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A Bayesian Expert System for Clinical Detecting Coronary Artery Disease

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Background: The purpose of this study was to use a data mining technique to develop an expert system of the Bayesian model for detecting coronary artery disease (CAD). In addition, this study provides an evaluation of CAD detection before an invasive cardiac angiography as well as a paradigm for implementing relevant expert systems in the future. **Methods:** The study samples were drawn from all patients with cardiac angiography between August 1, 2005 and July 31, 2006, from the cardiac department in a medical center (Tri-Service General Hospital, TSGH), excluding samples with acute myocardial infarction, dilated cardio myopathy and rheumatic heart disease. A total of 415 samples were studied. All CAD-related risk factors were data-mined using a training set of randomly extracted 204 samples. All risk factors were calculated for sensitivity and specificity for Bayesian modeling and the implementation of the localized rules of a knowledge based. Furthermore, this study also quoted the epidemiological results of the knowledge based external rules from the PROspective Cardiovascular Münster study (PROCAM). Two knowledge bases, the TSGH base and the PROCAM base, were validated by a testing set of 211 samples. **Results:** The accuracy rates of the TSGH and PROCAM bases were as high as 70%. For detecting CAD, the localized data mining of the TSGH-based AUC was more stable at 86.2%, outperforming the PROCAM-based AUC of 82.2%. **Conclusions:** In this study, an evidence-based clinical expert system of the Bayesian model provides an evaluation for detecting CAD before an invasive cardiac angiography as well as a paradigm for relevant expert systems.

Key words: Coronary Artery Disease (CAD), Bayesian Expert System, Hospital-based Epidemiology, Cut-off Point

INTRODUCTION

An expert system is a computer system that can use domain knowledge expertise in a specialized field and can perform specific analysis like an expert. An expert system could provide the following characters[1-11]. Expertise consists of arranged rules and must be extracted from evidence provided by experienced data. Expert systems must verify and utilize domain knowledge from evidence-based data.

Expert system contains three parts: inference engine, knowledge base and user interface. Inference engines lead static rules in knowledge bases to act as the intellect of dynamic reasoning. Suitable rules can be extracted from observed users or objective facts. These rules include new facts or rules that produce results. The domain knowledge base is the intelligent location of an expert system. Data-mined facts and deducted rules are formulated by experts interoperating with the inference engine. User interface is convenient for users communicating with expert systems. It contains the

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interfaces for acquiring expertise and catching evidence-based facts of the data mining.

A knowledge base can be extracted from an amount of real samples for evidence-based data mining and can, hence, perform Bayesian probability theory[1,2,5]. This approach can analyze experienced data and implement an expert system for evaluating and detecting coronary artery disease (CAD) before an invasive process of cardiac angiography is conducted.

This study aims to establish an expert system for assisting in the detection and evaluation of CAD according to the analysis of CAD risk factors from (1) a hospital-based data of local evidence-based samples and (2) an existing epidemiological study.

METHODS

A rule-based expert system shell, EXSYS for Windows of Albuquerque, NM, was used to establish an expert system. The knowledge base implemented a Bayesian model to detect CAD.

Evidence-based data mining

There were two evidence-based sources, one from hospital-based data and another from existing epidemiological data.

1. Evidence-based patient clinical records in a medical center (Tri-Service General Hospital, TSGH), the TSGH-based Bayesian model

This study designed a computerized sheet for extracting patient clinical records including patient demographic data, biomedical blood data, smoking and alcohol use, personal and familial medical history and cardiac angiographic results. The cardiac angiography was the golden standard for diagnosing CAD in the study. In this study, only selective patients received detailed history taking, CAD stratification, and non-invasive laboratory tests. However, this study did not conduct any costly examinations such as treadmill EKG and Thallium-201 myocardial perfusion imaging. There were 415 samples drawn from the department of cardiac angiography in TSGH of the National Defense Medical Center, for August 1st 2005 and July 31st 2006. 204 samples were randomized samples for training of the evidence-based knowledge rules and another 211 samples were used to test the trained TSGH-based knowledge.

