

Clinical Biomarkers and Prognosis in Taiwanese Patients with Non-Small Cell Lung Cancer (NSCLC)

Yixia Li¹, Yea-Jyh Chen², Li-Jung Chang³, Michael Hendryx^{1,4}, Juhua Luo^{1,4,5*}

¹Department of Community Medicine, School of Medicine, West Virginia University, Morgantown, USA; ²School of Nursing, West Virginia University, Morgantown, USA; ³Department of Nursing, Tzu Chi College of Technology, Hualien, Taiwan; ⁴West Virginia Rural Health Research Center, Morgantown, USA; ⁵Mary Babb Randolph Cancer Center, West Virginia University, Morgantown, USA.

Email: *jiluo@hsc.wvu.edu

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ABSTRACT

Introduction: Lung cancer is the leading cause of cancer death worldwide with poor survival rates. However, the prognostic factors for survival of patients with lung cancer are not well-established. In this study, we examined the impact of routine laboratory biomarkers and traditional factors on survival of patients with non-small cell lung cancer (NSCLC).

Method: Secondary data analysis was conducted from a retrospective study of 404 patients with newly diagnosed lung cancer in 2005-2007 in Taiwan. There were eight routine laboratory biomarkers and eight traditional factors investigated in the analyses. Cox proportional hazards model was used to assess the hazard ratios for the association between risk factors and patient overall survival. The Kaplan-Meier method was used to compare survival curves for each prognostic indicator. **Results:** High WBC counts (HR = 1.798, 95%CI: 1.225 - 2.639), low Hgb level (HR = 1.437, 95%CI: 1.085 - 1.903), and low serum albumin level (HR = 2.049, 95%CI: 1.376 - 3.052) were significant laboratory prognostic biomarkers for poor NSCLC survival. Additionally we confirmed the traditional prognostic factors for poor overall survival among NSCLC patients, including older age, comorbidity conditions, advanced cancer stage, and non-surgical treatment. **Conclusions:** This study identified three available laboratory biomarkers, high WBC counts, low Hgb level, and low serum albumin level, to be significant prognostic factors for poorer overall survival in NSCLC patients. Further prognostic evaluation studies are warranted to compare different ethnic groups on the prognostic values of these clinical parameters in NSCLC survival outcomes. These identified prognostic biomarkers should be included in early risk screening of hospitalized lung cancer patient population.

Keywords: Clinical Biomarkers; Non-Small Cell Lung Cancer (NSCLC); Prognostic Factors

1. Introduction

Lung cancer is the leading cause of cancer death worldwide [1]. An estimated 1.6 million new cases of lung cancer occurred worldwide in 2008, accounting for about 13% of total cancer diagnoses [2]; and an estimated 951,000 men and 427,400 women died from the disease worldwide in 2008. Histologically, lung cancer can be classified into two types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC accounts for 85% of lung cancer cases, and approximately 65% of patients with NSCLC present with advanced-stage (III or IV) disease [3]. In addition, lung cancer is predominantly a disease of elderly people: the median age of newly diagnosed lung cancer patients is approximately 68 years and as many as 40% of patients are older than 70 years [4]. The five-year survival rates among

patients with NSCLC after complete resection are 46% - 81% with stage IA to IIB, compared to 21% - 24% with stage IIIA to IV [5]. Furthermore, overall survival among patients receiving chemotherapy also remains poor with a median 4 to 15 month survival time [6]. Therefore, studying prognostic biomarkers as survival predictors may contribute to improved disease prognosis and treatment guidelines for lung cancer.

Prognostic predictors for lung cancer outcomes are inconsistent in previous literature. The most widely accepted prognostic factors for patients with NSCLC include tumor stage, performance status, and weight loss [7-12]. Besides these factors, biochemical or hematologic markers, such as white blood cell (WBC) counts, neutrophil counts and hemoglobin (Hgb) level, are also associated with NSCLC survival. A previous study performed by the North Central Cancer Treatment Group (NCCTG), which included 1053 lung cancer patients,

*Corresponding author.

revealed that patients who had high WBC counts and low Hgb levels had significantly worse survival than their counterparts [13]. However, the prognostic importance of complete blood count findings were inconsistent with other studies [14-18] where no significant association was found for WBC counts or Hgb level. In addition, neutrophil counts in a study by Ferrigno *et al.* were found to independently predict the survival of NSCLC patients [19]. Similar to Ferrigno's result, the European Lung Cancer Working Group found that a high-neutrophil count was an independent prognostic factor for poor survival in patients with unresectable advanced NSCLC [20]. Paddison also reported that high level neutrophil counts and low Hgb level predicted poor survival of NSCLC patients [21]. Furthermore, another study found that platelet counts were associated with poor overall survival in a univariate model but were not significant in multivariate analysis [22].

