Pretreatment prognostic factors to predict survival outcome in advanced non-small cell lung cancer with first line treatment in Thailand: a retrospective cohort study

Miss Sureerat Jaruhathai

A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science Program in Health Development
Faculty of Medicine
Chulalongkorn University
Academic Year 2017

การศึกษาปัจจัยพยากรณ์ที่มีผลต่ออัตราการรอดชีพในผู้ป่วยมะเร็งปอดที่ได้รับการรักษาด้วยยาขนานแรก

นางสาวสุรีรัตน์ จารุหทัย

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
สาขาวิชาการพัฒนาสุขภาพ
คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2560

Thesis Title	Pretreatment prognostic factors to predict survival outcome in advanced non-small cell lung cancer with first line treatment in Thailand: a retrospective cohort study
By	Miss Sureerat Jaruhathai
Field of Study	Health Development
Thesis Advisor	Associate Professor Ketchada Uerpairojkit, M.D.
Thesis Co-Advisor	Professor Pichet Sampatanukul

Accepted by the Faculty of Medicine, Chulalongkorn University in Partial Fulfillment of the Requirements for the Master's Degree

.....Dean of the Faculty of Medicine

(Professor Suttipong Wacharasindhu, M.D.)

THESIS COMMITTEE

.....Chairman

(Professor Thewarug Werawatganon, M.D.)

.....Thesis Advisor

(Associate Professor Ketchada Uerpairojkit, M.D.)

.....Thesis Co-Advisor

(Professor Pichet Sampatanukul)

.....Examiner

(Associate Professor Chulalak Komoltri, Ph.D.)

.....External Examiner

(Assistant Professor Eakphop Sirachainan, M.D.)

สุรีรัตน์ จารุหทัย : การศึกษาปัจจัยพยากรณ์ที่มีผลต่ออัตราการรอดชีพในผู้ป่วยมะเร็งปอดที่ได้รับการรักษาด้วยยาขนานแรก (Pretreatment prognostic factors to predict survival outcome in advanced non-small cell lung cancer with first line treatment in Thailand: a retrospective cohort study) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: รศ. พญ. เกศชาดา เอื้อไพโรจน์กิจ, อ.ที่ปรึกษาวิทยานิพนธ์ร่วม: ศ. นพ. พิเชฐ สัมปทานุกุล , หน้า.

ภูมิหลัง:การตรวจพันธุกรรมของมะเร็งและการตรวจ biologic marker มักถูกนำมาใช้เป็น prognostic factor อย่างไรก็ตามยังมีข้อจำกัดการใช้การส่งและการใช้ในเวชปฏิบัติทั่วไปและราคาแพง

วัตถุประสงค์: เพื่อศึกษาปัจจัยทีประเมินก่อนการรักษาที่สะดวกและราคาไม่แพงใดบ้างสัมพันธ์กับการมีชีวิตรอดในผู้ป่วยมะเร็งปอดชนิดเซลล์ไม่เล็กระยะลุกลาม

วัสดุและวิธีการ:เป็นการศึกษาแบบ retrospective cohort study โดยการทบทวนเวชระเบียนของผู้ป่วยที่ได้รับการวินิฉัยเป็นมะเร็งปอดระยะลุกลามที่ไม่เคยได้รับการรักษาใดๆมาก่อนในโรงพยาบาลจุฬาลงกรณ์ และโรงพยาบาลตำรวจระหว่างวันที่ 1 มกราคม พ.ศ. 2551-2556

ผลการศึกษา: ผู้ป่วย 301 รายในการศึกษา เป็นเพศชาย 68.1% ผลการศึกษาพบว่าปัจจัยก่อนการรักษาที่สามารถทำนายอัตราการมีชีวิตรอด ได้แก่ จำนวนอวัยวะที่กระจายของโรคมะเร็ง ($p<0.05$) สัดส่วน neutrophil lymphocyte ratio ($p<0.001$) สัดส่วน albumin globulin ratio ($p=0.010$) ECOG status ($p<0.005$)และการสูบบุหรี่ ($p<0.001$)

สรุป ปัจจัยก่อนการรักษาที่มีความสัมพันธ์กับอัตราการมีชีวิตรอดได้แก่ จำนวนอวัยวะที่มะเร็งแพร่กระจาย สัดส่วน neutrophil lymphocyte ratio สภาวะ ECOG ของผู้ป่วย และการสูบบุหรี่ ปัจจัยที่มีผลดังกล่าวสามารถนำมาพัฒนาsimple model เพื่อใช้ในการพยากรณ์โรคในผู้ป่วยมะเร็ง

สาขาวิชา การพัฒนาสุขภาพ ลายมือชื่อนิสิต .....

ปีการศึกษา 2560 ลายมือชื่อ อ.ที่ปรึกษาหลัก .....

ลายมือชื่อ อ.ที่ปรึกษาร่วม .....

5774653030 : MAJOR HEALTH DEVELOPMENT
KEYWORDS: PROGNOSTIC FACTORS / SURVIVAL / LUNG CANCER

SUREERAT JARUHATHAI: Pretreatment prognostic factors to predict survival outcome in advanced non-small cell lung cancer with first line treatment in Thailand: a retrospective cohort study. ADVISOR: ASSOC. PROF. KETCHADA UERPAIROJKIT, M.D., CO-ADVISOR: PROF. PICHET SAMPATANUKUL, pp.

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

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

Methods: Retrospectively reviewed the charts of patients diagnosed with having advanced NSCLC with no previous treatment seen at King Chulalongkorn Memorial Hospital and Police General Hospital during 1 January 2008-31 Dec 2013.

Results: A total of 301 patients were included in the study; 68.1% males. The pretreatment 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 ($p=0.010$)and the ,ECOG status ($p<0.005$),and current smoker($p=0.001$)

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

Field of Study: Health Development
Academic Year: 2017

Student's Signature .....
Advisor's Signature .....
Co-Advisor's Signature .....

