

Reference intervals of clinical chemistry parameters in adults at King Chulalongkorn Memorial Hospital

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Objective : *To establish reference intervals of clinical chemistry for helping the physician in differentiating between the healthy and diseased patients at Central Laboratory of King Chulalongkorn Memorial Hospital (KCMH).*

Study Design : *A descriptive study.*

Materials and Methods : *The study was done on 164 subjects, composed of 60 males and 104 females, age between 18 to 70 years old. All the subjects have normal vital signs, physical examination, chest X-ray, and laboratory investigation. Blood collection was performed by venepuncture after informed consent was obtained. Reference intervals of fasting blood glucose (FBG), blood urea nitrogen (BUN), creatinine (Cr), uric acid, cholesterol (Chol), triglyceride (Tg), high-density lipoprotein cholesterol (HDLc), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP), were performed by Hitachi 912. The study method was performed according to recommendation of the National Committee for Clinical Laboratory Standards (NCCLS).*

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Results : *Reference intervals of FBG, BUN, Cr, uric acid, Chol, Tg, HDLc, AST, ALT, and ALP were 74-106 mg/dL, 6-19 mg/dL, 0.5-1.1 mg/dL, 2.5-7.0 mg/dL, 150-220 mg/dL, 26-143 mg/dL, 41-91 mg/dL, 13-30 U/L, 10-38 U/L, and 28-93 U/L, respectively.*

Conclusion : *Our results agree with the previous studies and all our reference levels are in limitation of recommended reference level of the studies as well. We conclude that our reference level could be used as reference intervals for population at KCMH. In addition, reference intervals should not only be established for reason of requirement of standard service, but also should be used to support patients' care.*

Keywords : *Clinical chemistry, Reference intervals.*

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ค่าอ้างอิงของสารเคมีคลินิกในผู้ใหญ่ ณ โรงพยาบาลจุฬาลงกรณ์. จุฬาลงกรณ์เวชสาร 2547
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วัตถุประสงค์ : เพื่อหาค่าอ้างอิงของสารเคมีคลินิก สำหรับช่วยให้แพทย์ใช้แยกผู้ที่มีสุขภาพ
แข็งแรงและผู้ป่วย ที่มาใช้บริการการตรวจทางห้องปฏิบัติการ ณ ห้องปฏิบัติ
การกลาง โรงพยาบาลจุฬาลงกรณ์

รูปแบบการศึกษา : การศึกษาเชิงพรรณนา

วัสดุและวิธีการ : การศึกษานี้ทำในกลุ่มตัวอย่าง 164 คน เป็นเพศชาย 60 คน เป็นเพศหญิง
104 คน อายุระหว่าง 18-70 ปี ที่มีผลการตรวจร่างกายและการตรวจทาง
ห้องปฏิบัติการเป็นปกติ และได้ลงนามในใบยินยอมร่วมมือในการศึกษา
ค่าอ้างอิงของสารเคมีคลินิกที่ทำการศึกษา ได้แก่ fasting blood glucose
(FBG), blood urea nitrogen (BUN), creatinine (Cr), uric acid, cholesterol
(Chol), triglyceride (Tg), high-density lipoprotein cholesterol (HDLc),
aspartate aminotransferase (AST), alanine aminotransferase (ALT),
และ alkaline phosphatase (ALP) โดยทำการวิเคราะห์ด้วยเครื่อง Hitachi
912 วิธีการในการศึกษาทำตามคำแนะนำของ the National Committee
for Clinical Laboratory Standards (NCCLS)

ผลการศึกษา : ค่าอ้างอิงของ FBG, BUN, Cr, uric acid, Chol, Tg, HDLc, AST, ALT, and
ALP เท่ากับ 74-106 mg/dL, 6-19 mg/dL, 0.5-1.1 mg/dL, 2.5-7.0 mg/dL,
150-220 mg/dL, 26-143 mg/dL, 41-91 mg/dL, 13-30 U/L, 10-38 U/L,
และ 28-93 U/L ตามลำดับ