There may be additional biochemical markers related to lung cancer survival, such as serum albumin level and serum sodium level. Serum albumin level, a nutritional indicator, has been examined as a prognostic lung cancer marker among both SCLC and NSCLC patients in several previous studies [12,23,24]. Maeda *et al.* observed that serum albumin level was one of the most significant prognostic factors for advanced NSCLC in both univariate and multivariate analysis [12]. In Win's study, serum albumin level was identified to be a significant prognostic factor in univariate model but not in multivariate analysis for lung cancer patients [23]. A similar association between serum albumin level and lung cancer survival was observed by Tas *et al.* [24]. In addition, abnormal serum sodium level has been studied as a poor survival predictor for lung cancer. Previous research has reported that hyponatremia predicts poor survival of SCLC patients [15,25-27], but there appears to be no previous research on hyponatremia in relation to NSCLC survival outcome.

Because of incomplete and in some cases inconsistent evidence on prognostic biomarkers for NSCLC survival, the aim of this study was to examine the relationships between routine laboratory parameters including WBC counts, neutrophil percentage, lymphocyte percentage, Hgb level, platelet counts, serum albumin level, and serum sodium level on overall survival in NSCLC patients.

2. Materials and Methods

2.1. Study Design and Measures

This study is a secondary data analysis derived from a retrospective study of patients with newly diagnosed lung cancer in the years 2005-2007 in Taiwan. Detailed description of this study sample design and methods are available in Luo *et al.* [28]. In brief, the retrospective study screened potential patients through hospital medi-

cal records. Eligible patients were selected based on initial hospitalization with lung cancer as the primary diagnosis, who were discharged to home and were older than 40 years old. There were 404 patients eligible in the study for final analysis.

Patients' characteristics, extracted from hospital records, include age, gender, the Eastern Cooperative Oncology Group (ECOG) performance (PS) (0 - 5 with 0 denoting perfect health and 5 denoting death) [29], smoking status (never, former, current), body mass index (BMI; kg/m²), Charlson comorbidity Index (CCI; excluded lung cancer as the primary disease), tumor stage (less advanced—stage I, II and IIIA and advanced—stage IIIB and IV), cancer treatment (surgery with/without one or more types of supportive care [e.g. chemotherapy, radiation, tyrosin kinase inhibitor targeted therapy], chemotherapy with/without other supportive care, or no cancer treatment). The CCI, a weighted index score with a possible range of 0 - 35, was used to evaluate patients' comorbid conditions according to the influence of comorbidity on overall mortality risk [30,31]. The patients' BMI was calculated and classified into four categories: underweight (<18.5 kg/m²), normal (18.5 - <25 kg/m²), overweight (25 - <30 kg/m²) and obese (≥30 kg/m²). Laboratory data including WBC counts, Hgb level, neutrophil percentage, lymphocyte percentage, platelet counts, monocyte percentage, serum albumin level, and serum sodium level were measured at the index visit. These variables were considered as the main prognostic factors of interest for the study. We used the admission or first-time measure if more than one set of laboratory biomarkers were examined during the index visit. In order not to lose study power, we kept patients with missing data in the final analysis and categorized those patients as an additional group. The outcome of interest in this study was survival duration, which was defined as the interval in months from the discharge date of the index visit to death from any cause. Patients' survival data were followed through cancer registry records until the end of 2010.

2.2. Statistical Analysis

We categorized all potential prognostic variables including WBC counts, Hgb level, neutrophil percentage, lymphocyte percentage, platelet counts, monocyte percentage, albumin level, and sodium level into normal and abnormal values according to standard laboratory norms (cut-points are listed in **Table 1**) [32]. For sodium level, we divided it into two groups since there was only one patient with sodium level higher than 145 (mmol/l).