2. Epidemiological Results of PROCAM (PROspective CArdiovascular Münster) Study (PROCAM), the PROCAM-based Bayesian model

Meanwhile, the study also quoted the epidemiological results of the PROCAM study[12-18] to construct PROCAM-based knowledge. The PROCAM-based knowledge was also validated by the above TSGH testing set of 211 samples.

The risk factors analysis and the expert system prototype environment

The patients' clinical records were retrieved using Microsoft Access 2007. This study analyzed the relationship between every variable and cardiac angiographic results (indicating CAD morbidity) for odds ratios, confidence intervals, sensitivities and specificities. SPSS 17 and Clementine for Windows were used to compute Chi-square values and t-tests between every variable and the cardiac angiographic results that statistically analyzed significant risk factors associated with angiographic diagnosis.

Bayesian theory was employed to calculate the posterior CAD-morbid probability according to the CAD prevalence, sensitivity and specificity of every identified risk factor in the expert system of the evidence-based data mining[2,19,20], as shown in the algorithm below.

$$P(D+ \mid R_j) = P(D+ \mid R_i)\, Sen_j / (P(D+ \mid R_i)\, Sen_j + (1-P(D+ \mid R_i))\,(1-Spe_j)),\ j = i+1$$

In the formula, Ri and Rj indicate the ith and jth risk P (D+ | R+) is a posterior probability. According to Bayesian theory, that means a probability of a disease (D+) with a risk (R+). P (D) is a prior probability of a disease that is often estimated by prevalence of the disease. Sen and Spe indicate sensitivity and specificity in a 2 by 2 cross table between a status of disease (D+ or D-) and risk (R+ or R-). An iteration algorithm can perform the cumulative probabilities of a disease with multiple risks, as the above formula.

RESULTS

The study drew 415 samples who previously had not received any costly tests such as treadmill EKG and Thallium-201 myocardial perfusion imaging from the cardiac angiographic department in the TSGH of NDMC that were collected for 6 factors in the clinical records, 1) Personal demographic data, 2) Biomedical blood data, 3) Smoking and alcohol use, 4) Personal medical history, 5) Familial medical history and 6) Cardiac angiographic results. The cardiac angiographic results were the golden standard of CAD diagnosis in the study. There were 238 (57.3%) patients with CAD of the 415 samples.

The samples were randomized as a half sets (204 samples). The first set trained the Bayesian model construct a TSGH-based knowledge base and the other half set (211 samples) compared, testedand verifyed the trained TSGH-based and PROCAM-based Bayesian models.

Evidence-based Risk Factors Analysis and Knowledge Extraction

Table 1, the variables of sex, smoking, angina pectoris (AP), hypertension, personal medical history of diabetes mellitus (DM), familial medical history of hypertension, CAD, cardio-vascular diseases (CVD) and DM were significantly associated with CAD morbidity. The odds ratios of male versus female, smoking versus non-smoking were 3.97 and 2.71 times greater for CAD, respectively. The odds ratios of patients with personal medical history of AP, hypertension and DM were 9.47, 2.19 and 2.16, respectively. Moreover the odds ratios of patients with familial medical history with hypertension, CAD, CVD and DM were 2.97, 3.04, 2.72 and 2.62, respectively.

Table 2 shows the difference between continuous personal demographic data, biomedical blood data and CAD. The variables of age, body height, first hospitalized for DBP in the morning, glucose, total cholesterol, triglyceride, creatinine and inorganic phosphate were significantly associated with CAD.

