



## Diagnosis of splenomegaly with one-dimensional diameters in CT scan images in North-East of Iran and constructing a best-fit model for estimation of splenic volume

Masoud Pezeshki Rad<sup>1</sup>, Maryam Salehi<sup>2</sup>, Mohaddeseh Mohammadi<sup>3</sup>✉, Fatemeh Soati<sup>4</sup>

<sup>1</sup>Department of Radiology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran; Email: pezeshkiradm@mums.ac.ir

<sup>2</sup>Department of Community Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran; Email: salehim@mums.ac.ir

<sup>3</sup>Department of Radiology, Faculty of Medicine, Golestan University of Medical Sciences, Golestan, Iran; Email: mohaddese\_mohammadi@yahoo.com

<sup>4</sup>Department of Radiology, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran; Email: arezoosoati@yahoo.com

### ✉ Corresponding author

Department of Radiology, Faculty of Medicine, Golestan University of Medical Sciences, Golestan, Iran,  
Email: mohaddese\_mohammadi@yahoo.com

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## General Note

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## ABSTRACT

**Introduction:** The purpose of present study was to evaluate the accuracy rate of diagnosis of splenomegaly with one-dimensional diameters in computed tomography (CT) scan images and constructing a best-fit model for estimation of splenic volume from the standardized one-dimensional diameters of the spleen to estimates splenic volume with the prolate ellipsoid and a best-fit model. **Materials and Methods:** This cross-sectional study was performed retrospectively on 200 patients' abdominal CT scan images (100 with splenomegaly and 100 without splenomegaly). Six one-dimensional diameters were registered for each abdominal CT scan; splenic length (L), width (W) and four sizes of thickness (T1–T4). The volume of spleen was calculated by the following formula (volume =  $W \times T_3 \times \pi/6$ ) and also by MITK software. Also the formula for splenic volume was obtained by using linear regression. Sensitivity and specificity values were obtained for the one-dimensional index. Using ROC curve, the highest sensitivity and specificity for splenic length, width and thickness was determined to achieve a cutoff point for definition of splenomegaly unidimensionally. **Results:** In our study the length of 11.33 cm was the most sensitive and specific uni-dimensional parameter to define splenomegaly (sensitivity = 85% and specificity = 89%). The best regression model for predicting splenic volume was calculated  $\text{Volume} = 0.4 \times (L \times W \times T_3) + 5$  with  $R^2 = 90\%$ . **Conclusion:** We constructed this formula ( $0.4 \times (W \times T_3 \times L) + 5$ ) with less bias for estimation of splenic volume.

**Keywords:** Computerized Tomography scan; Splenic Volume; Volumetry

## 1. INTRODUCTION

Spleen is the largest organ of reticuloendothelial system. Spleen size had been used as an index for the activity of reticuloendothelial related diseases (Lamb et al., 2002). Various etiologies have been introduced for spleen enlargement including hematologic, infectious, and storage diseases, neoplasm, and connective tissue disorders (Knipe et al., 2015). Although splenomegaly has been categorized as rare diseases by National Institute of Health (NIH) and affects less than 200000 patients in United States ("Prevalence and Incidence of Splenomegaly", 2015), most of the clinical evaluations and decisions are done based on the determination of spleen size (Kaneko et al., 2008; Shen et al., 2005). For example, exact determination of spleen volume plays an important role in the patients who are splenectomy candidates before the surgery (Rezai et al., 2011).

Assessment of spleen size based on physical exam is subjective and unreliable and therefore has been largely supplanted by imaging studies which are more objective (Silverman et al., 1999; Spielmann et al., 2005; Robertson et al., 2001). Previous studies on ultrasound measurement of spleen size found a good correlation between in vivo ultrasound assessment of splenic size and true splenic volume (Lamb et al., 2002). But this kind of studies had some limitations because splenic volumetry by two-dimensional ultrasonography can be prone to error due to irregular spleen edge, and obscuring some parts of spleen by bowel gas, kidney and ribs (Lamb et al., 2002; Strijk et al., 1985). It also has been reported that the splenic weight in vivo is higher by 25-50% due to its dynamic blood storage ability (Prassopoulos et al., 1997; Griffith et al., 1990).

