Isocitrate Dehydrogenase 1 Is a Novel Plasma Biomarker for the Diagnosis of Non–Small Cell Lung Cancer

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Abstract

Purpose: Effective biomarkers for the diagnosis of non–small cell lung cancer (NSCLC) are needed. We previously showed that isocitrate dehydrogenase 1 (IDH1) is significantly increased in NSCLC tumors. This study aimed to examine the plasma levels of IDH1 in a large patient population to evaluate its effectiveness in NSCLC diagnosis.

Experimental Design: The plasma levels of IDH1, CA125, Cyfra21-1, and CEA were assayed by ELISA. Blood samples were obtained from 1,422 participants (943 patients with NSCLC and 479 healthy controls). The samples were randomly divided into a training set and a test set. Receiver operating characteristic and binary logistic regression analyses were applied to evaluate diagnostic efficacy and establish diagnostic mathematical models.

Results: Plasma IDH1 levels were significantly higher in patients with NSCLCs than in healthy controls (P < 0.001). The diagnostic use of IDH1 in lung adenocarcinoma [area under curve (AUC): 0.858 and 0.810; sensitivity: 77.1% and 76.2%; specificity: 82.9% and 76.6%; in the training set and test set, respectively] was significantly greater than that of CA125, Cyfra21-1, or CEA (P < 0.001). The model combining IDH1 with CEA, CA125, and Cyfra21-1 was more effective for lung adenocarcinoma diagnosis than IDH1 alone (sensitivity and specificity in the training set: 75.8%, 89.6%; test set: 86.3%, 70.7%). In addition, the plasma levels of IDH1 could contribute to the diagnostic model of lung squamous cell carcinoma.

Conclusions: IDH1 can be used as a plasma biomarker for the diagnosis of NSCLCs, particularly lung adenocarcinoma, with relatively high sensitivity and specificity. Clin Cancer Res; 19(18); 5136–45. ©2013 AACR.

Introduction

Lung cancer is the leading cause of cancer death worldwide (1). The goals of this study were to detect and determine the level of isocitrate dehydrogenase 1 (IDH1) in the plasma of patients with non–small cell lung cancer (NSCLC), to evaluate its diagnostic significance, and to show the feasibility of combining IDH1 with existing biomarkers on a large scale.

Reports from United States and China indicate that lung cancer has a high mortality rate; this mortality rate is usually ascribed to late diagnosis (2, 3). With the increases in aging populations and environmental pollution worldwide, the upward trend in lung cancer incidence will continue, and there will be an increased demand for improved lung cancer diagnosis. Current methods for the clinical diagnosis of lung cancer include chest X-ray, computed tomographic (CT) scans, and other imaging techniques. Although imaging data play an important role in diagnosis, they are limited by high false-positive rates and their inability to detect hidden lesions, subclinical lesions, and small metastases. In the National Lung Screening Trial (NLST), 53,454 participants at high risk for lung cancer were enrolled. The participants were randomly divided into different groups and underwent annual screenings with either low-dose CT (26,722 participants) or single-view posteroanterior chest radiography (26,732 participants) for 7 years. Although the use of low-dose CT reduced the mortality attributed to lung cancer, 96.4% of the positive screening results in the low-dose CT set and 94.5% in the radiography set were found to be false-positives (4). Furthermore, the harmful effects of radiation and the expense and overdiagnosis associated with CT scans have been points of controversy. In addition to CT scans, there are many invasive diagnostic methods for
IDH1 Is a Plasma Biomarker for Lung Cancer Diagnosis

Translational Relevance
Lung cancer is the leading cause of cancer death worldwide. Effective blood biomarkers for the diagnosis of non–small cell lung cancer (NSCLC) are urgently needed. In this study of a large number of participants, we showed for the first time that plasma levels of IDH1 are significantly higher in patients with NSCLCs than in healthy controls. The results show that IDH1 could be used in the diagnosis of NSCLCs and is more effective than the existing blood biomarkers of lung adenocarcinoma. Furthermore, by combining IDH1 with CEA, CA125, and Cyfra21-1, we created three mathematical models that had remarkably high diagnostic efficiency for NSCLCs. Thus, we propose that IDH1 is a promising auxiliary diagnostic biomarker for NSCLCs.

