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LETTER TO THE EDITOR

High serum YKL-40 is a poor prognostic marker in patients with advanced non-small cell lung cancer

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To the Editor,

Despite recent advances in the field of medical oncology, patients with advanced non-small cell lung cancer (NSCLC) have a disappointing long-term prognosis. Accurate prognostic and predictive factors are needed to evaluate and modify treatments for patients with advanced NSCLC, to minimize toxicity while improving treatment efficacy and quality of life (QOL). CYFRA 21-1, a tissue polypeptide antigen (TPA), CA 125, a neuro-specific enolase (NSE), and squamous cell carcinoma antigen (SCCAg) serum levels have been reported to be indicators of disease severity in NSCLC patients, especially for patients with squamous cell carcinoma [1]. To date, however, few proven biomarkers that allow for a prediction of prognosis for patients with NSCLC have been identified.

YKL-40 is a 40 kDa mammalian chitinase-like protein produced by cancer cells and tumor-associated macrophages [2]. It is also known as human cartilage glycoprotein-39 (HC gp-39), 38-kDa heparin-binding glycoprotein (Gp38k), chitinase-3-like-1 protein (CHI3L1), breast-regressing protein 39 Kd (brp-39), and chodrex [3]. YKL-40 may play a role in tissue remodeling, cancer cell proliferation, and angiogenesis [2]. Although it is not a cancer-specific biomarker, increased serum levels of YKL-40 have been reported in patients with different cancers, including breast cancer, colon cancer, and ovarian cancer [4–6]. The association between increased YKL-40 and a poor prognosis has been well documented [5,7,8], but the specific relationship between levels of YKL-40 and survival in patients with advanced NSCLC has not been studied.

Blood samples were obtained at the time of diagnosis from NSCLC patients that had been confirmed pathologically by bronchoscopy or percutaneous needle biopsy. This study was approved by the institutional review board, and all patients provided written informed consent. The normal range of serum YKL-40 was determined in 20 healthy volunteers (11 men and nine women). Individuals in the healthy control group were not taking medications and had no signs or clinical symptoms of cancer, joint, liver, metabolic or endocrine diseases. Their serum was separated from the cellular components by centrifugation within one hour after blood sampling, and all samples were stored at $-80°C$ until analysis.

Serum concentrations of YKL-40 were determined using a commercial two-site, sandwich-type enzyme-linked immunosorbent assay (ELISA; Quidel, San Diego, CA, USA) using streptavidin-coated micro-plate wells, a biotinylated-Fab monoclonal capture antibody, and an alkaline phosphatase-labeled polyclonal detection antibody, according to the manufacturer's instructions. The sensitivity of the ELISA was 20 μg/L, and the intra- and interassay variation coefficients were $<3.6\%$ and $<7.1\%$, respectively.

The optimal cut-off point for the YKL-40 level was determined using ROC analysis and the shortest distance method. Overall survival was calculated as the time from initial diagnosis to death or censoring. Survival curves were constructed using the Kaplan-Meier method, and a log-rank test was used for the comparisons. The Cox proportional hazard regression method was performed to evaluate the influence of prognostic factors on a patients' overall survival. Every independent variable was checked for statistical

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significance, and then if the p-value was >0.25, that variable was omitted for the Cox proportional hazard regression analysis. All statistical outcomes based on the two-sided test were calculated using STATA MP statistical software (Version 10.1, Stata Corporation, College Station, TX, USA). A p-value of <0.05 was considered to be statistically significant.

Thirty-nine blood samples were collected from patients with advanced NSCLC. The median age of the patients with NSCLC was 61 years (range, 31–82 years). At the time of diagnosis, most patients had stage IV lung cancer, except for nine patients with stage IIIb disease. Most patients had a good performance status and received palliative chemotherapy, although nine patients with a poor performance status were not treated with chemotherapy. Adenocarcinoma (56%) was the most common type of cancer, followed by squamous cell carcinoma (36%). Twenty-seven of the patients were male and 12 were female. The overall median survival of patients with NSCLC was 13 months (95% CI, 9–17 months). The median age of the control group was 50 years (range, 42–81 years).

The area under the ROC curve for YKL-40 levels was 0.903. The ROC curve also showed that the optimal cut-off value of YKL-40 was 165 μg/L (low vs. high) (sensitivity = 70% and specificity = 95%) (Figure 1). The median serum YKL-40 level was 34 μg/L in the control group (range, 14–273 μg/L), which was significantly lower than the YKL-40 level of patients with NSCLC (median, 193 μg/L, range, 25–464 μg/L; p = 0.004) (Figure 2).

The median survival of patients with high serum YKL-40 was seven months (95% CI, 5–10 months), while patients with low serum YKL-40 had a median survival time of 18 months (95% CI, 12–24 months). This difference was statistically significant (p = 0.007, log-rank test) (Figure 3).

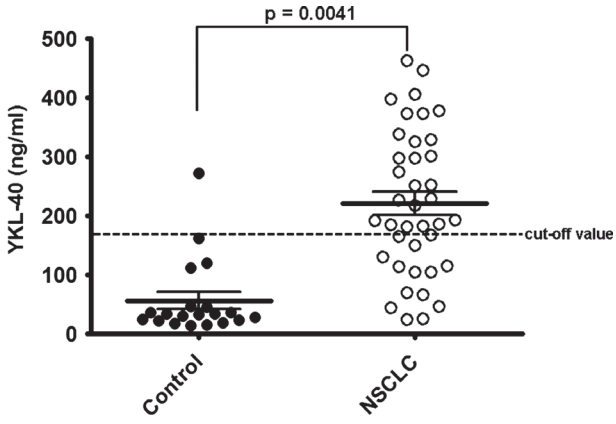

Figure 2. Serum YKL-40 levels in NSCLC patients and in the control group. Serum YKL-40 levels were elevated in the NSCLC group compared with that of the control group (p = 0.004).

