Purple-bluish tongue is associated with platelet counts, and the recurrence of epithelial ovarian cancer

Hao Jian, Zhu Cuihong, Cao Rui, Yang Xue, Ding Xiuli, Man Yanan, Wu Xiongzhi

OBJECTIVE: To evaluate the relationship between purple-bluish tongue and platelet counts, and further to examine their associations with the recurrence of epithelial ovarian cancer.

METHODS: A total of 82 epithelial ovarian cancer patients were enrolled in this study. Cluster analysis was used for grouping patients’ $P_{RGB}$ (Red-R; Green-G; Blue-B; Average percentage of RGB, $P_{RGB}$) values. Receiver operating characteristic (ROC) curve was performed for detecting the diagnostic standard of purple-bluish tongue. $\chi^2$ test was used to assess the relationship between purple-bluish tongue and platelet counts, and the recurrence of epithelial ovarian cancer. The perioperative (preoperative) platelet level was examined with tongue image and disease recurrence.

RESULTS: Tongue images were classified into two groups basing on $P_{RGB}$ values of images by cluster analysis. The numbers of cases in cluster "1" (normal color tongue) was 16 and cluster "2" (purple-bluish tongue) was 66. Two groups of $P_{RGB}$ values, classified by cluster analysis, were significantly correlated with vision-based tongue color recognition (Kappa = 0.852, $P < 0.001$). ROC curve showed that the ratio of PB to PR had the highest diagnostic value. The sensitivity and the specificity of the ratio of PB to PR were 95.3% and 88.9% respectively and the optimal cut-off point was 0.71. Purple-bluish tongue was significantly correlated with increased platelet counts ($P < 0.001$). Both the increased platelet counts ($P = 0.01$) and purple-bluish tongue were associated with recurrence of epithelial ovarian cancer ($P < 0.001$).

CONCLUSION: The ratio of $P_{s}$ to $P_{e}$ greater than 0.71 could serve as an indicator for purple-bluish tongue diagnosing used in symptom pattern identification in Traditional Chinese Medicine. Purple-bluish tongue, associated with increased platelet counts, was also closely correlated with the recurrence of epithelial ovarian cancer.

Key words: Ovarian epithelial cancer; Tongue inspection; Cluster analysis; Recurrence; Platelet count

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INTRODUCTION

Ovarian cancer is the fifth-leading cause of cancer death among women accounting for nearly 3% of all new cancer patients in the United States. Epithelial ovarian cancer (EOC), encompassing 90% of all ovarian malignant tumors, is an aggressive malignancy and one of the most lethal malignant gynecological tumors. Patients with EOC usually present with advanced stage disease due to the deep location of the ovary, as well as the lack of typical early symptoms and effective diagnostic methods clinically. Although serum CA125 is commonly used as a tumor marker for ovarian cancer clinically, its sensitivity and specificity is insufficient. So, while a high remission rate of EOC might be reached after surgical treatment and chemotherapy, the propensity for the common recurrence and early peritoneal dissemination of EOC ultimately result in high mortality. Therefore, exploring the clinical prognostic factor for EOC is of great significant.

For thousands of years, tongue diagnosis has been one of the four facets in the diagnostic method of symptom pattern identification used in Traditional Chinese Medicine (TCM). A tongue image can reflect the physical condition. Purple-bluish tongue is largely reflecting the status of physical hypercoagulation. Clinical experience shows that the recurrent EOC patients usually have purple-bluish tongues. Platelets play an important role in hypercoagulation phenomenon. Whether the purple-bluish tongue was related with the high platelet level is unclear (Figure 1). Thus, in this study, we investigated the relationship between tongue color and increased platelet counts in EOC patients and explored the possibility of purple-bluish tongue in predicting the relapse of EOC.

Figure1 Purple-bluish tongue versus normal color tongue
A is the representative picture for patient with epithelial ovarian cancer who has normal color tongue. The average percentage of RGB values: PR = 43.14, PB = 27.39, PG = 29.47. The ratio of PB to PR is 0.64; B is standing for patient with epithelial ovarian cancer whose tongue is purple-blue. Three points were chosen at random; for purple-bluish tongue, three points were chosen at the purple-bluish part by operators randomly. The average percentage of RGB values: PB = 34.07, PB = 35.37, PB = 30.56. The ratio of PB to PB is 1.04.

MATERIALS AND METHODS

Patients
The data of 82 EOC patients with their tongue photos in Tianjin Medical University Cancer Institute and Hospital from June 1999 to December 2011 were analyzed. All these tongue photos were taken at the time after surgeries or peri-recurrence. Among the total patients, 26 EOC patients underwent surgeries on other hospitals, whose perioperative platelet data were not found. The study was approved by the Hospital Ethics Committee. Pathological test was performed to confirm EOC and all patients were re-examined by ultrasound, pelvic CT and tumor markers detection periodically after surgery or systemic therapy (usually performed at three months, six months, and then once a year after surgery). All patients received primary surgical staging according to the International Federation of Gynecologists and Obstetricians (FIGO, 1989) guidelines. The tongue photos were taken in the same background by the camera (SONY DSC-H7). Patients were informed that the detail information of their faces was not been collected on photos. Informed consents were obtained from all participants involved in this study.

