ORIGINAL ARTICLE

Arch AHS

Archives of Allied Health Sciences 2020; 32(3): 1-12.

Clinical chemistry normal ranges of healthy adult population in Nong Khai, Thailand

Chanin Yotsakullert[1,2], Apisamart Klongkayan[3], Molin Wongwattanakul[2,4], Jureerut Daduang[2,4], Patcharee Jearanaikoon[2,4], Patcharaporn Tippayawat[2,4*]

[1] Biomedical science program, Graduate school, Khon Kaen University, Khon Kaen, Thailand.
[2] Centre of Excellence on Medical Biotechnology, Faculty of Associated Medical Sciences, Khon Kaen University, Khon Kaen, Thailand.
[3] Nong Khai hospital, Nong Khai, Thailand.
[4] Centre for Research and Development of Medical Diagnostic Laboratories, Faculty of Associated Medical Sciences, Khon Kaen University, Khon Kaen, Thailand.

KEYWORDS

Normal range; Reference interval; Liver function parameters.

ABSTRACT

Normal range is a range of values used for clinical decision-making in early diagnosis, prediction and therapeutic monitoring of diseases. Due to the lack of a locally-established normal range, western population ranges acquired from reagent companies are commonly used for patients. Clinical normal ranges are in high demand for clinical trials and practice studies. Improvement of the normal range for the population in northeastern Thailand would be valuable for the development of healthcare quality. A newly-established range could act as control for a normal population for laboratory testing in nearby regions and countries. This study was initiated in October 2010 and lasted until May 2018 using 2,589 healthy adults who visited a hospital in Nong Khai, Thailand for health check-ups. In terms of laboratory testing, 6 clinical chemistry tests consisted of AST, ALT, ALP, Creatinine, HDL, and LDL. For data management and statistical analysis, STATA 10.1 software was used to manage and analyze the laboratory result data. Each group of samples was tested with mean, median and percentile range for all parameters to establish new normal ranges for the population. Data mining and a filtering model were created based on normal reference ranges. This model was used to filter only a population of healthy adults. The dataset of 91,829 recorded laboratory results from 9,398 people, with only 30,296 records from 1,051 men and 1,538 women enlisted for further study. This study provides a simple guideline that can serve as a model for clinical laboratories intending to establish their own normal ranges with local data.

* **Corresponding author:** Patcharaporn Tippayawat, MT, PhD. School of Medical Technology, Faculty of Associated Medical Sciences, Khon Kaen University, Thailand. E-mail: patchatip@kku.ac.th
Received: 10 January 2020/ Revised: 16 March 2020/ Accepted: 4 May 2020

Introduction

Normal ranges comprise the range of values used for medical decision-making. For prompt diagnosis, estimation and therapeutic observation, especially for patients with certain diseases, clinical decisions can be critical. By assessing samples from a healthy population, normal ranges can be established. They are usually determined from the central 95% of values from a healthy and normal population[1]. For enhancing the quality of healthcare, population-based normal ranges can be a useful tool for clinical decision-making. These values become universally accepted and comprise the best method in clinical laboratory literature.

Currently, standard clinical laboratory ranges are widely available in scientific journals and publications for demographics from industrialized nations. However, the population in Thailand has limited data for normal ranges in various regions, with the most widely used range originating from articles or data appended from reagent companies. Further, the upper and lower limits can vary greatly and differ between hospitals[2]. Moreover, internal factors including race[3,4], and environmental factors such as lifestyle, biological changes with advanced age and sex[5,6] mean normal ranges can vary. Consequently, records from western countries may not be used for populations in other regions, as demonstrated by various studies[5,7-10], As a requirement before submission, the United States Food and Drug Administration (USFDA) states manufacturers of diagnostic reagents must establish a new normal range for their product[11]. Collecting statistics from all over the nation where the automations are to be used can fulfill this prerequisite. However, for people and patients in certain demographic regions, the population used for these studies may not be appropriate. Along with the Clinical Laboratory Improvement Act (CLIA), therefore, the laboratory standards allow a clinical laboratory to verify the suitability of normal ranges for certain demographics.

