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## Original Research

# The Association of Plasma Asymmetric Dimethylarginine Concentrations and Inflammation Markers in Non-small Cell Lung Cancer

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### Abstract

**Objectives:** Non-small cell lung cancer (NSCLC) accounts for about 85% of all lung cancers. Asymmetric dimethylarginine (ADMA) is an emerging molecule that is highlighted in carcinogenesis and tumor progression in lung cancer. Since elevated concentrations of ADMA are observed in lung cancer patients, we aimed to explore its associations with inflammation markers and established prognostic indices.

**Methods:** 78 newly diagnosed non-small cell lung cancer patients who were presented with brain metastases at the initial admission and 41 Stage 1 patients with NSCLC were included in the study. ADMA concentrations among the groups were correlated. Further, the relationship between ADMA levels and the other inflammatory markers was analyzed.

**Results:** ADMA levels were significantly higher in the group of NSCLC patients with brain metastases than in the Stage 1 patients control group ( $p<0.001$ ). A significant negative correlation was found between ADMA levels and BMI, albumin and hemoglobin ( $p<0.001$ ), whereas it was positively correlated with platelet, WBC, neutrophil-to-lymphocyte ratio, RDW, RDW/albumin ratio, LDH, CRP, fibrinogen, platelet, and CRP/albumin ratio ( $p<0.001$ ).

**Conclusion:** Increased circulating concentrations of ADMA were significantly correlated with higher NLR, CRP and LDH; which were accepted as indicators of poor prognosis in NSCLC patients. ADMA might contribute to tumor growth and dissemination via systemic inflammatory pathways.

**Keywords:** Advanced lung inflammation index, asymmetric dimethylarginine, lung cancer

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Lung cancer is one of the leading causes of cancer-related deaths and non-small cell lung cancer type (NSCLC) constitutes approximately 85% of all cases.<sup>[1]</sup> As tobacco use is increasing all around the world, smoking leads to

80% of lung cancer deaths.<sup>[2]</sup> More than half of the patients with NSCLC cannot be often diagnosed until its advanced stages or developing distant metastases.<sup>[2]</sup> World Health Organization categorized the subtypes of NSCLC as adeno-

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carcinoma approximately 40%, squamous cell carcinoma 25-30%, and large cell carcinoma 5-10%.<sup>[3]</sup> Brain metastases occur in about one-third of NSCLC patients which indicates poor survival.<sup>[4]</sup> Approximately 10% of NSCLC patients have brain metastases at the time of initial diagnosis.<sup>[5]</sup> Lung cancer remains the most common cause of brain metastases and nowadays the improvement in magnetic resonance imaging makes us detect brain metastases easier than in the past.<sup>[4]</sup>

Tumor proteins and genes which contribute to tumor formation and prognosis are hot topics for investigation with regard to novel therapeutic options. Asymmetric dimethylarginine (ADMA) is a molecule that is generated daily as a by-product during cellular protein metabolism and an endogenous dose-dependent competitive inhibitor of nitric oxide synthase (NOS).<sup>[6]</sup> The endothelial form of NOS synthesizes endothelium-derived nitric oxide (NO) from L-arginine. NO has an imperative role in the regulation of vascular function besides its antiatherogenic and antiproliferative properties.<sup>[7,8]</sup>

The enzymes termed protein arginine methyltransferases (PRMTs) catalyze the reaction of methylation of arginine residues in which ADMA is produced.<sup>[9,10]</sup> 80% of ADMA is catabolized intracellularly by dimethylarginine dimethylaminohydrolase (DDAH) after uptake from the circulation and the rest is excreted by urine.<sup>[11,12]</sup> To date, ADMA's impact on endothelial dysfunction, cardiovascular disorders, stroke, chronic renal failure and fibrotic pulmonary diseases has been demonstrated in various clinical studies.<sup>[13-15]</sup> The protein arginine methylation has several cellular roles such as cell signaling, cell differentiation, apoptosis, ribonucleic acid (RNA) processing and deoxyribonucleic acid (DNA) damage response.<sup>[16]</sup> From this standpoint, accumulating data reveals that ADMA is involved in tumor growth progression and carcinogenesis.<sup>[17]</sup> These findings stemmed from recent studies in which patients with cancer have dramatically higher levels of ADMA than the control groups, even though the possible mechanisms are not fully identified.<sup>[18]</sup> In this study, our intention was to investigate ADMA and its associations with the other inflammatory markers in patients with NSCLC during the first admission.

