Elevated Serum Concentration of Chitinase 3-Like 1 is an Independent Prognostic Biomarker for Poor Survival in Lung Cancer Patients

Jiying Wang a  Zhaoying Sheng b  Wenyan Yang b  Yong Cai b

aDepartment of Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, bDepartment of Radiation Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, PR China

Key Words
Chitinase 3-like 1 • Lung cancer • Prognosis

Abstract
Background/Aims: The chitinase 3-like 1 (CHI3L1) has an important role in cancer progression, and high CHI3L1 expression is associated with the development and progression of cancers. Previous studies had been controversial with respect to the association between CHI3L1 expression and lung cancer prognosis. Thus, we performed a meta-analysis to investigate the prognostic value of CHI3L1 expression in lung cancer. Methods: We searched Pubmed, Embase, and Wanfang databases to identify eligible studies. Overall survival and disease free survival were collected from included studies. Pooled hazard ratios (HRs) with 95% confidence interval (95%CI) were calculated to estimate the association. Seven studies comprising 911 lung cancer patients were included in this meta-analysis. Results: The results showed high CHI3L1 expression was independently associated with poorer overall survival in lung cancer patients (HR = 1.71, 95%CI 1.24-2.37, P = 0.001). Subgroup analysis by histological type showed that high CHI3L1 expression was independently associated with poorer overall survival in both non small-cell lung cancer patients (HR = 2.23,95%CI 1.43-3.47, P < 0.001) and small-cell lung cancer patients (HR = 1.45, 95%CI 1.06-2.00, P = 0.021). In addition, sensitivity analysis by omitting single study by turns did not change the pooled outcomes obviously. Conclusion: Our results suggest that elevated serum CHI3L1 concentration is an independent prognostic biomarker for poorer survival in lung cancer patients.
Introduction

Lung cancer is still the leading cause of cancer-related death in the world, and there are about 1.5 million newly diagnosed lung cancer cases each year [1]. Most of lung cancers are non small-cell lung cancer (NSCLC), while the left are mainly small-cell lung cancer (SCLC) [2, 3]. Both NSCLC and SCLC are fatal diseases, and have been the focus of medical researches. However, though there are many novel therapeutic methods developed for lung cancer, there is still no obvious improvement in patients' outcomes [4, 5]. In addition, not all patients can benefit from traditional chemotherapy or new targeted therapies, and finding of reliable biomarkers to select suitable treatments for individual patient is very important for patients to get the biggest benefit of treatment [6, 7]. Current studies have found some predictive and prognostic biomarkers in lung cancer patients, such as TP53 and EGFR mutations [8-13]. The chitinase 3-like 1 (CHI3L1; also known as YKL-40) has an important role in cancer progression, and high CHI3L1 expression is associated with human tumor development and progression. CHI3L1 is a secreted 40 kDa glycoprotein that is up-regulated in several human cancers and other diseases characterized by chronic inflammation [14]. Increased serum levels of CHI3L1 are associated with disease severity and shorter overall survival in many types of cancers. Given the important impact of CHI3L1 on the development and progression of several types of cancer, several studies have studied the prognostic role of CHI3L1 levels in patients with lung cancer [15-19]. However, the results of from those studies were controversial and the prognostic role of CHI3L1 in lung cancer still remained unclear. Thus, the objective of our meta-analysis was to evaluate the potential relationship of serum CHI3L1 levels with overall survival in patients with lung cancer.

Materials and Methods

Searching database and inclusion criteria

Relevant studies were searched by an electronic search in PubMed, Embase and Wanfang database from 1980 to June 2015. We used the following words: ("non small cell lung cancer", "lung cancer", "lung carcinoma" or "lung neoplasm") and ("chitinase 3-like 1", "CHI3L1" or "YKL-40"). There were no language restrictions or the minimum number of patients. Titles and abstracts were evaluated to identify related studies, and then full texts were read carefully.

The eligible studies for inclusion in this meta-analysis had to meet the following criteria: 1) Assessing the association between CHI3L1 levels with overall survival in patients with lung cancer; 2) The expression of IGF1R was measured by immunohistochemistry (IHC) or quantitative reverse transcription polymerase chain reaction (qRT-PCR), while the levels of serum CHI3L1 were measured by Enzyme-linked immunosorbent assay (ELISA); 3) Comparing the prognosis of patients with high CHI3L1 levels with those with low CHI3L1 levels; 4) Diagnosis of lung cancer was proven by histopathological method; 5) Offering sufficient data for estimating hazard ratios (HR) and 95% confidence intervals (95% CI). Studies without meeting the inclusion criteria were all excluded.

