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Significance of N-terminal pro-B-type natriuretic peptide levels in lung cancer

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Abstract

High blood levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) have been shown in various malignancies. In lung cancer, the importance of NT-proBNP is not clear. In this study, we aimed to investigate the significance of the correlation of NT-proBNP levels in lung cancer with tumor stage, tumor diameter, histopathology, and specific sites of mediastinal metastasis: lymphadenopathy; pericardial, cardiac, major vessel, other mediastinal organ or lymphatic involvement/invasion.

A total of 105 lung cancer and 120 control patients (chronic obstructive lung disease, interstitial lung disease, pulmonary thromboembolism, and pneumonia; 30/subgroup) with measured NT-proBNP levels were included retrospectively. Demographics, comorbidities, and echocardiographic findings in all patients, as well as histologic subtype, diameter, stage, and radiologic and/or pathologic mediastinal involvement/invasion of the tumor to the mediastinum in patients with lung cancer, were studied with regard to blood NT-proBNP levels.

When lung cancer and control groups were compared globally or as subgroups with comorbidities, NT-proBNP levels did not show meaningful differences. However, NT-proBNP levels were determined to be 249 pg/mL and 88 pg/mL in lung cancer (n=68) and control subgroups (n=58) without comorbidities, respectively (p=0.001). Among lung cancer patients without comorbidities and those with cardiac, pericardial, major vascular, or other mediastinal involvement/invasion (lymphadenopathy, lymphatic, or other organ invasion) (n=27), the NT-proBNP level was 303 pg/mL, whereas it was 166 pg/mL in those without these mediastinal invasions (n=41) (p=0.031).

There is a need for much larger, randomized studies to obtain evidence for the potential role of NT-proBNP as a helpful diagnostic biomarker for lung cancer. Clinical suspicion of malignancy may be raised if high NT-proBNP levels cannot be explained by all other risk factors and disorders or diseases. Furthermore, pericardial, cardiac, major vessel, or other mediastinal invasion/involvement should be sought when high NT-proBNP levels are determined in lung cancer patients without any comorbidities or risk factors for high NT-proBNP levels.

Key words: lung cancer, N-terminal pro-brain natriuretic peptide, mediastinal invasion, comorbidity, tumor stage, tumor histology.

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Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide. The chances of curing lung cancer are closely associated with the disease stage during diagnosis. Therefore, early diagnosis of lung cancer is crucial, but the majority of patients are diagnosed at an advanced stage [1]. The tumor, node, and metastasis (TNM) staging system for lung cancer is an internationally recognized system, based on tumor size and location, involvement of lymph nodes at specific sites, and presence of metastases either intrathoracic (other lung, pleural or/and pericardial) or distant ones [2].

B-type natriuretic peptide (BNP) and the N-terminal prohormone of BNP (NT-proBNP) are released by cardiomyocytes in response to ventricular wall stretching due to pressure and volume overload. These hormones are potent biomarkers in various cardiovascular diseases: coronary artery disease, valvular heart disease, constrictive pericarditis, pulmonary hypertension, and congenital heart diseases [3,4]. The levels of BNP and NT-proBNP are influenced by various factors [4]. Increased levels of these biomarkers have been reported in renal diseases, neurological disorders, sepsis, pulmonary embolism, and cor pulmonale resulting from pressure overload and structural anomalies of the right ventricle [5-9].

Few studies have examined NT-proBNP levels in lung cancer and other malignant diseases [10-18]. Elevated NT-proBNP levels observed in these studies may be associated with chemoradiotherapy [14,19,20], tumor-related fluid overload, hyperviscosity [21], paraneoplastic syndromes [22], tumor metastases, and tumor-released vasoactive peptides [15,23-25]. A few studies have indirectly demonstrated that these peptides can be produced and released by malignant cells [15].

In this study, we investigated the significance of the correlation

of NT-proBNP levels in lung cancer with tumor stage, tumor diameter, histopathology, and specific metastatic sites: pericardial, cardiac, major vessel, or other mediastinal involvement/invasion (lymphadenopathy, lymphatic or other organ invasion).

