Original Article

Pretreatment Prognostic Factors to Predict Survival Outcome in Advanced Non-Small Cell Lung Cancer with First Line Treatment in Thailand: A Retrospective Cohort Study

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Background: Tumor genetic information and biologic markers are often used as prognostic factors. However, these are limited in real daily practice due to their high cost.

Objective: To evaluate which inexpensive, convenient, and simple prognostic factors are associated with survival outcome with first line treatment among patients with advanced non-small cell lung cancer (NSCLC).

Materials and Methods: This retrospective cohort study reviewed the medical charts of patients diagnosed as advanced NSCLC with no previous treatment at King Chulalongkorn Memorial Hospital and Police General Hospital between January 1, 2008 and December 31, 2013.

Results: Three hundred one patients were included in the present study, 68.1% males. The pre-treatment prognostic factors found to be significantly associated with outcome were the number of organs involved ($p<0.05$), simple biomarkers, the absolute neutrophil/lymphocyte count ratio ($p<0.001$), albumin/globulin ratio ($p=0.010$), the ECOG status ($p<0.005$), and current smoker ($p=0.001$).

Conclusion: The pre-treatment prognostic factors significantly associated with outcome were the number of organs involved, the neutrophil/absolute lymphocyte ratio, the serum albumin/globulin ratio, the ECOG status, and the smoking status. These factors could potentially be used to develop a simple model to determine pre-treatment prognosis among NSCLC patients.

Keywords: Prognostic factors, Survival, Lung cancer

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Lung cancer is one of the five most common cancers among both males and females[1]. Approximately 85% of lung cancer diagnoses are non-small cell lung cancer (NSCLC)[2]. However, few countries screen for lung cancer and most NSCLC patients present in advanced stages of the disease and have a poor prognosis. Modern anti-cancer treatment for NSCLC clearly results in improved overall survival rates[3-9]. Many molecular biologic markers have been identified as prognostic factors for patients with NSCLC, including EGFR mutation[10,11], K-RAS[12], ERCC1, and RRM1[13,14]. However, there are barriers to tumor genetic testing for most NSLCLC patients in real practice.

Although many potential biomarkers have been identified, few are used routinely. It is important to identify simple, convenient, and inexpensive pre-treatment biomarkers for prognostic prediction, especially in countries with limited resources. Several recent studies have examined biomarkers to predict prognosis in both solid and hematologic malignancies[15,16]. For example, the serum albumin/globulin ratio has been found to be associated with

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patient nutritional status and the inflammatory process. These can be associated with cancer progression. The absolute neutrophil count over absolute lymphocyte count ratio is an indicator of systemic inflammation that plays a major role in tumor proliferation and migration. Both simple biomarkers may be related to overall survival[17-19]. However, interval time from diagnosis to treatment associated with survival is inconclusive.

The objective was to identify routinely measured factors, such as basic clinical features or routine laboratory tests including time from diagnosis to treatment that can predict prognosis of patients receiving first line treatment for advanced NSCLC. This knowledge could help physicians better discuss outcomes of treatment with their NSCLC patients and make treatment decisions.

Materials and Methods

Setting and data sources

This retrospective cohort study was conducted among patients with advanced NSCLC (IIIB, IV) treated at King Chulalongkorn Memorial Hospital and Police General Hospital. The ICD-10 diagnostic code was used for obtaining medical records of NSCLC patients treated between January 1, 2008 and December 31, 2013. Variables measurement were age, gender, smoking status, histological type of NSCLC whether squamous or non-squamous cell type, number of organ involvement, and time from diagnosis to treatment. Pretreatment laboratories, albumin/globulin ratio, and neutrophil/lymphocyte ratio within one month before starting treatment were recorded. ECOG status was used to evaluate the patient health status.

