Non-Small Cell Lung Carcinoma in Women: A Retrospective Cohort Study in Indonesia

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ABSTRAK

Latar belakang: *kanker paru merupakan kanker terbanyak di dunia baik pada pria maupun wanita. Kanker paru pada wanita berbeda dengan pada pria dalam berbagai aspek. Peningkatan trend kanker paru pada wanita terjadi di Indonesia. Studi ini dilakukan untuk melihat karakteristik dan kesintasan kanker paru karsinoma bukan sel kecil pada wanita di RS Pusat Kanker Nasional Dharmais.* ***Metode:*** *penelitian ini merupakan studi kohort retrospektif mengenai karateristik pasien wanita dengan kanker paru karsinoma bukan sel kecil dengan mengambil data sekunder mulai Januari 2005 sampai Desember 2015. Analisis kesintasan menggunakan kurva Kaplan-Meier. Faktor-faktor prognostik independen dianalisis dengan menggunakan model regresi Cox risiko proporsional dengan hazard ratio (HR) dan interval kepercayaan (CI) sebesar 95%.* ***Hasil:*** *dari studi didapatkan karsinoma paru bukan sel kecil sebanyak 956 kasus, 256 diantaranya adalah wanita. Rata-rata usia yang didapatkan adalah 56,9 (11,87) tahun. Riwayat merokok dijumpai pada 21 pasien (7,8%). Jenis histologi terbanyak adalah adenokarsinoma (91,1%), dan 261 pasien (98,0%) berada pada stadium lanjut (III-IV). Median kesintasan sedikit lebih panjang pada perempuan dibandingkan dengan laki-laki (14.9 bulan berbanding 12.2 bulan; log-rank p= 0,055). Faktor prognostik signifikan terhadap kesintasan adalah usia yang lebih dari 50 tahun (HR=0,681; 95% CI=0,467 – 0,992; p=0,045) dan mutasi eGFR positif (HR=0,393; 95% CI=0,251–0,615; p<0,001).* ***Kesimpulan:*** *dua puluh delapan persen kasus karsinoma paru bukan sel kecil diderita oleh perempuan. Sebagian besar tidak merokok, memiliki histopatologi adenokarsinoma, dan mutasi eGFR. Kesintasan ditemukan lebih baik pada pasien wanita dibandingkan dengan laki-laki. Faktor prognostik positif terhadap kesintasan pada pasien wanita dengan kanker paru adalah usia lebih dari 50 tahun dan adanya mutasi eGFR.*

Kata kunci: *karsinoma paru bukan sel kecil, wanita, karakteristik, mutasi eGFR, kesintasan.*

ABSTRACT

Background: *the increasing incidence of lung cancer in female patients has been observed in Indonesia. Lung cancer in female might have different biology process than male, but it has never been evaluated in Indonesia. This study aimed to know characteristics and survival of female patients with non-small-cell lung carcinoma (NSCLC) in Dharmais National Cancer Centre Hospital.* ***Methods:*** *a retrospective cohort study was performed among NSCLC female patients in Dharmais National Cancer Centre Hospital between January 2005 and December 2015. Survival analysis was done using the Kaplan-Meir estimation curve with proportional assumption test. Independent prognostic factors were analyzed using the Cox proportional hazard model with a hazard ratio (HR) and its 95% confidence interval (CI).* ***Results:*** *a total of 956 NSCLC cases were retrieved during the study; 268 (28.0%) were female patients. Mean of age in female patients was 56.9 (11.87) years old. Among female patients, 21 (7.8%) were smokers, 244 (91.1%) had adenocarcinoma subtype, and 261 (98.0%) were in advanced stage*