The categorical variables of EOC patients including age, histological type, stage, platinum combined with paclitaxel and postoperative residual disease were retrospectively abstracted from medical records under the institutional review board-approved protocol. Platelet counts were measured at perioperation (preoperative). Peripheral blood was obtained from the cubital vein of the patients.

Computerized analysis versus visual recognition method for tongue color

Vision-based tongue color recognition is widely used in symptom pattern identification in TCM practice. In this study, tongue colors were grouped into normal (not purple-blue) and purple-blue by three experienced doctors that ruled out the subjective factors basically. "2" was used to represent purple-bluish tongue and "1" was used to stand for normal color tongue. Cluster analysis operated by SPSS turned visual recognition into computerized identification. Three primary colors of light, R (red), G (green) and B (blue), were used to produce the color image. We used Adobe Photoshop CS5 to analyze three points on patients' tongues (for purple-bluish tongue, three points were chosen at the purple-bluish part by operators randomly; for normal color tongue, three points were chosen at random) and collected the data of the RGB values. 82 patients' tongues were analyzed by Photoshop CS5. The average percentage of R, G and B values (PR, PG, PB) were classified into two groups via cluster analysis. We assessed the relationship between the two cluster analytic groups and the groups classified via vision-based recognition, and tried to find out a computerized standard for visual-based recognition and process the tongue colors identification. Purple-bluish versus normal color tongue was shown in Figure 2.
Statistical analysis

Data were presented as numbers and frequencies for categorical variables, and mean ± standard deviation (\( \bar{x} \pm s \)) for continuous variables. Fisher exact test was used to compare the cluster results and visual recognition results of tongue color. Independent-\( T \) test was used to test the difference between the two groups classified by cluster analysis. We used receiver operating characteristic (ROC) curve to identify the optimal cut-off values of PRGB ratios for representing vision-based tongue color recognition. The sensitivity and specificity of optimal cut-off value were calculated from ROC curves. \( \chi^2 \) test was used to determine whether there were significant differences among the baseline characteristics, the recurrence of disease and the tongue images. Independent-sample T test was used to detect the relationship between the platelet counts and tongue color as well as recurrence. Statistical analysis was performed by SPSS (Version: 16.0, Chicago, IL, USA). \( P \) values < 0.05 were considered statistically significant.

RESULTS

Characteristics of patients

The median age of 82 patients was 53 years (range, 26-76 years). There were 24 patients with early stage (FIGO I / II) disease and 58 patients with stage III / IV disease. Among the 82 patients, 57 patients were diagnosed with serous carcinoma, and 25 patients with non-serous carcinoma. Chemotherapy, Platinum combined with paclitaxel, was used in 75 patients. 46 patients had postoperative residual disease. No significant difference was found between the population characteristics and tongue images (Table 1).

Computerized recognition, instead of visual recognition, was used for tongue color identification

PRGB values which were classified into two groups as cluster “1” (normal color tongue) and cluster “2” (purple-bluish tongue) by cluster analysis had significant difference (Table 2). The numbers of cases in normal color tongue was 16 and purple-bluish tongue was 66. Compared with purple-bluish tongue, the PR value was increased while PB, PG values were decreased in normal color tongue (Table 2). The result of Fisher exact test and correlation analysis reflected that the result of cluster analysis was consistent with visual recognition, correlation index was 0.852 (\( P < 0.001 \), Table 3). Thus the two groups classified by cluster analysis were represented normal color and purple-bluish tongue. In order to find a computerized standard to replace vision-based tongue color recognition, the ROC curves was used. Due to the reverse change of PRGB values in

<table>
<thead>
<tr>
<th>Clinicopathological parameter</th>
<th>Tongue image</th>
<th>( \chi^2 ) value</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Purple-bluish tongue</td>
<td>Normal color tongue</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>≤53</td>
<td>33</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>&gt;53</td>
<td>33</td>
<td>9</td>
</tr>
<tr>
<td>Histological type</td>
<td>Serous/Non-serous</td>
<td>46</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>TNM stage</td>
<td>I / II</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>III / IV</td>
<td>47</td>
<td>11</td>
</tr>
<tr>
<td>Chemical therapy</td>
<td>Yes</td>
<td>62</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Residual disease</td>
<td>Yes</td>
<td>39</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>27</td>
<td>9</td>
</tr>
</tbody>
</table>

Notes: chemical therapy refers to platinum combined with paclitaxel; residual disease refers to postoperative residual.
the two cluster analytic groups, we used the ratios among PRGB to process further exploration. The ratio of PB to PR (B/R) had a higher diagnostic value for tongue color classification compared to the ratio of PG to PR (G/R) and PB to PG (B/G) (Figure 3). In terms of the highest sensitivity and specificity of B/R, its optimal cut-off value (0.71), was used as a boundary point for distinguishing normal color and purple-bluish tongue, with which the sensitivity and specificity are 95.3% and 88.9% respectively.

