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

Author contributions: Jeffrey AW, Huang Y and Jeffrey GP were responsible for study design, data collection and analysis and manuscript preparation; de Boer WB, Adams LA, MacQuillan G, Speers D and Joseph J were involved in data interpretation and manuscript preparation.

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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.

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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. 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. 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.

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 to predict LRD, HCC or liver decompensation (LD) of all causes.

**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 (0.0-0.25, 0.26-0.5, 0.51-0.75, 0.76-1.0) and the delta Hepascore (delta ≤ -0.1, -0.1 < delta ≤ 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.

**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 ($n ≤ 0.001$), HCC ($n ≤ 0.001$), LD ($n ≤ 0.001$) 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 ≤ delta ≤ 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 worsened Hepascore reached a composite endpoint in contrast with those patients
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.

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

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**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)\(^2\)                | -      | -       | -      | -       | 30.3 | 1.0-1211 | 124.5| 16-1211 |
| A2M (µg/mL)\(^3\)              | -      | -       | -      | -       | 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 |

\(^1\)Serum 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               | < 0.001           | 96          |
| LRD                         | 0.048                            | 105               |
| LD                          | 0.001                            | 101               |
| HCC                         | 0.178                            | 100               |

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

**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.

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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
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\cite{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 ≤ delta ≤ 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.
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 progression/regression 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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