(III-IV). Median survival was slightly longer in female than male patients (14.9 months vs. 12.2 months; log-rank p=0.055). Significant prognostic factors for survival were older age (>50 y.o) (HR = 0.681; 95% CI = 0.467 – 0.992; p= 0.045) and positive eGFR mutation (HR = 0.393; 95% CI = 0.251 – 0.615; p<0.001). ***Conclusion:*** *female patients contributed to about 28% of all NSCLC cases. They were mostly non-smokers, had more adenocarcinoma histopathology and eGFR mutation. Survival tended to be longer in female than male patients. Age over 50 years and the presence of eGFR mutation were good prognostic factors to survival in female lung cancer patients.*

Keywords: *non-small cell lung carcinoma, female, characteristics, eGFR mutation, overall survival.*

INTRODUCTION

Lung cancer is the most common cancer diagnosed in the last decade. In 2012, there were 1.2 million new cases of lung cancer in male and 500,000 in female.[1] In 2017, there were 222,500 new cases and 155,870 deaths from lung cancer.[2] Historically, lung cancer was more common in male than in female, but this gender proportion has changed largely during the last two decades; lung cancer incidence is decreasing in male but continue to increase in female.[3] However, mortality rate is lower in female than male lung cancer patients. The 5-year survival rate is 21% for female and 15% for male patients.[4]

The increasing incidence of lung cancer in female was thought to be caused by increasing number of female passive smokers, particularly in developed countries. However, lung cancer among female may behave differently than male. Female patients tend to be younger, non-smokers, have more adenocarcinoma subtypes and longer survival rates than male patients.[5] Several factors have been associated with lung cancer in female, i.e. environmental exposures, genetic predisposition, hormonal factors and viral infection.[6]

Lung cancer in female has not been well studied in Indonesia. Therefore, this was the first study aimed to know characteristics and survival of non-small cell lung cancer (NSCLC) in female patients in Indonesia.

METHODS

A retrospective cohort study was performed in Dharmais National Cancer Centre Hospital Jakarta on NSCLC patients between January 2005 and December 2015. Data were obtained from patients' medical records which was correlated to other study on "characteristics at risk factors in lung cancer". Inclusion criteria were adult patients aged more than 18 years old and was diagnosed as NSCLC based on histopathology or cytology assessment. Speciments for NSCLC diagnosis were taken from lung tissues, bronchial swabs, lymph node aspirate or pleural effusion fluid. Clinical data from each patient were collected and included age, smoking status, histopathology type, staging and survival. Histopathology subtypes were grouped into adenocarcinoma, squamous cell carcinoma (SCC), and large cell carcinoma. The presence of mutation of epidermal growth factor receptor (EGFR) was also recorded. This study had been approved by the Ethical Committee for Medical Research, Dharmais Cancer Hospital, Jakarta with a reference number 031/KEPK/V/2016.

Statistical Analysis

Clinical data of female and male patients were compared and presented descriptively. Categorical data were expressed as frequency and percentage, while continuous data were presented as mean and standard deviation for normally distributed data or median and range for skewed data. Association between categorical variables was analyzed using the Chi-square test with calculated odds ratio (OR) and 95% confidence interval (CI). Mean difference was analyzed using the student t test. A p value of <0.05 was considered significant. Overall survival (OS) was calculated from the patient's initial diagnosis to the last visit during follow-up (December 31st, 2016) or death. Survival analysis was performed using Kaplan-Meier curve estimation with the proportional assumption test. A log-rank p of less than 0.05 was considered significant. Cox proportional hazard analysis were performed to identify significant prognostic factors to survival after adjusting for potential

significant confounders. Hazard ratios (HRs) and 95% confidence intervals (CI) were calculated for each variable. In the final adjusted multivariable Cox proportional hazard models, five potential confounding variables on the overall survival were evaluated, i.e. age, smoking history, the presence of distant metastasis, histopathological subtypes, and EGFR mutation. Statistical analysis were done using SPSS version 17.0 software.