Materials and Methods

The data of the patients followed up at our hospital from January 2010 to September 2017 were retrospectively analyzed following approval from the ethics committee of our hospital (5840, 21.08.2017). This study was conducted in accordance with the Declaration of Helsinki. We did not use artificial intelligence-assisted technologies (such as large language models, chatbots, or image creators) in the production of the submitted work.

The study group included 105 patients with histopathologically diagnosed lung cancer, and the control group included 120 patients, with 30 in each of four subgroups (Figure 1), for all of whom NT-proBNP levels, cardiology consultation, and echocardiographic reports were already available in the digital records. In all patients in the lung cancer and control groups, only the NT-proBNP levels before specific oncological treatment or specific treatments in the control group were taken into consideration for this study.

The chronic obstructive pulmonary disease (COPD) subgroup was diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease 2017 [26]. The interstitial lung disease (ILD) subgroup was diagnosed based on thoracic computed tomography and/or histopathology of bronchoscopic biopsy. The pulmonary thromboembolism (PTE) subgroup had thromboembolism-induced filling defects in the main/lobar/segmental pulmonary arteries on computed tomography pulmonary angiography, alongside compatible clinical findings. The pneumonia subgroup was diagnosed based on clinical, laboratory, and radiological findings.

In all patients, the relationships between NT-proBNP levels and demographic characteristics, comorbidities, and echocardiographic findings were analyzed. In the lung cancer group, histological subtype, tumor diameter, involvement/invasion of mediastinum (lymphadenopathy; heart, pericardium, major vessels, other organ or lymphatic invasion) based on radiological and/or pathological examination, and tumor stage according to the eighth TNM staging were examined in relation to NT-proBNP levels.

In all patients within the lung cancer and control groups, the presence/absence of heart failure (HF) or other heart disorder had already been confirmed through cardiology consultation, echocardiographic findings, and clinicoradiological assessments as obtained from the patient charts and digital records. During the study period, verification was requested from a cardiologist based on digital records and patient charts, where necessary.

