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Majalah Resmi Perhimpunan Dokter Paru Indonesia  
Official Journal of The Indonesian Society of Respiriology



*Lung Function Impairment Among Firefighter After Wildfire in Riau, Sumatra*

*The Differences in Urokinase Plasminogen Activator System in Lung Cancer Patients Before and After Chemotherapy*

*The Role of Neutrophil-Lymphocyte Ratio (NLR), Platelet-Lymphocyte Ratio (PLR), and D-Dimer in Predicting the Outcome of Confirmed COVID-19 patients*

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# Gender Disparities in Their Effects on Characteristics and Prognostics of Lung Cancer Patients in Pulmonary Ward of Dr. M Djamil Hospital, Padang

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## Abstract

**Background:** Lung cancer incidence in female tends to increase in many countries. Various studies have reported the characteristics of lung cancer in female are different from male. The purpose of this study was to determine the effect of gender on characteristics of lung cancer at Dr. M Djamil Hospital, Padang.

**Methods:** A retrospective analytic study of lung cancer patients treated in the Pulmonary Ward of Dr. M. Djamil Hospital Padang from January 1, 2004 to December 31, 2017, with recognized cancer cell types. Data were grouped according to gender.

**Results:** This study found that 451 lung cancer patients, male-dominant 77.8%. Female were younger than male (52.97±12.79 years vs. 57.81±11.23 years;  $P=0.0001$ ). Most of male (94.5%) were smokers and former smokers, while 93.9% of female were non-smokers ( $P=0.0001$ ). Most female were having prior history of tuberculosis (TB) (21.2% vs 11.0%;  $P=0.008$ ) and also prior history of other organs cancer (10.1% vs 3.4%;  $P=0.007$ ) than in male. Squamous cells were highest in males (41.1%), while females had adenocarcinoma (55.0%); with  $P=0.008$ . Advanced stage in female more than male (91.8% vs 82.7%;  $P=0.027$ ). The mean life expectancy of female was longer than male, respectively 8.7±1.56 and 7.29±0.64 months; ( $P=0.95$ ).

**Conclusion:** There are differences in the epidemiology of lung cancer between male and female in Dr. M. Djamil Hospital Padang in the form of age, cell type and staging. Non-smokers, a previous history of TB and a history of cancer in other organs were more dominant in female. (*J Respirol Indones 2021; 41(4): 245–51*)

**Key word:** lung cancer; gender; epidemiology

## Perbedaan Gender dalam Pengaruhnya pada Karakteristik dan Prognostik Pasien Kanker Paru di Bagian Paru RSUP Dr. M Djamil Padang

### Abstrak

**Latar belakang:** Kejadian kanker paru pada perempuan cenderung meningkat pada banyak negara. Berbagai penelitian melaporkan karakteristik kanker paru pada perempuan berbeda dengan laki-laki. Penelitian ini bertujuan untuk mengetahui pengaruh jenis kelamin terhadap karakteristik kanker paru di RSUP Dr. M. Djamil Padang.

**Metode:** Penelitian analitik retrospektif terhadap pasien kanker paru yang dirawat di Bangsal Paru RSUP Dr. M. Djamil Padang dari 1 Januari 2004 sampai 31 Desember 2017 dengan jenis sel sudah diketahui. Data dikelompokkan menurut jenis kelamin.

**Hasil:** Penelitian ini mendapatkan 451 orang pasien kanker paru, 77,8% diantaranya laki-laki. Usia perempuan lebih muda dari laki-laki (52,97±12,79 tahun vs 57,81±11,23 tahun;  $P=0,0001$ ). Sebagian besar laki-laki (94,5%) adalah perokok dan bekas perokok, sedangkan 93,9% perempuan bukan perokok ( $P=0,0001$ ). Riwayat TB sebelumnya pada perempuan lebih banyak dari laki-laki (21,2% vs 11,0%;  $P=0,008$ ) dan juga riwayat kanker pada organ lain (10,1% vs 3,4%;  $P=0,007$ ) dibandingkan pada laki-laki. Sel skuamosa terbanyak pada laki-laki (41,1%), sedangkan perempuan adeno karsinoma (55,0%); dengan  $P=0,008$ . Staging lanjut pada perempuan lebih banyak dibandingkan laki-laki (91,8% vs 82,7%;  $P=0,027$ ). Rerata harapan hidup perempuan lebih panjang dibandingkan laki-laki, masing-masing 8,74±1,56 dan 7,29±0,64 bulan; ( $P=0,95$ ).

