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A Systematic Review on Sonographic Assessment of Liver Size in Apparently Healthy Paediatrics

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Abstract
The size of the liver has been reported to be affected by intrinsic liver disease and other systematic pathologies. Ultrasound is usually the method of choice for screening, diagnosis, prognosis purposes and in the follow up after treatment because of its accuracy and easy accessibility. The study is aimed at reviewing published articles on sonographic assessment of liver size in apparently healthy pediatrics. The age of the selected subjects of the reviewed articles ranged 1 day to 18 years, the largest sample size was 1315subjectswhile the smallest sample size was 273subjects. All the 12 reviewed articles were prospective studies. With the exception of one article, all other articles used only one method of measurement of the liver dimension. None of the reviewed articles measured the right and the left lobes of the liver separately. The mean and standard deviation of the liver dimension ranged 5.10±1.10 - 11.6±1.06 cm. There was statistical difference ($p>0.05$) in the size of the liver between boys and girls in 5 of the articles and the remaining 7 articles, there was no statistical difference. All the reviewed articles showed strong positive correlation between the demographic variables and liver dimensions. Only two out of the twelve reviewed articles stated the type of sampling method employed in their studies and only three used a larger sample size. Only one took antero-posterior and longitudinal liver dimension and none of the studies measured the right and left lobes of the liver separately.

Keywords: Liver Size, Pediatrics, Systematic review, Ultrasound

INTRODUCTION

Paediatrics is the branch of medicine dealing with the health and medical care of infants, children and adolescents from birth up to the age of 18 (David *et al*., 2007). Age groups with their corresponding ages include neonate: 0 days to 30 days, infant: 1 month to 2years, young child: 2 to 6years, child: 6 to 12years, adolescent: 12 to 18years (David *et al*., 2007).Chronic liver diseases in children represent a rising problem with significant effects on public health. In fact, several pediatric liver diseases are precursors of adult chronic hepatopathies, cirrhosis

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and hepatocellular carcinoma. The prevalence of liver diseases in children is unknown (Della *et al*., 2016). In the USA, every year, 15,000 children are hospitalized for liver diseases, but these disorders continue to be under-recognized or diagnosed late. The main reason is due to the frequent absence of symptoms in the vast majority of liver diseases, especially in the early stages (Della *et al*., 2016). Pathological conditions affecting the liver include viral hepatitis which is the most common causes of cirrhosis in children. It tends to lead to cirrhosis later in life (Pinto *et al*., 2015). Acute liver failure is a bad condition that occurs in previously healthy children of all ages, usually a viral-like illness that worsens into jaundice, coagulopathy and mostly death (Squires *et al.,* 2014). Ascites is a common complication in pediatric cirrhosis, especially in younger children with terminal liver disease (Leonis&Balistreri,2008). Autoimmune hepatitis is a chronic inflammatory liver disease, with variable onset and duration. Establishing normal liver dimension is imperative in diagnosis of the pathological conditions affecting the liver in pediatric age group.

The liver size measurement during physical examination is to determine the size of the liver and identify possible hepatomegaly. Percussion of liver is the distance between the lower border of the liver in the mid-clavicular line obtained by palpation, and the upper border of the liver in the mid – clavicular line, however, upper border of the liver lies posterior to the ribs and cannot be palpated. More accurate ways of estimating liver size is the computed tomography, magnetic resonance imaging and ultrasound (Childs *et al*., 2016). Ultrasound scan is the first choice when diagnosing hepathopaties in pediatric patients because it is readily available, non-invasive, affordable and not associated with ionizing radiation. The study is aimed at reviewing published research articles on sonographic assessment of liver size in apparently healthy pediatrics, identifying the missing gaps and coming up with areas of further studies.