Materials and Methods
Patients
Patients with NSCLCs (1,000) and healthy individuals (500) were continuously enrolled from the Department of Thoracic Surgery and Department of Cancer Prevention in the Cancer Institute and Hospital of the Chinese Academy of Medical Sciences from 2007 to 2011. The patients and healthy individuals were enrolled according to the following criteria: patients had no antineoplastic therapy, radiotherapy, or chemotherapy before surgery or cancer diagnosis (10). Because our previous retrospective investigation only evaluated a small cohort of patients with lung cancer (100 cases), we could not precisely estimate the diagnostic efficiency of IDH1 in different subtypes or stages of lung cancer. As such, further analysis of the sensitivity and specificity of IDH1 as a diagnostic biomarker in NSCLCs in a larger population is needed.

Here, we measured the levels of IDH1, CEA, CA125, and Cyfra21-1 in a large clinical population to study the diagnostic efficiency of these markers in NSCLCs and to build models to improve NSCLC diagnosis.
and 454 had lung adenocarcinomas (ADC). NSCLC was defined on the basis of CT and confirmed by histopathology according to the World Health Organization Classification of Tumors of the Lung (17). Tumor stage was defined according to the 7th IASLC/AJCC staging system (18, 19). All samples were randomly separated into a training set and a test set (Supplementary Methods). The patient clinicopathologic information, including age, gender, pathology, differentiation, tumor–node–metastasis (TNM) stage, and history of smoking are shown in Table 1. The data collection and analyses were conducted by independent researchers. The study was approved by the medical ethics committee of the Cancer Institute and Hospital of the Chinese Academy of Medical Sciences.

### Specimen characteristics

Preoperative peripheral blood samples were collected in EDTA and anticoagulant-free tubes and processed according to standard protocols. Within 30 minutes of collection, the blood samples were centrifuged at 3,000 rpm at room temperature for 10 minutes, and the supernatants were divided into 200 μL aliquots, flash frozen, and stored at −80°C until testing.

### ELISA

Plasma IDH1 assays were conducted by a commercial laboratory (USCN Life Science Laboratories, Inc.). All samples were assayed simultaneously. All laboratory personnel were blinded to the identities of the samples. A commercially available ELISA kit (E97839Hu 96 Test, USCN Life Science) was used according to the manufacturer’s recommendations. The samples and kit components were equilibrated to room temperature before the assay. Aliquots of 100 μL of the plasma samples in standard diluent were added to the appropriate wells and covered with a plate sealer. The plates were incubated for 2 hours at 37°C. The liquid was removed from each well, and an aliquot of solution A containing secondary antibodies (diluted 1:200) was added, and the samples were incubated for another 1 hour at 37°C. After 5 washes with buffer, 100 μL solution B containing hydrogen peroxide was added, and the samples were incubated for 30 minutes. Color development was achieved by adding 90 μL 3,3,5,5-tetramethylbenzidine per well as a substrate. To stop the reaction, 50 μL sulfuric acid was added. The optical density (O.D.) was measured at 450 nm on a Synergy 2 multimode plate reader (Biotek). The concentration of IDH1 was

### Table 1. The characteristics of the patient population

<table>
<thead>
<tr>
<th>Training set</th>
<th>Healthy controls</th>
<th>Test set</th>
<th>Healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCC</td>
<td>ADC</td>
<td></td>
<td>SCC</td>
</tr>
<tr>
<td>No. of patients</td>
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<td>227</td>
<td>240</td>
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<tr>
<td>Age, y</td>
<td>Median (range)</td>
<td></td>
<td>Median (range)</td>
</tr>
<tr>
<td>Female/male</td>
<td>11/234</td>
<td>110/117</td>
<td>119/121</td>
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<tr>
<td>Lifetime smoking history (pack-years)*</td>
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<tr>
<td>0–25</td>
<td>60</td>
<td>35</td>
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<td>&gt;25</td>
<td>161</td>
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<td>TNM stage</td>
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<tr>
<td>I</td>
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</table>

*The relationship between the smoking history and IDH1 level (training and test sets: Pearson χ² test, SCC: P < 0.01; ADC: > 0.05; NSCLC: < 0.01).
calculated with a quadratic polynomial fitting curve. When the concentration of IDH1 was less than 0.53 U/L, the lower limit of the standard curve, the value was set to zero. The mean intra-assay coefficient of variation from the quality control samples was 6.7% (n = 20).

Analysis of tumor markers

The tumor markers CEA, CA-125, and Cyfra21-1 were analyzed with an Elecsys immunoassay analyzer (Roche Diagnostics). The upper normal limits for the tumor markers are 5 ng/mL for CEA, 35 U/mL for CA-125, and 3.3 ng/mL for Cyfra21-1.