## Methods

This was an observational study conducted in a tertiary care center in compliance with Helsinki Declaration after the ethical committee approved it. Between November 2019 and December 2023, newly diagnosed NSCLC patients who presented with brain metastases at the initial admission and treatment-naive Stage 1 NSCLC patients

were included in the study (using the 8th edition of the TNM classification).<sup>[19]</sup> Patients with active infections, other inflammatory/autoimmune diseases or having second malignancies were excluded. All the patients were informed about the study and a consent form was obtained from each participant.

Demographic characteristics, smoking status, and comorbidities of the patients were all recorded. The clinicopathological information, and positron emission tomography, cranial magnetic resonance imaging of the patients were extracted from the electronic medical records. Blood samples were drawn at the time of admission and examined for complete blood count, creatinine, albumin, lactate dehydrogenase (LDH), fibrinogen, and C-reactive protein (CRP). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters ( $\text{kg}/\text{m}^2$ ). We used several markers of systemic inflammation including red cell distribution width (RDW) to albumin ratio (RDW/albumin), CRP to albumin ratio (CAR) and absolute white cell and its components like neutrophil-to-lymphocyte ratio (NLR).

After a 12-hour fast, the patient's venous blood samples were collected into vacuum tubes for the measurement of ADMA. The samples were kept at room temperature for 2 hours, afterwards, they were centrifuged at +4 C for 15 minutes. The separated serums were stored at -80 C until the analysis was made by the method of enzyme-linked immunosorbent assay (ELISA).

## Statistical Analysis

SPSS 15.0 for Windows program was used for statistical analysis. In descriptive statistics; categorical variables were presented in numbers and percentages, and numerical variables were shown as mean, standard deviation, minimum, maximum and median. The rates in the groups were compared with the Chi-square test and Fischer's Exact test when the numerical variable satisfies the normal distribution condition, and two independent groups were compared with the Mann-Whitney U test when the normal distribution condition was not met. Kruskal Wallis analysis was used in comparing more than two independent samples. The linear relation between two continuous variables was assessed with Pearson correlation analysis. The statistical alpha significance level was considered as  $p < 0.05$ .

## Results

41 Stage 1 NSCLC patients (Group A) and 78 newly diagnosed NSCLC patients who presented with brain metastases (Group B) were enrolled in the study. As shown in Table 1 and Table 2, 70.5% (55) of patients with brain metastases

**Table 1.** The distribution of baseline characteristics of the groups

	Group A		Group B		X <sup>2</sup>	p
	n	%	n	%		
Gender						
Female	13	31.7	23	29.5	0.063	0.802
Male	28	68.3	55	70.5		
Comorbidity	31	75.6	69	88.5	3.308	0.069
Hypertension	8	19.5	21	26.9	0.801	0.371
CAD	8	19.5	36	46.2	8.185	<b>0.004</b>
DM	4	9.8	21	26.9	4.772	<b>0.029</b>
CRD	2	4.9	3	3.8	0.071	1.000
COPD	12	29.3	8	10.3	6.947	<b>0.008</b>
Smoking status						
Non-smoker	14	34.1	25	32.1	0.054	0.817
Current smoker	27	65.9	53	67.9		

Pearson Chi-Square, Fisher's Exact test; Group A: Stage 1 NSCLC patients Group B: NSCLC patients with brain metastases; CAD: Coronary Artery Diseases; DM: Diabetes Mellitus; CRD: Chronic Renal Diseases; COPD: Chronic Obstructive Pulmonary Diseases.

and 68.3% (28) of patients with Stage 1 NSCLC were males. The mean age for Group A was 65.71±8.66 (range 50-79) and for Group B was 64.64±8.3 (range 41-79). For Group A, the mean BMI was found as 24±1.5 (range 21.2-28.74) and 22.1±1.8 (range 18.2-28.1) for Group B. 67.9 % of metastatic patients and 65.9% of patients in Stage 1 NSCLC were current smokers.