A prospective study was conducted by Rousan *et al*. (2018) on sonographic assessment of liver and spleen size based on age, height and weight: evaluation of Jordanian children in Jordan. A total of 315 pediatric patients (142 males and 173 females) aged from newborns to 14 years were examined using a real time ultrasound machine (ALT, HDI 5000, USA) with 5-8 MHz or 4-7 MHz sector transducer equipped with electronic calipers. The mean liver size of neonates and infants; 0-3 months was 5.9 cm, infants 3-6 months was 7.0 cm, infants 6-12 months was 8.2 cm, toddler 1-2 years was 9.0 cm, 2-4 years was 8.9 cm, preschool 4-6 years 9.6 cm, school age 6-8years 10.6 cm, 8-10 years 11.5 cm, 10-12 years 12.2 cm, adolescent 12-14 years 13.1 cm.There was a statistical significant difference between males and females($P>0.05$). There was a steady increase in the size of the liver with age, except in the 2-4 year age group where there was a slight but non-significant decrease in the size of the liver. In the neonatal period there was a steady but mild increase in the size of the liver according to weight. After the neonatal period there was a steep increase in the size which then increases gradually with increasing weight. Age ($r = 0.80$ ($p<0.005$)), height ($r = 0.81$ ($p<0.005$)), and weight ($r = 0.77$ ($p<0.005$)) were strongly and directly correlated with liver size. Another prospective study was conducted by Wanakunasuriya *et al.* (2017) on ultrasonographic parameters of the liver, spleen and kidneys among a cohort of school children in Sri Lanka. A total of 332 (176 girls (53%) and 156 boys (47%) within the ages 5–13years were recruited into the study. Sonographic examination was done using a high resolution real-time scanner with a 3.5 MHz convex transducer. The longitudinal length of the liver was significantly higher among the females compared to the males (Mann Whitney $U = 11,830.5$, $p = 0.037$). Body weight significantly correlated with the longitudinal dimensions of the liver ($r = 0.742$, $p < 0.001$). Height was weakly but significantly correlated with liver dimensions ($r^2 = 0.247$, $p < 0.001$). On multiple regression analysis, weight and age were significant predictors of the longitudinal length of the liver after controlling for height.

A prospective cross-section study was also conducted by Thepa *et al.* (2017) on sonographic assessment of the normal dimensions of liver, spleen, and kidney in healthy children at tertiary care hospital in Nepal within October and December 2005. A total of 273 pediatric subjects (152male and 120female) within the ages 1 month to 15years. In 2015, US examination was performed with a high resolution real-time scanner. The mean age was 45.78 months (SD, 44.73), and median was 26 months. There was no statistically significant difference between the two sexes in any age group for the organ dimensions (t test, p> 0.05). Therefore, all data were rearranged without being separated according to sex. The longitudinal dimensions of each organ showed highest correlation with the body parameters (i.e. age, height, and weight). Among these variables also the correlation coefficients (Pearson r) was highly correlated with height and age for all the measured organs. The correlation coefficient for height for liver was 0.81. Another study was conducted by Weerakuljswe *et al.* (2017) on physical and ultrasonographic estimation of the liver size in healthy Thai children under two years old in Well Baby Clinic, Naresuan University Hospital in Thailand between October 2008 and April 2009. A total of 281 healthy children aged 0 to 2years (148 boys and 133 girls). This was performed in the supine lying position using a linear probe. The body weight (mean±SD), length (mean±SD), and body surface area (mean±SD) were 8.81±2.72 kg, 71.1±9.0 cm, and 0.28±0.06.

