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Editorial Board Member of *World Journal of Hepatology*, Veronika Lukacs-Kornek, MD, PhD, Assistant Professor, Department of Internal Medicine II, Saarland University Hospital, 66424 Homburg, Germany

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World Journal of Hepatology
 Baishideng Publishing Group Inc
 7901 Stoneridge Drive, Suite 501,
 Pleasanton, CA 94588, USA
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 Fax: +1-925-2238243
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PUBLISHER
 Baishideng Publishing Group Inc
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Retrospective Cohort Study

Improved Hepascore in hepatitis C predicts reversal in risk of adverse outcome

Angus W Jeffrey, Yi Huang, W Bastiaan de Boer, Leon A Adams, Gerry MacQuillan, David Speers, John Joseph, Gary P Jeffrey

Angus W Jeffrey, School of Medicine, University of Notre Dame, Fremantle, WA 6160, Australia

Yi Huang, Leon A Adams, Gerry MacQuillan, Gary P Jeffrey, School of Medicine and Pharmacology, University of Western Australia, Perth, WA 6009, Australia

Yi Huang, Leon A Adams, Gerry MacQuillan, Gary P Jeffrey, Department of Hepatology, Sir Charles Gairdner Hospital, Perth, WA 6009, Australia

W Bastiaan de Boer, Department of Anatomical Pathology, PathWest, QEII Medical Centre, Perth, WA 6009, Australia

David Speers, Department of Microbiology, PathWest, QEII Medical Centre, Perth, WA 6009, Australia

John Joseph, Department of Biochemistry, PathWest, QEII Medical Centre, Perth, WA 6009, Australia

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Correspondence to: Dr. Angus W Jeffrey, School of Medicine, University of Notre Dame, 32 Mouat St, Fremantle, WA 6160, Australia. angus.jeffrey1@my.nd.edu.au
Telephone: +61-8-94330555
Fax: +61-8-94330544

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Abstract

AIM

To establish if serial Hepascore tests (referred to as delta Hepascore) in those with chronic hepatitis C (CHC) correlate with the increase and/or decrease in risk of liver related complications.

METHODS

Three hundred and forty-six CHC patients who had two Hepascore tests performed were studied. During 1944 patient years follow-up 28 (8.1%) reached an endpoint. The Hepascore is a serum test that provides clinically useful data regarding the stage of liver fibrosis and

subsequent clinical outcomes in chronic liver disease.

RESULTS

Patients with a baseline Hepascore > 0.75 had a significantly increased rate of reaching a composite endpoint consisting of hepatocellular carcinoma, liver death, and/or decompensation ($P < 0.001$). In those with an initial Hepascore > 0.75, a subsequent improved Hepascore showed a significantly decreased risk for the composite endpoint ($P = 0.004$). There were no negative outcomes in those with a stable or improved delta Hepascore. The minimum time between tests that was found to give a statically significant result was in those greater than one year ($P = 0.03$).

CONCLUSION

In conclusion, Hepascore is an accurate predictor of liver related mortality and liver related morbidity in CHC patients. Of note, we have found that there is a decreased risk of mortality and morbidity in CHC patients when the patient has an improving delta Hepascore. Repeat Hepascore tests, when performed at a minimum one-year interval, may be of value in routine clinical practice to predict liver related clinical outcomes and to guide patient management.

Key words: Chronic; Prognosis; Direct acting antivirals; Serum; Hepatitis C

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Core tip: The growing burden of hepatitis C is well recognized. The use of serum fibrosis markers such as Hepascore to monitor change in clinical risk in hepatitis C has a significant potential benefit to optimise the management in these patients. However, there is no information on the value of serial serum fibrosis tests and their improvement over time in determining changes in liver related clinical outcomes. We have found that there is a decreased risk of mortality and morbidity in chronic hepatitis C patients when the patient has an improving delta Hepascore, and serial tests may be of use in clinical practice.