RESULTS

A total of 956 patients met the inclusion criteria during the study period; 268 (28.0%) of them were female patients. The mean of age in female patients was 56.9 (11.87) years, ranging from 24 to 91 years old. The peak age interval was between 51 and 60 years old (38.1%). Mean of age was slightly lower in female compare to male patients (56.9 vs. 58.2 years; p=0.117). Twenty-one (7.8%) of female patients were smokers, with a frequency between 3 and 48 cigarettes per day. Female patients significantly smoked less compared to male patients, had higher percentage of adenocarcinoma and EGFR mutation in histopathology, and diagnosed in advanced stage (**Table 1**). Cases of lung cancer tended to increase from 2005 to 2015 (**Figure 1**).

Female patients had increased odds ratio to develop adenocarcinoma (OR=5.587; 95% CI=3.572–8.470), stage IV B (OR=1.462; 95% CI=1.101-1.942) and EGFR mutation (OR=2.015; 95% CI=1.426–2.848) compared to male patients. On the contrary, female had decreased odds ratio

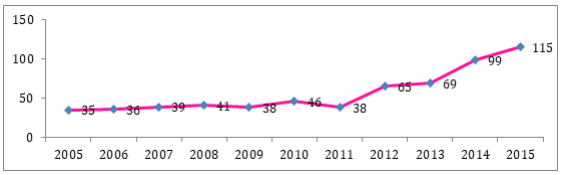

Figure 1. Incidence of lung cancer in female patients in Dharmais National Cancer Centre Hospital, 2005-2015.

Table 1. Comparison between female and male patients with NSCLC in Dharmais National Cancer Centre Hospital from January 2005 to December 2015

Charactersitcs	Female (n=268)	Male (n=688)	Total	p*
Age, n (%)				
- > 50 years old	201 (75.0)	524 (76.2)	725 (75.8)	0.706
- ≤ 50 years old	67 (25.0)	164 (23.8)	231 (24.2)	
Smoking				
- Yes	21 (7.8)	272 (39.5)	293 (30.6)	<0.001
- No	247 (92.2)	416 (60.5)	663 (69.4)	
Brinkman Index				
- Not smoking	247 (92.2)	416 (60.5)	663 (69.4)	<0.001
- Mild	8 (3.0)	21 (3.1)	29 (3.0)	
- Moderate	5 (1.9)	127 (18.5)	132 (13.8)	
- Heavy	8 (3.0)	124 (18.0)	132 (13.8)	
Histopathology				
- Adenocarcinoma	244 (91.1)	444 (64.5)	688 (72.0)	<0.001
- Squamous cell	17 (6.3)	221 (32.1)	238 (24.9)	
- Large cell	7 (2.6)	23 (3.4)	30 (3.1)	
Disease stage				
- I-II	7 (2.6)	26 (3.7)	33 (3.4)	0.119
- IIIA	21 (7.8)	69 (10.0)	90 (9.4)	
- IIIB	30 (11.2)	117 (17.0)	147 (15.4)	
- IVA	62 (23.1)	159 (23.1)	221 (23.1)	
- IVB	148 (55.2)	317 (46.1)	465 (48.6)	
EGFR mutation				
- Yes	69 (25.7)	101 (14.7)	170 (17.8)	<0.001
- No	199 (74.3)	587 (85.3)	786 (82.2)	

of smoking (OR=0.130; 95% CI = 0.081 – 0.208). Among patients with squamous cell carcinoma subtype, 5/17 (29.4%) were smokers, while in other histopathological subtypes, 16/251 (6.4%) were smokers; smoking was associated with higher odds ratio to develop SCC (OR=6.120; 95% CI =1.919 – 19.526; p = 0.002).

Survival Analysis

Females had a slightly longer overall survival than male patients (median 14.9 vs. 12.2 months, log-rank p = 0.055, **Figure 2**). Median survival was longer in patients aged >50 years than patients aged <50 years (15.3 vs. 13.6 months; log-rank p = 0.043; **Figure 3**). Patients with eGFR mutation had longer median survival time than patients without eGFR mutation (27.7 vs. 12.2 months; log-rank p <0.001; **Figure 4**). Older age (>50 years old) and positive eGFR mutation was significantly associated with lower mortality rate (**Table 2**). Cox proportional hazard model showed that age >50 years old and positive eGFR mutation were significant prognostic factors of survival in female NSCLC patients (**Table 3**).

