Dynamic change of LSM-HCC score and enhanced liver fibrosis score to predict hepatocellular carcinoma in chronic hepatitis B patients receiving antiviral treatment: abridged secondary publication

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KEY MESSAGES

1. A two-step algorithm combining LSM-HCC score and ELF score could improve the accuracy of predicting HCC in CHB patients after antiviral treatment.
2. The accuracy of predicting the risk of HCC after antiviral therapy may be further improved.
3. Clinicians could use this two-steps algorithm to better differentiate HBV patients and give a more specific surveillance method, which may save medical resources and help to decrease excessive medical care.
4. Better monitoring for CHB patients with the strategies of three-level prevention would improve the survival of patients and get economic benefits.
5. Further studies are needed to define the role of this algorithm to guide the need of intensity of HCC surveillance.
6. A prospective cohort study or a randomised controlled trial comparing this algorithm with existing recommendations would be warranted.

Hong Kong Med J 2022;28(Suppl 1):S11-3
HMRF project number: 13140651

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Introduction

Advanced fibrosis and cirrhosis are major risk factors of hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC).[1] Liver biopsy is often used to assess liver fibrosis in clinical trials,[2] but its invasiveness and potential complications limit its use. Transient elastography is widely used to assess liver fibrosis because of its non-invasive nature and reproducibility.[3] Liver stiffness measurement (LSM) based on transient elastography has an accuracy of >90% in diagnosing cirrhosis; LSM is also an important prognostic tool to predict HCC.[4] Enhanced liver fibrosis (ELF) is another non-invasive assessment for liver fibrosis, based on an algorithm that comprises three serum biomarkers. Combining LSM and ELF improves diagnostic accuracy for liver fibrosis by reducing the number of patients falling into the grey zone of LSM.[5] We aimed to evaluate the accuracy of a two-step algorithm that combined the LSM-HCC score and the ELF score to predict HCC in patients with chronic hepatitis B (CHB) receiving antiviral treatment.

Methods

Since 2006, we have performed transient elastography for patients with CHB. We classified the patients according to the LSM-HCC score, which comprises four parameters (age, serum albumin and HBV DNA levels, and LSM) and is very sensitive to predict HCC risk in 3 years.[6] Patients who were classified as at intermediate or high risk of HCC (LSM-HCC score of 11-20 and 21-30, respectively) at the first examination were invited to undergo repeated transient elastography at least 3 years later to assess the dynamic change of the LSM-HCC score.

On the day of examination, fasting blood sample was collected and serum was stored at -80°C. Serum aminoterminal propeptide of type III procollagen, hyaluronic acid, and tissue inhibitor of matrix metalloproteinase type-1 were measured using a CE-marked random-access automated clinical immunochemistry analyser that performs magnetic separation enzyme immunoassay tests (ADVIA CentaurTM, Siemens Healthcare Diagnostics, Tarrytown, NY, USA).

The ELF score was calculated using the algorithm recommended in the CE-marked assay (ELF=2.278+0.851 ln(hyaluronic acid)+0.751 ln(propeptide of type III procollagen)+0.394 ln(tissue inhibitor of matrix metalloproteinase type-1)].[7] The optimal cutoff values proposed by the manufacturer are 7.7 and 9.8 to stratify patients into none-to-mild fibrosis, moderate fibrosis, and severe