Statistical analysis

The standard curve was created in Curve Expert 1.3. SPSS (version 13.0) and MedCalc (version 9.6.2.0) were used for data analysis. The differences between plasma sample sets were evaluated by the Mann–Whitney U test using continuous variables and nonparametric analyses by GraphPad Prism version 5 for Windows. Receiver operating characteristic (ROC) curves were plotted to assess the sensitivity, specificity, and areas under the curves (AUC) with a 95% confidence interval (CI). The optimum cutoff value for diagnosis was determined by maximizing the specificity at 95% in the training set. To assess whether the diagnostic efficiency of IDH1 in combination with CEA, CA-125, and Cyfra21-1 was superior to that of the 4 individual biomarkers alone, new variable models for NSCLCs were created on the basis of equations obtained by binary logistic regression. The regression equations for all comparisons are provided in the appendix (Supplementary Table S1). Differences were considered statistically significant when the P value was lower than 0.05 (2-sided test).

Results

We recruited a total of 1,422 participants (943 patients with NSCLCs and 479 healthy controls). The NSCLCs and healthy control samples were randomly divided into a training set of 712 samples and a test set of 710 samples (Fig. 1). The characteristics of the patients in the training and test sets are summarized in Table 1. The training and test set populations were comparable with respect to age and sex.

IDH1 plasma levels in NSCLC patients and healthy controls

We analyzed the plasma IDH1 levels (median ± IQR; IQR, interquartile range) in each participant using an ELISA assay. In the training set, the median plasma IDH1 levels of patients with ADCs and SCCs were 2.42 ± 1.82 and 1.87 ± 2.01 U/L, respectively, higher than that of the healthy controls (0.79 ± 0.33 U/L; Fig. 2A, P < 0.0001, Mann–Whitney U test). In the test set, the median IDH1 levels of patients with ADCs and SCCs were 2.35 ± 1.51 and 2.03 ± 1.79 U/L, respectively, also higher than that of the healthy controls.
controls (0.95 ± 1.62 U/L; Fig. 2B, P < 0.0001, Mann–Whitney U test). In the whole set (i.e., the combined training and test sets), the median IDH1 levels in patients with ADCs and SCCs were 2.39 ± 1.77 and 1.96 ± 1.85 U/L, respectively, significantly higher than the level observed in healthy controls (0.88 ± 1.46 U/L; Fig. 2C, P < 0.0001, Mann–Whitney U test). In addition, the median level of plasma IDH1 in the patients with ADCs was significantly higher than that in the patients with SCCs (P = 0.012). These results indicate that plasma IDH1 can be used as a biomarker for the diagnosis of lung cancer and has a better diagnostic efficacy for identifying patients with ADCs than SCCs.

Next, we analyzed the correlation between the plasma IDH1 level and the clinical characteristics of patients with ADCs and SCCs. In the patients with ADCs, the median level of plasma IDH1 in patients with stage T2b–T4 (2.72 ± 2.23 U/L) was significantly higher than that in patients with stage T1a–T2a disease (2.31 ± 1.72 U/L; P < 0.05, Supplementary Fig. S1A). In contrast, although the median level of plasma IDH1 in patients with SCCs with stage T2b–T4 (2.11 ± 2.18 U/L) was higher than that in patients with SCCs with stage T1a–T2a (1.87 ± 2.56 U/L), this difference was not significant (Supplementary Fig. S1B). In addition, we did not observe any correlation between plasma IDH1 level and other patient clinical characteristics such as age, gender, smoking history, lymph node metastasis, or TNM stage.

**Discussion**

We previously showed that IDH1 mRNA and protein expression are elevated in tumor tissues compared with matched normal tissues (10). This suggests that IDH1 plasma levels might be a useful biomarker for the diagnosis of patients with NSCLCs. We have 2 hypotheses for the elevated levels of IDH1 in blood, which are currently being investigated: IDH1 may be secreted extracellularly under exceptional circumstances or released into the blood by cell damage and cell death. In addition, plasma IDH1 levels were positively correlated with T stage in patients with NSCLCs, strongly suggesting that IDH1 might be a useful diagnostic biomarker.

In this report, we showed that the plasma IDH1 level was significantly elevated in 976 patients with NSCLCs compared with 479 healthy controls. We also tested 3 existing clinical biomarkers, CEA, CA125, and Cyfra21-1, in all the samples and compared their diagnostic efficacy to that of IDH1. Then, we established the AUCs for biomarker panels and determined the appropriate balance between sensitivity and specificity in the choice of cutoff point. To reduce the misdiagnosis rate, we set the specificity at 95% and compared the sensitivity between panels. We identified several multiprotein panels that offer high sensitivity and specificity and provide a significant improvement over the use of single markers for the discrimination of NSCLCs from healthy controls.

