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Serial serum MHC class I chain-related A levels in predicting hepatocellular carcinoma in chronic hepatitis C patients with curative antiviral treatment

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Background/Aims

MHC class I chain-related A (MICA) genetic variants and their serum levels (sMICA) have been associated with the development of hepatitis C virus (HCV)-induced hepatocellular carcinoma (HCC) in untreated cohorts. However, the dynamic changes in serial sMICA levels in patients after anti-HCV treatment and their association with the development of HCC is elusive.

Materials and Methods

Single nucleotide polymorphism rs2596542 of MICA and serial sMICA levels were tested in chronic hepatitis C (CHC) patients with sustained virological response after antiviral treatment. Forty-two patients who developed HCC and another 84 age-, sex- and cirrhosis-propensity score matched non-HCC controls were compared. Serial sMICA levels were measured at three-time points: within 6 months of pretreatment (pre-sMICA), 6 months after the end of treatment (post-sMICA) and last visit before HCC occurrence or not (last-sMICA).

Results

Compared to patients who did not develop HCC, those with HCC had lower platelet counts, higher levels of post-sMICA (197.4±398.0 pg/mL vs. 57.6±89.6 pg/mL, P=0.03) and last-sMICA (320.4±508.4 pg/mL vs. 37.7±140.2 pg/mL, P<0.001). A Cox regression analysis revealed that last-sMICA was the only predictive factor of HCC development (hazard ratio [HR]/ 95 % confidence intervals [CI.]: 2.27 (per 1 log pg/mL increase)/1.672-3.082, P<0.001). Patients without HCC development showed a significantly reduced trend of sMICA levels during follow-up (trend P=0.001), which was observed only in MICA rs2596542 GG genotype (trend P<0.001) but not A allele carriers (P=0.88). In contrast, patients with HCC development showed an increased trend of sMICA levels (trend P=0.024). However, only the GG genotype “high expressors” (trend P=0.06) but not A allele carriers (P=0.18) showed a correlation of substantially increased trend of sMICA levels and HCC development.

Factors associated with HCC development

	All patients (n=126)	Non HCC (n=84)	HCC (n=42)	P value	HR	C.I.	P value
Age (years, mean±SD)	58.2 ±7.5	57.8±7.2	58.9±8.4	0.47			
Male gender, n (%)	81 (64.3)	52 (61.9)	29 (69.0)	0.43			
Body weight (kg, mean±SD)	67.9±10.8	67.5±9.5	68.5±13.1	0.63			
Liver cirrhosis, n (%)	65 (51.6)	42 (50.0)	23 (54.8)	0.61			
DM, n (%)	25 (19.8)	16 (19.0)	9 (21.4)	0.75			
Platelet count (x10^{3}u/L, mean±SD)	143±49	150±52	131±39	0.04			
Ferritin ng/ml, mean±SD)	432±359	450±359	395±361	0.43			
GOT (IU/L,mean±SD)	108±71	108±77	107±62	0.92			
GPT (IU/L,mean±SD)	150±117	156±127	139±95	0.44			
α-fetoprotein (ng/mL,mean±SD)	17.7±26.2	15.7±23.2	21.8±31.3	0.22			
r-GT (U/L, mean±SD)	75.9±65.1	71.4±64.0	84.9±67.1	0.28			
HCV RNA (log IU/mL, mean± SD)	5.30±1.10	5.39±1.14	5.13±0.99	0.20			
HCV genotype 1, n (%)	70 (55.6)	51 (60.7)	19 (45.2)	0.1			
MICA rs2596542 A allele, n (%)	68 (54.0)	46 (54.8)	22 (52.4)	0.80			
Pretreatment sMICA (pg/mL, mean±SD)	108.7±142.3	98.6±125.9	128.9±170.3	0.50			
Post-treatment sMICA (pg/mL, mean±SD)	104.2±248.3	57.6±89.6	197.4±398.0	0.03			
Last visit sMICA (pg/mL, mean±SD)	131.9±340.2	37.7±140.2	320.4±508.4	<0.001	1.001	1.001-1.002	<0.001
Follow up period (months, mean±SD)	46.4±31.3	47.2±33.1	44.7±27.8	0.08			

Note: HCC, hepatocellular carcinoma; MICA: MHC class Ipolypeptide-related chain A; sMICA: serum MICA level; *r*-GT: *r*-glutamyl transferase; SD: standard deviation; DM: diabetes mellitus; AST: aspartate aminotransferase; ALT: alanine aminotransferase; HR: hazard ratio; CI.: 95 % confidence intervals.