TABLE 1. Clinical characteristics of patients

	Baseline (n=453)*	Year 3 (n=453)*	P values
Male sex	337 (74.4)		
Age, y	51.7±10.3	54.7±10.3	
Body mass index, kg/m^2	24.8±3.7	25.2±4.0	0.761
Chronic alcohol use	18 (4.0)	21 (4.6)	0.743
Chronic smoking	39 (4.0)	33 (6.0)	0.539
Haemoglobin, g/dL	14.3±1.5	14.3±1.5	0.061
White cell count, ×10^9/L	6.1±1.9	6.0±2.2	0.591
Platelet count, ×10^9/L	180.6±66.1	170.8±55.7	<0.001
Albumin, g/L	42.6±3.6	43.4±3.7	<0.001
Total bilirubin, μmol/L	17.0±19.4	14.7±13.8	0.028
Alanine aminotransferase, IU/L	120.8 (41-115)	35.9 (22-42)	<0.001
American Association for the Study of Liver Diseases			
≤upper limit of laboratory normal	63 (13.9)	257 (57.1)	<0.001
>upper limit of laboratory normal	389 (86.1)	193 (42.9)	
Asian Pacific Association for the Study of the Liver			
≤upper limit of laboratory normal	112 (24.8)	330 (73.3)	<0.001
>upper limit of laboratory normal	340 (75.2)	120 (26.7)	
Creatinine, μmol/L	90.6±84.0	90.8±85.0	0.960
International normalised ratio	1.1±0.1	1.0±0.1	<0.001
Positive hepatitis B e antigen	155 (36.1)	97 (26.7)	<0.001
Hepatitis B virus DNA, log10 IU/mL	5.6±1.6	3.8±1.8	<0.001
Enhanced liver fibrosis panel			
Hyaluronic acid, ng/mL	163.9±201.4	102.9±159.9	<0.001
Propeptide of type III procollagen, ng/mL	14.8±14.6	9.6±4.3	<0.001
Tissue inhibitor of matrix metalloproteinase type-1, ng/mL	256.1±100.0	212.8±59.1	<0.001
Enhanced liver fibrosis score	10.24±1.16	9.47±1.06	<0.001
Transient elastography			
Liver stiffness measurement, kPa	14.0 (9.0-16.1)	8.7 (5.1-10.3)	<0.001
Interquartile range / liver stiffness measurement ratio	0.16±0.08	0.16±0.07	0.765
Success rate of acquisition, %	90.88±13.35	92.46±11.87	0.048
Aminotransferase platelet ratio index	3.33±20.65	0.62±0.49	0.024
Fibrosis-4 index	4.05±15.36	2.09±1.32	0.151
Forns index	8.53±1.95	9.21±1.45	0.235
Maintained virologic response	388 (85.65)		
Antiviral treatment			
Entecavir	414 (91.4)		
Tenofovir disoproxil fumarate	39 (8.6)		
Previous treatment exposure	53 (11.7)		
Antiviral treatment duration, months	47.2±13.3		

* Data are presented as mean ± standard deviation, median (range), or No. (%) of patients

fibrosis. In addition, LSM was performed using transient elastography (Fibroscan, Echosens, Paris, France). The LSM was considered reliable only if 10 successful acquisitions were obtained, and the ratio of interquartile range over LSM (IQR/LSM) was ≤0.3. The liver stiffness was expressed in kiloPascal (kPa).

Results

Of 1555 patients with CHB who underwent transient elastography between 2006 and 2008, 470 with intermediate and high risk of HCC (defined by LSM-HCC score) were invited to undergo repeated transient elastography at least 3 years later. Of them, 55 with HCC, 68 without antiviral treatment, 37 refusal to participate, and 11 with missing data were excluded. In addition, of 1072 patients with CHB who underwent transient elastography from 2009 onwards, 265 with intermediate and high risk of HCC were invited. Of them, 31 with HCC, 44 without antiviral treatment, 33 refusal to participate, and 3 with missing ELF data were excluded. The final number of patients recruited for repeated transient elastography and ELF test were 453.

Compared with the baseline results, the follow-up results had a lower platelet count (180.6±66.1 vs 170.8±55.7 ×10^9/L, P<0.001), higher serum albumin (42.6±3.6 vs 43.4±3.7 g/L, P<0.001), lower alanine aminotransferase (120.8 [IQR, 41.0-115.0] vs 35.9 [IQR, 22.0-42.0] IU/L, P<0.001), and lower HBV DNA (5.6±1.6 vs 3.8±1.8 log10 IU/mL, P<0.001) [Table 1].

Based on the LSM-HCC score, at baseline, 56.3% and 43.7% of patients were at intermediate- and high-risk of HCC, respectively. At the follow-up assessment, 56.3% of patients were at low risk, whereas 28.8% and 14.9% of patients were at intermediate- and high-risk of HCC, respectively. The difference in proportions of risk categories was significance (P<0.001). 71.4% of patients had improved LSM-HCC score, whereas 24.3% and 4.3% of patients had static and deteriorated LSM-HCC score, respectively.

Based on the ELF score, at baseline, 61.6%, 38.0%, and 0.4% of patients had severe, moderate, and mild liver fibrosis, respectively. At the follow-up assessment, the proportions were 31.3%, 66.2%, and 2.4%, respectively (P<0.001). ELF score improved, remained static, and deteriorated in 36.9%, 57.8%, and 5.3% of patients, respectively.