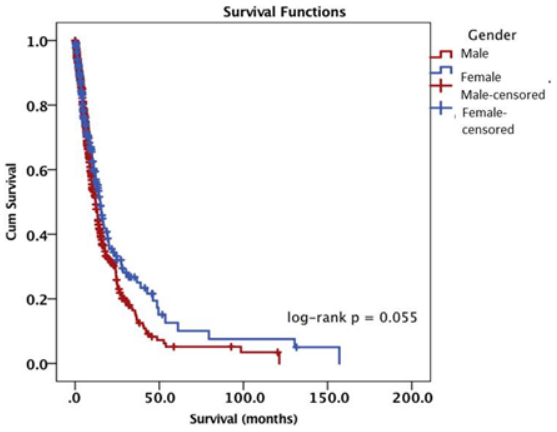

Figure 2. Kaplan Meier curves showing survival difference between male and female lung cancer patients in Dharmais National Cancer Centre Hospital, January 2005 – December 2015

DISCUSSION

This study was the first evaluation on NSCLC female patients in Indonesia. In this report, we found that females comprised 28% of lung cancer patients in Dharmais National Cancer Centre Hospital. However, the annual incidence was increasing from 2005 to 2015; if the trend continues, we may expect more female patients in the future. A large lung cancer registry in Poland during 1995-1998 found that female patients constitute 14.0% of all lung cancer cases (both NSCLC and SCLC cases).[7] A study in Pakistan reported an incidence rate of 11.8% of female patients from 830 cases of lung cancers.[8]

In this study, mean of age (56.9 years old) was slightly lower than a US study involving 485 NSCLC female patients with a mean age of 60.1 years old.[9] It was also lower than the Poland lung cancer registry (60.0 years old).[7] As

Table 2. Factors associated with mortality in NSCLC female patients (n=268)

Characteristic	Died (n=121)	Alive (n=147)	OR (95% CI)	p*
Age group, n (%)				
- > 50 years	78 (38.8)	123 (61.2)	0.354 (0.199– 0.629)	<0.001
- ≤ 50 years	43 (64.2)	24 (35.8)		
Smoking, n (%)				
- Yes	9 (42.9)	12 (57.1)	0.904 (0.368–2.223)	0.826
- No	112 (45.3)	135 (54.7)		
Histopathology, n (%)				
- SCC	10 (58.8)	7 (41.2)	0.555 (0.205–1.505)	0.242
- Others	111 (44.2)	140 (55.8)		
Distant metastasis, n (%)				
- Yes	73 (48.7)	77 (51.3)	1.383 (0.849–2.251)	0.192
- No	48 (40.7)	70 (59.3)		
EGFR mutation, n (%)				
- Yes	25 (36.2)	44 (63.8)	0.610 (0.347–1.072)	0.084
- No	96 (48.2)	103 (51.8)		

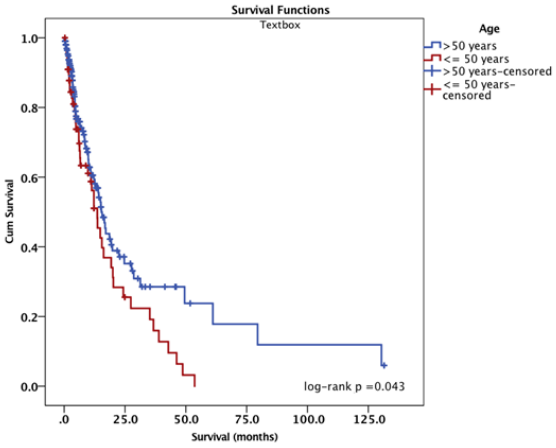

Figure 3. Kaplan Meier curves showing survival difference female lung cancer patients aged >50 years and < 50 years old in Dharmais National Cancer Centre Hospital, January 2005 – December 2015