ACKNOWLEDGEMENTS

I would like to sincere thanks to my advisor and co-advisor, Assoc.Prof.Ketchada uerpairojkit and Prof.Pichet Sampatanukul. This paper would not have been possible complete without good support. I'm grateful with whom i have had work during this thesis paper. I also would like to express my gratitude to the rest of my thesis committee : Prof.Thewarug Werawatganon, Assoc.Prof.Chulalak Komoltri and Asst.Prof.Eakphop Sirachainan for insightful comments,and encouragement. My sincere thanks to Dr.Nick Walter, and Alisara Sangviroon for the support.

CONTENTS

Page

LIST OF TABLES

LIST OF FIGURES

CHAPTER I
INTRODUCTION

TITLE: PRETREATMENT PROGNOSTIC FACTORS TO PREDICT SURVIVAL OUTCOME IN ADVANCED NON SMALL CELL LUNG CANCER WITH FIRST LINE TREATMENT IN THAILAND: A RETROSPECTIVE COHORT STUDY

BACKGROUND AND RATIONAL

Non-Small Cell Lung Cancer is approximately 85% of lung cancer. In Thailand, The National Cancer Center of Thailand recently reported Non-Small Cell Lung Cancer (NSCLC) is the first most common cancer in Male and the fourth most common cancer in Female.[1] At the present there is no evidence screening lung cancer in general population. Therefore most patients are diagnosed with advanced stage and the prognosis of advanced NSCLC is grim. Systemic chemotherapy is the mainstay treatment for advanced stage NSCLC. It has been shown chemotherapy can improve overall survival when compared to no treatment.[2-5] The median survival is improved from to 3.9 months to 8.1 months with 1 year survival rate at 30-40 %,[6-8] and 2 years survival rate at 18-23%.[9-11]. Recently, Tumor genetic information can also be used for predictive and prognostic factor, EGFR,[12-15] K-ras,[16-18] ERCC1,and RRM1[19-21] for example. Nevertheless, the new treatment, tumor genetic mutation testing or biologic markers are limited applicable in real daily practice due to high cost and few institutes are available. Most patients are unable to afford new treatment and test. Simple investigation such as routine blood chemistries and simple patient's factors that can use as prognostic factors is valuable. Albumin and globulin ratio also has been investigated. From basic knowledge albumin and globulin are involved with

nutritional status and the inflammatory process, and bring to tumor promotion. Neutrophil and lymphocyte is the indicator of systemic inflammatory response. The inflammatory process in tumor environment play a major role of malignant cells proliferation and migration.it has been shown the association of with survival in various solid tumors. The advantage is to help the physicians give information regarding the prognosis. Advanced lung cancer patients also can make decision about suitable optimal treatment plan, personal lives aspect for good quality of life. The aim of this study is to evaluate which simple prognostic factors related outcome with first line treatment in advanced stage NSCLC patients

CHAPTER II

REVIEW OF THE RELATED LITERATURES

All related literatures were searched from Pubmed database by using key word term prognostic factor AND survival outcome AND advanced Non-Small Cell Lung Cancer.191 articles that related simple biomarkers associated with survival outcome in advanced stage Non-Small Cell Lung Cancer were found. A repeated search by using key word prognostic factor AND long term survival AND NSCLC stage 4, then35 articles were found. By using Scopus database with key work term prognostic factor AND survival AND advanced Non-Small Cell Lung Cancer. Totally 126 articles were found. In general patient's factors widely used for predict survival such as ECOG status, extent of disease.[22, 23]

There are growing research studies regarding simple and easy applicable factors to predict prognosis both solid and hematologic malignancies. The definition of long term survival is derived from review literature mostly at 2 years.[23-25] Albumin and Globulin are 2 parts of protein in blood. Albumin is a protein 60% of total protein represents to nutritional status. It was used to assess the prognosis of the both non malignancies and malignancies disease.[26-29] Low pre-treatment serum albumin less than 3.5 g/dL was associated short survival in colorectal. In breast cancer study showed that patients who have high serum albumin can reduce risk of death by 72% (p=0.00233), ovarian cancer also showed that patients who have high serum albumin correlated with long term survival. (4.8 months: 95%CI 0-13.1 vs 43.2 months: 95%CI 16.-20.9 months) [26-29]. Globulin is 40% of total protein. Albumin and globulin ratio also has been investigated. Albumin and globulin are involved with nutritional status and the inflammatory process, and bring to tumor promotion. Previous studies showed that albumin globulin ratio is associated with survival in various type of cancer. Nasopharyngeal cancer study showed that low AGR was associated with poor survival (HR=1.439:95%CI 1.038-1.994, p=0.029).[30] breast cancer by HR=6.23:95%CI 2.73-13.98,(p<0.001)[31] .Colorectal cancer also showed the low AGR had higher mortality in comparison to high AGR (16.8 vs 6.6 vs

5.4%,p=0.012),[32][33] . It was wide range of cut point value in different studies. Neutrophil to lymphocyte ratio (NLR) is an interesting simple biomarker. NLR is an indicator of systemic inflammatory response. The inflammatory processes in tumor environment play a major role of malignant cells proliferation and migration.[34, 35] It has been shown the association of high NLR with shorter survival in various solid tumors.[36, 37] Regarding 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. Long term survival is referred to overall survival more than 2 years, definition by review previous related literature.[23-25]

RESEARCH QUESTION

PRIMARY QUESTION

Which factor is associated with overall survival with first line first line treatment in advanced NSCLC patients?

OBJECTIVES

To identify simple factors that can predict outcome with first line first treatment in advanced NSCLC patients

To determine the relationship between factors and overall survival with the first line treatment in advanced NSCLC patients.

CHAPTER III
MATERIALS AND METHODS

Keywords

Prognostic factors, survival, First line treatment, Advanced Non-Small Cell Lung Cancer

Operation Definitions

- Advanced Non-Small Cell Lung cancer(NSCLC) are referred to stage IIIB and IV staged with TNM staging of seven edition of TNM classification of malignant tumors

T = primary tumor size

N= Regional lymph nodes involvement

M= Distant metastasis

NSCL STAGE IIIB is referred to T4 or N3

T4 = Tumor of any size that invades any of adjacent organ

N3= Metastasis in contralateral mediastinum, contralateral hilar, supraclavicular node.