Jeffrey AW, Huang Y, de Boer WB, Adams LA, MacQuillan G, Speers D, Joseph J, Jeffrey GP. Improved Hepascore in hepatitis C predicts reversal in risk of adverse outcome. *World J Hepatol* 2017; 9(19): 850-856 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v9/i19/850.htm> DOI: <http://dx.doi.org/10.4254/wjh.v9.i19.850>

INTRODUCTION

The use of direct acting antivirals (DAA) therapy in chronic hepatitis C (CHC) treatment has resulted in up to 99% eradication of hepatitis C virus (HCV) in patients receiving treatment, depending on the genotype and type of DAA used^[1,2]. The increased efficacy and

minimal side effects of newer DAA's means that many more patients will access therapy, if financially able. To this end, in March 2016 the Pharmaceutical Benefits Scheme (PBS) in Australia listed sofosbuvir, ledipasvir/sofosbuvir and daclatasvir for the treatment with CHC (4) which will provide access to treatment for all Australians. It is estimated that there will be a 93% reduction in advanced liver disease cases due to the new DAA therapies compared to current regimens or no treatment^[3]. HCV eradication has been shown to reduce liver fibrosis and liver related complications but the time required for this reversal is not known^[2,4,5]. In addition, other co-factors such as NAFLD and alcohol use may be present and prevent or impair reversal of hepatic fibrosis. Therefore the problem remains that CHC patients with significant or advanced liver fibrosis at the time of successful HCV eradication may require long term monitoring for liver related complications for an uncertain period of time^[6].

Fibrosis severity is currently measured non-invasively using serum fibrosis markers or transient elastography (Fibroscan®). The histopathological staging of fibrosis using liver biopsy has historically been the best predictor of liver related mortality and liver related morbidity associated with CHC^[7]. However liver biopsy is now rarely used to stage CHC patients due to the risk of serious complications and issues with sampling error^[8]. Several non-invasive serum fibrosis markers have been developed and are currently used as non-invasive alternatives to liver biopsy. Recent advances have now demonstrated that some serum fibrosis markers are able to directly predict adverse liver related outcomes rather than just provide a surrogate marker of liver fibrosis^[9]. Hepascore is one of these markers, and it is used to predict liver related complications in patients with CHC. Hepascore has also been shown to be comparable to liver biopsy^[10-12]. The Hepascore result itself ranges from 0 to 1.0 with a lower value indicating less severe or absent liver fibrosis and consequently better liver related clinical outcomes^[10]. Measurement of the change in severity of liver fibrosis over time is also a strong prognostic tool in CHC^[7]. The use of non-invasive serum fibrosis markers to monitor regression/progression of fibrosis in CHC has a significant potential benefit to optimise the clinical management in these patients. However, there is no information on the value of serial serum fibrosis tests and their change over time in determining changes in liver related clinical outcomes.

This aim of this study is to establish if serial Hepascore tests (referred to as delta Hepascore) in those with CHC correlate with the increase and/or decrease in risk of liver related complications.

MATERIALS AND METHODS

Cohort

Hepatitis C patients who presented to Sir Charles Gairdner Hospital (SCGH) based in Western Australia

from 1992 to 2012 and who also had two Hepascore tests performed were studied. We defined our inclusion criteria as all patients with hepatitis C, both treated and untreated. We also included patients regardless of if they achieved a sustained virological response (SVR). Our exclusion criteria consisted those with co-existing hepatitis B infection, human immunodeficiency virus as well as any other liver diseases. We also excluded patients who had received a previous liver transplantation. We received ethics approval for this study from the Department of Health Ethics Committee and the SCGH Ethics Committee.

