PREDICTION OF TOTAL CHOLESTEROL: HIGH-DENSITY-LIPOPROTEIN-CHOLESTEROL RATIO IN YOUNG ADULTS

Wei-Hsi Chen[1], Yung-Yee Chang[1], Hsin-Ling Yin[2], Ming-Shon Chou[3], Jia-Shou Liu[1]

Departments of Neurology[1], Pathology[2] and Neuroradiology[3] Kaohsiung Medical College Hospital

Abstract. Abnormal cholesterol fraction is an essential risk factor for atherosclerosis of large cerebral arteries in young Asians. In order to reduce the medical cost and social resource for cholesterol electrophoresis, especially in undeveloped and developing Asian countries, we evaluated the validity of Nanji's GUT score for predicting TC: HDLC ratio in this population. Results showed that GUT score only predicted 71% of them. We also tested the predictive power of CUT index, and predicting rate was 81%. Therefore, Nanji's GUT score is not an ideal surrogate for cholesterol electrophoresis. We recommend CUT index to screen for high-risk subjects till a new method can satisfy the economic pattern in Asian countries.

INTRODUCTION

Similar to western countries, cerebral atherosclerosis of large cerebral artery is recently recognised as being not rare in young Asians (Jayakumar *et al*, 1991). Hypercholesterolemia and elevation of serum low-density-lipoprotein-cholesterol (LDLC) is positively related to cerebral atherosclerosis (Chen *et al*, 1996). A low serum high-density-lipoprotein-cholesterol (HDLC) level or hypercholesterolemia is notably associated with atherosclerosis of the internal carotid and basilar artery in Japanese residing in Japan (Yasaka, *et al*, 1993) or Hawaii (Reed *et al*, 1988). In Hong Kong Chinese, HDLC is a protective factor for stroke (Woo *et al*, 1991). The negative correlation of the epidemiological result for hypercholesterolemia and stroke in China may reflect a different nutritional status (Li *et al*, 1990). Therefore, further evaluation of abnormal cholesterol fraction is important for preventing cerebral atherosclerosis in young Asians, especially with the dietary and living habits in Asia shift towards a similar pattern to western countries in recent years.

Considering that unnecessary measurement of cholesterol fractions increases medical costs and takes social resources, especially in developing Asian countries, a cheap and accurate method is useful as a surrogate for cholesterol electrophoresis for screening high risk individuals. Nanji (1982) used 3 parameters (serum fasting glucose, uric acid and triglyceride) obtained from a multichannel analysis profile in the calculation of a GUT score to predict the TC:HDLC ratio in healthy subjects. The prediction rate was 91% in his series. Although Phillip *et al* (1989) wondered about the reliability of GUT scores, we achieved a 72% prediction rate in 150 healthy individuals aged between 25 to 65 years (Ngai *et al*, 1989). Herein, we evaluated the GUT score in predicting TC:HDLC in young Taiwanese in order to evaluate whether it is an adequate surrogate for cholesterol electrophoresis. Also, we assessed and compared the predicting power of CUT index and TU score (Ngai *et al*, 1989) for TC:HDLC ratio.

Correspondence: Dr Jia Shou Liu, Department of Neurology, Kaohsiung Medical College Hospital, No. 100, Shih-Chuan 1st Road, Kaohsiung 807, Taiwan.
Tel: 886-7-312-1101 ext 6756; Fax: 886-7-311-2516

MATERIALS AND METHODS

Our aim was to test the validity of Nanji's GUT score in predicting TC:HDLC in young Asians. In western countries, TC:HDLC ratio of 4.5 was considered a risk for coronary atherosclerosis. A cut-off point for cerebral atherosclerosis was not mentioned. In this study, we therefore enroled subjects of cerebral atherosclerosis first to estimate the cut-off point of TC:HDLC ratio for atherosclerotic stenosis of large cerebral artery. Then, we examined the predicting power of Nanji's GUT score, TU score and CUT index for TC:HDLC ratio in young healthy subjects.

