Short Communications

Editorial Process: Submission:08/10/2021 Acceptance:10/19/2023

High Proportion of Arsenic Detected in Bronchoalveolar Fluid among Newly Diagnosed Lung Cancer in Jakarta Indonesia

Jamal Zaini*, Indiane Putri Ningtias, Agus Dwi Susanto, Prasenohadi Pradono, Muhamad Rizqy Fadhillah, Sita Laksmi Andarini

Abstract

Objective: This study aims to measure arsenic concentration in bronchoalveolar lavage fluid (BALF) of newly diagnosed lung cancer and its corelation with clinical profiles. **Methods:** This study is a cross-sectional study to identify arsenic levels in newly diagnosed lung cancer patients. Bronchoalveolar lavage fluid was taken during the bronchoscopy. Arsenic concentration was measured using an ICP-EOS spectrometer. **Results:** Forty-two subjects who met inclusion criteria were recruited in this study. Arsenic metals were detected among 40% of subjects with mean, highest, and lowest values are 0.38 µg/L, 0.5 µg/L, and 0.3 µg/L, respectively. There is no significant difference between arsenic level and patients' demographic and clinical data. **Conclusion:** Arsenic was detected in BALF in majority of newly diagnosed lung cancer patients. Despite the insignificant relationship between arsenic level and patients characteristic, this results is evidence of which arsenic metal exposure in lung cancer during their lifetime and should raise public health awareness regarding mitigating the source of exposure and its potential as lung carcinogenic agent.

Keywords: Arsenic- lung cancer- bronchoalveolar lavage

Asian Pac J Cancer Prev, **24 (10)**, 3309-3313

Introduction

Lung cancer is still a significant problem globally (Cheng et al., 2015; Sung et al., 2021). Although generally, lung cancer is attributed to tobacco smoking, never-smoker contributed 10-25% of all lung cancer. Arsenic is a well-established lung cancer aetiology in never-smokers. Arsenic exposure has been linked to genetic and epigenetic alteration through oxidative stress (Hubaux et al., 2012).

Arsenic is a toxic metalloid element that could present in the air, water, and soil. Arsenic can be found in two forms, inorganic and organic compound. An inorganic compound is commonly found in industrial waste, building products ("pressure-treated" woods), and arsenic-contaminated water, whereas organic arsenic is found in food, including fish and shellfish. Inorganic form is toxic for humans and linked to cancer (American Cancer Society 2023). Smoking is also known as a source of arsenic metal (Chuan et al., 2012).

The primary source of arsenic exposure is contaminated water. Many countries have reported arsenic contamination in drinking water, for instance, Bangladesh, China, Chile, Taiwan, and United States. World Health Organization (WHO) has also set a dosage threshold value of 10 µg/L in drinking water as arsenic has potentially harmful effects on human health (Shuhui et al., 2019).

Since Indonesia is located in the ring of fire with high geothermal activity, it has an enormous potential area with considerably high arsenic concentration, such as hot springs and marine sediments (Ilyas et al., 2009). Moreover, some confined aquifers in Capital Jakarta contain high arsenic metal, and most residents used ground water as a source of fresh water in daily activity including drinking water. However, lack of complete data at the national level has raised concern for detailed studies related to the influence of arsenic metal on Indonesia's population health (Hosono et al., 2011).

To our knowledge, few study has been reported regarding arsenic concentration in certain body fluids of lung cancer patients, for instance, in bronchoalveolar lavage fluid. To find the correlation between arsenic and lung cancer occurrence, we aim to measure arsenic concentration in BALF, relating it with patients' characteristics. The collected data from this study hope could supply the basis for identifying lung cancer risk factors, creating public health awareness, and improving early detection in the future.

*Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia, Persahabatan National Respiratory Referral Hospital Jakarta, Indonesia. *For Correspondence: jamal.zaini@gmail.com*

Materials and Methods

Settings, Eligibility Criteria, and Variable Identification

We conducted a cross sectional study to measure arsenic level in lung cancer patients prepared for diagnostic procedures in Persahabatan National respiratory Referral Hospital Jakarta. Data were collected during the period of April-June 2019 and approved by the Research Committee of Persahabatan Hospital. The inclusion criteria including lung carcinoma cancer patients with age above 18 years, diagnosed as Non small cell lung carcinoma (NSCLC) or small cell lung carcinoma (SCLC), and agree to be assigned in this study. Subjects who had any contraindication for bronchoalveolar lavage procedure, for instance, hemodynamic problems, recent myocardial infarction, life-threatening arrhythmia, bronchospasm or bronchoconstriction, unstable angina, and hypercarbia were excluded.

