**Correlation of liver stiffness and histological features in healthy persons, and patients with occult hepatitis B, chronic active hepatitis B, and hepatitis B cirrhosis**

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**Abstract**

*Background:* Liver stiffness measurement using transient elastography has become a popular tool to assess liver fibrosis.

*Aim:* To determine liver stiffness values and histological features in healthy subjects and patients with chronic hepatitis B.

*Patients and Methods:* A total of 157 persons were included (28 healthy subjects, 18 occult hepatitis B infection, 102 active chronic hepatitis B, and 9 end-stage hepatitis B cirrhosis). Histology and liver stiffness measurements were obtained from all patients.

Results: The median liver stiffness in healthy subjects, occult hepatitis B, active hepatitis B, and end-stage cirrhosis were 4.6, 4.2, 8.7, and 33.8 kPa respectively. In healthy subjects and patients with occult hepatitis B infection, no one had significant fibrosis on histology and all had liver stiffness <7.2 kPa. In patients with chronic active hepatitis B, 32 (31%) had liver stiffness >11.0 kPa, but only 4 (12%) had cirrhosis on histology. Using liver stiffness to predict cirrhosis in this group had a sensitivity of 100%, specificity of 69%, a positive predictive value of 10%, and a negative predictive value of 100%. All 9 patients with end-stage liver cirrhosis had liver stiffness >11.0 kPa. The overall AUROC for diagnosing cirrhosis using a cut-off of 11.3 kPa was 0.89.

*Conclusion:* Liver stiffness measurement has an overall good diagnostic accuracy with excellent negative predictive value. However, in chronic active hepatitis B with elevated ALT levels, the positive predictive value for diagnosing cirrhosis is poor, and further studies are needed to optimize the use of transient elastography in this important group.

## Background

In patients with chronic liver diseases, determination of the degree of liver fibrosis and the presence of cirrhosis has important implications for prognostic, therapeutic and monitoring purposes. Although liver biopsy currently remains the gold standard in the assessment of liver fibrosis, it has associated risks of morbidity and less commonly, mortality.[1] There has been a rapid increase in the development of non-invasive methods to assess liver fibrosis. Measuring liver stiffness using transient elastography has recently become available for research and clinical practice to assess liver fibrosis and cirrhosis. The majority of the early validating studies have been performed in patients with chronic hepatitis C in the Western population. Subsequent validation studies with other liver diseases further support its usefulness.[2-5] However, compared to hepatitis C, there is still relatively limited data on liver stiffness in chronic hepatitis B.

The rationale for transient elastography is based on the theory that liver stiffness is positively correlated with the amount of fibrotic tissue within the liver. In a study of 429 healthy subjects without known liver diseases, the mean liver stiffness measurement was reported to be 5.49 kPa ± 1.59.[6] For patients with chronic liver disease, higher liver stiffness measurements are observed with increasing level of fibrosis, with higher liver stiffness cut-off values corresponding to increasing stages of fibrosis. In patients with cirrhosis, the optimal cut-off values used for patients with cirrhosis can range from 11.0 to 25.3 kPa, depending on the underlying liver disease.[2, 4, 7-9]

It is well established that the cut-off liver stiffness values used for different fibrosis stages are dependent on the underlying disease. However, there is increasing evidence to suggest that even within the same disease, the optimal cut-off values for different degrees of fibrosis may vary with the underlying inflammatory activity, as reflected by higher levels of serum alanine aminotransferase (ALT).[10] In patients with chronic hepatitis B (CHB), the inflammatory activity and its surrogate marker, ALT level, can fluctuate during the course of the disease. Several recent studies have shown that underlying inflammatory activity can increase liver stiffness values, causing an overestimation of the degree of fibrosis.[11-13]

In the current study, we determined liver stiffness values and histological features in subjects with no known liver disease, occult hepatitis B infection, active CHB, and hepatitis B-related cirrhosis, and to compare differences between these 4 groups of subjects.