The current research intends to improve the normal range in Northeastern Thailand, with Nong Khai chosen as the study area. About 517,260 people live in the province, which covers 3,027 square kilometers[12,13]. The study determines clinical chemistry parameters for normal ranges representing the population and compare them with other factors within the population, including age and gender. This article discusses the selected clinical chemistry laboratory normal ranges for healthy adults from Nong Khai Province, located in Northeastern Thailand. For normal populations in a laboratory for surrounding areas and nations, the locally determined normal range can act as control.

Materials and methods

Study subjects and sample size

This study was conducted from October 2010 to May 2018 with 2,589 healthy adults aged 18 years and older who visited Nong Khai Hospital, Nong Khai Province, Thailand for health check-ups (Figure 1). In terms of laboratory testing, 6 clinical chemistry tests consisted of AST, ALT, ALP, Creatinine, HDL and LDL. Data mining and a filtering model were created according to the normal reference range. From CLSI guidelines[14], the number of samples that permitted 90% confidence interval in order to estimate a normal range was 120 samples. The calculations were described as recommendations by Reed et al[15].

Figure 1 The population region in the study
(Retrieve from Google map: https://goo.gl/maps/12RdDWib2Am7wd269)

Data management

In statistical analysis, STATA software (1996–2019, StataCorp LLC) version 10.1 was used to manage laboratory results data. After inspection of the data, some records were excluded due to being defective (because of human errors in the laboratory or failure in automation) as they seemed to be physiologically unfeasible. The standardization procedure consisted of eliminating duplications and format checking of the records. These steps eliminated major errors and inconsistencies (e.g. incorrect, unsuitable, mistaken or irrelevant parts of the data) when multiple types of data were gathered into one dataset.

Inclusion and exclusion criteria

This study is a part of Mediage project, government funding project, which aims to create health data library and health index from the clinical and physical parameters for the Thai population. The inclusion criteria for healthy population are aged between 18-80 years, BMI < 30, systolic blood pressure < 140 mmHg, diastolic blood pressure < 90 mmHg. The exclusion criteria are subject regularly taking medication or has any underlying disease e.g. alcohol consumption, recent illness, blood donor, lactation, blood pressure, abnormal obesity, drug abuse, drug prescription, oral contraceptives, pregnancy, surgery, tobacco use, recent transfusion, hospitalization, current/recent vitamin abuse, presence of uncontrolled hypertension, diabetes, pulmonary, hepatic, pancreatic, or renal diseases. Subjects who reported clinical parameters not higher than the means and standard deviations (3 to 4 SD) of the reference value based on the normal range set by the American Medical Association (AMA): AST>60, ALT>80, ALP>350, creatinine <0.4 or >2.0, LDL>130, HDL<20 or >90, were also included based on a Korean study[16]. All

records from subjects who received more than one medical check-up were excluded, leaving only the results from their first check-up.

Continuity of the data and other disturbing factor effects

Principal component analysis (PCA) was used to test the continuity of the data between years to ensure that there was no effect from the disconnection of quality controls in the laboratory. Unscrambler X 10.4 software with PCA function was used to identify variations and draw out patterns in the dataset. There was no visual indication of subdivision from data distribution in the PCA score plot (Figure 2).