Changes of sMICA different time points between different time points in patients with or without HCC

△ of sMICA	post-treatment-pretreatment (pg/mL, mean±SD)		P value	last visit-post-treatment (pg/mL, mean±SD)		P value	last visit-pretreatment (pg/mL, mean±SD)		P value
	HCC	Non-HCC		HCC	Non-HCC		HCC	Non-HCC	
All patients	68.5±405.1	-41.0±113.3	0.1	123.0±336.7	-20.0±95.2	0.005	191.5±487.5	-61.0±157.7	<0.001
GG genotype	87.8±537.9	-90.1±136.8	0.1	212.2±432.2	-49.9±73.8	0.002	300.0±637.5	-139.9±141.6	<0.001
A allele	50.9±240.7	-0.5±67.7	0.1	42.0±194.5	4.7±104.2	0.44	92.9±273.7	4.2±140.6	0.16

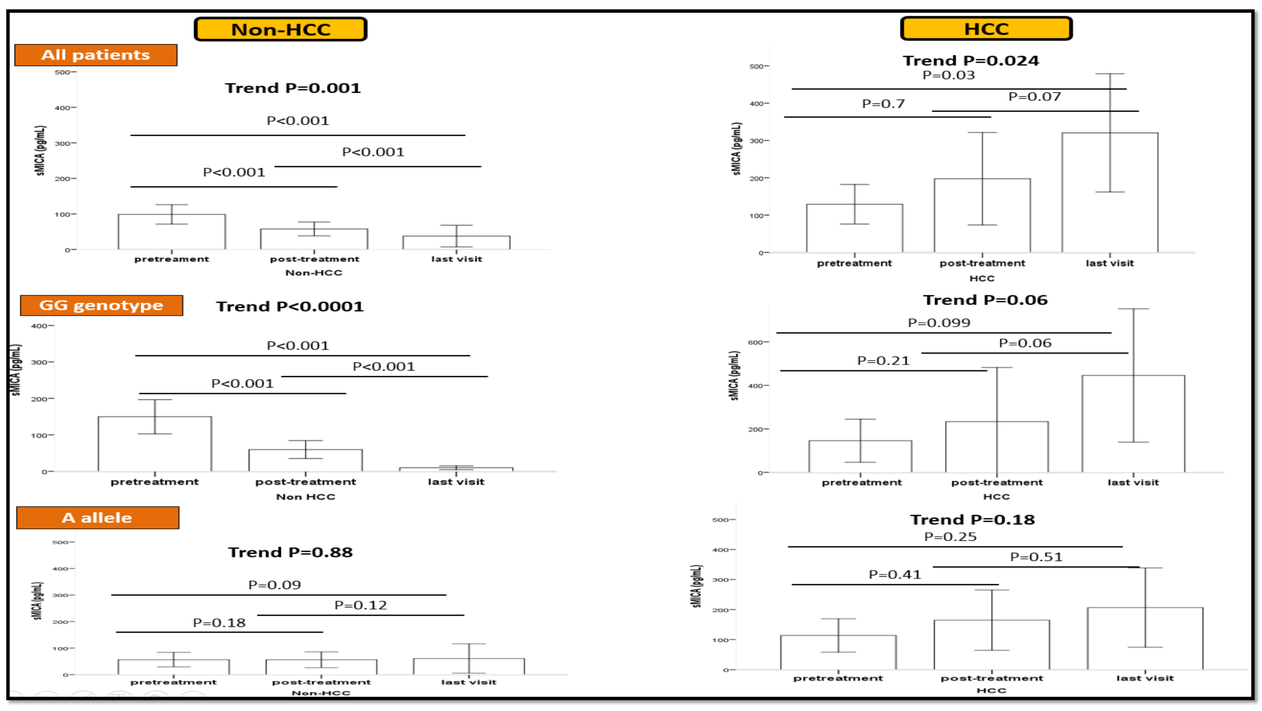
Note: MICA: MHC class I polypeptide-related chain A; sMICA: serum MICA level; GG genotype: MICA rs2596542 genotype; A allele: MICA rs2596542 A allele.

