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LETTER TO THE EDITOR

How well does liver span as part of the consensus criteria for liver involvement in AL amyloidosis perform?

Criteria for organ involvement and treatment response in AL amyloidosis were formulated in 2005 by a consensus panel comprising 13 medical experts actively involved in the treatment of patients with amyloidosis, based upon the clinical criteria used by each of them at that time [1]. Hepatic involvement is defined as *proven* when there is evidence of liver dysfunction and interstitial amyloid deposits found on liver biopsy. Hepatic involvement is *implicated* when amyloid is diagnosed at another site in a patient with hepatomegaly (defined as total craniocaudal liver span greater than 15 cm in the absence of heart failure) or when the serum alkaline phosphatase (ALP) value is above 1.5 times the upper limit of the institutional normal value.

In patients with AL amyloidosis liver involvement can be asymptomatic, but does affect prognosis and should be taken into account during follow up [2]. At the Groningen Amyloidosis Centre of Expertise, the presence of liver involvement is routinely evaluated using serum alkaline phosphatase, liver span and serum amyloid P component (SAP) scintigraphy [3]. The computerised tomography (CT) scan provided by the SAP scintigraphy is used for measuring the craniocaudal liver span in mid-clavicular line of the frontal plane. Over the years we observed that a significant proportion of patients with AL amyloidosis have a liver span greater than 15 cm without further evidence of liver involvement (no clinical symptoms, normal ALP and no increased tracer uptake in the liver on SAP scintigraphy) or heart failure. Given these discrepancies and the fact that reported reference values for liver span were mainly established on the basis of ultrasound, we wondered how well our method of measuring liver span using CT scan corresponds with liver span measured using ultrasound.

We therefore measured liver span in 43 treatment-naive AL amyloidosis patients with both ultrasound and CT scan. The baseline characteristics of the patients are presented in the Supplemental Data Table 1. The Bland-Altmann plot and Pearson's correlation coefficient were performed to analyse the agreement between the results of ultrasound and CT scan. Analysis was performed with GraphPad Prism version 8 (GraphPad Software, Inc., La Jolla, CA, USA) and SPSS version 23 (IBM Corp, Armonk, New York, USA).

The mean liver span was 16.2 cm (SD 2.6) measured with transabdominal ultrasound and 17.1 cm (SD 2.5) measured with CT scan. On average CT scan results were 0.9 cm higher (95% CI −2.8 to 4.6 cm) compared to transabdominal ultrasound results. A strong correlation was found between both measurements ($r = .72$, $p < .0001$) (Figure 1). Although liver span measured with CT scan did not significantly differ from liver span measured with ultrasound, considerable variation in individual measurements was found. Therefore, we also looked at the percentage of patients in whom both measurements gave discrepant results based on the cut-off value of 15 cm. Corresponding results between CT scan and ultrasound were found in 34 patients (79%), of whom 26 patients (60%) were classified as having an increased liver span and 8 patients (19%) were classified as having a normal liver span. In nine patients (21%), CT scan and ultrasound gave discrepant results. In six patients (14%), the CT scan showed an increased liver span whereas ultrasound showed a normal liver span and in three patients (7%), it was the other way around. Of the 32 patients (74%) that were classified as having an increased liver span based on CT scan, 14 (44%) showed tracer uptake on SAP scintigraphy and only 7 (22%) had an ALP above the upper limit of the institutional normal value. Of the 29 patients (67%) that were classified as having an increased liver span based on ultrasound, 12 (41%) showed tracer uptake on SAP scintigraphy and only 8 (28%) had an ALP above the upper limit of the institutional normal value. In total, 10 patients (23%) had an ALP above the upper limit of the institutional normal value of whom 8 (80%) had an increased liver span based on ultrasound and 7 (70%) based on CT scan. Weak correlations between ALP and liver span measured with CT scan ($r = .397$, p −.012) and liver span measured with ultrasound ($r = .368$, $p = .015$) were found. As liver span may be affected by heart failure [1] we performed multivariate analysis with liver span based on ultrasound or CT scan as dependent variable and NT-proBNP and liver involvement based on SAP scintigraphy as independent variables. Only liver involvement significantly predicted liver span in these models. Also, when we replaced NT-proBNP for presence of manifest heart failure (defined as signs of fluid overload in a patient with cardiac involvement at the time of liver span measurement) only liver involvement significantly predicted liver span.

