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KLİNİK ÇALIŞMA
RESEARCH ARTICLE

High serum YKL-40 level is associated with poor prognosis in patients with lung cancer

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SUMMARY

High serum YKL-40 level is associated with poor prognosis in patients with lung cancer

Introduction: *YKL-40 is a glycoprotein that plays role in inflammation and malignant processes. High serum YKL-40 levels are associated with short survive in cancer and chronic obstructive pulmonary disease (COPD) is another reason to increase its' level. However, limited knowledges are known in YKL-40 along with lung cancer and COPD.*

Materials and Methods: *One hundred patients were involved to study with lung cancer (84 men, 16 women, and median age 62). Results were compared with 30 healthy volunteers. Thirteen patients were small cell lung cancer (SCLC), 87 patients were non-small cell lung cancer (NSCLC). 62% of patients were inoperable.*

Results: *Median YKL-40 level was 222.7 ± 114.1 ng/mL in patients and was 144.5 ± 105.7 ng/mL in controls (p< 0.001). Stage,*

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tumour size, lymph node involvement and distant metastasis weren't associated with serum YKL-40 level. Above all cut-off values (133.159 and 162 ng/mL) survival was shorter (p> 0.05). Patients with COPD had worse survive above all cut-off values (p< 0.05), especially according to 133 ng/mL (p= 0.01).

Conclusion: *YKL-40 level is useful in lung cancer however it's not related to cell type and prognosis. It is associated with poor prognosis in lung cancer patients with COPD.*

Key words: *Lung cancer; chronic obstructive pulmonary disease; prognosis; YKL-40*

ÖZET

Yüksek serum YKL-40 düzeyi akciğer kanserinde kötü prognozla ilişkilidir

Giriş: *YKL-4 inflamasyon ve malign süreçlerde rol oynayan bir glikoproteindir. Yüksek YKL-40 düzeyi inflamasyonda görüldüğü gibi kanserde kısa yaşam beklentisiyle ilişkilidir. Akciğer kanseri ve kronik obstrüktif akciğer hastalığı (KOAH)'nın serum YKL-40 düzeyi ile ilişkisinin birlikte incelendiği yayın sayısı kısıtlıdır.*

Materyal ve Metod: *Çalışmaya 84 erkek ve 16 kadın olmak üzere 100 hasta dahil edildi. Yaş ortalaması 62 idi. Sonuçlar 30 sağlıklı gönüllü ile karşılaştırıldı. Hastalardan 13 tanesi küçük hücreli akciğer kanseri (KHAK) 87 küçük hücre dışı akciğer kanseri (KHDAK) tanısı aldı. Yüz hastanın 42'sinde KOAH eşlik ediyordu.*

Bulgular: *Hasta grupta ortalama YKL-40 düzeyi 229 ± 110.7 ng/mL iken kontrol grubunda 114.5 ± 105.7 ng/mL saptandı (p< 0.001). Evre, tümör çapı, nodal infiltrasyon ve uzak metastazla YKL-40 düzeyi arasında ilişki saptanmadı. Tüm eşik değerler üzerinde (133.159 ve 162 ng/mL) yaşam süresi daha kısa bulundu (p> 0.05). Özellikle 133 ng/mL'ye göre KOAH tanılı 42 hastada KOAH olmayanlara göre yaşam süresi anlamlı derecede daha kısaydı (p= 0.01).*

Sonuç: *YKL-40 akciğer kanserinde yararlı bir belirteç ancak hücre tipi ve yaşam süresiyle ilişkisiz. KOAH'ın eşlik ettiği akciğer kanserli hastalarda ise yüksek serum düzeyleri kötü prognozla ilişkili bulunmuştur.*

Anahtar kelimeler: *Akciğer kanseri; kronik obstrüktif akciğer hastalığı (KOAH); prognoz; YKL-40*

INTRODUCTION

In cancer treatments new therapy options are needed to be developed to improve survive. Recently some biomarkers were discussed whether they can allow new treatment modalities in cancer like agents against growth factors and their receptors (1). YKL-40 is a newly defined marker expressed by both malignant and non-malignant cell has role in tumour and inflammatory processes. Several solid tumour cells produce YKL- 40 such as breast, colon, lung, kidney, prostate. Myelocyte series, chondrocytes and fibroblasts secrete YKL-40 as non-malignant cells causing increased serum YKL-40 levels during inflammatory process (2).