For univariate analyses, we estimated survival curves using the Kaplan-Meier method and compared these curves by the log-rank test. Survival duration was also estimated by fitting the data with a Cox regression model [33]. All variables reaching statistical significance ($p <$

Table 1. Characteristics of lung cancer patients during the study follow-up (N = 404).

Variable	No. (%)	Death within follow-up (N)	Death within follow-up (%)
Age (years)			
<70	201(49.75)	167	83.08
≥70	203 (50.25)	185	91.13
Gender			
Female	148 (36.63)	124	83.78
Male	256 (63.37)	228	89.06
Smoking status			
Never	179 (44.31)	149	83.24
Former	156 (38.61)	141	90.38
Current	69 (17.08)	62	89.86
ECOG Performance status			
<2	264 (65.35)	217	82.20
≥2	140 (34.65)	135	96.43
BMI (kg/m²)			
<18.5	39 (9.65)	36	92.31
18.5 - <25	225 (55.69)	193	85.78
25-<30	86 (21.29)	70	81.40
≥30	13 (3.22)	12	92.31
Missing	41 (10.15)	41	100.00
Co-morbidity score			
<4	136 (33.66)	105	77.21
4 - 8	200 (49.50)	184	92.00
≥8	68 (16.83)	63	92.65
Cancer stage			
Less advanced	41 (10.15)	25	60.98
Advanced	363 (89.85)	327	90.08
Cancer treatment			
Surgery	24 (5.94)	8	33.33
Chemotherapy and /or other supportive care	300 (74.26)	268	89.33
None	80 (19.80)	76	95.00
WBC counts (10³/μL)			
≤5.5	63 (15.59)	52	82.54
5.5 - 15.5	300 (74.26)	260	86.67
>15.5	41 (10.15)	40	97.56
Neutrophil (%)			
27 - 55	35 (8.66)	25	71.43
>55	339 (83.91)	299	88.20
Missing	30 (7.43)	28	93.33
Lymphocyte (%)			
<16	175 (43.32)	162	92.57
16 - 46	220 (54.46)	187	85.00
>46	9 (2.23)	3	33.33

Continued

Hemoglobin (g/dL)			
<11.5	122 (30.20)	118	96.72
11.5 - 13.5	152 (37.62)	129	84.87
>13.5	130 (32.18)	105	80.77
Platelet counts (Thou/μl)			
<150	157(38.86)	133	84.71
150 - 400	164 (40.59)	144	87.80
>400	51 (12.62)	48	94.12
Missing	32 (7.92)	27	84.38
Monocyte (%)			
<4	99 (24.50)	85	85.86
4 - 11	280 (69.31)	243	86.79
>11	25 (6.19)	24	96.00
Albumin (g/dl)			
<3.1	40 (9.90)	40	100.00
3.1 - 4.3	175 (43.32)	151	86.29
>4.3	28 (6.93)	20	71.43
missing	161 (39.85)	141	87.58
Sodium (mmol/l)			
<136	189 (46.78)	177	93.65
136 - 147	215 (53.22)	175	81.40

0.05) at the univariate level were included in the multivariate analysis. We performed Pearson correlations among the selected variables for collinearity before the multivariate analysis. If any two variables were highly correlated ($r > 0.6$), only one was selected in the multivariate model. We used the Cox proportional hazards model to perform the multivariate analysis to adjust for all included variables. The hazard ratios were calculated to assess the death risk for various prognostic factors. All statistical analyses were done using SAS version 9.2 with a significant p-value criterion of 0.05 or less.

3. Results

3.1. Baseline Patient Characteristics

Of the total 404 patients with newly diagnosed NSCLC, the median follow-up duration time was 10.7 months (range, 0 - 70 months). Mean age of the study sample population was 67.6 years (SD = 11.0). Over 60% of the patients (N = 256) were male; approximately 39% of patients were former smokers and 17% were current smokers. The majority of patients (90%) were diagnosed at an advanced stage (stage IIIB or stage IV). Overall, 352 patients (87%) died by the end of 2010. **Table 1** summarizes the study patient characteristics.