Data extraction and quality assessment

Two reviewers evaluated the articles, extracted data and checked all potentially relevant studies independently. All disagreements between the findings of the two reviewers in the data extraction were resolved by discussion and reaching consensus. The following information from each article were extracted: first author; year of publication, country, types of lung cancer; number of patients, follow-up period, disease stage, detection method, and adjusted HR estimation. From all published researches, the HR and 95% CI could be directly obtained by using survival analysis.

The quality of included studies was assessed by using the Newcastle-Ottawa Scale (NOS) [20]. The quality of those included studies was evaluated by assessing three items, which mainly included the selection of participants, comparability of groups, and assessment of outcomes. A study can be awarded a maximum of 3 stars for each item, and higher scores represent studies of higher quality.
Statistical analysis

The associations between CHI3L1 expression and overall survival were described as HR, and a value of HR over 1 indicated worse prognosis in patients with high levels of CHI3L1. The heterogeneity among studies was examined by the Cochrane’s Q test and I² inconsistency statistic, and p < 0.05 or I² more than 50% was considered to be statistically significant [21, 22]. When there was no significant heterogeneity among studies, the fixed effects model was employed to pool the HR estimates [23]. Otherwise, when there was significant heterogeneity among studies, the random effects model was used [24]. Subgroup analysis was performed by types of lung cancer, such as NSCLC and SCLC. To evaluate the stability of the results, a sensitivity analysis was performed, in which one study was removed to know the influence of the individual study on the pooled HR. Publication bias was investigated by Egger’s regression test, Begg’s test and funnel plot, and P < 0.05 was considered to indicate statistically significant publication bias [25, 26]. STATA 12.0 software (STATA Corp., College Station, TX) was used to perform statistical analysis.

Results

Study selection and characteristics

42 studies were retrieved initially using the above search strategy. Titles and abstracts screened, a total of 8 independent studies were preliminarily identified and were further assessed by reading full-text [15-19, 27-29]. After reviewing the full-text, one study [29] was excluded and seven studies were eventually used in the present meta-analysis [15-19, 27, 28]. There were five studies published in English, and one study published in Chinese (Table 1). Table 1 showed the main characteristics of those 7 studies included in the meta-analysis [15-19, 27, 28]. Of these studies, three were conducted in the China, two in Denmark, one in Germany, and one in Korea [15-19, 27, 28]. Overall, 911 lung cancer patients were included, with sample sizes ranging from 39 to 242 individuals (Table 1). In addition, four studies focused on NSCLC patients, two studies focused on SCLC patients, and the other one study were on all types of lung cancer (Table 1). Six of those 7 studies measured the level of CHI3L1 in the serum, while only one study measured the CHI3L1 expression in tumor tissue.

Table 1. Main characteristics of studies included in the meta-analysis. (NSCLC, Non-small Cell Lung Cancer; SCLC, Small Cell Lung Cancer; ELISA, Enzyme-linked immunosorbent assay; qRT-PCR, quantitative reverse transcription polymerase chain reaction)

| Study [Ref.] | Country      | Participants (Mean age:Female, number) | Testing methods     | Adjusted factors                                                                 | Quality |
|--------------|--------------|----------------------------------------|---------------------|----------------------------------------------------------------------------------|---------|
| Wang XW 2015 [18] | China       | 95 NSCLC patients (62 years, 50 females) | QT-PCR              | Age, gender, smoking, histology, histological grade, intratumoral microvessel density | 8       |
| Xu CH 2014 [19]    | China       | 120 patients with SCLC (64.5 years, 25 females) | ELISA              | Age, gender, disease stage, smoking status, performance status, chemotheraphy regimen | 8       |
| Zhou F 2011 [28]   | China       | 95 NSCLC patients (60 years, 32 females) | Immuno-histochemical staining | Pathological stage, operation model, chemotheraphy, tumor-associated macrophage | 6       |
| Thom I 2010 [27]   | Germany     | 189 patients with NSCLC (62 years, 46 females) | ELISA              | Serum lactate dehydrogenase, bone metastases, age, gender, tumor stage, grade, baseline therapy | 8       |
| Choi IK 2010 [15]  | Korea       | 39 NSCLC patients (61 years, 12 females) | ELISA              | Age, gender, stage, smoking status, performance status, pathology | 6       |
| Johansen JS 2004 [17]| Denmark   | 131 SCLC patients (57 years, 49 females) | Radioimmunoassay    | Age, gender, disease stage, performance status, chemotheraphy regimen, serum lactate dehydrogenase, Sex, age, smoking habits, alcohol consumption, and body mass index at the time of blood sampling | 7       |
| Johansen JS 2009 [16]| Denmark   | 242 lung cancer patients(Not reported, not reported) | ELISA              |                                                                                  | 9       |
Meta-analysis of total 7 studies showed that high levels of CHI3L1 expression was independently associated with poorer overall survival in lung cancer patients (HR = 1.71, 95%CI 1.24-2.37, P = 0.001) (Fig. 1). When excluding the study focusing on CHI3L1 expression in tumor tissue, high levels of CHI3L1 expression was independently associated with poorer overall survival in lung cancer patients (HR = 1.65, 95%CI 1.17-2.34, P = 0.005).