Inclusion criteria were: 1) patients aged 18 years or older, 2) with histological or cytological confirmation of having NSCLC, 3) having advanced stage NSCLC as classified by the American Joint Committee on Cancer (AJCC) TNM staging criteria system, and 4) had no previous history of specific treatment for their advanced NSCLC. All study patients received standard chemotherapy and/or radiation therapy for their advanced NSCLC. Exclusion criteria were 1) patients who had early NSCLC, 2) patients who had chronic liver disease, a chronic infection, an autoimmune disease, and 3) patients who had a diagnosis of advanced NSCLC as a second primary cancer. Patients who received targeted therapy as first line treatment or who had received supportive treatment were excluded from the study. Patients were followed until death or to their most recent hospital visit. Patients who were still living at the most recent medical record date were censored. The date of death for each patient was extracted from the population-based registry. The missing data will be approached by using listwise deletion. The primary end point was overall survival and disease-free survival as a secondary end point. The sample size was calculated by using rule of thumb (Comrey and Lee, 1992[20]) 5 to 10 events at least were needed to avoid fitting a model. The second sample size calculation method was based on equation of N = 10 k/p (based on the work of Peduzzi et al, 1995[21]) for Cox proportional-hazard model. The proportion for long-term survival by using from previous literatures was 0.23[15,16]. Thus, the suitable sample size should be 300 to 345.

Statistical analysis

Categorical variables were presented as percentages and continuous variables were presented as means and standard deviations, or medians with minimum and maximum levels, depending on the distribution of the variable. The primary inferential analysis was the clinical endpoint, overall survival, which was measured from the date of diagnosis to the date of death due to any cause. Disease-free survival time, the secondary outcome, was defined as being from the date of diagnosis to the time to the first incidence of recurrence, death by any cause or time to last follow-up prior to death. The Kaplan-Meier and Cox proportional hazards regression were used to assessing the association between each variable (e.g., demographic variable, laboratory result) and the outcome. The serum albumin/globulin ratio and the absolute neutrophil count/lymphocyte count ratio were examined using Lowess lines to find the proper ratio related to survival. To minimize bias, all analyses were stratified by variables, the univariate and multivariate logistic regression model were used for analysis. Statistically significant variables were included in the multivariate Cox regression model. Statistical analyses were performed using Stata, version 13. Significance was set at p-value less than 0.05 for all analyses. The protocol of the present study was approved by the Institutional Review Board (IRB) of King Chulalongkorn Memorial Hospital and the Police General Hospital.

Results

Six hundred forty cases were considered for the present study. After cleaning the data, 336 cases were excluded. One hundred three cases were missing more than two interested variables data, 66 cases were in early stage of NSCLC (stage I-IIIA), 52 cases

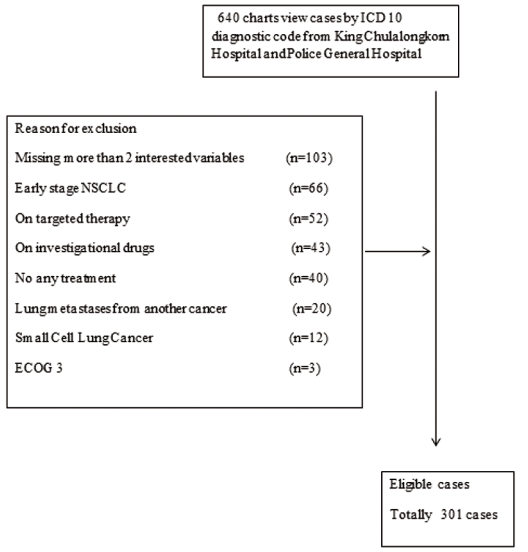

Figure 1. Flow diagram summarizing cases eligible for the present study.

