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Elevated serum bilirubin levels are associated with improved survival in patients with curatively resected non-small-cell lung cancer

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ABSTRACT

Background: Bilirubin levels have been associated with risk of several malignancies. The association between pretreatment serum bilirubin levels and survival of curatively resected non-small-cell lung cancer (NSCLC) is unclear.
Methods: This analysis was performed retrospectively in a cohort of 1617 consecutive patients with bilirubin levels within the range considered normal, who received curative resection for NSCLC. The receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off points. The significance of pretreatment serum total bilirubin (TBIL), direct bilirubin (DBIL), and indirect bilirubin (IBIL) levels in the prognosis of patients with curatively resected NSCLC was investigated.
Results: The cutoff points of serum TBIL, DBIL and IBIL were 9.50 μmol/L, 3.45 μmol/L and 6.95 μmol/L, respectively. High TBIL was observed in 65.2% of entire patient population, high DBIL 50%, and high IBIL 56.8%. The high-TBIL group had significantly lengthened overall survival (OS; hazard ratio [HR], 0.73; 95% confidence interval [CI] 0.63–0.84; $P < 0.001$), disease-free survival (DFS; HR, 0.72; 95% CI 0.64–0.82; $P < 0.001$) and distant metastasis-free survival (DMFS; HR, 0.74; 95% CI 0.60–0.91; $P = 0.004$). Similarly, high-DBIL and high-IBIL levels were associated with longer OS, DFS, and DMFS with significant differences. In multivariable analysis, IBIL level was identified as an independent significant prognostic factor.
Conclusions: Moderately elevated pretreatment bilirubin levels are associated with longer OS, DFS, and DMFS for patients with curatively resected NSCLC. IBIL is an independent prognostic factor in curative resected NSCLC.

1. Introduction

Annually, among more than 1 million new lung cancer cases worldwide [1], non-small-cell lung cancer (NSCLC) constitutes 80–85% [2]. Despite improvements in chemotherapy and target therapy, the 5-year survival of all stages of lung cancer remains under 15%, with less than 7% sufferers living more than 10 years [3]. Diagnosis and treatment of early-staged NSCLC are valued since improving the prognosis of locally advanced and metastatic NSCLC is a tough impediment. Identifying novel prognostic factors of this usually fatal disease is important for early diagnosis, prognosis assessment and more appropriate treatment.

Bilirubin, the major end product of heme degradation, is cleared from the liver, where it is conjugated to form water-soluble direct bilirubin that is secreted into bile [4]. Unconjugated bilirubin, namely indirect bilirubin, accounts for more than 80% of total

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bilirubin. Owning to its potential properties of antioxidation, anti-inflammation and anticancer [5], bilirubin has no longer been regarded only as a marker of hepatobiliary and hematological disorders. In recent years, the relationship between serum bilirubin and cancer risk has drawn much interest. The inverse association between bilirubin and cancer risk has been suggested in lung cancer [6,7], breast cancer [8] and colorectal cancer [9]. Elevated bilirubin is also associated with longer survival in non-metastatic breast cancer [10]. *In vitro* studies indicated that bilirubin induces apoptosis in colon cancer cells [11], exhibits an antiproliferative effect on human adenocarcinoma cells [12], and inhibits cell growth in various tumor cells [13]. However, the relationship between bilirubin levels and survival of lung cancer has not been studied previously.

Bilirubin levels may be a useful marker for cancer prognosis. We hypothesized that lung cancer patients with moderately elevated pretreatment serum bilirubin levels would have a longer survival, given the cytoprotective effects of bilirubin. Thus, we conducted this study to investigate whether serum bilirubin levels at the time of diagnosis are associated with the survival of NSCLC patients who received curative resection as the primary treatment.

2. Patients and methods

This analysis was performed retrospectively in a cohort of 1617 consecutive patients that received curative resection for stage I-IIIA NSCLC at Sun Yat-sen University Cancer Center (SYSUCC) from January 1, 2005 and December 31, 2009. All patients were restaged by the seventh international classification system for lung cancer [14]. The medical Ethics Committee and Clinical Trial Review Committee of SYSUCC approved this study.

Information was collected from electronic and papery individual patient records, and information about survival was obtained from the follow-up registry of SYSUCC. The information collected included age, sex, smoking history, histology, pathological stage, time of diagnosis and relapse/metastasis, and pretreatment serum total bilirubin (TBIL), direct bilirubin (DBIL) and indirect bilirubin (IBIL) levels. All biochemical analyses were performed in the Department of Clinical Laboratory, SYSUCC.