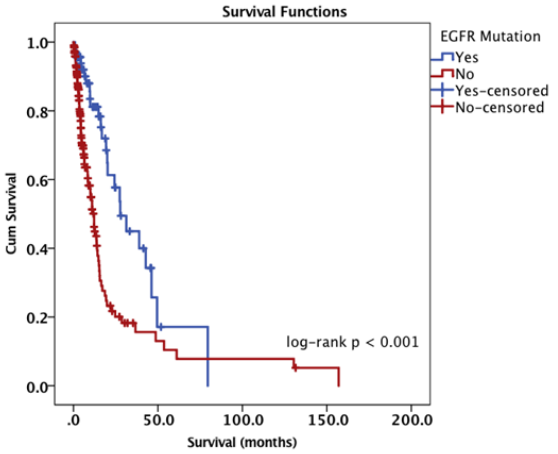

Figure 4. Kaplan Meier curves showing survival difference between female lung cancer patients with and without EGFR mutation in Dharmais Cancer Hospital, January 2005 – December 2015

comparison, the Pakistani study found a mean age of 57.5 years old, which were significantly lower than the male patients (60.1 years old).[8] In a recent study from China, the mean age was 59.7 years old for female and 62.7 years old for male patients.[10] Most of female patients (75.0%) were diagnosed at the age of more than 50 years old. This is comparable with the data from the Poland lung cancer registry (76.7%).[7]

Adenocarcinoma was the predominant subtype in female patients (91.1%), while SCC was only found in a small percentage (6.3%). Similar pattern was also reported in China, which showed that adenocarcinoma was found in 86.9%, while SCC was only 5.8% of female patients.[10]

Mutation of the EGFR gene was higher in female than male patients. This finding is also observed in other Asian studies. For example, the study from China found that EGFR mutation was present in 66% of female patients with adenocarcinoma subtype.[10] EGFR mutation is lower in European population. New report from Spain found EGFR mutation in 34.4% of 1,775 NSCLC female patients.[11] It is generally accepted currently that EGFR mutations are more common in female patients, in non-smokers and in those with adenocarcinoma histology.[12,13]

Table 3. Cox proportional hazard model to predict survival in NSCLC female patients (n=268)

Variable	β	SE	HR (95% CI)	p
Age >50 years	-0.385	0.192	0.681 (0.467–0.992)	0.045
Positive EGFR mutation	-0.934	0.229	0.393 (0.251–0.615)	<0.001

In our study, only a small proportion of female patients were smokers. Male sex was associated with 7.6 times higher odds ratio of being smoker than female patients. A study in Japan found that less than 10% of female lung cancer patients had smoking history, either current or former smoker.[14] The study in China even found less proportion; only 2.7% of the female patients were smokers.[10] Data from Singapore showed that 79.4% of female patients with advanced NSCLC were non-smokers.[15] Apparently, female lung cancer patients who reported tobacco smoking were lower in Asia than the Western countries. Recent meta-analyses showed that the prevalence of smoking worldwide was 11.7 – 97.5% in male and 5.9 – 67.7% in female.[16] Furthermore, unlike in males, current data did not support the hypothesis that smoking increases lung cancer risk in female.[17] However, recent result from a prospective cohort study in UK found that moderate and heavy smokers among females have a higher risk of lung cancer than male.[18]

The association between smoking and lung cancer was stronger for small cell carcinoma, SCC, and large cell carcinoma than for adenocarcinoma.[19] In this current study, smoking was associated with 6.1 times higher risk of having SCC subtype in female patients. A Japan study found that lung cancer risk was 10- to 20-

fold higher for SCC and small cell carcinoma but only 2- to 3-fold higher for adenocarcinoma in male and female patients.[14] Recent study showed that both in males and females, adenocarcinoma was more frequently found in non-smokers than in former or current smokers.[20]