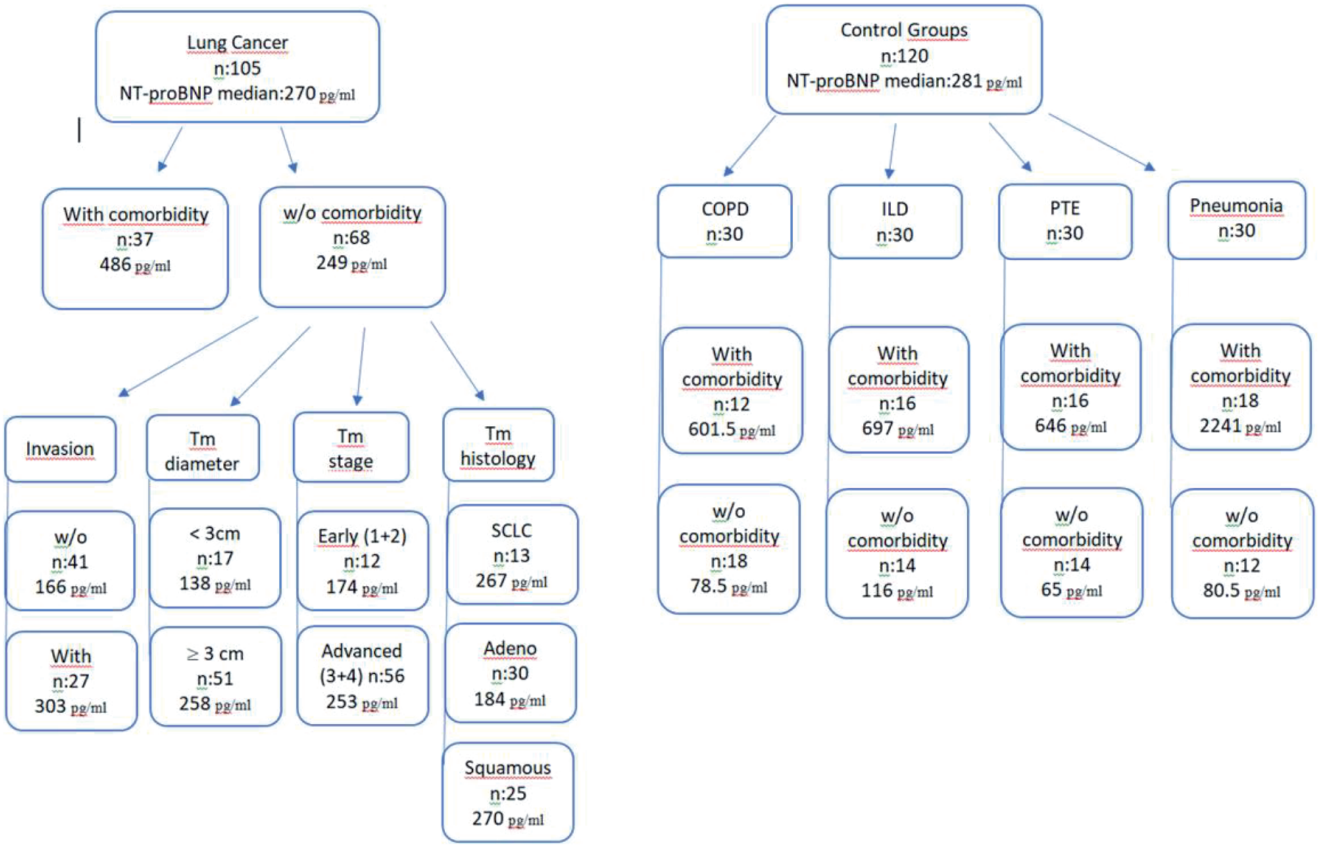

Figure 1. The flowchart shows the study design and the number of patients and N-terminal pro-B-type natriuretic peptide levels in lung cancer group, the control group, and their subgroups. NT-proBNP, N-terminal pro-B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; PTE, pulmonary thromboembolism; mediast., mediastinal; tm, tumor; SCLC, small cell lung cancer; Adeno, adenocarcinoma; Squamous, squamous cell carcinoma; w/o, without.

Comorbidities included heart disease, hypertension, diabetes mellitus, thyroid disease, neurological and renal diseases, cor pulmonale, obesity, and malignancies other than lung cancer. As some patients in the lung cancer and control groups were not clinically stable regarding comorbidities, NT-proBNP levels in the subgroups with and without comorbidities were analyzed and compared.

The absence of any of the following data led to the exclusion of the patient from the study: i) NT-proBNP measurement within the period from 1 month before to 1 month after the definitive diagnosis; ii) NT-proBNP measurement before treatment (chemotherapy, radiotherapy or surgery for lung cancer, and specific treatments for the diseases in control subgroups); iii) a histopathological diagnosis of lung cancer, iv) Cardiology consultation and/or echocardiography findings. Patients aged >75 years were also excluded.

The upper limit of normal for NT-proBNP level was considered 125 pg/mL, with levels >125 pg/mL classified as high [27]. Serum NT-proBNP level was measured by ECLIA (electrochemiluminescence immunoassay) using an Elecsys 1010/2010 analyzer (Roche Diagnostics, Mannheim, Germany) on an E170 device by the sandwich method.

Statistics

Statistical analysis was performed using the IBM SPSS 22.0 for Windows (SPSS Inc, Chicago, IL) program. For categorical data, a contingency table was generated, and a chi-square analysis was conducted. A *t*-test was used to compare normally distributed numerical variables between the two groups. Non-normally distributed numerical variables were compared using the Mann–Whitney *U* test or Kruskal-Wallis analysis. A p-value <0.05 was considered statistically significant. Receiver operating characteristic (ROC) curve analysis was used to determine the NT-proBNP threshold level. Descriptive statistics included numbers and percentages for categorical variables, and the numerical variables were expressed as median (minimum–maximum) or arithmetic mean ± standard deviation.

Results

Of the patients included in the study, 167 (74.2%) were males; 58 (25.8%) were females. The mean age of the lung cancer group was 64±8.1 years, and 84.8% were male, whereas the mean age of the control group was 62.2±11.6 years, and 65% were male. No differences were found between the lung cancer and control groups in terms of age and gender (Table 1).

