Regression of liver stiffness assessed through transient elastography in patients with chronic hepatitis C receiving direct acting antiviral agents

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Background & Aim

- Transient elastography (TE) is a validated non-invasive tool to evaluate liver fibrosis in patients with hepatitis C virus (HCV) infection.
- We aimed to investigate the effect of direct acting antiviral (DAA) therapy on liver stiffness measurement (LSM) in patients with HCV infection.

Methods

- This study enrolled 46 patients with HCV who had LSM using TE before treatment (baseline) and at 12 weeks after the completion of DAA therapy at Taipei Medical University Hospital between February 2016 and June 2017.
- Liver stiffness measurement (LSM) more than 9.5 and 12.5 kPa indicated LSM-defined advanced fibrosis and cirrhosis, respectively.
- A significant decline in the LSM was defined as a ≥30% drop from the baseline.
- The APRI score was calculated as ([AST/upper limit of normal value] / platelet counts [109/L]) * 100. FIB-4 was calculated as age (years) x AST/[platelet count (10^9/L) x $ALT^{1/2}$]. The ALBI score was calculated using the formula: −0.085× (albumin g/L + 0.66×log (bilirubin μmol/L)
- A multivariate logistic regression model was utilized to identify the factors associated with a significant decline in LSM.

Table 1. Demographic data between baseline and SVR (n=46)

	Baseline	SVR12	*P* value
Age, years (mean ± SD)	65.5±11.6	NA	NA
Sex (M/F) (%)	18/28 (39.1/60.9)	NA	NA
BMI, kg/m²	25.2; 23.3-27.2	NA	NA
Treatment-naïve (%)	43 (93.5)	NA	NA
DAA regimens (%)		NA	NA
PrOD±RBV	40 (87.0)	NA	NA
SOF/LDV+RBV	3 (6.5)	NA	NA
DCV+ASV	2 (4.3)	NA	NA
SOF+DCV	1 (2.2)	NA	NA
Treatment duration (%)	44/2 (95.6/4.4)	NA	NA
12weeks/24weeks			
HCV RNA, 10^3 IU/mL	2480; 743-3648	NA	NA
HCV RNA level < 6,000,000 IU/mL (%)	38 (82.6)	NA	NA
HCV Genotype (%)	2/41/1/2	NA	NA
1a/1b/2/mixed genotype*	(4.3/89.2/2.2/4.3)		
Sustained virologic response (%)	44 (95.7)	NA	NA
HBsAg positivity (%)	2 (4.3)	NA	NA
DM (%)	5 (10.9)	NA	NA
Hemoglobin level, g/dL	14.0; 12.7-14.8	NA	NA
White blood cell count, /μL	5235; 3992-6422	5425; 4200-6328	<0.001
Platelet, 10^3 /mm3	131.5; 105.0-159.3	133.0; 88.0-172.8	0.874
Total bilirubin, mg/dl	0.6; 0.5-0.8	0.7; 0.5-0.9	0.290
Direct bilirubin, mg/dl	0.3; 0.2-0.4	0.2; 0.2-0.3	0.142
AST, U/L	65.5; 51.5-93.5	24.5; 19.8-28.0	<0.001
ALT, U/L	76.5; 47.5-123.8	19.0; 16.0-22.5	<0.001
Creatinine, mg/dl	0.7; 0.6-0.9	0.7; 0.6-0.9	0.163
eGFR, mL/min/1.73m²#	102.0; 80.0-125.0	90.5; 62.3-107.3	0.002
eGFR ≥ 60 mL/min/1.73m² (%)	40 (87.0)	35 (76.1)	<0.001
Albumin, g/dl	4.3; 4.1-4.6	4.5; 4.3-4.7	0.088
PT-INR	1.1; 1.0-1.2	1.0; 0.9-1.1	<0.001
Neutrophil-lymphocyte ratio	1.68; 1.26-2.31	NA	NA
AFP (ng/ml)	7.1; 4.8-17.1	3.7; 2.7-6.0	<0.001
APRI	1.18; 0.74-2.12	0.37; 0.23-0.66	<0.001
FIB-4	4.53; 2.76-5.63	2.27; 1.45-4.05	<0.001
ALBI	-2.92; -3.2-(-2.77)	-3.12; -3.29-(-2.87)	0.074
HCC (yes/no) (%)	6/40 (13.0/87.0)	8/38 (17.4/82.6)	<0.001
LSM (E score)	13.9; 10.2-18.5	9.8; 6.5-13.7	<0.001
IQR of E score (%)	9.5; 5.8-13.5	10.0; 6.5-12.5	0.680
Stage of hepatic fibrosis by METAVIR§ (%)			<0.001
F0-1	5 (10.9)	14 (30.4)	
F2	1 (2.2)	8 (17.4)	
F3	14 (30.4)	10 (21.7)	
F4	26 (56.5)	14 (30.4)	

