3D VOLUMETRIC MEASUREMENT OF NORMAL PEDIATRIC LIVERS: CREATING A REFERENCE DATABASE AND PREDICTIVE MODEL

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3D Volumetric Measurement of Normal Pediatric Livers: Creating a Reference Database and Predictive Model

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ABSTRACT

Background: Accurate and reproducible measurements of pediatric organs are necessary for defining normal organ volume, size, growth rates, and patterns of development, which aids in determining pathological variants. Currently, no modern reliable database exists for normal liver volume (LV) in children, and although predictive equations have been proposed, many are based on adult data, ethnically homogenous populations, or are derived from smaller samples and have not utilized advanced imaging technology in determining LV in vivo.

Objective: To establish normal LV measurements in children, using a three-dimensional (3D) volumetric approach, with additional consideration for height, weight, body surface area (BSA), and body mass index (BMI), and to develop a predictive model using these parameters.

Materials and methods: A retrospective review of normal contrast enhanced abdomen and pelvis CT images of 184 patients from 1 month to 18 years, identified within the Phoenix Children's Hospital picture archive communications system (PACS) was performed. Gender, age, height and weight were recorded for each patient; BSA and BMI were calculated. LV measurements were obtained using segmentation images software (IntelliSpace, Phillips Healthcare, Haifa, Israel).

Results: Univariate analysis of LV was most strongly correlated with and predicted by BSA ($R^2 = 0.90$, $p < 0.0001$), which could be defined by: LV = -115.5 + 941.7*BSA. In multivariate analysis, BSA ($p < 0.0001$), gender ($p = 0.01$), and height ($p = 0.001$) were the covariates that best predicted LV with an adjusted R^2 value of 0.90.

Stratifying the model by age did not modify the predictive capabilities of the covariates. Further stratifying by gender revealed inconsistent effect modification in some age groups.

Conclusion: Univariate analysis of LV was most strongly correlated with and predicted by BSA, which can be defined by: LV = -115.5 + 941.7*BSA.

Keywords: Children, Liver, Organ, Normal measurements, Volumes, Three-dimensional (3D), Radiography, Database

INTRODUCTION

Before knowing and understanding what is abnormal, one must first confidently know what is normal. The importance of this point in medical training and throughout medical practice is paramount. Louis Pasteur has been quoted and paraphrased on this matter for more than 150 years, "In the fields of observation chance favors only those minds which are prepared", uttered during an inaugural lecture delivered as professor and dean of the faculty of science at University of Lille, Douai, France, December 7, 1854 [1Respectfully quoted: A dictionary of quotations. Dover Publications, New York. p. 38 (2010).]].

From the neonatal stage of human life, through infancy, childhood, and adolescence, the human body changes dramatically as it grows. Each organ occupies a specific location in normal human anatomy, but its size in relation to the body, as a whole, changes in proportion. The complex shape of the liver also makes it challenging to understand what denotes normal organ size, how linear measurements of the organ should be made, and whether the typical growth rate and pattern of development are normal, delayed, or perhaps increasing at a pathological rate. Pediatric Radiologists must have confidence in their knowledge of normal organ development, size, and growth rates and be readily able to make accurate and reproducible measurements, or at least have a reliable source to reference.

Currently, no modern reliable database exists for normal liver volume (LV) in children. Though several authors have proposed calculations and equations as a method to predict normal LV in children [2], many of these formulas are based on adult data [2, 3, 4] which does not account for variation in growth rates or a child's unique anatomy, or are derived from smaller samples [2, 3, 4], and have not utilized the most advanced technology in determining LV from imaging in vivo [2, 5].

The purpose of this study is to establish accurate normal LV measurements using a three-dimensional (3D) volumetric approach, in neonates, infants, children, and adolescents, with additional consideration for height, weight, body surface area (BSA), and body mass index (BMI) and to determine a predictive model for LV in children using these parameters.