Quantification of volume in vivo by counting CT voxels within the boundaries of an organ results in an accurate estimate of volume and has been considered the reference standard for volumetry (Lamb et al., 2002; Rezai et al., 2011). There has been a great association between estimated splenic volume by CT scan and the real splenic volume measured by water displacement (Lamb et al., 2002). But voxel counting technique of an organ in CT scan is time consuming labor-intensive, and clinically impractical (Robertson et al., 2001). Using multiple indices for spleen volumetry is time consuming and more complicated and there is the need for one reliable index for assessment of splenomegaly.

Radiologic estimation of splenic size usually relies on determination of splenic length (craniocaudal extension) is simple and doesn't need a special guideline (Rezai et al., 2011). But there is no consensus on a standard length for splenomegaly, for example the length of 9.76 cm (Bezerra et al., 2005), 12 cm (Rezai et al., 2011; Gerspacher-Lara et al., 1997), 13 cm (Hellstrom et al., 2004), and 13-14 cm (Robertson et al., 2001) have been reported for the estimation of splenomegaly by various authors and in the study of Shen et al., Splenic width was the most accurate one-dimensional predictor of splenomegaly (Rezai et al., 2011). In the survey by Hellstrom et al., splenic thickness had the most association with splenomegaly (Hellstrom et al., 2004).

Although the initial reports have suggested various methods on the definition of splenomegaly, there is still need for further survey on the comparison of these indexes and identification of a simple and practical method capable of diagnosis of splenomegaly with high accuracy rate. To this end, the purpose of present study was to evaluate the accuracy rate of diagnosis of splenomegaly with one-dimensional diameters in CT scan images and constructing a best-fit model for estimation of splenic volume from the standardized one-dimensional diameters of the spleen to estimates splenic volume with the prolate ellipsoid and a best-fit model.

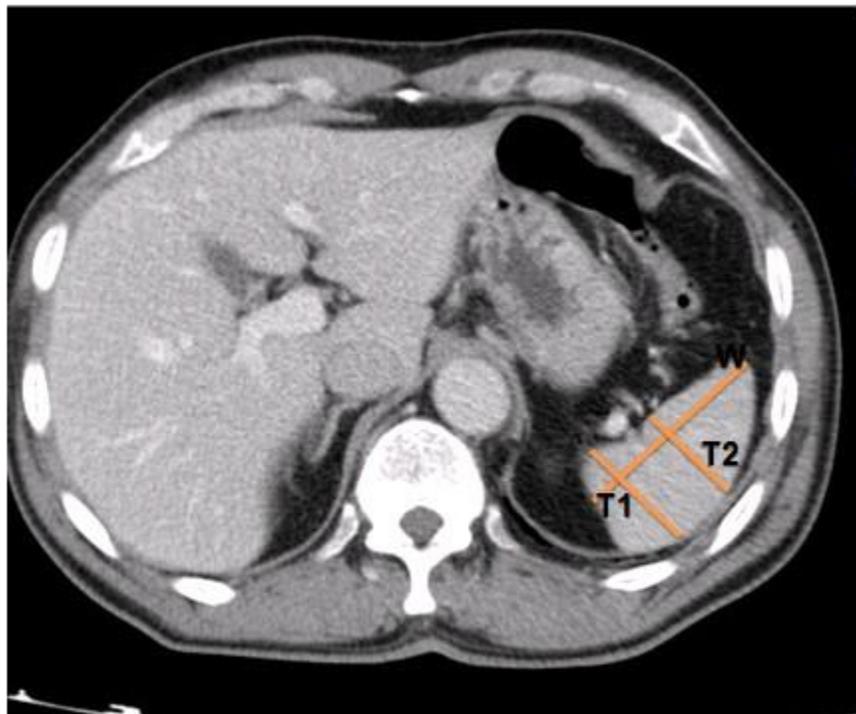
## 2. MATERIALS AND METHODS AND ETHICAL CONSIDERATION

### Patient population

This cross-sectional study was performed retrospectively in our institution on 200 patients abdominal CT scan images (100 with splenomegaly and 100 without splenomegaly) referred for abdominal CT scan for different causes from January 2012 to July 2014. A written informed consent has been obtained from each patient. The study was approved by Mashhad University of Medical Sciences (911249) and the Ethical Committee of Mashhad University of Medical Sciences (98/307352). Patients with a prior splenectomy, focal splenic lesions, hard recognition of splenic boundaries, breathing artifacts, history of nephrectomy, kidney atrophy or tumor, age of less than 12 years; and CT scans were done with multiple breath-hold were excluded.