**Patients and Methods**

The present study recruited a total of 187 subjects from Queen Mary Hospital, University of Hong Kong, Hong Kong, between the periods of November 2005 to November 2008. There were 4 groups of subjects (28 healthy subjects, 18 occult hepatitis B patients, 121 active CHB patients, and 20 end-stage cirrhosis patients). The group without known underlying liver disease (healthy subjects) was living-related donors recruited from the liver transplant program at Queen Mary Hospital. Subjects in this group were negative for hepatitis B surface antigen (HBsAg), antibody to hepatitis C virus, significant alcohol

intake history (as defined by an intake of >20g/day), or any other known liver diseases. Patients with occult hepatitis B infection were recruited from healthy blood donors who were negative for HBsAg, but positive for hepatitis B core antibody (anti-HBc) with detectable HBV DNA (method described below). Patients with active CHB were recruited from the hepatitis clinic at Queen Mary Hospital. These patients were positive for HBsAg for over 6 months, with elevated ALT and HBV DNA levels >20,000 IU/mL. The hepatitis B-related cirrhosis group was liver transplant recipients recruited from the liver transplant program. Written and verbal consent was obtained for liver biopsy and liver stiffness measurements respectively. This study has been approved by the Institutional Review Board of the University of Hong Kong.

*Liver histology*

All patients included in the current study had liver histology available. Liver biopsy was performed on the patient groups with occult hepatitis B and active CHB using a 16G Menghini needle after written informed consent. The liver histology was graded using the modified hepatic activity index (HAI) score.[14, 15] In the groups with normal subjects and HBV-related cirrhosis, histology was obtained at the time of liver transplantation from the donor (intra-operative biopsy specimen) and from the recipient (explant specimen).

*Liver stiffness measurements*

Liver stiffness was measured using transient elastography (Fibroscan, Echosens, Paris, France). All patients had transient elastography performed either on the same day or

within one week of obtaining the liver histology. The procedure has been well described in earlier studies.[2, 5] Patients who had a success rate of <50%, interquartile range-to-liver stiffness ratio of >30%, or less than 10 validated measurements, were excluded. Liver stiffness scores were expressed as the median value of the validated measurements in units of kilopascals (kPa).

*Liver biochemistry and viral load*

Complete blood count, coagulation profile, and routine liver biochemistry were determined at the time of liver biopsy or surgery. In patients with active CHB, the HBV DNA levels were determined using the Cobas Taqman assay, with a lower limit detection of 12 IU/mL (Roche Diagnostics, Branchburg, NJ). For detection of occult hepatitis B in blood donors, HBV DNA was extracted from 500 μL of serum using the QIAamp DSP Virus Kit (Qiagen GmbH, Hilden, Germany) according to the manufacturer's instructions, with a final elution of 26 μL. HBV DNA in the extracts was then quantitatively measured by the Artus HBV RG PCR Kit (Qiagen Hamburg GmbH, Hamburg, Germany), using the Rotor-Gene 3000 Real-time Multiplexing System (Corbett Research, Mortlake, Australia), according to the manufacturer's instructions. This test has a 95% lower limit of quantitation of 3.8 IU/mL of serum and a linear range of detection from 1.1 IU/mL to $4 \times 10^9$ IU/mL of serum. Since the serum HBV DNA levels of these occult HBV subjects were very low, in order to eliminate the chance of false positive or negative results, Artus HBV test was performed 3 times. Genuine HBV DNA-positive result was defined as having ≥2 out of 3 positive HBV DNA signals by 3 independent Artus test runs.

*Statistical analysis*

All statistical analyses were performed using the SPSS version 14.0 (SPSS Inc, Chicago, IL). Continuous variables with skewed distribution were analyzed using Mann Whitney test. Related data were analyzed using the Wilcoxon paired test. Continuous variables with more than 2 independent samples were analyzed using the Kruskal-Wallis test. Correlation between liver stiffness and liver biochemistry and histology score was performed using Spearman's bivariate correlation. Multivariate analysis was performed using multiple regressions on variables significant on univariate analysis. The receiver-operating characteristic (ROC) curves and area under ROC (AUROC) were calculated. The optimal cut-off values were defined as the value giving the highest sensitivity and specificity. A p-value of $<0.05$ was considered statistically significant.