MATERIALS AND METHODS

Patient selection

In a retrospective manner, 485 children from 1 month to 18 years, who underwent contrast enhanced abdomen and pelvis CT with reported normal findings at our institution between January 2016 and February 2017, were randomly identified using a search function in our picture archive communications system (PACS) (iPACS, Philips Healthcare, Cleveland, OH, USA), following Institutional Review Board (IRB) approval. Of these, 60 patients were excluded due to suboptimal image quality, typically due to motion artifact. Gender, age, weight, and height were recorded for each patient, BMI was calculated, and BSA was determined using the Monsteller formula [6] for children who weighed greater than 10 kg, and the Haycock formula [7] for children less than 10 kg. An additional 241 patients were excluded if height and weight measurements contemporaneous within 30 days of the CT exam were not available in the electronic medical record. CT images were anonymized using random patient identifiers and blinded from the investigators to protect private health information (PHI); anonymized images were stored securely in a password protected computer workstation. The remaining 184 patients were grouped as follows: < 5 years (n=48), 5-9 years (n=51), 10-15 years (n=48), and > 15 years (n=37). Abdomen and pelvis CT scans were performed for a variety of indications, most commonly related to trauma, nonspecific abdominal pain, or to rule out appendicitis.

Data collection protocol

Using a software program designed specifically to segment the liver, (IntelliSpace Portal, Liver Health, Philips Healthcare, Haifa, Israel) volumetric measurement of the liver was performed. The software program is designed to automatically detect the contours of liver; the operator is then able to edit the automatically generated contour using a cursor in a manner similar to a paint brush in order to refine definition of the liver contour. The liver parenchyma is colorized during this process of segmentation so that its clear demarcation is distinct from adjacent organs and anatomic structures which are excluded. Subsequently, the volume of the segmented liver tissue is automatically calculated and displayed (Fig. 1). Liver segmentation was performed by a fourth year medical student under the guidance and supervision of two technologists with over 5 years of experience in 3D post-processing of cross-sectional imaging or an attending Pediatric Radiologist to ensure accuracy.

Statistical Analysis

Demographic and clinical characteristics were reported as means, standard deviations for continuous variables and frequencies, and percentages for categorical variables (Table 1). Mean and range for each variable were recorded (Table 2). Univariate linear regression was used to independently associate each covariate with total LV (Fig. 2, 3, & 4). Furthermore, each variable was entered into a second linear regression model where a backwards stepwise variable selection determined the best covariates that predicted total LV (Table 3). The final model was stratified by age to ascertain whether age modified the predictive capabilities of the covariates (Table 4). The stratified models were further stratified by gender to assess gender's roles in effect modification. All p-values were 2-sided and $p < 0.05$ was considered statistically significant. All data analyses were conducted using STATA version 15 (College Station, Texas).

RESULTS

The cohort of 184 patients was evenly distributed between genders, including 92 females (50%) aged from 1 month to 18 years, with an average age of 9.38 years *(SD*=5.35) at the time of the exam. Average weight of 39.4 kg (*SD*=26.2), an average height of 131.5 cm (*SD*=32.6), an average BMI of 20 m^2/kg (*SD*=6.27), and an average BSA of 1.17 m^2 (*SD*=0.52) were recorded (Table 1).

In univariate analysis, LV was significantly related to age ($R^2 = 0.72$, $p < 0.001$), BMI ($R^2 = 0.59$, $p < 0.0001$), weight ($R^2 = 0.87$, $p < 0.0001$), and height ($R^2 = 0.75$, $p < 0.0001$) (Fig. 2 & 3). Univariate analysis also showed that LV was most strongly correlated with and predicted by BSA ($R^2 = 0.90$, $p < 0.0001$), which could be defined by: LV = -115.5 + 941.7*BSA (Fig. 4).

In multivariate analysis, BSA ($p < 0.0001$), gender ($p = 0.01$), and height ($p = 0.001$) were the covariates that best predicted LV with an adjusted R^2 value of 0.90 (Table 3). Stratifying the model by age did not modify the predictive capabilities of the covariates (Table 3). Further stratifying by gender revealed an inconsistent effect modification in some age groups (Table 4).