### CT scans

All imaging examinations were performed with MDCT scanners (16slic-MDCT, NEOSOFT) under standard abdominal protocol with 2-mm slice thickness and 1.5 mm reconstruction interval undertaken in one breath-holding period. The abdominal CT scans were done from the diaphragmatic dome to the pubic symphysis. A total of 125 ml of nonionic contrast material (omnipaque) was injected IV at a rate of 3 ml/s through an antecubital vein with an 18-gauge catheter, using an injector, in the portal venous phase (70 second after initiation of injection).



**Figure 1** Measurement of largest width (W) of spleen, greatest thickness at section where W was determined (T1), and thickness at midpoint of section where W was determined (T2).

### Volumetry of the Spleen

Medical Imaging Interaction Toolkit (MITK) software which was designed by division of medical and biological informatics of German Cancer Research Center (DKFZ) was used for splenic volumetry. Splenic volume more than 314.5 cm<sup>3</sup> was introduced as splenomegaly (Rezai et al., 2011; Prassopoulos et al., 1997; Bezerra et al., 2005).

Six one-dimensional diameters were recorded for each patient; Splenic length (L) was quantified by multiplying the number of sections where spleen was seen by the thickness of each section. Splenic width (W) was determined as the largest diameter of the spleen on transaxial slices; And four measures of thickness (T1–T4), the image where scrolled at axial section where W was measured, greater thickness was determined (T1), thickness at midpoint of this level was determined (T2), the maximum thickness on any section was determined (T3) and thickness at midpoint of this level was determined (T4) (Figure 1).

Four multidimensional indexes were derived using the one-dimensional splenic measures recorded as explained here. The L was multiplied by the W, and this result was then multiplied by each of the four thickness values ( $L \times W \times T1-T4$ ) that were obtained, for a total of four multidimensional indexes (indexes 1–4, based on whether T1–T4 was used). Also the abutment of splenic tissue with the left lobe of the liver, including the anatomical normal variant of the lateral segment extending around the splenic margin, and the relevance between the lowest point of the splenic margin and the inferior third of kidney were considered as signs of splenomegaly.

### Statistical analysis

To define the relationship between the different uni-dimensional and multi-dimensional indexes with the splenomegaly, as data didn't have a normal distribution, Spearman regression index was used and a linear regression analysis was performed for each of the indexes.

The volume of spleen was calculated by the following formula ( $\text{volume} = W \times T_3 \times \pi/6$ ). Splenic volume was also calculated by MITK software. Also the formula for splenic volume was obtained by using linear regression. Sensitivity and specificity values were calculated for the uni-dimensional index. Chi-square test was performed to determine correlation between a splenomegaly and the relationship it has with the liver and the kidney. Presence (sensitivity) and absence (specificity) of enlarged spleen were obtained when the uni-dimensional index or the relationship between splenic margin and the inferior third of the left kidney was concordant with the reference test.