Subgroup analysis by histological type showed that high CHI3L1 expression was independently associated with poorer overall survival in both NSCLC patients (HR = 2.23, 95%CI 1.43-3.47, P < 0.001) and SCLC patients (HR = 1.45, 95%CI 1.06-2.00, P = 0.021) (Fig. 2).
Publication bias and sensitivity analysis

The funnel plot in the meta-analysis of total 7 studies seemed symmetrical and didn't detect publication bias (Fig. 3). In addition, publication bias was also not detected in Egger's regression test (P = 0.45) and the Begg's test (P = 0.55).

When performing sensitivity analysis by excluding single study by turns, the pooled HRs were similar when any single study was removed. Therefore, our pooled risk estimates were statistically reliable.

Discussion

CHI3L1 has an important role in cancer progression, and high CHI3L1 expression is associated with human tumor development and progression. Considering the important role of CHI3L1 in cancer, its expression has been proposed as a possible prognostic biomarker of lung cancer. Currently, there are several studies available to assess the prognostic significance of CHI3L1 in lung cancer, but no conclusive result is available. Our meta-analysis is based on published data and was performed using adjusted risk estimate from multivariate analysis. To the best of our knowledge, this study is the first meta-analysis on the prognostic significance of CHI3L1 expression in lung cancer. The results showed that high CHI3L1 expression was independently associated with poorer overall survival in lung cancer patients (Fig. 1). Subgroup analysis by histological type showed that high CHI3L1 expression was independently associated with poorer overall survival in both NSCLC patients and SCLC patients. Therefore, our results suggest that elevated serum CHI3L1 concentration is an independent prognostic biomarker for poorer survival in lung cancer patients.

The CHI3L1, which is also known as YKL-40, is a secreted 40 kDa glycoprotein that is upregulated in several human cancers and other diseases characterized by chronic inflammation [14]. CHI3L1 has been considered to have important roles in the carcinogenesis of many types of cancers [30-36]. Considering the important role of CHI3L1 in cancer, its expression has been proposed as a possible prognostic biomarker of several types of cancer, such as colorectal cancer, hepatocellular carcinoma, prostate cancer, and breast cancer [31, 32, 37-41].

CHI3L1 is a highly conserved protein and is expressed by different types of cancer cells [14]. Previous studies have suggested that CHI3L1 can influence the proliferation and differentiation of cells, and it also can influence the metastatic potential and angiogenesis of cancer cells. The biologic functions of CHI3L1 above suggest that it can reflect the aggressiveness and progression of cancer. Therefore, patients with cancer cells producing high level of CHI3L1 may show more aggressive phenotype and a high metastatic potential,
both of which are associated with shorter survival. However, more studies are needed to further explore possible explanations for the prognostic role of CHI3L1 in cancer.

Elevated serum YKL-40 levels, compared with age-matched healthy subjects, are found in some patients with both malignant diseases and some nonmalignant diseases, such as rheumatoid arthritis and osteoarthritis. However, not all patients with cancer had elevated serum YKL-40 levels compared with healthy age-matched controls, suggesting that not all tumors secrete YKL-40 or that the protein is secreted at a low level. Therefore, the significance of YKL-40 as the diagnostic biomarker of cancer is not well established. However, the prognostic value of YKL-40 in several cancers has been identified. The findings in the meta-analysis suggest that elevated serum CHI3L1 concentration is an independent prognostic biomarker for poorer survival in lung cancer patients.

However, there were some potential limitations in this meta-analysis. Firstly, most included studies were retrospective cohort studies of patients in hospital, and no prospective cohort had been found. Owing to limitations in retrospective cohort studies, we could not get the adjusted risk estimates after adjusting all confounding factors. Secondly, six of those 7 studies measured the level of CHI3L1 in the serum, while only one study measured the CHI3L1 expression in tumor tissue. Owing to the only one study measuring the expression of CHI3L1 in the tumor tissue, its prognostic role in lung cancer needs the validation of results from future studies. Thirdly, the cut-off values for high level of CHI3L1 expression were arbitrarily selected and varied greatly between studies, which might produce the high heterogeneity. Nevertheless, due to the limited information of the original studies, we were unable to conduct further subgroup analysis by cut-off values. Finally, although we didn’t observe risk of publication bias, it cannot be ignored, since positive results tend to be accepted by journals, whereas negative results often are rejected or even not be submitted.