In the ROC curve analysis for the NT-proBNP levels in the study groups, the area under the curve value was 0.621 (close to 0.5) and not sufficient to determine a cut-off value. Therefore, a cut-off value was not calculated for the lung cancer and control groups.

In both the lung cancer and control groups, there was no difference in NT-proBNP levels between patients under and over 50 years or 60 years of age (p>0.05).

Comorbidities were present in 99 cases (44%). A higher number of comorbidities was observed in the control group (n=62, 51.7%) compared to that in the lung cancer group (n=37, 35.2%) (p=0.013). The highest number of patients was observed in the heart disease group [congestive HF (CHF), coronary artery disease, and valvular heart disease] (n=59, 26.2%). There were 32 (30.5%) and 27 (22.5%) patients with heart disease in the lung cancer and control groups (p=0.175), respectively. A total of 14 (11%) patients in the lung cancer group and 31 (25.8%) in the control group were diagnosed with hypertension (p=0.019) (Table 1).

The study and control groups were analyzed regarding the presence of left HF as well as pulmonary hypertension and/or right HF caused by respiratory failure due to COPD, ILD, PTE, and pneumonia. At least one was present in four (3.8%) patients in the lung cancer group and 25 (20.8%) in the control group (p<0.001) (Table 1).

Comparison of lung cancer and control groups in total and according to comorbidity

The median serum NT-proBNP values in patients with lung cancer and those in control were analyzed (Figure 1). The NT-proBNP

Table 1. Patient demographics and comorbidities in total lung cancer group, the total control group and control subgroups.

	Control subgroups				Total control group (n=120), n (%)	Lung cancer group (n=105), n (%)	p*
	COPD (n=30), n (%)	ILD (n=30), n (%)	PTE (n=30), n (%)	Pneumonia (n=30), n (%)			
Gender, F Gender, M	8 (6.6) 22 (18.3)	12 (10) 18 (15)	11 (9.1) 19 (15.8)	11 (9.1) 19 (15.8)	42 (35) 78 (65)	16 (15.2) 89 (84.8)	0.996
Age (mean±SD)	63.8±8.38	60.4±13.7	59.7±16.1	58.5±15.9	62.2±11.6	64±8.1	0.177
Heart disease	2 (1.66)	7 (5.83)	6 (5)	12 (10)	27 (22.5)	32 (30.5)	0.175
HT	3 (2.5)	7 (5.83)	5 (4.16)	16 (13.33)	31 (25.8)	14 (13.3)	0.019
DM	3 (2.5)	4 (3.3)	5 (4.16)	8 (6.66)	20 (16.7)	12 (11.4)	0.262
Thyroid disease	1 (0.83)	1 (0.83)	1 (0.83)	1 (0.83)	4 (3.3)	2 (1.9)	0.507
Neurological disease	0	0	0	1 (0.8)	1 (0.8)	1 (1)	0.924
Renal disease	0	0	0	0	0	1 (1)	0.284
Cor pulmonale	7 (5.83)	12 (10)	6 (5)	0	25 (20.8)	4 (3.8)	<0.001
Other malignancies	0	1 (0.83)	1 (0.83)	0	2 (1.7)	3 (2.9)	0.546
Obesity	1 (0.83)	1 (0.83)	2 (1.)	0	4 (3.3)	2 (1.9)	0.507
Total comorbidities	12 (10)	16 (13.33)	16 (13.33)	18 (15)	62 (51.7)	37 (35.2)	0.013

F, female; M, male; SD, standart deviation, DM, diabetes mellitus; HT, hypertension; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; PTE, pulmonary thromboembolis; NT-proBNP, N-terminal pro-B-type natriuretic peptide; *p-values show the comparisons between total control and total lung cancer groups.

level was 270 pg/mL (n=105) in the lung cancer group and 281 pg/mL (n=120) in the control group (p=0.885).

When the groups were analyzed according to comorbidities, the NT-proBNP level was comparable (486 pg/mL) in the lung cancer group with comorbidities (n=37) to that (914 pg/mL) in the control group with comorbidities (n=62) (p=0.155) (Table 2). However, when patients with comorbidities that could affect NT-proBNP were eliminated, the NT-proBNP level was significantly higher (249 pg/mL) in the lung cancer group without comorbidities (n=68) than that (88 pg/mL) in the control group without comorbidities (n=58) (p=0.001) (Table 2).