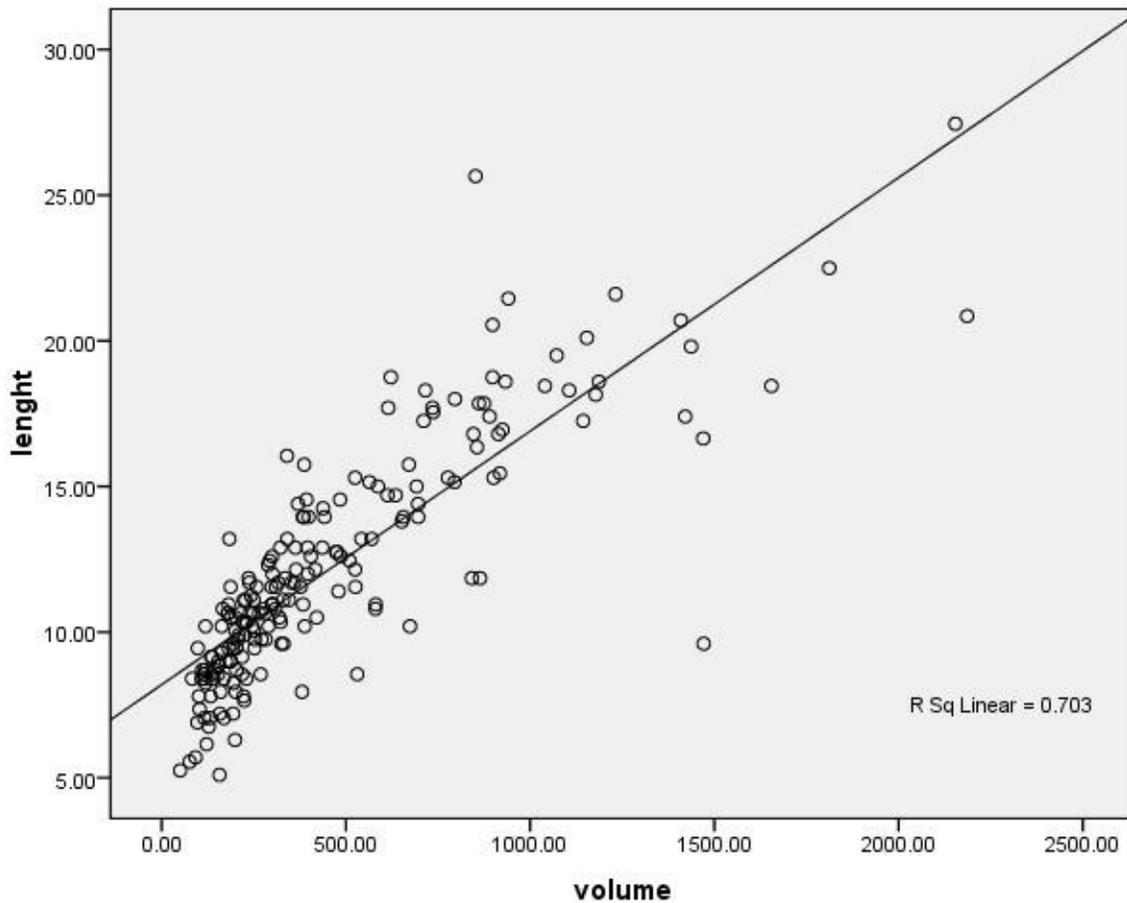
Data analysis was performed in SPSS 16 software. Data were assessed for normality by using the Kolmogorov–Smirnov test. Categorical variables were evaluated using the chi-square test and the t-test/Mann–Whitney tests was utilized to analyze continuous variables between the two groups and Pearson /Spearman correlation test was used for assess the relation between two continuous variables Receiver operating characteristic (ROC) curves were used to determine the most appropriate cut-off point for the selected discrimination endpoint which corresponds to the best possible trade-off between sensitivity and specificity. We analyzed our data using a linear regression model for estimate the spleen volume. A p value of less than 0.05 is used as the cut off significance.

## 3. RESULTS

Previous studies showed that the normal upper limit of splenic volume was  $314.5 \text{ cm}^3$  (Rezai et al., 2011; Prassopoulos et al., 1997; Bezerra et al., 2005). In our study, among 200 patients, 100 had splenomegaly (splenic volume  $> 314.5 \text{ cm}^3$ ) and 100 patients had normal splenic size (splenic volume  $< 314.5 \text{ cm}^3$ ). The mean age of the patients was  $48 \pm 20$  (range 12-91) years. The mean age of the patients with normal spleen was  $49 \pm 21$  (range 13-91) years, while the patients with splenomegaly had the mean age of  $46 \pm 18$  (range 12-88) years. There was no significant difference between the age and gender of the patients with and without splenomegaly ( $P = 0.08$  and  $P = 0.35$ , respectively).