NSCLC stage IV is referred to T any N any M1

- ECOG Performance is the scale and criteria are used to assess how a patient's disease is progressing, assess how the disease affects the diary living ability of patient, and determine appropriate treatment and prognosis. In this study will use to assess patient status before start first line treatment. The definition by Eastern Cooperative oncology group, the clinical cancer research organization in United States.

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confine to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

- Definition of smoking status

Current smoker is smoking at least 100 cigarettes in life time, and still smoke every day or someday.

Former smoker is smoking at least 100 cigarettes in life time, and did not smoke at all.

Never smoker is never smoke or less than 100 cigarettes in life time

Chemotherapy regimen is referred to standard platinum based chemotherapy regimen.

There are consist of either carboplatin based or cisplatin based chemotherapy

For elderly who age>65 can have either single agent chemotherapy.[6-8]

- Albumin to globulin ratio is calculated by formula

$$AGR = \frac{\text{Albumin}}{\text{(total protein-albumin)}}$$

- Neutrophil to lymphocyte ratio is calculated by dividing the number of neutrophils by number of lymphocytes from peripheral blood sample.
- Time from diagnosis to date of start first line treatment is referred to the duration date start that know the pathological diagnosis to the date that start first line treatment for advanced stage NSCLC patients.
- Overall survival is referred to time from date of diagnosis to death from any cause.

RESEARCH METHODOLOGY

A retrospective cohort study conducted among patients with advanced NSCLC 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 during 1 January 2008 to 31 December 2013. Patient who were dead before 31st Dec 2013 will be censored at date of death. Patient who has first visit with oncology unit at 31th Dec 2013 were allowed to include in this study. Variables measurement were age, gender, smoking status, histological type of NSCLC whether squamous or non-squamous cell type, number of organ involvement, time from diagnosis to treatment. Pretreatment laboratory, within 1 month before starting treatment albumin/globulin ratio, neutrophil/lymphocyte ratio were recorded. ECOG status was used to evaluate the patient health status. 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 that had died was extracted from the population based registry. Patient's data who were loss to follow up will keep for final analysis. 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.

Inclusion criteria

1. Patients aged ≥18 years
2. With histological or cytological confirmation of having NSCLC
3. Patients who were having advanced stage NSCLC as classified by the American Joint Committee on Cancer (AJCC) TNM staging criteria system, and
4. Patients who had no previous history of specific treatment for their advanced NSCLC.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2

Exclusion criteria

1. Previous treatment of chemotherapy or chemo radiotherapy
2. Patients who have NSCLC as a new second primary cancer.
3. Patients who have history of any infection within 2 weeks before chemotherapy
4. Patients who have history of chronic liver disease, or autoimmune disease

THE SAMPLE SIZE CALCULATION

☐ By using sample size calculations for Cox proportional-hazard regression model (based on the work of Peduzzi et al.1995)

☐ N =10 k/p

K = 10 variables in this study

P= proportion for long term survival by using from previous literature that 2 years survival =0.23 [23-25] Therefore the 435 at least 435 subjects are needed.

The second method by using a rule of thumb (Comrey and Lee 1992) 5-10 events are needed to avoid fitting a model, thus the suitable sample size should be 300-435.

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 or time to last follow up prior to death. 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 in documented medical record. 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 and the univariate and multivariate logistic regression analysis. Statistically significant variables were included in the multivariate Cox regression model. A statistical analysis was performed using STATA, version 13. Significance was set at $p<0.05$ for all analyses. The protocol of the study was approved by the Institutional Review Board (IRB) of King Chulalongkorn Memorial Hospital and the Police General Hospital.

CHAPTER IV
RESULTS

A total of 640 cases were considered for this study. After cleaning the data, 336 cases were excluded. There were 103 cases that missing more than 2 interested variables data, 66 cases were in early stage of NSCLC (stage I-IIIA), 52 cases were on targeted therapy, 43 cases were 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 3 cases had ECOG 3. Therefore 301 cases were eligible, 299 cases (98.36%) were dead, and 5 cases (1.64%) were still alive at the censored date (figure 1). The patient characteristics are shown in (Table 1). The mean participant age was 61.4 years, 172 cases (57.1%) were aged < 65 years and 129 (42.9%) were aged ≥ 65 years. 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 ECOG score more than 1. One hundred fifth teen 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 0-180 days). The average serum albumin globulin ratio was 1.03 (±0.3) (range: 0.35-2.50) and the average absolute neutrophil count lymphocyte count ratio was 3.72 (range: 0.56-32.1). In terms of number of organ involvement, it was classified into 3 groups. There were 106 cases (35.2%) and 141 cases (46.8%) with1 and 2 organ involvement respectively. There were 54 cases (18%) with more than 2 organ involvement. There were 234 cases (77.7%) didn't have palliative radiation, and 67 cases (22.3%) didn't receive radiation. Because of no consensus on time from diagnosis to treatment, this study used 30 days as a cut point. There were 152 cases (97.4%) received the treatment within 30 days, and 144 cases (99.3%) started the treatment after definite diagnosis of NSCLC more than 30 days. The median follow up was 10.5 months (range 0.2-68.3 months). Using the Lowess line graph, the best value correlated with survival with the neutrophil lymphocyte ratio

was 4 and with the albumin globulin ratio was 1.2 (Figure2) (Figure3). There were 176 cases had neutrophil lymphocyte count ratio less than 4, and 125 cases had neutrophil lymphocyte count ratio more than or equal to 4. There were 242 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 HR: 2.34; 95%CI: 1.73-3.18; p<0.001), the ECOG status 2 (Crude HR: 2.14; 95%CI: 1.49-3.08; p<0.001), number of organs involvement more than 2 (Crude HR: 1.74; 95%CI: 1.12-2.430; p=0.001). Two simple biomarkers, the absolute neutrophil lymphocyte ratio (Crude HR: 2.04; 95%CI: 1.61-2.58; p<0.001) and serum albumin globulin ratio less than 1.2 (Crude HR: 1.47; 95%CI: 1.10-1.97; 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: 1.30-2.99; p=0.001), ECOG score 2 (HR: 1.87; 95%CI: 1.28-2.73; p=0.001), number of organs involvement more than 2 organs (HR: 1.49; 95%CI: 1.05-2.13; p=0.02). The simple biomarker absolute neutrophil lymphocyte ratio was a strongly prognostic overall. Perusal of the Hazard Ratio represents a significant risk for death compared to the reference group. The albumin globulin ratio had a trend to related to prognosis but not reach the statistically significance (HR: 1.33; 95%CI: 098-1.80; p=0.06) (Table2). Regarding the analyses of the second outcome, on univariate analysis, smoking status, number of organs involved, the neutrophil lymphocyte ratio and time from diagnosis to treatment were not reach the statistically significant associated with disease free survival. (Table3).

