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EXPLORING THE ASSOCIATION BETWEEN AIR POLLUTANT EXPOSURE AND KREBS VON DEN LUNGEN-6 (KL 6) SERUM LEVELS IN OUTDOOR AND INDOOR WORKERS IN BANYUMAS DISTRICT, CENTRAL JAVA

Euis Tia Istianah[1,2], Nendyah Roestijawati[3], Joko Mulyanto[3]*

[1]Master of Biomedical Science Program, Faculty of Medicine, Universitas Jenderal Soedirman, Purwokerto 53112, Indonesia
[2]Medical Laboratory Technology Diploma Program, STIKes Muhammadiyah Ciamis, Ciamis 46216, Indonesia
[3]Department of Public Health and Community Medicine, Faculty of Medicine, Universitas Jenderal Soedirman, Purwokerto 53112, Indonesia

Corresponding Author:
*) joko.mulyanto@unsoed.ac.id

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Abstract

Introduction: *Indonesia ranks 8th globally in the air pollution index, with poor air quality causing premature deaths from lung ailments such as interstitial lung diseases. Krebs von den Lungen-6 (KL 6) can be used to detect lung disease caused by air pollution. However, the number of studies investigating the link between air pollutant exposure and KL-6 levels is inadequate. The present study explores the association between air pollutant exposure and KL-6 levels in workers in different settings.* ***Methods:*** *This cross-sectional study recruited 70 individuals who were divided into two groups. Dust levels were measured using a particle counter as a proxy for air pollutant levels. KL-6 levels were measured with ELISA. The Spearman correlation test, Mann-Whitney test, and generalized linear model were used in statistical analyses.* ***Results and Discussion:*** *Air pollutant exposure differed significantly between outdoor and indoor settings ($p = 0.000$). A significant difference was found in KL-6 serum levels between outdoor and indoor workers ($p = 0.000$). Air pollutant levels were inversely associated with KL-6 serum levels in outdoor ($r = -0.557$, $p < 0.05$) and indoor workers ($r = -0.360$, $p < 0.05$). Working duration did not significantly correlate with KL-6 serum levels in either group. A tendency of linear association among air pollutant exposure, overall working duration, and KL-6 serum levels was found in the multivariable model.* ***Conclusion:*** *Work settings were associated with varying exposures to air pollutants and KL-6 serum levels. Higher exposure to pollutants may be associated with an increase in KL-6 serum levels.*

INTRODUCTION

Indonesia ranked 8th in the global air pollution index between 2015 and 2017 (1). Globally, air pollution is a serious threat to the health of the population and has been identified as the fourth most significant risk factor contributing to approximately three million premature deaths, mainly due to outdoor air pollution in urban areas (2-3). The International Energy Agency (IEA) recorded more than 60,000 air pollution-related deaths in Indonesia in 2016, and this figure is expected to increase to 120,000 fatalities in 2040 (4). Respiratory disorders, particularly lung diseases such as asthma, chronic obstructive pulmonary disease (COPD), lung carcinoma, and lung inflammation-related diseases, are the most significant contributors to these mortalities (5).

Early detection of respiratory disorders due to air pollution, particularly chronic progressive lung diseases, is crucial for preventing an increase in air pollution-related morbidity and mortality (6). Early diagnosis and intervention can prevent or slow disease progression, maintain patients' quality of life, and reduce the economic burden of disease (7). Spirometry tests, radiologic examinations, and biomarkers have been used in the early detection of air pollution-related diseases. Spirometry tests can accurately predict the progression of the disease but are less sensitive and specific in detecting early pathological changes in respiratory disorders (8-9). High-resolution computed tomography can detect respiratory disorders in the early stages, but the high costs of this procedure render it impractical for mass-screening purposes (10-11).

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Biomarkers such as surfactant protein-A (SP-A), surfactant protein-D (SP-D), monocyte chemoattractant protein-1 (MCP-1), matrix metalloproteinase-7, and chemokine CCL-18 can potentially detect respiratory disorders early and effectively when these biomarkers are tested in regular laboratory settings (12-13). Krebs von den Lungen 6 (KL-6) is a potential biomarker for interstitial lung diseases (ILD) due to its role as a fibroblast chemoattractant in the pathophysiology of ILD (14). Type II pneumocytes release KL-6, a glycoprotein, as a prognostic marker for Chronic Hypersensitivity Pneumocystis (CHP). Overexpression of KL-6 in type II epithelial cell regeneration increases the KL-6 serum level and may indicate fibrotic lung lesions (15).