Potentially eligible patients had to have curatively resected pathologically confirmed stage I-IIIA NSCLC without previous therapy other than surgical resection and neoadjuvant chemotherapy. Exclusion criteria included evidence of hepatobiliary or hemolytic disease, previous malignancies, perioperative death, and insufficient data of survival or pretreatment hematology test data. We also excluded patients with total bilirubin levels lower than 3 μmol/L for both sexes, and higher than 40 μmol/L for men and 30 μmol/L for women. To avoid the potential impact of surgery or chemotherapy on bilirubin level, we ensured that each eligible patient had a pretreatment biochemical test.

3. Statistical analysis

The receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of bilirubin (TBIL, DBIL and IBIL) to predict for long-term outcomes and to determine the optimal cut-off points. The cut-off points with highest sum of sensitivity and specificity dichotomized the entire cohort. Chi-square test was used to compare categorical variables.

The following end points were evaluated: overall survival (OS), defined as the interval from the time of being diagnosed to the time of death from any cause; disease-free survival (DFS), defined as the interval from the time of being diagnosed to the time of disease recurrence/metastasis or death from any cause; locoregional relapse-free survival (LRFS) and distant metastasis-free survival (DMFS), defined as the interval from the time of being diagnosed to the time of locoregional relapse and distant metastasis, respectively. Kaplan–Meier curves were drawn for these endpoints, and differences were compared by the log-rank test. The Cox proportional hazards model was used to perform multivariate analyses. Variables reaching a significant level of 0.1 in univariate analyses suggested a trend, and were included in multivariate analysis. Two-tailed *P* values of less than 0.05 were considered as statistically significant.

4. Results

4.1. Patient population

A total of 1617 patients with curative resection for primary stage I-IIIA NSCLC were included in this study (Fig. 1). Table 1 shows the baseline characteristics of the study patient population. The TBIL cut-off points for OS, DFS, LRFS, and DMFS were 9.50, 9.55, 14.95, and 9.95 μmol/L, respectively (Supplementary Fig. 1). The TBIL cut-off point of 9.50 μmol/L for OS was selected as the uniform point in the survival analyses. Similarly, DBIL level of 3.45 μmol/L and IBIL level of 6.95 μmol/L were selected as the cut-off points for survival analyses (Supplementary Figs. 2 and 3). High TBIL was observed in 65.2% of entire patient population, high DBIL 50%, and high IBIL 56.8%. All of the high-TBIL group, the high-DBIL group and the high-IBIL group had more older patients. There were more never smokers, more adenocarcinomas and more advanced tumors in the high-TBIL group and the high-IBIL group. Male patients were more prevalent in the high-DBIL group than the low-DBIL group (Table 1). The distribution of serum TBIL was right-skewed (Fig. 2).

Supplementary material related to this article found, in the online version, at http://dx.doi.org/10.1016/j.canep.2015.06.007.

5. Survival

After a median follow-up of 80.9 (95% CI, 78.8–83.0) months, 360 patients developed locoregional relapse, 371 developed distant metastases, and 815 died for the entire cohort. The high-TBIL group had significantly lengthened OS compared with the low-TBIL group, with a median OS of 78.0 months versus 56.9 months (HR, 0.73; 95% CI 0.63–0.84; $P < 0.001$; Supplementary Fig. 4A). The 5-year OS rates were 58.7% and 48.2%, respectively, among the patients with high TBIL and those with low TBIL. Also, DFS (HR, 0.72; 95% CI 0.64–0.82; $P < 0.001$; Supplementary Fig. 4B) and DMFS (HR, 0.74; 95% CI 0.60–0.91; $P = 0.004$; Supplementary Fig. 4D) were significantly longer among those in the high-TBIL group. The 5-year DFS and DMFS were, respectively, 47.3% and 76.5% for patients in the high-TBIL group, and 36.3% and 69.9% for patients in the low-TBIL group. No significant difference was

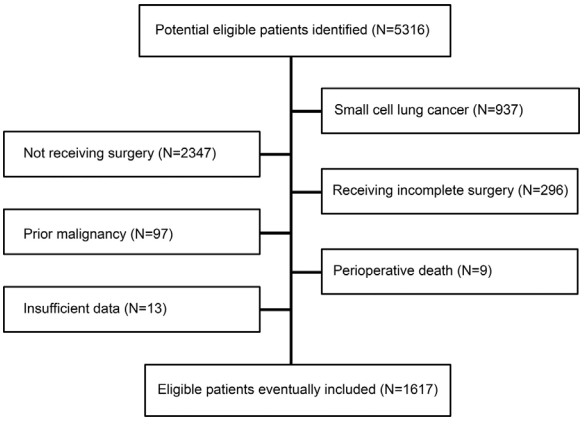

Fig. 1. Flow diagram.

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