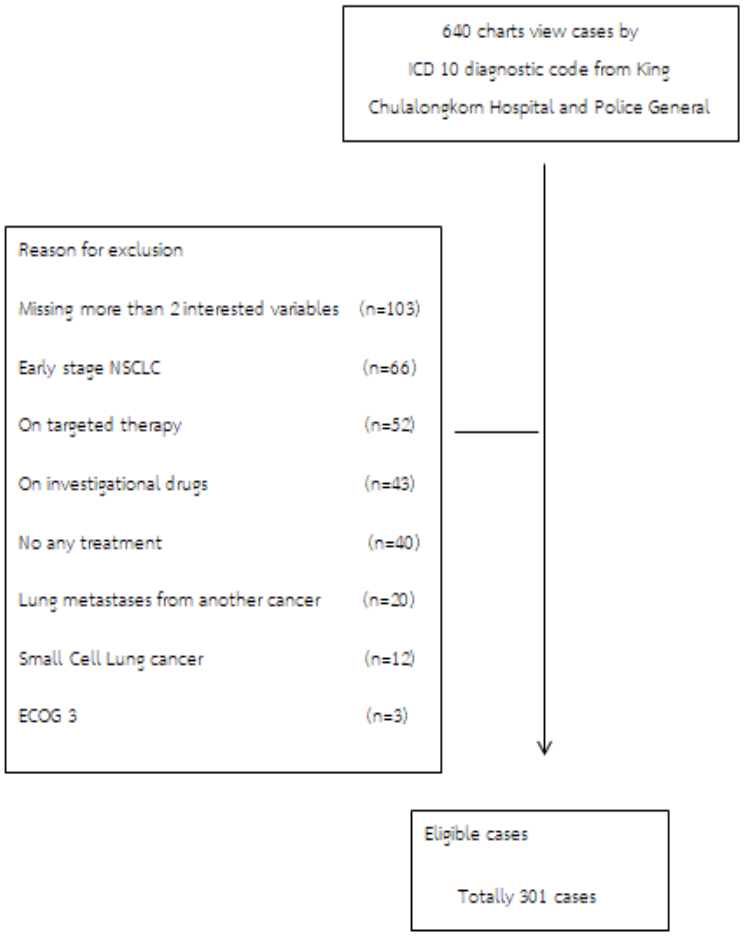

Figure 1.Flow diagram summarizing cases eligible for this study

Table 1.Baseline patient characteristics # Median (p25,p75)

Patient characteristics	Number (%) 0r Mean±SD	Min, Max
Gender		
Female	96 (31.9)	
Male	205 (68.1)	
Age (Years)	61.4±11.5	26, 92
< 65	172 (57.1)	
≥65	129 (42.9)	
ECOG		
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	2 (1,4)	
≤ 1	106 (35.2)	
2	141 (46.8)	
3-5	54 (18.0)	
Neu/lym ratio#	3.72 (2.51,5.35)	0.56, 32.1
Alb/glob ratio#	1.03±0.31	0.35, 2.50
Time from dx to treatment	28 (14,43)	0, 180
< 30	156 (51.8)	
≥ 30	145 (48.2)	
Palliative radiation		
No	234 (77.7)	
Yes	67 (22.3)	