Studies have investigated the differences in KL-6 serum levels between individuals with respiratory disorders and healthy individuals. One study showed that KL-6 serum levels in individuals with ILD were significantly higher than those in healthy individuals (16). KL-6 serum levels are also correlated with early clinical and functional variables of lung diseases (17). Another study showed higher KL-6 serum levels in individuals with Langerhans cell histiocytosis compared to healthy individuals (18). Moreover, exposure to environmental hazards such as particulate matter (PM) from air pollution, titanium dioxide (TiO_2) from paint, and toner from copying machines is associated with an increase in KL-6 serum levels (19-21). Studies in Indonesia investigating KL-6 serum levels among high-risk asymptomatic populations exposed to risk factors related to lung disease are still lacking. An epidemiological study among workers in the bird market showed an increase in average KL-6 serum levels compared to that healthy individuals from the general population (22). Previous studies on the adverse effects of air pollution in Indonesia were limited to investigating the association between air pollutant exposure and demographic and clinical characteristics, such as anthropometric measurements (23-24).

Banyumas is one of the largest and most populated districts in Central Java Province. Air pollution levels in Banyumas are currently still below the maximum safety threshold; however, they have tended to increase over time due to a substantial increase in the number of motor vehicles over the past decade (25). The high degree of air pollution in Banyumas allowed this study to explore the association between air pollutant exposure and specific biomarkers for early detection. The present study aimed to examine the possible relationship between exposure to air pollutants and KL-6 serum levels in working individuals employed in various settings in Purwokerto, Banyumas District, Central Java by measuring the differences in air pollutant levels between indoor and outdoor settings, the differences in KL-6 serum levels between outdoor and indoor workers, and the correlation between the exposure of air pollution (levels and duration) with KL-6 serum levels in both outdoor and indoor workers.

METHODS

This study was an observational analytic study with a cross-sectional design. A total of 70 working individuals were recruited and divided into two groups. One group consisted of 35 outdoor workers, and the other group consisted of 35 indoor workers. The sample size was calculated based on the sample size formula for the correlation analysis, with the assumption of α = 0.05, a power of 80%, and r = 0.5, which resulted in a minimum sample size of 30 participants (26). The study participants were consecutively recruited based on the following inclusion criteria: male; < 60 years of age; normal body mass index (BMI); current smoker or a history of smoking; working for at least one year before data collection; provided consent to participate in the study. The exclusion criteria for the study participants were the following: a history of lung-related diseases such as pneumonia, bronchitis, asthma, or lung cancer. Data collection was conducted in March 2021, and the study participants were recruited on the spot in Jenderal Soedirman street, the main street in Purwokerto, Banyumas District, Central Java. All eligible subjects who participated in the study completed and signed the informed consent form following an oral explanation of the purpose of the study from the study team. Ethical clearance for this study was issued by the Health Research Ethics Commission, Faculty of Medicine, Universitas Jenderal Soedirman, reference number 022/KEPK/II/2021.

The primary independent variable in the study was the level of airborne dust, which was used as a proxy for the level of air pollutants. Particulate Matter 2.5 ($PM_{2.5}$) and Particulate Matter 10 (PM_{10}) were used to representing the dust levels and were measured using a particle counter. The dust level was measured three times per day at five different points on the roadside of Jenderal Sudirman Street, the main street in Purwokerto where the study participants were working. The dust level was measured during the periods from 06.00-07.00 am, 12.00-1.00 pm, and 4.00-5.00 pm, which represents the busiest periods of the day and with the highest concentration of traffic. The average results from the three measurements combining $PM_{2.5}$ and PM_{10} were used to determine the dust levels and as a proxy for the levels of air pollutants. The secondary independent variables were included to provide a comprehensive assessment of air pollutant exposure. Working duration, both overall (in years) and per day (in hours), was calculated to determine the extent of air pollutant exposure, given that the effects of air pollutant exposure depend on the level and duration of exposure. Data on working duration were collected from the study participants through direct interviews and from the data provided on written forms.

The primary dependent variable in the study was the KL-6 serum level of each participant. Blood samples were drawn from the median cubital vein, 2-3 cc of blood was drained into the tube and subsequently stored in a cooling box with a temperature of 1-5 °C. The centrifugation of frozen specimens was carried out at 3000 rpm for 5 min. The resulting serum was stored in the freezer at -80 °C. A sandwich-type enzyme-linked immunosorbent assay (ELISA) was employed to evaluate the frozen serum using BT-Lab Human Protein KL-6/MUC 1 ELISA Kit from Elabsience (27). The absorbance was observed at a wavelength of 450 nm, and the absorbance values were converted into KL-6 serum levels using tools from arigobio.com. Data on age, smoking status, the use of personal protective equipment (PPE) such as face masks, history of lung diseases such as asthma, pneumonia, bronchitis, and lung cancer; and nutritional status measurements such as BMI, were collected from study participants. These data were used in multivariate analysis to control for confounders.