were on targeted therapy, 43 cases participated in investigational drugs, 40 cases had no any treatment, 20 cases were lung metastases from another cancer, 12 cases were diagnosed of Small cell lung, and three cases had ECOG 3. Therefore 301 cases were eligible, 299 cases (98.36%) were dead, and five cases (1.64%) were still alive at the censored date (Figure 1). Median follow-up time and median survival time were 13.7 months (range 0.2 to 68.3 months) and 10.5 months respectively. The patient characteristics are shown in (Table 1). The mean participant age was 61.4 years; 172 cases (57.1%) were younger than 65 years and 129 (42.9%) were 65 years or older. In terms of the ECOG scoring, 46 cases (15.3%) had ECOG score of 0, 164 cases (54.5%) had ECOG score of 1, and 91 cases (30.2%) had an ECOG score more than 1. One hundred fifteen cases (38.2%) had never smoked, 115 (38.2%) were former smokers, and 71 (23.6%) were current smokers. There were 43 cases (14.3%) with squamous cell type and 258 cases (85.7%) with non-squamous cell type. The average time from diagnosis to treatment was 28 days (range 0 to 180 days). The average serum albumin/globulin ratio was 1.03±0.3 (range 0.35 to 2.50) and the average absolute neutrophil count over lymphocyte count ratio was 3.72 (range 0.56 to 32.1). In terms of number of organ involvement, it was classified into three groups. There were 106 cases (35.2%) and 141 cases (46.8%) with one and two organ involvement respectively. There were 54 cases (18%) with more than two organs involvement. Two hundred thirty-four cases (77.7%) did not have palliative radiation, and 67 cases (22.3%) did not receive radiation. Because of no consensus on time from diagnosis to treatment, the present study used 30 days as a cut point. One hundred fifty-two cases (97.4%) received the treatment within 30 days, and 144 cases (99.3%) started the treatment after definite diagnosis of NSCLC, which took longer than 30 days.

Table 1. Baseline patient characteristics

Patient characteristics	n (%)
Sex	
Female	96 (31.9)
Male	205 (68.1)
Age (years), Mean±SD	61.4±11.5
Min-max	26 to 92
<65	172 (57.1)
≥65	129 (42.9)
ECOG status	
0	46 (15.3)
1	164 (54.5)
2	91 (30.2)
Smoking status	
Never	115 (38.2)
Former	115 (38.2)
Current	71 (23.6)
Histological type	
Squamous	43 (14.3)
Non-squamous	258 (85.7)
Number of organ involvement, Median (p25, p75)	2 (1, 4)
≤1	106 (35.2)
2	141 (46.8)
3 to 5	54 (18.0)
Neutrophil/lymphocyte ratio, Median (p25, p75)	3.72 (2.51, 5.35)
Min-max	0.56 to 32.1
Albumin/globulin ratio, Mean±SD	1.03±0.31
Min-max	0.35 to 2.50
Time from dx to treatment, Median (p25, p75)	28 (14, 43)
Min-max	0 to 180
<30	156 (51.8)
≥30	145 (48.2)
Palliative radiation	
No	234 (77.7)
Yes	67 (22.3)

SD=standard deviation; ECOG=Eastern Cooperative Oncology Group; dx=diagnosis

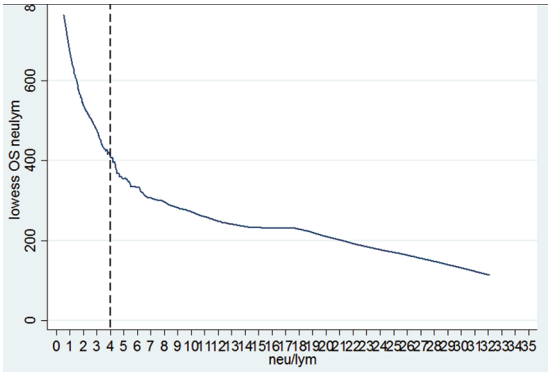

Figure 2. Lowess line of absolute neutrophil/lymphocyte count ratio.

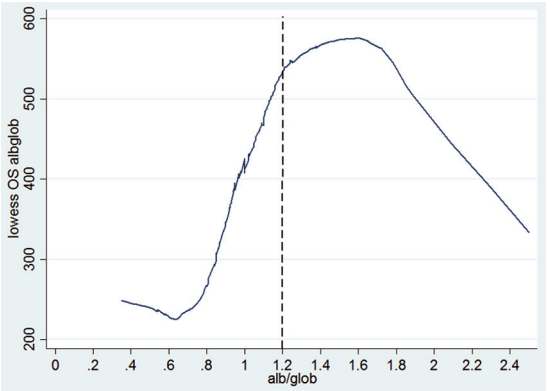

Figure 3. Lowess line of albumin/globulin ratio.