สรุป : ผลการศึกษาหาค่าอ้างอิงของสารเคมีคลินิกของคณะผู้วิจัย มีความ
สอดคล้องและมีช่วงค่าการตรวจวิเคราะห์ใกล้เคียงกับการศึกษาที่ผ่านมา
คณะผู้วิจัยสรุปว่า ค่าอ้างอิงที่ศึกษานี้สามารถนำมาใช้เป็นค่าอ้างอิงของ
ห้องปฏิบัติการกลาง โรงพยาบาลจุฬาลงกรณ์ นอกจากนี้การหาค่าอ้างอิง
ไม่ใช่เป็นเพียงการหาตามมาตรฐานในการให้บริการทางห้องปฏิบัติการ
เท่านั้น หากแต่ยังมีความสำคัญต่อการสนับสนุนการดูแลผู้ป่วยด้วย

คำสำคัญ : เคมีคลินิก, ค่าอ้างอิง

Generally laboratory tests are the most common noninvasive investigation that ordered by clinicians. In order to interpret a laboratory test, a clinician needs to know the reference intervals or values of the test run in healthy population. However, most of biochemical substances in circulation are influenced by several factors, therefore each laboratory is recommended to establish their own reference intervals of laboratory tests. To establish proper reference intervals for any laboratory tests, three important criteria are needed to be considered. Firstly, the subject populations must be evaluated for their health conditions. In another word, ostensible subjects should not be recruited into the study without adequate evaluation for their health status. Secondly, the size of the population must be adequate for statistical calculation. Thirdly, the selected statistical methods should be suitable. In order to establish proper reference intervals of laboratory tests for worldwide laboratories, the National Committee for Clinical Laboratory Standards (NCCLS) had provided a standard method to determine reference intervals.⁽¹⁻²⁾

In order to establish clinical chemistry reference intervals for helping the physician in differentiating between the healthy and diseased patients at Central Laboratory of King Chulalongkorn Memorial Hospital (KCMH), the authors designed a descriptive study based on the recommendation method of NCCLS. In addition, all laboratory services at the Central Laboratory of KCMH have been performed under the standard of ISO 15189: 2003⁽³⁾ since August 2003. The laboratory has been audited and accredited for the standard by the Department of Medical Science, Ministry of Public Health,

since April 2004. It is the first laboratory in Asia that has been audited and accredited for ISO 15189: 2003.

Materials and Methods

This study protocol has been approved by the Research Ethics Committee (REC), Faculty of Medicine, Chulalongkorn University. All subjects were checked for vital signs, blood pressure, and also inspected by doctors. Those who had abnormal vital signs or abnormal blood pressure or abnormal doctoral inspection were not recruited for further chest X-ray (CXR) and laboratory investigation, for this study. After informed consent was obtained, blood was collected by venepuncture. Four hundred and eighty volunteers were randomly selected, composed of 240 males and 240 females, age between 16 to 81 years old. Most of them were employees of private or governmental organizations enrolling in annual checkup program, at KCMH, during July to November 2003. Some of them were having their own annual checkup. All volunteers were filmed for CXR and investigated according to the laboratory menu for complete blood count (CBC), fasting blood glucose (FBG), blood urea nitrogen (BUN), creatinine (Cr), uric acid, cholesterol (Chol), triglyceride (Tg), high-density lipoprotein cholesterol (HDLc), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), urinalysis (UA), and stool examination. In addition, CBC was analyzed by Advia 120, and FBG, BUN, Cr, uric acid, Chol, Tg, HDLc, AST, ALT, and ALP were determined by Hitachi 912.⁽⁴⁾ The principles of determination of FBG, BUN, Cr, uric acid, Chol, Tg, HDLc, AST, ALT, and ALP were hexokinase, kinetic UV assay, kinetic colorimetric assay, uricase/PAP,

enzymatic colorimetric assay, enzymatic colorimetric assay, homogeneous enzymatic colorimetric assay, IFCC/SFBC, IFCC/SFBC, IFCC/liquid, respectively. Subjects who had abnormal CXR and/or laboratory results were excluded from the study. After careful investigation, only 164 (34.2 %) healthy subjects were accepted for the study, they were 60 males and 104 females, between 18 to 70 years old.