Data of other non-invasive markers, namely APRI, FIB-4, and Forns index were analysed in a subgroup of patients with complete parameters of the serum formulae. The changes in APRI, FIB-4, and Forns index results were of similar trend of ELF.

The cutoff of 20 in LSM-HCC score at baseline had 53.3% sensitivity and 57.4% specificity to predict HCC. The cutoff of 9.8 in ELF score at baseline had

75.6% sensitivity and 40.0% specificity. A combined LSM-HCC and ELF score had an improved sensitivity of 86.7% yet lower specificity of 29.7%, with the highest negative predictive value (95.3%), compared with that of ELF score (93.7%) and that of LSM-HCC score (91.8%). Using the combined LSM-HCC-ELF score, the number of patients with HCC missed was reduced (13%, 6 of 45 HCC patients), compared with the LSM-HCC score alone (47%, 21 of 45 HCC patients) and ELF score alone (24%, 11 of 45 HCC patients) [Table 2].

We therefore propose a stepwise algorithm combining LSM-HCC and ELF scores to predict HCC. Patients with intermediate risk, based on the LSM-HCC score, should be assessed using the ELF score. Of 255 patients with intermediate risk at baseline, according to the ELF score, 127 were classified as low or intermediate risk and 128 were classified as high risk at follow up. HCC occurred in 6 (4.7%) of 127 patients and 15 (11.7%) of 128 patients, respectively. Of 198 patients at high risk of HCC defined by LSM-HCC score, 24 (12.1%) had HCC.

TABLE 2. Liver stiffness measurement - hepatocellular carcinoma (LSM-HCC) score and enhanced liver fibrosis (ELF) score of patients

	Baseline*	Year 3*	P values
LSM-HCC score			<0.001
Low risk (0-10)	-	238 (56.3)	
Intermediate risk (11-20)	255 (56.3)	122 (28.8)	
High risk (21-30)	198 (43.7)	63 (14.9)	
Change in LSM-HCC score			
Improved	302 (71.4)		
Static	103 (24.3)		
Deteriorated	18 (4.3)		
ELF score			<0.001
None to mild fibrosis (<7.7)	2 (0.4)	11 (2.4)	
Moderate fibrosis (7.7-<9.8)	172 (38.0)	300 (66.2)	
Severe fibrosis (≥9.8)	279 (61.6)	142 (31.3)	
Change in ELF score			
Improved	167 (36.9)		
Static	262 (57.8)		
Deteriorated	24 (5.3)		

* Data are presented as No. (%) of patients

Discussion

The dynamic changes of risk of HCC in patients with antiviral treatment are mostly related to liver fibrosis regression and viral suppression, both of which result in reduced HCC risk.[5] The accuracy of predicting the risk of HCC after antiviral therapy may be further improved by this two-step algorithm, which can better differentiate patients with HBV and give more specific surveillance to save medical resources and decrease excessive medical care. Better monitoring of patients with CHB using the strategies of three-level prevention would improve patient survival and economic benefits.

Conclusion

A two-step algorithm combining LSM-HCC score and ELF score could improve the accuracy of predicting HCC in patients with CHB after antiviral treatment.

Acknowledgements

We thank Prof Henry Lik-Yuen Chan for sharing his idea on the conception and design of the study and the development of methodology. We also thank Dr Lilian Y Liang for clinical and laboratory data collection and analysis, Mr Yee-Kit Tse for his support on statistical analysis.

Funding

This study was supported by the Health and Medical Research Fund, Food and Health Bureau, Hong Kong SAR Government (#13140651). The full report is available from the Health and Medical Research Fund website (https://rfs1.fhb.gov.hk/index.html).

Disclosure

The results of this research have been previously published in:

1. Liang LY, Wong VW, Tse YK, et al. Improvement in enhanced liver fibrosis score and liver stiffness measurement reflects lower risk of hepatocellular carcinoma. Aliment Pharmacol Ther 2019;49:1509-17.
2. Liang LY, Wong VW, Tse KY, Chan HL, Wong GL. Enhanced liver fibrosis (ELF) score improves the accuracy of LSM-HCC score for predicting hepatocellular carcinoma (HCC) in patients with chronic hepatitis B received antiviral treatment. Hepatol Int 2019;13(Suppl 1):S9-10.

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