Furthermore, prospective study was conducted by El-Afifi *et al.* (2015) on Correlation between clinical examination and ultrasound of liver and spleen span in normal children between 12 and 18 years in Menoufia University Egypt (included 300 healthy Egyptian school children whose ages range from 12-18years (156 boys 52.0% and 144 girls 48.0%). The $\chi 2$-test was used to compare qualitative variables between groups. The unpaired t-test was used to compare quantitative variables in parametric data. The Mann–Whitney test was used instead of the unpaired t-test for nonparametric data. The analysis of variance test was used for comparison of quantitative data among different time points in the same group. P values less than 0.05 were considered significant and P values less than 0.01 were considered highly significant. A cross-sectional prospective study was also conducted by Ezeofor *et al.* (2014) on sonographic evaluation of normal liver sizes of school children in south east Nigeria in Enugu carried out between 2009 and 2010. A total of 1315 children were used where 633(48.1%) were boys and 682(51.9%) were girls. US examinations were performed with a high resolution real time scanner. The longitudinal and diagonal axes of the liver were assessed. Age and all the body size indices correlated positively and significantly with the liver dimensions (p<0.01, p<0.05). BSA correlated best with the liver dimensions. Eze *et al.*(2013) conducted a cross-sectional study was on sonographic biometry of liver size among Igbo school age children of South east, Nigeria at university of Nigeria Medical Centre, Nsukka in Enugu used between January 2011 and June 2011. Convenience sampling method was used on a total of 940 Igbo school age children within the ages of 6 to 17years with 496 (52.48%) being male and 451 (49.6%) being female. US examinations were performed with a high resolution real time scanner. Association between liver dimension and sex, age, height, weight, BSA, and BMI was assessed with Pearson's correlation coefficient; to determine the exact pattern of the relationship, non-linear regression analysis was performed. The mean of the liver length was 116.3±10.6 mm. Dimension of the liver was not statistically different in boys and girls (p > 0.05). Height correlated best with the liver dimension followed by age, body surface area, weight, body mass index, and sex.

A cross-sectional study was conducted by Rocha *et al*. (2009) on sonographic determination of liver size in healthy newborns, infants and children less than 7 years of age in Sao Paolo between April 2003 and April 2005 using B – mode ultrasonography. The sample included 584 subjects where 301 where girls (51.54%) and 238 were boys (48.46%) aged between 7 days and 6 years. Ultrasound machine was used with the children lying in a supine position. (Mean

=42.2 months). The transducer was positioned below the costal cage, with longitudinal orientation, in orthogonal position relative to spine plane. The following measurements were performed: a) cranio-caudal diameter in the mid-sternal line (CCMSL), through a horizontal line parallel to the abdominal wall, extending from the diaphragmatic surface to the lower hepatic border; b) cranio-caudal diameter of the posterior surface of the liver on the hemi-clavicular line (CCPHCL), through an oblique line traced between the upper extremity and the lower hepatic border. The measurements were correlated with age, height and weight of the children evaluated, with the Pearson's correlation coefficient. The non-paired Student's t test was utilized for comparing measurements between the female and male groups. The significance level utilized was 0.05.A cross- sectional study was conducted by Dhingra *et al.* (2009) on normal values of liver and spleen size by ultrasonography in Indian children subjects in a tertiary-care pediatric teaching hospital between January – December 2005 in India. A total of 597 healthy children between the ages of 1 month to 12 years were used as subjects. US assessment of the liver was done by a Philips envisor color Doppler system with a multi frequency 3.5-5mHz probe with the subject lying supine. The liver length was measured with the child in supine position and the section level along the MCL. The upper and lower points of the measurement of the liver span were marked and then measured from the sonographic image. The measurements were made during quiet breathing in younger children and during breath-holding in older children. The age-group 1 month to 12 years (mean (SD) age 56.5 (41.9). The median age was 48 month (range, 1-156 month). The liver size increased significantly with the age ($P<0.05$). Liver length correlated significantly with the height ($r=0.84$) and weight ($r=0.79$). The regression analysis with height/length as the independent continuous variable yielded a high multiple correlation liver length and height/length ($R^2=0.70$).A prospective cross sectional survey was conducted by SriPriya. (2008) on clinical and sonographic assessment of liver span in children in Institute of Child Health and Hospital for Children, Egmore, Chennai from October, 2006 to October, 2007. Six hundred children were enrolled from newborn to 12years; sampling was done using stratified and random sampling methods. The examination was performed using high resolution real time scanner LOGIQ 500MD with 3.5 MHz convex transducer. The mean liver size for newborn was 5.7 cm, for infants was 6.5, for one year age group was 7.1 cm, 2 years 8.0 cm, 3 years 8.3 cm, 4 years 8.7 cm, 5 years 8.8 cm, 6 years 9.1 cm, 7 years 9.4 cm, 8 years 9.8 cm, 9 years 10.1 cm and for 10-12 years 10.3 cm. The correlation existed in all the age group and was found to be significant. The liver span had significant correlation with height (r=0.89) and weight (r=0.86). It also had significant correlation with age (r=0.90). There was no significant correlation between sex and mean liver span. Multiple linear regressions revealed that age, height and weight had significant influence on liver span with age being the most important factor.