• Continuous variables are expressed as median; 25 and 75 percentiles
* Mixed genotype: two patients had HCV genotype 1a and 1b
# Determined by Cockcroft-Gault equation
§ Determined by transient elastography (FibroScan®, Echosens, Paris, France). The reference range of hepatic fibrosis by transient elastography was as follows: F0-F1(≤ 7.0 kPa), F2 (7.1-9.4 kPa), F3 (9.5-12.4 kPa), F4 (≥ 12.5 kPa)

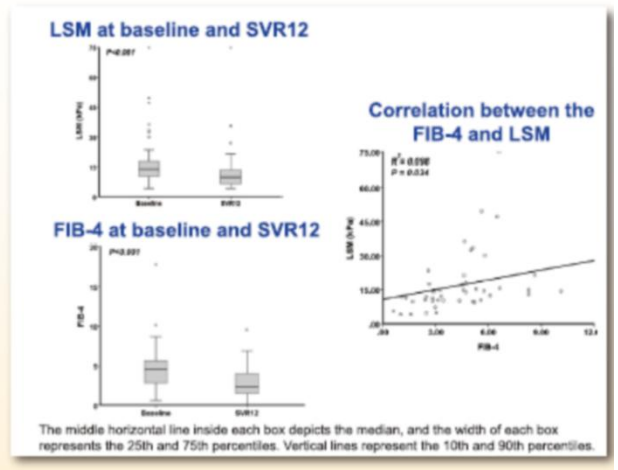
Table 2. Demographic data between LSM ≥30% and LSM<30% drop from the baseline groups

	LSM ≥30%(n=23)	LSM<30%(n=23)	*P* value
Age, years (mean ± SD)	68.4±9.6	62.6±12.9	0.135
Sex (M/F) (%)	10/13(43.5/56.5)	8/15(34.8/65.2)	0.763
BMI, kg/m²	24.9; 23.2-27.0	25.7; 23.4-27.8	0.517
Treatment-naïve (%)	22 (95.7)	21 (91.3)	0.308
DAA regimens (%)			0.255
PrOD±RBV	22 (95.7)	18 (78.3)	
SOF/LDV+RBV	1 (4.3)	2 (8.7)	
DCV+ASV	0	2 (8.7)	
SOF+DCV	0	1 (4.3)	
Treatment duration (%)	23/0 (100/0)	21/2 (91.3/8.7)	0.489
12weeks/24weeks			
HCV RNA, 10^3 IU/mL	3025; 954-3640	1590; 1290-8410	0.317
HCV Genotype (%)	0/22/0/1 (0/95.7/0/4.3)	2/19/1/1	0.359
1a/1b/2/mixed genotype*		(8.7/82.7/4.3/4.3)	
Sustained virologic response (%)	22 (95.7)	22 (95.7)	1.000
HBsAg positivity (%)	0	2 (8.7)	0.512
DM (%)	5 (21.7)	0	0.049
Hemoglobin level, g/dL	14.0; 12.0-14.7	13.9; 12.7-15.0	0.733
White blood cell count, /μL	5250; 3830-6570	5180; 4340-6410	0.852
Platelet, 10^3/mm3	130; 100-169	132; 106-156	0.965
Total bilirubin, mg/dl	0.6; 0.5-0.8	0.7; 0.5-0.8	0.828
Direct bilirubin, mg/dl	0.3; 0.2-0.4	0.3; 0.2-0.3	0.153
AST, U/L	80.0; 54.0-101.0	55.0; 46.0-74.0	0.015
ALT, U/L	89.0; 62.0-140.0	57.0; 44.0-96.0	0.049
Creatinine, mg/dl	0.8; 0.7-0.9	0.6; 0.5-0.8	0.021
eGFR, mL/min/1.73m²#	92.0; 70.0-103.8	108.0; 86.0-132.0	0.027
eGFR ≥ 60 mL/min/1.73m² (%)	20 (87.0)	20 (87.0)	1.000
Albumin, g/dl	4.2; 4.1-4.4	4.4; 4.2-4.6	0.070
PT-INR	1.1; 1.0-1.2	1.1; 1.-1.2	0.585
Neutrophil-lymphocyte ratio	1.4; 1.2-2.0	1.8; 1.4-2.3	0.124
AFP (ng/ml)	9.2; 5.9-31.6	5.7; 3.4-12.4	0.069
APRI	1.59; 0.87-2.83	1.1; 0.6-1.5	0.093
FIB-4	5.13; 2.88-6.49	3.3; 2.5-4.7	0.070
ALBI	-2.90; -3.10-(-2.76)	-3.00; -3.36-(-2.77)	0.397
HCC (yes/no) (%)	2/21 (8.7/91.3)	4/19 (17.4/82.6)	0.665
LSM (E score)	14.8; 11.4-21.3	11.9; 7.3-14.8	0.013
IQR of E score (%)	10.0; 5.0-16.0	9.0; 6.0-13.0	0.792
Stage of hepatic fibrosis by METAVIR§ (%)			0.010
F0-1	0	5 (21.7)	
F2	0	1 (4.3)	
F3	7 (30.4)	7 (30.4)	
F4	16 (69.6)	10 (43.6)	