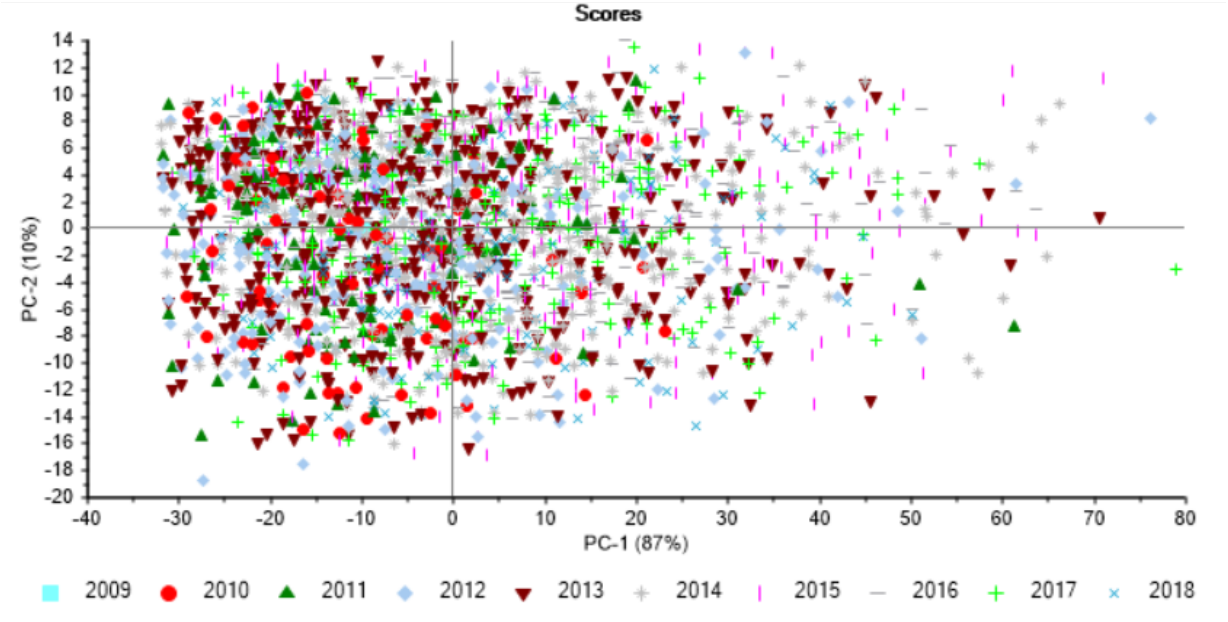

Figure 2 Unsupervised dataset in PCA scores plotted by year (differences in symbols and colors)

Statistical analysis

In statistical analysis, STATA version 10.1 was used to analyze the laboratory result data. To test mean, median and 95 percentile range for each parameter to determine the new normal range for the population, descriptive statistics were applied. Based on the Shapiro–Wilk test for normality, not all measured parameters followed Gaussian distribution[17]. Nonparametric statistical methods were used to summarize the normal range from the data. This method is recommended in the CLSI guidelines[14]. Independent sample T-test (Wilcoxon two-sample for nonparametric data) and one-way ANOVA (Kruskal–Wallis for nonparametric data) were utilized to ascertain the variation between sex and age, respectively. *p*-values ≤ 0.05 were deemed to be statistically significant.

Ethical consent

This study is a part of the project called "Health Index of the elderly in Northeastern Thailand for the Purpose of Lifestyle Modification and Health Monitoring before Disease Occurrence" (HE602172). According to the affirmation of Helsinki and ICH good clinical practice guidelines, the Khon Kaen University Ethics Committee for Human Research reviewed this work[18]. Any information acquired during the study remained private.

Results

Study population

In order to screen for a healthy, adult population and eliminate errors as well as inconsistencies in the raw data, including incorrect, unsuitable, mistaken and irrelevant parts of the data, a dataset comprising 91,829 result records from 9,398 people were filtered, leaving only 30,296 records from 1,051 men and 1,538 women. Data management and inclusion criteria were applied to this step. The data was enlisted in Table 1, consisting of the population categorized by gender and age. More than half of the population comprised people ranging in age between 35 and 54 years old.

Normal range of Nong Khai population

After the pre-analysis step, the organized data was ready to be used in the normal range calculation. Tables 2 and 3 show the investigated mean, median and 2.5th-97.5th percentile range values for clinical chemistry parameters according to gender and age, respectively. Conventional mean values for AST, ALT, ALP, creatinine, LDL and HDL among contributors were 23.7 U/L, 20.1 U/L, 67.9 U/L, 0.77 mg/dL, 85.3 mg/dL and 55.5 mg/dL, respectively.