A prospective study was conducted by safak *et al.*(2005) on sonographic assessment of the normal limits and percentile curves of liver, spleen, and kidney dimensions in healthy school-aged children in Turkey.712 children i.e. 357 boys(50.1%) and 355 girls(49.9%) in age group 1 to 15years.There were no significant differences in liver dimensions with respect to sex. Liver measurements were performed in a supine position. The longitudinal axis was measured after clear visualization of the liver in the midclavicular plane. The uppermost edge under the dome of the diaphragm was defined as the upper margin, whereas the lowermost edge was defined as the lower margin. There were no significant differences in organ dimensions with respect to sex (P >0.05). The mean right kidney length was shorter than the left kidney length, and the difference was significant (P =0.009). Body weight showed the best correlation with liver dimensions. The results were also supported by the variance and covariance of the correlation coefficients. There were no significant differences in organ dimensions with respect to sex (P > .05). The results were also supported by the variance and covariance of the correlation coefficients. Another prospective study was conducted by Konus *et al.* (1998) on normal liver, spleen, and kidney dimensions in neonates, infants, and children: evaluation with sonography involving 307 subjects (169 girls and 138 boys) with ages ranging from 5 days to 16 years. With the subjects lying supine, a high resolution real -time sonograph scanners were used in December 1998. 307).In a subject lying in the supine position, longitudinal and antero-posterior dimensions were obtained in the mid-clavicular and mid-sagittal planes for the right and left lobe. In both planes, the upper margin of the liver was defined as the uppermost edge under the dome of the diaphragm, whereas the lower margin was defined as the lowermost edge of the lobe. No statistically significant differences were found between the two sexes in any age group for any measured organ dimension (t test, p>.05). Therefore, all data were rearranged without being separated according to sex.

Table showing summary of findings

Author(s) & year of publ-Ication	Study location	Study design	Sampling method	Sample size	Age group (years)	Method of measurement	Mean (SD) of liver dimension	Sex difference	Correlation with dem-ographic variables
RousanJodan *et al.* 2018		Prospective	-	315	0-1y	Longitudinal	9.1±1.26	p>0.05	r= 0.087
Warnakulasuriya *et al.* 2017	Sri lanka	Prospective	-	332	5-13y	Longitudinal	8.7±1.05	p>0.05	r= 0.742
Thapa*et al.* 2017	Nepal	Prospective	-	273	1m-15y	Longitudinal	9.1±0.86	p>0.05	r= 0.82
Weerakuljswe *et al.* 2017	Thailand	Prospective	-	281	0-2y	Craniocaudal	5.1±1.10	P<0.05	r= 0.75
El-Afifi*et al.* 2015	Egypt	Prospective	-	300	12-18y	Longitudinal	11.3±0.88	P<0.05	r= 0.83
Ezeofor *et al.* 2014	Enugu	Prospective	-	1315	1-7y	Longitudinal	11.1±1.3	P<0.01	r= 0.86
Eze*et al.* 2013	Enugu	Prospective	Convenience	940	6-12y	Craniocaudal	11.6±1.06	p>0.05	r= 0.84
Dhingra*et al.* 2009	India	Prospective	-	759	1m-12y	Longitudinal	9.6±1.98	P=0.0001	r= 0.79
Rocha *et al.* 2009	Sao paolo	Prospective	-	584	7d-6y	Craniocaudal	5.6±0.70	p>0.05	r= 0.70
Sri Priya. 2008	Vellore	Prospective	Random	600	1d-12y	Longitudinal	5.7±0.38	p=0.05	r= 0.88
Safak*et al.* 2005	Turkey	Prospective	-	712	1-15y	Longitudinal	8.3±1.22	p>0.05	r= 0.76
Konus*et al.* 1998	Turkey	Prospective	-	307	5d-1y	Longitudinal & antero-posterior	9.6±1.16	p>0.05	r= 0.82