However its function in malignant process hadn't been shown with in vivo studies yet, YKL-40 may play role in proliferation, differantiation, angiogenesis and inhibition of apoptosis. According to twenty retrospective studies, serum YKL-40 concentration is exactly 10 times higher than healthy group. There is no well-defined cut-off value because it depends on methodology of studies and types of malignancies. YKL-40 isn't a specific marker for a particular cancer but when we analyse twenty retrospective studies (2). One prospective study about gliomas (overall 2543 patients) is suggestive for survival (3). But depending on the current studies; some cancer cells don't secrete YKL-40. This indicates the variation of tumour cell biological behaviour. According to all these data's; we can't use YKL-40 for diagnosis or during follow up period in a specific kind of malignancy (2).

In lung cancer, serum YKL-40 level is expected to be increased like other malignancies. Especially in advanced non-small cell lung cancer (NSCLC) high serum levels are associated with poor prognosis. In a study with 189 NSCLC (88% advanced stages) patients, cut-off value was calculated 209 ng/mL. Above this value surveys were extremely low (32 weeks versus 41 weeks). So it was a statistically significant prognostic factor in advanced NSCLC (4). In an another study with 61 NSCLC patients' cut-off value was 165 ng/mL and survey analyses were statistically significant. (In high serum levels survey was seven months, in the low group survey was 18 months). Also this study revealed the correlation with performance status and YKL-40 level (5). SCLC is less frequent type of lung cancer but extensive disease has a median survival duration of 6 months. There is no routinely used serological biomarker to detect SCLC earlier. Although it is not a specific biomarker, YKL-40 has been discussed in a study for SCLC with 131 patients. In extensive disease YKL-40 level was higher than limited disease. High serum YKL-40 level had been associated with poor prognosis within the 6 months after starting the chemotherapy (6).

In this study we planned to evaluate YKL-40 level for all subtypes of lung cancer by considering all stages. Due to YKL-40 is important in inflammatory process, we have discussed results taking into account presence of choronic obstructive pulmonary disease (COPD).

MATERIALS and METHODS

One hundred patients with lung cancer were enrolled study (84 men, 16 women, median age of 62 years). Biopsy materials were obtained by bronchoscopic mucosal biopsy, trans bronchial lymph node aspiration, transthoracic fine needle aspiration or surgery. Blood samples were collected before any treatment. Time interval between the drawing of blood and centrifugation of blood stored at room temperature is less than 3 hours. Blood was spun at 3000 revolutions per minute for 10 minutes. Supernatant was placed into 2 cc eppendorf tubes after centrifugation and stored at -80°C deep-freezer.

Patients enrolled study between 2009-2011 and the median following time is 8.7 months. At the end of the study only 39% of patients was alive. Exclusion criterias were; age under 18 and previous cancer history. TNM staging was done according to International Association for the Study of Lung Cancer (IASLC)-7th edition. Eastern Cooperative Oncology Group (ECOG) performance status, age, sex, smoking status (packet/year), hemogram, biochemical parameters (LDH and calcium specifically discussed) and coexistence of COPD are recorded for each patient. Inoperable patients were given chemotherapy/radiotherapy according to treatment protocols.

We evaluate normal serum level of YKL-40 in 30 healthy adults (15 men, 15 women, median age 60 years). None of the participants in control group had a chronic disease that requires regular drug use or symptom of malignancies.

Study protocol was approved by ethical committee of university and all participants were informed about study design.

Procedure of detection of serum concentration of YKL-40 is based on enzyme-linked immunosorbent assay (ELİSA) (MicroVue™, YKL-40 EIA Summary, Quidel, San Diego, CA 92121, USA). Principle of procedure consists of three steps; a micro assay plate coated with streptavidin and a biotinylated murine monoclonal antibody to human YKL-40, an AP-conjugated rabbit polyclonal antibody to YKL-40, and a chromogenic substrate (1-3). In third step an incubation period is needed and the colour intensity is measured spectrophotometically. All serums were studied duplicate to increase accuracy. This part of the study was done by a microbiologist who doesn't know the study's parameters and endpoints.

