | 1.915| 0.989–3.708| 0.054   |
| Mesothelioma              | 0.425| 0.209–0.866| 0.019*  |
| Others                    | 0.643| 0.269–1.538| 0.321   |
| ECOG PS                   |      |            |         |
| ≤ 2                       | 1.372| 1.026–1.836| 0.033*  |
| > 2                       |      |            |         |
| Hematological index       |      |            |         |
| Leukocyte ×10⁹/L          |      |            |         |
| ≤ 6.8                     | 1.344| 1.012–1.784| 0.041*  |
| > 6.8                     |      |            |         |
| Neutrophil ×10⁹/L         |      |            |         |
| ≤ 4.6                     | 1.569| 1.181–2.084| 0.002** |
| > 4.6                     |      |            |         |
| Monocyte ×10⁹/L           |      |            |         |
| ≤ 0.5                     | 1.438| 1.083–1.908| 0.012*  |
| > 0.5                     |      |            |         |
| LMR                       |      |            |         |
| ≤ 3.1                     | 0.658| 0.496–0.872| 0.004** |
| > 3.1                     |      |            |         |
| CRP mg/dL                 |      |            |         |
| ≤ 1.12                    | 1.486| 1.088–1.979| 0.012*  |
| > 1.12                    |      |            |         |
| ESR mm/h                  |      |            |         |
| ≤ 18                      | 1.367| 1.017–1.873| 0.038*  |
| > 18                      |      |            |         |
| NT-pro-BNP pg/mL          |      |            |         |
| ≤ 72.7                    | 1.413| 1.011–1.974| 0.043*  |
| > 72.7                    |      |            |         |
| CEA ng/mL                 |      |            |         |
| ≤ 4.6                     | 1.686| 1.209–2.349| 0.002** |
| > 4.6                     |      |            |         |
| Cl mmol/L                 |      |            |         |
| ≤ 105.9                   | 0.605| 0.453–0.809| 0.001** |
| > 105.9                   |      |            |         |

Note: *p<0.05, ** p<0.001.

Abbreviations: NT-pro-BNP, N-terminal pro B-type natriuretic peptide; CEA, carcinoembryonic antigen; CI, confidence interval; CRP, C reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status; ESR, erythrocyte sedimentation rate; HR, hazard ratio; LMR, lymphocyte-to-monocyte ratio; UVA, Univariate analysis; SCC, squamous cell carcinoma antigen; SCLC, small cell carcinoma; SQC, squamous cell carcinoma.

### Table 3 Prognostic Scoring Method and Multivariate Analysis of Prognostic Factors

| Predictors                  | HR   | MVP  | 95% CI      | P value |
|-----------------------------|------|------|-------------|---------|
| CEA ng/mL                   |      |      |             |         |
| ≤ 4.6                       | 1    | 1    | 1.065–2.851 | <0.001**|
| > 4.6                       | 1.966| 1.365–2.851| 0.001**    |
| Monocyte ×10⁹/L             |      |      |             |         |
| ≤ 0.5                       | 1    | 1    |             |         |
| > 0.5                       | 1.534| 1.058–2.225| 0.024*    |
| NT-pro-BNP pg/mL            |      |      |             |         |
| ≤ 72.7                      | 1    | 1    | 1.021–2.116 | 0.038*  |
| > 72.7                      | 1.470| 1.021–2.116| 0.038*    |
| Pleural effusion Cl mmol/L  |      |      |             |         |
| ≤ 105.9                     | 0.623| 0.433–0.895| 0.011*    |
| > 105.9                     |      | 1    | 0.433–0.895 | 0.011*  |

Note: *p<0.05, ** p<0.001.

Abbreviation: NT-pro-BNP, N-terminal pro B-type natriuretic peptide.
present study, we identified CEA as an independent indicator of prognosis for patients with MPE, and an elevated level of serum CEA on admission indicated a shorter survival.

The monocyte count in peripheral blood was determined to be a predictor for patients with MPE, according to our data. As an immature member of the reticuloendothelial system, monocytes are capable of developing into macrophages or histiocytes and then participating in the multiple functions of this system, especially in phagocytosis. Although none of our patients met the diagnostic criteria for infectious mononucleosis, an enhanced monocyte count may occur in a variety of conditions, most notably infectious diseases and several hematologic disorders. In addition, monocyte proliferation related to obesity, chronic stress, acute alcoholic liver disease, pre-eclampsia, idiopathic pulmonary fibrosis and hyperlipidemia has drawn attention. The monocyte count also tends to increase in patients with various cardiovascular diseases, most frequently left ventricular (LV) dysfunction and LV aneurysm.

