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SERUM METALLOPROTEINASE-3 (MMP-3) LEVELS IN PATIENTS WITH LUNG CANCER AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) and lung cancer are among the leading causes of mortality and share a similar genetic predisposition. COPD is recognized as a significant risk factor for lung cancer. Matrix metalloproteinases (MMPs) degrade the extracellular matrix (ECM) and contribute to tissue damage by activating cytokines such as tumor necrosis factor (TNF), thereby exacerbating inflammation and cellular damage characteristic of COPD pathogenesis. Several inclusion criteria were applied in this study, including healthy individuals as controls, patients diagnosed with lung cancer confirmed through histopathological examination, and lung cancer patients with coexisting COPD. Matrix metalloproteinase-3 (MMP-3) is a protein involved in cancer progression and is believed to

play a role in the transition from COPD to lung cancer. This descriptive observational study aimed to compare plasma MMP-3 levels among four groups: healthy individuals, lung cancer patients, COPD patients, and patients with both lung cancer and COPD. The study included 40 participants, selected using a total sampling technique. The findings revealed that plasma MMP-3 levels were lowest in the healthy group and elevated in the other groups. The increase in plasma MMP-3 levels among patients suggests a potential association between serum MMP-3 levels and the development of lung cancer in COPD patients. Abnormal MMP activity induces pathological metabolic cascades, which can trigger complex cellular changes leading to tumorigenesis. However, further research is required to better understand this relationship.

Keywords: Chronic Obstructive Pulmonary Disease, Lung Cancer, Matrix Metalloproteinase-3.

ABSTRAK

Penyakit Paru Obstruktif Kronik (PPOK) dan kanker paru merupakan dua penyakit dengan tingkat mortalitas tinggi yang memiliki predisposisi genetik serupa. PPOK diketahui sebagai faktor risiko signifikan terhadap kanker paru. Matriks metaloproteinase-3 (MMP-3) adalah protein yang berperan dalam perkembangan kanker dan berpotensi menyebabkan PPOK menjadi kanker paru. Studi observasional deskriptif ini bertujuan untuk membandingkan kadar MMP-3 plasma pada empat kelompok: individu sehat, pasien kanker paru, pasien PPOK, serta pasien dengan kanker paru dan PPOK. Jumlah sampel dalam penelitian ini adalah 40 orang dengan teknik total sampling. Hasil penelitian menunjukkan kadar MMP-3 plasma paling rendah terdapat pada kelompok sehat dan lebih tinggi pada kelompok lainnya. Peningkatan kadar MMP-3 plasma pada subjek menunjukkan terdapat potensi hubungan antara kadar MMP-3 serum dan perkembangan kanker paru pada pasien PPOK. Peningkatan aktivitas MMP, sebagai proses abnormal, menginduksi kaskade metabolik abnormal. Kaskade tersebut adalah sinyal yang memicu munculnya jalur sel abnormal yang kompleks, yang memunculkan sel fenotipe tumor/kanker.Namun, penelitian lebih lanjut diperlukan untuk memperjelas hubungan ini.

Kata kunci: Penyakit Paru Obstruktif Kronik, Kanker Paru, Matriks Metaloproteinase-3.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory condition characterized by persistent symptoms and an increased inflammatory response to harmful particles and gases. Currently, COPD affects approximately 8–10% of the adult population in developed countries and 15–20% of smokers. The World Health Organization (WHO) predicts that by 2030, COPD will become the third leading cause of death worldwide (Parris et al., 2019). Late-stage COPD cases have been identified to have a higher rate of disease progression to lung cancer. Lung cancer is one of the leading causes of death worldwide, causing more than 1.3 million deaths annually (Nader et al., 2019). COPD and lung cancer are respiratory disorders that can significantly affect an individual's ability to work. Many patients are forced to leave the workforce early due to disability or premature death (Pens et al., 2022). An estimated 400,000 deaths occur each year due to COPD, while the five-year survival rate for late-stage lung cancer patients is only 15.0%. Additionally, 85% of newly diagnosed lung cancer cases are associated with smoking. Recent studies indicate that COPD and lung cancer share a similar genetic predisposition (Friedlaender et al., 2020). Elastolysis, mediated by specific matrix metalloproteinases secreted by macrophages, plays a key role in the progressive decline of lung function in COPD patients (Christopoulou et al., 2023).