Data collection

Baseline and second Hepascore test dates and results were collected for each patient. The WA based Data Linkage System, called WADLS was used to collect long term patient morbidity and mortality figures^[13]. This is a wide scale population based linkage system that has been used extensively in the past and validated in previous population and cohort studies^[14,15]. The WADLS contains records of cancer registrations as well as in-patient hospital morbidity and death records of the Western Australian population, from 1966 to the present. For this study, the events collected were all-cause mortality, liver related mortality, liver related morbidity and cancer registration. The WADLS database has previously been used as part of published and validated studies on liver fibrosis assessment and use of other non-invasive markers including Hepascore^[10,11].

The primary endpoint for this study was liver related death (LRD) or liver transplantation. Secondary endpoints included onset of hepatocellular carcinoma (HCC) and liver decompensation (LD) of all causes. A composite endpoint included all of these endpoints but patients were only included once. The follow-up time used for the analysis of the baseline Hepascore test was from the time of the test until a primary or secondary endpoint or the conclusion of the study. The follow-up time used for the analysis of delta Hepascore was from the time of the second Hepascore test until an end point or end of study was reached. Delta Hepascore was calculated as the second Hepascore minus the baseline Hepascore. Patients who reached an endpoint before the second Hepascore test were excluded from delta Hepascore analysis. Hepascore is a serum marker that incorporates gamma glutamyl transpeptidase, hyaluronic acid and alpha 2 macroglobulin.

Statistical analysis

Statistics were undertaken using the SPSS Statistics software package and Kaplan-Meier survival analysis. Multivariate cox regression was used to assess the prognostic significance of an initial Hepascore, second Hepascore, and delta Hepascore to predict LRD, HCC or LD. Significance was defined as $P < 0.05$. Patients were placed into groups based on the baseline Hepascore

value (0-0.25, 0.26-0.5, 0.51-0.75, 0.76-1.0) and the delta Hepascore (delta < -0.1 , $-0.1 \leq \text{delta} \leq 0.1$, delta > 0.1) for the analysis. Survival probabilities for using baseline Hepascore values and delta Hepascore values were then calculated using Kaplan-Meier curves with significance calculated using the log rank test.

Area under Receiver Operating Characteristic (AUROC) curves were calculated to assess the capacity of baseline Hepascore and delta Hepascore values to predict liver related outcomes. The optimal time interval between Hepascore tests was assessed by Kaplan-Meier analysis according to the time between tests: < 1 year and ≥ 1 year.

RESULTS

A total of 346 patients met the inclusion criteria and were followed for a mean of 5.5 years, during which 28 (8.1%) had a LRD, developed LD and/or HCC (Table 1). The mean age of the cohort was 53.6 years and 220 (63.6%) were male. Of the total cohort, 8 (2.3%) had a LRD, 15 (4.6%) developed LD and 16 (4.3%) developed HCC. The mean baseline and second Hepascore values were 0.48 (SD ± 0.34) and 0.57 (SD ± 0.34) respectively and the mean delta Hepascore was 0.09 (SD ± 0.23). The time between Hepascore tests ranged from 0.03 and 12.5 years, with a mean of 3.3 and the mean follow-up time after the second Hepascore was 2.4 years. Multivariate cox regression showed that baseline Hepascore and delta Hepascore were independently predictive of reaching a composite clinical endpoint (LRD, HCC or LD), with P values of 0.02 and 0.013 respectively (Table 2).

Patients were grouped into 4 categories according to their baseline Hepascore (0-0.25, 0.26-0.5, 0.51-0.75 and 0.76-1.0). One hundred and twenty-nine (37%) had a Hepascore ≤ 0.25 , 73 (21%) had a Hepascore from 0.26 to 0.5, 43 (12%) had a Hepascore from 0.51 to 0.75 and 100 (29%) had a Hepascore > 0.75 . Kaplan-Meier survival curve analysis found that those patients with a baseline Hepascore > 0.75 had a significantly increased rate of LRD ($n \leq 0.001$), HCC ($n \leq 0.001$), LD ($n \leq 0.001$) and composite endpoint ($P < 0.001$) (Table 3 and Figure 1). Hazard ratios could not be calculated because of the lack of adverse liver related outcomes in the other three lower value Hepascore groups.