Key: y=year(s), m=month(s), d=day(s)

Discussion

Abdominal organs can be demonstrated using ultrasography more especially liver, right after delivery through all the pediatrics age group. The advantage ultrasound has over other imaging modalities includes; not being associated with ionizing radiation, availability, affordability non-invasiveness and does not requires additional power supply for its operation. All the reviewed articles conducted prospective study; therefore, their strength is the same in terms of the study design. Among all the reviewed articles only two; Rousan *et al.* (2018) &Eze *et al.*(2013) reported the sampling method employed in their studies, the former used random sampling method which is a probability sampling method, therefore, served as a strength over the later that used convenience sampling method which is a non-probability sampling method. However, 9 articles cannot be criticized based on sampling method because it has not been stated. The study conducted by Ezeofor *et al.*(2014) has strength over all the reviewed articles in terms of sample size because it has the largest sample size. However, the study conducted by Thapa *et al.*(2017) in terms of sample size because it used the smallest sample size. The larger the sample size, the more accurate the results, but the smaller the sample size the lees accurate the results more especially when establishing a normative value. The study conducted by SriPriya *et al.*(2008) has strength over all the reviewed articles in this study in terms of aged ranged of the studied subjects with aged ranged from delivery to 12 years while the study conducted by Rousan *et al.*(2018) is the weakest because it studied subjects with aged ranged 0-1 year. When establishing a normative value it is important to wider age groups so that comparison could be made between the different ages which the findings could be very important in making diagnosis. The study conducted by Konus *et al.*(1998) has strength over reviewed articles in this study in terms of the method of measurement of the liver size because it is the study measured liver size using anterior-posterior and longitudinal dimensions. All other articles measured either anterior-posterior, cranio-caudal or longitudinal liver dimensions. The studies conducted by El-Afifi *et al.*(2015); Ezeofor *et al.*(2014), & Eze *et al.*(2013) reported a higher liver dimensions than the other reviewed articles. The studies conducted by Sri Priya. (2017); Weerakuljswe *et al.*(2017) &Rocha *et al.*(2005) reported a lower liver dimensions. The studies conducted by SriPriya. (2008); Weerakuljswe *et al.*(2011) &Dhingra *et al.*(2009)showed statistical significance difference in liver dimension between males and females selected sublects. However, studies conducted by Rousan*et al.*(2019);Warnakulasuriya *et al.(*2017);El-Afifi *et al.*(2016); Thapa *et al.(*2015); Ezeofor *et al.*(2014), Eze *et al.*(2013), Rocha *et al.*(2005); Safak *et al.*(2005) & Konus *et al.*(1998) showed no statistical significance difference in liver dimensions between males and females selected subjects. All the reviewed articles showed strong positive correlation between the demographic variables and liver dimensions. The study conducted by SriPriya. (2008) has strength over all the reviewed articles considering the sampling method employed, sample size used and the age ranged of the selected subjects.

Conclusion

Only two out of the twelve reviewed articles stated the type of sampling method employed in their studies and only three used a larger sample size. Only one took antero-posterior and longitudinal liver dimension and none of the studies measure the right and left lobes of the liver separately. Further studies should consider using the most appropriate sampling method, used a larger sample size and measure the right and left lobes of the liver separately.

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