Subjects

From 1986 to 1992, individuals aged from 20 to 45 years admitted to Kaohsiung Medical College Hospital (KMCH) on account of cerebral infarct were enroled. The exclusion criteria were : [1] an evidence of cardioembolic or systemic embolic source, infectious arteritis, positive lupus study, brain tumor or abscess, dysmetabolic, cancerous or mitochondrial encephalopathy; [2] a history of recent head or neck injury; [3] consumption of herbal remedy, estrogen, androgen, or corticosteroid; [4] a previous recurrent optic neuritis or unexplained focal neurological deficit with spontaneous recovery; [5] an abnormal renal (serum creatinine > 1.4 mg/dl) or hepatic (SGOT > 40 IU/l, SGPT > 40 IU/l, serum albumin < 3.8 g/dl) function; [6] an abnormal thyroid or adrenal function; [7] confined venous thrombosis, vascular malformations or specific vasculopathy (fibromuscular dysplasia, Moyamoya disease, Takayasu arteritis, arterial dissecting, etc); [8] a history or laboratory evidence of diabetes mellitus or glucose intolerance; or [9] an incomplete or absence of cerebral angiography study.

A total of 56 individuals, consisting of 35 men and 21 women, were eligible in this study.

Another group of 155 healthy subjects was randomly chosen as controls. They were 92 men and 63 women. The age ranged from 30 to 45 years. They were under a good physical condition. None of them suffered from focal neurological deficit, unexplained optic deficit, recent head or neck injury, or any familial disease. They had normal hemogram, biochemistry and diurnal cortisol levels, as well as a normal thyroid, renal and hepatic function. All of them were tested negative on the lupus test. The electrocardiogram, cardiac echogram, and extracranial carotid dopscan were all normal.

Blood sample collection and laboratory tests

After an overnight 14-hour fast, patients and healthy controls remained supine and blood was collected from the antecubital vein. Blood for cholesterol electrophoresis was centrifuged and the serum was stored in -20°C and subjected to batch measurement within 72 hours. Blood samples for total cholesterol (TC), triglyceride (TG), uric acid, fasting glucose (FAG), total proteins, albumin, hepatic enzymes and creatinine were proceeded for analysis within 2 hours by the Beckman ASTRA autoanalyser.

Cholesterol electrophoresis

Five µl serum was applied into each well of a Titan III-Lipo cellulose acetate plate in Tris-barbital-sodium barbital buffer (pH 8.8) and electrophoresis was run. After electrophoresis, lipoproteins were stained with oil red O, then observed and scanned under 525 nm for quantitation. The level of α, β and pre-β lipoprotein was determined by multiplying the ratio of each individual with the value of total lipids.

Nanji's GUT score, TU score and "CUT" index

The Nanji's GUT score was calculated by a scoring system depending on three parameters - serum FAG, uric acid and TG (Nanji, 1984). There is no maximum of this score. The TU score, a modified Nanji's GUT score, and "CUT" index had been reported by us before (Ngai *et al*, 1992). In TU score, we excluded the glucose factor (Table 1). While in CUT index, we replaced FAG by serum creatinine (Table 1).

Cerebral angiography

Biplanar cerebral angiography via transfemoral approach was done in the study subjects for evaluation the severity of atherosclerosis of cerebral artery. The procedure had been described in prior (Chen *et al*, 1996). In brief, the internal carotid (ICA), anterior cerebral (ACA), middle cerebral (MCA) and vertebrobasilar arteries (VBAs) were observed and evaluated by a neuroradiologist (Dr Chou) who did not know the clinical and biochemical data. The selection of the portion of each artery was: [1] from the level above the carotid bulb to the MCA and ACA stem in ICA; [2] A1 (horizontal part) in ACA; [3] M1 (sphenoid part) in MCA; [4] vertebral artery segment above atlas (V4) to the bifurcation of the posterior cerebral artery in vertebrobasilar artery (VBA). The luminal diameter was measured by Alter's method (Alter *et al*, 1972). In practice, the luminal width at the narrowest point (A) to the beginning of the stenosis (B) was measured. The degree of stenosis was calculated as (B -

Table 1

The calculation method of Nanji's GUT score, TU score and CUT index. The GUT score depends on the total scores calculated from three parameters, fasting glucose, triglyceride and uric acid. TU score is calculated by excluding fasting glucose. A substitution of fasting glucose by creatinine is CUT index.

Score	Fasting glucose (mg/dl)	Triglyceride (mg/dl)	Uric acid (mg/dl)	Creatinine (mg/dl)
1	75-85	0-50	uric acid level	< 0.6
2	86-95	51-100	2	0.7-0.9
3	96-105	101-150		1.0-1.1
4	106-115	151-200		1.2-1.5
5		> 200		

A)/B and expressed as percentage. If there were more than one artery to have atherosclerotic stenosis, the most severe one was selected. In this study, luminal stenosis less than 25% in the ICA, and 35% in the ACA, MCA or VBAs was regarded as insignificant.