Patients with a baseline Hepascore > 0.75 were then analysed using the delta Hepascore value. The delta Hepascore values were divided into those with an improved Hepascore (delta < -0.1), a stable Hepascore ($-0.1 \leq \text{delta} \leq 0.1$) and a worsened Hepascore (delta > 0.1). Survival curve analysis found that in those with an improved Hepascore there was a significantly decreased risk of LRD, LD and a composite endpoint ($P = 0.048$, $P = 0.001$, $P = 0.004$ respectively) as shown in Figure 2. Twelve (17%) patients with a stable or worsened Hepascore reached a composite end point in contrast with those patients

Table 1 Patient characteristics and outcomes

Characteristic	All patients		Patients with first Hepascore > 0.75		All patients		Patients with first Hepascore > 0.75	
	Number	Percent	Number	Percent	mean	Range	mean	Range
Number	346	-	100	-	-	-	-	-
Gender (male)	220	63.6	76	76	-	-	-	-
SVR	38	11.0	16	16	-	-	-	-
Composite endpoint	28	8.1	21	21	-	-	-	-
LRD	8	2.3	8	8	-	-	-	-
LD	16	4.6	12	12	-	-	-	-
HCC	15	4.3	12	12	-	-	-	-
Result								
Bilirubin (μmol/L) ¹	-	-	-	-	9.0	1.0-200	12	2.3-200
GGT (U/L) ¹	-	-	-	-	55.0	8.0-1005	93.5	17-713
HA (μg/L) ¹	-	-	-	-	30.3	1.0-1211	124.5	16-1211
A2M (μg/mL) ¹	-	-	-	-	2.5	0.6-6	3.6	1.5-6.0
Age (yr)	-	-	-	-	53.6	30-80	58.3	36-80
Baseline Hepascore	-	-	-	-	0.48	0.02-1.0	0.93	0.77-1.0
Second Hepascore	-	-	-	-	0.57	0.04-1.0	0.87	0.13-1.0
Delta Hepascore	-	-	-	-	0.09	-0.80-0.94	-0.06	-0.8-0.23
Time between baseline and second Hepascore (yr)	-	-	-	-	3.3	0.03-12.5	2.8	0.03-10.3
Follow-up after second Hepascore (yr)	-	-	-	-	2.2	0.01-7.3	1.9	0.01-5.7

¹Serum markers used in Hepascore calculation. GGT: Gamma glutamyl transpeptidase; HA: Hyaluronic acid; A2M: Alpha 2 macroglobulin.

Table 2 Predictors of composite clinical endpoint (liver related death, hepatocellular carcinoma, liver decompensation) using Multivariate Cox Regression

Variable	Follow-up from the baseline Hepascore		Follow-up from the second Hepascore	
	P	Hazard ratio (95%CI)	P	Hazard ratio (95%CI)
Baseline Hepascore	< 0.001	5.85 (2.25-15.18)	0.020	12.86 (1.49-111.17)
Second Hepascore	-	-	0.891	3288.82 (0.0-4.6E + 53)
Delta Hepascore	-	-	0.013	4.77 (1.35-16.45)

Table 3 Predictors of survival using Kaplan-Meier survival curves

Test	End point	P value (log rank)	Cohort size
Baseline Hepascore alone	Composite Endpoint	< 0.001	346
	LRD	< 0.001	352
	LD	< 0.001	348
	HCC	< 0.001	350
Delta Hepascore	Composite Endpoint	0.004	96
	LRD	0.048	105
	LD	0.001	101
	HCC	0.178	100

LRD: Liver related death; LD: Liver decompensation; HCC: Hepatocellular carcinoma.

who had an improved Hepascore, who had no negative outcomes. Comparison between those patients with a stable Hepascore and those with a worse Hepascore was not possible as 19.5% of patients had a baseline Hepascore value > 0.9 (the maximum Hepascore value is limited to 1.0). Thirty-eight (11%) patients had anti-viral treatment and reached a SVR. Of those achieving SVR only 4 patients reached an endpoint. Excluding these patients from the analysis made no difference to the results.