Comparison of lung cancer subgroups with and without comorbidities

The median NT-proBNP level was 249 pg/mL in the lung cancer group without comorbidities (n=62) and 486 pg/mL in that with comorbidities (n=37) (p=0.003). In the control group, NT-proBNP levels were also higher in patients with comorbidities compared with those without comorbidities (Figure 1 and Table 3).

Comparison of noncomorbid lung cancer subgroups with and without mediastinal involvement

The lung cancer patients without comorbidities (n=68) were analyzed according to the presence of mediastinal involvement/invasion; tumor diameter (<3 cm and ≥3cm); cancer stage; and histopathological subtypes [squamous, adenocarcinoma, small cell lung cancer (SCLC)] (Figure 1).

The NT-proBNP level was 303 pg/mL in patients with lung cancer invading the heart, pericardium, major vessels, or with other mediastinal involvement/invasion (lymphadenopathy, lymphatic or other organ invasion) (n=27), and was 166 pg/mL in those without mediastinal involvement/invasion (n=41) (p=0.031) (Table 4).

Comparisons by tumor size, early/advanced stage, site/number of metastasis, and histopathology

The NT-proBNP level was 258 pg/mL in patients with a tumor diameter ≥3 cm (n=51) and 138 pg/mL in those with a tumor diameter <3 cm (n=17) (p=0.075). However, 78.4% (n=40) of patients with a tumor diameter ≥3 cm and 58.8% (n=10) of those with a tumor diameter <3 cm had an NT-proBNP level above the threshold. This insignificant difference of 20% was attributed to the small sample size.

The patients were further divided into early (stages 1 and 2) and advanced (stages 3 and 4) stages. The NT-proBNP value was 174 pg/mL in stages 1 and 2 (n=12) and 253 pg/mL in stages 3 and 4 (n=56) (p=0.330) (Table 4). There were no statistically significant differences in NT-proBNP levels in stage 4 patients regarding the site or number of metastases (p>0.05).

Evaluation of the lung cancer patients without comorbidity according to histopathologic subtypes showed 13 (19.1%) SCLC, 30 (44.1%) adenocarcinoma, and 25 (36.7%) squamous cell lung can-

Table 2. Comparison of N-terminal pro-B-type natriuretic peptide levels between lung cancer and control subgroups with comorbidities and between those without comorbidities.

		NT-proBNP median levels (pg/mL) (min-max), n (%)		p
		Lung cancer group	Control group	
Comorbidity	(+)	486 (29-35000), 37 (35.2)	914 (13-22701), 62 (51.7)	0.155
	(-)	249 (20-3063), 68 (64.8)	88 (10-5787), 58 (48.3)	0.001
Total		270 (20-35000), 105	281 (10-22701), 120	0.885

NT-proBNP, N-terminal pro-B-Type natriuretic peptide.

Table 3. Comparison of N-terminal pro-B-type natriuretic peptide levels between the subgroups with and without comorbidities within the lung cancer group and within the control subgroups.

		NT-proBNP median levels (pg/mL) (median-min/max)		p
		With comorbidities	Without comorbidities	
Lung cancer (n=105)		486 (29-35,000) (n=37)	249 (20-3063) (n=68)	0.003
Control	COPD (n=30)	601.5 (17-2575) (n=12)	78.5 (10-1120) (n=18)	0.016
	ILD (n=30)	697 (13-20,808) (n=16)	116 (17-5787) (n=14)	0.020
	PTE (n=30)	646 (61-8926) (n=16)	65 (10-710) (n=14)	0.001
	Pneumonia (n=30)	2241 (91-22,701) (n=18)	80.5 (27-1399) (n=12)	0.001

NT-proBNP, N-terminal pro-B-type natriuretic peptide; PTE, pulmonary thromboembolism; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease.

Table 4. N-terminal pro-B-type natriuretic peptide levels according to mediastinal invasion, tumor diameter, and stage in the lung cancer subgroup without comorbidities.