Using the Lowess line graph, the best value correlated with survival with the neutrophil over lymphocyte ratio was 4 and with the albumin/globulin ratio was 1.2 (Figure 2, 3). One hundred seventy-six cases had neutrophil over lymphocyte count ratio less than 4, and 125 cases had neutrophils/lymphocyte count ratio more than or equal to 4. Two hundred forty-two cases had albumin/globulin ratio less than 1.2 and 59 cases had value greater than or equal to 1.2. Factors significantly associated with overall survival on bivariate Cox regression analysis were being a current smoker (crude hazard ratio (HR) 2.34; 95% CI 1.73 to 3.18; p<0.001), the ECOG status 2 (crude HR 2.14; 95% CI 1.49 to 3.08; p<0.001), number of organs involvement more than two (crude HR 1.74; 95% CI 1.12 to 2.430; p=0.001). Two simple biomarkers, the absolute neutrophil over lymphocyte ratio (crude HR 2.04; 95% CI 1.61 to 2.58; p<0.001) and serum albumin/globulin ratio less than 1.2 (crude HR 1.47; 95% CI 1.10 to 1.97; p=0.01). Regarding histological type, the result showed that non-squamous cell type was significantly associated overall survival (crude HR 0.68; 95% CI 0.49, 0.95; p=0.022). When adjusted for potential prognostic factors with the multivariable model, only current smoker (HR 1.97; 95% CI 1.30 to 2.99; p=0.001), ECOG score 2 (HR 1.87; 95% CI 1.28 to 2.73; p=0.001), number of organs involvement more than two organs (HR 1.49; 95% CI 1.05 to 2.13; p=0.02). The simple biomarker absolute neutrophils/lymphocyte ratio was a strongly prognostic overall. Perusal of the HR represents a significant risk for death compared to the reference group. The albumin/globulin ratio had a trend that related to prognosis but it did not reach statistical significance (HR 1.33; 95% CI 098 to 1.80; p=0.06) (Table 2). Regarding the analyses of the second outcome, on univariate analysis, smoking status, number of organs involved, the neutrophils/lymphocyte ratio and time from diagnosis to treatment did not reach statistical significant associated with disease-free survival (Table 3, Figure 4-8).

Discussion

A number of biomarkers have been developed to give the prognosis for patients with advanced NSCLC. However, new biomarkers are often costly and not widely available. Few of these biomarkers make it into clinical practice making prognostication in the clinical setting difficult and not routinely used. Biomarkers that are easy to obtain and inexpensive to determine are needed for clinical use. Although many studies have demonstrated the prognostic utility of novel biomarkers, much of these researches have not made them to the clinical setting and not routinely used. These are likely due to cost and difficulty in translating them into clinical practice. Ideally, prognostic biomarkers should be easily available to clinicians and developed into clinically useful prognostic models, where they can be brought into standard practice. In the present study, the authors investigated simple pretreatment factors easily determined in daily clinical practice. The authors examined three aspects to provide a more holistic approach to prognostication. The first aspect is the clinical characteristics of patient such as age, gender, health status determined using the ECOG score, and smoking status. Regarding time from diagnosis to start of treatment, it showed to improve outcome in early stage cancer treatment. Nevertheless it is seldom explored in advanced stage cancer and is controversial[22]. The second aspect examined was specific to the tumor and included histological type. The histological type was divided into squamous cell and non-squamous cell carcinoma, and number