Statistical analysis

Student's *t*-test and single variable regression test were used in this study. Statistical significance was accepted as p value < 0.05.

RESULTS

In 56 CI patients, 17 out of them had atherosclerotic stenosis (AST) of large cerebral artery by angiographic criteria. They were 10 men and 7 women. The average age was 32.3 years. In another 39 patients without angiographic evidence of atherosclerotic stenosis (NAT) were 25 men and 14 women. The average age was 36.5 years.

In those 17 AST patients, the TC:HDLC ratio was 5.98 ± 1.40, in contrary to 5.13 ± 1.48 in NAT individuals ($p < 0.05$) or 4.349 ± 1.86 in controls ($p < 0.005$). Therefore, the TC:HDLC ratio was significantly higher in young AST subjects, suggesting a reduction of HDLC fraction may attribute to atherosclerotic change of large cerebral artery in young Asians. Only 3 (17.65%) AST and 19 (48.72%) NAT patients had their TC:HDLC ratio less than 5.0 (Fig 1). Accordingly, we selected TC:HDLC ratio of 5.0 to be the cut-point risk for cerebral atherosclerosis in our series.

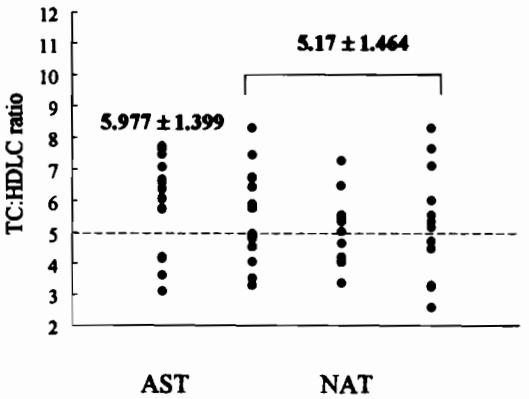

Fig 1–The mean TC:HDLC ratio of AST (atherosclerotic) subjects was 5.977 and of NAT (non-atherosclerotic) was 5.13 ($t = 2.77$, $p < 0.05$). Only 3 out of 17 (17.65%) AST but 19 out of 39 (48.72%) NAT subjects had a TC:HDLC ratio below 5.0. Therefore, we chosed TC:HDLC ratio of 5.0 as cut-point.

In our 155 control subjects, TC:HDLC ratio correlated well to TG ($r = 0.4305$, $F = 35.3$, $p < 0.0001$), uric acid ($r = 0.2957$, $F = 14.85$, $p < 0.01$) but less FAG ($r = 0.0046$, $F = 0.00327$, $0.01 < p < 0.05$) (Fig 2). This data was similar to prior (Phillip *et al*, 1989) that TG was the most dominant factor reported for predicting TC:HDLC ratio, while FAG was a less significant determinant. This data also compared well with our previous findings that FAG was not a notable factor predicting TC:HDLC ratio (Ngai *et al*, 1992).

In our data, TC : HDLC ratio correlated well to GUT score ($r = 0.40044$, $p < 0.01$). From the correlation plot, a GUT score of 8.3564 was chosen

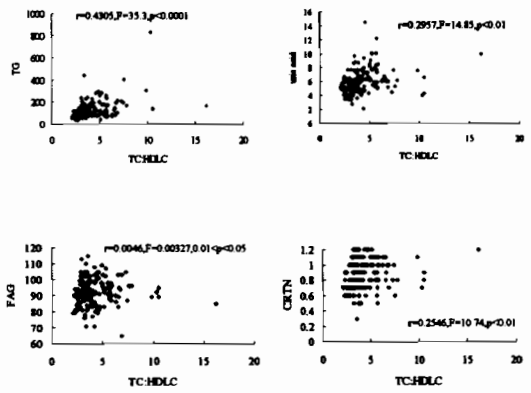

Fig 2–The correlation plot between TC:HDLC ratio and triglyceride (TG), uric acid (UA), fasting glucose (FAG) and creatinine (CRTN). TG is the most significant factor correlating to TC:HDLC ratio amongst them. UA and CRTN are similar. FAG is the less one.

