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Reevaluation of the critical flicker frequency in patients with liver cirrhosis reveals new perspectives of its diagnostic impact in the detection of hepatic encephalopathy

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Introduction

• The assessment of the critical flicker frequency (CFF) is a widely-used diagnostic tool for the detection of minimal hepatic encephalopathy (mHE) in patients with liver cirrhosis.

• For CFF assessment patients must repeatedly mark a flicker threshold for light pulses with decreasing frequency presented by the HEPAtonorm™-Analyzer.

• If the standard deviation (SD) of the mean CFF of 8 runs is above 1, as many runs are added as needed to achieve 8 runs with a SD below 1.

• In our experience the latter applies especially to patients with cognitive alterations. Thus, we aimed to investigate the use of CFF variation as diagnostic tool for mHE.
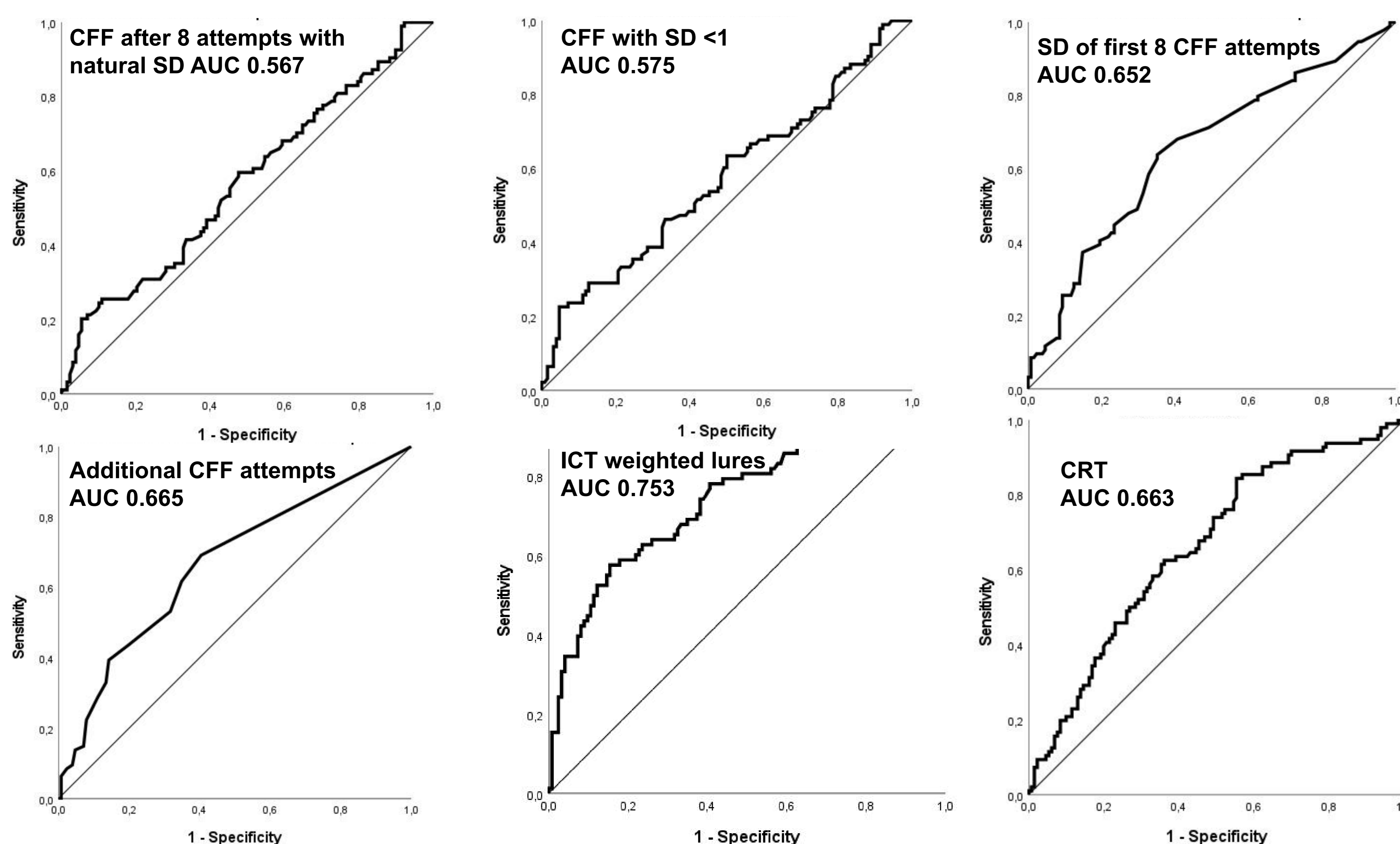
Results

• Neither CFF <39, nor the age corrected CFF correlated with abnormal PHES results.