3.2. Univariate Analysis

Univariate analysis revealed the following patient characteristics to be significant prognostic factors for poor survival: older age (≥ 70 years), male, current smoker, poor performance status (PS ≥ 2), low BMI (≤ 18.5 kg/m²), high CCI score (≥ 4), advanced cancer stage (IIIB and IV), cancer treatment (chemotherapy with/without other supportive cancer treatment or no cancer treatment), high WBC ($>15.5 \times 10^3/\mu\text{L}$), high neutrophil percentage ($>55\%$), lower ($<16\%$)/ higher ($>46\%$) lymphocyte percentage, low Hgb level (<11.5 g/dl), lower (<3.1 g/dl)/ higher (>4.3 g/dl) albumin level, and low sodium level (<136 mmol/l). Other variables, including platelet counts and monocyte percentage were not observed to be significantly associated with overall NSCLC survival ($p > 0.05$; see **Table 2**).

In patients with advanced cancer stage, the median survival time was 10.1 (95%CI: 8.6 - 12.0) months compared with 26.2 survival months among those patients with less advanced stage ($p < 0.0001$). In patients with high WBC counts, the median survival was 1.93 (95%CI: 1.1 - 4.1) months, compared with the patients with normal and low WBC counts (11.9 vs 14.3 survival months, respectively; $p < 0.0001$). Similarly, patients with low

Table 2. Univariate analyses of prognostic factors and survival in patients with NSCLC (N = 404).

Variable	Hazard ratio	95%CI	p-value
Age (years)			
<70	1		
≥70	1.703	1.380 - 2.102	<0.0001
Gender			
Female	1		
Male	1.273	1.023 - 1.585	0.0306
Smoking status			
Never	1		
Former	1.263	0.939 - 1.699	0.1228
Current	1.410	1.119 - 1.777	0.0035
ECOG performance status			
<2	1		
≥2	2.236	1.798 - 2.781	<0.0001
BMI (kg/m²)			
<18.5	1.430	1.002 - 2.043	0.0490
18.5 - <25	1		
25 - <30	0.969	0.541 - 1.738	0.9166
≥30	0.949	0.722 - 1.247	0.7068
missing	4.013	2.838 - 5.674	<0.0001
Co-morbidity score			
<4	1		
4 - 8	1.479	1.162 - 1.883	0.0015
≥8	1.873	1.366 - 2.568	<0.0001
Cancer stage			
Less advanced	1		
Advanced	2.375	1.575 - 3.582	<0.0001
Cancer treatment			
Surgery	1		
Chemotherapy and/ or other supportive care	4.877	2.408 - 9.877	<0.0001
None	11.481	5.522 - 23.868	<0.0001
WBC counts (10³/μL)			
≤ 5.5	0.789	0.586 - 1.063	0.1192
5.5 - 15.5	1		
>15.5	2.642	1.889 - 3.697	<0.0001
Neutrophil (%)			
27 - 55	1		
>55	1.942	1.290 - 2.923	0.0015
Missing	1.897	1.105 - 3.257	0.0203
Lymphocyte (%)			
<16	1.620	1.311 - 2.003	<0.0001
16 - 46	1		
>46	0.240	0.077 - 0.752	0.0143

Continued

Hemoglobin (g/dL)			
<11.5	1.908	1.482 - 2.455	<0.0001
11.5 - 13.5	1		
>13.5	0.786	0.607 - 1.018	0.0679
Platelet counts (Thou/μl)			
<150	0.803	0.634 - 1.016	0.6628
150 - 400	1		
>400	1.295	0.933 - 1.797	0.1227
Missing	0.913	0.605 - 1.377	0.6628
Monocyte (%)			
<4	0.858	0.670 - 1.099	0.2248
4 - 11	1		
>11	1.310	0.861 - 1.993	0.2080
Albumin (g/dl)			
<3.1	3.728	2.598 - 5.350	<0.0001
3.1 - 4.3	1		
>4.3	0.609	0.381 - 0.972	0.0374
Missing	1.070	0.850 - 1.346	0.5657
Sodium (mmol/l)			
<136	1.783	1.443 - 2.201	<0.0001
136 - 147	1		

Hgb level (<11.5 g/dL) had 5.4 (95%CI: 4.1 - 7.2) survival months, compared with 12.2 months for patients with normal Hgb level and 7.5 months for patients with high Hgb level. For patients with low albumin level, the overall survival time was shorter (2.4 months; 95%CI: 1.2 - 5.9), compared with those having normal and high albumin levels (12.4 months vs 22.0 months, respectively; $p < 0.0001$). Survival curves for these four markers are shown in **Figures 1(a)-(d)**.