Matrix metalloproteinases (MMPs) contribute to extracellular matrix (ECM) degradation and tissue damage by activating cytokines such as tumor necrosis factor (TNF), thereby intensifying inflammation and cellular damage characteristic of COPD pathogenesis. Moreover, MMPs play a crucial role in cancer progression by facilitating proteolytic ECM degradation and disrupting cell-ECM interactions, thereby promoting invasion and metastasis (Nader et al., 2019). Homozygosity for the MMP-3 polymorphism has been identified as a potential marker of increased susceptibility to

lung cancer progression in COPD patients (Brzóska et al., 2014). Elevated MMP-3 levels have been observed in COPD patients, suggesting a strong likelihood of progression to lung cancer (Christopoulou et al., 2023). The main mechanisms linking COPD and lung cancer are oxidative stress, inflammation, genetic predisposition, epigenetics in lung cancer and COPD, extracellular vesicles (EVs), epithelial-mesenchymal transition (EMT), endothelial-mesenchymal transition (EndoMT), extracellular matrix (ECM), and angiogenesis. It is known that COPD is a risk factor for lung cancer, with a six times higher risk of developing lung cancer compared to smokers with normal lung function (Eapen et al., 2018). Therefore, further research is essential to evaluate plasma matrix metalloproteinase-3 (MMP-3) as a potential biomarker for predicting lung cancer in COPD patients.

The objectives of this study were to analyze the demographic characteristics of COPD and lung cancer patients, examine the distribution of MMP-3 levels in relation to lung cancer incidence in COPD patients, assess the correlation between MMP-3 levels and lung cancer type in COPD patients, and evaluate the association between MMP-3 levels and COPD severity in lung cancer patients.

METHOD

This descriptive observational study aimed to evaluate plasma MMP-3 levels in four groups: healthy individuals, lung cancer patients, COPD patients, and individuals with both lung cancer and COPD. Conducted over five months, the study employed a total sampling technique, which was chosen because when the population is fewer than 100 individuals, the entire population is included as the study sample. A total of 40 participants were included. The control group consisted of healthy individuals with normal spirometry and radiology results and aged over 40 years. The sample group included patients diagnosed with lung cancer through histopathological examination, lung cancer patients with COPD, and individuals aged over 40 years. Exclusion criteria encompassed individuals with systemic and/or autoimmune diseases such as rheumatoid arthritis or sepsis, other lung diseases, or HIV infection.

The diagnosis of COPD is established based on spirometry values, while the diagnosis of lung cancer is confirmed through histological testing. The data collected included age, performance status, cancer pain level, cancer stage, lung cancer type, Brinkman index, PUMA score, post-bronchodilator Forced Expiratory Volume in 1 second (FEV1)/ Forced Vital Capacity (FVC) ratio, and MMP-3 levels. MMP-3 analysis was conducted using the Human Total MMP DuoSet ELISA kit protocol. Patient data were obtained from medical records. In this study, each of the 2 variables was tested using the unpaired T test, but previously a normality test was carried out. In this study the analysis was carried out using a one way ANOVA test because there were more than 2 groups. This test was included in the parametric test so that the assumption of using a parametric test must be met, namely that the data was normally distributed. The next test was a post hoc test to see which was the most different between the 3 groups.

RESULTS AND DISCUSSION

This study was conducted from June to September 2024, with a total sample of 40 participants who met the inclusion criteria and were equally divided into four research groups. The sample characteristics by group are presented in table 1. All participants in this study were male. The age distribution was relatively balanced across categories within each group, although the cancer group was predominantly aged >60 years, whereas the COPD and cancer + COPD groups were primarily ≤60 years. The performance status of participants in the cancer and cancer + COPD groups was predominantly scored 1 and 2, while cancer pain waw mostly reported on a scale of on a score of 1-3. Among these groups, 85% were diagnosed with non-small cell lung cancer (NSCLC), with varying