Table 4 Predictors of survival Using Area under Receiver Operating Characteristic

Test	End point	AUROC
Baseline Hepascore alone	Composite endpoint	0.80
	LRD	0.89
	LD	0.75
	HCC	0.87
Baseline Hepascore > 0.75 and Delta Hepascore	Composite endpoint	0.84
	LRD	0.95
	LD	0.77
	HCC	0.93

AUROC: Area under Receiver Operating Characteristic; LRD: Liver related death; LD: Liver decompensation; HCC: Hepatocellular carcinoma.

AUROC analysis was performed using the baseline Hepascore alone and with a combination of the baseline Hepascore and delta Hepascore (Table 4). There was a marked improvement in the AUROC for the combined baseline and delta Hepascore values compared to baseline Hepascore values alone with an AUROC for LRD of 0.95 and 0.89, for LD of 0.77 and 0.75 and for HCC of 0.93 and 0.87, respectively (Table 4).

Sub-group analysis was then completed to determine the minimum time required between Hepascore tests to determine delta Hepascore. Survival curve

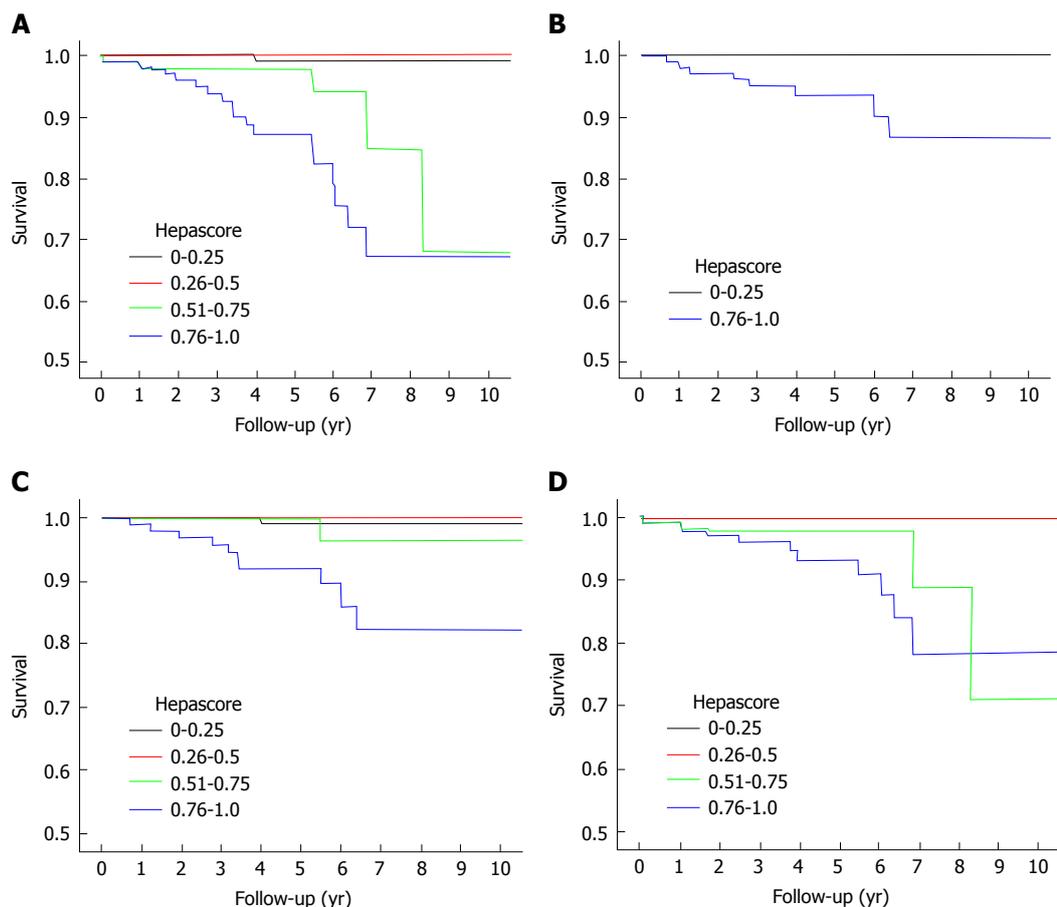


Figure 1 Kaplan-Meier curves specifying survival for liver related death, liver decompensation, hepatocellular carcinoma and a composite end point as a function of baseline Hepascore in the whole cohort. A: Time to composite end point using baseline Hepascore ($P < 0.001$); B: Time to LRD according to Hepascore ($P < 0.001$); C: Time to LD according to Hepascore ($P < 0.001$); D: Time to HCC according to Hepascore ($P < 0.001$). LRD: Liver related death; LD: Liver decompensation; HCC: Hepatocellular carcinoma.

analysis found that in those patients with a baseline Hepascore > 0.75 , delta Hepascore is only predictive of a composite endpoint if the time between Hepascore tests is more than one year ($P = 0.03$) (Figure 3).

DISCUSSION