3.3. Multivariate Analysis

After performing the Pearson correlations, gender and smoking status were highly correlated ($r = 0.68$). Gender remained in the multivariate model for analysis because 1) it is a common characteristic for analysis; and 2) in an analysis of males only, smoking status was not a significant independent predictor for NSCLC (data not shown). After simultaneously adjusting for all potential prognostic factors (see **Table 3**), significantly lower survival rates were identified for patients with older age (≥ 70 years), lower performance status, higher co-morbidity score (>8), advanced lung cancer stage, cancer treatment rather than surgery, high WBC counts, low Hgb levels and low albumin levels. Correspondingly, similar results were found while performing a multivariable analysis stratified by cancer stage (data not shown). However, our data were insufficient to perform a similar analysis for

patients with less advanced cancer stage, as only 7.1% patients with less advanced cancer diagnosis died within the study period.

4. Discussion

Our study demonstrated that older age, poor performance status, poor comorbid condition, advanced cancer stage, treatment other than surgery, high WBC counts, low Hgb levels and low albumin levels were significant prognostic factors for shorter NSCLC survival in multivariate analysis.

Tumor stage, performance status and weight loss at the time of diagnosis have been found to have a negative impact on patient survival from NSCLC in previous research [34,35]. The present study confirmed that advanced cancer stage and poor performance status were prognostic factors for NSCLC survival. However, low BMI ($<18.5 \text{ kg/m}^2$) was a significant prognostic factor in univariate analysis but not in multivariate analysis in our study. This may be due to the fact that BMI data were missing in 10% of cases. We observed that patients with missing BMI all died within the study follow-up period, indicating that patients with unavailable BMI data during hospitalization were more likely to be severely ill with relatively higher mortality rate. In addition, individuals with missing BMI data tended to be older, with advanced cancer stage, and have poor performance status.

