Evaluation of the Accuracy of Human Kallikrein-6, Cancer Antigen-125, and Human Epididymis - 4 in Predicting Ovarian Cancer

Evaluasi Akurasi Human Kallikrein-6, Cancer Antigen-125, dan Human Epididymis-4 dalam Memprediksi Kanker Ovarium

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Abstract

Objective: To evaluate the accuracy of hK6, HE4, and CA125 in predicting the malignancy of ovarian mass.

Methods: The design of this study was cross-sectional. This study was conducted in the Obstetrics and Gynecology Clinic, Sanglah Hospital, Denpasar, between the period of September 2014 and August 2016. Samples were all patients with ovarian tumors who underwent surgery at Sanglah Hospital, Denpasar. Data analysis was performed using McNemar and chi square test in SPSS for windows version 17.0.

Results: 22 samples were obtained. P > 0.05 value of age and parity variables indicated no differences between the two groups. There is no accuracy differences (sensitivity, specificity, positive predictive value, negative predictive value) of hK6 compared to histopathology examination in diagnosing ovarian cancer (p = 1). There is no accuracy differences (sensitivity, specificity, positive predictive value, negative predictive value) of HE4 compared to histopathology examination in diagnosing ovarian cancer (p = 1). There is no accuracy difference (sensitivity, specificity, positive predictive value, negative predictive value) of CA125 compared to histopathology examination in diagnosing ovarian cancer (p = 0.687).

Conclusion: There was no accuracy differences (sensitivity, specificity, positive predictive value, negative predictive value) found between hK6, CA125, HE4 compared to histopathology examination in predicting ovarian cancer.

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Keywords: cancer antigen 125, human epididyism-4, human kallikrein 6, ovarian cancer

INTRODUCTION

Ovarian cancer is a major burden in the field of gynecology oncology, due to high rate of mortality resulted from this cancer.1 Increasing ratio of morbidity and mortality in ovarian cancer patients is due to progression of disease that shows no symptoms found until metastasis. 70% of women with ovarian cancer are diagnosed at advanced stage. The five year survival rate of ovarian cancer is 85% when diagnosed at early stage (stage I and II), but may decrease to less than 20% if diagnosed at advanced stage (stage III or IV).2

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Serum of CA125 tumor marker to predict the presence of malignancy in patients with ovarian mass has lower sensitivity and specificity in pre and postmenopausal women.\(^3\) Several studies conducted to diagnose ovarian cancer in patients with ovarian mass using tumor marker HE4 and combination of HE4 and CA125 have shown that HE4 has higher sensitivity and specificity compared to CA125.\(^4\)

Kallikrein 6 gene is a trypsin-like serine protease of human gene, family kallikrein that has great potential to be developed as a tool for early detection for ovarian cancer and various preliminary research have been conducted to support towards it and result of the research can be used as rationale that hK6 can be used as a medium or tool for early detection of ovarian cancer.\(^5\)

Based on explanation elaborated above, assessment of the correlation or relationship between hK6 with ovarian cancer will be performed. This study is expected to be a reference or additional consideration to support usage hK6 as the early detection of ovarian cancer diagnostic.

**METHOD**

We used cross-sectional study design. This study was conducted at the Obstetrics and Gynecology Clinic, Sanglah Hospital, Denpasar, during the period between September 2014 and August 2016. The subjects were all patients with ovarian tumors who came to Obstetrics Clinic of Sanglah Hospital and underwent surgery in Sanglah Hospital, Denpasar. Data analysis was performed using SPSS for Windows version 17.0.

**RESULT**

In this study, T-independent test was conducted toward age and parity variable between the two groups. As seen in Table 1, \(p\) value > 0.05 of age and parity was obtained, indicated no differences between both groups.

To determine diagnostic test of hK6 toward histopathology in the diagnosis of ovarian cancer, it was analyzed using Chi-Square test. The results of the analysis are presented in the following table.

Table above with 2x2 cross table, showed 80.0% sensitivity, 75.0% specificity, 72.7% positive predictive value, 81.8% negative predictive value, 27.3% false positive, 18.2% false negative values, and 77.3% accuracy. McNemar test showed no accuracy differences of hK6 (sensitivity, specificity, positive predictive value, negative predictive value) compared to histopathology examination in diagnosing ovarian cancer (\(p = 1.00\)).