The subjects' performance status was defined according Eastern Cooperative Oncology Group Performance Status (ECOG-PS). Histology of Lung cancer was determined using 2015 World Health Organization classification of lung tumors (Travis et al., 2015). Moreover, staging of lung cancer is determined by American Joint Committee on Cancer (Edge et al., 2010).

Data collection

The patient's demographic and clinical data regarding his diagnosis was collected in the first visit. Entire patients were also undergone standard diagnosis procedure (i.e., history taking, physical and lab examination) for determining their performance of status using Eastern Cooperative Oncology Group Performance Status (ECOG-PS), and Staging.

Bronchoalveolar lavage procedure was utilized for collecting the specimen. 100-150 ml NaCl 0,9% with 37°C was used for preventing cough, bronchospasm, and lung function in BAL. Hence, this could increase the volume of the sample produced. The fluid was inserted in bolus using a syringe with a velocity of 5 ml/s or driven using hydrostatic force. The specimen collected was aspirated using a negative pressure of about 25-100 mmHg. A minimum of 50 ml volume sample was collected using this procedure. For the sampling location, we choose the location of the suspected malignant lesion. However, if there is not a localized lesion, the medial lobe and lingula were chosen. Inductively Coupled Plasma-Optical Emission Spectrometry (ICP-OES) was used to measure arsenic level and presented as µg/L. the minimal detection threshold was 0,03 µg/L. During BAL procedure, biopsy procedure was also performed. Further, our subjects is also tested the presence of Epidermal Growth Receptor Factor (EGFR) mutation.

Statistical Analysis

For data analysis, SPSS for Window 23.0 was used and perform descriptive analysis, including frequency and distribution. In order to assess the associations between demographic and clinical profile with arsenic metal positivity, chi-square or fisher exact test was used. p-value <0.05 was considered as statistically significant.

Results

Among 60 subjects newly diagnosed lung cancer during study period, Forty-two lung cancer patients that met inclusion criteria and included in this study. Eighteen subjects were excluded because inability to performed bronchoscopic procedure due to its clinical condition. Whole patients' characteristics and clinical data were presented in Table 1. Female mainly predominates study subjects with mean age of 57.1 ± 10.5 years. Arsenic metal are detected among 17 of 42 subjects (40 %) with mean, highest, and lowest value are 0.38 µg/L, 0.5 µg/L, and 0.3 µg/L, respectively. Based on cancer type, the arsenic concentration on BALF were similar among different types

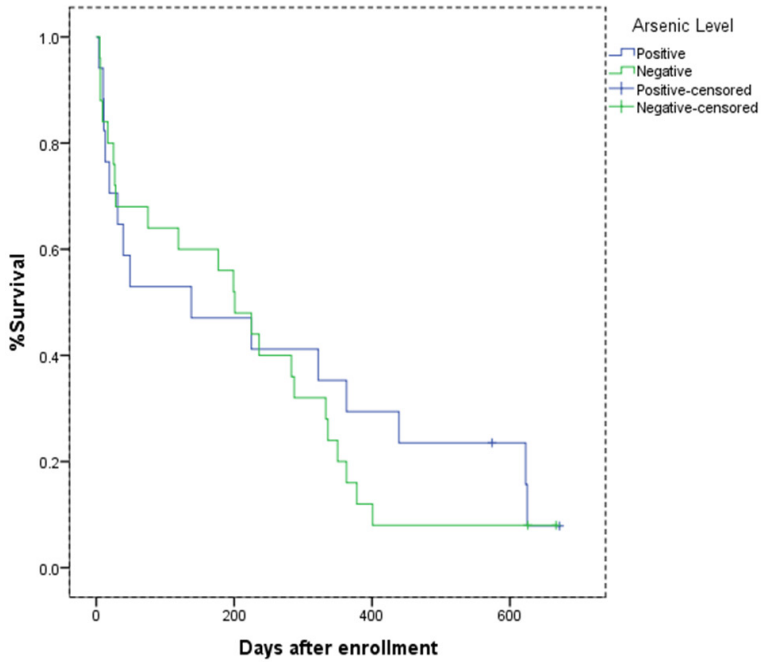

Figure 1. Kaplan Meier: Survival Analysis of Arsenic Level in BALF

Table 1. Baseline Characteristics and Clinical Data associated with Arsenic Level in BALF