To cover 95 % of the population (95 % reference intervals or ranges) according to NCCLS recommendation, the reference intervals were calculated with the formula $\text{mean} \pm 2$ standard deviation ($\text{mean} \pm 2\text{SD}$) for those laboratory parameters that have Gaussian distribution. For those laboratory parameters that have skewed distributions, the 95 % reference intervals are calculated from 2.5 and 97.5 percentiles.⁽⁵⁾

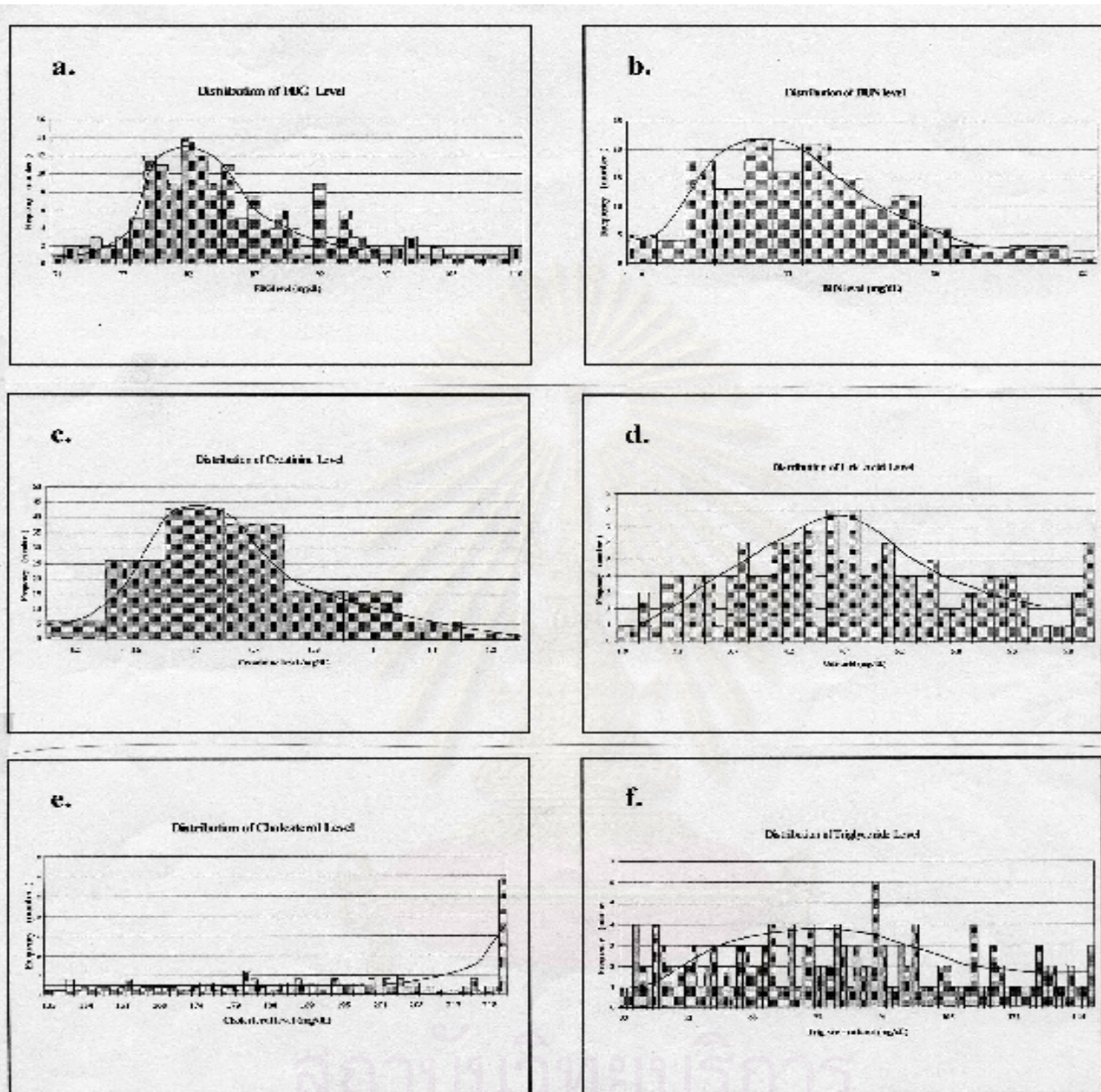
Results

The reference means and intervals are shown in Table 1. The distributable patterns of each parameter are shown in Figure 1 (a-j). From our data the distributable patterns of most of parameters are not Gaussian distributions even using 164 subjects that higher than 120 subjects recommended by NCCLS,⁽⁵⁻⁷⁾ so we decided to use the 95 % reference intervals calculated from 2.5 and 97.5 percentiles for FBG, BUN, Cr, AST, ALT, and HDLc parameters. Only the reference intervals of uric acid, Tg, and ALP were calculated from $\text{mean} \pm 2$ standard deviation ($\text{mean} \pm 2\text{SD}$). However, we noticed that the reference intervals of Cr calculated by $\text{mean} \pm 2\text{SD}$ was equal to the reference intervals calculated from 2.5 and 97.5 percentiles.

Discussion