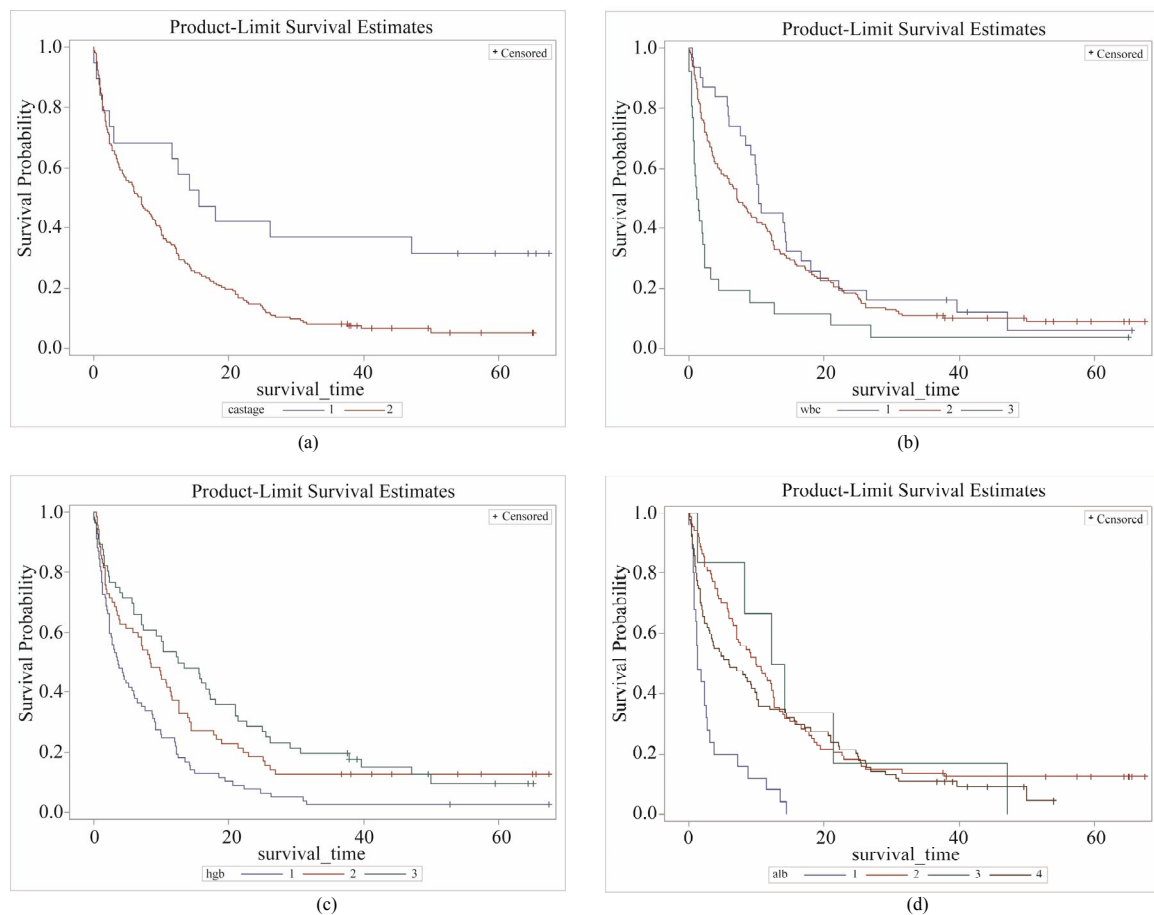


Figure 1. NSCLC survival curve by cancer staging and laboratory biomarkers (N = 404). (a) Survival curves by cancer stage: 1 for less advanced stage, 2 for advanced stage ($p < 0.0001$); (b) Survival curves by WBC counts: 1 for $\leq 5.5 \times 10^3/\mu\text{L}$, 2 for $5.5 \times 10^3/\mu\text{L} - 15.5 \times 10^3/\mu\text{L}$, 3 for $> 15.5 \times 10^3/\mu\text{L}$ ($p < 0.0001$); (c) Survival curves by hemoglobin (Hgb) level: 1 for ≤ 11.5 g/dL, 2 for 11.5 g/dL - 13.5 g/dL, 3 for > 13.5 g/dL ($p < 0.0001$); (d) Survival curves by serum albumin (alb) level: 1 for ≤ 3.1 g/dL, 2 for 3.1 g/dL - 4.3 g/dL, 3 for > 4.3 g/dL, 4 for missing value ($p < 0.0001$).

Table 3. Multivariate analyses of key prognostic factors and survival in patients with NSCLC (N = 404).

Variable	Hazard ratio	95%CI	p-value
Age			
<70	1		
≥ 70	1.445	1.147 - 1.819	0.0017
Gender			
Female	1		
Male	1.183	0.936 - 1.494	0.1597
BMI (kg/m²)			
<18.5	0.980	0.658 - 1.460	0.9207
18.5 - <25	1		
25 - <30	0.998	0.750 - 1.329	0.9898
≥ 30	1.129	0.619 - 2.065	0.6924
missing	2.269	1.514 - 3.399	<0.0001

Continued

ECOG Performance status			
<2	1		
≥2	1.506	1.167 - 1.943	0.0017
Co-morbidity score			
<4	1		
4 - 8	1.354	1.023 - 1.791	0.0340
≥8	1.557	1.103 - 2.199	0.0118
Cancer stage			
Less advanced	1		
Advanced	1.818	1.153 - 2.867	0.0101
Cancer treatment			
Surgery	1		
Chemotherapy and/ or other supportive care	2.513	1.202 - 5.257	0.0144
None	5.704	2.665 - 12.211	<0.0001
WBC counts (10³/μL)			
≤5.5	0.798	0.577 - 1.104	0.1724
5.5 - 15.5	1		
>15.5	1.798	1.225 - 2.639	0.0027
Neutrophil (%)			
27 - 55	1		
>55	1.308	0.826 - 2.070	0.2521
Missing	1.650	0.891 - 3.055	0.1112
Lymphocyte (%)			
<16	0.931	0.705 - 1.230	0.6157
16 - 46	1		
>46	0.475	0.139 - 1.622	0.2350
Hemoglobin (g/dL)			
<11.5	1.437	1.085 - 1.903	0.0115
11.5-13.5	1		
>13.5	0.901	0.686 - 1.183	0.4522
Albumin (g/dl)			
<3.1	2.149	1.376 - 3.052	0.0004
3.1 - 4.3	1		
>4.3	0.943	0.580 - 1.534	0.8131
Missing	1.279	1.006 - 1.625	0.0443
Sodium (mmol/l)			
<136	1.141	0.895 - 1.454	0.2875
136 - 147	1		