stages of cancer, though stages IVA and IVB were the most common. Based on the Brinkman index, all groups were primarily categorized as moderate severe. However, when excluding the healthy group, 45% of participants in the non- healthy groups fell into the severe category. The same thing was also obtained in the PUMA score, where if the healthy group was excluded, the number of PUMA scores ≥6 is obtained as much as 97% of the entire non-healthy group. Table 2 presents the results of post bronchodilator (BD) FEV1/FCV spirometry and the average MMP-3 levels for each group. In the healthy group, which met one of the inclusion criteria, no abnormalities were found in the spirometry results, with post BD FEV1/FCV values exceeding 70% in all sampels. The highest average MMP-3 level was observed in the cancer group at 73.62, while the lowest was obtained in the healthy at 11.42. Tables 3 and 4 summarize the results of bivariate analysis, and the unpaired the results of the bivariate analysis, and the unpaired T-test results are detailed in Table 7.3. The T test in this study excluded the healthy group, except for the PUMA score. According to the table, all test items yielded p value> 0.05, indicating no statistically significant difference in the means. Data analysis using the One-Way ANOVA test initially did not meet the requirements for normal distribution and homogeneity. Therefore, data transformation was performed to satisfy these requirements. The One-Way ANOVA test revealed a statistically significant difference in the mean MMP-3 levels between all groups, with a p-value of 0.006. However, testing the mean MMP-3 between Brinkman index categories obtained a p-value of 0.146, which was not statistically significant. To further explore differences in mean MMP-3 levels between groups, a post-hoc analysis was conducted, as detailed in table 4

Table 1
Sample Characteristic

Item description	Healthy	COPD	Cancer	Cancer + COPD	Total
Age					
>70	-	-	1 (10%)	-	1 (2,5%)
61-70	1 (10%)	4 (40%)	5 (50%)	-	10 (25%)
51-60	4 (40%)	5 (50%)	2 (20%)	4 (40%)	15 (37,5%)
41-50	5 (50%)	1 (10%)	2 (20%)	6 (60%)	14 (35%)
Performance status					
1	-	-	5 (50%)	5 (50%)	10 (50%)
2	-	-	5 (50%)	2 (20%)	7 (35%)
3	-	-	-	3 (30%)	3 (15%)
4	-	-	-	-	-
Cancer pain					
1	-	-	-	5 (50%)	5 (25%)
2	-	-	5 (50%)	2 (20%)	7 (35%)
3	-	-	1 (10%)	3 (30%)	4 (20%)
4	-	-	3 (30%)	-	3 (15%)
7	-	-	1 (10%)	-	1 (5%)
Cancer type					
NSCLC	-	-	9 (90%)	8 (80%)	17 (85%)
SCLC	-	-	1 (10%)	2 (20%)	3 (15%)
Cancer stages					
IIIA	-	-	-	3 (30%)	3 (30%)
IIIB	-	-	1 (10%)	1 (10%)	2 (10%)
IVA	-	-	4 (40%)	3 (30%)	7 (35%)
IVB	-	-	4 (40%)	3 (30%)	7 (35%)
Extensive disease	-	-	1 (10%)	-	1 (5%)
Brinkman index					
Mild	5 (50%)	2 (20%)	1 (10%)	-	8 (20%)
Moderate	5 (50%)	5 (50%)	4 (40%)	4 (40%)	18 (45%)
Severe	-	3 (30%)	5 (50%)	6 (60%)	14 (35%)
PUMA score					
≥6	-	10 (100%)	9 (90%)	10 (100%)	29 (72,5%)
<6	10 (100%)	-	1 (10%)	-	11 (27,5%)

Table 2
Univariat Analysis of Each Group

	Healthy	COPD	Cancer	Cancer + COPD
Post BD VEP1/FCV				
< 70%	-	10 (100%)	-	8 (80%)
> 70%	10 (100%)		10 (100%)	2 (20%)
MMP-3 mean (mcg/dl)	11,42	64,10	73,62	51,01

The age of patients in the COPD and cancer + COPD groups was predominantly lower (≤ 60 years) compared to the the cancer groups. However, although given the small size of sample, this finding may not be statistically meaningful. According to a consensus from Asia, lung cancer screening is recommended for individuals aged 50 to 75 years with a smoking history of at least at least 20 packs-years (Lam et al., 2023). In Indonesia, lung cancer screening is recommended for individuals with high risk (heavy smokers, occupational/environmental exposure, family history) starting at the age of 40 years.