**Table 1** Correlation between the splenic volume and uni- and multi-dimensional indexes

	r	P
Splenic length	0.87	< 0.001
Splenic width	0.84	< 0.001
T1	0.76	< 0.001
T2	0.75	< 0.001
T3	0.80	< 0.001
T4	0.76	< 0.001
Index 1 ( $L \times W \times T_1$ )	0.94	< 0.001
Index 2 ( $L \times W \times T_2$ )	0.947	< 0.001
Index 3 ( $L \times W \times T_3$ )	0.946	< 0.001
Index 4 ( $L \times W \times T_4$ )	0.950	< 0.001



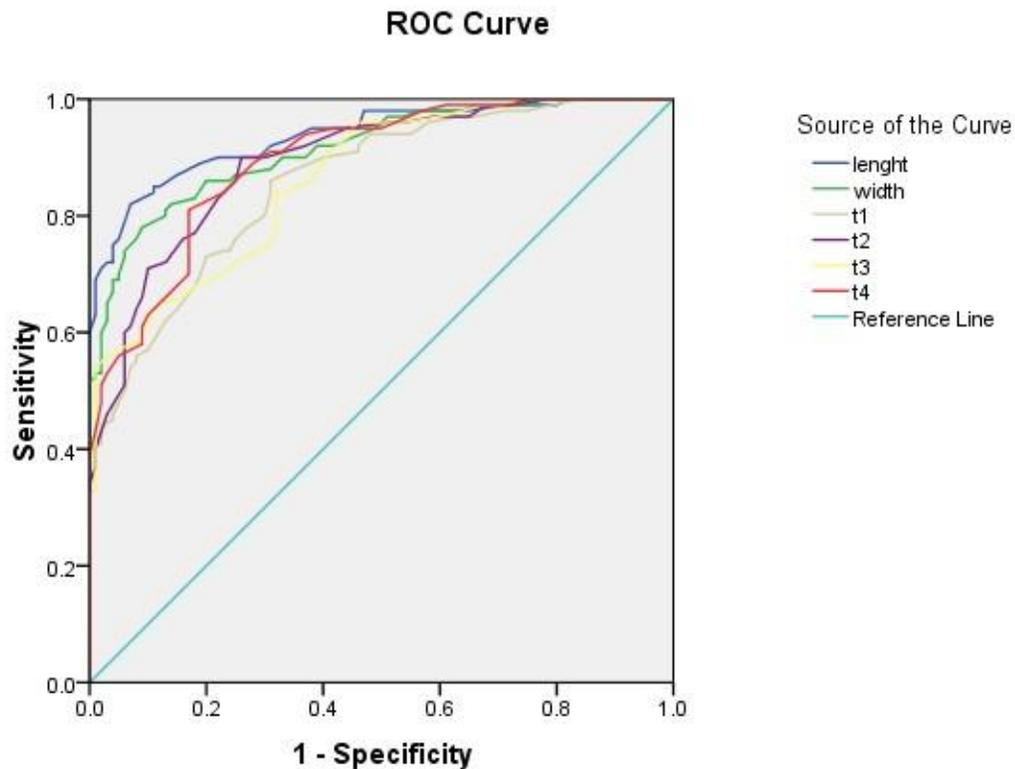
**Figure 2** Correlation between the length and the volume of spleen

The mean volume of spleen among all the patients was  $385 \pm 5 \text{ cm}^3$  (range = 50-2186  $\text{cm}^3$ ). The range of patients' splenic length, width and largest thickness were 5-28 cm, 5-22 cm, and 3-12 cm, respectively. Table 1 shows the relationship of uni-dimensional and multi-dimensional indexes with the splenic volume. Among the uni-dimensional indexes, splenic length and among multi-dimensional indexes, Index 4 ( $L \times W \times T_4$ ) showed the higher correlation with the splenic volume ( $r=0/87$ ,  $P<0/001$  and  $r=0/95$ ,  $P<0/001$ , respectively) (Figure 2).

The highest sensitivity and specificity for splenic length, width and thickness was determined to achieve a cutoff point for definition of splenomegaly uni-dimensionally (Table 2, Figure 3).

