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Urine Biomarker Calibration for Ovarian Cancer Diagnosis

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Abstract. This paper proposes a correction method for urine biomarkers for better diagnosis of the ovarian cancer. The biomarkers were obtained from each urine sample of 163 patients (cancer: 42, benign: 121). The logistic regression of the combinations of 2 biomarkers calibrated by creatinine concentration was compared with that of the 3 biomarkers including creatinine. The average AUC over 100 repeated 5-fold cross validations was employed to evaluate the performance. The logistic regression of the calibrated biomarkers showed better performance than that without calibration for the top 10 combinations.

Keywords: Biomarker, ovarian cancer, calibration, logistic regression, urine, creatinine

1 Introduction

Ovarian cancer is a malignant tumor frequently arising in the age between 50~70, ranking the second most frequently occurring cancer in gynecology following cervical cancer. Early diagnosis is associated with the 5-year survival rate of 50-95%, but when diagnosed in the late stage the survival rate decreases to only 25%. It is evident that the development of a biomarker or a combination of biomarkers for early detection of ovarian cancer has become paramount [1-2]. Biomarkers are defined as markers that can objectively measure whether an organism is in a pathologically normal or abnormal state and the degree of reaction to certain drugs. More specifically, biomarkers can express a pathological state of illness, measure the degree of reaction that an organism shows when treated with certain drugs, and predict a viable treatment to a disease. An ideal tumor biomarker will be the protein fragments detected in the patient's urine or blood that cannot be found in healthy people [3-4]. The possibility of early detection of ovarian cancer using biomarkers found in urine is reported in a research done in the cancer institute at the University of Pittsburgh [5]. However, more researches on developing the method for precise and accurate early diagnosis of ovarian cancer are needed.

Although urine samples are not useful after 24 hours of collection, blood samples are disfavored over urine samples due to the invasive collection procedure and blood-

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borne diseases. The American Conference of Governmental Hygienists (ACGIH) recommends random urine sampling on basis of the Biological Exposure Indices (BEIs). However random urines have drawbacks due to the variability of urinary output. When measuring the biomarkers in urine samples, the protein quantity in urine can change due to the digested food or the amount of water, and the concentration might also vary according to the time of collection or the sampling method. Much of this variability can be compensated for by adjustment of the concentration of the measured analyte based on the level of creatinine in the urine sample. Creatinine is the metabolite of the muscle tissue and normally exists in urine. According to ACGIH, approximately 1.2 g of creatinine is produced per day. If the average daily urine volume is 1.2 L (range: 600-2500 ml), the average of creatinine concentration is approximately 1 g/L. Based on this assumption, the urine sample concentration can be calibrated to an average concentration of 1 g/L using creatinine as the standard. Some urine samples during a day will be above 1 g/L and others will be below 1 g/ L, but the analyte concentration will be calibrated to a value which would be theoretically equivalent to the value of a urine specimen which has the concentration of 1 g/L [6].

This paper presents a function to calibrate urine biomarkers. The logistic regression of the two calibrated biomarkers are tested and compared with that of the three not-calibrated biomarkers including creatinine which is utilized for calibration.

2 Experiments and results

In this paper, the concentration of each biomarker is divided by the power of the creatinine concentration, that is, the corrected concentration will be $m\ C^r$ when the concentrations of the biomarker and creatinine are m and C^r , respectively. The powering of the creatinine concentration is employed from the idea that the increment rate tends to be rapidly reduced when the concentration becomes greater. The power factor r was determined to maximize the area under the receiver operating curve (AUC) of the calibrated biomarker [7]. 14 biomarkers were measured from each of the urine samples of 163 patients (42: cancer, 121: benign). The 91 combinations of 2 calibrated biomarkers were regressed by logistic regression, and the average AUC of each combination was calculated where the average was taken over 100 random partitions of 5-fold cross validation. The logistic regression for three biomarkers (two not-calibrated biomarkers and the creatinine) was also evaluated to prove if the calibration is a better approach than the simple logistic regression.