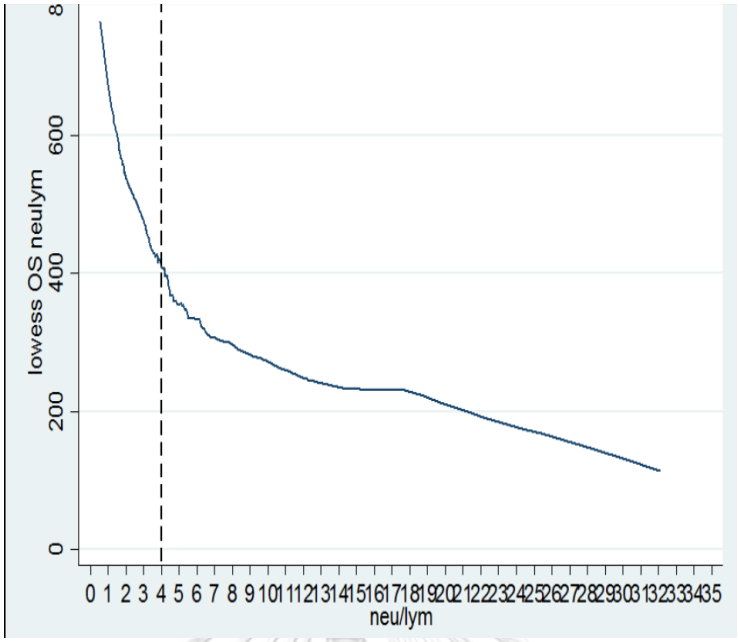

Figure 2.Lowess line of absolute neutrophil lymphocyte count ratio

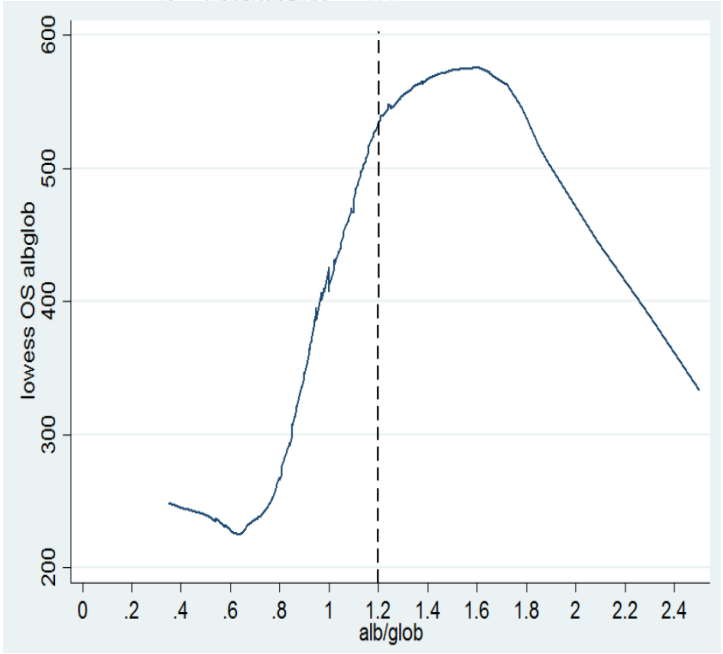

Figure 3.Lowess line of albumin globulin ratio

Table 2.Factors affecting overall survival

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

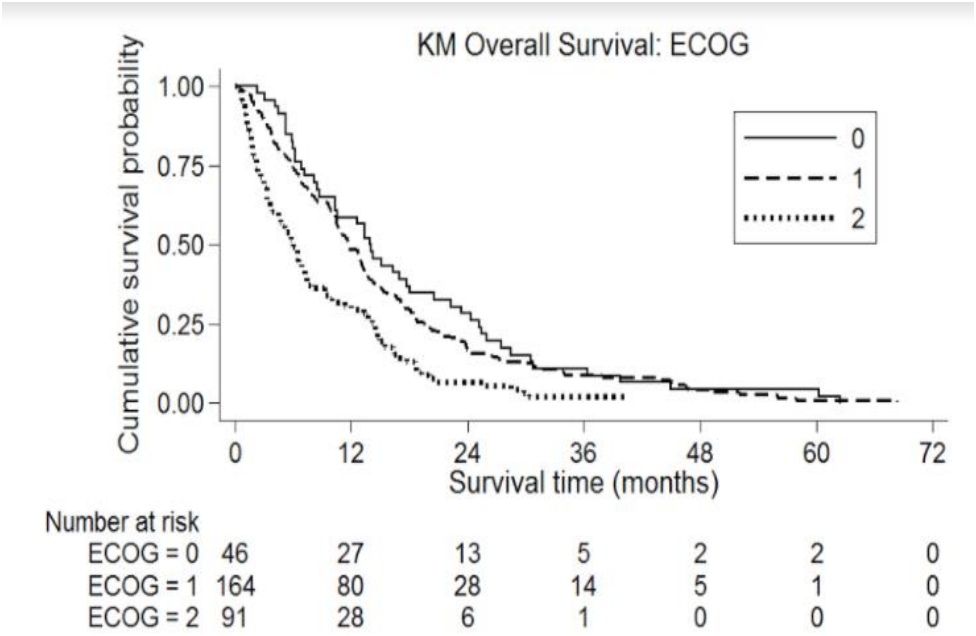

Figure 4.Comparison of overall survival curves by ECOG status

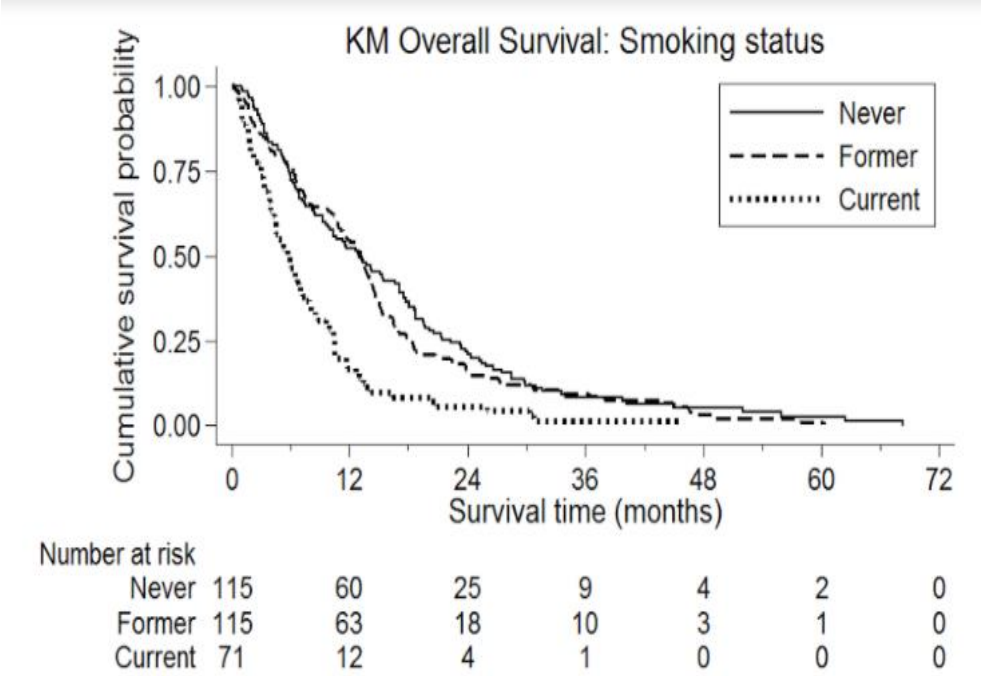

Figure 5.Comparison of overall survival curves by Smoking status

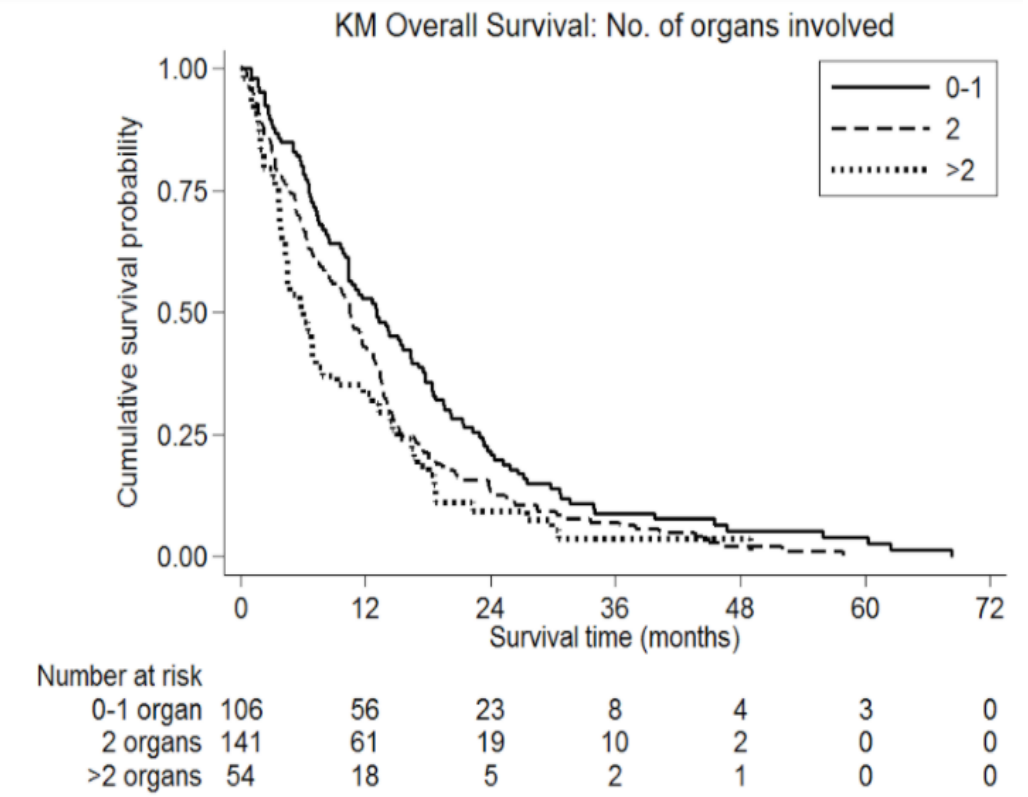

Figure 6.Comparison of number of organ involvement

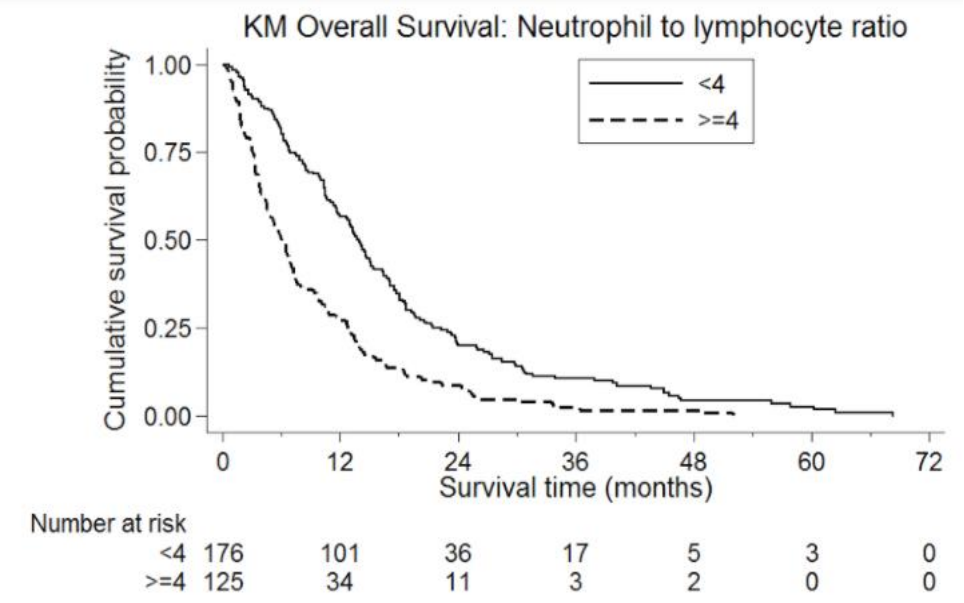

Figure 7.Comparison of value neu/lym ratio

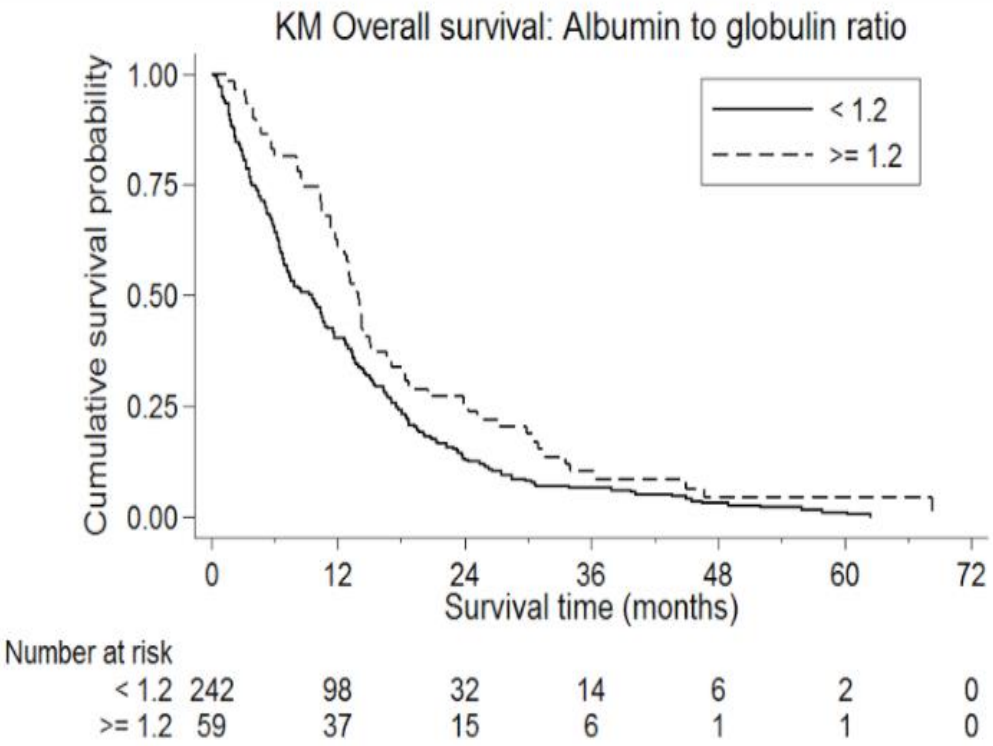

Figure 8.Comparison of value alb/glob ratio

Table 3.Factors affecting disease free survival

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

CHAPTER V
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 this research has not made it to the clinical setting and not routinely used. This is 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 this study we investigated simple pretreatment factors easily determined in daily clinical practice. The authors examined 3 aspects to provide a more holistic approach to prognostication. The first aspect is the clinical characteristics of patient: age, gender, health status determined using the ECOG score, 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 [38]. The second aspect examined was specific to the tumor and included histological type. The histological type was divided into squamous cell and non-squamous carcinoma, and number of organs involved. The third aspect was comprised of laboratories biomarkers that are commonly available clinically, the pretreatment neutrophil lymphocyte ratio and the serum albumin/serum globulin ratio. The simple laboratories biomarker ratios were strongly associated with patient overall survival. The result of this study, after adjusted for confounding factors, the ECOG score, smoking status, number of organs involved, neutrophil lymphocyte ratio were strong prognostic factors. Serum albumin/serum globulin ratio had tended to predict overall survival, although the result didn't reach the statistically significant. An increase in the neutrophil lymphocyte ratio was