To investigate differentiation in the normal range for demographic groups (gender and age), a laboratory can derive a separate normal range for different demographic groups. One criterion reinforcing this decision is the *p*-value for the variance between male and female contributors. Males had normal ranges of AST at 16-35 U/L compared to females at 15-33 U/L, ALT value of 12-32 U/L against females of 12-31 U/L, ALP of 40-114 U/L against females of 40-111 U/L, creatinine of 0.64-1.28 mg/dL against females of 0.51-0.91 mg/dL, LDL of 40-98 mg/dL against females of 47-99 mg/dL and HDL of 40-78 mg/dL against females of 41-86 mg/dL. Compared to males, females had much (p-value < 0.05) higher mean values for HDL. Conversely, much higher (p-value < 0.05) mean values for AST, ALT and creatinine were seen in males compared to females (Table 2). In the mean values for AST, ALT and HDL, there was no significant difference across all groups of participants (p-value > 0.05). The reverse was true for ALP and creatinine. Both of these parameters tend to increase with higher age. As shown in Table 2 and 3, a normal range was not seen for some parameters (LDL and HDL) among groups of participants based on sex and age because the sample size was small. This result suggests that there is no age dependency in these parameters. There is no increasing or decreasing trend in the same direction for ALP and creatinine. However, this result showed that the normal range for these tests should be derived in separated gender groups rather than a combined gender group, especially for creatinine.

Comparison between the present study and currently used

To compare clinical chemistry parameters for normal range between the currently used at hospital and the present study (Table 4), the upper limits of ALT, ALP and creatinine were lower in the present study compared to those currently used. The lower limits for AST, ALT, creatinine and HDL were higher in the current study compared to those currently used. This result made overall normal ranges for AST, ALT, ALP, creatinine, LDL and HDL for adults, narrower than those currently used at hospital.

Table 1 Statistical data relating to the individualities of the study contributors

	Number of Person	Percent	Number of Result Records					
			AST	ALT	ALP	Creatinine	HDL	LDL
Sex								
Male	1,051	40.6	830	884	804	927	154	26*
Female	1,538	59.4	1,258	1,311	1,232	1,333	265	52*
Age (years)								
18-24	127	3.9	66*	80*	58*	83*	37*	7*
25-34	366	11.2	192	194	174	208	123	14*
35-44	971	29.6	637	680	622	685	119*	20*
45-54	1,032	31.5	674	710	667	720	96*	15*
55-64	625	19.1	412	420	409	445	36*	15*
≥ 65	156	4.8	107*	111*	106*	119*	8*	7*

Note: *n < 120

Table 2 Average, standard, and 2.5th-97.5th percentile of clinical chemistry orientation values concerning the sex of healthy adults in Nong Khai

Parameters	Male			Female				Combined		
	Mean	Median	2.5th-97.5th Percentile Range	Mean	Median	2.5th-97.5th Percentile Range	*P*-value	Mean	Median	2.5th-97.5th Percentile Range
AST (U/L)	25.20	25.00	16-35	22.77	22.00	15-33	0.00	23.73	23.00	15-34
ALT (U/L)	21.97	22.00	12-32	18.89	18.00	12-31	0.00	20.13	19.00	12-31
ALP (U/L)	68.95	66.00	40-114	67.26	65.00	40-111	0.128	67.93	65.50	40-113
Creatinine (mg/dL)	0.92	0.91	0.64-1.288	0.67	0.66	0.51-0.91	0.00	0.77	0.74	0.53-1.17
LDL (mg/dL)	80.73	87.50	40-98*	87.71	91.50	47-99*	0.506	85.38	89.50	48-99*
HDL (mg/dL)	52.13	50.00	40-78	57.48	56.00	41-86	0.00	55.51	53.00	41-85

Note: *n < 120

Table 3 Average, standard, and 2.5th-97.5th percentile of clinical chemistry orientation values concerning the age summary of healthy adults in Nong Khai