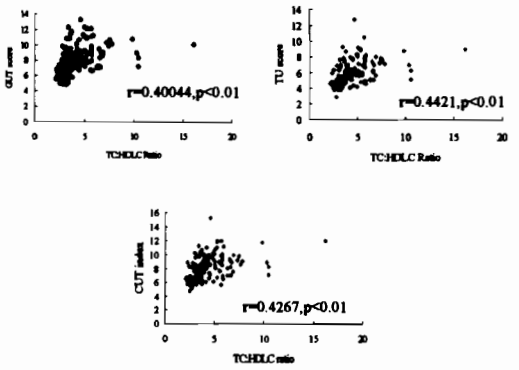

Fig 3–The correlation plot between TC:HDLC ratio and GUT score, TU score and CUT index.

to correspond to TC:HDLC ratio of 5.0 (Fig 3). Eighty-two of 113 (72.57%) healthy subjects with a TC : HDLC ratio of < 5.0 had a GUT score of < 8.3564 (true-negative). And 28 of 42 (66.67%) subjects with a TC : HDLC ratio of > 5.0 had a GUT score of < 8.3564. Thus, 70.97% of them correctly classified into their risk categories by use of the GUT score. This data was similar to our previous result encompassing subjects with a variety of age. Accordingly, GUT score is not an ideal predictor for TC : HDLC ratio. When subjects were classified into normocholesterolemic (NT) (TC ≤ 200 mg/dl) or hypercholesterolemic (HC) (TC > 200 mg/dl), the GUT score predicted TC : HDLC ratio 73.56% in NT and 67.65% in HC subjects.

Since FAG displayed no significant effect on predicting TC : HDLC ratio, we examined if either TG, uric acid or creatinine differed in individuals who had TC : HDLC ratio > 5.0 and < 5.0. The results showed that uric acid and creatinine were more higher in individuals with TC : HDLC ratio > 5.0 than who with ratio < 5.0 (Table 2). It indicated that a prediction of TC : HDLC ratio might be more better if uric acid or creatinine was emphasized. Therefore, we tested the predicting power of TU score and CUT indexes, which contained uric acid and creatinine. The correlation coefficient of TC : HDLC ratio to creatinine was 0.2546 and F value was 10.74, which were similar to uric acid eventually (Fig 2).

TU score also correlated well with TC : HDLC ratio ($r = 0.4421$, $p < 0.01$). From the correlation plot, a TU score of 6.3935 was selected to correspond to TC : HDLC ratio of 5.0 (Fig 3). A total 75.64% of controls were correctly classified into their risk categories by TU score. TU score predicted accurately the TC : HDLC ratio 74.71% in NT and 77.94% in HC subjects. Similar to GUT score, TU score deems also not an ideal system in predicting TC : HDLC ratio.

CUT index also correlated well to TC:HDLC ratio ($r = 0.4267$, $p < 0.01$). From the correlation plot, a CUT index of 8.6403 was chosen to correspond to TC:HDLC ratio of 5.0 (Fig 3). Totally, there were 81.29% of them were correctly classified into the risk category by CUT index. CUT predicted TC:HDLC ratio 81.06% in NT and 80.88% in HC subjects respectively. Accordingly, CUT index seems to be better on predicting the TC: HDLC ratio than GUT or TU score.

Comparing the three scoring systems, the true-negative and false-negative rate were eventually similar amongst them (Table 3). However, CUT index had a more lower false-positive rate than other two, suggesting that CUT index is more accurate for predicting TC:HDLC ratio than GUT or TU score in individuals with an above cut-point value. In our series, the frequency of false-positive rate was more than false-negative one, therefore, a reduction of erroneous false-positive prediction by CUT index will relatively save a large pool of medical cost in this group of population.

Table 2

The fasting glucose, triglyceride, uric acid and creatinine level between TC:HDLC ratio < 5.0 and ≥ 5.0 in healthy subjects. Only uric acid and creatinine reach significant difference.

Parameters	TC:HDLC < 5.0 (n = 114)	TC:HDLC ≥ 5.0 (n = 41)	p-value
Fasting glucose (mg/dl)	91.09 ± 12.44	90.52 ± 15.96	NS
Triglyceride (mg/dl)	113.4 ± 61.4	170.8 ± 128.3	NS
Uric acid (mg/dl)	5.688 ± 1.63	6.944 ± 1.80	< 0.01
Creatinine (mg/dl)	0.834 ± 0.20	0.927 ± 0.17	< 0.05

Table 3

The predictive rate of Nanji's GUT score, TU score and CUT index for TC:HDLC ratio in 155 healthy Asian young subjects. The predicting rate by CUT index is better than GUT score for TC:HDLC. Actually, the true-negative rate is similar amongst these 3 scoring systems. But CUT index has a better predictive rate due to a high true-positive rate, as well as a low false-positive rate. Therefore, CUT index is the ideal one amongst them to predict TC:HDLC ratio, especially in individual who has an above-cut point CUT index. From our data it is clearly that the serum total cholesterol level has no effect no prediction amongst these three scoring systems. True-positive rate seems to be better in > 200 mg/dl individuals.