significantly associated with a shorter overall survival (HR: 1.69; 95%CI: 1.32-2.18; p<0.001). This finding is 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 neutrophils and lymphocytes are 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: 1.10-1.97; p=0.01) and Recent clinical studies investigated colorectal cancer, breast cancer, urothelial cancer and nasopharyngeal cancer [30-32, 39], low serum albumin globulin ratio is associated with shorter survival. However, these studies used various different cut-off levels for an abnormal serum albumin/serum globulin ratio. Our findings are consistent with those of a previous retrospective study of lung cancer from a single institute in Turkey [40]. However, there are no previous published reports in East Asian populations. Regarding whether time from diagnosis to treatment had prognostic effect [38], 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: 0-180) did not have a significant impact on survival (HR: 0.90; 95%CI: 0.72-1.13; p=0.36). This might be because of the advanced stage of the disease at presentation. More than fifty percent of 301 patients in this study had an ECOG score of 0-1 (Table 1). Patients with an ECOG score 2 had a significantly shorter survival than patients with ECOG score 0 and 1. This confirmed to our knowledge that performance status evaluation before treatment is crucial. Patients who continued to sue tobacco during treatment had a shorter survival than never smokers and former smokers (HR: 1.97; 95%CI: 1.30-2.99; p<0.001). Although this result is not surprising, it is a modifiable prognostic factor.

There were some limitations of the study. First, it was retrospective; the results are based on medical records. Some data was due to incomplete medical records. 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 this study did not have tumor genome testing and most received standard chemotherapy rather than novel treatment limiting the applicability of our results to other situations where newer treatment is used. We did identify several prognostic factors in our study which can be useful, such as educating the patient on the added benefit of cessation of smoking during treatment and can encourage patients to improve nutritional status. A strength of the 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.

CHAPTER VI
CONCLUSIONS

This multicenter retrospective cohort study found three factors that are associated with prognosis pretreatment. These were the ECOG score, the patient's smoking status and 2 easily available biomarkers: the neutrophil 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. We recommend using these factors to develop a prognostic model and then testing this 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 pretreatment factors can be use for predicting survival outcome for advanced NSCLC patients such as albumin/globulin ratio. It is guided to develop simple prognostic model that which factors should be considered in the model.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