Comorbidity condition was also observed as a predictor of lung cancer survival. Previous findings on comorbidity are inconsistent. Janssen *et al.* reported no independent prognostic effect of comorbidity condition for patients with non-small cell lung cancer [36]. However, in line with our study, Wang and colleagues revealed that patients with CCI score ≥ 2 had higher perioperative

mortality and death from NSCLC compared with patients with CCI score < 2 [37]. Firat *et al.* and Moro-Sibilot *et al.* also studied the significance of comorbidity scores in stage I NSCLC patients and found it to be a significant prognostic impact [38,39].

Our study confirmed that elevated WBC counts were significantly associated with poor prognosis among

NSCLC patients, which aligned with most previous observations [13]. In a nationally representative adult cohort study, WBC counts were found to be positively and independently associated with cancer mortality after adjusting for age, gender and race [40]. In that study, inflammation was associated with WBC counts as well. WBC as a marker of inflammatory level reflects either a greater burden of tumor cells within the bone marrow, a possible concomitant subclinical infection, or the effect of a yet undescribed chemokine or cytokine secreted by the tumor into the circulation. Stromal tissues of tumors contain large numbers of WBC counts, and the inflammatory cell number and their cytokine production correlate with tumor severity and prognosis [41-44].

We also identified the relationship of both low Hgb and serum albumin levels with poor survival as reported in other studies [12,13,23,24,45,46]. Takugawa *et al.* stated low Hgb level correlated with overall survival among patients with NSCLC [47]. Similar findings were reported in Albain's study [48]. For serum albumin level, Phillips reported a marked increase in mortality rate with decreasing serum albumin concentrations among cancer and cardiovascular patients [49]. Another study found an approximate 25% reduction in cancer mortality among middle aged men with a one standard deviation increase in serum albumin [50]. Similar to the elevated WBC counts, low Hgb and serum albumin levels also play an influential role in body inflammation. Serum albumin is a negative acute phase protein; its concentration in the blood is reduced in response to inflammation [51]. Hypoalbuminemia is the result of the combined effects of inflammation and inadequate protein and caloric intake in patients with chronic disease and cancer. Inflammation and malnutrition both reduce albumin concentration by decreasing its rate of synthesis, while inflammation alone is associated with a greater fractional catabolic rate (FCR) and, when extreme, increased transfer of albumin out of the vascular compartment [50]. This study is the first to assess clinical prognostic factors in a Taiwanese population, although several other Asian research articles have identified the traditional factors for lung cancer survival including old age, no surgery treatment, performance status, and advanced lung cancer stage [28,52,53].

The findings of this study should be considered in the context of its strengths and limitations. Study strengths include the fact that 1) all lung cancer cases were newly diagnosed which ruled out impact on patients' outcomes by possible cancer pretreatment that patients may have received. In addition, 2) the outcome measure (death yes/no) was tracked up to 3 - 5 years in order to predict long term prognosis for NSCLC; and 3) we were able to collect and adjust for most potential prognostic factors such as smoking status, BMI, and performance status.

However, the present study was also limited in several

respects. Using data derived from retrospective hospital records review, we found that routinely examined laboratory item such as albumin level was not available for every individual during the hospital stay. These missing data limited the ability of our study to conduct a complete data analysis. In addition, the study uses a sample from a Taiwanese patient population most of whom reside in a rural area, which may limit the generalizability of study findings of NSCLC survival outcomes to other populations.

5. Conclusion

This study contributes to research on overall NSCLC survival by concurrently identifying significant laboratory biomarkers for survival, including WBC counts, Hgb level, and serum albumin level. Additionally we confirmed the widely accepted prognostic factors of lung cancer survival such as old age, advanced cancer, severe comorbidity, performance status, and lack of surgery treatment. Because these identified biomarkers are routinely checked during hospital admissions, the findings of this study could help in the early identification of patients at risk of shorter NSCLC survival to provide better clinical patients care. Moreover, to extend and confirm the current study findings, future studies should apply more comprehensive prognostic assessments, conduct longer follow-ups, and study additional ethnic populations.

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