**Results**

A total of 187 patients had both liver biopsy and transient elastography performed during the study period. Of these, thirty (16%) patients were excluded because of suboptimal liver stiffness measurements. Of these suboptimal measurements, eleven patients were liver recipients with very small livers and ascites, accounting for the overall higher-than-expected failure rate of liver stiffness measurements. The remaining 19 patients were excluded due to suboptimal measurements secondary to overlying adipose tissue. One hundred and fifty-seven patients were included in the final analysis. The demographics and laboratory data are summarized in table 1.

*Healthy subjects*

Twenty-eight liver donors were recruited as healthy subjects, with a median age of 32 years (range, 18-56) and ALT of 16 U/L (range, 4-51). None of the healthy subjects had fibrosis on liver histology. The median liver stiffness was 4.6 kPa (range, 2.0-7.1). Twenty-six (93%) subjects had liver stiffness of less than 6.0 kPa. All healthy subjects had liver stiffness values of less than 7.2 kPa, the optimal cut-off for F2 as defined in a previous study of CHB patients.[7]

*Occult hepatitis B*

Eighteen patients with evidence of occult hepatitis B infection were included, with a median age of 47 years (range, 20-59) and ALT of 24 U/L (range, 8-48). Fourteen (78%) patients had no fibrosis on liver biopsy. The remaining 4 (22%) patients had minimal stage 1 fibrosis. The median liver stiffness in patients with occult hepatitis B was 4.2 kPa (range, 3.4-6.9), with all patients having liver stiffness values of less than 7.2 kPa.

*Active chronic hepatitis B*

One hundred and two patients had active CHB, with a median age of 41 years (range, 18-63). The median ALT was 89 U/L (range, 46-501). The median liver stiffness was 8.7 kPa (range, 3.6-44.3). Thirty-two (31%) patients had liver stiffness value >11.0 kPa, the optimal cut-off value for cirrhosis defined in a previous study of CHB patients.[7] Of these 32 patients, 12 (38%) had minimal fibrosis (stage 0-1), and a further 16 (50%) patients had moderate fibrosis (stage 2-3). The remaining 4 (12%) patients had histological cirrhosis with HAI fibrosis stage 5-6. In active CHB, using liver stiffness

measurements to predict cirrhosis had a sensitivity of 100%, specificity of 69%, a positive predictive value of 10%, and a negative predictive value of 100%.

Of these 102 patients with chronic active hepatitis B, 15 patients underwent repeat liver biopsies with valid liver stiffness measurements at 12 months after commencing oral antiviral therapy with subsequent normalization of ALT. None of these patients had cirrhosis at either the first or second biopsy. However, 3 patients had liver stiffness measurement of >11.0 kPa indicating cirrhosis before treatment. Of these 3 patients, 2 had liver stiffness of <11.0 kPa (8.5 and 6.8 kPa) after 1 year of antiviral therapy with normalization of ALT. There was a significant decline in liver stiffness after ALT normalization compared to the time of active hepatitis (8.6 vs 6.0 kPa, p=0.001) without associated significant decline in fibrosis stages.

*End-stage CHB cirrhosis*

Nine patients had end-stage liver cirrhosis secondary to CHB requiring liver transplantation. The median age was 55 years (range, 51-59), with a median liver stiffness of 33.8 kPa (range, 11.9-75.0) and ALT of 91 U/L (range, 16-324). All patients had liver stiffness value of >11.0 kPa, the cut-off for cirrhosis in CHB patients.[7]

*Comparison of groups*

The demographic and laboratory data of the four different groups are shown in table 2. The liver stiffness value of the study population is summarized in figure 1 according to their groups. There was no significant difference in median liver stiffness between healthy subjects and occult hepatitis B (4.6 vs 4.2 kPa respectively, p=0.796). Patients

with active CHB had a significantly higher median liver stiffness compared with occult hepatitis B patients (8.7 vs 4.2 kPa respectively, $p<0.001$) and healthy subjects (8.7 vs 4.6 kPa respectively, $p<0.001$). In patients with minimal (F1) fibrosis in the occult hepatitis B and active CHB groups, there was a trend for higher liver stiffness measurement in the active CHB group (5.2 vs 7.0 kPa respectively, $p=0.066$). Patients with end-stage CHB cirrhosis had a significantly higher median liver stiffness compared with active CHB patients (33.8 vs 8.7 kPa respectively, $p<0.001$), occult hepatitis B patients (33.8 vs 4.2 kPa respectively, $p<0.001$), and healthy subjects (33.8 vs 4.6 kPa respectively, $p<0.001$).

