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A longitudinal 5-year study for the prediction of HCC, death and liver decompensation by ARFI elastography

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Abstract

Aim: Numerous studies have evaluated elastography for the staging of liver fibrosis. Fewer studies were performed investigating the prognostic relevance using transient elastography (TE), although with promising results. This study was designed to evaluate the prognostic relevance of ARFI elastography. **Material and method**: Patients receiving ARFI elastography in our ultrasound department between 2010 and 2012 were initially screened for an ARFI examination with a clinical follow-up of at least 5 years. The following events were recorded: liver related death, liver unrelated death, HCC, liver decompensation/variceal bleeding. **Results**: A total of 335 patients were included in the final analysis with an ARFI examination of the liver and a follow-up of 60 months. Within the observation interval the number of events with corresponding AUROCs (shown with 95% confidence interval) were: overall death (n=49, 0.76 [0.69 – 0.83]), liver related death (n=25, 0.85 [0.77 – 0.93]), liver unrelated death (n=24, 0.66 [0.55 – 0.77]), HCC (n=15, 0.80 [0.72 – 0.87]), liver related complications/variceal bleeding (n=34, 0.87 [0.82 – 0.93]). In the group of patients with ARFI values suggestive of cirrhosis (equal to or above 1.80 m/s; n=110) higher values (<2.5 m/s vs. >= 2.5 m/s) where associated with a significant decline in liver related survival (p=0.007). **Conclusion**: ARFI elastography seems to have a good diagnostic accuracy for the prediction of liver related death and decompensation. Further it seems to allow a risk stratification in patients with cirrhosis suspicious elastography values.

Keywords: ARFI; elastography; prognosis; cirrhosis

Introduction

In the year 2003, transient elastography (TE) was introduced to the European market [1]. Since then, numerous studies with different elastography systems have been published, mainly focusing on the staging of liver fibrosis, revealing an overall good diagnostic accuracy [2,3]. Generally, elastography performs rather better at excluding than confirming liver cirrhosis [4,5]. Today, elastography is a widely accepted clinical tool in the work up of patients with liver disease [6]. For instance, the EASL-ALEH Clinical Practice Guidelines recommend, for patients with hepatitis B, that TE can be used to exclude cirrhosis for values <6 kPa and to consider treatment, screening for varices and hepatocellular carcinoma (HCC) if values are greater than 9 kPa or 12 kPa, depending on ALT (alanine transaminase) values [6].

Comparatively fewer studies have focused on the prognostic relevance of elastography. This, however, could have important implications for treatment and surveillance strategies. One of the first studies assessing the prognostic value of elastography was published by Verginol et al. They included 1457 patients with hepatitis C and found that liver stiffness was a good predictor for survival [7]. Another study on 600 patients with hepatitis B found similar results [8]. Also for rare liver diseases

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one study with 150 primary biliary cholangitis (PBC) patients and another study on 120 primary sclerosing cholangitis (PSC) patients showed very promising results for the prognostic relevance of elastography on liver related survival [9,10]. Those longitudinal studies usually had observational intervals of several years and were mainly performed with TE. Compared to TE, acoustic radiation force impulse (ARFI) elastography has the advantage of being integrated in routine ultrasound machines and therefore can easily be performed during an ultrasound exam with the same probe [5]. Also, it does allow measurements in patients with ascites. Only very few data are available on the prognostic values of ARFI elastography.

We designed this longitudinal study over an observation interval of 5 years to assess the prognostic potential of ARFI elastography for the prediction of liver related death, HCC development or the development of hepatic decompensation.

Material and methods

Patients

The hospital database was searched for patients with an ARFI examination of the liver performed between June 2010 and December 2012. Patients with a follow-up for at least 5 years in our hospital were included in the study. The observation period for the study and consequently for the events counted were 5 years after the ARFI examination. It was intended to include patients with known liver disease as well as others where ARFI elastography was performed in the work up process of excluding relevant liver disease. The goal of this preliminary study was to investigate prognostic relevance solely focusing on shear wave velocity of the liver. Patients under the age of 18 were excluded from the study. The first occurrence of the following events was recorded: death (divided in liver related and liver unrelated death), variceal bleeding, liver decompensation, HCC. Liver decompensation was defined as therapeutically relevant ascites, hepatic encephalopathy or newly occurring esophageal varices. Studies using ARFI elastography were approved by the local ethics committee and conform to the ethical guidelines of the 1975 Declaration of Helsinki. The study was registered at the German Clinical Trials Register (https://www.drks.de, ID: DRKS00031824).