Our glucose, BUN, Cr, uric acid, Chol, Tg, HDLc, AST, ALT, and ALP are all close to reference intervals recommended by manufacturer⁽⁸⁾, including the reference intervals of Fischbach F⁽⁹⁾, (Table 1). Because of distribution of levels of most of parameters were skewed distributions, so most of reference intervals were calculated from 2.5 and 97.5 percentiles. Only the reference intervals of uric acid, Tg, and ALP were calculated from $\text{mean} \pm 2\text{SD}$. In addition, the reference intervals of Cr calculated by $\text{mean} \pm 2\text{SD}$ was equal to that calculated from 2.5 and 97.5 percentiles.

From the study, the distributable patterns of FBG, BUN, Cr, AST, ALT, and HDLc were leftward skewed, while the distributable patterns of Chol was in the opposite direction. These suggested that the blood levels of FBG, BUN, Cr, AST, ALT, HDLc, and ALP in healthy population trend to shift to the lower levels, whereas the blood level of Chol in healthy population shifts toward the opposite direction, to the higher levels. The distributable pattern of Chol suggested the tendency of high cholesterol in healthy population. Because of high cholesterol and low HDLc associated with coronary heart diseases (CHD)⁽¹⁰⁾, hence the distributable pattern of Chol and HDLc should urge the society to be concerned with dyslipidemia,⁽¹¹⁾ and the further policy for the promotion of health of the people and prevention should be stimulated. Furthermore, the blood level of uric acid, and Tg are almost equally distributed to both sides of the curves. Our reference intervals of Chol and Tg are close to those recommended by that of the manufacturer but both Chol and Tg are lower