Table 2. Factors affecting overall survival

Variables	n	Dead n (%)	Univariable analysis			Multivariable analysis	
			Median survival time (months)	Crude HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Age (years)						-	-
<65 (reference)	172	168 (97.7)	10.1	1			
≥65	129	128 (99.2)	11.7	1.04 (0.83 to 1.32)	0.730		
Sex							
Female	96	92 (95.8)	12.8	1		1	
Male	205	204 (99.5)	9.9	1.21 (0.94 to 1.55)	0.133	1.05 (0.73 to 1.51)	0.795
ECOG status							
0	46	46 (100)	14.0	1		1	
1	164	160 (97.6)	11.7	1.17 (0.84 to 1.63)	0.351	1.22 (0.87 to 1.71)	0.245
2	91	90 (98.9)	6.1	2.14 (1.49 to 3.08)	<0.001	1.87 (1.28 to 2.73)	0.001
Smoking							
Never	115	112 (97.4)	12.9	1		1	
Former	115	113 (98.3)	13.1	1.12 (0.86 to 1.45)	0.410	1.02 (0.70 to 1.48)	0.927
Current	71	71 (100)	5.7	2.34 (1.73 to 3.18)	<0.001	1.97 (1.30 to 2.99)	0.001
Histology							
Squamous	43	43 (100)	6.9	1		1	
Non-squamous	258	253 (98.1)	10.8	0.68 (0.49 to 0.95)	0.022	1.06 (0.75 to 1.52)	0.737
Number of organ involvement							
≤1	106	103 (97.2)	13.1	1		1	
2	141	140 (99.3)	10.5	1.37 (1.06 to 1.77)	0.017	1.18 (0.90 to 1.54)	0.238
3 to 5	54	53 (98.1)	5.8	1.74 (1.24 to 2.43)	0.001	1.49 (1.05 to 2.13)	0.027
Neutrophil/lymphocyte ratio							
<4	176	171 (97.2)	13.7	1		1	
≥4	125	125 (100)	6.1	2.04 (1.61 to 2.58)	<0.001	1.69 (1.32 to 2.18)	<0.001
Albumin/globulin ratio							
<1.2	242	239 (98.8)	9.3	1.47 (1.10 to 1.97)	0.010	1.33 (0.98 to 1.80)	0.067
≥1.2	59	57 (96.6)	14.0	1		1	
Time from dx to treatment (days)						-	-
<30	156	152 (97.4)	8.2	1			
≥30	145	144 (99.3)	12.6	0.90 (0.72 to 1.13)	0.366		
Radiation						-	-
No	234	230 (98.3)	10.4	1			
Yes	67	66 (98.5)	10.6	0.89 (0.67 to 1.17)	0.387		

HR=hazard ratio; CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; dx=diagnosis

of organs involved. The third aspect comprised of laboratories biomarkers commonly available clinically, the pretreatment neutrophils/lymphocyte ratio and the serum albumin over serum globulin ratio. The simple laboratories biomarker ratios were strongly associated with patient overall survival. The result of the present study, after adjusted for confounding factors, shows that the ECOG score, smoking status, number of organs involved, and neutrophils/lymphocyte ratio were strong prognostic factors.

Table 3. Factors affecting disease-free survival

Variables	n	Recurrence n (%)	Univariable analysis			Multivariable analysis	
			Median survival time to recurrence (months)	Crude HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Age (years)						-	-
<65	172	107 (62.2)	222	1			
≥65	129	74 (57.4)	261	0.88 (0.65 to 1.18)	0.379		
Sex							
Female	96	67 (69.8)	223	1		1	
Male	205	114 (55.6)	250	0.80 (0.59 to 1.08)	0.151	0.80 (0.59 to 1.09)	0.155
ECOG status							
0	46	37 (80.4)	210	1		1	
1	164	103 (62.8)	251	0.73 (0.50 to 1.07)	0.105	0.74 (0.51 to 1.08)	0.119
2	91	41 (45.1)	238	0.81 (0.52 to 1.26)	0.350	0.75 (0.48 to 1.18)	0.216
Smoking						-	-
Never	115	78 (67.8)	230	1			
Former	115	79 (68.7)	250	1.02 (0.74 to 1.39)	0.918		
Current	71	24 (33.8)	269	0.83 (0.52 to 1.32)	0.431		
Histology						-	-
Squamous	43	20 (46.5)	184	1			
Non-squamous	258	161 (62.4)	240	1.02 (0.64 to 1.62)	0.944		
Number of organ involvement						-	-
≤1	106	78 (73.6)	238	1			
2	141	77 (54.6)	251	0.92 (0.67 to 1.27)	0.617		
3 to 5	54	26 (48.1)	193	1.16 (0.74 to 1.81)	0.524		
Neutrophil/lymphocyte ratio						-	-
<4	176	123 (69.9)	250	1			
≥4	125	58 (46.4)	197	1.13 (0.82 to 1.55)	0.449		
Albumin/globulin ratio						-	-
<1.2	242	140 (57.9)	222	1.19 (0.84 to 1.69)	0.333		
≥1.2	59	41 (69.5)	278	1			
Time from dx to treatment (days)						-	-
<30	156	85 (54.5)	212	1			
≥30	145	96 (66.2)	252	0.86 (0.64 to 1.15)	0.305		
Radiation							
No	234	133 (56.8)	252	1		1	
Yes	67	48 (71.6)	178	1.39 (1.00 to 1.93)	0.053	1.42 (1.01 to 1.99)	0.042