Variables	Values n=184
Age At Exam, years (mean, SD)	9.38 (5.35)
Gender (Female, %)	92 (50.0)
Weight, kg (mean, SD)	39.4 (26.2)
Height, cm (mean, SD)	131.5 (32.6)
BMI, $kg.m^2$ (mean, SD)	20.0 (6.27)
BSA, m^2 (mean, SD)	1.17 (0.52)

Table 1 Descriptive characteristics of pediatric study subjects

Age categories (years)	Age (years) Mean (range)	Weight (kg) Mean (range)	Height (cm) Mean (range)	BMI (kg/m^2) Mean (range)	BSA (m^2) Mean (range)	Liver Volume (cc) Mean (range)
< 5 (n=48)	2.06 (0 – 4)	13.2 (4.01 – 22.6)	88.7 (51.5 – 117)	16.2 (11.4 – 24.1)	0.57 (0.24 – 0.85)	443.2 (133.9 – 688)
5 – 9 (n=51)	7.05 (5 – 9)	28.4 (10.2 – 59.8)	125.2 (84.5 – 146.4)	17.7 (11.5 – 30.4)	0.98 (0.49 – 1.56)	811.5 (371 – 1717.4)
10 – 15 (n=48)	12.0 (10 – 14)	53.6 (27 – 131.4)	154.6 (92 – 191)	22.1 (13.4 – 42.4)	1.50 (0.91 – 2.53)	1280.0 (702.3 – 2245)
>15 (n=37)	16.3 (15 – 18)	70.2 (41.5 – 128.6)	165.6 (150.1 – 188)	25.5 (17.2 – 44.9)	1.78 (1.32 – 2.45)	1553.6 (1026 – 2707.9)

Table 2 Summary of pediatric LV data stratified by age; mean weight, height, BMI, BSA, and LV in each age group

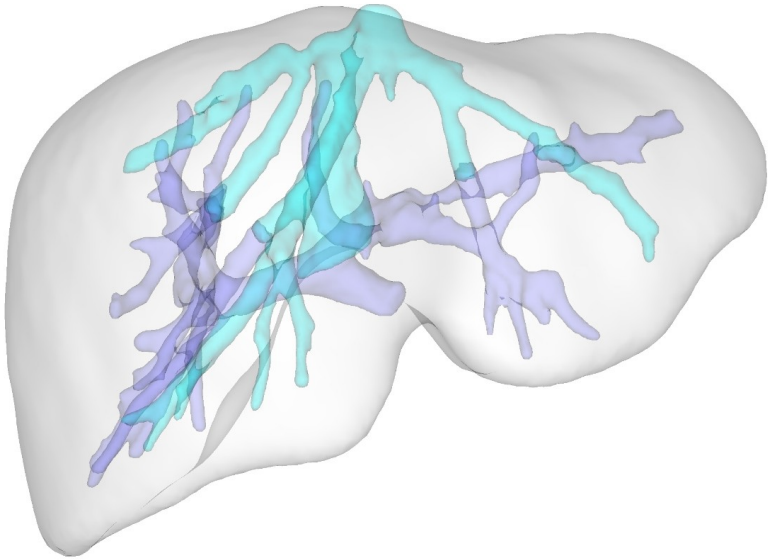

Fig. 1 From contrast enhanced CT data, automatic definition of liver parenchyma was performed with subsequent user assisted confirmation of accurate organ segmentation. Hepatic veins (aqua) and portal veins (blue) are also defined

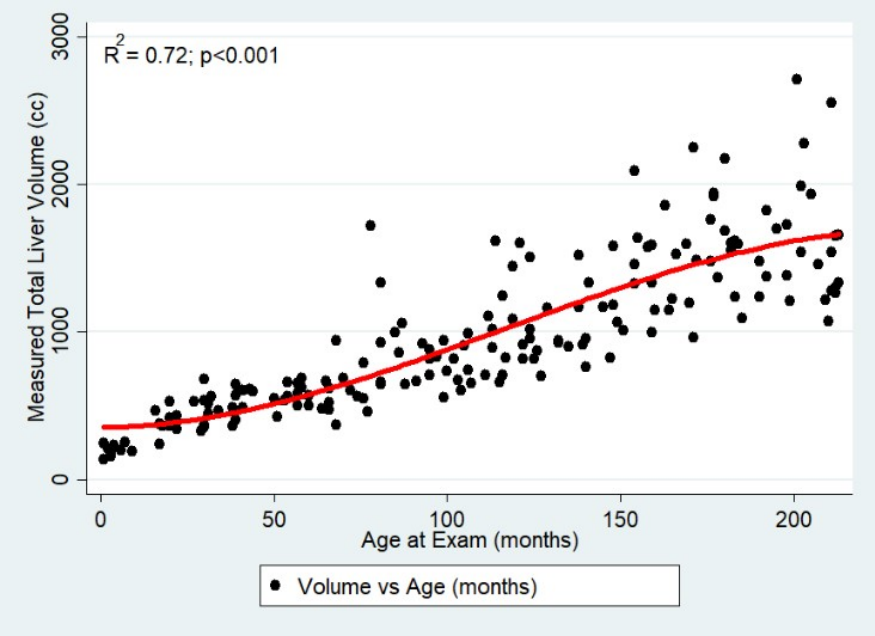
R^2 = 0.72; p<0.001
Measured Total Liver Volume (cc)
0
1000
2000
3000
0
50
100
150
200
Age at Exam (months)
Volume vs Age (months)