	With comorbidities NT-proBNP median (min/max)	Without comorbidities NT-proBNP median (min/max)	p
Mediastinal invasion (lymphadenopathy, cardiac, pericardial, major vascular, other mediastinal organ or lymphatic invasion)	303 (40-3063) (n=27)	166 (20-1704) (n=41)	0.031
Tumor diameter (≥3 cm)	258 (40-3063) (n=51)	138 (20-573) (n=17)	0.075
Tumor stage (3+4)	253 (20-3063) (n=56)	174 (40-573) (n=12)	0.330

NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table 5. N-terminal pro-B-type natriuretic peptide levels according to histological subtypes in lung cancer subgroup without comorbidities.

	NT-proBNP median level, pg/mL (min-max)	p
SCLC (n=13)	267 (57-1016)	
Adenocarcinoma (n=30)	184 (20-1704)	0.208
Squamous cell carcinoma (n=25)	270 (53.6-3063)	

NT-proBNP, N-terminal pro-B-type natriuretic peptide; SCLC: small cell lung cancer.

cer cases. The NT-proBNP level was 267 pg/mL in SCLC, 184 pg/mL in adenocarcinoma, and 270 pg/mL in squamous cell lung cancer (p=0.208) (Table 5).

Comparison of small cell lung cancer and non-small cell lung cancer groups in total and by the absence of comorbidity

The comparison of the NT-proBNP levels in SCLC (n=19) and non-small cell lung cancer (NSCLC) groups (n=86) showed no significant difference [267 pg/mL (29-1016) *vs.* 277 pg/mL (20-35000), respectively; p=0.790]. Similarly, when the subgroups of SCLC (n=13) and NSCLC (n=55) without comorbidities were compared [267 (57-1016) *vs.* 204 pg/mL (20-3063), respectively], there was no significant difference (p=0.628).

Comparisons within non-small cell lung cancer by early/advanced stages, and by tumor diameter in early stage (stage 1+2) in the total groups and noncomorbid subgroups

There were no significant differences between the early stage (stage 1+2) (n=18), stage 3 (n=44) and stage 4 (n=24) within the total NSCLC group regarding NT-proBNP levels [178 pg/mL (40-1112), 418.5 pg/mL (48-35000), 211 pg/mL (20-2252), respectively (p=0.226)].

Similarly, between the subgroups with a tumor diameter of <3 cm (n= 10) and ≥3 cm (n=8) within the total group of early stage NSCLC, the NT proBNP levels did not show a significant difference [162 pg mL 1 (80-1112), 264 (40-920), respectively (p=0.300)].

No significant difference was found also between the early stage (stage 1+2) (n=12), stage 3 (25), and stage 4 noncomorbid NSCLC subgroups (n=18) [174 pg/mL (40-573), 250 pg/mL (53-3063), 156.5 pg/ mL (20-1704) pg/ mL, respectively (p= 0.632)].

The subgroups with a tumor diameter <3 cm (n=6) and ≥3 cm (n=6) within the early stage noncomorbid NSCLC group did not differ significantly [221 pg/mL (83-573), 170 pg/mL (40-342), respectively (p=0.7367]].

Comparisons within small cell lung cancer by limited/extensive stage in the total group and noncomorbid subgroup

Between the limited (n=3) and extensive stages (n=16) of the total SCLC group, the NT-proBNP levels were comparable [258 pg/mL (138-325), 276 pg/mL (29-1016), respectively (p=0.798)].

Between the limited (n=2) and extensive stages (n=11) within the noncomorbid subgroup of SCLC, the NT-proBNP levels were also comparable [198 pg/mL (138-258), 303 pg/mL (57-1016), respectively (p=0.204)].

Discussion

Our study yielded two key findings. First, NT-proBNP levels were significantly higher in lung cancer patients without comorbidities compared to those in control patients without comorbidities. Second, among patients with lung cancer without comorbidities, those with mediastinal involvement/invasion (lymphadenopathy; cardiac, pericardial, major vascular, other mediastinal organ or lymphatic invasion) had higher NT-proBNP levels than those without.