HR=hazard ratio; CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; dx=diagnosis

Serum albumin over serum globulin ratio tended to predict overall survival but the result did not reach statistical significance. An increase in the neutrophils/lymphocyte ratio was significantly associated with a shorter overall survival (HR 1.69; 95% CI 1.32 to 2.18; p<0.001). These findings are compatible with previous studies of patients with hematological malignancies and solid tumors, such as breast cancer, gastrointestinal cancer, hepatobiliary tract cancer, and renal cell carcinoma. It is hypothesized that

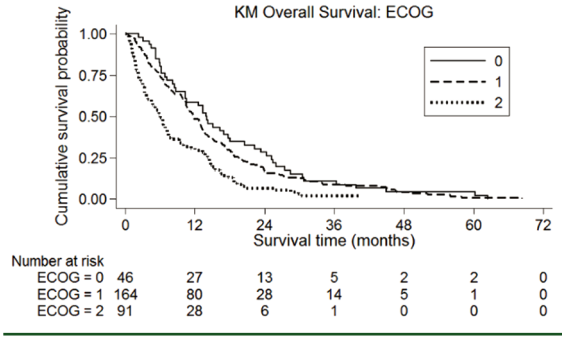

Figure 4. Comparison of overall survival curves by ECOG status.

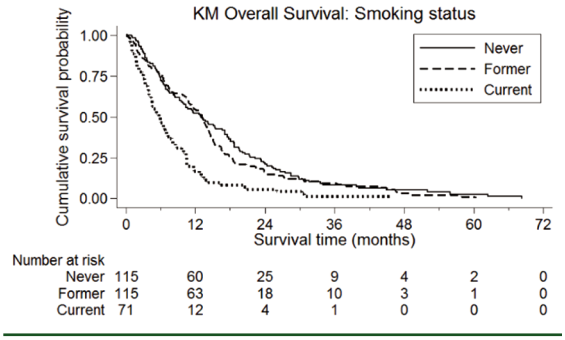

Figure 5. Comparison of overall survival curves by smoking status.

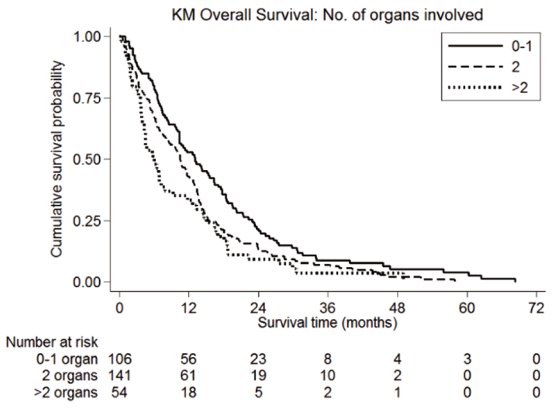

Figure 6. Comparison of number of organ involvement.

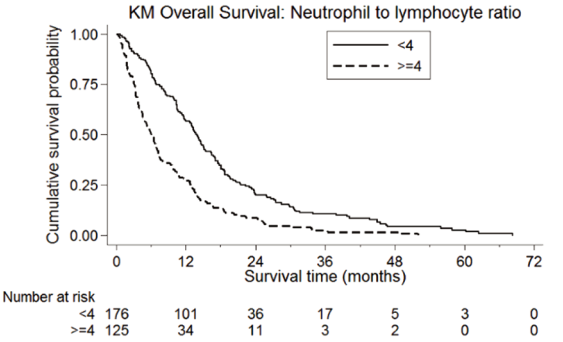

Figure 7. Comparison of value neutrophil/lymphocyte ratio.