*Relationship between liver stiffness and biological parameters*

The correlation between liver stiffness and biological parameters is shown in table 3. There were significant correlations with age, necro-inflammatory activity, histological fibrosis, bilirubin, ALP, ALT, AST, GGT, platelets, and INR. After stratification into different age groups and levels of ALT and platelets, there were higher liver stiffness measurements in patients with higher age groups, higher ALT levels, and lower platelet counts (Table 4). After multivariate analysis, histological fibrosis, ALT, AST, GGT, and platelets remains significantly correlated with liver stiffness.

*Diagnostic performance*

The AUROC, optimal cut-offs, sensitivity and specificity for diagnosing stage 2, 3, and ≥4 fibrosis for our study population is shown in table 5. The ROC curves for stage 2, 3, and ≥4 fibrosis are shown in figure 2.

**Discussion:**

Transient elastography has been used increasingly as a non-invasive method for assessing liver fibrosis. There have been many validating studies performed to date in patients with various underlying liver diseases, including chronic hepatitis C, primary biliary disease, alcoholic liver disease, fatty liver disease, and CHB.[2, 4, 5, 8, 9] A recent meta-analysis on the diagnostic performance of transient elastography has also been published showing an AUROC of 0.89 and 0.94 for F3 and F4 respectively.[16] Although earlier studies did not show any significant effect of underlying inflammatory activity on liver stiffness values, more recent studies have shown that in severe flares of hepatitis, liver stiffness may be spuriously elevated.[11-13]

At present, there are less reports regarding liver stiffness on CHB as the technology was developed in Europe where hepatitis C is more common. Therefore, most of the earlier studies were performed on patients with chronic hepatitis C. In the current study, we determined the liver stiffness of healthy subjects and patients at different ends of the spectrum of hepatitis B-related diseases ranging from occult infection to end-stage cirrhosis. Although the diagnostic accuracy of transient elastography appeared excellent with an AUROC of 0.89 for stage 3 and 4 fibrosis, the performance was dependent on the underlying disease activity. In both healthy subjects and occult hepatitis B patients (none had histological grade of F2, F3 or F4 fibrosis), all subjects had liver stiffness values of <7.1 kPa. There were no false positive liver stiffness results indicating advance fibrosis or cirrhosis. This suggests that liver stiffness of <7.1 kPa can be safely adopted as defining insignificant fibrosis. In patients with end-stage hepatitis B cirrhosis, there were

no false negative results with transient elastography, with all subjects having liver stiffness values of >11.0 kPa.

In patients with active CHB, the diagnostic accuracy of transient elastography appeared to be dichotomous. It had an excellent negative predictive value of 100% in excluding cirrhosis. However, transient elastography had a poor positive predictive value of 10% in active CHB; 28 out of 32 patients with liver stiffness >11.0 kPa had no evidence of cirrhosis on histology. Therefore, in active CHB, additional tests such as liver biopsy or serum markers of fibrosis are required to confirm the presence of severe fibrosis or cirrhosis in patients with liver stiffness >11.0 kPa.

Although previous studies have shown that severe necro-inflammatory activity (as defined by ALT>1000) can affect liver stiffness, the current study suggests that a much lesser degree of inflammation may also increase liver stiffness, and therefore reduce the accuracy of transient elastography.[11, 12] These results are also in accordance with a previous large population study which have shown that even milder degrees of ALT elevation are associated with significantly higher median values of liver stiffness.[17]