The finding that more than 90% of female patients with adenocarcinoma in this study were non-smokers suggested that other factors may contribute to the pathogenesis of this subtype of lung cancer in female. One of the major differences between female and male is the presence of estrogen and progesterone in female that has been suggested to play an important role in lung carcinogenesis.[21,22] Both type of estrogen receptor (ER) α and β are found in NSCLC and mediated cell proliferation.[23] High expression of ER-β1 but low progesterone receptor was associated with more aggressive biology and poor survival in lung cancer.[24] Moreover, aromatase enzyme involved on estrogen synthesis is also associated with prognosis; lower level of tumor aromatase is associated with better survival in NSCLC patients.[25] Other study showed that post-menopausal female who received hormone replacement therapy with estrogen and progesterone had a higher risk of developing lung cancer.[26] If the hormonal therapy are used more than 10 years, the risk of developing lung cancer increase up to 50%.[27] Another study reported that female patients who received tamoxifen (anti-estrogen) had a decreased risk of developing lung cancer.[28]

Compared to male patients, our study showed that female patients had only slightly longer survival (about two months). However, more than 70% of the patients came with stage IV disease, which had poor prognosis. In general, female NSCLC patients have longer survival time trend than male in all stages and histology type.[29]

Analysis within the female patients group showed that patients aged more than 50 years had significantly longer survival than those aged less than 50 years. It was also an independent prognostic factor after adjusting disease stage and histopathology. This finding was similar to several studies that observed better survival in NSCLC postmemopausal female patients than premenopausal ones.[30,31] A study by Moore et al.[31] showed that premenopausal women had more extensive disease at presentation and increased frequency of adenocarcinoma compared to postmenopausal women. On multivariate analysis, postmenopausal women also had fewer lung cancer-related deaths compared to older men. This findings may be related to hormonal status in women. Sex hormone in female does not only correlate to higher incidence in lung cancer, but also the outcome.[21] However, the underlying mechanism to explain the association between sex hormone and survival in female patients with lung cancer need further studies.

In this study, the presence of EGFR mutation was protective against early death as the median survival of these patients was more than 2 years (27.7 months). Another study in female with stage IV NSCLC showed similar result; median overall survival was reported to be longer in mutated than wild type EGFR (25.6 vs. 16.2 months, $p = 0.20$).[32] Longer survival found in the patients harboring EGFR mutation could be due to the administration of EGFR tyrosine kinase inhibitor (TKI), as the standard treatment in DCH. Recent study from Spain showed that NSCLC female patients treated with EGFR TKI achieved an OS of 23.0 months.[11] Another data from Iressa Pan-Asia Study (IPASS) showed improved overall survival in patients with EGFR mutation-positive NSCLC, whether they receive treatment with gefitinib or chemotherapy.[33] However, the underlying mechanism is still unknown.

There are several limitations in our study. We used data from lung cancer registry and the study was not designed as a prospective cohort study. However, given the large sample size, findings from this registry data may provide clue on the incidence and trends of female lung cancer patients, particularly NSCLC. Secondly, we did not assess menopausal or hormonal status of the female patients. The fact that estrogen may affect lung carcinogenesis in female deserves further study. Similarly, smoking assessment did not evaluate the role of environmental tobacco smoke or secondhand smoker. As non-smoker patients tend to be dominant in Indonesian female, study about risk factors for developing lung cancer should be elaborated more in the future.

CONCLUSION

Lung cancer in females is increasing in Indonesia. Female patients had different profile than males; they were mostly non-smokers, had higher percentage of adenocarcinoma histopathology, and more EGFR mutation. Although most of patients were already in advanced stage, overall survival was slightly better in female than male patients. Age over 50 years and the presence of EGFR mutation were the positive prognostic factors of survival in female lung cancer patients.

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