ACTA FACULTATIS
MEDICAE NAISSENSIS

UDC: 616.24-006.6-07
DOI: 10.5937/afmnai39-35741

Original article

Could Nucleolin and Nucleophosmin Levels Be Prognostic Indicators in Non-Small Cell Lung Cancer?

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SUMMARY

Aim: Lung cancer is the leading cause of mortality from cancer across the world. In this study, the use of serum nucleolin (NCL) and nucleophosmin (NPM1) levels as a marker in the diagnosis, prognosis and treatment response evaluation in lung cancer was investigated.
Materials and Method: NCL and NPM1 levels of serum samples taken before chemotherapy and after 3-4 courses of chemotherapy from the control group and the patients diagnosed with lung cancer were studied using ELISA method.
Results: Serum NCL and NPM1 levels of the patients were higher than of the controls ($p = 0.085$ for NCL, $p = 0.000$ for NPM1). NCL and NPM1 levels by histopathologic type were significantly higher in adenocarcinoma than in squamous cell carcinoma ($p < 0.05$ for each). In view of the treatment responses to chemotherapeutic agents, there was a statistically insignificant difference between the values before and after chemotherapy ($p > 0.05$ for each).
Conclusion: High serum NCL and NPM1 levels were found to correlate with poor prognosis, poor treatment response and low survival rate. It can be concluded that serum NCL and NPM1 levels in lung cancer can be used as diagnostic and prognostic markers for the disease.

Keywords: **cancer, nucleolin, nucleophosmin**

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INTRODUCTION

Lung cancer is the leading cause of death from cancer across the world (1) and comprises 18% of all cancer deaths. The percentage of non-small cell lung cancer (NSCLC) among lung cancers is about 83% (2). Although a wide range of treatments, such as chemotherapy, radiotherapy, and radical surgery are available for lung cancer patients, the 5-year survival rate of lung cancer has remained below 18% (3).

The nucleolin, called NCL or C23, is one of the amplest proteins, accounting for about 10% of nucleolar proteins. NCL plays a key role in nucleolar chromatin remodeling, pre-RNA maturation, rDNA transcription, and ribosome splicing (4). It also has an important function in numerous physiological processes, including the regulation of cell proliferation, survival and apoptosis, especially in cancer cells. NCL on cell surface of malign cells has been shown to be capable of binding specifically to ligands to regulate cancer progression. Expression of NCL in cancer cells was reported to be excessive, with the extent of NCL expression correlating with cancer prognosis (5).

Nucleophosmin (otherwise referred to as NPM1, B23, No38, numatrin) is a phosphoprotein localized primarily in the nucleolus (6). Being a crucial cellular protein involved in a series of pathways, such as mRNA transport, chromatin remodeling, genome stability and apoptosis, NPM1 plays important roles in the response to various stress stimulators. It is typically overexpressed in solid tumors, being associated with mitotic index and metastasis in most cases (7). Thus, both NCL and NPM1 might be new targets in monitoring cancer progression and improving diagnosis and treatment of cancer.

Identification of new markers and approaches that can be used in differentiation of malignant and benign lesions is very important for strengthening and reliability of diagnostic success. To our knowledge, there is no study in the literature that has investigated serum nucleolin and nucleophosmin levels, which can be used as an indicator of the proliferative and metabolic activity of cells in lung cancer patients. In our study, we investigated whether serum NCL and NPM1 levels established by ELISA method correlate with prognosis, treatment response and lower survival in NSCLC patients.

PATIENTS AND METHODS

A total of 69 people, including 34 diagnosed with lung cancer and 35 from the control group, were recruited for the study. The study was approved by the Ethics Committee of Duzce University Medical Faculty with the decision number of 2020/02, date of 02.03.2020. The patients were divided into subgroups by the eighth edition of the tumor, node, and metastasis (TNM) classification (8). The response status of the patients was evaluated according to RECIST 1.1 (“Response Evaluation Criteria in Solid Tumors) (9). While patients with complete response, partial response and stable disease were grouped as "responders", patients with progressive disease were grouped as "no response". While overall survival (OS) is the time from the date of first diagnosis to the date the files were scanned for surviving patients, it is the time elapsed from the date of the first diagnosis to death for deceased patients. The progression-free time/time till progression (TTP) was defined as the time from the date of diagnosis to progression of patients in the current study.