Table 1 shows the performance comparison between the calibrated and not-calibrated combinations for the top 20 combinations. The combinations of the calibrated biomarkers showed better performance for the top 9 combinations. The average AUC for the combinations of the not-calibrated biomarkers that are absent in the table was less than 0.9, and the best performance of the combination of not-calibrated biomarkers was 0.916, which is the same value to the performance of the 8th ranked combination of the calibrated biomarkers. Therefore, it can be said that the performance of the combination of calibrated biomarkers is generally higher than that of the not-calibrated biomarkers. Figure 1 shows the ROC curves with a combination of calibrated and non-calibrated biomarker having the best performance. The solid line

represents the ROC curve of logistic regression of the calibrated M5 and M7. The dashed curve is for that of M5, M8, and creatinine. They seem to have very similar performance over the specificity range. The results show that the creatinine calibration enhances the performance than simply being combined with other biomarkers.

Table 1. The Performance Comparison of the Top 20 Combinations

No	*m*1	*m*2	*AUC(LR(m*1/C^{γ}, *m*2/C^{γ}*))*	*AUC(LR(m*1, *m*2, *C))*
1	M5	M7	**0.922**	0.905
2	M5	M3	**0.921**	0.909
3	M5	M8	**0.921**	0.916
4	M5	M6	**0.921**	0.904
5	M5	M9	**0.921**	0.907
6	M5	M10	**0.921**	0.903
7	M5	M11	**0.918**	0.905
8	M5	M14	**0.916**	0.907
9	M5	M1	**0.909**	0.905
10	M5	M19	0.903	**0.914**
11	M5	M4	0.901	**0.906**
12	M5	M12	0.892	**0.905**
13	M5	M13	0.892	**0.905**
14	M5	M2	0.868	**0.909**
15	M2	M10	**0.755**	0.748
16	M2	M7	**0.733**	0.716
17	M1	M6	0.715	**0.721**
18	M7	M9	0.693	**0.728**
19	M6	M9	0.67	**0.754**
20	M9	M10	0.657	**0.771**

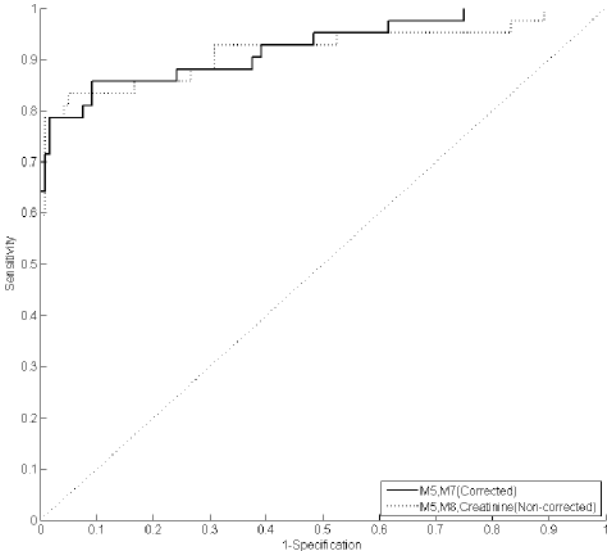

Fig. 1. The ROC of the Best Performance Combination of the Calibrated Biomarker (M5, M7) and Non-calibrated Biomarker (M5, M8, Creatinine)

3 Conclusion and discussion

A function to calibrate the urine biomarker with creatinine was proposed to increase the performance of early diagnosis for ovarian cancer. Every calibrated pair of 14 biomarkers were combined by logistic regression and calculated for the average AUCs. They were compared with the not-calibrated combinations, and the results show that calibration enhances the performance of early diagnosis using biomarkers from urine. The experimental results showed that creatinine should be utilized to calibrate other biomarkers, rather than simply combining with them.

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