Elastography

The 4 MHz transducer was used for ARFI measurements (S2000 ultrasound system, Siemens Medical Solutions, Erlangen, Germany). An intercostal approach to the right liver lobe during a relaxed breathing arrest in a supine position was chosen. The region of interest (10 x 5 mm) was placed in liver parenchyma with a distance of more than 2 cm from the liver capsule ensuring not to include visible vessels. Partly based on cut-offs proposed by Friedrich-Rust et al, ARFI categories for elastography measurements were defined as: normal (<1.34 m/s), moderately elevated (1.34-<1.80 m/s), severely elevated (1.8-<2.5 m/s) and profoundly elevated (>2.5 m/s) [2]. The cut-off of 1.8 m/s has been proposed for liver cirrhosis [2]. Examples of ARFI measurement of a healthy liver and a cirrhotic liver with a profound increase in shear wave velocity can be found in one of our former publications [11]. Measurements were performed by doctors who were very experienced in ultrasound (6 months to over 10 years of full-time ultrasound).

Statistical analysis

The diagnostic capability of ARFI to discriminate between overall survival, liver unrelated or liver related death, HCC and no HCC, and liver decompensation and no liver decompensation was examined by means of ROC analysis. Areas under the ROC curves (AUROCs) and their 95% confidence intervals are given [12]. Survival and incidence of HCC and liver decompensation were examined by Kaplan-Meier and cumulative incidence plots. Differences between patients with different ARFI categories (normal, moderately elevated, severely elevated, profoundly elevated) were tested with the log rank test. The significance level was set to 0.05. All the statistical analysis was performed using the programming language R V 4.0.3 [13]. Patients which already presented with an event at baseline were excluded in subgroup analysis for that event.

Results

Patients

We included 335 patients in the final analysis as outlined in figure 1. Overall, 110 (32.8%) patients had a median ARFI value equal to or over 1.8 m/s. Patient characteristics are shown in Table I. The observation period was 5 years for every patient or shorter for those patients who died during the observation period. The following events were recorded: 49 deaths (25 liver related and 24 liver unrelated), 15 HCCs, 7 variceal bleeding, 32 liver decompensations.

Survival

The AUROC was 0.76 [0.69 – 0.83] for overall death, 0.85 [0.77 – 0.93] for liver related death and 0.66 [0.55 – 0.77] for liver unrelated death (fig 2A-C). The Kaplan-Meier plot for liver related survival over a time period of 5 years is shown in figure 3A. Comparing patients with normal elastography values (<1.34 m/s) to patients with a moderate elevation in elastography values (1.34 - <1.80 m/s) the occurrence of liver related death was simi-

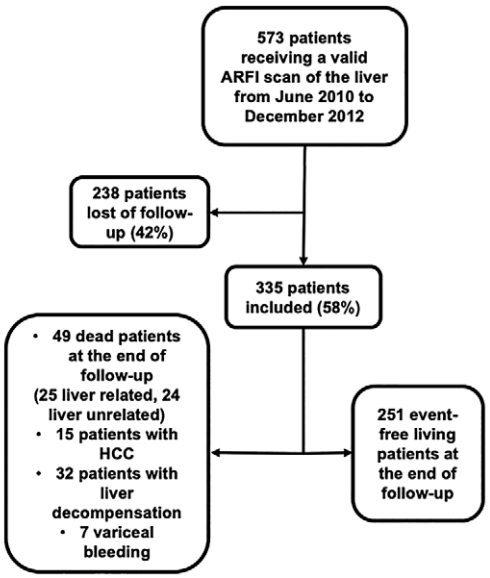

Fig 1. Flowchart of the study population.

lar (1.24% (2 patients) vs. 3.13% (2 patients), p=0.324). Liver related death was recorded more often in patients with a severe elevation in elastography values (>1.8 m/s; p<0.001). Interestingly, in those patients with values >1.8 m/s, liver related death occurred significantly more often in the subgroup of individuals with values >2.5 m/s (>1.8 m/s to <2.5 m/s: 7%/3 patients vs. ≥2.5 m/s: 28%/18 patients; p=0.007). At inclusion there were 14 patients (4%) with an HCC at baseline. Of those patients 7 died in the observation period of 5 years after 19, 46 ,4, 42, 1, 23, and 7 months respectively.