Demographic characteristics, clinical and laboratory results of the patients were determined. Blood samples were collected from 35 healthy people and 34 patients with NSCLC after diagnosis but prior to any treatment. Serum samples were collected from the patient group after they received 3 - 4 cycles of chemotherapy. For this purpose, the blood samples of individuals were promptly centrifuged at 1500 g for 15 minutes and the supernatant stored at − 80°C until study time.

The serum concentrations of NCL and NPM1 were determined by a commercial, two-site, sandwich-type ELISA (eBioscience, China).

In statistical evaluation of the data, the distribution of continuous variables was examined using the Shapiro-Wilk and Kolmogrov-Smirnov tests. Based on the distribution of data, Mann-Whitney U test was used to compare two groups, and Kruskal-Wallis tests was used to compare disease stages and more than two groups. Also, polynomial regression analysis was performed. The SPSS v.22 software package was used to perform statistical analyses, and significance level was specified as 0.05.

RESULTS

Mean age of the study subjects was 63.9 years in the patient group and 57.4 years in the control group. Fifteen (44%) patients were diagnosed with adenocarcinoma (AC) and 19 (56%) with squamous cell carcinoma (SCC). When stages of the patients were examined by the eighth TNM, 18 (53%) patients were in stage 3 and 16 (47%) were in stage 4. When the patients were grouped by tumor size (T), 10 patients (29.4%) were T1-2 and 24 (70.6%) were T3-4, and when they were grouped by lymph node metastases (N), 28 (82.4%) patients had lymph node metastasis and 6 (17.6%) patients had none. At the end of the study, file records and hospital computer system were used to check whether the patients were alive or not. At the end of the study, it was concluded that 11 patients (32%) had passed away.

Pre-chemotherapy serum NPM1 levels of the patient group were significantly higher than in the

Table 1. *Correlation between serum levels of nucleolin and nucleophosmin in NSCLC and clinicopathological features of patient samples*

	n	NCL median (min-max) ng/dl	P	NPM1 median (min-max) ng/dl	P
Patient group	34	19.78 (13.99-26.77)	0.085	19.95 (15.99-24.35)	< 0.001*
Control group	35	17.29 (11.00-24.92)		14.32 (9.93-20.81)	
AC	15	21.58 (18.75-30.43)	<0.001*	22.42 (18.86-26.08)	0.008*
SCC	19	17.62 (12.37-22.05)		19.16 (14.65-22.25)	
T1-2	10	19.65 (12.46-35.10)	0.955	21.14 (18.78-23.80)	0.364
T3-4	24	19.80 (5.96-35.00)		19.50 (7.67-26.94)	
N0	6	19.05 (10.51-19.66)	0.354	18.09 (10.51-19.69)	0.022*
N1-3	28	20.21 (5.96-35.10)		21.14 (7.67-26.94)	
M0	18	19.78 (9.86-35.0)	0.691	19.65 (7.67-26.94)	0.814
M1	16	20.21 (5.96-35.10)		19.95 (16.78-26.10)	