Score	Nanji's GUT score %	TU score %	CUT index %
False-negative			
≤ 200 mg/dl TC	43.75	56.25	42.86
> 200 mg/dl TC	26.92	34.16	32.00
overall	33.34	42.86	35.90
False-positive			
≤ 200 mg/dl TC	64.00	65.00	55.56
> 200 mg/dl TC	44.12	26.09	22.72
overall	52.54	44.19	37.50
True-negative			
≤ 200 mg/dl TC	88.71	86.57	92.20
> 200 mg/dl TC	79.41	80.00	84.45
overall	85.42	83.93	88.60
True-positive			
≤ 200 mg/dl TC	36.00	35.00	44.45
> 200 mg/dl TC	55.88	73.91	77.27
overall	47.46	55.81	62.50
predictive rate			
≤ 200 mg/dl TC	73.56	74.71	81.61
> 200 mg/dl TC	67.65	77.94	80.88
overall	70.97	76.13	81.29

DISCUSSION

Despite Nanji (1982) achieved a 91% prediction, we showed that Nanji's GUT score predicted only 71.0% of TC:HDLC ratio in our young adults. The prediction rate is similar to our previous data from a study including healthy subjects encompassing with a variety of age (Ngai *et al*, 1989). In both studies, the correlation of the score with TC:HDLC ratio was relatively good. It implicates that the Nanji's GUT score is rather consistent with TC : HDLC ratio independent of age.

In our series, all three scoring systems actually achieved a good true-negative predicting rate. But the true-positive rate was rather low. Even the GUT score was below 50%. Since false-negative rate was similar amongst them, this low true-positive rate was possibly due to a high false-positive rate, which implies to a heterogenous group having disproportionally high serum level of parameters in face of a normal TC:HDLC ratio. Individuals classified into this group constituted 9.7% to 20% of total subjects. Since this group of individuals are proposed to be high-risk on screening by either scoring system but actually have a normal TC:HDLC ratio, how to define them more accurately will obviously save unnecessary medical cost for cholesterol electrophoresis.

The Nanji's GUT score depends on 3 parameters, fasting glucose, uric acid and triglyceride, which relate tightly to the cholesterol metabolism. Although Nanji restricted the range of fasting glucose to avoid diabetic effect on cholesterol metabolism, there are still a number of factors known to influence. Like an alteration of thyroid function, cortisol, hepatic microsomal and ductal enzymes or recent drug history is capable of affecting cholesterol metabolism but was not clearly described in his report. In our series, they were examined to be normal.

Besides, dietary and living habits are essential factors in influencing TC:HDLC ratio. Food abundant with animal fat and proteins will cause an increase of serum total cholesterol level and its LDLC component. Another possible factor is smoking and alcohol consumption. They are becoming more prevalent in young Asians and can induce a great change of cholesterol metabolism, including an elevation of apoB containing lipoproteins or a decrease of HDLC. Since cholesterol metabolism is modified by a variety of endogenous and exogenous factors, a low prediction rate of GUT or TU score may partially relate to a disturbance by other factors in ours and Phillips *et al* (1989). A variety of factors interfering the cholesterol metabolism complicates the predicting power of single factor for TC:HDLC ratio and further evaluation is necessary.

HDLC is metabolized partially in kidney and renal function is another essential determinant for TC:HDLC ratio. Therefore, we had included creatinine in predicting TC :HDLC ratio and termed it the "CUT" index (Ngai *et al*, 1992). It achieved a more better predictive power than GUT score in our previous study. In this series, CUT index predicted 81% of TC:HDLC ratio. Accordingly, we suggest CUT index can be used for predicting TC:HDLC ratio currently.

In conclusion, Nanji's GUT score is not an ideal surrogate for cholesterol electrophoresis. We recommend the "CUT" index, if possible, for screening individuals at risk for cerebral atherosclerosis. But a more cheap and accurate method is still an objective looking forwards to reduce medical cost in developing countries.

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