The basic characteristics of study participants were described using frequency distribution (percentage) for variables measured in categorical (nominal and ordinal) scales. For variables measured in numerical scales, the characteristics of the study participants were presented using central tendency measurements (mean and standard deviation) (28). The Shapiro-Wilk test was applied to test the normality of the data distribution before the bivariate analysis was conducted. The results from the normality test showed that the data were not normally distributed. Further efforts to transform the data failed to normalize the data distribution. Therefore, non-parametric tests were used in the bivariate analysis (29). Two different analyses were conducted to assess the relationship between air pollutant exposure and KL-6 serum levels. First, the Mann-Whitney test compared the air pollutant level between indoor and outdoor settings, and KL-6 serum levels between indoor and outdoor workers. Second, the Spearman-rank correlation test was used to test the correlation between air pollutant levels, working duration, and the KL-6 serum levels for indoor and outdoor workers. A generalized linear model (GLM) was used to control confounding variables to analyze the linear correlation between air pollutant levels, working duration, and KL-6 serum levels, adjusted for age and other characteristics. The GLM was used because it has more flexible assumptions than the ordinary linear regression, which allows for the analysis of data with an abnormal distribution and provides a straightforward interpretation (30). All analyses were conducted using IBM SPSS Statistics v22.0 software.

RESULTS

Table 1 shows the characteristics of the study participants. In terms of age, outdoor workers were typically older than indoor workers, with 77.1% of the outdoor workers aged 40 to 60 years, whereas only 8.6% of the indoor workers were in this age category. All study participants in the outdoor groups were smokers, whereas 80% of the indoor workers were current smokers. In both indoor and outdoor groups, all study participants reported always wearing PPE when working, having a normal BMI, and having no history of lung disease. Outdoor workers tended to have a longer overall working duration, with 51.4% having worked for more than ten years, whereas in the indoor group, only 20% of the participants had been working for more than ten years. Most workers, 51.4% of indoor workers and 71.5% of outdoors workers, respectively, worked less than eight hours per day.

Table 1. Characteristics of Study Participants

Characteristics	Frequency (%)		
	Outdoor	Indoor	Total
Age group (years)			
20-40	8 (22.9)	32 (91.4)	40 (57.1)
41-60	27 (77.1)	3 (8.6)	30 (42.9)
Smoking status			
Yes	35 (100.0)	28 (80.0)	63 (90.0)
No	0 (0.0)	7 (20.0)	7 (10.0)
Use of personal protective equipment (PPE)			
Yes	35 (100.0)	35 (100.0)	70 (100.0)
No	0 (0.0)	0 (0.0)	0 (0.0)
Body mass index (BMI)			
Normal	35 (100.0)	35 (100.0)	70 (100.0)
Underweight/overweight	0 (0.0)	0 (0.0)	0 (0.0)
History of lung diseases			
Yes	0 (0.0)	0 (0.0)	0 (0.0)
No	35 (100.0)	35 (100.0)	70 (100.0)
Working duration (overall)			
< 10 years	17 (48.6)	28 (80.0)	45 (64.3)
≥ 10 years	18 (51.4)	7 (20.0)	25 (35.7)
Working duration per day			
< 8 hours	25 (71.5)	18 (51.4)	43 (61.4)
≥ 8 hours	10 (28.5)	17 (48.6)	27 (38.6)

Table 2 shows the association between air pollutant levels, KL-6 serum levels, and the study setting (outdoors vs. indoors). The average air pollutant level, based on the dust level ($PM_{2.5}$ and PM_{10}), was significantly higher in the outdoor setting (26.67 ± 3.31 μg/m³) compared to the indoor setting (16.21 ± 1.96 μg/m³), as indicated by the p-value = 0.000. Similarly, the KL-6 serum levels of individuals who worked in outdoor settings were much higher than those who worked in outdoor settings. The average KL-6 serum level of the outdoor workers was 3.23 ± 2.11 ng/ml, which was considerably higher than that of the indoor workers, with an average KL-6 serum level of 1.29 ± 0.79 ng/ml (p = 0.000).