Statistical Analysis

Frequency (percent) for categorical variables, mean ± standard deviation [median (minimum-maximum)] for metric variables was given as descriptive statistics. In order to compare two/more independent groups, Mann-Whitney U test/Kruskal-Wallis variance analysis for metric variables, chi-square test for categorical variables was used. Spearman correlation coefficient was used to assess the degree of association between two variables. The area under the ROC curve gives an estimate of the overall accuracy of YKL-40 level. An area of 0.50 implies that the variable adds no information. The area under the ROC curve and 95% confidence interval for YKL-40 level was calculated in the manner described by Hanley and McNeil (7). The sensitivity, specificity, positive and negative predicted values, likelihood ratios and overall accuracy were calculated for diagnostic performance of YKL-40 level. Overall survival was estimated by Kaplan-Meier survival analysis. The log-rank test was used to compare survival estimates between subgroups. $p< 0.05$ was considered as statistically significant.

RESULTS

One hundred patients (16 female and 84 male) were enrolled to the study and results were compared to 30 healthy volunteers. Mean ages were 62 ± 8.2 in group of patients and 60.9 ± 10.3 in control group. There were no statistically significant differences between control and study group in terms of demographic characteristics. Fourty-two patients were in stage 4 at time of diagnosis. There were thirty-three operable patients but surgery was performed only twenty-six of them because of poor medical conditions. Eighty-seven of patients were diagnosed with NSCLC and most frequent cell type was squamous cell lung cancer. Patients were analysed by dividing into groups according to existence of COPD and comorbidity. Characteristics of patients were summarized in Table 1.

Serum YKL-40 Levels and Patient Characteristics

While the median serum YKL-40 level was 229.0 ± 110.7 ng/mL in patients, it was 144.5 ± 105.7 ng/mL in control group and it was statistically significant

Table 1. Characteristic of patients

		Number	Serum YKL-40 level ng/mL	p
Control group	Male/Female	15/15	119.57 ± 105.7	**< 0.001**
	Age	60.9 ± 10.3		
Patient group	Male/Female	84/16	197.37 ± 114.1	**< 0.001**
	Age	62 ± 8.2		
Pathological subtype	SCLC	13	202.7 ± 114.1	0.4
	NSCLC	87	225.8 ± 115.6	
Subtypes of NSCLC	Adeno	28	251.1 ± 122.5	0.16
	Squamous	59	213.7 ± 111.2	
Tumour status	T1-T2	55	227.5 ± 114.2	0.83
	T3-T4	32	222.8 ± 119.6	
Nodal status	N0	39	240.4 ± 130.3	0.45
	N1-2-3	48	213.9 ± 197.3	
Metastasis	M0	42	234.2 ± 125.2	0.57
	M1	58	211.6 ± 101.1	
Operability	Operable	33	238.3 ± 138.2	0.76
	Inoperable	54	218.1 ± 99.9	
SCLC	Extensive	9	201 ± 94	> 0.05
	Limited	4	203.2 ± 143	
Presence of comorbidity	Yes	55	238.6 ± 105.4	0.1
	No	45	203.2 ± 122	

SCLC: Small cell lung cancer, NSCLC: Non-small cell lung cancer.

Table 2. Serum YKL-40 levels and NSCLC stages

NSCLC stages	Number	Serum YKL-40 level ng/mL
IA	6	318.5933
IB	9	272.2789
IIA	6	150.5267
IIB	12	216.5825
IIIA*	12	223.1800
IV	42	216.7300

* There was only one patient in Stage IIIB so it is discussed in group IIIA,

NSCLC: Non-small cell lung cancer.

(p< 0.001). Serum YKL-40 level wasn't related to age, gender, performance status and histopathologic type of tumour (p> 0.05). In NSCLC group there was no association between YKL-40 and stage (Table 2). In group of SCLC mean YKL-40 levels were similar between extended and limited disease (p> 0.05). Operability, histopathological type, tumour size and nodal status did not affect YKL-40 level. Existence of COPD (n= 42 patients) wasn't correlated with high level of YKL-40 (Table 3). Patients who have any of chronic diseases (hypertension, diabetes mellitus, renal disease, congestive heart failure and coronary artery disease) had higher serum YKL-40 levels than those without comorbidity (238.6 ± 105.4 ng/mL versus 218.5 ± 117.2 ng/mL) (Table 1).