APPENDIX

REFERENCES

1. National cancer institute doms, Ministry of public health Thailand. Hospital-Based Cancer Registry annual report. 2012.

2. Natukula K, Jamil K, Pingali UR, Suresh Attili VS, Naidu Madireddy UR. Survival analysis in advanced non small cell lung cancer treated with platinum based chemotherapy in combination with paclitaxel, gemcitabine and etoposide. Asian Pac J Cancer Prev. 2013;14(8):4661-6.

3. Hotta K, Fujiwara Y, Kiura K, Takigawa N, Tabata M, Ueoka H, et al. Relationship between response and survival in more than 50,000 patients with advanced non-small cell lung cancer treated with systemic chemotherapy in 143 phase III trials. J Thorac Oncol. 2007;2(5):402-7.

4. Marino P, Pampallona S, Preatoni A, Cantoni A, Invernizzi F. Chemotherapy vs supportive care in advanced non-small-cell lung cancer. Results of a meta-analysis of the literature. Chest. 1994;106(3):861-5.

5. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group. BMJ. 1995;311(7010):899-909.

6. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med. 2002;346(2):92-8.

7. Scagliotti GV, De Marinis F, Rinaldi M, Crino L, Gridelli C, Ricci S, et al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. J Clin Oncol. 2002;20(21):4285-91.

8. Fossella F, Pereira JR, von Pawel J, Pluzanska A, Gorbounova V, Kaukel E, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol. 2003;21(16):3016-24.

9. Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol. 2008;26(21):3543-51.

10. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006;355(24):2542-50.

11. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012;13(3):239-46.

12. Pan JB, Hou YH, Zhang GJ. Correlation between efficacy of the EGFR tyrosine kinase inhibitor and serum tumor markers in lung adenocarcinoma patients. Clin Lab. 2014;60(9):1439-47.

13. Fang S, Wang Z, Guo J, Liu J, Li C, Liu L, et al. Correlation between EGFR mutation status and response to first-line platinum-based chemotherapy in patients with advanced non-small cell lung cancer. Onco Targets Ther. 2014;7:1185-93.

14. Fang S, Wang Z. EGFR mutations as a prognostic and predictive marker in non-small-cell lung cancer. Drug Des Devel Ther. 2014;8:1595-611.