**Table 2** Sensitivity and specificity of uni-dimensional indexes for splenomegaly

		Sensitivity	Specificity
Length	$\geq 11.33$	85%	89%
Width	$\geq 11.3$	86%	80%
T1	$\geq 6.25$	73%	80%
T2	$\geq 3.95$	90%	74%
T3	$\geq 6.25$	84%	68%
T4	$\geq 4.45$	84%	78%



**Figure 3** ROC curve for obtaining a uni-dimensional cutoff point for definition of splenomegaly

The length of 11.33 cm was the most sensitive and specific uni-dimensional parameter to define splenomegaly (sensitivity = 85% and specificity = 89%) (Table 2). The second uni-dimensional index which had the highest correlation with the splenic volume was splenic width ( $r = 0.84$ ,  $P < 0.001$ ). Splenic width was also the second most sensitive and specific uni-dimensional index to define splenomegaly (sensitivity = 86%, and specificity = 80%) (Table 2). The best regression model for predicting splenic volume was calculated  $\text{Volume} = 0.4 \times (L \times W \times T_3) + 5$  with  $R^2 = 0.90$ . The mean estimated splenic volume based on the prolate ellipsoid formula and the volume calculated by MITK software was compared with this formula. The mean splenic volume estimated by MITK formula, prolate ellipsoid formula, and regression model were  $454.7 \pm 385$ ,  $454.7 \pm 364.25$ ,  $590.6 \pm 478.41$ , respectively.

The mean splenic volume estimated by prolate ellipsoid formula was  $136 \text{ cm}^3$  higher than the mean splenic volume estimated by MITK software and regression model, but the mean splenic volume by MITK software was similar to the mean splenic volume by regression model. There was a significant difference between MITK mean splenic volume and ellipsoid formula mean splenic volume ( $P < 0.001$ ), but the difference between the mean splenic volume estimated by MITK software and regression model was not significant ( $P = 0.104$ ).

There was a significant concordance between the contact of splenic margin and the inferior third of the left kidney and enlarged spleen ( $P < 0.001$ , Table 3). Also the contact of left liver lobe and spleen showed a significant association with splenomegaly ( $P < 0.001$ , Table 4).

**Table 3** Distribution of case in accordance with splenic volume and position of the inferior splenic margin in relation to the kidney

	Spleen below the inferior	Volume	Volume	Total
	third of left kidney	$>314.5 \text{ cm}^3$	$<314.5 \text{ cm}^3$	
YES		48 (94%)	3 (6%)	51
NO		52 (35%)	97 (65%)	149
Total		100	100	200

**Table 4** Distribution of case in accordance with splenic volume and contact of left liver lobe and spleen

Contact of left liver lobe and spleen	Volume >314.5 cm <sup>3</sup>	Volume <314.5 cm <sup>3</sup>	Total
YES	33 (75%)	11 (35%)	44
NO	67 (43%)	89 (57%)	156
Total	100	100	200

#### 4. DISCUSSION

Attention has been given to the imaging role in the diagnosis and follows up of splenomegaly (Bezerra et al., 2005). Several prior surveys have reported the accuracy of various imaging methods in determining splenomegaly based on different indexes (Lamb et al., 2002; Prassopoulos et al., 1994; Singer, 1973; Schlesinger et al., 1994; Picardi et al., 2002). We have shown that CT scan can evaluate variations of splenic volume with high sensitivity and specificity, although ultrasonography can also be useful.

We showed that uni-dimensional indexes had higher concordance for the diagnosis of splenomegaly compared to the multi-dimensional indexes. However, using multi-dimensional indexes is time consuming and more complicated and there is the need for one simple reliable index for assessment of splenomegaly.

In this study, we found that among uni-dimensional indexes, splenic length had shown the highest correlation with splenomegaly compared to width and various thicknesses. This was similar to the results of the investigations by Bezerra et al. (Bezerra et al., 2005) and Lamb et al. (Lamb et al., 2002). However in the study by Rezai et al. (Rezai et al., 2011) on 193 CT scans of consecutive cases for splenomegaly, splenic width showed the highest correlation with splenic volume. In a report by Prassopoulos and Cavouras (Prassopoulos et al., 1994) on 150 children, they concluded that measuring the thickness in splenic hilum should be considered for predicting splenomegaly; however there are variations of this index in different age groups.