In parallel to these findings of our study, Aujollet *et al.* found that in patients with lung cancer without risk factors that might affect NT-proBNP levels, NT-proBNP levels were seven-fold higher than in those without cancer [10]. Lafaras *et al.* reported that NT-proBNP levels increased because of restrictive-type cardiomyopathy secondary to cardiac/pericardial metastases in NSCLC [12]. In our study, three patients with lung cancer and elevated NT-proBNP levels had pericardial and cardiac invasion, with only one of them having CHF.

The NT-proBNP levels in the entire lung cancer group and control group were comparable. This result can be attributed to the fact that each group was mixed with comorbidities/risks, causing confounding results regarding NT-proBNP levels. When the patients with risk factors/comorbidities were eliminated in both groups, the lung cancer group had a significantly higher NT-proBNP level. The same approach of excluding patients with comorbidities/risk factors for elevated NT-proBNP levels in lung cancer and control groups was used in quite a number of pertinent studies [10,13,28,29], and higher NT-proBNP levels were determined in lung cancer groups [10,13].

Some previous studies suggest that BNP, with results similar to NT-proBNP [30], leads to a reduction in distant metastases by inhibiting the production of collagen 1 and fibronectin proteins along with cell proliferation induced by TGF-β, which plays a role in tumor invasion and metastasis in NSCLC [31,32]. In contrast, another study involving 80 patients with various malignancies found elevated NT-proBNP levels, particularly in those with advanced cancer. Thus, NT-proBNP was suggested as a marker for the advanced stage and prognosis [13]. In the current study, we did not study the effect of NT-proBNP on the prognosis of lung cancer. However, lung cancer patients without any comorbidities/risks for high NT-proBNP levels but with mediastinal involvement/invasion (stage 3B) had higher NT-proBNP levels than those without, which might suggest higher NT-proBNP levels in the advanced stage with worse prognosis. Our study cannot confirm the relationship between high NT-proBNP and prognosis, as we have not analyzed survival or mortality. In studies on lung cancer and other malignancies, higher levels of NT-proBNP have been shown in more extensive, advanced, metastatic, or progressive disease with worse prognosis and shorter survival [28,29,33].

The current study found no difference in NT-proBNP levels between patients with early-stage (stage 1-2, n=12) and advanced-stage (stage 3-4, n=56) lung cancer. The lack of a significant increase in NT-proBNP levels in advanced stages may be attributed to the limited number of patients in the early stage or the heterogeneity in the tumor inhibitory effect of NT-proBNP [13,31,32]. Furthermore, there were no significant differences in NT-proBNP levels in stage 4 regarding the site and number of metastases.

In the lung cancer group without comorbidities, there was no significant difference in NT-proBNP values between those with a tumor diameter ≥3 cm and those with a tumor diameter <3 cm. The 20% insignificant difference between the NT-proBNP levels exceeding the upper limit of normal in tumors ≥3 cm (78.4%) and in those <3 cm (58.8%) may be attributed to the small sample size. To our knowledge, there is no study directly assessing the NT-proBNP levels according to the size of primary lung cancer or other malignancy.

In our study, further analyses were performed to show the differences between the NSCLC and SCLC groups and between particular stages in NSCLC and SCLC separately regarding NT-proBNP levels. No significant differences were found between NSCLC and SCLC groups, and between their subgroups without comorbidities. The comparisons between TNM stages 1+2, stage 3, and stage 4 within the total NSCLC group, as well as comparisons between these stages within the noncomorbid NSCLC subgroup, did not show any significant differences. Similarly, the NT-proBNP levels did not show significant differences between the subgroups with a tumor diameter of <3 cm and ≥3 cm within the total group or noncomorbid subgroup of early-stage NSCLC. Comparisons within SCLC, between limited and extensive stages in the total and noncomorbid subgroups, were comparable with no significant differences. These nonsignificant differences between NSCLC and SCLC, between stages within NSCLC or SCLC, and between tumor sizes within early-stage NSCLC might be due to the small number of cases in the subgroups.