Our data show that CT scan-based measurements are in good agreement with ultrasound-based measurements of liver span. Many patients have a liver span > 15 cm irrespective of the method of measuring, while these patients do not have liver tracer uptake on SAP scintigraphy and/or an elevated ALP indicating liver involvement. Another large study comprising 2080 individuals in a nonselected population sample showed a liver span of > 15 cm (measured by transabdominal ultrasound) in 539 (26%) of the subjects [4].

Supplemental data for this article can be accessed online at https://doi.org/10.1080/13506129.2023.2222878.

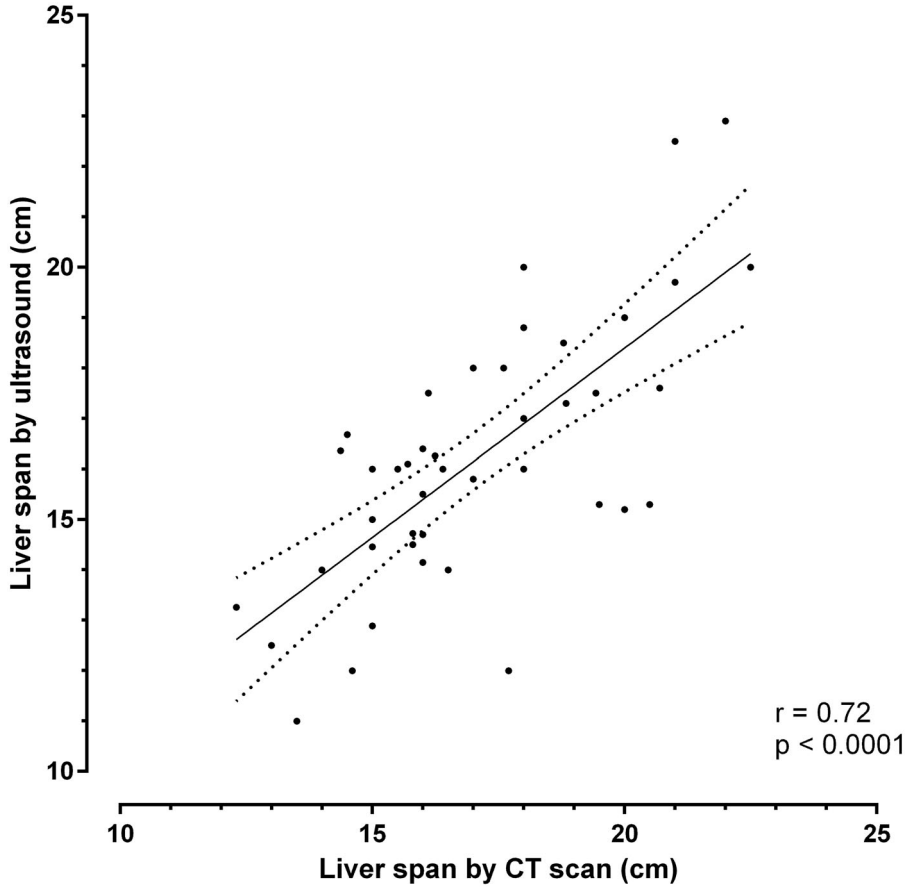

Figure 1. (A) Correlation between liver span based on echography versus CT scan ($N = 43$). The dotted lines represent the 95% confidence interval.

The results of this study, with the knowledge that 26% of average population has a liver span > 15 cm, raises doubt about the specificity of a liver span > 15 cm as criterion for liver involvement. Time may have come to validate liver span and ALP as the two key elements of the non-invasive criteria for liver involvement.

Disclosure statement

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