In addition to the benign conditions mentioned above, solid tumor malignancies were associated with a significant elevation in the monocyte count in comparison with the count in normal individuals. Several lines of studies have revealed that a low monocyte count may be associated with favorable outcomes in patients with some types of malignancy. In accordance with previous studies, we found that MPE patients with high monocyte levels had poor survival rates. Instead of initially suppressing the immune system, monocytes or macrophages assist in cancer progression by being educated by the tumor microenvironment, which may be part of the underlying mechanisms. In addition, a recent study showed that glycolysis levels in the peritumoral area of hepatocellular carcinoma can be significantly enhanced by monocytes, which induces PD-L1 expression and weakens cytotoxic T lymphocyte responses. These studies identified the pro-tumour effects of monocytes in the tumor microenvironment.

NT-pro-BNP, along with BNP secreted in equal molar, is known to be secreted in relation to cardiac stretch and left ventricular hypertrophy, which have been generally considered to be vital biomarkers guiding the management of patients with cardiovascular disease. Increased NT-pro-BNP levels are associated with cardiovascular disease (including heart failure, chronic coronary disease, and acute coronary syndromes) or renal disease due to decreased clearance. Furthermore, some studies have confirmed that plasma NT-pro-BNP is an independent indicator of the prognosis of patients with chronic renal disease, cardiovascular diseases, and multiple myeloma.

In general, cardiac dysfunction in patients with cancer may result from anticancer-treatment-induced myocardial

| Variable                        | n   | Median Survival (IQR) Months | HR   | 95% CI          | P value |
|---------------------------------|-----|-----------------------------|------|-----------------|---------|
| Low Risk Group (score 0–1)      | 66  | 17 (9–44)                   | 1    | —               | —       |
| Medium Risk Group (score 2–3)   | 112 | 11 (5–22)                   | 1.586| 1.047–2.402     | 0.029   |
| High Risk Group (score 4)       | 23  | 5 (1–8)                     | 4.389| 2.432–7.921     | <0.001  |

Figure 1 Survival curves estimated by the Kaplan–Meier survival function for the 3 groups stratified by the CONCH score system.
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Although very few studies have assessed the levels of chloride in body fluids, we identified chloride levels in pleural effusion as an independent indicator of prognosis for patients with MPE. A decreased chloride level in pleural effusion indicates a shorter survival, which may be related to total-body chloride depletion resulting from poor nutrition. Other relevant mechanisms should be investigated further.

We include 281 patients in our study, which is very large population in this subject. The CONCH score model based on four indicators shows great practical value in the prognosis of patients with MPE. This model highlights the stratified survival prospects in different patients and identifies routinely tested markers as key predictors. Although more studies are needed to further confirm its effectiveness, this convenient and clinically relevant score may help guide the selection of appropriate treatment options for patients with MPE.

Abbreviations
ADA, adenosine deaminase; ALP, alkaline phosphatase; CEA, carcinoembryonic antigen; CI, confidence interval; CRP, C reactive protein; CYFRA, Cytokeratin 19 fragment; ECOG PS, Eastern Cooperative Oncology Group performance status; ESR, erythrocyte sedimentation rate; HGB, hemoglobin; HR, hazard ratio; LDH, lactate dehydrogenase; LMR, lymphocyte-to-monocyte ratio; MPE, malignant pleural effusion; MPV, mean platelet volume; MVA, multivariate analysis; NLR, neutrophil-to-lymphocyte ratio; NSE, neuron specific enolase; NT-pro-BNP, N-terminal pro B-type natriuretic peptide; OS, overall survival; PLR, platelet-to-lymphocyte ratio; PLT, platelet; SCC, squamous cell carcinoma antigen; SCLC, small cell carcinoma; SQC, squamous cell carcinoma; UVA, Univariate analysis.

Statement of Ethics
The study was approved by the Institutional Review Board of Beijing Chao-Yang Hospital. Patients’ consent was not required because this is a retrospective study. We declare to keep patients’ data confidential and comply with the Declaration of Helsinki.

Author Contributions
Huan-Zhong Shi and Feng-Shuang Yi conceived the idea, supervised the study; Xin Zhang and Feng-Shuang Yi collected data. All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.
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Disclosure
The authors have no financial or other conflicts of interest.

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