We conducted univariate and multivariate analysis of the baseline characteristics, including age, sex, stage, performance status, pathology, smoking history, alcohol use, and YKL-40 level, in order to evaluate the prognostic factors for overall survival. After the univariate analysis, age, performance status, and YKL-40 were utilized for the multivariate analysis of overall survival (Table I). Among these three variables, performance status and YKL-40 were statistically significant in the multivariate analysis (Table I).

YKL-40 is expressed in several types of solid tumors (breast, colon, lung, kidney, ovarian, prostate, uterine, pancreas, osteosarcoma, thyroid, oligodendroglioma, glioblastoma, and germ cell tumors) [2]. YKL-40 is also known to be expressed in human small cell lung cancer [9,10], but there have been no prior reports of YKL-40 expression in NSCLC. As far as we know, this study is the first report about the relationship between the serum levels of YKL-40 and survival in patients with NSCLC. We found that YKL-40 may be a useful prognostic marker in

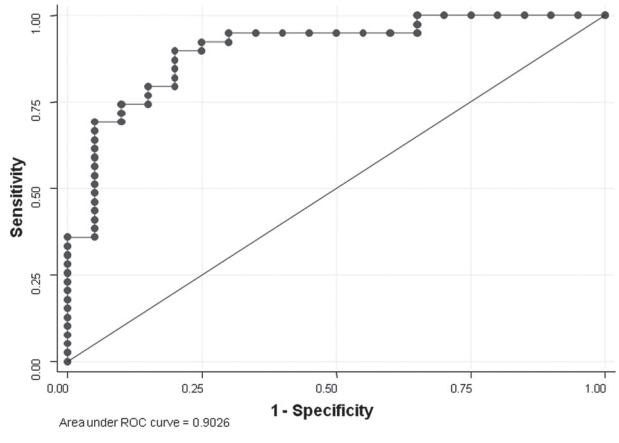

Figure 1. Receiver-operating characteristic (ROC) curve for YKL-40 levels.

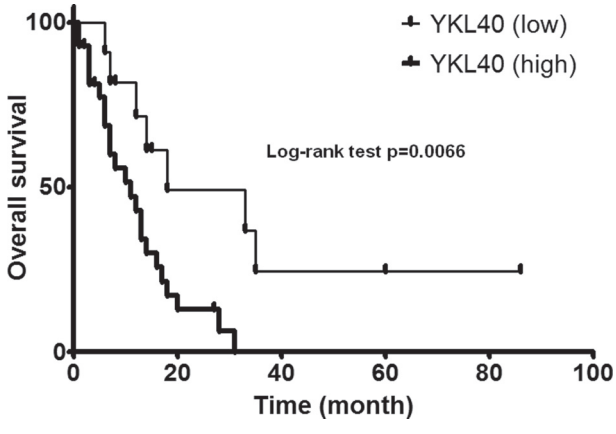

Figure 3. Overall survival analysis for enrolled patients according to serum YKL-40 level. The log-rank test was statistically significant (p = 0.007).

Table I. Cox proportional hazard regression analysis of overall survival.

		Hazard ratio (95% CI)			
Variable	Number	Univariate	p-value	Multivariate	p-value
Age (years)					
<60	16	1			
≥60	23	2.25 (1.06–4.75)	0.033	1.74 (0.79–3.84)	0.172
Sex					
Female	12	1			
Male	27	0.80 (0.38–1.69)	0.559		
Stage					
IIIB	9	1			
IV	30	1.38 (0.60–3.14)	0.448		
Performance status					
0, 1	26	1			
2, 3	13	2.38 (1.22–6.59)	0.016	3.94 (1.58–9.82)	0.003
Pathology					
Adenocarcinoma	22	1			
Squamous cell carcinoma	14	1.49 (0.67–3.28)	0.325		
Poorly differentiated	3	0.48 (0.06–3.63)	0.477		
Smoking					
No	11	1			
Yes	28	1.16 (0.52–2.55)	0.708		
Alcohol					
No	16	1			
Yes	23	0.75 (0.36–1.60)	0.466		
YKL-40					
Low	11	1			
High	28	3.55 (1.32–9.56)	0.012	3.60 (1.25–10.39)	0.018

NSCLC patients. The previously reported median concentration of YKL-40 in healthy adults (43 μg/L) [11] was similar to the median serum YKL-40 level in our control group (34 μg/L). YKL-40 does not show circadian variability, and there is no gender difference in its levels [2].

The mechanism involved in the association between YKL-40 and a poor prognosis is poorly understood. Recently, Saidi et al. suggested that poor survival in cancer patients with elevated YKL-40 might be attributed to the promotion of angiogenesis [12]. Mylin et al. also reported an association between YKL-40 and shortened survival in patients with multiple myeloma, suggesting that the mechanism may involve bone marrow angiogenesis [13]. And serum YKL-40 also can be elevated in patients with inflammation and tissue remodeling, therefore, there is a risk for false positive results [14].

In conclusion, YKL-40 appears to be a good candidate for a predictive survival marker in patients with advanced NSCLC. As NSCLC is not a homogeneous disease, however, this finding warrants further study and clinical confirmation in patients with NSCLC.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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