Table 2. Comparison of Air Pollutant and KL-6 Serum Levels Between Outdoor and Indoor Settings

Variables	Setting		p-value (Mann-Whitney test)
	Outdoor (mean ± SD)	Indoor (mean ± SD)	
Air pollutant level (μg/m³)	26.67 ± 3.31	16.21 ± 1.96	0.000
KL-6 serum level (ng/ml)	3.23 ± 2.11	1.29 ± 0.79	0.000

The results related to the correlation between air pollutant exposure and KL-6 serum level for indoor and outdoor workers are presented in table 3. The air pollutant level significantly correlated with the KL-6 serum level in both outdoor (r = -0.557; p = 0.001) and indoor workers (r = -0.360, p = 0.034). The negative correlation indicated the inverse association between these variables (lower air pollutant level correlated with higher KL-6 serum level). The correlation between overall working duration and KL-6 serum level was not significant both for outdoor (r = 0.304; p = 0.076) and indoor workers (r = -0.290; p = 0.091). Similar results were also found when the correlation between working duration per day and KL-6 serum level was assessed in both outdoor (r = 0.023; p = 0.895) and indoor workers (r = 0.302; p = 0.078).

Table 3. Correlation Between Air Pollutant Exposure (Level and Duration) and KL-6 Serum Levels in Indoor and Outdoor Settings

Variables	Setting			
	Outdoor		Indoor	
	r	p-value	r	p-value
Air pollutant level	-0.557	0.001	-0.360	0.034
Overall working duration	0.304	0.076	-0.290	0.091
Working duration per day	0.023	0.895	0.302	0.078

The relationship between the degree and duration of air pollutant exposure with KL-6 serum levels was further analyzed using the GLM to control for age as a confounding variable (table 4). After adjusting for age, the findings showed no significant linear association between air pollution levels, overall working duration, working duration per day, and KL-6 serum levels. However, the tendency of a positive linear association with KL-6 serum levels was observed in the variables of overall working duration (B = 0.052; p = 0.100) and air pollutant levels (B = 0.044; p = 0.153).

Table 4. Multivariate Analysis of the Association Between Air Pollutant Exposure and Kl-6 Serum Levels Using a Generalized Linear Model (GLM)

Variables	B (coefficient)	Standard error (SE)	p-value
Age	-0.007	0.029	0.813
Overall working duration	0.052	0.031	0.100
Working duration per day	0.038	0.145	0.791
Air pollutant level	0.044	0.031	0.153

DISCUSSION

The present study assessed the association between exposure to air pollutants and KL-6 serum levels among indoor and outdoor workers in Purwokerto, Banyumas District, Central Java Province. Findings from this study show that outdoor settings had much higher levels of air pollutants compared to those indoor settings. Similarly, KL-6 serum levels in individuals who worked in outdoor settings were significantly higher than in individuals who worked in indoor settings. Correlation tests revealed significant inverse correlations between levels of air pollutants and KL-6 serum levels for both outdoor and indoor workers. There were no significant correlations between working duration (overall and daily) and KL-6 serum levels in outdoor and indoor workers. After adjusting for age and working duration, air pollutant levels tended to have a linear association with KL-6 serum levels in the total population in the study, although this association was not statistically significant.

The present study showed that air pollutant levels, in terms of $PM_{2.5}$ and PM_{10}, were significantly higher in outdoor settings than in indoor settings. This finding was expected due to the different environmental conditions between outdoor and indoor working areas. Outdoor areas were directly exposed to air pollutants from various sources (31). Because the study site in this investigation was located in the main street of Purwokerto City, which is a relatively high traffic area for motor vehicles, the air pollutant levels, particularly the dust levels, were considerably higher. In contrast, the indoor setting, although situated in the same area, was located inside a building with concrete walls, which provided a physical barrier to protect the indoor workers from exposure to dust. Furthermore, most indoor working settings were equipped with an air conditioner capable of filtering pollutants (such as PM) from the ambient air, consequently decreasing the levels of indoor dust. A good ventilation system inside a building will typically decrease dust levels and reduce exposure to air pollutants (32).

One of the results from this study showed that KL-6 serum levels in outdoor workers were significantly higher than that in indoor workers. Several possible mechanisms could explain this finding. First, the dust level in the outdoor setting was higher than that in the indoor setting, as shown in the previous result. Greater exposure to air pollutants, particularly over a longer duration (chronic exposure), is likely to induce more pathological responses, such as respiratory tract inflammation, thereby increasing the KL-6 serum level. Chronic inhalation of PM from polluted air can induce a response in the respiratory tract via oxidant-mediated cellular damage that produces reactive oxygen species (ROS), oxidative stress, and induces both innate and adapted immune system responses (33-34). Second, the outdoor workers were much older than the indoor workers. Older age has been associated with an increase in individual KL-6 serum levels. Older individuals arguably experience more episodes of disease that may induce cellular damage in respiratory organs, particularly in the lungs and connective tissue (35). Several non-respiratory diseases, including rheumatoid arthritis, measles, and Sjogren's Syndrome, have been linked to an increase in serum levels of KL-6 (36-38). Some of these diseases are primarily found in older individuals, which may accelerate the degenerative process of lung tissue and lead to higher KL-6 serum levels in older individuals.