**Kesimpulan:** Terdapat perbedaan epidemiologi kanker paru antara laki-laki dan perempuan di RSUP Dr. M. Djamil Padang berupa umur, jenis sel dan staging. Bukan perokok, riwayat TB sebelumnya dan riwayat kanker pada organ lain lebih dominan pada perempuan. (*J Respirol Indones 2021; 41(4): 245–51*)

**Kata kunci:** kanker paru; jenis kelamin; epidemiologi

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## INTRODUCTION

Reports from various countries show changes in the proportion of lung cancer in male and female in the last two decades. The incidence of lung cancer in male in the United States began to decline since 1982; in 2008–2013, the decline in incidence reached 2.9%. Whereas in female, the incidence of lung cancer only decreased in 2006 after previously continuing to increase. The decrease in the incidence of lung cancer in female in 2006–2013 was only 1.4%. Differences in lung cancer incidence patterns between male and female are caused by differences in smoking history in both sexes. The peak prevalence of smoking in female is less than 20 years later than in male.<sup>1,2</sup>

Smoking is not the only affluent factors of lung cancer gender disparities. Several other factors have also been reported to control lung cancer, including exposure to environmental fumes such as ecological cigarette smoke, workplace exposures and indoor smoke. Genetic mutations, hormonal factors and infections have also been reported to affect these differences. In addition, there are differences in life expectancy for each gender. Various studies show that the 5-year life expectancy of female is higher than that of male. Radzikowska et al. found that the relative risk for death in males was higher (RR = 1.15) than females and was statistically significant.<sup>3,4</sup>

The tendencies of lung cancer being treated in the Pulmonary Ward of Dr. M. Djamil Padang needs to be researched. In addition, complete data are needed on the differences in epidemiology and risk factors for lung cancer in both sexes at RSUP Dr. M Djamil Padang.

## METHOD

This study is a retrospective analysis of lung cancer patients whose histopathologically diagnosed at the Pulmonary Ward, Dr. M. Djamil Padang, from January 1, 2004, to December 31, 2017. Metastatic lung tumors were not included in the study.

Data collected in the form of morbidity, age, risk factors, cell type, staging and life expectancy are grouped by sex. The risk factors studied were smoking, history of TB, history of cancer in other organs, and family history of cancer. Categorical data are expressed in terms of number and percentage in each category. Continuous data with normal distribution are expressed in mean and SD, continuous data with non-normal distribution is described in median and percentile. Differences between male and female with continuous data were assessed using t-test if the data were normally distributed, and Mann-Whitney if not normally distributed. Differences in categorical data were evaluated using the Pearson Chi-Square; if they did not meet the requirements, they were assessed using the Fisher's Exact test. The difference was declared statistically significant when  $P < 0.05$ . Life expectancy was assessed using the Kaplan-Meier curve.

## RESULT

Lung cancer patients treated in the Pulmonary Ward, Dr. M. Djamil Padang, histopathologically diagnosed from January 1, 2004, to December 31, 2017, were 451 people. Male dominant (77.8%). The trend of lung cancer incidence in male and female from year to year is relatively unstable (Figure 1). The lowest incidence of lung cancer in male was in 2011 as many as 9 cases (64.3%), while in female, the lowest incidence was in 2008 as many as 3 cases (11.1%). The lowest overall incidence of lung cancer was found in 2011 with 14 points and gradually increased. This is due to broken scope for bronchoscopy, so patients were referred to Jakarta. Incidence trends for both genders were gradually increased every year, but the increase in cases in female is relatively stable.

The average age of male lung cancer patients treated at the Pulmonary Ward, Dr. M. Djamil Padang  $57.81 \pm 11.23$  years, while female are  $52.97 \pm 12.79$  years. The youngest age of the patient is male, 20 years old, female 25 years old, while the oldest age male is 85 years old and female is 83

years old. Based on the Pearson Chi-Square analysis, it was found that the age difference between male and female was significantly different, with  $P=0.0001$  (Table 1).

The risk factors that were significantly different between male and female lung cancer were smoking, prior history of TB and cancer in other organs. The number of smokers and ex-smokers were higher in male (94.5%), while 93.9% in female

are non-smokers. Pearson chi-square analysis found a significant difference between smoking risk factors in the male and female groups with  $p=0.00$ . Prior history of TB in female was more common in female than male (21.2% vs. 11.0%;  $p=0.008$ ). In addition, female were more likely to have a history of cancer in other organs than male (10.1% vs. 3.4%;  $p=0.013$ ).