Age (years)		AST (U/L)	ALT (U/L)	ALP (U/L)	Creatinine (mg/dL)	HDL (mg/dL)
18-24	Mean	21.74	18.39	65.98	0.76	55.22
	Median	21.00	16.50	61.50	0.76	54.00
	2.5th Percentile	14.00*	12.00*	37.00*	0.52*	40.00*
	97.5th Percentile	34.33*	30.98*	130.58*	1.13*	77.00*
25-34	Mean	22.64	19.40	63.03	0.74	55.23
	Median	22.00	18.00	59.00	0.71	53.00
	2.5th Percentile	14.83	12.00	38.00	0.52	40.10
	97.5th Percentile	34.00	31.00	105.88	1.09	82.80
35-44	Mean	22.84	19.40	63.39	0.74	55.88
	Median	23.00	18.00	61.00	0.70	54.00
	2.5th Percentile	15.00	12.00	39.58	0.52	41*
	97.5th Percentile	33.00	31.00	105.43	1.11	83*
45-54	Mean	24.08	20.63	69.10	0.78	55.66
	Median	24.00	20.00	67.00	0.75	52.00
	2.5th Percentile	16.00	12.00	40.00	0.53	40.43*
	97.5th Percentile	34.00	31.23	113.30	1.17	91.45*
55-64	Mean	24.81	21.04	74.47	0.81	55.03
	Median	24.00	21.00	72.00	0.78	51.50
	2.5th Percentile	17.00	12.00	42.50	0.53	40.00*
	97.5th Percentile	34.00	31.00	119.00	1.29	105.00*
>64	Mean	25.86	20.52	71.08	0.86	56.13
	Median	26.00	20.00	68.00	0.82	52
	2.5th Percentile	16.00*	12.00*	40.68*	0.57*	47.00*
	97.5th Percentile	34.00*	31.00*	112.28*	1.33*	87.00*
	P-value	0.39	0.17	0.00	0.00	0.13

Note: *n < 120

Table 4 Divergence between orientation range values for clinical chemistry parameters in the current study with hospital used at present

Parameters	Sex	Present study (Nong Khai, Northeast Thailand)	AMS Laboratory, Khon Kaen University (Northeast Thailand)	Han population[26] (Northern China)	American population[10] (USA)		
		Thai	Thai	Chinese	White	Black	Hispanic
AST (U/L)	Combined	15.00-34.00	12.00-32.00	12.00-38.00	N/A	N/A	N/A
	Male	16.00-35.00	N/A	13.00-38.00	N/A	N/A	N/A
	Female	15.00-33.00	N/A	11.00-37.60	N/A	N/A	N/A
ALT (U/L)	Combined	12.00-31.00	4.00-36.00	7.00-49.00	N/A	N/A	N/A
	Male	12.00-32.00	N/A	8.10-55.90	12.00-87.00	11.00-64.00	12.00-102.00
	Female	12.00-31.00	N/A	6.20-44.40	11.00-58.00	9.00-41.00	10.00-62.00
ALP (U/L)	Combined	40.00-113.00	42.00-121.00	36.20-112.00	N/A	N/A	N/A
	Male	40.00-114.00	N/A	45.10-113.00	35.00-107.00	38.00-114.00	43.00-126.00
	Female	40.00-111.00	N/A	30.20-108.60	31.00-115.00	33.00-121.00	40.00-123.00
Creatinine (mg/dL)	Combined	0.53-1.17	0.50 -1.50	0.50-1.05	N/A	N/A	N/A
	Male	0.64-1.29	N/A	0.62-1.13	0.70-1.27	0.73-1.45	0.65-1.34
	Female	0.51-0.91	N/A	0.47-0.87	0.50-1.10	0.52-1.15	0.46-0.99
HDL (mg/dL)	Combined	41.00-85.25	20.00-35.00	16.92-41.94	N/A	N/A	N/A
	Male	40.00-75.00	N/A	16.20-39.24	N/A	N/A	N/A
	Female	41.00-86.25	N/A	19.08-43.20	N/A	N/A	N/A