Cox regression analysis of factors associated with HCC development in patients stratified by different MICA rs2596542 genotypes

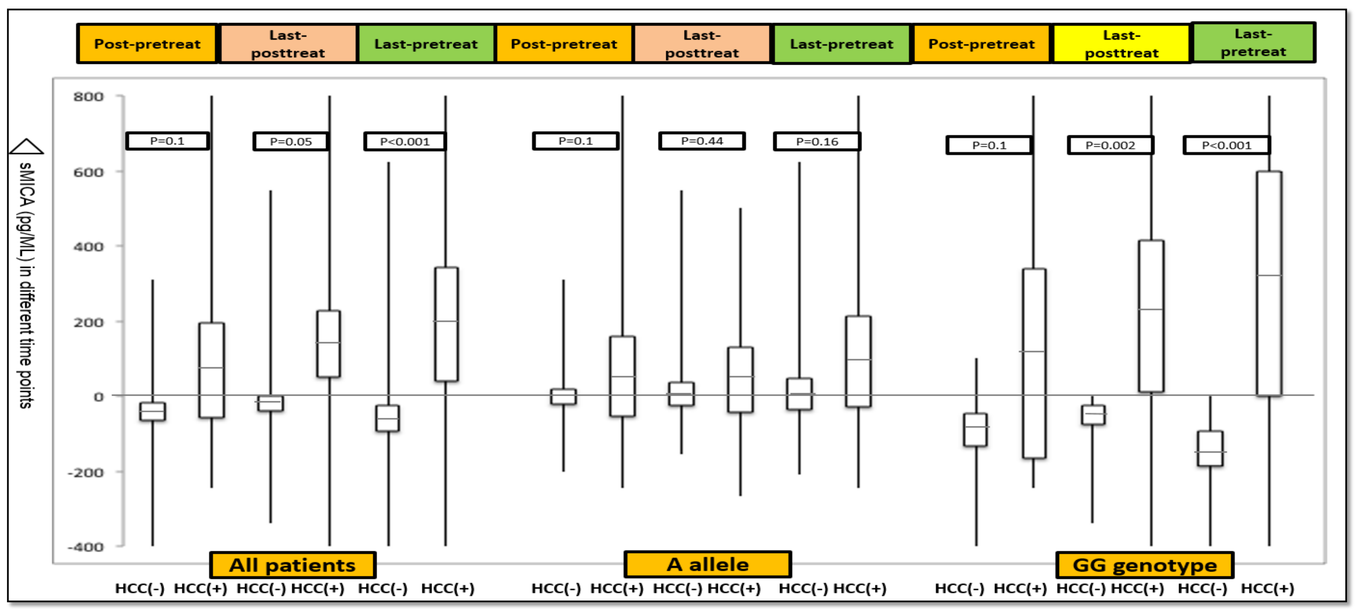
Variables	HR	95% CI	P value
MICA rs2596542 GG genotype			
Last visit sMICA			
Per 1 log pg/mL increased	2.22	1.450-3.401	<0.001
MICA rs2596542 A allele			
Last visit sMICA			
Per 1 log pg/mL increased	2.54	1.544-4.164	<0.001

Note: sMICA, serum MICA level. HR, hazard ratio; CI., 95 % confidence intervals.

Serial changes of sMICA in patients with or without HCC stratified by different MICA rs2596542 SNP



Changes of sMICA between different time points in patients with or without HCC



Box area represented mean value and 95 % confidence intervals. Allele: MICA rs2596542 A allele. sMICA: serum MHC class I polypeptide-related chain A

Conclusions

Serum MICA levels were ameliorated after HCV eradication. Serial sMICA levels were associated with HCC development in CHC patients after achieving an SVR. The clinical utility of serial sMICA in identification of HCC occurrence is restricted to MICA rs2596542 GG genotype carriers.