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Evaluation of Difference between Benign and Normal in Ovarian Cancer

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Abstract. We evaluate the contribution of the biomarker combination to classify benign tumor from cancer and normal patients from cancer patients. For the performance evaluation, the AUC of the ROC curves are used. The logistic regression was hired as a main classification algorithm. The best biomarker combination shows 87.97% and 91.38% when two and three markers are combined to classify benign and cancer class, respectively. And 87.39% and 90.68% of AUC value are shown when classifying normal patients to cancer patients, respectively.

Keywords: Ovarian Cancer, Benign-Cancer, Normal-Cancer, Biomarker Combination

1 Introduction

Ovarian cancer typically causes very few specific symptoms in an early stage and over 60% of patients who are diagnosed with ovarian cancer ultimately die from the disease. In addition, seventy percent of patients are diagnosed with advanced stages, where 5-year survival rates are less than 30%. Consequently, the great way of improving clinical outcome to detect at an early stage should be required[1,2].

Many researches for early diagnosis have been developed for distinguishing between benign tumor and cancer[3,4]. However, in public medical examination, many of patients want to know whether they have some problem or not. That's why this research was promoted. Unlike many related researched above, this research is for the patients who do not have any symptoms in their ovary.

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In this paper, we try to compare the performance of classification between benign tumor and cancer and between normal and cancer, and to check that normal-cancer classification is also stable like benign-cancer classification.

2 Data Collection

Samples consist of 79 healthy women, 119 patients with benign tumor, and 137 patients with ovarian cancer. The total 335 urine samples of Korean women were provided from ASAN Medical Center. The concentrations of urine protein biomarkers were measured using the multiplex immunoassay method with Luminex antibody microbeads: thereby, we used a multiplexed immunoassay kit consisting of cancer biomarkers specific to ovarian cancer [5]. Analyses were performed following the protocol of the manufacturer provided by Luminex Corp., and the sample were analyzed using the Bio-Plex Suspension Array System [6]. The biomarker expression levels are shown in terms of median fluorescent intensities generated from analyzing microbeads in quantities of 50-100 for an analyte of each sample. Analyte concentrations were quantified on the basis of the median fluorescent intensity using the standard curves generated by Bio-Rad (5-parameter curve fitting) [7].

3 Methods

To use urine samples in a clinical study, various variables should be calibrated to correct the collection time differences. The relatively stable creatinine protein level was used as a reference for calibration to correct the concentration differences in the total protein level in the urine samples [8].

A cancer diagnostic model with high specificity and sensitivity should be selected to classify different types of cancer. The conventional method of measuring the specificity and sensitivity is to determine an area under the receiver operating characteristic curve (AUC), which is used to evaluate the efficacy of cancer classification [9].

This paper uses Logistic regression to evaluate ROC AUC values and selects the marker combination that has the highest value. To minimize the biomarker selection time, the primary top 20 biomarker combinations were determined after performing evaluation 100 times with 5-fold cross validation. The 5-fold cross validation was re-performed 1000 times for the top 20 biomarker combinations to rank them based on AUC values. This cross validation was repeated for reducing the deviation between the population and sample. The repetition of 1,000 times could reduce the deviation of sampling processes.

The combinations selected consist of 2 and 3 biomarkers out of 21 markers, and the score threshold for Logistic Regression was set to be 0.5 to evaluate the diagnosis performance of the selected combinations.

4 Result

For the best biomarkers combination of two markers (M2,M5) to distinguish normal from cancer, the AUC was 87.97%, and accuracy was 78.7%, and, for the best biomarkers combination with three markers (M2,M5,M15), the AUC was 91.38% and accuracy was 83.8%. The performances to distinguish benign tumor from cancer with the above combinations of two markers and three markers, are 82.71% of AUC and 74.22% of accuracy and 73.23% of AUC and 75.39% of accuracy, respectively.

For the best biomarkers combination of two markers (M5,M21) to distinguish benign tumor from cancer, the AUC was 87.39% , and accuracy was 81.64%, and for three markers (M5,M21,M19), the highest AUC was 90.68% and accuracy was 84.38%. The performance to distinguish normal from cancer with the above combination of two markers is 81.83% of AUC and 74.54% of accuracy. For biomarkers combination of three markers has the AUC of 85.15%, and accuracy of 76.39%.

The normal-cancer classification and benign-cancer classification could not select the same marker combination. With this result, the normal-cancer classification and benign-cancer classification should be considered to be a totally different problem although they select a same marker, M5.

Generally, people could have intuition that the classification of normal and cancer would be easier than that of benign and cancer. However, the best biomarker combinations was failed to prove the intuition.

5 Conclusion

In this research, we tried to compare the biomarker combinations showing the highest performance to classify the normal patient and cancer patient and the highest performance of the benign patient and cancer patient.

The research shows that different biomarkers are selected, except M5, in case of normal-cancer and benign-cancer classification. It means that two classification problems should be treated as two different problems.

For the further study, we will develop another application to utilize the normal-abnormal classification as well as normal-cancer classification.

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