The patients with Stage 1 NSCLC had higher rates of accompanying Chronic Obstructive Pulmonary Diseases whereas Coronary Artery Diseases and Diabetes Mellitus were higher among the patients with brain metastases (p<0.05). But as shown in Table 2, there was no statistically significant difference in the Charlson comorbidity index among the groups (p=0.843).

**Table 2.** The demographic characteristics and the laboratory findings of the patients

	Group A Mean±SD	Group B Mean±SD	Z	p
Age	65.71±8.66	64.64±8.32	-0.703	0.482
BMI kg/m <sup>2</sup>	24±1.5	22.12±1.88	-5.859	<b>0.000</b>
ADMA mol/L	628.03±416.55	2437.5±1714.47	-6.426	<b>0.000</b>
Albumin g/L	36.1±5.13	31.46±3.65	-4.769	<b>0.000</b>
Creatinine ng/dL	0.93±0.15	0.88±0.21	-1.581	0.114
CRP mg/L	8.65±10.36	15.04±8.55	-5.151	<b>0.000</b>
LDH u/L	214.24±40.97	262.18±71.82	-4.097	<b>0.000</b>
NLR	4.2±1.31	5.52±1.48	-5.004	<b>0.000</b>
RDW	12.3±0.87	13.18±1.13	-4.122	<b>0.000</b>
Hgb g/L	12.88±1.32	11.47±1.2	-4.885	<b>0.000</b>
Platelet 10 <sup>9</sup> /L	241.46±93.12	270.28±77.38	-1.742	0.081
WBC 10 <sup>9</sup> /L	7636.59±2638.82	9082.05±2254.16	-3.457	<b>0.001</b>
Eos%	2.54±1.82	2.08±1.55	-1.069	0.285
RDW/albumin	0.35±0.05	0.43±0.07	-5.690	<b>0.000</b>
Fibrinogen mg/L	339.51±41.83	448.6±86.64	-6.683	<b>0.000</b>
Charlson comorbidity index	3.07±1.08	3.12±1.18	-0.198	0.843
CAR	0.24±0.28	0.48±0.28	-5.525	<b>0.000</b>

Mann Whitney U analysis; Group A: Stage 1 NSCLC patients Group B: NSCLC patients with brain metastases; BMI: Body mass index kg/m<sup>2</sup>, ADMA: Asymmetric dimethyl arginine, CRP: C reactive protein, LDH: Lactate dehydrogenase, NLR: Neutrophil-to-lymphocyte ratio, RDW: Red cell distribution width, Hgb: Hemoglobin, WBC: White blood cell count, Eos %: Blood eosinophil %, CAR: CRP/albumin ratio; SD: Standard Deviation.

The mean BMI, and concentrations of albumin and hemoglobin of Group B were found to be statistically significantly lower than Group A ( $p < 0.001$ ). The levels of ADMA, CRP, LDH, RDW, platelet, white blood cell count, and fibrinogen were statistically significantly higher among the patients with brain metastases than the patients in Stage 1 NSCLC patients ( $p < 0.05$ ). Also the inflammation markers such as NLR, CAR, and RDW/albumin ratios were found to be statistically significantly higher in the metastatic NSCLC patients than the ones in Stage 1 ( $p < 0.05$ ) (Table 3).

Among the patients with brain metastases, a diagnosis of adenocarcinoma was made in 68 (87%), squamous cell carcinoma in 6 (7%), large cell cancer in 3 (3.8%), mucinous cancer in 1 (1.3%). 24 (58%) of patients with Stage 1 NSCLC were diagnosed as adenocarcinoma and 17 (41.5) were as squamous cell carcinoma.

Subsequently, we investigated the association between the levels of ADMA and the demographic and laboratory variables of the patients (Table 4).

There was a negative correlation between the levels of ADMA and BMI and hemoglobin values, and a positive correlation between CRP, LDH, NLR, platelet, fibrinogen, and CAR values which were statistically significant in patients with brain metastases ( $p < 0.05$ ).