Patient's Characteristics	n(%), n=42	Arsenic Level		P-Value
		Positive n (%) n=17 (40.5)	Negative n (%) n=25 (59.5)	
Sex				0.972
Male	32 (76.2)	13 (40.6)	19 (59.4)	
Female	10 (23.8)	4 (40.0)	6 (60.0)	
Age				0.551
<65 years	32 (76.2)	13 (43.3)	17 (56.7)	
>65 years	10 (23.8)	4 (33.3)	8 (66.7)	
Type of Carcinoma				0.191
Adenocarcinoma	25 (59.5)	9 (36.9)	16 (64.0)	
Squamous cell Carcinoma	13 (30.9)	5 (35.7)	9 (64.3)	
Small cell Carcinoma	2 (4.7)	1 (100.0)	0 (0.0)	
Neuroendocrine carcinoma	2 (4.7)	2 (100.0)	0 (0.0)	
Staging				0.08
Early Stage	11 (26,2)	2 (18.2)	9 (81.2)	
Advanced Stage	31 (73,8)	15 (48.4)	16 (51.6)	
Performance Status				0.489
PS 0	2 (4.8)	0 (0.0)	2 (100.0)	
PS 1	26 (61.9)	11 (42.3)	15 (57.7)	
PS 2	14 (33.3)	6 (42.9)	8 (57.1)	
EGFR Mutation				0.199
EGFR Mutation	6 (14.3)	1 (16.7)	5 (83.3)	
No Mutation	36 (85.7)	16 (44.4)	20 (55.6)	
Smoking status				0.414
Non smoker/passive smoker	18 (42.8)	6 (33.3)	12 (66.7)	
Active smoker/former	24 (57.2)	11 (50.0)	13 (50.0)	

of cancer, with adenocarcinoma (n=9, mean: 4 µg/L); squamous cell carcinoma (n=5, mean:3.4 µg/L) and small cell and neuroendocrine carcinoma (n=3, mean: 4 µg/L).

However, based on the comparative test, sex, age, smoking status, type of carcinoma, staging, performance status, and EGFR mutation were not shown statistically significantly different with arsenic metal positivity. ($p<0.05$). Kaplan Meier survival analysis also shown not significant different between arsenic detected vs non detected group (Figure 1).

Discussion

This study aimed to define and analyze BAL fluid arsenic metal content among lung cancer patients in tertiary respiratory hospital in Jakarta, Indonesia. Although this study did not show a significant correlation between patients' characteristics and clinical data with arsenic metal positivity, high proportion of patients with arsenic positive in their BAL specimen are found among subjects (40%) with mean arsenic level of 0,38 µg/L.

Arsenic metal is well known carcinogenic substrate among some studies and has been investigated through epidemiological, molecular, and animal studies. Model of carcinogenesis has been proposed, both in genetic and epigenetic (Hubaux et al., 2012; Tsuji et al., 2019; Lamn et al., 2018). At the molecular level, arsenic in humans is metabolized to toxic monomethylmarsonus acid (MMAIII) and dimethylarsinic acid (DMAIII). Both metabolites cause depletion of natural antioxidants in human cells, which promote oxidative stress and directly damage DNA. Moreover, these metabolites influence DNA and protein changed on the epigenetic level due to the deletion of methyl group donors. Direct genetic impairment is also thought to produce DNA mutations that could defect protein translation, such as EGFR Protein (Tsuji et al., 2019). Nevertheless, our study has not shown any correlation between the presence of arsenic in BALF and EGFR mutation; therefore, higher-quality studies are needed to reveal this conclusion.

Even higher dosage of inorganic arsenic is an evident carcinogen, It is uncertain whether low dose (<10-50 µg/L) exposure could increase lung cancer risk (Lamn et al., 2018). A study in Central Italia has concluded that lung cancer risk is identified as low as 10 ug/L arsenic exposure (D'Ippoliti et al., 2015). Recent meta-regression conducted by Lamm et al., (2015) reported statistically significant carcinogenic activity of a high dose arsenic level and anticancer activity arsenic in low dosage (<50 µg/L). Other study also supports this conclusion that a low dosage of arsenic shows a protective effect (Snow et al., 2005).