Due to the fact that the Bayesian model requires sensitivity and specificity between CAD and a risk factor, particularly for a risk factor of a continuous variable, thus, it is an issue to determine a cut-off point to discriminate the risky threshold factor of CAD, e.g. variables of age, body height, blood pressure, glucose, cholesterol, triglyceride, creatinine and inorganic phosphate. Similarly, as a categorical variable, we proposed to examine the cross table between the CAD morbid status (CAD versus non-CAD) and a risk factor of continuous values at various cut-off points (risk versus non-risk) that determined proper cut-off points of significant odds ratio and narrow confidence interval. The algorithm was used in the following steps.

1. To compute the odds ratio of every risk factor and its confidence interval at each cut-off threshold from the minimum to maximum value, as shown in below cross table between cholesterol and CAD, which obtained odds ratios at various cholesterol cut-off points, as in Figure 1.

Table 1 The Knowledge Extraction of Categorical Risk factors for Detecting Coronary Artery Disease (CAD)

	CAD (n=124)	Non CAD (n=80)	Odds Ratio	95% C.I.
Sex***				
Male	97	38	3.97	7.32-2.15
Female	27	42	1	
Personal Lifestyle				
Smoking**				
Ever	75	25	3.37	6.11-1.86
Yes	58	24	2.71	5.00-1.47
Cessation	10	1	11.22	90.88-1.39
Social	7	0	n.a.	
No	49	55	1	
Alcohol				
Ever	49	25	1.44	2.61-0.79
Yes	12	6	1.47	4.15-0.52
Cessation	34	19	1.31	2.54-0.68
Social	3	0	n.a.	
No	75	55	1	
Personal Medical History				
Angina pectoris ***				
Yes	118	54	9.47	24.35-3.68
No	6	26	1	
Hypertension**				
Yes	72	31	2.19	3.89-1.23
No	52	49	1	
Diabetes mellitus*				
Yes	39	14	2.16	4.31-1.08
No	85	66	1	
Family Medical History				
Hypertension**				
Yes	45	13	2.97	5.97-1.47
No	77	66	1	
Unknown	2	1		
CAD**				
Yes	43	12	3.04	6.23-1.48
No	79	67	1	
Unknown	2	1		
Cardio-vascular diseases*				
Yes	40	12	2.72	5.60-1.32
No	82	67	1	
Unknown	2	1		
Diabetes mellitus*				
Yes	39	12	2.62	5.40-1.27
No	83	67	1	
Unknown	2	1		

***, p<0.001; **, p<0.01; *, p<0.05; n.a., non available

Table 2 The Risk Factors of Continuous Personal Demographic and Biomedical Data of CAD

	CAD		Non-CAD			
	mean	S.D.	Mean	S.D.	t	P-value
Age*	62.2	8.92	59.4	10.41	2.05	0.042
Body height (cm)**	163.6	7.35	160.5	8.66	2.75	0.007
Body weight (kg)	68.1	9.86	65.6	11.99	1.59	0.113
Body Mass Index (kg/m^2)	25.5	3.56	25.5	4.40	-0.02	0.987
Hospitalized systolic blood pressure at morning						
First	130.6	20.66	129.1	18.98	0.51	0.612
Second	128.7	18.56	127.3	17.63	0.54	0.590
Last	126.1	17.84	125.9	16.51	0.08	0.937
Average	128.4	16.33	127.5	15.28	0.42	0.673
Hospitalized diastolic blood pressure at morning						
First *	80.7	9.95	77.6	10.49	2.17	0.031
Second	79.5	9.60	78.6	9.65	0.66	0.511
Last	76.9	8.27	77.7	9.29	-0.59	0.553
Average	79.1	7.32	77.9	7.81	1.07	0.285
Hospitalized pulse at morning						
First	74.8	11.53	74.5	13.80	0.19	0.850
Second	73.0	10.98	74.7	12.39	-1.03	0.306
Last	74.3	10.63	73.8	9.37	0.35	0.725
Average	74.1	8.87	74.3	9.87	-0.20	0.842
Glucose*	121.0	55.68	104.9	39.71	2.22	0.027
Total cholesterol***	193.6	49.47	167.6	40.10	3.80	0.001
triglycride*	185.7	116.32	151.4	92.39	2.17	0.032
HDL-cholesterol	41.6	12.90	47.1	14.30	-1.46	0.150
LDL-cholesterol	115.1	47.27	99.1	30.00	1.34	0.186
Blood urea nitrogen	18.7	8.04	17.0	7.40	1.49	0.137
Creatinine**	1.3	0.85	1.0	0.30	2.63	0.009
Uric acid	7.1	2.22	7.6	4.56	-1.03	0.303
Total calcium	8.6	1.03	8.7	0.47	-0.86	0.390
Inorganic phosphorus**	3.4	0.81	3.7	0.76	-2.73	0.007
Aspartate transaminase	27.1	21.29	28.4	27.92	-0.38	0.704
Alanine aminotransferase	23.4	20.73	23.6	26.38	-0.07	0.944
Alkaline phosphatase	119.6	43.75	110.1	40.64	1.50	0.137
Total bilirubin	0.8	0.56	1.0	0.91	-1.66	0.099
Total protein	6.8	0.93	7.0	0.72	-1.71	0.090
Albumin	3.8	0.42	3.9	0.61	-0.97	0.333
Albumin/globulin ratio	1.3	0.26	1.2	0.21	0.89	0.372
Sodium	144.6	5.27	145.2	3.58	-0.93	0.356
Potassium	4.0	1.02	3.8	1.29	1.05	0.294