15. Liang W, Zhang Y, Kang S, Pan H, Shao W, Deng Q, et al. Impact of EGFR mutation status on tumor response and progression free survival after first-line chemotherapy in patients with advanced non-small-cell lung cancer: a meta-analysis. J Thorac Dis. 2014;6(9):1239-50.

16. Dong X, Zhao X, Hao Y, Wei Y, Yin Q, Du J. Response to first-line chemotherapy in patients with non-small-cell lung cancer according to epidermal growth factor receptor and K-RAS mutation status. Clin Lung Cancer. 2013;14(6):680-7.

17. Meng D, Yuan M, Li X, Chen L, Yang J, Zhao X, et al. Prognostic value of K-RAS mutations in patients with non-small cell lung cancer: a systematic review with meta-analysis. Lung Cancer. 2013;81(1):1-10.

18. Deng LL, Deng HB, Lu CL, Guo Y, Wang D, Yan CH, et al. Mutations of EGFR or KRAS and expression of chemotherapy-related genes based on small biopsy samples

in stage IIIB and IV inoperable non-small cell lung cancer. J Cancer Res Clin Oncol. 2014;140(12):2097-105.

19. Zhang Q, Zhu X, Zhang L, Sun S, Huang J, Lin Y. A prospective study of biomarker-guided chemotherapy in patients with non-small cell lung cancer. Cancer Chemother Pharmacol. 2014;74(4):839-46.

20. Li P, Kang X, Chen K. [Clinical significance of ERCC1, RRM1 and TS in non-small cell lung cancer]. Zhongguo Fei Ai Za Zhi. 2014;17(6):496-500.

21. Zhao H, Zhang H, Du Y, Gu X. Prognostic significance of BRCA1, ERCC1, RRM1, and RRM2 in patients with advanced non-small cell lung cancer receiving chemotherapy. Tumour Biol. 2014;35(12):12679-88.

22. Caglayan B, Fidan A, Salepci B, Kiral N, Torun E, Salepci T, et al. Effects of prognostic factors and treatment on survival in advanced non-small cell lung cancer. Tuberk Toraks. 2004;52(4):323-32.

23. Satoh H, Ishikawa H, Ohara G, Kagohashi K, Kurishima K, Ohtsuka M, et al. Long-term survivors after chemotherapy in advanced non-small cell lung cancer. Anticancer Res. 2007;27(6C):4457-60.

24. Dujon C, Azarian R, Petitpretz P. [Long-term survivors of advanced non-small-cell lung cancer: characterisation and prognostic factors in a retrospective study]. Rev Mal Respir. 2009;26(9):952-60.

25. Giroux Leprieur E, Lavole A, Ruppert AM, Gounant V, Wislez M, Cadranel J, et al. Factors associated with long-term survival of patients with advanced non-small cell lung cancer. Respirology. 2012;17(1):134-42.

26. Lis CG, Grutsch JF, Vashi PG, Lammersfeld CA. Is serum albumin an independent predictor of survival in patients with breast cancer? JPEN J Parenter Enteral Nutr. 2003;27(1):10-5.

27. Asher V, Lee J, Bali A. Preoperative serum albumin is an independent prognostic predictor of survival in ovarian cancer. Med Oncol. 2012;29(3):2005-9.

28. Fujii T, Sutoh T, Morita H, Katoh T, Yajima R, Tsutsumi S, et al. Serum albumin is superior to prealbumin for predicting short-term recurrence in patients with operable colorectal cancer. Nutr Cancer. 2012;64(8):1169-73.

29. Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. Nutr J. 2010;9:69.

30. Du XJ, Tang LL, Mao YP, Sun Y, Zeng MS, Kang TB, et al. The pretreatment albumin to globulin ratio has predictive value for long-term mortality in nasopharyngeal carcinoma. PLoS One. 2014;9(4):e94473.

31. Azab BN, Bhatt VR, Vonfrolio S, Bachir R, Rubinshteyn V, Alkaied H, et al. Value of the pretreatment albumin to globulin ratio in predicting long-term mortality in breast cancer patients. Am J Surg. 2013;206(5):764-70.

32. Azab B, Kedia S, Shah N, Vonfrolio S, Lu W, Naboush A, et al. The value of the pretreatment albumin/globulin ratio in predicting the long-term survival in colorectal cancer. Int J Colorectal Dis. 2013;28(12):1629-36.

33. Yao Y, Zhao M, Yuan D, Gu X, Liu H, Song Y. Elevated pretreatment serum globulin albumin ratio predicts poor prognosis for advanced non-small cell lung cancer patients. J Thorac Dis. 2014;6(9):1261-70.

34. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002;420(6917):860-7.

35. Roxburgh CS, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. Future Oncol. 2010;6(1):149-63.

36. Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, McMillan DC, Clarke SJ. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. Crit Rev Oncol Hematol. 2013;88(1):218-30.

37. Templeton AJ, McNamara MG, Seruga B, Vera-Badillo FE, Aneja P, Ocana A, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst. 2014;106(6):dju124.

38. Neal RD, Tharmanathan P, France B, Din NU, Cotton S, Fallon-Ferguson J, et al. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. Br J Cancer. 2015;112 Suppl 1:S92-107.

39. Zhang B, Yu W, Zhou LQ, He ZS, Shen C, He Q, et al. Prognostic Significance of Preoperative Albumin-Globulin Ratio in Patients with Upper Tract Urothelial Carcinoma. PLoS One. 2015;10(12):e0144961.

40. Duran AO, Inanc M, Karaca H, Dogan I, Berk V, Bozkurt O, et al. Albumin-globulin ratio for prediction of long-term mortality in lung adenocarcinoma patients. Asian Pac J Cancer Prev. 2014;15(15):6449-53.

VITA

Dr. Sureerat Jaruhathai

Education

Doctor of medicine.Mahidol University, year 1999

Diploma of general medicine,2006

Diploma of medical oncologist,2008

Office address

Medical oncology unit,department of medicine.Police General Hospital

492/1 Rama 1 RD.

Ptumwan district

BKK 10330

email. sjaruhathai@gmail.com