Necroinflammatory effects on noninvasive liver stiffness measurement using acoustic radiation force impulse elastography in Asian patients with chronic hepatitis B

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Background

- Necroinflammatory effects on ARFI LSM have been widely reported. Patients with CHB usually manifest abrupt and fluctuating ALT levels. Necroinflammatory effects are crucial for CHB patients in liver fibrosis evaluation using ARFI elastography. However, few studies have uniformly analyzed Asian patients with CHB.
- This prospective study, therefore, aimed to estimate the effects of concurrent host factors, especially the histological necroinflammatory grades on ARFI LSM, and the adjusted effects of METAVIR F staging on ARFI LSM, to compare the diagnostic performances of concurrent FibroTest and the simple and noninvasive single indicator ARFI LSM, and to establish the optimal ARFI LSM cutoff values for liver fibrosis staging in Taiwanese patients with CHB.

The effects of hepatic necroinflammatory activity on liver stiffness measurement (LSM) have varied in previous studies.

Positive correlation
- Yoon et al
- Chen et al, BMC Gastroenterology 2012
- Chen et al, JVH 2012
- ...

Insignificant correlation
- Rizzo et al.
- Colombo et al.
- ...

Negative correlation
- Harata et al.

Modes of analysis to delineate the necroinflammatory effects on LSM

- Longitudinal or cross-sectional analyses
- Pearson's or Spearman's correlations
- Univariate or multiple linear regressions
- Univariate or multiple logistic regressions to explain the false positivity
- ALT-specific cutoffs to attempt to compare or enhance the diagnostic performances
- …

Table 1 Patient characteristics

	n = 115
Age, year	44.4(1.0)
Gender (n) male/female	45/70
BMI, kg/m^2	23.90(0.41)
HBeAg (n) positive/negative	55/60
HBV DNA, x 10^4 IU/L	6457.34(1826.00)
ALT, IU/L	118.32(10.75)
$<$1x ULN (n)	26
$\geq$1$<$2x ULN	38
$\geq$2$<$3x ULN	16
$\geq$3$<$4x ULN	11
$\geq$4x ULN	24
Bilirubin, umol/L	18.80(0.67)
Cr, umol/L	77.03(6.55)
INR	1.08(0.01)
Na, meq/L	137.72(0.23)
Platelet, x 10^9/L	166.91(4.94)
Child-Pugh grade (n) A/B/C	21/0/0
METAVIR F (n) 0/1/2/3/4	0/51/26/17/21
METAVIR A (n) 0/1/2/3	28/55/25/7
Hepatic steatosis (n) 0/1/2/3/4	25/35/46/7/2
Liver SWV, m/s	1.75(0.07)

Continuous variables were presented as mean (standard error)

Box plot

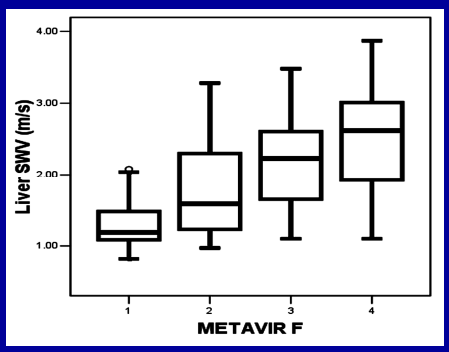

Table 2 The diagnostic performances of liver SWV and FibroTest to classify METAVIR fibrosis (F) stages

	METAVIR		
	F1 *vs* F2-4	F1-2 *vs* F3-4	F1-3 *vs* F4
	Liver SWV		
AUC (95% CI)	0.835(0.762-0.908)	0.844 (0.767-0.921)	0.834 (0.735-0.932)
SE of AUC	0.037	0.039	0.050
Cutoff (m/s)	1.44	1.64	1.86
	FibroTest		
AUC (95% CI)	0.635(0.534-0.737)	0.717 (0.615-0.819)	0.697 (0.579-0.816)
SE of AUC	0.052	0.052	0.060