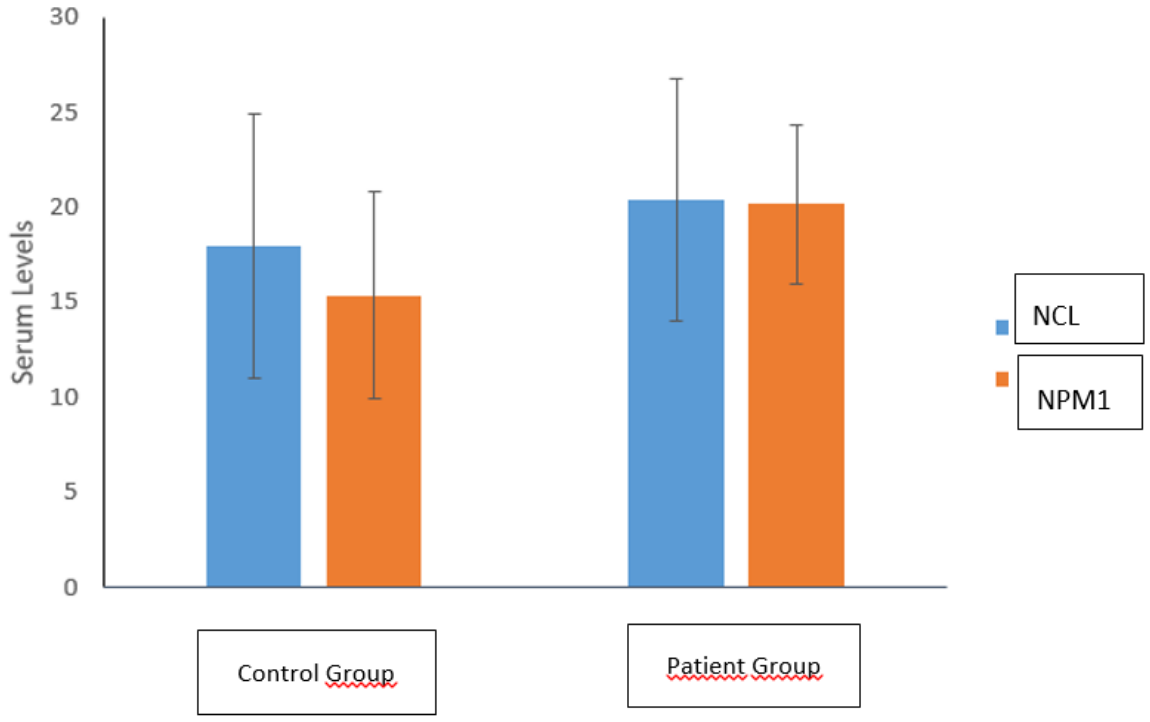

Figure 1. *A graph showing NCL and NPM1 serum levels of control and patient groups*

healthy control group ($p < 0.001$). Although serum NCL levels were higher in the patient group vs the control group, this difference was statistically insignificant ($p > 0.05$) (Table 1) (Figure 1).

In view of histopathologic subgroups and pre-chemotherapy serum NCL, NPM1 levels of the patients, serum NCL, NPM1 levels of patients diagnosed with AC were statistically significantly higher than in patients diagnosed with SCC ($p < 0.05$ each) (Table 1).

Table 2. *Correlation between serum NCL and NPM1 levels before chemotherapy and after 3-4 courses of chemotherapy*

		Pre-chemotherapy levels Median (min-max) ng/dl	Levels after 3-4 courses of chemotherapy Median (min-max) ng/dl	P
NCL	Responders (n:24)	19.72(5.96-35.10)	19.25(10.90-41.00)	0.123
	Non-responders (n:10)	20.99 (14.18-31.16)	21.27(15.54-42.0)	0.575
NPM1	Responders (n:24)	19.82 (7.67-26.90)	18.67 (6.44-43.61)	0.543
	Non-responders (n:10)	20.44 (16.78-26.94)	20.00(9.58-28.50)	0.799