To determine diagnostic test of HE4 compared to histopathology in diagnosis of ovarian cancer, Chi-Square test analysis was conducted. Results are presented in Table 3.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Malignancy group (n=10)</th>
<th>Benign tumor group (n=12)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>Mean 52.80 DS 16.72</td>
<td>Mean 50.50 DS 14.94</td>
<td>0.737</td>
</tr>
<tr>
<td>Parity</td>
<td>Mean 2.10 DS 1.10</td>
<td>Mean 2.08 DS 1.88</td>
<td>0.981</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ovarian cancer</th>
<th>Malignant</th>
<th>Benign</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>hK6</td>
<td>High</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>12</td>
<td>22</td>
</tr>
</tbody>
</table>
Table above with a 2x2 cross table showed 70.0% sensitivity, 83.3% specificity, 77.8% positive predictive value, 76.9% negative predictive value, 22.2% false positive, 23.1% false negative values, and 77.3% accuracy. McNemar test showed no differences of accuracy (sensitivity, specificity, positive predictive value, negative predictive value) HE4 compared to histopathology examination in diagnosing ovarian cancer (p = 1.00).

To determine diagnostic test of CA125 compared to histopathology in diagnosis of ovarian cancer, Chi-Square test analysis was conducted. The results of analysis is presented in Table 4.

Table above with a 2x2 cross table showed 60.0% sensitivity, 83.3% specificity, 75.0% positive predictive value, 71.4% negative predictive value, 25.0%, false positive, 28.6%, false negative values, and 72.7% accuracy. McNemar test showed no accuracy differences (sensitivity, specificity, positive predictive value, negative predictive value) of HE4 compared to histopathology examination in diagnosing ovarian cancer (p = 1.00).

**DISCUSSION**

Result of the research revealed p value > 0.05 of age and parity variable, suggesting no differences between the two groups.

Diagnostic test of HK6 toward histopathology in diagnosis of ovarian cancer revealed sensitivity, specificity, positive predictive value, negative predictive value, false positive value, false negative value, and accuracy of 80%, 75%, 72.7%, 81.8%, 27.3%, 18.2%, and 77.3%, respectively. McNemar test showed p-value of diagnostic tests of HK6 toward histopathology examination in diagnosing ovarian cancer is p = 1.00. It shows that no accuracy differences (sensitivity, specificity, positive predictive value, negative predictive value) of HK6 compared to histopathology examination in diagnosing ovarian cancer. This can be explained that, in ovarian cancer, the increment of HK5, HK6, HK8, HK10, HK11 and HK14 in serum make kallikrein become a potential biomarker. Several studies on the association of HK6 with ovarian cancer showed that among many types of cancer, only in ovarian cancer, HK6 levels in circulation showed remarkable increase.6

Diagnostic test of HE4 toward histopathology showed 70.0% sensitivity, 83.3% specificity, 77.8% positive predictive value, 76.9% negative predictive value, 22.2% false positive, 23.1% false negative values, and 77.3% accuracy. McNemar test showed no differences of accuracy (sensitivity, specificity, positive predictive value, negative predictive value) HE4 compared to histopathology examination in diagnosing ovarian cancer (p = 1.00). This result is supported by another research conducted Wang et al which examined HE4 level in the differential diagnosis of pelvic mass in the population of Chinese women. The
study demonstrated that the sensitivity and specificity of HE4 were 86.7% and 98.0%, respectively. Diagnostic test of CA125 toward histopathology showed 70.0% sensitivity, 83.3% specificity, 77.8% positive predictive value, 76.9% negative predictive value, 22.2% false positive, 23.1% false negative values, and 77.3% accuracy. McNemar test showed no differences of accuracy (sensitivity, specificity, positive predictive value, negative predictive value) CA125 compared to histopathology examination in diagnosing ovarian cancer (p = 1.00). In initial report, it is known that level of CA125 increased by about 80% in women with advanced ovarian cancer and only 1-2% in the normal population. While in stage I ovarian cancer, CA125 level increased less than 50%. Specificity of CA125 is also low in differentiating between benign and malignant cases. In a retrospective study of 9233 women, sensitivity 62% of CA125 was obtained.

CONCLUSION
There were no accuracy differences (sensitivity, specificity, positive predictive value, negative predictive value) between hK6, CA125, HE4 compared to histopathology examination in diagnosing ovarian cancer. Each of hK6, CA125 and HE4 value can be used as an ovarian cancer biomarker.

REFERENCES