Limited studies has evaluated the correlation between BAL arsenic metal level and lung cancer occurrence. Corhay et al. performed the mineralogical analysis of BAL using the PIXE method between two groups, in white-collar and blast furnace workers, then further divided into smokers and nonsmokers. No significant difference in arsenic concentration is found between those groups. Blast furnace workers have more dusty BAL fluid containing other metals than arsenic (Corhay et al., 1995). In line with the results, confounding factors, such as smoking status and occupation, could influence this study's results. Moreover, other carcinogens found in cigarettes or subjects' occupations could act synergistically with arsenic, increasing the probability of developing lung cancer (Corhay et al., 1995; Jarup et al., 1989).

Arsenic is ubiquitously found in the environment and could expose humans from ingestion, notably from contaminated drinking water. The primary source of inorganic arsenic came from the earth's crust as a result of geothermal activities. Geothermal water, located near magma, has a high temperature and seeps through subterranean and faults to underground. Further high-temperature water could circulate back to the surface, reacting to the rock and dissolute minerals. Hence, geothermal water contains a high concentration of arsenic and heavy metals. About 251 sources of geothermal energies are distributed around 26 provinces in Indonesia, which could become a potential source of arsenic exposure (Ilyas et al., 2009). Still, few studies discuss arsenic contamination in Indonesia. Some high concentration sources of arsenic reported in Indonesia are hot spring from West Java Province (Herdianita and Priadi, 2008) and Groundwater in South Sumatra Province (winkel et al., 2007).

Anthropogenic activity, for instance, mining and wood processing, arsenic usage in pesticides, and oil refineries could also increase arsenic contamination. In Indonesia, these activities, for example, are found in sediment pore and gold mine tailing Buyat Bay, North Sulawesi (Ilyas et al., 2009; Blackwood et al., 2007) and also gold mine tailing in Selogiri Central Java which is affected by gold-mine tailing (Harijoko et al., 2010). Following the arsenic BAL profile in this study and Indonesia's arsenic exposure status, this study's subjects are at higher risk of exposure.

As there is no significant correlation between arsenic positivity with demographic and clinical data, pathogenic of arsenic positivity in BAL is uncertain. However, the subjects enrolled in this study was limited and need larger population for verification. Other limitation is the absence of exposure analysis in each subject, such as groundwater usage and potential anthropogenic activities around their home environment. Because of the cross-sectional study design, the BAL procedure and assessment were only conducted once. Thus, arsenic exposure towards lung cancer progression could not be concluded. Considering many centers in Indonesia are treating lung cancer patients, this study finding could be generalized into Indonesian population.

Based on this study, it can be concluded that arsenic was detected in majority of lung cancer patients in BAL fluid. Although it could not verify how these results correlate with subjects' conditions, the presence of arsenic in BAL of lung cancer patients is an evidence of arsenic exposure and should raise public health awareness regarding source control of exposure which might be drinking water. In conjunction with these results, we encourage any study in the future on this field in purpose of mitigating risk factors and develop novel strategy in preventing arsenic contamination in water.

Author Contribution Statement

Conceptual: JZ, P, SA. Design: JZ, IPN, P, ADS. Data collection/processing: IPN, P, MRF. Analysis/interpretation: JZ, IPN, SA. Writing and critical review: JZ, IPN, ADS, P, MRF,SA. ALL authors has reviewed the final manuscript.

Acknowledgements

Funding Statement

This study was supported by Universitas Indonesia, grant no BA-562/UN2.RST/PPM.00.03.01/2021.

Ethical Decralation

The Ethics Committee of the Faculty of Medicine, Universitas Indonesia with regards of the protection of human rights and welfare in medical research has reviewed and approved the protocol including the information given to the potential subjects. Ref no KET-452/UN2.F1/ETIK/PPM.00.02/2019.

Availability of data

The data are available upon request and should be approved by ethical committee.

Conflict of interest

All authors declared no conflict of interest.