Fig. 2 This scatter plot shows the distribution of measured total LV (y axis) and age in months (x axis) in all patients age 1 month to 220 months. The trend line represents univariate linear regression of LV vs. age. The R^2 value is 0.72 with a p-value < 0.001

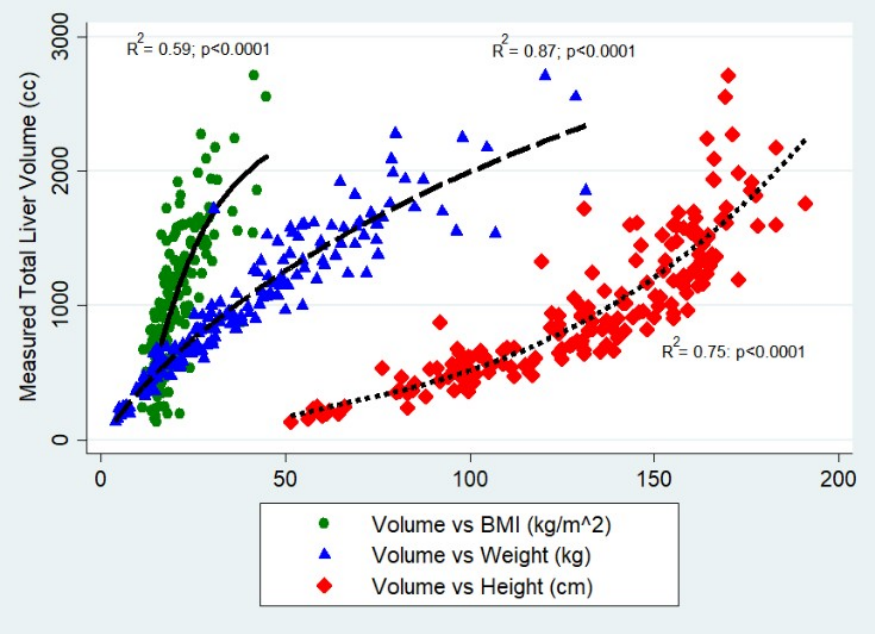
Measured Total Liver Volume (cc)
0
1000
2000
3000
0
50
100
150
200
R2= 0.59; p<0.0001
R2= 0.87; p<0.0001
R2= 0.75: p<0.0001
Volume vs BMI (kg/m^2)
Volume vs Weight (kg)
Volume vs Height (cm)

Fig. 3 This scatter plot shows the distribution of measured total LV (y axis) and BMI in kg/m^2 (x axis) represented in green; measured total LV (y axis) and weight in kg (x axis) represented in blue; and measured total LV (y axis) and height in cm (x axis) represented in red. The trend lines represent univariate linear regression of LV vs. BMI ($R^2 = 0.59$, $p < 0.0001$), LV vs. weight ($R^2 = 0.87$, $p < 0.0001$), and LV vs. height ($R^2 = 0.75$, $p < 0.0001$), respectively from left to right