***, p<0.001 **, p<0.01 *, p<0.05

	Cut-off value	CAD	Non CAD
Total cholesterol	>=160mg/dl	88	42
	<160mg/dl	27	32

OR=2.49, S.D. (OR)=0.31, X^2=14.63

	Cut-off value	CAD	Non CAD
Total cholesterol	>=165mg/dl	83	39
	<165mg/dl	32	35

OR=2.37, S.D. (OR)=0.31, X^2=13.90

2. To choose an optimal cut-off point that suits two criteria, one being an odds ratio that is as statistically significant as possible. Such a ratio indicates the cholesterol cut-off point more effectively to discriminate CAD. The other criteria is that the confidence interval of odds ratio is as narrow (stable) as possible, in which case, the cholesterol cut-off point is more reliable in discriminating CAD.

In Figure 1, the vertical axles indicated Chi-square values on the left and log10 transposed odds ratios on the right that were calculated from cross tables between various cut-point values of cholesterol for samples with and without CAD. The left vertical axle indicated the Chi-square values and the right vertical axle indicated the transformation of $\log_{10}$ (odds ratio) and its upper and lower bounds a 95% confidence interval. The patterns of odds ratios and Chi-square values were similar. The Chi-square values obviously indicated that the two highest cholesterol peaks of statistical significances were at about 177 and 217 mg/dl, where odds ratios also denoted the most significant statistics and the narrowest bounds of the 95% confidence interval. This signifies that the two cholesterol cut-off points were the most effective and stable in discriminating whether or not samples had CAD. The other cut-off points of glucose, triglyceride and other continuous variables were determined for the Bayesian model in the same way.

Moreover, in the instance of cholesterol (Fig. 1), there were two or more peaks that we observed with significant Chi-square values that indicated several peaks for multiple cut-off points. The following cross tables demonstrated why the highest two peaks should be considered as multiple cut-off points at about 175mg/dl and 215mg/dl (integrals from 177 and 217 were applied for the sake of convenience). According to the cross tables below, the first odds ratio (2.48) was over-estimated when a single peak of cut-off point was at 175mg/dl, and the second one (odds ratio=2.62) was

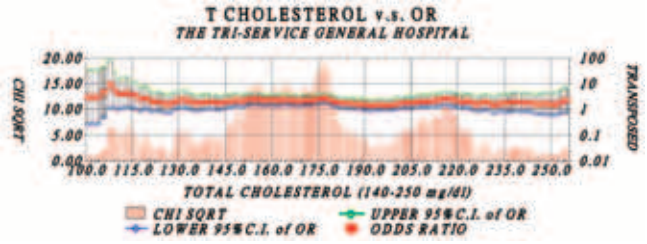


Fig. 1 The Chi-square value and transposed Odds Ratio of respective cut-point cholesterol point in samples with CAD to without CAD

