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Comparison of biomarkers performance from Urine and Serum for the early diagnosis of ovarian cancer

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Abstract. This paper compares of biomarker combinations performance extracted from urine and serum samples for the early diagnosis of ovarian cancer. The sample consists of 22 benign and 10 cancer patients. The concentrations of 15 ovarian cancer-specific biomarkers were measured by antibody microbead-assisted multiplexed immunoassay technology. To determine the optimal combination that best distinguish benign from cancer, the AUC of the ROC curve of marker combinations consisting of two biomarkers was estimated. The diagnosis performance was evaluated with Logistic Regression. The highest AUC value of the biomarker combination consisting of two biomarkers was 93.81% and 87.27% for the biomarkers extracted from urine and serum, respectively. This result represents that biomarker combinations extracted from urine has higher performance than those from serum.

Keywords: biomarker, Tumor markers, Multianalyte, Ovarian Cancer, IVDMIA, Logistic Regression

1 Introduction

These symptoms of ovarian cancer in an early stage are not noticeable, and it is hard to distinguish the benign tumor from cancer using nonradioactive diagnosis such as ultrasonography. Therefore the diagnosis of ovarian cancer is generally accompanied by expensive and unnecessary surgical diagnosis. Epithelial ovarian cancer, which takes up to 90% of ovarian cancer, is usually detected after the tertiary period, and as a result, the survival rate after 5 years from diagnosis is less than 40%. Therefore early detection of ovarian cancer is becoming paramount [1-2]. Diagnosis of cancer with biomarkers is relatively simple since it uses only urine or blood samples, and can detect the cancer in an early stage without expensive diagnosis methods [3].

The U.S. Food and Drug Administration (FDA) approved protein biomarkers as a way of diagnosing cancer, and announced the regulations and instructions in 2007 according to

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'IVDMIA: In Vitro Diagnostic Multivariate Index Assay'. IVDMIA by definition is combining the values of multiple variables using an interpretation function to yield a single, patient-specific result such as “classification,” “score,” “index,” that is intended for use in the diagnosis of disease or other condition, or in the cure, migration, treatment or prevention of disease [4]. In cancer diagnosis, IVDMIA is used to improve the accuracy of the diagnosis by combining multiple biomarkers and quantifying the analysis by statistic means, since there is no single biomarker that has a cancer-specificity close to 100% for a specific cancer.

The advantages of IVDMIA in comparison with a single biomarker assay are based on the premise that the single-valued index, with its aggregated information from complementary biomarkers, will outperform each of its component biomarkers used individually [5].

OVA1 is the first in IVDMIA of protein biomarkers cleared by FDA (2009) developed by Vermillion that uses five of serum proteins to diagnose the ovarian cancer. They tested pelvic tumor patients who needed surgery and diagnosed whether the tumor was benign or malignant on a scale of 0-10 [5].

Although serum protein is used in biomarker researches concerning ovarian cancer diagnosis, urine biomarkers have higher advantage in that it is clinically easier to handle and is a perfect non-surgical cancer diagnosis method that enables the detection of ovarian cancer patients among the benign tumor patients [5-8]. This paper compares the early diagnosis performance of biomarker combinations extracted from urine and serum.

2 Data collection

The sample pool consists of 22 benign and 10 cancer samples, and 15 biomarkers from urine and serum each were used. The 32 samples were from Korean women and were also provided by the Seoul ASAN Medical Center.

Protein biomarker concentrations were measured in antibody microbead-assisted multiplexed immunoassays with Luminex technology. The samples were incubated with Luminex-beads that were bound to 15 biomarkers, and the fluorescence from each antibody on the beads was measured with Luminex. The measured fluorescence intensities were converted to concentrations according to the standard curves generated by Bio-Rad (5-parameter curve fitting) [2].

3 Methods

To find the optimum biomarker combination for an accurate early diagnosis of ovarian cancer, the performance of the biomarker combination from urine and serum were compared. When classifying cancer, an appropriate model that can specifically and sensitively distinguish cancer from benign must be selected. The area under the curve (AUC) of a ROC curve is a general method of evaluating both sensitivity and specificity method of evaluating both sensitivity and specificity, and thus the classification performance.

In this research, the score gained by Logistic regression is used to evaluate the ROC AUC, and select the biomarker combination with the highest AUC. A 5-fold cross validation was repeated 1000 times for both urine and serum biomarker combinations, and the combinations having the top three average values of AUC for each urine and serum biomarkers were selected.

4 Results

Table 1 shows the performance of the top three combinations consisting of 2 biomarkers from urine, and table 2 shows those from serum. The performance was measured with the score resulting from Logistic regression, and the AUC, sensitivity, specificity, classification accuracy, PPV (positive predictive value), and NPV (negative predictive value) was evaluated.

Table 1. Top three diagnosis performance of combinations consisting of two biomarkers from urine (%)

Markers	*M14,M15*	*M7,M15*	*M1,M15*
AUC	*93.81*	*93.33*	*92.38*
95% CI	*70.65~100*	*69.21~100*	*71.43~100*
Sensitivity	*70.00*	*70.00*	*60.00*
Specificity	*100*	*100*	*95.24*
Accuracy	*90.32*	*90.32*	*83.87*
PPV	*100*	*100*	*85.71*
NPV	*87.50*	*87.50*	*83.33*

Table 2. Top three diagnosis performance of combinations consisting of two biomarkers from serum (%)

Markers	*M6,M13*	*M1,M6*	*M6,M10*
AUC	*86.32*	*85.03*	*83.79*
95% CI	*55.85~97.08*	*58.12~96.52*	*71.38~96.87*
Sensitivity	*60.00*	*60.00*	*50.00*
Specificity	*78.13*	*90.91*	*90.91*
Accuracy	*78.13*	*81.25*	*78.13*
PPV	*66.67*	*75.00*	*71.43*
NPV	*82.61*	*83.33*	*80.00*

The AUC of the biomarker combination from urine (M14, M15) was 94.31%, and the accuracy was 90.32%. The AUC and accuracy of the combination from serum protein (M6, M13) was 86.32% and 78.13%, respectively.

5 Conclusion

The paper compares the performance of biomarker combinations for the early diagnosis of ovarian cancer extracted from urine and serum. The combinations from the 15 biomarkers specific to ovarian cancer were evaluated and the classification performance was compared. The optimal marker combination from the combinations consisting of two biomarkers was determined by comparing the ROC AUC. The AUC in the early diagnosis of ovarian cancer was 94.31% and 86.32% for the marker combinations from urine and serum, respectively. This result shows that the biomarkers from urine have better performance than those of the serum proteins.

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