HCC

For the development of an HCC during a time period of 5 years ARFI elastography had an AUROC of 0.80 [0.72 – 0.88] as shown in fig 2D. The incidence of HCC was 0%, 7.8%, 8.7% and 9.4% for patients with elastography values of <1.34 m/s, 1.34 - <1.80 m/s, 1.8 - <2.5 m/s, and >2.5 m/s, respectively, with a statistic significance (p<0.001; fig 3B).

Liver decompensation/variceal bleeding

In total, 34 patients developed liver decompensation and/or variceal bleeding (30 cases with paracenteses, 15 cases with hepatic encephalopathy and 7 cases with variceal bleeding). The AUROC for liver decompensation/variceal bleeding was 0.87 [0.82 – 0.93]. In patients with ARFI elastography values under 1.34 m/s or between 1.35 and under 1.80 m/s, there were only a few events (2% and 2%, respectively, p=0.895). In the group of patients with ARFI elastography values from 1.8 to 2.49 m/s events were recorded in 22% (n=10) compared to 31% (n=20) in patients with elastography values >2.5 m/s without a statistical significance (p=0.22).

Table I. Characteristics of patients at baseline.

Characteristics	Patients (n = 335)
Male, n (%)	193 (57.6)
Age (years), mean ± SD	52.3 ± 13.7
Body mass index (kg/m²), mean ± SD	25.7 ± 5.1
Aetiology of liver disease, n (%)	
No chronic liver disease	27 (8.1)
HBV	43 (12.8)
HCV	69 (20.6)
HBV/HCV	4 (1.2)
Alcohol	34 (10.1)
NASH	7 (2.1)
AIH	11 (3.3)
PBC	17 (5.1)
PSC	7 (2.1)
unknown or other causes	116 (34.6)
Hepatocellular carcinoma, n (%)	14 (4.2)
Present Ascites, n (%)	28 (8.4)
Oesophageal varices, n (%)	
No endoscopy	219 (65.3)
No varices	78 (23.3)
Varices stage I	24 (7.2)
Varices stage II	12 (3.6)
Varices stage III	2 (0.6)
History of variceal bleeding, n (%)	9 (2.7)
History of hepatic encephalopathy, n (%)	3 (0.9)
Biological characteristics, median (IQR)	
Hemoglobine (g/dl)	13.7 (12.2-14.9)
Platelet count (x10³/µl)	192 (140-257)
Prothrombin time (%)	89 (77-100)
INR	1.07 (0.99-1.15)
AST (U/l)	44 (28-79)
ALT (U/l)	46 (26-95)
GGT (U/l)	75 (36-218)
Serum creatinine (mg/dl)	0.85 (0.68-1.1)
Total bilirubin (mg/dl)	0.8 (0.6-1.5)
Serum albumin (g/l)	41.7 (36.5-45.3)
Median number of ARFI measurements (per patient)	8
ARFI measurement	
<1.34 m/sec, n (%)	161 (48.1)
1.34 and <1.55 m/sec, n (%)	45 (13.4)
1.55 and <1.8 m/sec, n (%)	19 (5.7)
≥1.8 and <2.5 m/sec, n (%)	46 (13.7)
≥2.5 m/sec, n (%)	64 (19.1)

The absolute number or the median value with SD are shown.

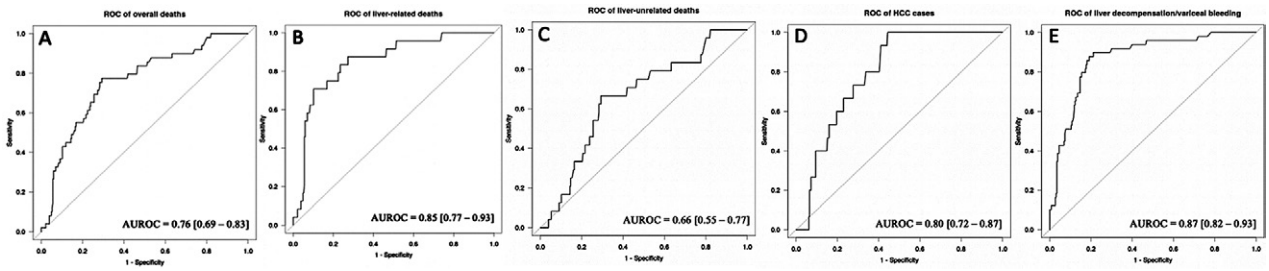

Fig 2. ROC curve for overall death (A), liver-related death (B), liver-unrelated death (C), HCC (D) and decompensation (E) with corresponding AUROCs.