References

American Cancer Society (2020). Arsenic and Cancer Risk. Available on : https://www.cancer.org/cancer/cancer-causes/arsenic.html[Cited on 2023 May 9].

Blackwood GM, Edinger EN (2007). Mineralogy and trace element relative solubility patterns of shallow marine sediments affected by submarine tailings disposal and artisanal gold mining, Buyat-Ratototok district, North Sulawesi, Indonesia. *Environ Geol*, **52**, 803–18.

Cheng TYD, Cramb SM, Baade PD, et al (2015). The International Epidemiology of Lung Cancer: Latest Trends, Disparities, and Tumor Characteristics. *J Thoracic Oncol*, **11**, 1653-71.

Chuan L, Wright CG, Mcadam K, et al (2012). Arsenic Speciation in Tobacco and Cigarrette Smoke. *Beiträge zur Tabakforschung Int*, **25**, 375-80.

Corhay JL, Bury T, Delavignette JP, et al (1995). Nonfibrous mineralogical analysis of bronchoalveolar lavage fluid from blast-furnace workers. *Arch Environ Health*, **50**, 312-9.

D'Ippoliti D, Santelli E, De Sarlo M, et al (2015). Arsenic in Drinking Water and Mortality for Cancer and Chronic Diseases in Central Italy, 1990–2010. *PLoS One*, **10**,

e0138182.
Edge SB, Compton CC (2010). The American Joint Committee on Cancer: The 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol*, **17**, 1471–4.
Harijoko A, Htun TM, Saputra R, et al (2010). Mercury and Arsenic Contamination from Small Scale Gold Mining activities at Selogiri Area, Central Java, Indonesia. *J SE Asian Appl Geol*, **2**, 56–64.
Herdianita NR, Priadi B (2008). Arsenic and mercury concentration at several geothermal systems in west Java, Indonesia. *ITB J Sci*, **40**, 1-14.
Hosono T, Nakano T, Shimizu Y, et al (2011). Hydrogeological constraint on nitrate and arsenic contamination in Asian metropolitan groundwater. *Hydrol Process*, **25**, 2742–54.
Hubaux R, Becker-Santos DD, Enfield KS, et al (2012). Arsenic, asbestos and radon: emerging players in lung tumorigenesis. *Environ Health*, **11**, 89.
Ilyas M, Sudaryanto A, Anantasena Y, et al (2009). Is Arsenic a Potential Threat for Human Health in Indonesia? In: Interdisciplinary studies on Environmental Chemistry—Envirnmental Research in Asia, Eds. Obayashi Y, Isobe T, Subramanian A. Terrapub, Tokyo, pp 185-9.
Järup L, Pershagen G, Wall S (1989). Cumulative arsenic exposure and lung cancer in smelter workers: A dose-response study. *Am J Ind Med*, **15**, 31-41.
Lamm SH, Boroje IJ, Ferdosi H, et al (2018). Lung Cancer Risk and Low (≤50 µg/L) Drinking Water Arsenic Levels for US Counties (2009–2013)—A Negative Association. Int J *Environ Res Public Health*, **15**, 1200-5.
Lamm SH, Ferdosi H, Dissen EK, et al (2015). A Systematic Review and Meta-Regression Analysis of Lung Cancer Risk and Inorganic Arsenic in Drinking Water. *Int J Environ Res Public Health*, **12**, 15498–515.
Shuhui W, Hong Z, Shasha T (2019). A Review of arsenic exposure and lung cancer. *Toxicol Res*, **8**, 319.
Snow ET, Sykora P, Durham TR, et al (2005). Arsenic, mode of action at biologically plausible low doses: What are the implications for low dose cancer risk?. *Toxicol Appl Pharmacol*, **207**, 557–64.
Sung H, Ferlay J, Siegel RL, et al (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*, **71**, 209-49.
Travis WD, Brambilla E, Nicholson AG, et al (2015). The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. *J Thorac Oncol*, **10**, 1243–60.
Tsuji JS, Chang ET, Gentry PR, et al (2019). Dose-response for assessing the cancer risk of inorganic arsenic in drinking water: the scientific basis for use of a threshold approach. *Crit Rev Toxicol*, **49**, 36-84.
Winkel L, Berg M, Amini M, et al (2018). Predicting groundwater arsenic contamination in Southeast Asia from surface parameters. *Nat Geosci*, **1**, 536-42.