In this study, it was found that the performance status in the cancer and cancer + COPD groups was 50% at score 1, while the remaining patients had scores of 2 or 3. The performance status score might serve as an indicator of prognostic factors based on the patient's ability to perform daily activities and was designed to measure of impairment as a function of tumor burden (Lilenbaum et al., 2008). A score of 2-4 was generally interpreted as indicating poor performance status. The predominant type of cancer in this study was NSCLC, which accounted for 85% of case in both the cancer and cancer + COPD groups. NSCLC is the most common type of lung cancer (Parris et al., 2019). However, no studies heve been reported that specifically examine the relationship between COPD and lung cancer types.

Based on cancer stage, patients in the cancer and cancer + COPD groups were predominantly classified as stage IVA & IVB. High MMP expression is associated with poor survival, TNM stage and high metastasis (Wei, 2023). In this study, most of the samples had a severe Brinkman index category (45%). The Brinkman index, calculated as the number of cigarettes smoked per day multiplied by the number of years of smoking, is commonly used to estimate the cumulative dose of smoking. Cigarette smoking is one of the main risk factors for COPD and lung cancer. A high Brinkman index reflects the extent of smoke exposure, which contains carcinogenic component (Mulyawan & Setiawan, 2024). To date, no studies have directly reported a relationship between smoking and MMP-3. However, research has documented the effects of cigarette smoke exposure on other types of matrix metalloproteinases. Exposure to e-cigarette smoke has been shown to increase in matrix metalloproteinase-8 (MMP-8) expression while decreasing type-2 collagen expression in lung tissue (Suryadinata et al., 2022). Additionally, MMP-9 was thought to play a role in the pathogenesis of airflow obstruction caused by cigarette smoke. Another study reported that MMPs 1, 2, 7, and 9 were elevated in emphysema subjects and were associated with GOLD COPD grade criteria (Dimic-Janjic et al., 2023).

Respiratory diseases such as chronic bronchitis and emphysema have previously been reported to have a positive association with lung cancer development (Ahn et al., 2020). Other studies have reported the modulation of molecular pathways activated in emphysema conditions leads to the production of proteases that affect tumor growth and lung metastasis (Woode et al., 2015). Additionally, another study reported that the presence of emphysema and obesity in COPD increases the risk of lung cancer in COPD patients (Husebø et al., 2019). Based on these findings, COPD can be said to be one of the risk factors for lung cancer. In this study, the cancer group had a higher cancer

stage than the cancer + COPD group. It is possible that the cancer grups experienced more extensive tissue damage, which may have contributed to increased MMP-3 expression. However, the reason for the higher MMP-3 in n the COPD group compared to the cancer + COPD group remains unclear. In general, tissue damage that occurs in cancer + COPD cases is expected to be more extensive than pure COPD, yet in this study, higher MMP-3 expression was observed in the pure COPD group. Nevertheless, the mean difference in MMP-3 expression between pathological group was not statistically significant

Matrix metalloproteinase (MMP) activity was involved extracellular matrix (ECM) degradation, remodeling, and turnover, which under physiological conditions, contributes to homeostasis as part of ECM modulation. However, in cancer, homeostasis is disrupted, leading to extensive ECM alterations. Increased MMP activity, as part of abnormal process, induces dysregulated metabolic cascades. These cascades act as signals that trigger the emergence of complex, abnormal cell pathways, ultimately contributing to development of tumor or cancer phenotype cells. A study that reported elevated biomarker levels of MMP 1, 2, 7, and 9 in emphysema subjects, with associated to GOLD COPD grade criteria (Dimic-Janjic et al., 2023; Mahor et al., 2020). However, another study reported that MMP 1, 2, 7, 9, and 10 levels were not associated with emphysema (Tsay et al., 2020). Other studies have shown that MMP-3 increases in COPD, which causes worsening lung function due to excessive degradation of the extracellular matrix (Christopoulou et al., 2023). Overall, there is no strong evidence of the role of MMPs, including MMP-3, as reliable markers for evaluation or therapy of COPD or lung cancer. The complexity of these disease suggests that multiple factors their progression. In this study, MMP-3 levels in the pathological group were significantly elevated compared to the healthty subject. The use of MMP-3 as a therapeutic target in COPD and cancer still requires further research and cannot be the main therapeutic target considering the other biomarkers involved.