In summary, our results suggest that elevated serum CHI3L1 concentration is an independent prognostic biomarker for poorer survival in lung cancer patients. However, since the limitations mentioned above, these findings need to be explained with caution when applied to clinical practice. More prospective cohort studies with large samples are needed to further demonstrate the correlations between CHI3L1 expression and the survival in lung cancer patients.

Disclosure Statement

None.

References

1 Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D: Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
2 van Meerbeeck JP, Fennell DA, De Ruyscher DK: Small-cell lung cancer. Lancet 2011;378:1741-1755.
3 Goldstraw P, Ball D, Jett JR, Le Chevalier T, Lim E, Nicholson AG, Shepherd FA: Non-small-cell lung cancer. Lancet 2011;378:1727-1740.
4 Powell JW, Dexter E, Scalzetti EM, Bogart JA: Treatment advances for medically inoperable non-small-cell lung cancer: Emphasis on prospective trials. Lancet Oncol 2009;10:885-894.
5 Pennathur A, Lukeitch JD: Multimodal treatment with surgical resection for stage iiiib non-small-cell lung cancer. Lancet Oncol 2009;10:742-743.
6 Wu F, Zhang J, Liu Y, Zheng Y, Hu N: Hif1 alpha genetic variants and protein expressions determine the response to platinum based chemotherapy and clinical outcome in patients with advanced nsclc. Cell Physiol Biochem 2013;32:1566-1576.
Wang et al.: Chitinase 3-Like 1 in Lung Cancer

Shi C, Qian J, Ma M, Zhang Y, Han B: Notch 3 protein, not its gene polymorphism, is associated with the chemotherapy response and prognosis of advanced nsclc patients. Cell Physiol Biochem 2014;34:743-752.

Scoccianti C, Vesin A, Martel G, Ollivier M, Brambilla E, Timsit JF, Tavecchio L, Brambilla C, Field JK, Hainaut P: Prognostic value of tp53, kras and egfr mutations in non small cell lung cancer: The euelc cohort. Eur Respir J 2012;40:177-184.

Sadiq AA, Salgia R: Met as a possible target for non-small-cell lung cancer. J Clin Oncol 2013;31:1089-1096.

Oxnard GR, Binder A, Janne PA: New targetable oncogenes in non-small-cell lung cancer. J Clin Oncol 2013;31:1097-1104.

Coate LE, John T, Tsao MS, Shepherd FA: Molecular predictive and prognostic markers in non-small-cell lung cancer. Lancet Oncol 2009;10:1001-1010.

Tian Z, Yao G, Song H, Zhou Y, Geng J: Igf2r expression is associated with the chemotherapy response and prognosis of patients with advanced nsclc. Cell Physiol Biochem 2014;34:1578-1588.

Zhang L, Qian J, Qian Y, Huang H, Wang C, Li D, Xu B: Down-regulation of mir-4500 promoted non-small cell lung cancer growth. Cell Physiol Biochem 2014;34:1166-1174.

Coffman FD: Chitinase 3-like-1 (chi3l1): A putative disease marker at the interface of proteomics and glycomics. Crit Rev Clin Lab Sci 2008;45:531-562.

Choi IK, Kim YH, Kim JS, Seo JH: High serum ykl-40 is a poor prognostic marker in patients with advanced non-small cell lung cancer. Acta Oncol 2010;49:861-864.

Johansen JS, Bojesen SE, Myllin AK, Frikke-Schmidt R, Price PA, Nordestgaard BG: Elevated plasma ykl-40 predicts increased risk of gastrointestinal cancer and decreased survival after any cancer diagnosis in the general population. J Clin Oncol 2009;27:572-578.

Johansen JS, Drivsholm L, Price PA, Christensen IJ: High serum ykl-40 level in patients with small cell lung cancer is related to early death. Lung Cancer 2004;46:333-340.

Wang XW, Cai CL, Xu JM, Jin H, Xu ZY: Increased expression of chitinase 3-like 1 is a prognosis marker for non-small cell lung cancer correlated with tumor angiogenesis. Tumour Biol 2014

Xu CH, Yu LK, Hao KK: Serum ykl-40 level is associated with the chemotherapy response and prognosis of patients with small cell lung cancer. PLoS One 2014;9:e96384.

Wells G, Shea B, O'connell D, Peterson J, Welch V, Losos M, Tugwell P: The newcastle-ottawa scale (nos) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Health Research Institute Web site, 2014.