In the present study, a cut-off level of liver stiffness of 11.3 kPa for cirrhosis is associated with high sensitivity and specificity (93% and 82% respectively) for the overall group . This is in accordance with another validating study of CHB patients in which the sensitivity and specificity for diagnosing cirrhosis using a cut-off of 11.0 kPa were 93% and 87% respectively.[7] The low positive predictive value of 11.0 kPa in the present

study for the group with active hepatitis can be explained by the different population studied. The median ALT of the current study was higher than that of the previous study (89 vs 54 U/L respectively). In addition, after multivariate analysis, both ALT and AST were significantly associated with liver stiffness in addition to histological fibrosis and platelet levels, whereas only histological fibrosis and platelet levels were significantly associated with liver stiffness in the previous validation study. A recent study on CHB patients has also shown that patients with the same fibrosis stage albeit higher ALT levels tend to have higher liver stiffness values, and the diagnostic performance of transient elastography is reduced.[10] It emphasizes the role of abnormal ALT on liver stiffness measurement.

Transient elastography remains one of the most promising non-invasive techniques in assessing liver fibrosis. As this technology matures with increasing experience, we are now beginning to understand the finer intricacies of measuring liver stiffness. The current study shows that liver stiffness measurement is not accurate in diagnosing cirrhosis in patients with active hepatitis and elevated ALT using the current cut-off values. Unfortunately, these patients are also a group in which clinicians are very interested to know whether underlying advance fibrosis or cirrhosis is present, so that the decision to start antiviral therapy can be made. To increase the diagnostic accuracy of transient elastography, the optimal timing of performing a scan needs to be established, that is, whether it should be performed (or repeated) after ALT is normalized. An alternative approach would be to adopt different cut-off values depending on the ALT, or to combine

liver stiffness values into a more complex model, including markers of inflammation, to improve the diagnostic accuracy.

One limitation of the current study was that even though the study had a wide spectrum of disease severity, further useful information can be gained with the availability of patients with inactive CHB, and with the inclusion of more patients with well-compensated cirrhosis. Nevertheless, the current study was able to demonstrate the performance of transient elastography in a wide range of disease severity. Furthermore, the current study provides histological correlation with liver stiffness for the first time in healthy patients and in patients with occult hepatitis B. The median liver stiffness in healthy subjects in the current study was similar to the mean level of liver stiffness in an earlier study of healthy subjects without histological correlation (4.6 and 5.5 kPa respectively).[6] Another limitation of the study is that the body weight and body mass index was not measured, which may affect the liver stiffness measurements.

In conclusion, liver stiffness measurement has an overall good diagnostic accuracy, particularly with an excellent negative predictive value in patients with CHB. However, in patients with active hepatitis and elevated ALT, measuring liver stiffness has a poor positive predictive value, and further studies are required to determine both the optimal timing for performing transient elastography, and the optimal cut-off values for different levels of inflammatory activity.

**Table 1. Baseline demographics of study population**

| Parameter | Value |
|---|---|
| Total patients | 187 |
| Invalid liver stiffness measurements | 30 (16%) |
| Number in final analysis | 157 |
| Male gender | 101 (64%) |
| Age (years) | 41 (18-63) |
| Groups | |
| Healthy subjects | 28(18%) |
| Occult hepatitis B | 18 (11%) |
| Active chronic hepatitis B | 102 (65%) |
| End-stage hepatitis B cirrhosis | 9 (6%) |

Continuous variables are shown as median values, with range in brackets.

**Table 2. Demographics and laboratory values of normal subjects, occult hepatitis B, active chronic hepatitis B, and hepatitis B-related cirrhosis**