When all the patients were analyzed, a negative correlation between the levels of ADMA and BMI, albumin and hemoglobin values, and a positive and statistically significant correlation between CRP, LDH, NLR, RDW, platelet, WBC, RDW/albumin, fibrinogen and CAR values were noted as well ( $p < 0.05$ ).

We found no correlation between the levels of ADMA and the laboratory variables of the patients in Stage 1 NSCLC ( $p > 0.05$ ).

## Discussion

Non-small cell lung cancer represents the leading cause of death from cancer worldwide and is more frequent in males.<sup>[1]</sup> In this current study, the plasma concentrations of ADMA were found significantly higher in NSCLC patients presented with brain metastases than the patients in Stage 1 NSCLC. ADMA is one of the three types of methyl arginines, a natural analog of L-arginine; basically produced by the enzyme PRMT via arginine methylation.<sup>[6]</sup> Yoshimatsu et al.'s study<sup>[17]</sup> included patients with various types of cancer which 33 cases had lung cancer, they demonstrated elevated levels of ADMA in cancer patients. They suggested that overexpression of PRMT1 led to an increase in ADMA concentration. ADMA is formed in all cells during protein turnover as a result of many cellular processes.<sup>[7]</sup> As new evidence of the pathological roles and oncogenic functions of protein arginine methylation are reported in the literature, the link between PRMT, ADMA and lung cancer is the focus of interest. Bayraktutan et al.<sup>[20]</sup> conducted a study in which they compared the levels of ADMA, NO and eNOS gene expression in healthy controls and patients with a diagnosis of lung cancer (including both SCLC and NSCLC), they showed the elevation of ADMA in patients with lung cancer. Their study stemmed from the influences of NO molecule in DNA modification and hypothesized that eNOS gene expression and increased levels of ADMA in plasma might play

**Table 3.** The distribution of ADMA levels based on histological subtype

Histological subtype	ADMA		X <sup>2</sup>	p
	Mean±SD	Median (Min.-Max.)		
Group A				
Squamous cell carcinoma	723.11±532.18	598 (256.1-2200)	0.793	0.673
Adenocarcinoma	552.27±311.97	419.52 (236.2-1233)		
Others	653.15±289.7	653.15 (448.3-858)		
Group B				
Squamous cell carcinoma	2677.72±1814.27	2033.9 (136.8-6009.7)	1.693	0.429
Adenocarcinoma	2381.82±1685.34	2033.9 (207.4-6885.6)		
Others	1363.5±1245.18	1056.4 (300.6-2733.5)		
Total				
Squamous cell carcinoma	1886.57±1726.33	1260.35 (136.8-6009.7)	0.89	0.641
Adenocarcinoma	1822.79±1646	1503.35 (207.4-6885.6)		
Others	1079.36±973.45	858 (300.6-2733.5)		

Kruskal Wallis H analysis; ADMA: Asymmetric dimethyl arginine; Group A: Stage 1 NSCLC patients Group B: NSCLC patients with brain metastases; SD: Standard Deviation; There was no statistically significant difference between the groups when ADMA levels were analyzed according to groups and histological subtypes ( $p > 0.05$ ).

**Table 4.** The correlation of ADMA levels and the laboratory variables of the patients

	ADMA					
	Total		Group A		Group B	
	r	p	r	p	r	p
Age	-0.017	0.852	0.116	0.471	0.006	0.957
BMI kg/m <sup>2</sup>	-0.476	<b>0.000</b>	0.096	0.549	-0.376	<b>0.001</b>
Albumin g/L	-0.254	<b>0.005</b>	-0.219	0.168	0.020	0.863
Creatinine ng/dL	-0.058	0.529	-0.118	0.463	0.014	0.901
CRP mg/L	0.479	<b>0.000</b>	0.051	0.751	0.515	<b>0.000</b>
LDH u/L	0.695	<b>0.000</b>	-0.091	0.572	0.713	<b>0.000</b>
NLR	0.610	<b>0.000</b>	-0.037	0.817	0.617	<b>0.000</b>
RDW	0.278	<b>0.002</b>	-0.251	0.114	0.143	0.212
Hgb g/L	-0.601	<b>0.000</b>	0.057	0.722	-0.616	<b>0.000</b>
Platelet 10 <sup>9</sup> /L	0.529	<b>0.000</b>	0.138	0.389	0.688	<b>0.000</b>
WBC 10 <sup>9</sup> /L	0.202	<b>0.027</b>	0.286	0.070	0.050	0.665
Eos%	-0.080	0.385	-0.167	0.297	0.008	0.942
RDW/Albumin	0.313	<b>0.001</b>	0.075	0.642	0.070	0.543
Fibrinogen mg/L	0.722	<b>0.000</b>	-0.029	0.856	0.651	<b>0.000</b>
Charlson comorbidity index	0.091	0.323	-0.015	0.927	0.119	0.300
CAR	0.518	<b>0.000</b>	0.063	0.696	0.494	<b>0.000</b>