This study is a case-control study, where there are many confounding variables that might influence MMP-3 expression. The number of samples in this study is still small, which could result in bias in the results. Apart from that, there is no data regarding the history of the duration of the disease and its course in the pathological group. The timing of the diagnosis of COPD and cancer, or COPD + cancer, which were not included in this study, may be able to answer the variations in the mean differences found. A diagnosis of COPD that precedes cancer, or vice versa, may explain the reason for the variation in mean differences in MMP-3 found in this study. Factors that are directly or indirectly related to the variables studied should be excluded, or if not possible, tested simultaneously with multivariate analysis.

CONCLUSIONS AND SUGGESTIONS

Based on the results of the study, it can be concluded that serum MMP-3 levels increased in COPD, lung cancer, and combination of both compared to healty subject. The distribution of demographic characteristics varied in each study group. There is no relationship between MMP-3 levels and the stage, type of lung cancer, and COPD Severity.

ETHICAL CONSIDERATIONS

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Conflict of Interest Statement
The author reports no conflicts of interest in this work.

List of Abbreviations

Chronic Obstructive Pulmonary Disease (COPD); Matrix metalloproteinases (MMPs); Matrix Metalloproteinase-3 (MMP-3); World Health Organization (WHO); Extracellular Matrix (ECM); Tumor Necrosis Factor (TNF); Forced Expiratory Volume in 1 second (FEV1); Forced Vital Capacity (FVC); Non-Small Cell Lung Cancer (NSCLC)

REFERENCES

Ahn, S. V., Lee, E., Park, B., Jung, J. H., Park, J. E., Sheen, S. S., Park, K. J., Hwang, S. C., Park, J. B., Park, H.-S., & Park, J. H. (2020). Cancer development in patients with COPD: a retrospective analysis of the National Health Insurance Service-National Sample Cohort in Korea. *BMC Pulmonary Medicine*, *20*(1), 170. https://doi.org/10.1186/s12890-020-01194-8

Brzóska, K., Bartłomiejczyk, T., Sochanowicz, B., Cymerman, M., Grudny, J., Kołakowski, J., Kapka-Skrzypczak, L., Kruszewski, M., Śliwiński, P., & Roszkowski-Śliż, K. (2014). Matrix metalloproteinase 3 polymorphisms as a potential marker of enhanced susceptibility to lung cancer in chronic obstructive pulmonary disease subjects. *Annals of Agricultural and Environmental Medicine*, *21*(3), 546–551. https://doi.org/10.5604/12321966.1120599

Christopoulou, M. E., Papakonstantinou, E., & Stolz, D. (2023). Matrix Metalloproteinases in Chronic Obstructive Pulmonary Disease. *International Journal of Molecular Sciences*, *24*(4). https://doi.org/10.3390/ijms24043786

Dimic-Janjic, S., Hoda, M. A., Milenkovic, B., Kotur-Stevuljevic, J., Stjepanovic, M., Gompelmann, D., Jankovic, J., Miljkovic, M., Milin-Lazovic, J., Djurdjevic, N., Maric, D., Milivojevic, I., & Popevic, S. (2023). The usefulness of MMP-9, TIMP-1 and MMP-9/TIMP-1 ratio for diagnosis and assessment of COPD severity. *European Journal of Medical Research*, *28*(1), 127. https://doi.org/10.1186/s40001-023-01094-7

Friedlaender, A., Liu, S. V, Passaro, A., Metro, G., Banna, G., & Addeo, A. (2020). The Role of Performance Status in Small-Cell Lung Cancer in the Era of Immune Checkpoint Inhibitors. *Clinical Lung Cancer*, *21*(6), e539–e543. https://doi.org/10.1016/j.cllc.2020.04.006