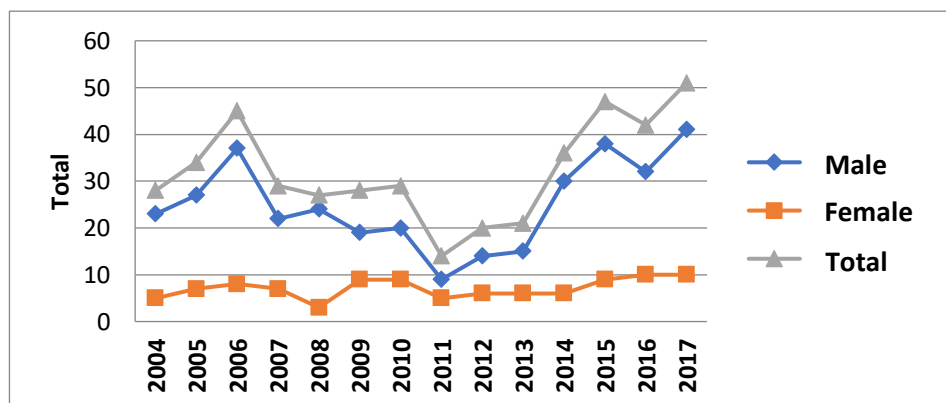


Figure 1. Trends in lung cancer by gender treated in the Pulmonary Ward, RSUP Dr. M. Djamil Padang 2004–2017

Table 1. Differences in the epidemiology and risk factors of lung cancer by sex (N=451)

| Risk factors                      | Male<br>N (%) | Female<br>N (%) | P                   |
|-----------------------------------|---------------|-----------------|---------------------|
| Age (Mean ± SD)                   | 57,81 ± 11,23 | 52,97 ± 2,79    | 0,0001*             |
| Smoking History                   |               |                 |                     |
| Non smokers                       | 19 (5,5)      | 92 (93,9)       |                     |
| Smokers                           | 258 (74,8)    | 6 (6,1)         | 0,0001 <sup>f</sup> |
| Ex-smokers                        | 69 (19,7)     | 0 (0)           |                     |
| TB History                        |               |                 |                     |
| There is                          | 38 (11,0)     | 21 (21,2)       |                     |
| There is no                       | 309 (89,0)    | 78 (78,8)       | 0,008 <sup>f</sup>  |
| History of cancer in other organs |               |                 |                     |
| There is                          | 12 (3,4)      | 10 (10,1)       |                     |
| There is no                       | 337 (96,6)    | 89 (89,9)       | 0,013 <sup>z</sup>  |
| History of cancer in the family   |               |                 |                     |
| There is                          | 4 (1,1)       | 2 (2,0)         |                     |
| There is no                       | 344 (98,9)    | 97 (98,0)       | 0,527 <sup>z</sup>  |
| Cell type                         |               |                 |                     |
| Small cell                        | 16 (4,6)      | 1 (1,0)         |                     |
| Adenocarcinoma                    | 123 (35,1)    | 55 (55,0)       |                     |
| Squamous cells                    | 144 (41,1)    | 31 (31,0)       |                     |
| Big cell                          | 22 (6,3)      | 6 (6,0)         |                     |
| Mix**                             | 17 (4,9)      | 1 (1,0)         |                     |
| Not a small cell***               | 28 (8,0)      | 6 (6,0)         | 0,008 <sup>f</sup>  |
| Staging                           |               |                 |                     |
| Early stage (I & II)              | 59 (17,3)     | 8 (8,2)         |                     |
| Advanced stage (III & IV)         | 283 (82,7)    | 90 (91,8)       | 0,027 <sup>f</sup>  |
| Total                             | 351 (77,8)    | 100 (22,2)      |                     |

Note:  $P<0,05$ ; \* *t*-test; <sup>f</sup>Pearson chi-square; <sup>z</sup>Fisher's Exact test



The most common cell type in male was squamous cell (41.1%), while in female it was adenocarcinoma (55.0%). Based on statistical analysis with Pearson Chi-Square, there was a significant difference with  $P < 0.05$ . More advanced stages in both sexes (84.8%). Advanced stage in female was much more (91.8%) than male (82.7%), with  $P < 0.05$ .