There are already several good markers for the diagnosis of SCCs, such as Cyfra21-1 and SCCA, whereas good markers for ADCs are lacking (6). Cyfra21-1 was shown to have good diagnostic capability in a small cohort of patients with SCCs, with a high sensitivity (69%–79%) but an unsatisfactory efficacy, similar to other ADC diagnostic markers.
As such, we focused on ADC markers such as CEA and CA125. CA125 is used mainly for ovarian cancer screening and diagnosis (23, 24), whereas CEA is used for the diagnosis and prognosis of several types of cancer, including colon cancer (25, 26). Both CEA and CA125 were useful for monitoring recurrence and evaluating prognosis in NSCLCs but only performed moderately in diagnosing NSCLCs (27–33). We also included Cyfra21-1 because it is useful for the diagnosis of both SCCs and overall NSCLCs. Finally, we included CEA, CA125, and Cyfra21-1 in our panel. Our results confirmed that Cyfra21-1 is a good marker for SCC diagnosis, with a much better sensitivity than IDH1, CEA, or CA125 (Table 2). In contrast, for ADC diagnosis, IDH1 showed higher sensitivity than CEA, CA125, or Cyfra21-1 (Table 2). In the training set, the combination of IDH1 with CEA, CA125, and Cyfra21-1 improved the diagnostic sensitivity to 63.4% in ADCs, 63.3% in SCCs, and 60.4% in NSCLCs, with a specificity of 95%. These results were further validated in the test set (Table 2). Our analyses of a large cohort of 943 NSCLC patients established that IDH1 is a highly effective auxiliary diagnostic marker for ADCs.

Figure 3. ROC curve analyses of the use of IDH1, CEA, CA125, and Cyfra21-1 to differentiate NSCLC cases and controls. A, ROC curves for IDH1, CEA, CA125, and Cyfra21-1 for patients with ADCs versus controls in the training (left) and test sets (right), respectively. B, ROC curves for IDH1, CEA, CA125, and Cyfra21-1 for patients with SCCs versus controls in the training (left) and test sets (right), respectively. C, ROC curves for IDH1, CEA, CA125, and Cyfra21-1 for patients with NSCLCs versus controls in the training (left) and test sets (right), respectively.
In this study, the SCC and NSCLC groups had a significantly greater smoking history than the control group (Table 1). However, there were no significant differences between the smoking histories of the ADC group and the control group (Table 1). Pearson correlation analysis indicated no correlation between IDH1 levels and smoking history (pack-years) in any of the groups (Supplementary Table S2). We also stratified the patients and controls in our study according to smoking history. The AUCs of the ROC curves were similar for smokers and non-smokers (Supplementary Table S3).