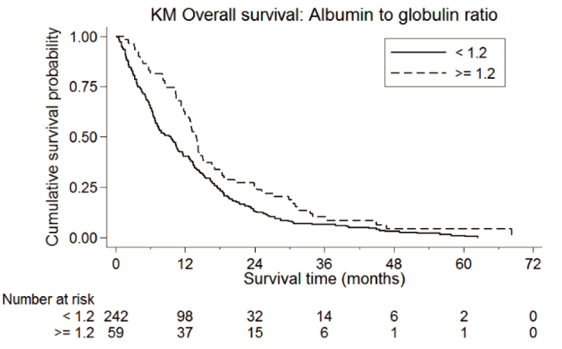

Figure 8. Comparison of value albumin/globulin ratio.

neutrophils and lymphocytes involved immunity and inflammatory processes, which are associated with the invasiveness of cancers, as migration, angiogenesis, and stimulating tumor growth factor. The lower serum albumin/globulin ratio is most likely related to nutritional status and immunity through tumor cytokine pathways. It was significantly associated with shorter overall survival (crude HR 1.47; 95% CI 1.10 to 1.97; p=0.01). Recent clinical studies investigated colorectal cancer, breast cancer, urothelial cancer, and nasopharyngeal cancer[18,23-25] and found that low serum albumin/globulin ratio is associated with shorter survival. However, these studies used various different cut-off levels for an abnormal serum albumin over serum globulin ratio. The present findings are consistent with those of a previous retrospective study of lung cancer from a single institute in Turkey[26]. However, there are no previous published reports in East Asian populations. Regarding whether time from diagnosis to treatment had prognostic effect[22], this has an impact in early stages of malignancy but this is unclear in advanced stages. Studies from Canada, Sweden, Ireland, and Finland found early treatment was associated with shorter survival in advanced lung cancer, with a median survival time of 50 to 120 days. The mean time from diagnosis to treatment of 28 days (range 0 to 180) did not have a significant impact on survival (HR 0.90; 95% CI 0.72 to 1.13; p=0.36). This might be because of the advanced stage of the disease at presentation. More than fifty percent of 301 patients in the present study had an ECOG score

of 0 to 1 (Table 1). Patients with an ECOG score 2 had a significantly shorter survival than patients with ECOG score 0 and 1. This confirmed that performance status evaluation before treatment is crucial. Patients who continued to use tobacco during treatment had a shorter survival than those who never smoke and former smokers (HR 1.97; 95% CI 1.30 to 2.99; p<0.001). Although this result is not surprising, it is a modifiable prognostic factor.

There were some limitations of the present study. First, it was retrospective, the results were based on medical records. Some data were incomplete. It also had little control over data quality, including missing values. This not only reduced the number of cases reviewed but also the data available for analysis (reducing power) and could result in bias, especially if certain data were not missing at random. Second, most of the patients in the present study did not have tumor genome testing and most received standard chemotherapy rather than novel treatment limiting the applicability of the results to other situations where newer treatment is used. The authors did identify several prognostic factors in the study that can be useful such as educating the patient on the added benefit of cessation of smoking during treatment and improvement of nutritional status. A strength of the present study was that it was multi-centered making it more likely to be more generalizable. The patients are typical for daily practice with standard first line chemotherapy, which plays a major role in the treatment of NSCLC, in spite of newer treatments introduced. Physicians can use this information at the bedside to evaluate and educate patients prior to receiving standard first line chemotherapy. This can guide decision making on the part of the physician and the patient.

Conclusion

The present multicenter retrospective cohort study found three factors that are associated with prognosis pre-treatment. These were the ECOG score, the patient's smoking status and two easily available biomarkers, the neutrophils/lymphocyte ratio and the serum albumin/globulin ratio. These factors should be included in the practical care of patients with NSCLC and added to the prognostic model. The authors recommend using these factors to develop a prognostic model and then testing the model in a larger, prospective cohort of patients with NSCLC.

What is already known on this topic?

Although many prognostic factors especially new tumor genetic, and biomarkers were used, there are still barrier and high cost.

What this study adds?

The simple pre-treatment factors can be used for predicting survival outcome of advanced NSCLC patients such as albumin/globulin ratio. It is guided to develop a simple prognostic model to select the right factors that should be considered.

Conflicts of interest

The authors declare no conflict of interest.

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