Tumor markers for HCC-screening in patients with liver cirrhosis and hepatic inflammation

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Background and aims:

The incidence of hepatocellular carcinoma (HCC) is rising in the Western world especially due to chronic hepatitis c (HCV) infection. Screening for HCC is mainly based on ultrasound performance as tumor markers such as α-fetoprotein (AFP) are not recommended in the current AASLD guidelines. In patients with inflammatory active, HCV-associated liver cirrhosis, AFP is often elevated as a result of a high cell turnover resulting in impaired diagnostic accuracy. Other possible biomarkers are the lens culinaris agglutinin-reactive fraction of AFP (AFP-L3) and des-γ-carboxyprothrombin (DCP).

The aim of this study was to determine if AFP-L3 and DCP are influenced by hepatic inflammation.

Methods:

Serum samples of 93 patients with chronic HCV were prospectively collected. Patients with other liver diseases were excluded. 69 patients had liver cirrhosis without evidence of HCC. In 24 patients diagnosis of HCC was confirmed according the current AASLD guidelines. Hepatic inflammation was determined if alanin-aminotransferase (ALT) was elevated (> 50 U/l). AFP, AFP-L3 and DCP were measured using a micro-total analysis system (Wako Chemicals GmbH, Neuss, Germany). Diagnostic accuracy was evaluated using ROC analyses. Differences in biomarker values were determined by non-parametric tests.

Results:

	Liver cirrhosis n=69	HCC n=24
Sex – no (%)		
male	45 (65%)	20 (83%)
female	24 (35%)	4 (17%)
Age – median (range)	58 (32 -80)	71 (45 – 80)
Child-Score		
A	55 (81%)	19 (79%) #
B	9 (13%)	3 (13%)
C	4 (6%)	-
BCLC		
A	-	14 (58%)
B		5 (21%)
C		5 (21%)

Table 1: Baseline characteristics of patients with HCV-associated liver cirrhosis and HCC. # 2 patients (8%) with HCC had no liver cirrhosis.

	Liver cirrhosis n=69	HCC n=24	p value
AST [U/l]	45 (25-206)	98 (29-226)	0.065
ALT [U/l]	65 (19-208)	69 (17- 248)	0.507
AFP [ng/ml]	6.8 (1.4 - 265.6)	21.7 (0.8 - 149413.8)	0.005
AFP-L3 [%]	4.1 (0 -26.9)	15.7 (0 - 90.7)	<0.001
DCP [ng/ml]	0.29 (0 -1.9)	2.09 (0.16 -1835.60)	<0.001

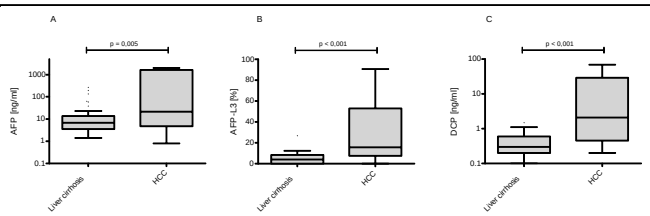

Fig. 1: AST, ALT and biomarker in patients with liver cirrhosis and HCC. Biomarker and ALT values are reported as median and range.

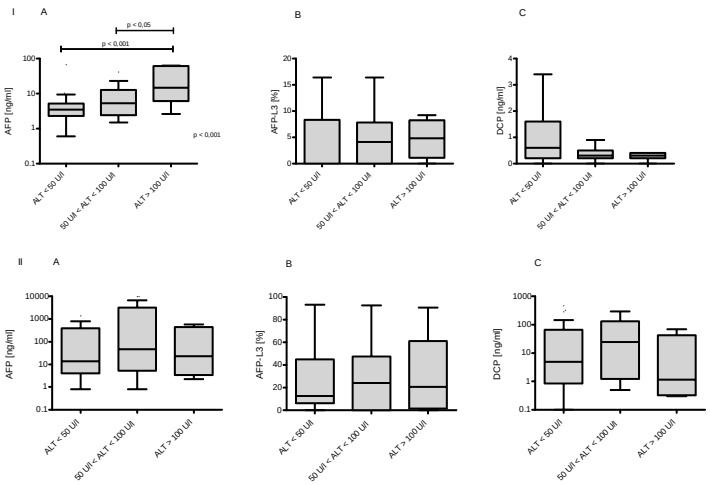

Fig. 2: **I** Patients with liver cirrhosis and elevated ALT have higher AFP values than patients without elevation of ALT (A). AFP-L3 (B) and DCP (C) are not influenced by hepatic inflammation. **II** In patients with HCC there are no significant differences in biomarker values with regard to elevation of ALT.

Patients with liver cirrhosis were stratified according to elevation of ALT and diagnostic accuracy of the biomarkers were calculated. Cut-offs were set at 10 ng/ml for AFP, 10% for AFP-L3 and 2.85 ng/ml for DCP.

	cut-off	Sensitivity *(95%CI)*	Specificity *(95%CI)*	AUC
ALT < 50 U/l				
AFP [ng/ml]	10	67 (36– 97)	**93** (83 – 99)	**0.767**
AFP-L3 [%]	10	78 (51 – 99)	93 (83 – 99)	0.860
DCP [ng/ml]	2.85	44 (12 – 77)	99 (95 – 100)	0.774
ALT > 50 U/l				
AFP [ng/ml]	10	64 (39– 89)	**51** (39 – 89)	**0.632**
AFP-L3 [%]	10	64 (39 – 68)	97 (92 – 99)	0.772
DCP [ng/ml]	2.85	50 (24 – 77)	99 (96 – 100)	0.838

Table 2: ROC analyses stratified according to elevation of ALT indicating hepatic inflammation.

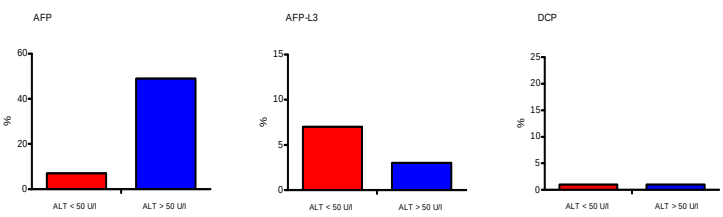

Fig. 2: False positive rate of AFP, AFP-L3 and DCP in patients with elevated ALT compared to those without elevation.

Conclusions:

Hepatic inflammation indicated by elevated ALT results in elevated AFP values. Therefore AFP may be an insufficient screening tool in patients with inflammatory active liver cirrhosis. AFP-L3 and DCP are not influenced by hepatic inflammation. These two biomarkers may provide better diagnostic accuracy in these patients and may compensate the limitations of AFP.