In the present study, KL-6 serum levels increased in indoor and outdoor workers, even when air pollution decreased. This finding contradicts the hypothesis that an increase in air pollutant exposure will adversely affect the condition of respiratory organs through the inflammation process, which induces the hypersecretion of mucin and the production of mediators such as serum KL-6, which can lead to respiratory disorders (39). Findings from a previous study indicated that the increase in KL-6 serum levels was in line with a reduction in lung function, which can be interpreted as a decrease in lung function, as indicated by pathological changes in the lung (8). It should be noted that the present study did not include air pollutant exposure as a variable that could influence lung function. Therefore, the relationship between air pollutant exposure, lung function, and KL-6 serum levels remains unclear. Such a relationship is likely influenced by multiple factors. When tested separately in bivariate analysis, the interaction among the multiple determinants of KL-6 serum levels may affect the association between pollutant exposure and KL-6 serum levels. The multivariate analysis in this study confirms that after adjusting for confounding variables, the correlation between air pollutant exposure and KL-6 serum levels becomes positively linear. This finding implies that interactions among variables have been controlled through statistical analysis, resulting in findings that reflect the relationship between air pollution with KL-6 serum levels.

This study showed that overall working duration and daily work duration did not correlate with the KL-6 serum level in outdoor and indoor workers. KL-6 serum levels are markers of pathological processes such as inflammation and organ damage, particularly in lung tissue caused by air pollutant exposure (40-41). The effects of air pollutant exposure on respiratory organs are influenced by the concentration of the air pollutants and the duration of exposure (42). In the present study, although the exposure time was quite long (i.e., chronic), the level of air pollutants was still relatively low, and far below the maximum threshold. Chronic exposure to low-level air pollutants is likely insufficient to induce substantial pathological processes in respiratory organs and results in relatively low KL-6 serum levels. This finding is reflected by the nonsignificant correlation observed between working duration and KL-6 serum levels.

The final finding from this study showed the tendency of a linear association between air pollutant levels, overall working duration, and KL-6 serum levels after adjusting for confounding variables. Although these associations were not statistically significant, this finding supports the hypothesis that air pollutant exposure may induce the pathological process in respiratory organs mainly through chronic inflammation in the lungs and associated tissues, thereby producing ROS and triggering the immune response, which causes organ damage and increases KL-6 serum levels (34). The statistically nonsignificant results may be due to the relatively small sample size. The sample size used in this study was only appropriate for two-variable correlation and may have been underpowered to detect significant associations when multiple variables were included in the multivariate analysis. This finding sheds light on the nature of the relationship between air pollutant exposure and KL-6 serum levels, which showed that an increase in air pollutant exposure will increase the level of KL-6 in the serum due to pathological processes in respiratory organs, particularly the lungs. It is worth mentioning that this finding reiterates the principle of environmental hazards. Exposure to air pollutants requires two major components to have an adverse effect on health: exposure time of sufficient duration and a concentration of air pollutants above the safety threshold.

The strength of this study lies in the assessment of KL-6 serum levels with ELISA, which meets international standards, but is still rarely used to detect respiratory organ disorders, particularly in Indonesia. However, this study is not without limitations. Although adequate for use in bivariate analysis, the relatively small sample size may have been insufficient to reflect an association among variables in the multivariate analysis. Moreover, the assessment of confounding variables was conducted with the data obtained in direct interviews with the study participants. This situation is likely prone to recall bias and may inaccurately reflect the actual conditions of the study participants.

CONCLUSIONS

This study found that individuals working in different settings experienced various degrees of air pollution and had different KL-6 serum levels. Although results from the bivariate analysis showed unexpected and nonsignificant correlations between air pollutant exposure and KL-6 serum levels, the effect of air pollutant exposure on KL-6 serum levels as an indicator of the pathological process in respiratory organs cannot yet be determined. Based on the results from multivariate analysis, it is likely that air pollutant exposure may increase KL-6 serum levels after adjusting for confounding variables. Further studies with a larger sample size, improved measurements of air pollutant levels, and a more precise assessment of confounding variables are still required to determine the link between levels of air pollution, duration of exposure, KL-6 serum levels, and other possible determinants, as well as the utility of KL-6 serum levels as a biomarker for lung disorders.

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