Table 3. Survival in patients with COPD

	Serum YKL-40 level (ng/mL)	Survival (day) (< 133 ng/mL)	Survival (day) (≥ 133 ng/mL)	p value for survival
Patient with COPD (n= 42)	210.9	730	116	**0.01**
Patient without COPD (n= 58)	231.2	261	534	0.51

COPD: Choronic obstructive pulmonary disease.

Serum YKL-40 Levels and Survival

Survival was analysed for TNM staging, histopathologic type of tumour, operability and coexistence of COPD regardless of serum YKL-40 level. In NSCLC group, as the stage increased and tumour growed survival got lower. Similarly as the number of involvement lymph node increased, coexistence of COPD and inoperability were related to poor prognosis ($p< 0.05$). In terms of cell type patients diagnosed with SCLC had shorter survival than NSCLC patients ($p= 0.019$).

Survey was analysed according to three cut-off values of serum YKL-40 level, 133 ng/mL (high specifity and sensitivity), 159 ng/mL (high sensitivity) and 162 ng/mL (high specifity) (Figure 1). There was no association between serum YKL-40 levels and other parameters described in Table 1. Above all cut-off values survival was shorter ($p> 0.05$). The highest p value was found ($p= 0.09$) in limited disease in SCLC for 162 ng/mL. Although it had no significance, above all cut-off values inoperability was related to poor prognosis. Patients with COPD had shorter life expectancy according to 133 ng/mL ($p= 0.01$) (Table 3, Figure 2).

Although serum calcium level, age, gender and performance status was not related with YKL-40 level, serum LDH level had low correlation with YKL-40 level for only NSCLC ($p= 0.009$, $r= 0.262$).

DISCUSSION

This study evaluated association between pre-treatment serum YKL-40 level and clinicopathologyc parameters in lung cancer. In patient group median YKL-40 level was significantly higher than control group ($p< 0.001$). This result is similar to study that Thöm et al. had investigated 189 advanced NSCLC for YKL-40 (4). According to other studies YKL-40 was poor prognostic factor. Similar result was reported by Johansen et al. with 131 SCLC including mostly extended disease patients (6). Differently in current study both early and advanced stage patients were evaluated together.

Lung cancer is an aggressive malignancy especially diagnosed in advanced stage. So various biomarkers were investigated if they had an importance to detect lung cancer earlier. Nowadays angiogenetic biomarkers are being investigated and there are ongoing studies to develop therapies that block these growth factors (8). YKL-40 has some differences physiological role from others. It is produced by both non-malignant (human cells like granulocytes, chondrocytes and vessel endothelia) and malignant tissues. Elevated serum YKL-40 levels were detected with chronic inflammation like osteoarthritis, chronic bowel disease, cirrhosis and COPD (9). So obviously it should not be dedicated as only a tumour biomarker, it takes place in inflammatory process.

In current study, existence of COPD was evaluated with YKL-40 in patients with lung cancer in respect of survival. Patients with COPD had shorter survey above all cut-off values. It's remarkable that despite there is no correlation between COPD existence and serum YKL-40 level, survival had changed significantly. That can be explained by using bronchodilator drugs, theophylline and smoking status. Because in a study designed by Letuve et al. they report that serum and BAL YKL-40