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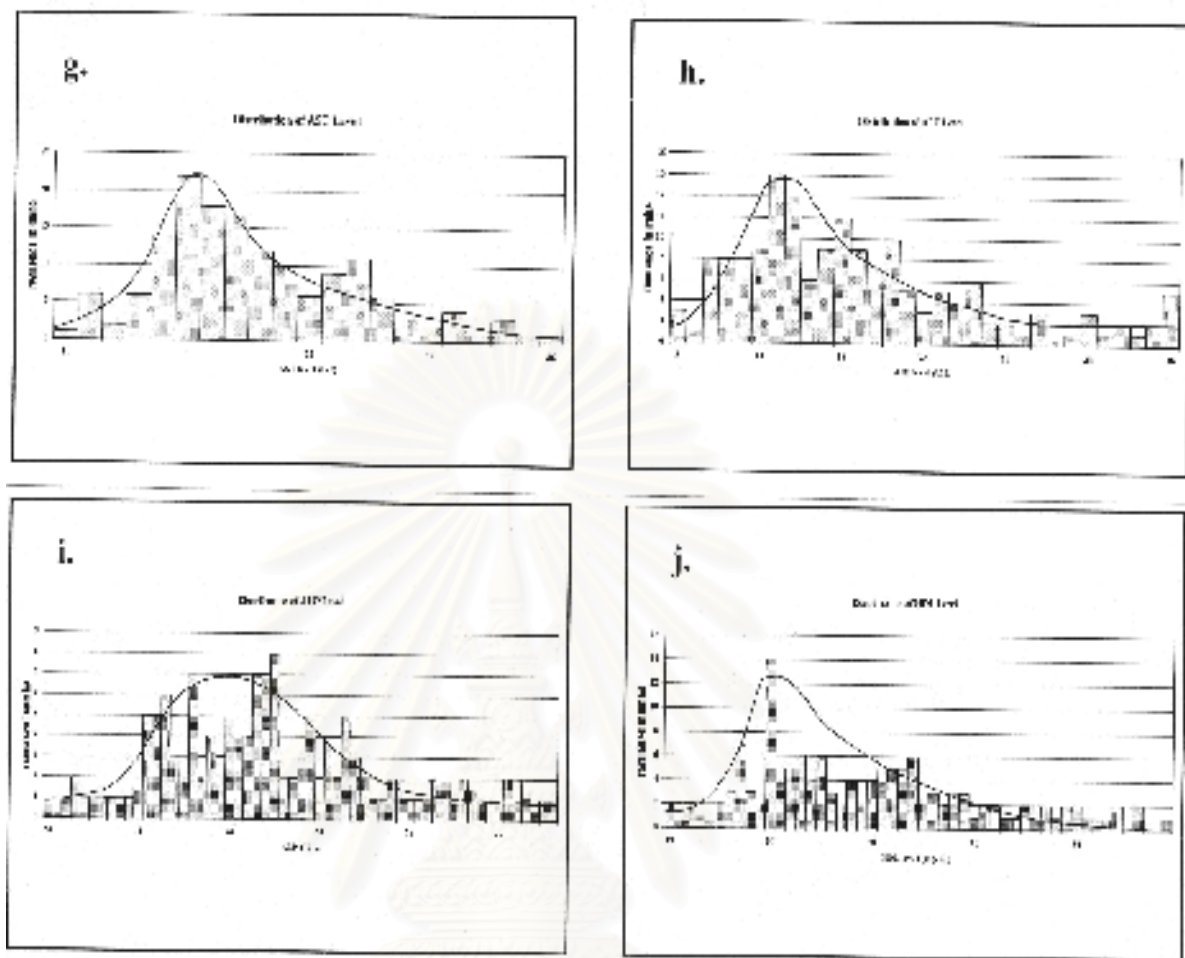


Figure 1. The distributable pattern of laboratory parameters; a.) FBG, b.) BUN, c.) Cr, d.) uric acid, e.) Chol, f.)Tg, g.) AST, h.) ALT, i.) ALP, and j.) HDL.

Table 1. Comparison of our reference intervals and others reference intervals.

Laboratory parameters	Reference intervals (our study)	Reference intervals (manufacturer) ⁽⁵⁾		Reference intervals (Fischbach F) ⁽⁶⁾
Glucose (mg/dL)	74-106	70-110		62-110
BUN (mg/dL)	6-19	10-20		6-25
Creatinine (mg/dL)	0.5-1.1	0.5-2.0		0.4-1.3
Uric acid (mg/dL)	2.5-7.0	2.0-7.0	Men	2.9-8.5
			Women	2.2-6.5
Cholesterol (mg/dL)	150-220	150-220	<29 years old	<200
			30-39 years old	<225
			40-49 years old	<245
			>50 years old	<265
Triglyceride (mg/dL)	26-143	40-155		50-200
HDLc (mg/dL)	41-91	50-100		-
AST (U/L)	13-30	0-38		5-40
ALT (U/L)	10-38	0-38		5-40
ALP (U/L)	28-93	39-117		35-110

than in previous studies.⁽¹²⁾ Several reasons could be stated to explain the outcome, such as the inclusion criteria for healthy subjects in this study is different, the study is done in different population at different time, and by different methods. In this study, however, all ostensive subjects were examined for physical examination but were investigated for CXR, and laboratory tests such as; CBC, FBG, BUN, Cr, uric acid, Chol, Tg, HDLc, AST, ALT, ALP, UA, and stool examination. Then only the subjects with physical examination, CXR, and normal laboratory results were recruited into the study. We also compare our results with reference level recommended by manufacturer⁽⁸⁾ and Fischbach F⁽⁹⁾ (Table 1). We found that our results agree with the previous studies. All our reference levels are in limitation of recommended reference level of the studies as well. The important reason to explain the study result is; our study had performed using a strict criterion of subject inclusion according the recommendation of NCCLS.