• The number of attempts needed to achieve a SD <1 for CFF <39 and the SD of the first 8 uncorrected CFF attempts were strongly associated with pathological PHES.

• The number of additional attempts for CFF assessments was also associated with abnormal CRT (p=0.017) and ICT (p=0.027) but did not correlate with MELD or Child Pugh Score.

• Multiple linear regression analysis, including age, significant comorbidities, concomitant medication, laboratory parameters and PHES results indicated PHES results the only cofactor with independent impact upon CFF variability (B= -0.052; 95% CI= -0.084 - -0.019, p=0.002).

Materials & Methods

• 228 patients with liver cirrhosis were included

• Patients underwent PSE-Syndrome test (leading to PHES), inhibitory control test (ICT), continuous reaction time test (CRT) and CFF assessment. PHES <-4, ICT weighted lures >24, CRT Index <1.9 and CFF <39 Hz were rated abnormal.

• Additionally, age adjusted norms for CFF were applied, and the total number of CFF runs required to achieve a SD <1 as well as the uncorrected standard deviation of the first eight CFF attempts were registered.

• Clinical characteristics, demographic data and laboratory findings were recorded.

	Entire cohort	Normal PHES	Pathological PHES	p-value
Number of patients	N=228	N=131 (57.5%)	N=97 (42.5%)	
Age in years	57 (50-64)	56 (49-63)	58 (54-66)	**0.017**
Sex female	67 (29.4%)	41 (31.3%)	26 (26.8%)	0.401
Etiology				0.335
Alcohol related	98 (43%)	51 (38.9%)	47 (48.5%)	
Alcohol plus other etiology	24 (10.5%)	14 (10.7%)	10 (10.3%)	
Non Alcohol related	106 (46.5%)	66 (50.4%)	40 (41.2%)	
Diabetes	59 (25.9%)	27 (20.6%)	32 (33%)	**0.035**
Previous oHE episodes	76 (33.3%)	35 (26.7%)	41 (42.3%)	**0.014**
Years of school education	10 (9-11)	10 (9-11)	10 (9-10)	**0.028**
PHES	-4 (-2 - -7)	-2 (-3 – 0)	-8 (-6 - -11)	**<0.001**
ICT weighted lures (=Lures/ Target Accuracy[2])	19.4 (10.5-34)	14 (7.5-24.7)	33.5 (18.5-44.5)	**<0.001**
ICT abnormal	103 (46.6%)	38 (29.7%)	65 (69.9%)	**<0.001**
CRT	1.84 (1.4-2.3)	2.04-1.56-2.46)	1.6 (1.27-2.05)	**<0.001**
CRT abnormal	122 (53.7%)	58 (44.6%)	64 (66%)	**0.001**
CFF with SD <1	42.5 (38.7-48)	42 (38.7-46.8)	40.7 (36.5-46.1)	0.175
Number of additional CFF attempts needed for SD <1	1 (0-4.75)	0 (0-3)	3 (0-7)	**<0.001**
CFF of first 8 attempts (Hz)	42 (38.38-46)	42.2 (38.7-46.65)	41.4 (36.6-45.4)	0.086
SD of first 8 CFF attempts	1.1 (0.8-1.9)	0.9 (0.7-1.6)	1.4 (0.9-2.6)	**<0.001**
CFF abnormal (<39Hz)	69 (31.4%)	34 (27%)	35 (37.2%)	0.105
CFF abnormal (age corrected)	54 (24.7%)	26 (20.6%)	28 (30.1%)	0.108
Sodium (mmol/l)	136 (134-139)	137 (135-139)	136 (132-138)	**0.003**
Creatinine (µmol/l)	87 (71-111.5)	84 (70-105)	93 (78.5-133.5)	**0.006**

CFF after 8 attempts with natural SD AUC 0.567

CFF with SD <1 AUC 0.575

SD of first 8 CFF attempts AUC 0.652

Additional CFF attempts AUC 0.665

ICT weighted lures AUC 0.753

CRT AUC 0.663

Above: Table 1.: Baseline characteristics of the study cohort with differences in patients with normal and pathological psychometric hepatic encephalopathy score (PHES).

Conclusion

The necessity of additional runs for CFF assessment indicates cognitive dysfunction and gives -rather than CFF results- a worthwhile hint for the presence of mHE in patients with liver cirrhosis.

Left figure 1: ROC analysis for different diagnostic tools to detect cognitive dysfunction, defined by PHES < -4
Abbreviations: ICT: inhibitory control test; CRT: continuous reaction time test; CFF: critical flicker frequency; SD: standard deviation