Pearson correlation analysis; Group A: Stage 1 NSCLC patients Group B: NSCLC patients with brain metastases; ADMA: Asymmetric dimethyl arginine, BMI: Body mass index kg/m<sup>2</sup>, CRP: C reactive protein, LDH: Lactate dehydrogenase, NLR: Neutrophil-to-lymphocyte ratio, RDW: Red cell distribution width, Hgb: Hemoglobin, WBC: White blood cell count, Eos %: Blood eosinophil %, CAR: CRP/albumin ratio.

a role in the formation and progression of lung cancer. Besides, Bayraktutan et al.<sup>[20]</sup> observed higher concentrations of ADMA in their study participants with SCLC than NSCLC.

PRMTs play a vital role in diverse cellular processes including cell cycle progression, DNA damage and repair processes.<sup>[21]</sup> Several studies revealed overexpression or dysregulation of PRMT and increasing levels of ADMA in lung cancer.<sup>[22-24]</sup> To date, the possible mechanisms for the interaction between ADMA and lung cancer biology remain incompletely understood whereas, the contribution of PRMTs to the pathogenesis of lung cancer is clearly confirmed in a number of studies. The knockdown of PRMT1 and PRMT6 was shown to influence the pathways in the cell cycle and lead to the suppression of lung cancer cell growth in a study.<sup>[17]</sup> Smith et al.<sup>[25]</sup> demonstrated coronary artery endothelial cell gene expression in their study as a response to the increasing concentrations of ADMA. Moreover, ADMA was found to alter the expression of PRMTs in the same study. These pathways may be involved in the control mechanisms of ADMA in the pulmonary cell behavior also. Even though the molecular mechanisms for the link between ADMA and tumor growth remain unclear, in a very recent study, Malicka et al.<sup>[26]</sup> have confirmed the expression of ADMA within mammary tumor cells by histologi-

cal assessment and they have speculated that tumor cells are the main source of ADMA. ADMA was also found to be elevated in different types of hematological malignancies and colon cancer.<sup>[18,27]</sup>

ADMA is metabolized intracellularly by the enzyme DDAH, and overexpression of DDAH may lead to tumor neovascularization as ADMA functions as an endogenous inhibitor of angiogenesis.<sup>[28]</sup> When oxidative stress is induced in endothelial cells by stimuli like inflammatory cytokines, that may cause a decrease in DDAH activity and an increase in ADMA concentrations, as DDAH is highly sensitive to oxidative stress.<sup>[29]</sup> Moreover, as accumulated ADMA inhibits endothelial NOS, the reaction results in a shift from NO production to superoxide production, which in turn induces oxidative stress.

Wang et al.<sup>[30]</sup> demonstrated that in air pollution-exposed macrophages of animal lungs, ADMA administration triggered the inflammatory response and reactive oxygen species generation which in turn changed the antioxidant system of the airways. Aside from this, in an earlier study Liu et al.<sup>[31]</sup> reported increased levels of iNOS expression in NSCLC patients also with the exhalation of elevated levels of NO, where hypoxia was thought to stimulate iNOS expression, novel vessel generation and tumor necrosis.