No previous studies have reported the use of repeated non-invasive serum fibrosis markers to predict improved liver related clinical outcomes. In this well documented cohort of CHC patients with a long follow-up period, 8.1% had an adverse liver related outcome after a mean of 5.5 years of follow-up. Cox regression found that a high (> 0.75) baseline Hepascore value was independently associated with increased rates of adverse liver related outcomes ($P < 0.001$), consistent with previous reports^[11,12]. Importantly the delta Hepascore was also independently associated with predicting a composite clinical endpoint (LRD, HCC, LD) ($P = 0.004$). The AUROC for predicting the composite end point using the initial Hepascore and delta Hepascore was 0.84, which was increased compared to the AUROC using Hepascore alone (0.80).

Patients with an initial Hepascore value greater than 0.75 had an increased risk of developing an

adverse liver related end point and this equated to a 5-year risk of 10% and a 10-year risk of 35%. CHC patients with an initial Hepascore less than or equal to 0.75 had a negligible (%) risk for developing these complications over 10 years. Further analysis found that in patients with a baseline Hepascore greater than 0.75 and who had a subsequent improvement in their second Hepascore of more than 0.1 (delta < -0.1), no adverse liver related end points occurred after a mean of 2.5 years. In contrast, those CHC patients with an initial Hepascore greater than 0.75 and who had a stable or worsened delta Hepascore there was an increased risk of experiencing an adverse liver related outcome. Hepascore has a range of values from 0 to 1.0, therefore only those patients with a baseline Hepascore below 0.9 could have an increased delta Hepascore (delta > 0.1) on subsequent testing. This limited the value of sub-group analysis comparing worsening (delta > 0.1) or stable ($-0.1 \leq \text{delta} \leq 0.1$) delta Hepascore values in those with an initial Hepascore greater than 0.75.

The minimum time interval between Hepascore tests that resulted in useful clinical information was one year. Only when the Hepascore test interval was one year or more was there a significant association