Obuchowski measures of the two diagnostic modalities- liver SWV and FibroTest F score

Pairwise accuracy for liver SWV		Pairwise accuracy for FibroTest F score	
	SE		SE
1 *vs* 2: 0.7330317	0.06439579	1 *vs* 2: 0.5045249	0.07268760
1 *vs* 3: 0.8869666	0.05044829	1 *vs* 3: 0.7018454	0.08128390
1 *vs* 4: 0.9267040	0.03898447	1 *vs* 4: 0.7605042	0.06278666
2 *vs* 3: 0.6595023	0.08522372	2 *vs* 3: 0.6764706	0.08708497
2 *vs* 4: 0.7710623	0.06990761	2 *vs* 4: 0.7261905	0.07492219
3 *vs* 4: 0.6540616	0.09036897	3 *vs* 4: 0.5350140	0.09964546
0.9247125	0.01519396	0.8476893	0.02233475

two-sided hypothesis test: *P* = 6.103992e-05

Table 3 Three multiple linear regression models to identify independent significant factors that explain liver stiffness

	Model 1			Model 2			Model 3		
Variable	B	SE	*P*	B	SE	*P*	B	SE	*P*
Age, year	.001	.005	.900	-.003	.005	.601	.001	.005	.858
Male gender	.023	.110	.835	.065	.107	.545	-.055	.102	.593
METAVIR									
F2	.452	.123	**<.001**	.407	.130	**.002**	.451	.118	**<.001**
F3	.975	.162	**<.001**	.750	.154	**<.001**	.909	.149	**<.001**
F4	1.287	.157	**<.001**	1.164	.153	**<.001**	1.276	.147	**<.001**
ALT/ULN									
ALT ≧1x <2x	.206	.138	.138						
ALT ≧2x <3x	.308	.182	.093						
ALT ≧3x	.550	.153	**.001**						
METAVIR A									
A1				-.040	.117	.735			
A2-3				.281	.141	**.048**			
ActiTest A score							.842	.190	**<.001**
Na, meq/L	-.055	.021	**.009**	-.062	.021	**.003**	-.046	.020	**.023**
Platelet, x10⁹/L	-.002	.001	**.026**	-.002	.001	**.043**	-.002	.001	**.031**
R^2		.746			.727			.760	
adjusted R^2		.514			.488			.546	

Table 4 Factors associated with false positivity in patients with METAVIR F1-3

	Non FP	FP		
	n = 57	n = 37	OR(95% CI)	*P* value
METAVIR F (n)				
F1	38	13		
F2	13	13		
F3	6	11		
ALT, ULN (n)				
ALT <1x	19	6	reference	
ALT ≧1x <2x	15	6	0.789(0.211-2.951)	.725
ALT ≧2x <3x	8	5	1.562(0.361-6.759)	.550
ALT ≧3x	15	20	3.333(1.045-10.628)	.042
METAVIR A (n)				
A0	28	10	reference	
A1	55	21	1.177(0.414-3.344)	.760
A2-A3	32	11	6.001(1.798-20.020)	.004
ActiTest A score				
<0.25			reference	
≧0.25 <0.5			2.286(0.480-10.883)	.299
≧0.5 <1.00			5.531(1.446-21.158)	.012

Limitations

- Cross-sectional or baseline rather than dynamic or kinetic analysis of the necroinflammatory effects
- Larger sample sizes for validation of cutoffs and for examination of effects of several of the covariates e.g. more severe forms of steatosis
- Bias from stage sizes
- Binary gold standard of fibrosis stages
- Direct tissue markers e.g. hydroxyproline to construct more optimal explanatory models

Conclusion

- The degree of concurrent hepatic necroinflammatory activity independently and significantly exaggerates liver fibrosis staging results using ARFI LSM.
- However, results from comparisons with concurrent FibroTest reflect that ARFI LSM alone remains a promising alternative, or adjunctive indicator for liver fibrosis evaluation in patients with CHB.