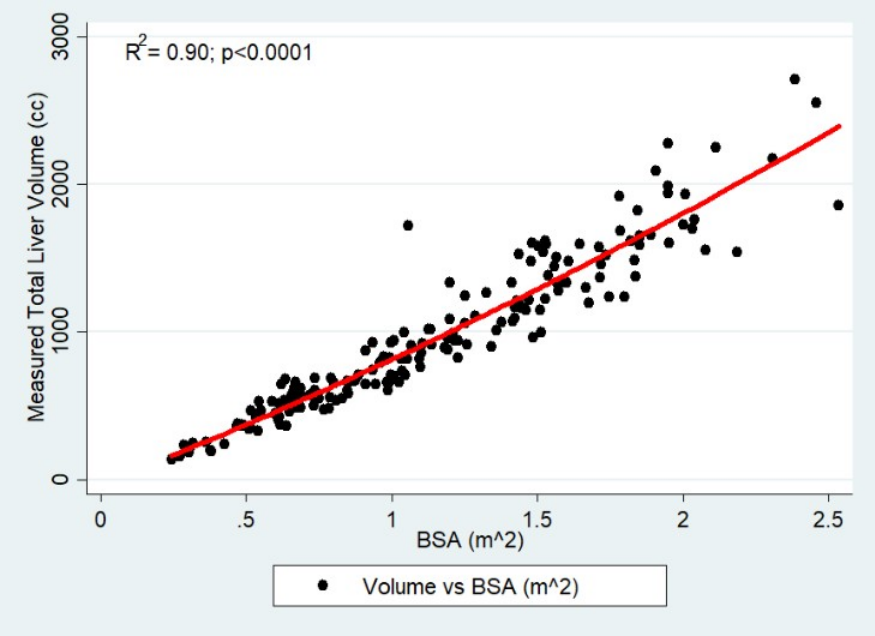
R^2= 0.90; p<0.0001
Measured Total Liver Volume (cc)
0
1000
2000
3000
0
.5
1
1.5
2
2.5
BSA (m^2)
Volume vs BSA (m^2)

Fig. 4 This scatter plot shows the distribution of measured total LV (y axis) and BSA in m^2 (x axis). The trend line represents univariate linear regression of LV vs. BSA and can be defined by the equation: LV = -115.5 + 941.7*BSA. The R^2 value is 0.90 with a p-value < 0.0001

Variables	Beta (95%CI)	p-value	Adjusted R^2
Overall			
BSA	1159.9 (1026.5, 1293.4)	<0.0001	0.90
Gender (female)	-61.3 (-110.2, -12.3)	0.01	
Height	-3.69 (-5.82, -1.55)	0.001	
< 5 years of Age (n=48)			
BSA	906.1 (358.8, 1453.3)	0.002	0.80
Gender (female)	-48.5 (-92.1, -4.89)	0.03	
Height	-0.44 (-5.39, 4.50)	0.86	
5 – 9 years (n=51)			
BSA	1448.3 (1071.8, 1824.7)	<0.0001	0.71
Gender (female)	-79.0 (-168.8, 10.8)	0.08	
Height	-6.82 (-13.1, -0.55)	0.03	
10 – 15 years (n=48)			
BSA	1105.9 (815.6, 1396.4)	<0.0001	0.75
Gender (female)	21.7 (-95.4, 138.7)	0.71	
Height	-2.99 (-8.97, 2.98)	0.32	
>15 years (n=37)			
BSA	1218.1 (896.6, 1539.6)	<0.0001	0.67
Gender (female)	-181.4 (-352.4, -10.4)	0.04	
Height	-6.83 (-17.9, 4.24)	0.22	

Table 3 Multivariate linear regression following a backwards, stepwise variable selection adjusting for all other variables within the model with subsequent stratification by age

Variables	Males only		Females only	
	Beta (95%CI)	p-value	Beta (95%CI)	p-value
Overall	(n=92)		(n=92)	
BSA	1199.4 (988.7, 1410.1)	<0.0001	1127.1 (954.5, 1299.6)	<0.0001
Height	-4.18 (-7.47, -0.89)	0.013	-3.26 (-6.06, -0.45)	0.024
< 5 years of Age	(n=25)		(n=23)	
BSA	1094.1 (237.5, 1950.6)	0.02	731.8 (-15.3, 1478.9)	0.054
Height	-2.80 (-10.8, 5.21)	0.47	1.42 (-5.19, 8.05)	0.65
5 – 9 years	(n=24)		(n=27)	
BSA	1348.6 (557.7, 2139.4)	0.002	1517.2 (1183.2, 1851.3)	<0.0001
Height	-3.17 (-16.3, 9.93)	0.62	-9.35 (-14.9, -3.76)	0.002
10 – 15 years	(n=28)		(n=20)	
BSA	902.1 (556.4, 1247.8)	<0.0001	1585.3 (1029.3, 2141.3)	<0.0001
Height	-0.17 (-6.79, 6.45)	0.95	-10.6 (-27.4, 6.05)	0.19
>15 years	(n=15)		(n=22)	
BSA	1637.3 (1108.3, 2166.3)	<0.0001	914.5 (497.2, 1331.8)	<0.0001
Height	-14.7 (-27.9, -1.54)	0.03	8.60 (-16.0, 33.2)	0.47