| Parameter | Healthy Subjects N=28 | Occult Hepatitis B N=18 | Active Chronic Hepatitis B N=102 | Hepatitis B Cirrhosis N=9 |
|---|---|---|---|---|
| Age | 32 (18-56) | 47 (20-59) | 41 (18-63) | 55 (51-59) |
| Male sex | 17 (61%) | 14 (78%) | 63 (62%) | 7 (78%) |
| Bilirubin | 9 (4-17) | 8 (4-13) | 13 (6-30) | 28 (18-565) |
| ALT | 16 (4-51) | 24 (8-48) | 89 (46-501) | 91 (16-324) |
| AST | 18 (11-40) | 26 (12-40) | 55 (27-255) | 110 (29-512) |
| Albumin | 45 (38-50) | 45 (41-49) | 47 (41-54) | 33 (22-45) |
| Platelets | 246 (173-355) | 236 (155-365) | 210 (102-334) | 64 (33-189) |
| INR | 0.9 (0.8-1.1) | 0.9 (0.7-1.0) | 1.0 (0.9-1.4) | 1.4 (1.0-1.9) |
| HAI activity | 0 (0-0) | 1 (0-4) | 5 (2-12) | 4 (0-12) |
| Fibrosis stage | 0 (0-0) | 0 (0-1) | 1 (0-6) | 6 (6-6) |
| F≤2 | 28 (100%) | 18 (100%) | 88 ((86%) | 0 (0%) |
| F3-4 | 0 (0%) | 0 (0%) | 10 (10%) | 0 (0%) |
| F5-6 | 0 (0%) | 0(0%) | 4 (4%) | 9 (100%) |
| Liver stiffness | 4.6 (2.0-7.1) | 4.2 (3.4-6.9) | 8.7 (3.6-44.3) | 33.8 (11.9-75) |

Units: age in years, bilirubin in umol/L, ALT in U/L, AST in U/L, albumin in g/L, platelets in $10^9$/L, fibrosis stage in HAI, liver stiffness in kPa. Continuous variables are

displayed as median values. HAI=histology activity index, ALT=alanine aminotransferase, AST=aspartate aminotransferase, INR=international normalized ratio

**Table 3. Correlation between liver stiffness and demographic and laboratory data**

| Parameter | Correlation co-efficient | P value |
|---|---|---|
| Age | 0.204 | 0.010 |
| HAI activity | 0.626 | <0.001 |
| HAI fibrosis | 0.636 | <0.001 |
| Bilirubin | 0.408 | <0.001 |
| ALP | 0.342 | <0.001 |
| ALT | 0.550 | <0.001 |
| AST | 0.624 | <0.001 |
| GGT | 0.397 | <0.001 |
| Albumin | 0.021 | 0.794 |
| Platelets | -0.513 | <0.001 |
| INR | 0.531 | <0.001 |

* HAI=histology activity index, ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=gamma-glutamyl transferase, INR=international normalized ratio

**Table 4. Liver stiffness stratified by age groups, and levels of ALT and platelets**

| Parameter | Numbers | Liver stiffness (kPa) | P value |
|---|---|---|---|
| Age (years) | | | 0.027 |
| <35 | 61 | 5.6 (2.4-34.3) | |
| 36-55 | 74 | 7.3 (2.0-75.0) | |
| >55 | 22 | 8.7 (3.3-49.6) | |
| ALT | | | <0.001 |
| <1x ULN | 50 | 4.7 (2.0-75.0) | |
| 1-2x ULN | 52 | 8.6 (3.4-44.3) | |
| >2x ULN | 55 | 9.5 (4.5-75.0) | |
| Platelets ($x10^9$/L) | | | <0.001 |
| <150 | 23 | 16.0 (5.3-75.0) | |
| 150-250 | 94 | 6.8 (2.0-34.3) | |
| >250 | 40 | 5.3 (2.7-20.5) | |

* ALT=alanine aminotransferase, ULN=upper limit of normal.

**Table 5. The AUROC and optimal cut-off values for liver stiffness measurement in diagnosing stage 2, 3, and 4 or more fibrosis.**

| | Fibrosis Stage ≥2 | Fibrosis Stage ≥3 | Fibrosis Stage ≥4 |
|---|---|---|---|
| AUROC | 0.87 | 0.89 | 0.89 |
| Cut-off (kPa) | 9.4 | 9.9 | 11.3 |
| Sensitivity | 81% | 91% | 93% |
| Specificity | 82% | 80% | 82% |

* AUROC=area under the receiver operating characteristic curve, kPa=kilopascals

**Figure Legends**

Figure 1. Liver stiffness measurements in healthy subjects, occult hepatitis B, active chronic hepatitis B, and end-stage liver hepatitis B cirrhosis