Discussion

The basis for laboratory testing is the normal range, which helps differentiate the healthy population. A normal range is important for disease screening, diagnosis, progression, and treatment monitoring. Consequently, patients in the area of study are the people who get the most benefit from establishing a distinctive normal range. In the same way, physicians can have more confidence in the interpretation of their test results. For clinical trials and practice, applicable clinical normal ranges are compulsory. For laboratories in adjacent districts and nations, the determined range could also be a reference and comparison source. Physicians frequently require normal range data from the local population to conduct clinical trial studies[19]. In addition, various organizations value the importance of normal ranges, such as the USFDA[11]. The International Organization for Standardization (ISO) 15189 standard for laboratory certification circumstances must be regularly re-evaluated by laboratories for their own normal range[20]. The Joint Commission on International Accreditation Standards for Laboratories (JCI) also requires laboratories to establish their own normal ranges for cytogenetics testing[21].

In present study, the criteria for enlisting candidate was only the subject who visited health check-up at Nong Khai hospital. Consequently, it was difficult to declare that this group of population are accurately healthy. In current study, subjects were excluded as outlier that based on standard deviations of the reference value, possibly leadings to bias result. Ideally, candidate who participate in reference value study should have done a questionnaire to exclude subject with underlying disease. CLSI guideline recommend that a minimum of 120 observations

are required, before applying statistical analysis with 90% confidence[14,15].

To assess the homogeneity of data collection over eight years, an unsupervised statistical method was employed in the dataset by PCA[22, 23]. The results from PCA only showed discrete patterns in one large group from PC1 but did not show any sign of clustering in the whole dataset. There was no data disturbance from unexpected factors such as human or machine error in the process of accumulating data. Moreover, this indicated the homogeneity of the dataset gathered over a period of eight years. Furthermore, quantitative methods based on information selection, such as the Gaussian (Normal) distribution, are referred to as "parametric" since they make particular suppositions concerning population-based data. Thus, the reference interval would be: RI = $\mu \pm 1.96\sigma$ if a normal range study for a Gaussian distribution of the data was assumed, when μ is the average and σ is the standard deviation for the dataset. Conversely, non-parametric methods do not conceive of distributed data and offer ways to assess and compare data sets with undetermined or unstable distributions. The central 95% of the data can be regulated by arranging from the lowest to the highest values and excluding the highest 2.5% and lowest 2.5% of values when distribution is not Gaussian. The residual highest and lowest values delineate the orientation interval mentioned previously in the method[12]. Based on the Shapiro–Wilk test for normality, not all measured parameters in this study followed a Gaussian distribution[14]. Consequently, this research selected nonparametric statistical methods.

In the values for ALP and LDL between men and women, this study identified a non-significant difference (p-value > 0.05) (Table 2). In the values for AST, ALT and creatinine, the result exhibited a noteworthy difference (p-value < 0.05). Normal ranges of AST and ALT have changed slightly in practical use. On the other hand, creatinine has an entirely different normal range. For analyzing chronic kidney disease (CKD) under UK guidelines, the appraised glomerular filtration rate (eGFR) from statistical models, such as Modification of Diet in Renal Disease (MDRD) is suggested[24]. For physicians to contrast patients' results, therefore, details to evaluate renal function, normal ranges of serum creatinine (Scr) are needed. The reference value displayed deterioration in renal function with age, causing a trend of intensifying serum creatinine. Creatinine is the product of muscle metabolism. Serum creatinine ranges are lower in women because women have less muscle mass and, therefore, a lower rate of creatinine excretion. In the present study, the reference values for serum creatinine were significantly different in men and women (p-value < 0.05). Another study in a Caucasian population likewise revealed Scr-age reliance begins to diverge between men and women at around the age of 15. Further, this disparity between men and women increases to a value of 0.25 mg/dL by the time they reach the age of 30 years[25]. The normal range of creatinine is superior when based on patient gender because of this.