Cochran WG: The combination of estimates from different experiments. Biometrics 1954;10:101-129.

Higgins JP, Thompson SG, Deeks JJ, Altman DG: Measuring inconsistency in meta-analyses. BMJ 2003;327:557-560.

Mantel N, Haenszel W: Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719-748.

DerSimonian R, Laird N: Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-188.

Begg CB, Mazumdar M: Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088-1101.

 Egger M, Davey Smith G, Schneider M, Minder C: Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-634.

Thom I, Andritzky B, Schuch G, Burkholder I, Edler L, Johansen JS, Bokemeyer C, Schumacher U, Laack E: Elevated pretreatment serum concentration of ykl-40 an independent prognostic biomarker for poor survival in patients with metastatic nonsmall cell lung cancer. Cancer 2010;116:4114-4121.

Zhou F, Hu XE, Yang L: The expression of ykl-40 and tumor-associated-macrophage in non-small cell lung cancer and its relationship with prognosis [article in chinese]. CHINA MODERN MEDICINE 2011;18:11-13.

Kirankaya Gunes A, Gul S, Tutar N, Ozgul MA, Cetinkaya E, Zengi O, Onaran H: The place of ykl-40 in non-small cell lung cancer. Tuberk Toraks 2014;62:273-278.

Tanwar MK, Gilbert MR, Holland EC: Gene expression microarray analysis reveals ykl-40 to be a potential serum marker for malignant character in human glioma. Cancer Res 2002;62:4364-4368.

Ozdemir E, Cicek T, Kaya MO: Association of serum ykl-40 level with tumor burden and metastatic stage of prostate cancer. Urol J 2012;9:568-573.

Pan J, Ge YS, Xu GL, Jia WD, Liu WF, Li JS, Liu WB: The expression of chitinase 3-like 1: A novel prognostic predictor for hepatocellular carcinoma. J Cancer Res Clin Oncol 2013;139:1043-1054.
33 Andersen CL, Bjørn ME, McMullin MF, Harrison C, Samuelsson J, Ejerblad E, Zweegman S, Fernandes S, Bareford D, Knapper S, Lofvenberg E, Lindner O, Andreasson B, Ahlstrand E, Jensen MK, Bjerrum OW, Vestergaard H, Larsen H, Klausen TW, Skov V, Thomassen M, Kruse T, Gronbaek K, Hasselbalch HC: Circulating ykl-40 in patients with essential thrombocytemia and polycythemia vera treated with the novel histone deacetylase inhibitor vorinostat. Leuk Res 2014;38:816-821.

34 Cheng D, Sun Y, He H: Diagnostic role of circulating ykl-40 in endometrial carcinoma patients: A meta-analysis of seven related studies. Med Oncol 2014;31:326.

35 Jeet V, Tevz G, Lehman M, Hollier B, Nelson C: Elevated ykl40 is associated with advanced prostate cancer (pca) and positively regulates invasion and migration of pca cells. Endocr Relat Cancer 2014;21:723-737.

36 Zhang JP, Yuan HX, Kong WT, Liu Y, Lin ZM, Wangs WP, Guo JM: Increased expression of chitinase 3-like 1 and microvessel density predicts metastasis and poor prognosis in clear cell renal cell carcinoma. Tumour Biol 2014;35:12131-12137.

37 Cintin C, Johansen JS, Christensen IJ, Price PA, Sorensen S, Nielsen HJ: Serum ykl-40 and colorectal cancer. Br J Cancer 1999;79:1494-1499.

38 Cintin C, Johansen JS, Christensen IJ, Price PA, Sorensen S, Nielsen HJ: High serum ykl-40 level after surgery for colorectal carcinoma is related to short survival. Cancer 2002;95:267-274.

39 Shao R, Cao QJ, Arenas RB, Bigelow C, Bentley B, Yan W: Breast cancer expression of ykl-40 correlates with tumour grade, poor differentiation, and other cancer markers. Br J Cancer 2011;105:1203-1209.

40 Zhu CB, Chen LL, Tian JJ, Su L, Wang C, Gai ZT, Du WJ, Ma GL: Elevated serum ykl-40 level predicts poor prognosis in hepatocellular carcinoma after surgery. Ann Surg Oncol 2012;19:817-825.

41 Tschirdeiwahn S, Reis H, Niedworok C, Nyirady P, Szendroi A, Schmid KW, Shariat SF, Kramer G, vom Dorp F, Rubben H, Zarvas T: Prognostic effect of serum and tissue ykl-40 levels in bladder cancer. Urol Oncol 2014;32:663-669.