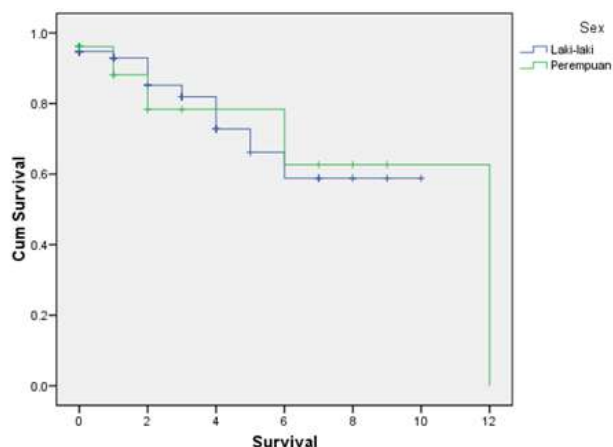


Figure 2. Kaplan-Meier curve for life expectancy of lung cancer patients

The average life expectancy of female ( $8.74 \pm 1.56$  months) is longer than that of male ( $7.29 \pm 0.64$  months). However, the Log Rank test showed that there was no statistically significant difference ( $P = 0.95$ ).

## DISCUSSION

The number of people with lung cancer in male is more than in female with a 3.5: 1. Data from Ramdhani et al. in 2008–2012 obtained relatively the same results with a balance of male to female 3.1:1.<sup>5</sup> The number of male patients, both male and female, tend to increase from 2011, but the increase in cases in female is relatively slower than male. Chen et al.'s research in China found an increased incidence of lung cancer, but the increased incidence in female was more significant than male (2.34% vs. 1.30%;  $P < 0.05$ ).<sup>6</sup> Statistical data from Siegel et al. on cancer in the United States until 2017 get different results. The number of male sufferers tends to decrease twice as fast as female, while the decline in female is relatively slow. Changes in lung cancer trends in male and female

in the United States are associated with changes in smoking habits. The habit of smoking large amounts of smoking in female is late and carried out at an older age than male, and is slower to quit.<sup>1</sup> A study by Costa et al. in Brazil found that both male and female were more smokers and ex-smokers, but the number was higher in males compared to females (87.1% vs. 71.1%), female non-smoker only 28.9%.<sup>7</sup>

The habit of smoking in Indonesia is currently on the rise with the second-largest cigarette consumption globally after China; it is estimated that 316,075 cigarettes were sold to the public in Indonesia in 2016. This number decreased slightly in 2019 to 301,144 cigarettes. It is estimated that 36.3% of adults smoked daily in Indonesia in 2013, with a smoking prevalence of 66% in male and 6.7% in female. The percentage of teenage smokers aged 13–15 years in Indonesia were also high, 35.5% for boys and 3.4% for girls. The number of smokers continues to increase every year, in 2014 an increase of 1.1% compared to 2007.<sup>8–10</sup> This is thought to have caused an increase in the number of lung cancer patients in male in this study, where 74.8% of male with lung cancer were smokers, and 19.7% were ex-smokers so that the total male lung cancer patients associated with smoking was 94.5%. Different results were found in female, where 93.9% of female with lung cancer were not smokers.

Lung cancer in non-smokers is estimated to occur in 10–25% of lung cancer patients globally, more commonly found in female, with the predominant cell type being adenocarcinoma. Exposure to environmental cigarette smoke, especially in female and exposure to carcinogens in the workplace, especially in male, are two alternative risk factors.<sup>10</sup> A meta-analysis study by Sheng et al. found a significant relationship between exposure to environmental cigarette smoke and the incidence of lung cancer in non-smokers in China. The results of this study showed the odds ratio (OR) of the population with exposure to environmental cigarette smoke was 1.64 (95% CI: 1.34–2.01) compared to the unexposed population, male (OR: 1.62; 95% CI: 1.16–2.28), in female (OR=1.57; 95% CI: 1.43–1.72).<sup>11</sup> Study from Ermawati et al. found

that exposure to cigarette smoke from parents is a significant risk factor in female who have lung cancer treated at RSUP M. Djamil Padang and RSUD Solok (OR=13.46, 95% CI: 4.04–44.82;  $P=0.001$ ).<sup>12</sup>