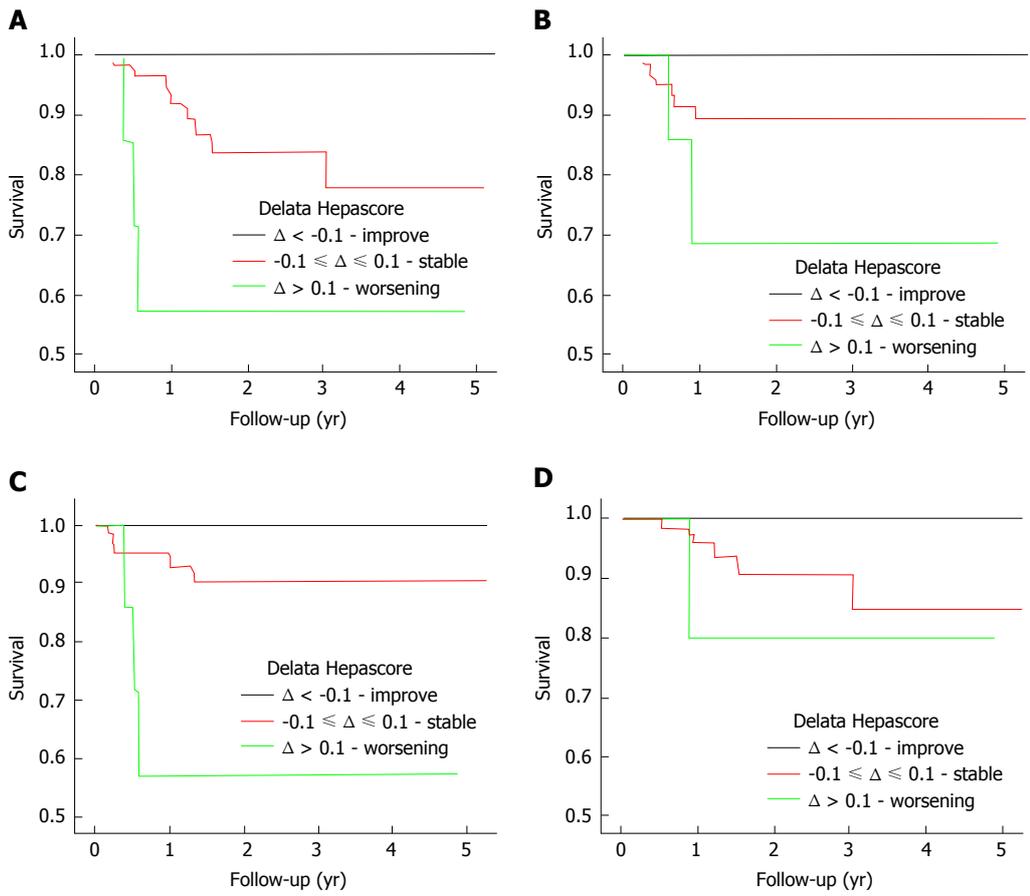


Figure 2 Kaplan-Meier curves specifying survival for liver related death, liver decompensation, hepatocellular carcinoma and a composite end point as a function of Delta Hepascore in the cohort with a baseline Hepascore > 0.75. A: Composite end point according to delta Hepascore, with a baseline Hepascore result of > 0.75 ($P = 0.004$); B: LRD according to delta Hepascore, with a baseline Hepascore result of > 0.75 ($P = 0.048$); C: LD according to delta Hepascore, with a baseline Hepascore result of > 0.75 ($P = 0.001$); D: HCC according to delta Hepascore, with a baseline Hepascore result of > 0.75 ($P = 0.178$). LRD: Liver related death; LD: Liver decompensation; HCC: Hepatocellular carcinoma.