To assess whether or not joint or gender-specific normal ranges should be employed, this research used p-value as a value. The percentage of laboratory values that would be organized differently if a common range instead of the gender-specific range is used is an alternative approach to estimating whether a normal range for both sexes is appropriate. However, this approach will need a new dataset from the population in Nong Khai in order to be arranged as 'normal' or 'abnormal'. Thus, testing could be carried out on the combined normal range and separate ranges.

Reference interval of liver enzyme including AST, ALT and ALP in Han population[26] are found similar to Thai population. But the liver enzyme ranges from our study are narrower than the ranges from Han population. While ALT of other American ethnic groups[10] are diverse and difficult to apply to East Asian population. On the other hand, reference value of HDL in present study has a distinct value from Chinese result which has a tendency to increase. Reference values of creatinine from present study are similar to Han population which men are higher than women in every ethnic group. It shows that reference interval should base on their own population.

Including sample data being greater, including the broadest age range, and making it possible to fill the gaps revealed by healthy-volunteer studies using these results to confirm the theories or re-assessed normal range between ethnic groups, there are various advantages for indirect (data mining) methods over direct methods (study in healthy individuals) when applied for retrospective hospital data[10]. All of the datasets from this study can contribute to larger projects that may require data from thousands of subjects in a healthy population. In this context, it can be used to create a model to predict or assess the health and aging statuses of people in the Thai population based on their laboratory test results and other related factors[16].

Conclusion

Based on the orientation values produced from a western population, the normal range for healthy adults in Nong Khai displayed disparity concerning the study of clinical chemistry parameters. Compared to those from the manufacturer and developed countries, the inclusive normal ranges for AST, ALT, ALP, creatinine, LDL and HDL for adult were more limited. Likewise, there were differences in the normal ranges in terms of age and sex. Additional research is needed to determine the normal ranges for the population in Thailand because there is no national database and a shifting standard for data management. In order to advance quality healthcare and reduce excessive costs of healthcare, the results highlight the need for assessing normal ranges in various populations.

Take home messages

Normal range of clinical chemistry parameters for healthy adults in Nong Khai showed disparity, compared to those from the manufacturer and developed countries. Establishment of normal range for individual population is necessary to distinguish between groups, especially between normal and abnormal subjects. Therefore, every population group requires specific reference values.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

The Center of Excellence on Medical Biotechnology (CEMB), S & T Postgraduate Education and Research Development Office (PERDO), Office of Higher Education Commission (OHEC), Thailand provided financial support for the completion of this study, for which we are grateful. We acknowledge Nong Khai Hospital for granting permission to use its laboratory results in this study, as well as for the time and patience provided.

References

1. Ashwood ER, Burtis CA, Tietz NW. Tietz fundamentals of clinical chemistry: Elsevier; 2001.
2. Solberg HE. The IFCC recommendation on estimation of reference intervals. The RefVal program. Clinical Chemistry and Laboratory Medicine (CCLM) 2004; 42(7): 710-4.
3. Horn PS, Pesce AJ. Effect of ethnicity on reference intervals. Clinical chemistry 2002; 48(10): 1802-4.
4. Nduka N, Aneke C, Maxwell-Owhochuku S. Comparison of some haematological indices of Africans and Caucasians resident in the same Nigerian environment. Haematologia 1988; 21(1): 57-63.
5. Rödöö P, Ridefelt P, Aldrimer M, Niklasson F, Gustafsson J, Hellberg D. Population-based pediatric reference intervals for HbA1c, bilirubin, albumin, CRP, myoglobin and serum enzymes. Scandinavian journal of clinical and laboratory investigation 2013; 73(5): 361-7.
6. Kratz A, Ferraro M, Sluss PM, Lewandrowski KB. Laboratory reference values. N Engl J Med 2004; 351: 1548-64.
7. Furruqh S, Anitha D, Venkatesh T. Estimation of reference values in liver function test in health plan individuals of an urban south Indian population. Indian J Clin Biochem 2004; 19(2): 72-9.