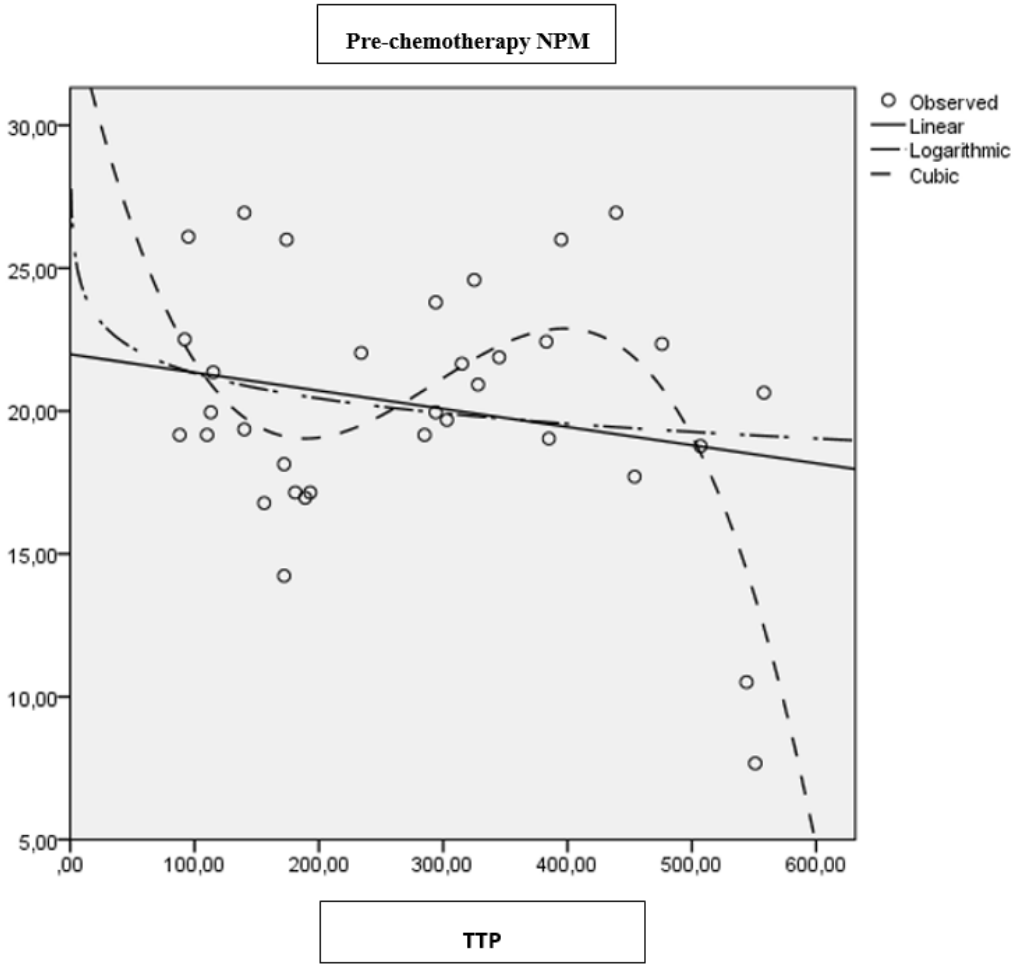

Figure 2. *Correlation between serum NPM levels before chemotherapy (pre-chemotherapy NPM) and time to progression (TTP)*

The patients were divided into two groups as responders after chemotherapy (full, partial or stable) and non-responders (those that progressed), and their serum NCL and NPM1 levels before chemotherapy and after 3-4 courses of chemotherapy were studied. No statistically significant difference was identified between serum NCL and NPM1 levels of the patients before chemotherapy and after 3-4 courses of chemotherapy, however, the levels of these molecules decreased in the group responding to chemotherapy, whereas the levels of these molecules were stable or increased in non-responding group (Table 2).

The levels of NCL and NPM1 molecules increased in patients with metastatic lymph nodes compared to those without, and such difference was statistically significant for serum NPM1 level ($p < 0.05$). Moreover, serum NCL and NPM1 levels were higher in patients with metastasis than in patients without them and the difference was statistically insignificant ($p > 0.05$) (Table 1).

In the correlation analysis made between pre-chemotherapy serum NCL levels of the patients and both TTP and OS, statistically significant correlations were not found ($p > 0.05$, r: 0.055; $p > 0.05$, r: 0.027, respectively). Additionally, the post-chemotherapy serum NCL levels of the patients and both TTP and OS were considered and statistically significant correlations were not found ($p > 0.05$, r: 0.019; $p > 0.05$, r: 0.008, respectively).

In the correlation analysis made between pre-chemotherapy serum NPM1 levels of the patients and TTP, serum NPM1 level significantly increased with decreasing TTP ($p < 0.05$, r: -0.351) (Figure 2). No statistically significant correlation was found between pre-chemotherapy serum NPM1 levels and OS ($p > 0.05$, r: 0.076). Additionally, the post-chemotherapy serum NPM1 levels of the patients and both TTP and OS were considered and statistically significant correlations were not found ($p > 0.05$, r: 0.048; $p > 0.05$, r: 0.005, respectively).