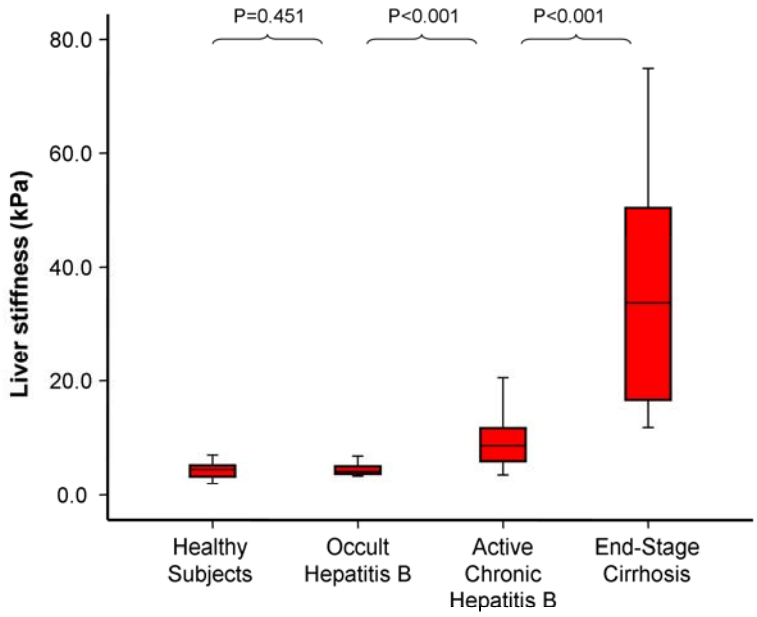
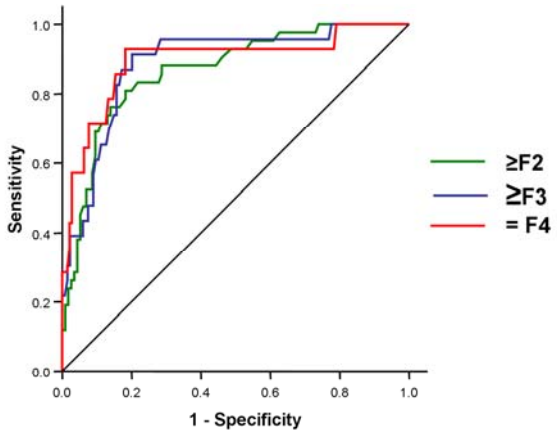


Figure 2. Receiver Operator Characteristic Curve for Liver Stiffness and greater than stage 2 fibrosis, stage 3 fibrosis, and cirrhosis



**Study Highlights**

1. **What is current knowledge**
    a. **Transient elastography is useful as a non-invasive method for assessing liver fibrosis in chronic hepatitis B**
    b. **Severe hepatitis flares can affect liver stiffness**
2. **What is new here**
    a. **Transient elastography has an excellent negative predictive value for cirrhosis in chronic hepatitis B**
    b. **Moderate inflammatory activity can also affect liver stiffness measurements and the accuracy of transient elastography**
    c. **A cut-off of <7.1 kPa can be used to exclude underlying significant fibrosis in chronic hepatitis B**
    d. **Patients with occult hepatitis B infection have liver stiffness values which are similar to healthy subjects**

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**Authors contributions:**

James Fung: Patient recruitment, data accumulation, performance of transient elastography, responsible for liver histology, writing of paper

Ching-Lung Lai: Supervision of study, responsible for liver histology, intellectual contribution, and finalizing of manuscript

See-Ching Chan: Responsible for liver explant and donor histology, intellectual contribution, reviewing of manuscript

David But: Patient recruitment, performance of transient elastography, reviewing of manuscript

Wai-Kay Seto: Patient recruitment, performance of transient elastography, reviewing of manuscript

Charles Cheng: Patient recruitment, performance of transient elastography, logistics arrangements

Danny Ka-Ho Wong: Performance of virological studies on both active hepatitis B and occult hepatitis B subjects, reviewing of manuscript

Chung-Mau Lo: Responsible for liver explant and donor histology, intellectual contribution, reviewing of manuscript

Sheung-Tat Fan: Responsible for liver explant and donor histology, intellectual contribution, reviewing of manuscript

Man-Fung Yuen: Supervision of study, responsible for liver histology, performance of transient elastography, intellectual contribution, and finalizing of manuscript

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