Ohsaki *et al*. suggested that SCLC cells release BNP by demonstrating BNP mRNA in SCLC cells [15]. In another study, high NT-proBNP levels were found in lung cancer other than SCLC [10]. In our study, lung cancer patients without comorbidities were categorized into histopathological subgroups: adenocarcinoma, squamous cell lung cancer, and SCLC. In each of these histological subtypes, NT-proBNP levels were elevated. However, when the histological subgroups were compared, no significant difference in NT-proBNP levels was observed. Our results suggest that NT-proBNP levels may also be elevated in histological subtypes of lung cancer other than SCLC. However, the subgroups are too small to derive a definite conclusion.

A recent study reported an association between high NT-proBNP levels and an increased risk of breast, prostate, and colorectal cancers [34]. Another study found that high NT-proBNP levels were associated with disease severity as an independent risk factor for ultra-high-risk in newly diagnosed multiple myeloma patients [35].

In patients with multi-organ malignancies, those with hematologic malignancies often have very high levels of NT-proBNP (>50,000 pg/mL). This has been attributed to hyperviscosity resulting from paraproteinemias observed during the disease prognosis, frequent blood transfusion, and fluid overload secondary to cardiac dysfunction caused by systemic amyloidosis [21]. In contrast, Burjonroppa *et al*. argued that there was no relationship between high BNP levels and volume overload or left ventricular diastolic dysfunction in cancer patients with multiple comorbidities [11]. In the current study, we also found that among lung cancer patients without comorbidities, NT-proBNP was elevated in those without evidence of fluid overload based on echocardiography and physical examination findings.

The reason for elevated NT-proBNP levels in lung cancer patients and those with other organ malignancies has not yet been established through evidence-based findings, but is suggested through indirect results. The causes may include tumor-related fluid overload and an increase in hydrostatic pressure due to major mediastinal vessel and/or heart invasion or compression, and a decrease in lymphatic drainage due to mediastinal lymphadenopathy. Other related causes might be hyperviscosity, paraneoplastic syndromes, tumor metastases, various mechanisms related to cytokines, vasoactive peptides, and growth factors released from tumor cells, or the production of NT-proBNP by malignant cells [15,21-25]. Treatment of lung cancer and other malignancies by chemotherapy, radiotherapy, or surgery can also affect the NT-proBNP levels. In patients with a favorable or stable response, NT-proBNP levels are lower than in those with progressive disease [28,29]. On the other hand, cardiotoxicity due to chemotherapy or other oncological treatments can lead to high NT-proBNP levels [28,36].

The limitations of the current study include its retrospective design, absence of a healthy control group, performance in a single center, and the small sample sizes, particularly in the subgroups, which may have affected the obtention of strong statistical findings and results.

As high NT-proBNP levels have been shown mostly in advanced stages of lung cancer, the value of NT-proBNP in the era of thoracic computed tomography scan and lung cancer screening can be questioned. However, the exact mechanism of the elevated natriuretic peptides is not clear yet in lung cancer and other malignancies. They may be produced by cancer cells and may also decrease the number of cancer cells by inhibiting vasculogenesis. Although currently providing no use as a screening tool in early-stage lung cancer, NT-proBNP can be a useful marker in monitoring the disease, determining extension of the tumor, and checking the effect and toxicity of therapy [13,18,37]. On the other hand, inflammatory conditions are generally present prior to a malignant change, and an oncogenic process produces a microenvironment of inflammation promoting tumor development. Several pro-inflammatory cytokines (tumor necrosis factor-α and interleukins) may stimulate NT-proBNP synthesis before oncogenic change. Based on this mechanism, the use of NT-proBNP as a potential screening molecular marker in early-stage lung cancer can be investigated [13,38].

Larger, prospective, multicentric, and randomized controlled trials are needed to explore the relationship between lung cancer and NT-proBNP more accurately and reliably by investigating all possible aspects related to the tumor and its treatment.

Conclusions

Thoracic malignancy, primarily lung cancer, can be considered in cases with clinical suspicion and high NT-proBNP levels that cannot be explained by other risk factors and diseases. Furthermore, pericardial, cardiac, major vessel, or other mediastinal organ invasion, mediastinal lymphadenopathy, or a tumor invading/compressing lymphatics that causes a decrease in lymphatic drainage should be sought when high NT-proBNP levels are determined in lung cancer patients without any comorbidities or risk factors for high NT-proBNP levels.

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