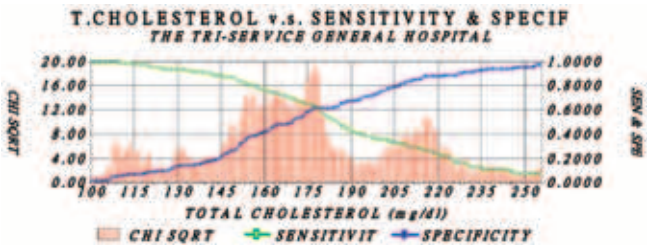


Fig. 2 Sensitivity and specificity of respective significant risk factor with morbid CAD

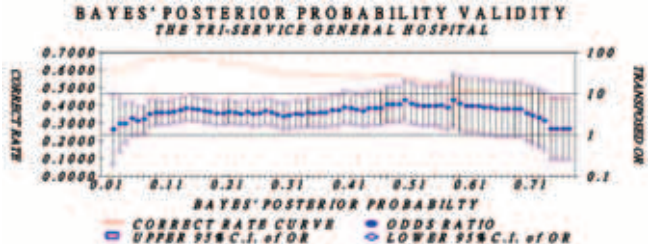


Fig. 3 The correct rate and transposed Odds Ratio of respective Bayes' posterior Probability with CAD in Tri-Service General Hospital data-driven approache.

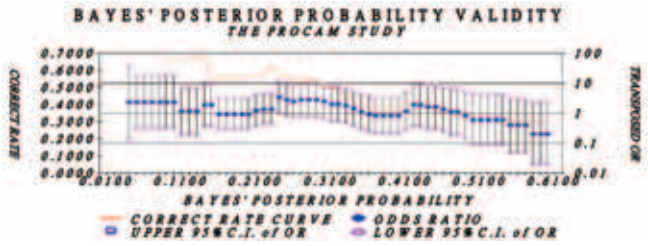


Fig. 4 The correct rate and transposed Odds Ratio of respective Bayes' posterior Probability with CAD in PROspective Cardiovascular Münster study data-driven approache.

under-estimated when a single peak of the cut-off point was at 215mg/dl. This phenomenon is similar to misclassification in epidemiology. To be accurate, the two peaks should be simultaneously picked as multiple cut-off points at the first peak 175mg/dl and the second peak 215mg/dl. The band is well established as a gray area between the first and second peaks, which was from 175 to 215 mg/dl.

		CAD	Non CAD
Total cholesterol	>=175mg/dl	74	32
	<175mg/dl	40	43

OR=2.48

		CAD	Non CAD
Total cholesterol	>=215mg/dl	30	9
	<215mg/dl	84	66

OR=2.62

The following cross table demonstrated that the accurate odds ratios of CAD were 3.58 and 2.06, respectively, for patients with cholesterol over 215 mg/dl and 175-215 mg/dl versus under 175 mg/dl.

		CAD	Non CAD	
Total cholesterol	>=215mg/dl	30	9	OR=3.58
	215-175mg/dl	44	23	OR=2.06
	<175mg/dl	40	43	

Figure 2 shows, for the example of cholesterol, how this study analyzed sensitivity and specificity from the cross tables of association between CAD and cholesterol at various cut-off points. In table 3, the evidence-based knowledge was extracted from the mining of 204 samples of the TSGH-based training data set. The highest three Bayesian posterior probabilities were 0.018 for HDL, 0.0138 for pulse of the hospitalized patient on the last morning and 0.0115 for familial CAD history. The lowest three Bayesian posterior probabilities were 0.0059 for patient BMI (Body Mass Index), 0.0063 for hospitalized patient DBP on the first morning and 0.0063 for patient age. Every CAD morbid probability of the 211 samples of the testing data set was calculated, according to Bayesian iteration (Table 3 footnote).