The mean age of female lung cancer patients was younger than male (52.97 years vs. 57.81 years,  $p<0.05$ ). Based on data from the Surveillance, Epidemiology, and End Results Program (SEER) from 1975 to 2008, the median age of female lung cancer patients in the United States (52.3 years) is younger than male (75.2 years).<sup>13</sup> Study by Radzikowska et al. in 2002 also found female with lung cancer younger than male (60.02 vs. 62.18 years;  $P<0.001$ ). Patients aged  $<50$  years were more common in female (23.3% vs 12%;  $P<0.001$ ).<sup>4</sup>

The same thing was also found in Japan by Funakoshi et al. The comparison between male and female aged  $<50$  years who had lung cancer was smaller than those aged  $>50$  years (1.99 vs. 2.89;  $P=0.003$ ). This shows that female with lung cancer are found at a younger age.<sup>14</sup> The age difference between female and male in this study can be related to the results of Ermawati et al. which that female have been exposed to environmental cigarette smoke from an early age from their parents.<sup>12</sup> Research by Lee et al. in Taiwan has shown that exposure to environmental cigarette smoke in childhood can be a risk factor for lung cancer in adulthood as much as 1.8 times (95% CI: 1.2–2.9) in non-smokers.<sup>15</sup>

Other risk factors that were significantly different in female with lung cancer than male in this study were a previous history of TB ( $P=0.008$ ) and a history of cancer in other organs ( $P=0.013$ ). Study from Yu et al. demonstrated that the incidence of lung cancer increased 11 times in TB patients, with a hazard ratio of 4.37 (95% CI: 3.56–5.36) for the TB cohort after adjustment for demographic variables. The hazard ratio became 3.32 (95% CI: 2.70–4.09) after adjustment for other risk factors such as COPD, other cancers associated with smoking, etc.<sup>16</sup> Chronic inflammatory processes and fibrosis due to TB can induce genetic mutations. Various hypotheses of the role of TB in causing lung

cancer have been proposed by experts, including variations in vascular morphology, the process of lymphocytosis, the formation of immune system mediators such as interleukins (IL). Induction of necrosis and apoptosis or reactivation of TB, especially in immunocompromised patients, can increase IL-17 and Tumor Necrosis-alpha (TNF- $\alpha$ ), which can reduce p53 activity or increase B-cell lymphoma 2 (Bcl-2) expression, reduce B-cell Lymphoma associated x (Bax-T) and cause inhibition of caspase-3 expression, resulting in mitochondrial expression, decreased cytochrome oxidase.<sup>17</sup>

Data in the United States found about 880,300 people from 11 million cancer patients who survived until January 1, 2005, were diagnosed with more than one cancer called multiple primary cancer. Lung cancer is among the ten most common cancer sites, both in male and female, with an observation/expectation ratio (O/E ratio) for female being more significant than male (1.53 vs. 1.32). The causes of multiple primary cancers are grouped into three categories, namely familial cancer syndromes and other genetic susceptibility factors, concurrent risk factors such as smoking and the effects of previous cancer treatment. Specifically for smoking-related cancers, the O/E ratio in female for lung cancer ranged from 1.17 to 7.01 according to primary cancer, while in male, it was only 0.97 to 3.82.<sup>18</sup>

The most common cell type in female were adenocarcinoma (55%), While most men got squamous cell carcinoma (41.1%) with  $p<0.001$ . Study by Sagerup et al. In 2010 showed that squamous cell types were still dominant in male. In 1998–2002 were relatively the same between adenocarcinoma and squamous cells. But since 2003–2007, the number of adenocarcinomas was dominant in male. The cell type in female since 1988 has been dominated by adenocarcinoma.<sup>19</sup> This change in lung cancer cell types is associated with changes in smoking patterns. Study by Muhas et al. in 2018 showed that squamous cell type was dominant in male smokers (63.25%), while adenocarcinoma type was prevalent in non-smoker



female (66.67%).<sup>20</sup> This was also found in this study, where 74.8% of male are smokers, while 93.9% of female are non-smokers.

Female's life expectancy was longer than male's (8.74±1.56 months vs. 7.29±0.64 months,  $P=0.95$ ). A study by Radkiewicz et al. in 2019 obtained the same results where male with non-small cell lung cancer had a poorer prognosis than female, both in the type of adenocarcinoma and squamous cell.<sup>21</sup>

## CONCLUSION

This study shows that gender disparities affluent by various risk factors such as history of smoking and prior TB infection. And this could affect the prognostic of lung cancer patients at M Djamil Hospital Padang (history of smoking and TB) and prognostic of lung cancer patients at M Djamil Hospital, Padang

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