DISCUSSION

NCL was discovered to play a vital role in nucleolar chromatin remodeling, pre-RNA maturation, rDNA transcription, and ribosome splicing (5). NCL was shown to serve a critical function in numerous physiological processes, including the regulation of cell proliferation, survival and apoptosis, especially in cancer cells and to be capable of binding specifically to ligands to regulate progression of cancer; it was detected in certain types of cancer (4).

Hsu et al.'s study on levels of tissue NCL expression identified that the nucleolin splits to form C-terminal nucleolin (TNCL) in lung cancer, that TNCL is capable of increasing expression of MMP9, anaplastic lymphoma kinase (ALK) and HIF1a and reducing expression of tumor suppressor genes by regulating mRNA. They identified higher NCL expression in tissues with lung cancer versus normal lung tissue, and demonstrated that high NCL expression correlates with poor prognosis in lung cancer patients (10). Zhao et al. stated that nucleolin expression in tumor tissues of surgically resected NSCLC patients might be a negative prognostic factor for OS (11). Zuang et al.'s study showed that the expression of nucleolin in tumor tissue of NSCLC patients increased compared to normal lung tissue, being associated high nucleolin expression with increased lymph node metastasis and low OS (12). Xu et al.'s study reported that high NCL expression in NSCLC tissues are independent prognostic factors for both TTP and OS, with no statistically significant difference identified between histopathological subtypes in terms of NCL expression (13).

NPM1 is a vital cellular protein involved in a series of pathways, including mRNA transport, chromatin remodeling, genome stability and apoptosis, which plays a crucial role in responding to various stress stimulators. Abnormal expression of NPM1 has been shown to affect prognosis in various cancers. Previous evidence reveals that high expression of NPM1 in tissues is a marker correlating with poor prognosis for glioblastoma, oral squamous cell carcinoma, hepatocellular carcinoma, bowel cancer, ovarian cancer, and uterine cancer (14).

Sekhar et al.'s study identified a higher NPM1 level in tumor tissues of NSCLC patients than in normal tissues (15). He et al. proved that high NPM1 expression in tumor tissue of AC patients correlates with high disease stage and low differentiation and that patients with high NPM1 levels have low chemotherapy sensitivity (16). Zohou et al. found that high NPM1 expression in neoplasms of AC patients correlates with lymph node metastasis, poor overall survival and advanced stage, and noted that NPM1 expression is more sensitive and specific than TTF1 expression in tumor tissues diagnosed with AC (17).

Both nucleolin (NCL) and nucleophosmin (NPM1 are AgNOR proteins. The studies about the use of these protein as biomarkers in xeroderma pigmentosum group E (18), hypoxic damage caused by testicular torsion (19), different doses of carbon monoxide poisoning in brain (20) and both heart tissue (21, 22) and lung (23), ST-elevation myocardial infarction (24), clinical exacerbation of chronic obstructive pulmonary disease (25), colon adenocarcinoma (26), Ehrlich's ascitic carcinoma (27, 28), oncocytology (29), fine-needle aspiration samples of thyroid (30), cytologic discrimination of follicular thyroid lesions (31), discrimination of benign thyroid nodules and normal thyroid tissue (32) in non-diagnostic fine needle aspiration samples (due to insufficient cell groups) of thyroid nodules (33), comparison of fine needle aspiration biopsy and paraffin embedded tissue sections (34), renal ischemia/reperfusion (I/R) injury (35), hair root cells of humans at different developmental stages and sex (36), human hair loss (37, 38), buccal epithelial cells of healthy individuals (39), developmental stages of Down syndrome infants (40), peripheral blood lymphocytes of babies/children with Down syndrome (41), wound healing (42) etc. were done.

Previous studies in the literature have investigated NCL and NPM1 levels in tissues, and our study is the first to investigate the serum NCL and NPM1 levels in NSCLC and healthy control groups. In our study, higher serum NCL and NPM1 levels were detected in NSCLC patients than in healthy control group (for NCL $p > 0.05$; for NPM $p < 0.05$). Previous tissue studies observed no significant difference in NCL expression between histopathologic subtypes (13). In our study, patients diagnosed with AC had higher NCL and NPM1 levels than those diagnosed with SCC ($p>0.05$). Such difference between serum NPM1 levels of AC and SCC patients has not been investigated in previous tissue studies, therefore, our result is important because it is the first finding reported in the literature. This result suggested that serum levels of these molecules could be used in diagnostic stage and histopathologic subtype differentiation of lung cancer.