In the present study splenic length has shown the higher concordance with the splenic volume. Measuring splenic volume by multiplying the number of sections by the thickness of each section in CT scan is however easier than splenic width measurement which is done manually in the section with highest width. Measurement of splenic length is simple and practical and reliably can be used. But there is controversy on a standard length for splenomegaly, for reported for the estimation of splenomegaly by various authors. In the present study, this standard length has been calculated 11 cm. In routine measurements, this 11 cm can be considered as the upper normal limit of splenic length which is easy to use and remember. This cut off point has the sensitivity and specificity of 85% and 89% respectively.

In the present survey no significant difference was seen in the splenic volume and age of the sample groups similar to the previous reports (Elstein et al., 1997; Geraghty et al., 2004; Niederau et al., 1983). Relationship between splenic margins and surrounding structures is an easy method for evaluation splenomegaly. Splenic contact with left liver lobe for proving splenomegaly was statistically relevant in our investigation similar to the report by Yetter et al. (Yetter et al., 2003); however Bezerra et al. (Bezerra et al., 2005) didn't find any significant association between this parameter and splenomegaly. Also, in consistent with Bezerra et al. report, our study showed a significant relationship between extension of the splenic margin to or over the inferior third of the left kidney and splenomegaly.

The aim of the present study was to find an accurate formula to define splenomegaly simply. As splenic morphologic characteristics are complex and unpredictable, prolate ellipsoid formula may not be accurate for measuring splenic volume. Similar to the previous investigations (Rezai et al., 2011; Prassopoulos et al., 1997; Singer, 1973), counting CT voxels has been considered standard reference for estimating splenic volume in our survey. We standardized transaxial diameters by measuring the largest transaxial distance and the perpendicular distance through it. This method is similar to WHO guidelines for assessment of treatment response of solid tumors (Kaneko et al., 2002) and minimizes the variability of transaxial measurements.

In the present study we calculated splenic volume by prolate ellipsoid formula to estimate splenomegaly through a uni-dimensional standard formula. The mean splenic volume has been measured 136 cm<sup>3</sup> higher by this formula; this emphasizes the need for a more accurate formula for estimating splenic volume and also is indicative of the non-ellipsoid structure of the spleen. Because of the strong correlation between splenic volume and one diameter of the spleen (Lamb et al., 2002; Bezerra et al., 2005; Prassopoulos et al., 1994; Singer, 1973; Yetter et al., 2003; Miller et al., 1981) and as prolate ellipsoid formula is not the most accurate formula for splenic volumetry, the best formula for estimating splenic volume uni-dimensionally has been calculated splenic volume =  $0/4 \times (W \times T \times L) + 5$ . The difference between splenic volume calculated by this formula and MITK has decreased from 136 cm<sup>3</sup> to zero in comparison to the difference between splenic volume calculated by prolate ellipsoid formula and MITK software and the mean splenic volume measured by this formula was similar to the mean splenic volume measured by MITK software.

This study had some limitations. It was retrospective and was done on adults while its accuracy on the children population is not proved. There is no gold standard method for splenic volumetry within the boundaries of an organ and splenic volume is decreased while and after splenectomy because of blood circulation changes and duration of circulation ligation and uncontrolled blood loss while surgery (Strijk et al., 1985). Also it has been reported that the splenic weight in vivo is higher by 25-50% due to its dynamic blood storage ability (Prassopoulos et al., 1997; Griffith et al., 1990). In this condition using CT scan for measuring splenic volume quantitatively has been considered reliable (Rezai et al., 2011). We recommend further studies with larger sample size according to age (pediatric), race and geometrical shape of spleen (round shapes vs cuboid figures).

## 5. CONCLUSION

For daily routine assessment of splenomegaly, we can use one-dimensional diameters in CT scan. A splenic length of 11.33 cm had the highest sensitivity and specificity for splenomegaly diagnosis. Prolate ellipsoid formula is not the most accurate formula for splenic volumetry because of the shape of spleen, we constructed this formula  $(0.4 \times (W \times T^3 \times L) + 5)$  with less bias for estimation of splenic volume.

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### Conflicts of interest

The authors declare that they have no financial interests related to the materials in the manuscript.

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