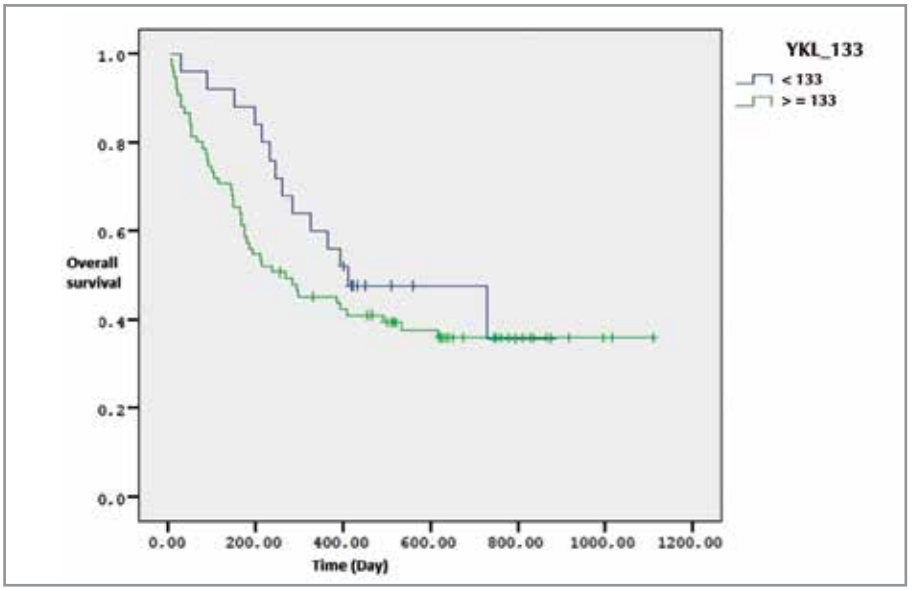

Figure 1. Overall survival for cut-off value of 133 ng/mL.

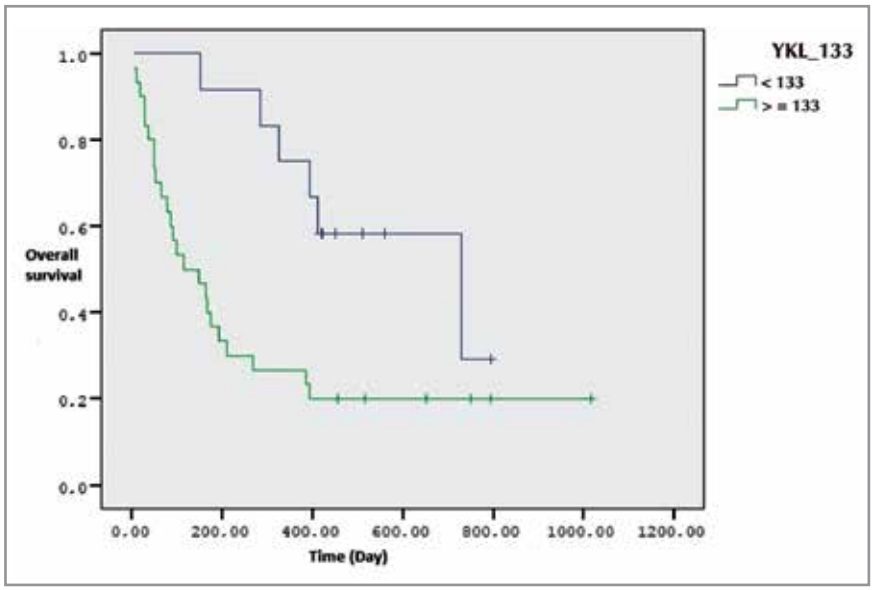

Figure 2. Overall survival for patients with COPD according to cut-off 133 ng/mL.

level reflect positive correlation in patient with COPD. Also by immunohistochemically staining they demonstrate alveolar macrophages are major cells to produce YKL-40 in lung tissue (9). We didn't record patients' medications or stage of COPD, however, bronchodilators and theophylline can reduce inflammation hereby we detect YKL-40 level lower than expected in patients with COPD. Again, Letuve et al. presents increased serum YKL-40 levels in smoking patients compared to non-smokers (9). Current study smoking frequency is 81%. So YKL-40 level is increased in smokers without COPD. Therefore, drugs especially working in inflammatory process should be considered when designing a study with serum YKL-40.

It has been investigated in several studies for different type of tumours. Eventually it was detected as a poor prognostic factor but it wasn't specific to any cell type. However, its biological function in malign process isn't well known yet it's suggested to take place in proliferation, differantiation, protecting tumour cells from apoptosis. But more in vivo studies are needed (10). There are limited reports that YKL-40 is associated with survival in lung cancer. We followed patients for fifteen months and after this period 61 patients had been died. In our study we defined three cut-off values. Despite survival was shorter above all cut-off values it wasn't significant (p> 0.05). Because we had patients who diagnosed in early stages and most of study group was NSCLC; so this heterogeneity in patient distribution may be effective on results.