Zuang et al. suggested that high tissue NCL levels correlate with increased lymph node metastasis in NSCLC cancer (12). Subgroup analyses in our study revealed that serum NCL levels were high, though statistically insignificant in patients with metastatic lymph nodes or metastatic distant organs. Previous studies investigating the tissue NPM1 levels reported that high NPM1 expression correlates with poor overall survival, metastatic lymph nodes and advanced stage (16, 17). In our study, serum NPM1 levels of patients with metastatic lymph nodes were significantly higher than in patients without ($p < 0.05$). Moreover, serum NPM1 levels of patients with metastasis were higher than in patients without them, with statistically insignificant difference. In the correlation analysis made between serum NPM1 level and TTP, serum NPM1 level increased with decreasing TTP, which suggested that high serum NCL and NPM1 levels identified before chemotherapy could be an indicator of poor prognosis.

To our knowledge, our study is the first to evaluate the correlation between serum NCL and serum NPM1 levels, chemotherapy response and prognosis in NSCLC. In this study, the relationship between chemotherapy response, serum NCL levels before chemotherapy and after 3 - 4 courses of chemotherapy was investigated. Serum NCL and NPM1 levels before chemotherapy were higher in the group responding to treatment versus the group not responding, which implied that high serum NCL and NPM1 levels might be associated with poor chemotherapy response and poor prognosis. Serum NCL vs NPM1 levels before chemotherapy of the group responding to treatment were lower, though not statistically significant, than those after 3 - 4 courses of chemotherapy, whereas such levels remained stable or increased in the group not responding. This finding implies that serum NCL and NPM1 levels could be used to assess a response to chemotherapy and predict prognosis.

CONCLUSION

In view of the literature, our study is the first to evaluate the correlation between serum NCL-NPM1 levels and chemotherapy response and prognosis in NSCLC. In the light of these data, we consider that serum NCL and NPM1 levels that are monitored consecutively could be used as markers in the assessment of response to chemotherapy and prediction of prognosis.

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Article info

Received: January 4, 2022
Revised: July 29, 2022
Accepted: October 12, 2022
Online first: December 12, 2022

Da li nivoi nukleolina i nukleofosmina mogu biti prognostički indikatori karcinoma malih ćelija pluća?

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SAŽETAK

Cilj. Karcinom pluća je vodeći uzrok smrtnosti širom sveta. U ovoj studiji ispitivana je upotreba nivoa nukleolina (NCL) i nukleofosmina (NPM1) u serumu, kao markera kod uspostavljanja dijagnoze, prognoze i procene odgovora na lečenje karcinoma pluća.
Bolesnici i Metode. Korišćenjem ELISA metode ispitivani su nivoi nukleolina i nukleofosmina u uzorcima seruma, uzetim pre hemioterapije i nakon tri četiri ciklusa hemioterapije, kod kontrolne grupe i bolesnika kod kojih je dijagnostikovan karcinom pluća.
Rezultati. Nivoi serumskog nukleolina i nukleofosmina bili su viši kod bolesnika nego u kontrolnoj grupi ($p = 0,085$ za NCL, $p = 0,000$ za NPM1). Nivoi NCL i NPM1 po histološkom tipu bili su značajno povišeni kod adenokarcinoma u poređenju sa karcinomom skvamoznih ćelija ($p < 0,05$, kod oba). U pogledu odgovora na hemoterapijske agense zabeležena je statistički beznačajna razlika između vrednosti pre i posle hemioterapije ($p > 0,05$ za obe vrednosti).
Zaključak. Utvrđeno je to da su visoki nivoi NCL i NPM1 u serumu u korelaciji sa lošom prognozom, lošim odgovorom na terapiju i niskom stopom preživljavanja. Može se zaključiti da se nivoi NCL i NPM1 kod karcinoma pluća mogu koristiti kao dijagnostički i prognostički markeri bolesti.

Klučne reči: **karcinom, nukleolin, nukleofosmin**