8. Yadav D, Mishra S, Gupta M, John PJ, Sharma P. Establishment of reference interval for liver specific biochemical parameters in apparently healthy north Indian population. Indian J Clin Biochem 2013; 28(1): 30-7.
9. Lugada ES, Mermin J, Kaharuza F, Ulvestad E, Were W, Langeland N, Asjo B, Malamba S, Downing R. Population-based hematologic and immunologic reference values for a healthy Ugandan population. Clin Diagn Lab Immunol 2004; 11(1): 29-34.
10. Lim E, Miyamura J, Chen JJ. Racial/ethnic-specific reference intervals for common laboratory tests: a comparison among Asians, Blacks, Hispanics, and White. Hawai'i J Med Public Health 2015; 74(9): 302.
11. US Food and Drug administration. "Replacement Reagent and Instrument Family Policy" for in vitro diagnostic (IVD) devices; 2003 [cited 2019Oct21]. Available from: https://www.fda.gov/media/111186/download.
12. Area of each district in Nong Khai Province [Internet]. [cited 2020 Dec 10]. Available from: http://www.e-report.energy.go.th/area/Nongkai.htm
13. The Royal Gazette published the number of citizens across the Kingdom 66.5 million people, [Internet]. [cited 2020 Dec 10]. Available from: https://moe360.blog/2020/02/01/ ราชกิจจานุเบกเผยแพร่-2/
14. Clinical and Laboratory Standards Institute. Defining, establishing, and verifying reference intervals in the clinical laboratory; approved guideline. CLSI Document C28-A3 (3rd Edition). 2008.
15. Reed AH, Henry RJ, Mason WB. Influence of statistical method used on the resulting estimate of normal range. Clinical chemistry 1971; 17(4): 275-84.
16. Kang YG, Suh E, Lee JW, Kim DW, Cho KH, Bae CY. Biological age as a health index for mortality and major age-related disease incidence in Koreans: National health Insurance service–health screening 11-year follow-up study. Clin Interv Aging 2018; 13: 429.
17. Royston P. Approximating the Shapiro-Wilk W-Test for non-normality. Statistics and computing 1992; 2(3): 117-9.
18. General Assembly of the World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. J Am Coll Dent 2014; 81(3): 14.
19. Eller LA, Eller MA, Ouma B, Kataaha P, Kyabaggu D, Tumusiime R, Wandege J, Sanya R, Sateren WB, Wabwire-Mangen F, Kibuuka H. Reference intervals in healthy adult Ugandan blood donors and their impact on conducting international vaccine trials. PLOS one 2008; 3(12): e3919.
20. Pereira P. ISO 15189: 2012 Medical laboratories-Requirements for quality and competence.
21. Joint Commission International. Joint Commission International; 1017 [cited 2019Oct10]. Available from: https://www.jointcommissioninternational.org/assets/3/7/JCI_Standards_for_Laboratories_STANDARDS-ONLY.pdf
22. Lima DC, dos Santos AM, Araujo RG, Scarminio IS, Bruns RE, Ferreira SL. Principal component analysis and hierarchical cluster analysis for homogeneity evaluation during the preparation of a wheat flour laboratory reference material for inorganic analysis. Microchemical Journal 2010; 95(2): 222-6.
23. Dobos L, Abonyi J. On-line detection of homogeneous operation ranges by dynamic principal component analysis based time-series segmentation. Chemical Engineering Science 2012; 75: 96-105.
24. Joint Specialty Committee on Renal Medicine (Great Britain), Renal Association (Great Britain). Chronic kidney disease in adults: UK guidelines for identification, management and referral. Royal College of Physicians.
25. Pottel H, Vrydags N, Mahieu B, Vandewynckele E, Croes K, Martens F. Establishing age/sex related serum creatinine reference intervals from hospital laboratory data based on different statistical methods. Clinica chimica acta 2008; 396(1-2): 49-55.

26. Yang S, Qiao R, Li Z, Wu Y, Yao B, Wang H, Cui L, Yang Y, Zhang J. Establishment of reference intervals of 24 chemistries in apparently healthy adult Han population of Northern China. Clin Biochem 2012; 45(15): 1213-8.