A study from Turkey designed with NSCLC patient serum YKL-40 level is higher in locally advanced/advanced staged NSCLC (240.20 ng/mL (104.91-408.07) vs. 82.28 ng/mL (56.53-265.61)) (11). In contrast to this study, serum YKL-40 levels were slightly higher in operable groups than inoperable group. So it's suggestible that YKL-40 is released to serum from tumour cells since early stages or existence of an inflammatory disease changes result. If post-operative YKL-40 levels and effect of comorbidities had also been measured it would be easy to have a healthy comparison. Unfortunately, this the missing point of current study.

Although it was not statistically significant, serum YKL-40 level was higher in SCLC than NSCLC. But sample sizes were quite different between groups and only 13 of 100 patients were diagnosed SCLC. Both groups should be analysed again for an equal number of patients in each histological types.

There are limited reports that YKL-40 is associated with survival in lung cancer. We followed patients for fifteen months and after this period 61 patients had been died. In our study we defined three cut-off values. Despite survival was shorter above all cut-off values it wasn't significant (p> 0.05). Because we had patients who diagnosed in early stages and most of study group was NSCLC; so this heterogeneity in patient distribution may be effective on results.

In current study, existence of COPD was evaluated with YKL-40 in patients with lung cancer in respect of surviv-

al. Patients with COPD had shorter survey above all cut-off values. It's remarkable that despite there is no correlation between COPD existence and serum YKL-40 level, survival had changed significantly. That can be explained by using bronchodilator drugs, theophylline and smoking status. Because in a study designed by Letuve, et al. they report that serum and BAL YKL-40 level reflect positive correlation in patient with COPD. Also by immunohistochemically staining they demonstrate alveolar macrophages are major cells to produce YKL-40 in lung tissue (9). We didn't record patients' medications or stage of COPD, however, bronchodilators and theophylline can reduce inflammation hereby we detect YKL-40 level lower than expected in patients with COPD. Again, Letuve, et al. presents increased serum YKL-40 levels in smoking patients compared to non-smokers (9). Current study smoking frequency is 81%. So YKL-40 level is increased in smokers without COPD. Therefore, drugs especially working in inflammatory process should be considered when designing a study with serum YKL-40.

Similar to other studies YKL-40 wasn't related to age, gender, cell type, site of metastasis except LDH level. Serum LDH level had low correlation with YKL-40 value ($p= 0.009$, $r= 0.262$) in patients with NSCLC. In contrast to literature there was no correlation between performance status and YKL-40 because of patients with early stages.

The role of YKL-40 in malign process is still unknown and very few studies have evaluated the functional role of YKL-40 expression in cancer cells. It has been suggested that playing roles in proliferation, differentiation and neovascularization of malignant cells, protects the cells from undergoing apoptosis. But also it's obviously defined that it has importance for inflammatory events like extracellular tissue remodelling, fibroblast activity, however there is not enough in vivo studies to prove yet. In literature YKL-40 is mentioned for both malignant and non-malignant diseases. So its' signalling pathways, molecular interactions, receptors and if present different molecular isoforms needed to be defined. After these questions are answered we can start to work on therapies targeting YKL-40.

In conclusion we have demonstrated that YKL-40 level is higher in patients with lung cancer than healthy people. But we couldn't define any prognostic value in lung cancer except for patients with COPD. To understand the biological function of serum YKL-40 in lung cancer, expression in tissue and correlation with serum level should be demonstrated. Then neutralizing antibodies targeted against YKL-40 can be an alternative treatment in lung cancer.

CONCLUSION

YKL-40 level is useful in lung cancer however it's not related to cell type and prognosis. Also co-morbidities that increase inflammation should be considered when analysing. Current study demonstrated that it is associated with poor prognosis in lung cancer patients with COPD, supporting that YKL-40 is a both tumour and inflammation related biomarker.

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