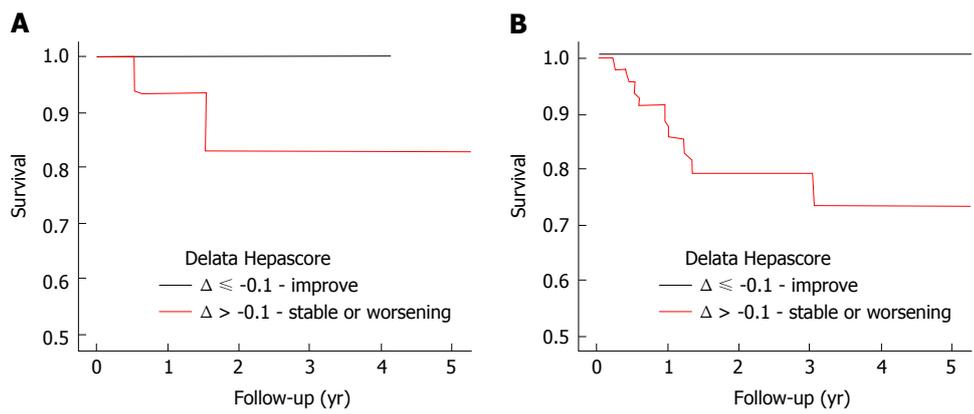


Figure 3 Kaplan-Meier curves specifying survival for a composite end point as a function of Delta Hepascore calculated at varying time intervals between tests. A: Time between tests - 0 to 12 mo ($P = 0.347$); B: Time between tests from - 1 year onwards ($P = 0.03$).

between delta Hepascore and the risk of adverse liver related outcomes ($P = 0.03$). Our findings show that there is a reduced risk of negative outcome in CHC patients who have an initial Hepascore over 0.75, but have an improved delta Hepascore, and will potentially allow a change in clinical management whereby the need for surveillance for varices and hepatocellular

cancer may be reduced.

This study has some limitations. Firstly, due to the retrospective nature of this study, the second Hepascore test was not performed after a fixed time period. This time period was sufficient to demonstrate variation in delta Hepascore, however a fixed follow-up period could be established for future research.

Secondly, the data linkage system, which has allowed the collection of comprehensive data from a central source did not include information on alcohol consumption, diet and exercise. However, we believe that this data would not impact on the results of this study.

In conclusion, Hepascore is an accurate predictor of liver-related mortality and morbidity in CHC patients. Of note, we have found that there is a decreased risk of mortality and morbidity in CHC patients when the patient has an improving delta Hepascore. Repeat Hepascore tests, when performed at a minimum one-year interval, may be of value in routine clinical practice to predict liver related clinical outcomes and to guide patient management.

COMMENTS

Background

Several non-invasive serum fibrosis markers have been developed and are currently used as non-invasive alternatives to liver biopsy. Hepascore is one such marker that is able to predict severity of fibrosis, comparable to liver biopsy. Recent advances have now demonstrated that serum fibrosis markers such as Hepascore are able to directly predict adverse liver related outcomes rather than just provide a surrogate marker of liver fibrosis. Hepascore can also be used to monitor regression/progression of fibrosis in chronic hepatitis C (CHC).

Research frontiers

The use of Hepascore to monitor regression/progression of fibrosis in CHC has a significant potential benefit to optimise the clinical management in these patients. However, there is no information on the value of serial serum fibrosis tests and their change over time in determining changes in liver related clinical outcomes.

Innovations and breakthroughs

Hepascore was found to an accurate predictor of liver-related mortality and morbidity in CHC patients. Of note, the authors have found that there is a decreased risk of mortality and morbidity in CHC patients when the patient has an improving delta Hepascore. Repeat Hepascore tests, when performed at a minimum one-year interval, are of value in routine clinical practice to predict liver related clinical outcomes and to guide patient management.

Applications

Repeat Hepascore tests, when performed at a minimum one-year interval, may be of value in routine clinical practice to predict liver related clinical outcomes and to guide patient management.

Terminology

SVR: Sustained viral response. SVR is specific to hepatitis C and is the absence of HCV RNA for 24 wk after the cessation of treatment.

Peer-review

Current study was from the group who originally described Hepascore as a non-invasive marker of fibrosis in patients with chronic hepatitis C. In the current study, the authors use "baseline" Hepascore as a prognostic indicator. In addition, the authors also found the change in Hepascore over time ("Delta Hepascore") was also a predictor of liver related events or death.

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