Husebø, G. R., Nielsen, R., Hardie, J., Bakke, P. S., Lerner, L., D'Alessandro-Gabazza, C., Gyuris, J., Gabazza, E., Aukrust, P., & Eagan, T. (2019). Risk factors for lung cancer in COPD - results from the Bergen COPD cohort study. *Respiratory Medicine*, *152*, 81–88. https://doi.org/10.1016/j.rmed.2019.04.019

Lam, D. C.-L., Liam, C.-K., Andarini, S., Park, S., Tan, D. S. W., Singh, N., Jang, S. H., Vardhanabhuti, V., Ramos, A. B., Nakayama, T., Nhung, N. V., Ashizawa, K., Chang, Y.-C., Tscheikuna, J., Van, C. C., Chan, W. Y., Lai, Y.-H., & Yang, P.-C. (2023). Lung Cancer Screening in Asia: An Expert Consensus Report. *Journal of Thoracic Oncology : Official Publication of the International Association for the Study of Lung Cancer*, *18*(10), 1303–1322. https://doi.org/10.1016/j.jtho.2023.06.014

Lilenbaum, R. C., Cashy, J., Hensing, T. A., Young, S., & Cella, D. (2008). Prevalence of poor performance status in lung cancer patients: implications for research. *Journal of Thoracic Oncology : Official Publication of the International Association for the Study of Lung Cancer*, *3*(2), 125–129. https://doi.org/10.1097/JTO.0b013e3181622c17

Mahor, D., Kumari, V., Vashisht, K., Galgalekar, R., Samarth, R. M., Mishra, P. K., Banerjee, N., Dixit, R., Saluja, R., De, S., & Pandey, K. C. (2020). Elevated serum matrix metalloprotease (MMP-2) as a candidate biomarker for stable COPD. *BMC Pulmonary Medicine*, *20*(1), 302. https://doi.org/10.1186/s12890-020-01323-3

Mulyawan, E., & Setiawan, J. A. (2024). The correlation between smoking cumulative dose based on Brinkman Index with peak expiratory flow rate. *Journal of General and Family Medicine*, *25*(4), 193–197. https://doi.org/10.1002/jgf2.694

Nader, C. P., Cidem, A., Verrills, N. M., & Ammit, A. J. (2019). Protein phosphatase 2A (PP2A): A key phosphatase in the progression of chronic obstructive pulmonary disease (COPD) to lung cancer. *Respiratory Research*, *20*(1), 1–18. https://doi.org/10.1186/s12931-019-1192-x

Parris, B. A., O'Farrell, H. E., Fong, K. M., & Yang, I. A. (2019). Chronic obstructive pulmonary disease (COPD) and lung cancer: Common pathways for pathogenesis. In *Journal of Thoracic Disease* (Vol. 11, pp. S2155–S2172). AME Publishing Company. https://doi.org/10.21037/jtd.2019.10.54

Suryadinata, R., Wirjatmadi, B., Andriani, M., & Sri Sumarmi, M. (2022). The Expression Change of Mmp-8 and Collagen Type-2 Intracell in Lung Tissue Due to Electronic Smoke Exposure. *Jurnal Kesehatan Masyarakat*, *18*, 31–40. https://doi.org/10.15294/kemas.v17i2.26557

Tsay, J.-C. J., Hu, Y., Goldberg, J. D., Wang, B., Vijayalekshmy, S., Yie, T.-A., Bantis, K., Sterman, D. H., & Rom, W. N. (2020). Value of metalloproteinases in predicting COPD in heavy urban smokers. *Respiratory Research*, *21*(1), 228. https://doi.org/10.1186/s12931-020-01496-9

Wei, C. (2023). The multifaceted roles of matrix metalloproteinases in lung cancer. *Frontiers in Oncology*, *13*, 1195426. https://doi.org/10.3389/fonc.2023.1195426

Woode, D., Shiomi, T., & D'Armiento, J. (2015). Collagenolytic matrix metalloproteinases in chronic obstructive lung disease and cancer. *Cancers*, *7*(1), 329–341. https://doi.org/10.3390/cancers7010329