Table 4 Multivariate linear regression following a backwards, stepwise variable selection adjusting for all other variables within the model with stratification by age and additional gender stratification

DISCUSSION

This study begins to address a gap in medical knowledge regarding normal liver size by providing reliable, potentially reproducible in vivo 3D measurement of the liver in the pediatric population and reveals a potential path to develop similar simple methods to calculate organ volume.

Although knowledge of organ size and volume is paramount in clinical practice and diagnostic reasoning, no reliable reference for LV, or any other organ, exists in the pediatric population, and current reference guidelines for organ size in children are antiquated. Oregon Health & Sciences University has compiled data for pediatric normal organ measurements [8] based on currently available sources; however, liver measurement data is not included, and the gallbladder and biliary tract data are taken from sonographic linear measurements that bear a publication date from 1982 [9]. Urata was the first to use BSA to predict LV using any pediatric population in 1995, but was limited by a small ethnically homogeneous population of 96 Japanese patients ranging in age from 1 year to 27 years old [3], and was later shown to have significantly underestimated LV through erroneous calculation of BSA and LV [10]. Noda in 1997 also utilized a relatively small sample size of 54 children aged 10 days to 22 years to predict LV based on age [4]. The most comprehensive summary of predictive LV models is by Johnson in 2005, which provided a meta-analysis of data published between 1933-1999 with 5036 patients from birth to 18 years old utilizing a wide variety of methodologies including various imaging modalities to evaluate autopsy and in vivo liver size measurements to determine LV and subsequently evaluate predictive models based on a number of covariates [2].

Organ measurements on medical imaging studies are typically performed in one or more anatomic planes using a linear measurement tool. Subsequently, using linear measurements to calculate an organ volume is heavily dependent on slice selection by the Radiologist and patient positioning during the scan and is therefore inherently biased and inter-reader and intra-reader variability of linear measurements is considerable. Additionally, calculation of liver volume from simple linear measurements is further complicated by its irregular and complex shape, creating a wholly unreliable method of measurement. These factors contribute to making linear measurements less accurate and reproducible compared to 3D volumetric methods [11].

It is known that 3D volume measurement of an organ or tissue is a more accurate and reproducible method of in vivo measurement compared to utilizing linear measurements [11]. Volumetric measurements may be performed using readily available image post-processing software. Image post-processing software of CT scans have been touted as the gold-standard technology for measuring total LV [12]. Future work is necessary to verify both inter-reader and intra-reader reproducibility of the organ segmentation process. Other limitations of this technology include cost of the software, training time for technologists, and overall accessibility particularly in resource limited settings. Our equation is simple and can act as a substitute for this individual 3D software when applicable.

In a previous study by Pomposelli [12], it was noted that inclusion of the vasculature overestimates LV by approximately 9% in adult patients. We chose to include the vasculature in our 3D volumetric measurements of LV, as including the blood flow provides a more accurate representation of living patients and provides more clinically relevant data for application in a clinical setting. Additionally, it has been noted that overestimating LV in children has less clinical consequences than underestimating [5], especially in the context of surgical planning for liver transplantation.

In addition to the applications related to determining graft size for liver transplantation [5,12], other clinically relevant applications for determining normal LV in the pediatric population include recognition of hepatic enlargement or disease states with small liver, determining drug dosing [10], and estimating hepatic drug metabolism [2].

Additional studies are necessary for continued increase in sample size and further refinement of the predictive equation for determining LV. The method by which we derived a predictive equation for LV can lay the foundation for application to other organs. Other considerations for future study also include further stratification by ethnic background to determine the effect modification potential of this variable within an ethnically heterogeneous population.

- **CONCLUSION**

BSA was found to be the most predictive of LV in children in univariate analysis, which was not significantly altered in multivariate analysis or with stratification by age. Gender stratification offered inconsistent effect modification of the ability to predict LV. This equation may be used in clinical applications to predict normal LV in children: LV = -115.5 + 941.7*BSA

COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of Interest

None

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