Figures 3, 4 and 5 show the performances of the two evidence-based Bayesian models from the 205 samples of the TSGH-based training set and the quoted figures from the PROCAM-based epidemiological study, respectively. In the 211 samples of the testing set given, the prior probability was 0.005. The TSGH-based Bayesian posterior probabilities (between 0.07 and 0.58, Fig. 3) performed statistical significances for discriminating patients with and without CAD when the lower bounds of the confidence intervals of odds ratios were greater than

Table 3 The Evidence-based Knowledge Extraction of TSGH-based Risk factors for Detecting CAD of Bayesian Model

	Cut-off point[a]	Sensitivity	Specificity	Bayesian post probability[b, §]
Sex	male vs. female	78.23%	52.50%	0.0082
Smoking	ever vs. no	60.48%	68.75%	0.0096
Personal Medical History				
Angina pectoris[c]	yes vs. no	95.16%	32.50%	0.007
Hypertension	yes vs. no	58.06%	61.25%	0.0075
Diabetes mellitus	yes vs. no	31.45%	82.50%	0.009
Familial Medical History				
Hypertension	yes vs. no	36.89%	83.54%	0.0111
CAD	yes vs. no	35.25%	84.81%	0.0115
Cardio-vascular Diseases	yes vs. no	32.79%	84.81%	0.0107
Diabetes Mellitus	yes vs. no	31.97%	84.81%	0.0105
Age	60 yr.-old	67.29%	46.85%	0.0063
Body Mass Index	24 kg/m^2	67.76%	42.66%	0.0059
Systolic Blood Pressure_first	145 mm-Hg	22.90%	86.71%	0.0086
Diastolic Blood Pressure_first	75 mm-Hg	71.03%	44.06%	0.0063
Pulse_last	80 times/min	36.92%	86.71%	0.0138
Glucose	85 mg/dl	80.00%	44.06%	0.0071
	110 mg/dl	39.05%	74.13%	0.0075
Total cholesterol	175 mg/dl	64.88%	58.33%	0.0078
	215 mg/dl	26.83%	87.88%	0.011
Triglyceride	145 mg/dl	55.01%	61.36%	0.0071
	220 mg/dl	25.37%	85.61%	0.0088
High Density Lipoprotein	45 mg/dl	78.46%	78.46%	0.018

a: Contradistinction for dichotomous variable, b: Given 0.005 as a prior probability, c: patients ever complained paroxysmal chest pain which is precordial, temporary, exertional, emotional, burning like and relieved by rest, § footnote: For instance, given a patient data with age 65, glucose 100, cholesterol 220 and triglyceride 200 in a population prevalence 0.005 (PD, as a prior disease probability) that a Bayesian model calculates the patient morbid probability 0.0713 (PDagct) according to the following iteration:

- P (CAD| age=65)= PD * 0.6729 / ((PD * 0.6729) + (1-PD) * (1-0.4685))= 0.00063= PDa
- P (CAD| glucose=100 and age=65)= PDa * 0.8000 / (PDa * 0.8000 + (1-PDa) * (1-0.4406))= 0.009= PDag
- P (CAD| cholesterol=220 and glucose=100 and age=65)= PDag * 0.2683 / (PDag * 0.2683 + (1- PDag) * (1-0.8788))= 0.0197= PDagc
- P (CAD| triglyceride=200 and cholesterol=220 and glucose=100 and age=65)= PDagc * 0.5501 / (PDagc * 0.5501 + (1- PDagc) * (1-0.8561))= 0.0713= PDagct

1 (Fig. 3 on the right axel). The best accuracy rate was about 70% with a Bayesian posterior probability of 0.12. The PROCAM-based Bayesian posterior probabilities did not perform statistical significances for discriminating patients with or without CAD because the lower bounds of the confidence intervals of the odds ratios were all less than 1 (Fig. 4 on the right axel). Therefore, the accuracy rates were not credible. The TSGH-based Bayesian model outperformed the PROCAM-based model as their AUCs were 0.862 and 0.822, respectively (Fig. 5).