We conclude that our reference level could be used as reference intervals for population at KCMH. In addition, reference intervals should not only be established for reason of requirement of standard service, but should also be used to support patients' care. We agree with the recommendation of NCCLS⁽¹⁾, ISO⁽²⁾, etc, that suggested every laboratory to establish it own reference intervals. In order to achieve the standard requirement and the need of patients' care for laboratory services in developing countries such as Thailand, reference intervals should be considered as one of the basic requirements. Supporting grants for establish the reference intervals from the associated or research organizations should be managed and available to the laboratories.

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References

1. National Committee for Clinical Laboratory Standards. How to define and determine reference intervals in the clinical laboratory: Approved guideline. Second Edition NCCLS Document C28-A. Villanova, PA: NCCLS, 1995
2. National Committee for Clinical Laboratory Standards. How to define and determine reference intervals in the clinical laboratory: Approved guideline, NCCLS Document C28-A2. Wayne, PA: NCCLS, 2000
3. Technical Committee ISO/TC 212, Clinical laboratory testing and in vitro diagnostic test system. ISO 15189, Medical laboratories – particular requirements for quality and competence. 1st edition, Feb 15, 2003
4. Roche/Hitachi 912: Operator's Manual. version 1.2, Roche Diagnostic Corporation, Technical Publication Department: Indianapolis, 2000
5. Horn PS, Pesce AJ. Reference intervals: an update. Clin Chim Acta 2003 Aug; 334 (1-2): 5 - 23
6. Sasse EA. Determination of reference intervals in the clinical laboratory using the proposed Guideline National Committee for Clinical Laboratory Standards C28-P. Arch Pathol

- Lab Med 1992 Jul; 116 (7): 710 - 3
7. Reed AH, Henry RJ, Mason WB. Influence of statistical method used on the resulting estimate of normal range. Clin Chem 1971 Apr; 17 (4): 275 - 84
8. Reagent leaflets. Glu-quant[®], Glucose/HK 2001-08-21787700010102; Urea/Bun, Kinetic UV assay for urea/urea nitrogen 2000-09-19824860010106; Crea, HiCo creatinine Jaffe method, rate-blanked and compensated 2000-08-19721980010105; UA Plus, Uric acid plus 2001-03-19653520010108; Chol, Cholesterol CHOD-PAP 2001-11-19439010010106; Tg, Triglycerides GPO-PAP 2001-05-19214280010107; HDL-c plus, HDL cholesterol, no pretreatment 2002-10-30393660010102; AST, AST (ASAT/GOT) AST IFCC without/with pyridoxal phosphate activation 2001-01-21722750010102; ALT (ALAT/GPT) ALT IFCC without/with pyridoxal phosphate activation 2002-01-21721860010103; ALP, ALP IFCC liquid 2001-05-21734090010102, Roche Diagnostic Corporation, Customer Technical Support: Indianapolis
9. Fischbach F. A Manual of Laboratory and Diagnostic Tests. 7th edition, Philadelphia: Lippincott Williams & Wilkins, 2004: 1113 - 7
10. Pingsuthiwong S, Charuruks N. Importance and management of hyperlipidemia. Bull Chiang Mai Assoc Sci 1995 Sep; 28 (3): 9 - 23
11. Pingsuthiwong S, Charuruks N, Krailadsiri P. Screening for cholesterol and triglyceride levels in a middle-aged population. Chula Med J 1994 Oct; 38 (10): 571 - 7
12. Charuruks N, Krailadsiri P, Pingsuthiwong S. Reference range values for blood lipids and CHD guidelines for risk classification in middle-aged subjects. Chula Med J 1994 Aug; 38 (8): 461 - 70