• Continuous variables are expressed as median; 25 and 75 percentiles
* Mixed genotype: two patients had HCV genotype 1a and 1b
§ Determined by transient elastography (FibroScan®, Echosens, Paris, France). The reference range of hepatic fibrosis by transient elastography was as follows: F0-F1(≤ 7.0 kPa), F2 (7.1-9.4 kPa), F3 (9.5-12.4 kPa), F4 (≥ 12.5 kPa)

Table 3. Factors associated with a significant decline in LSM (≥30% drop from the baseline) after DAA treatment

		Univariate analysis		Multivariate analysis	
Variable	No.	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age (per years)	46	1.048 (0.990-1.109)	0.103		
Sex (M/F)	18/28	1.442 (0.439-4.741)	0.546		
BMI (per kg/m²)	46	0.959 (0.798-1.153)	0.658		
HCV RNA (per 1000 IU/ml)	46	1.000 (1.000-1.000)	0.378		
HCV Genotype 1b/non-1b	41/5	4.632 (0.476-45.085)	0.187		
SVR (yes/no)	44/2	1.000(0.059-17.015)	1.000		
Non-PrOD/PrOD	40/6	0.164(0.017-1.530)	0.113		
Total bilirubin (per mg/dl)	46	1.094(0.185-6.480)	0.921		
AST (per U/L)	46	1.026(1.002-1.050)	0.033	1.026(1.002-1.050)	0.033
ALT (per U/L)	46	1.011(0.999-1.024)	0.077		
Creatinine (per mg/dl)	46	3.224(0.385-27.010)	0.280		
Albumin (per g/dl)	46	0.267(0.042-1.686)	0.160		
Platelet (per 1000/mm³)	46	1.001(0.989-1.012)	0.897		
PT-INR (per sec)	46	0.409(0.001-136.067)	0.763		
AFP (per ng/ml)	46	1.002(0.993-1.011)	0.702		
APRI	46	1.583(0.916-2.738)	0.100		
FIB-4	46	1.241(0.950-1.622)	0.113		
ALBI	46	0.754(0.311-1.831)	0.533		
LSM (per kPa)	46	1.072(0.997-1.153)	0.060		
Neutrophil-lymphocyte ratio	46	1.113(0.809-1.530)	0.512		
HCC (yes/no)	6/40	0.452(0.074-2.757)	0.390		



Results

- The sustained virologic response rate (SVR) was achieved 44 of 46 patients (95.7%). Forty-one (89.2%) patients had genotype 1b HCV infection and 40 (87.0%) patients received paritaprevir/ritonavir, ombitasvir, and dasabuvir (PrOD) with and without ribavirin.
- All patients tolerated treatment well without treatment interruption. Two patients had newly-diagnosed hepatocellular carcinoma (HCC) and 3 of 6 patients with HCC had recurrent HCC after treatment.
- 14 (30.4%) and 26 (56.5%) patients had LS-defined advanced fibrosis and cirrhosis before treatment. LSM decreased from the baseline median value of 13.9 (interquartile range: 5.8–13.5) kPa to a post-treatment week 12 score of 9.8 (interquartile range: 6.5–12.5) kPa (P<0.001). 23 (50.0%) achieved at least a 30% reduction in LSM.
- Univariate analysis showed patients with a significant decline in LSM group had higher alanine aminotransferase, aspartate aminotransferase (AST), LSM and lower creatinine levels than those without a significant decline in LSM.
- Multivariate logistic regression analysis disclosed that high baseline AST level was associated significantly with this reduction (P=0.033). LSM exhibited a correlation with fibrosis-4 index (R2 = 0.098, P = 0.034).

Conclusions

- Patients with HCV infection receiving DAA therapy was associated with a significant improvement in LSM by TE.
- High baseline AST level was the only independent factor associated with the regression in LSM.
- Further large cohort long-term effects of DAA therapy studies are warranted.