Although the CT scan, which is the currently recommended method of diagnosis, has several advantages, including its noninvasive nature, there are also some disadvantages to this method, such as radiation, cost, and low specificity (34–36). In contrast, our blood-based test is more practical than a CT scan because it uses a peripheral blood sample obtained by routine venipuncture. Our tests require less than 100 μL of plasma, do not require significant operator expertise, and are inexpensive and highly reproducible. In addition, our samples do not require special treatment such as extraction, purification, or reverse
Table 2. The diagnostic efficiency of models in differentiating NSCLC cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Training set</th>
<th></th>
<th></th>
<th>Test set</th>
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<tbody>
<tr>
<td></td>
<td>AUC (95% CI)</td>
<td>SN (%)</td>
<td>SP (%)</td>
<td>PPV (%)</td>
<td>NPV (%)</td>
<td>Positive LR</td>
</tr>
<tr>
<td>ADC vs. control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDH1</td>
<td>0.858 (0.823–0.889)</td>
<td>56.0</td>
<td>95.0</td>
<td>91.4</td>
<td>69.5</td>
<td>11.19</td>
</tr>
<tr>
<td></td>
<td>CEA</td>
<td>0.600 (0.553–0.644)</td>
<td>38.8</td>
<td>82.9</td>
<td>68.2</td>
<td>58.9</td>
</tr>
<tr>
<td></td>
<td>CA125</td>
<td>0.704 (0.661–0.746)</td>
<td>14.1</td>
<td>99.2</td>
<td>94.1</td>
<td>55.0</td>
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<td></td>
<td>Cyfra21-1</td>
<td>0.648 (0.603–0.691)</td>
<td>30.8</td>
<td>97.5</td>
<td>70.0</td>
<td>57.2</td>
</tr>
<tr>
<td>IDH1 + CEA + CA125 + Cyfra21-1</td>
<td>0.890 (0.858–0.917)</td>
<td>63.4</td>
<td>95.0</td>
<td>92.3</td>
<td>73.3</td>
<td>12.69</td>
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<tr>
<td>SCC vs. control</td>
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<tr>
<td>IDH1</td>
<td>0.778 (0.739–0.815)</td>
<td>42.0</td>
<td>95.0</td>
<td>89.6</td>
<td>61.6</td>
<td>8.41</td>
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<tr>
<td></td>
<td>CEA</td>
<td>0.534 (0.488–0.579)</td>
<td>15.1</td>
<td>82.9</td>
<td>47.4</td>
<td>48.9</td>
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<tr>
<td></td>
<td>CA125</td>
<td>0.747 (0.706–0.785)</td>
<td>12.2</td>
<td>99.2</td>
<td>93.7</td>
<td>52.5</td>
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<tr>
<td></td>
<td>Cyfra21-1</td>
<td>0.846 (0.811–0.877)</td>
<td>64.9</td>
<td>87.5</td>
<td>84.1</td>
<td>70.9</td>
</tr>
<tr>
<td>IDH1 + CA125 + Cyfra21-1</td>
<td>0.914 (0.886–0.938)</td>
<td>63.3</td>
<td>95.0</td>
<td>92.8</td>
<td>71.7</td>
<td>12.65</td>
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<tr>
<td>NSCLC vs. control</td>
<td></td>
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<tr>
<td>IDH1</td>
<td>0.817 (0.786–0.845)</td>
<td>48.7</td>
<td>95.0</td>
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<td>48.5</td>
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<td>CEA</td>
<td>0.565 (0.528–0.602)</td>
<td>26.5</td>
<td>82.9</td>
<td>75.3</td>
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<td>CA125</td>
<td>0.726 (0.692–0.759)</td>
<td>13.4</td>
<td>99.2</td>
<td>96.9</td>
<td>36.8</td>
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<td>Cyfra21-1</td>
<td>0.751 (0.717–0.782)</td>
<td>48.5</td>
<td>87.5</td>
<td>88.4</td>
<td>46.4</td>
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<td>IDH1 + CA125 + Cyfra21-1</td>
<td>0.896 (0.871–0.918)</td>
<td>60.4</td>
<td>95.0</td>
<td>96.0</td>
<td>54.9</td>
<td>12.08</td>
</tr>
</tbody>
</table>

Abbreviations: LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

*The diagnostic cut-off value was 2.19 U/L.
transcription (37). Thus, measuring IDH1 levels in patient blood can be a convenient, efficient, and reliable auxiliary method for the diagnosis of NSCLCs, particularly ADCs. Integrated analyses of plasma IDH1, CEA, Cyfra21-1, and CA125, in conjunction with imaging and clinicopathologic examination information, may provide a better panel of diagnostic tools for the rapid diagnosis of NSCLCs. This will enable the timely and effective treatment of NSCLCs and the improvement of cancer patient mortality.

However, because most of the participants in our study originated from northern China, common confounding variables and comorbid conditions cannot be eliminated. Because of the complexity of the causes of lung cancer and the potential differences in the genomic and molecular signatures of patients from different populations, future studies with an independent cohort of patients are needed. It will also be necessary to determine whether plasma IDH1 is a specific biomarker of NSCLCs by examining it in patients with other cancer types. Although the IDH1 levels in patients and controls are highly significantly different in our study, and the sensitivity and specificity of IDH1 are relatively good compared with the existing markers, there is some overlap in patients and controls (Fig. 2). Therefore, at this stage, IDH1 can only be used as an adjunct approach for diagnosis. In addition, the molecular mechanisms and clinical implications of elevated IDH1 require further investigation.

This is the first large-scale study to report the clinically diagnostic relevance of IDH1 as a plasma marker for NSCLCs in a training set and a test set. Our results show that plasma IDH1 could be used to assist the diagnosis of NSCLCs, particularly ADCs. Hence, we recommend detecting IDH1 along with CEA, CA125, and Cyfra21-1 and using the presented models to aid in diagnosis.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: N. Sun, F. Tan, X. Tan, J. He
Development of methodology: N. Sun, F. Tan, X. Tan, J. He
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): N. Sun, Z. Chen, B. Zhang, R. Yao, C. Zhou, X. Tan, K. Shao, B. Qiu, Y. Yu, Y. Zhao, X. Shi, J. He
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): N. Sun, Z. Chen, J. Li, X. Tan, M. Y. F. He, J. Sun, J. He
Writing, review, and/or revision of the manuscript: N. Sun, Z. Chen, F. Tan, Z. Liu, X. Tan, J. He
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): N. Sun, B. Zhang, X. Tan, F. Zhou, N. Li, S. Wang, J. He
Study supervision: Y. Gao, X. Tan, J. He

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References
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