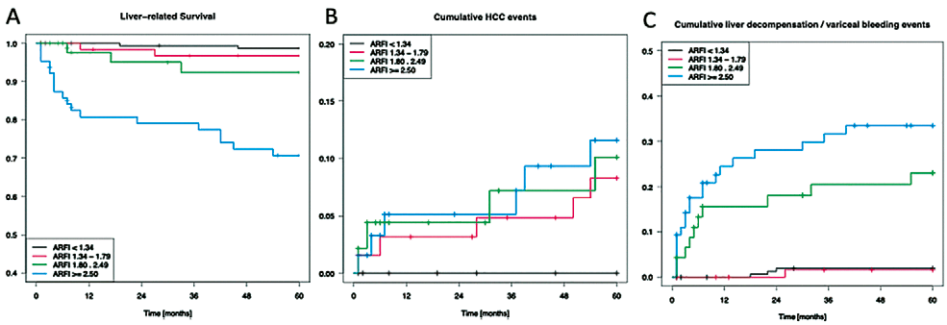

Fig 3. Kaplan-Meier plot for liver related survival (A), cumulative incidence of HCC development (B) and cumulative incidence of liver decompensation (C) for different groups of elastography values: <1.34 m/s, >1.34 - <1.80 m/s, >1.8 - <2.5 m/s, >2.5 m/s.

Discussion

This retrospective longitudinal study on 335 individuals with an observational interval of 5 years is one of the first longitudinal studies assessing the prognostic relevance of ARFI elastography for the prediction of liver related death, HCC development and liver decompensation.

In our study, liver related death occurred significantly more often in patients with ARFI values over 1.8 m/s, which has been proposed as the cut-off for cirrhosis [2]. Furthermore, a risk stratification concerning liver related death of patients with values >1.8 m/s was possible. Therefore, elastography might be a helpful clinical tool for selecting patients at higher risk for liver related death. Those patients, at least theoretically, bear the highest potential for preventing liver related death and might therefore especially profit from closer follow-up and therapy strategies. Prior studies using TE in HCV, HBV or NAFLD patients showed the potential of elastography to predict survival [7,8,14]. A recent retrospective longitudinal study assessing ARFI elastography in 254 patients with chronic viral hepatitis found that patients with liver related events (defined by either HCC development, liver transplantation or liver related death) showed overall higher ARFI values. Even though this study did not analyze the single liver related events by itself, it also supports the overall prognostic value of ARFI elastography which we found in our study [15].

Regarding the HCC risk, several studies, mainly in patients with viral hepatitis, have shown that higher values in transient elastography are associated with a higher risk for the development of an HCC[16–19]. For example, a Japanese study on 1149 HCV patients looking at six subgroups defined by transient elastography (cut-offs 5 kPa, 10 kPa, 15 kPa, 20 kPa, 25 kPa) found a rising 5 year incidence of 2%, 3%, 17%, 25%, 36%, 44% with a higher TE group, respectively [17]. In our study with ARFI elastography we also found an increased risk for HCC development with higher ARFI values. The risk was already increased in patients with ARFI values between 1.34 m/s to 1.8 m/s and was interestingly quite similar for higher values. A further significant improvement may be the combination of elastography with other patient characteristics such as age or blood values. This has been particularly studied for transient elastography and hepatitis B (HBV) [20]. A recent longitudinal study in Caucasians with HBV found that even in year 5 to 12 after starting treatment a rather simple combination of age and transient elastography values was very efficient for HCC risk stratification [21].

Besides survival and HCC risk, we also looked at the risk of liver decompensation/variceal bleeding. One longitudinal Japanese study found that ARFI measurements of the spleen can predict liver decompensation [22]. In our longitudinal study we found an overall good accuracy for ARFI elastography of the liver to predict variceal

bleeding or hepatic decompensation. Those patients with increased risk may potentially profit from closer weight controls, blood controls and more frequent consultation of their doctors.

It is important to keep in mind the heterogenous population from this study which is based on the exams performed in one German university hospital. Around 8% of participants had no signs of liver disease and the causes of liver disease were diverse. Also due to its retrospective character, we lost quite a high number of individuals on follow-up who had to be excluded from the study. Another drawback is that only 35% of the studied patients had an upper GI-endoscopy.

In **conclusion**, this study supports the potential of ARFI elastography for the prediction of liver related death, HCC development and liver decompensation. Further preferentially longitudinal studies should focus on the promising ability of elastography to be integrated in surveillance and therapeutic strategies.

Conflict of interest: none

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