**DISCUSSION**

In this study, we changed vision-based recognition of purple-bluish tongue into computerized recognition and tried to find out a computerized standard to represent the experienced recognition for purple-bluish tongue. Normal color and purple-bluish tongue, classified by experienced doctors were re-grouped by cluster analysis based on PRGB values. Because of the highest sensitivity and specificity of B/R for vision-based tongue color recognition, we chose the optimal cut-off value of B/R as the boundary point for diagnosing purple-bluish tongue, and we considered that the standard of purple-bluish tongue was B/R > 0.71.

Our data showed that EOC patients with purple-bluish tongue had a higher risk of recurrence. Thus, the long-term character of tongue image can predict EOC patient’s relapse in an early stage. Plasmatic hypercoagulation, a well-recognized phenomenon in patients, is associated with numerous cancers such as breast, lung, as well as ovarian cancer. The mainly cause of plasmatic hypercoagulation is increased and activated platelet. Growing cancer cells activate and aggregate platelets. Conversely, platelets contribute to cancer process. Platelets play in abetting cancer progression through numerous pathways: integrating with tumor cells for protecting tumor against natural killer (NK) cells attack, stimulating tumor angiogenesis, and correlate with tumor recurrence.

### Table 2 Colorimetric analysis of purple-bluish tongue and normal color tongue ( \( \bar{x} \pm s \) )

<table>
<thead>
<tr>
<th>Item</th>
<th>Average percentage of RGB</th>
<th>( P_s )</th>
<th>( P_t )</th>
<th>( P_b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purple-bluish tongue</td>
<td>38.6±2.0</td>
<td>29.6±1.2</td>
<td>31.7±1.6</td>
<td></td>
</tr>
<tr>
<td>Normal color tongue</td>
<td>44.8±2.6</td>
<td>27.2±2.3</td>
<td>27.6±2.9</td>
<td></td>
</tr>
</tbody>
</table>

*Notes: RGB: red-R, green-G, blue-B.*

### Table 3 Computerized and visual recognition of tongue color analyzed by Fisher exact test

<table>
<thead>
<tr>
<th>Item</th>
<th>Computerized</th>
<th>Correlation index (Kappa)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual recognition</td>
<td>+</td>
<td>63</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>1</td>
<td>15</td>
</tr>
</tbody>
</table>

*Notes: +: Purple-bluish tongue; -: Normal color tongue.*

### Table 4 Relationship between purple-bluish tongue and recurrence

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>Tongue image</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Purple-bluish tongue</td>
<td>61</td>
</tr>
<tr>
<td>No</td>
<td>Normal color tongue</td>
<td>5</td>
</tr>
</tbody>
</table>

### Table 4 Relationship between purple-bluish tongue and recurrence

**Tongue images for recurrence predicting**

Among the 67 patients who suffered the recurrence of EOC, 61 patients had purple-bluish tongues. \( \chi^2 \) test was identified that patients with purple-bluish tongues were significantly correlated with EOC recurrence (\( P < 0.001 \), Table 4).

**Association of platelet counts with tongue images, and EOC recurrence**

Elevated platelet level was observed in patients with purple-bluish tongue group and normal color tongue group. The platelet levels of the two groups had significantly difference (\( P = 0.001 \)) and the \( \bar{x} \pm s \) of platelet level was (306 ± 86) × 10^9/L (purple-bluish tongue group), (197 ± 93) × 10^9/L (normal color tongue group), respectively. The recurrence of EOC was significantly associated with platelet count increasing. The \( \bar{x} \pm s \) of platelet level for patients relapse in this study was (300 ± 84) × 10^9/L, which was significantly higher than that of patients without recurrence (\( P = 0.01 \), Table 5).
mor-derived thrombopoietic cytokines and platelet-derived growth factor receptor alpha are believable to foster tumor growth in ovarian cancer. The vitro research also proved human ovarian carcinoma cells proliferation rate increased significantly after co-incubation with platelets. Our study showed that the platelet level of the purple-bluish tongue group was \((306 \pm 86) \times 10^9/L\), which was higher than that of normal color tongue group. The purple-bluish tongue was related with the high platelet level. In addition, the increased platelet was also correlated with the recurrence of EOC patients. It also had been proved that increasing platelet could promote tumor growth. We also investigated that patients with purple-bluish tongue were significantly correlated with EOC recurrence. Thus, we could explain the relationship between purple-bluish tongue and EOC recurrence by the platelet level objectively. Due to the promotion effect of platelet on EOC progression, its biological superficial sign-tongue with purple-bluish color can play a role in predicting the recurrence of EOC.

In conclusion, the purple-bluish tongue might be mainly caused by platelet count increasing. Patients with purple-bluish tongue have a higher risk for the recurrence of EOC.

REFERENCES