DISCUSSION

A non-invasive expert system for detecting CAD before an invasive process of cardiac angiography is worthy of evaluation[19]. This study demonstrated how to implement an evidence-based clinical expert system of a Bayesian model to detect coronary artery disease. The two datasets used as evidence included one from data mined from localized hospital samples and another from epidemiological results quoted from a previous study[21-27]. The Bayesian model has an advantage compared to logistic and linear regression models. That is, it is still workable when several variables are missing[19,28-32].

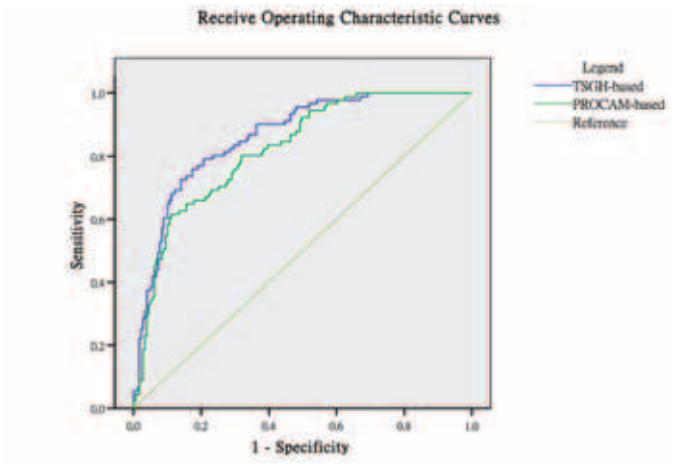
The Implementation of Clinical CAD Expert System

When using a Bayesian theorem, sensitivities and specificities drawn from cross tables between the status of risk factors and of CAD in a training set, should be extracted as the inferring rules in the knowledge base. A prior probability can be borrowed from the population prevalence of CAD. Consequently, a series of posterior CAD probabilities can be used to calculate the risk factors of patients one by one in a trained Bayesian model. The final posterior probability can discriminate probability and detect whether or not a patient is morbid with CAD.

The Verification of Clinical CAD Expert Systems

A testing set can evaluate performances of a trained Bayesian model, that is, transplanting can be confirmed how to detecting CAD in new patients. The TSGH-based Bayesian model outperformed the PROCAM-based model, indicating that the data mining of localized data is more suitable for local patients than quoted extractions of epidemiological literature.

In addition, the sensitivities and specificities in knowledge-based rules should be dynamically revised and updated due to changes in the characteristics of patients' morbidity over time. This can prolong the usability and life cycle of expert systems[2,19,20,29]. The



Data Sets	AUC	Standard Errors [a]	P Values [b]	95% Confidence Intervals	
				Lower	Upper
TSGH-based	0.862	0.023	< 0.001	0.818	0.906
PROCAM-based	0.822	0.026	< 0.001	0.772	0.873

a, non-parametrics

b, null hypothesis: AUC= 0.5

Fig. 5 The Receiver Operating Characteristic Curves (ROC) and Area under Curves (AUCs) of TSGH-based and PROCAM-based Data Mining Sets

development of expert systems should refine a database system that will provide the capacity to explore samples and modify and transport knowledge bases.

The rules of knowledge bases should be influenced by the characteristics of population, time change and disease prevalence. The transplant of rules should be carefully used in different populations that feature a variety of causes, such as TSGH-based and PROCAM-based models shown in this study. A clinical expert system can extract more suitable localized rules and cut-off points from data mining by using its own datasets. This could make the Bayesian model even more accurate for detection. Computer-based decision support systems can be useful clinical applications for improving clinician performance. Additional samples can enhance the detective application.

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