Histopathologically, 85% of lung cancer are classified as non-small cell lung cancer and 15% are small cell lung cancer. As the early symptoms of lung cancer are not evident, more than half of the patients with lung cancer are already at an advanced stage and about 10%–20% of them have brain metastases when they are diagnosed.<sup>[3]</sup>

In all our patients with NSCLC, we showed that ADMA has been strongly correlated with the indicators of inflammation like NLR, RDW, RDW/albumin, fibrinogen, platelet, LDH, hypoalbuminemia, CRP and CAR which reflected the systemic host inflammation in cancer patients. These inflammatory parameters are known to play an important role in the cell-mediated destruction of tumor cells.<sup>[32-34]</sup> It is suggested that individuals who had higher levels of systemic inflammation at the time of diagnosis may have had more aggressive disease and should receive immediate and effective treatment.<sup>[35]</sup> Systemic inflammation is described as a condition that promotes tumor growth and cellular proliferation, induces angiogenesis and activates metastatic dissemination.<sup>[36]</sup> In chronically inflamed tissue, augmented macrophage recruitment and increased reactive oxygen species may constitute the tumor microenvironment and cancer may easily arise in this microenvironment.<sup>[36]</sup> The neutrophil-to-lymphocyte ratio has been shown to predict the progression of the disease in NSCLC patients.<sup>[37]</sup> Red blood cell size is reflected by the red cell distribution width (RDW), and it has been shown that an increase in RDW is strongly correlated with a response to inflammation, as bone marrow is stimulated to produce premature erythrocytes.<sup>[38]</sup> Moreover, RDW/albumin ratio and all-cause mortality in critically ill patients have previously been linked favorably in previous studies.<sup>[39]</sup> According to numerous studies, platelet activation plays a crucial role in metastasis and the development of cancer and thrombocytosis may occur in nearly half of the patients with solid tumors.<sup>[40]</sup>

Inflammation is also closely linked to cancer-related symptoms such as cachexia, pain and anorexia.<sup>[33]</sup> Impairment in nutritional status and changes in tumor-related inflammatory status are the characteristics of lung cancer. Systemic inflammation induces a catabolic state which causes immune dysregulation and subsequent cancer progression.<sup>[36]</sup> Consistent with the previous reports, the patients with brain metastases in our study group, had a lower BMI than the patients in Stage 1 NSCLC.<sup>[41]</sup>

In this current work, ADMA was correlated with low BMI and low hemoglobin values but increased NLR, CRP, fibrinogen, and LDH levels. All those variables were suggested as important determinants of oncologic outcomes in several studies.<sup>[42]</sup> It has been a well-known fact that chronic inflammatory response has contributed to the development

and the progression of tumors with the inflammatory cells including lymphocytes, and platelets.<sup>[43]</sup> As cancer triggers inflammation, it leads to the stimulation of pro-inflammatory cytokines and the synthesis of CRP in the hepatocytes.<sup>[44]</sup> CRP activates the complement system and alters the functions of the innate immune system.<sup>[45]</sup> CAR as a novel parameter, may reflect not only the inflammatory but also the nutritional status in patients with lung cancer.<sup>[46,47]</sup>

In the published literature, it was noted that the association between elevated levels of CRP and ADMA were indicating the shared mechanisms of inflammation in atherosclerosis which was demonstrated in published literature.<sup>[13]</sup> These findings may be commented on as ADMA contributes to the development of cancer through inflammatory pathways.

This study harbored some limitations; the sample size was small and the information about survival was not available during the study period. Nevertheless, our findings have clinical value regarding ADMA and the complex biochemistry of this molecule in lung cancer biology.

## Conclusion

We detected higher levels of ADMA in NSCLC patients who presented with brain metastases initially than the patients in Stage 1 NSCLC. Also, increased levels of ADMA were found to correlate with well-recognized inflammatory and prognostic markers in all the patients with NSCLC. As there are still many outstanding questions remain surrounding the role of methyl arginines in tumor growth and progression, prospective investigations will further characterize the biological significance of ADMA's functions in lung cancer development and dissemination.

## Disclosures

**Ethics Committee Approval:** The study was approved by the Sisli Hamidiye Etfal Training and Research Hospital Ethics Committee (date: 30.04.2019, no: 1234).

**Peer-review:** Externally peer-reviewed.

**Patient Informed Consent:** Oral consent were received from the individuals that participated in the study.

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