

**Research Assessment Exercise 2020**  
**Impact Case Study**

**University:** The Chinese University of Hong Kong

**Unit of Assessment (UoA):** 3 (Clinical Medicine)

**Title of case study:** Non-invasive assessment has transformed management of liver fibrosis

**(1) Summary of the impact** (indicative maximum 100 words)

This case describes the impact of research from CUHK into the value of the non-invasive assessment of liver fibrosis. It has changed clinical practice and driven government policy by reducing 80% of liver biopsy, which led to an estimated healthcare saving of HK\$10 million in the last 5 years. The research also influenced international clinical practice and guidelines, and reshaped clinical trial protocols in for viral hepatitis B and fatty liver disease. The impact occurred through wide-ranging engagement with healthcare workers and public via training of overseas doctors, government advisory, an award-winning website, online talks, and various media activities.

**(2) Underpinning research** (indicative maximum 500 words)

In 2007 to 2008, Prof. Henry Lik-Yuen Chan, Dr. Vincent Wai-Sun Wong and Dr. Grace Lai-Hung Wong, working at CUHK, were the first in the world to validate of transient elastography using computerized morphometry, which led to the understanding of the relationship between distribution of liver fibrosis and liver stiffness measurement [3.1]. Subsequently we developed the algorithm of liver stiffness measurement in chronic hepatitis B, and that study is one of the most cited paper in *Journal of Viral Hepatitis* in the past 10 years [3.2] (276 citations up to 8 August 2019). Our algorithms of liver stiffness measurement have been adopted in most hospitals and medical centres in Hong Kong and Asia-Pacific regions since it was published. We developed a few combined algorithms of liver stiffness measurement and serum test formulae and Enhanced Liver Fibrosis panel to diagnose advanced fibrosis in chronic hepatitis B. We also provided guidance to interpretation of liver stiffness measurement in the presence of confounding factors, including elevated liver enzymes, high body-mass index and the presence of liver mass. All these studies have set a solid background of knowledge these new tools.

From 2008 to 2015, we published extensively on the clinical applications of this non-invasive tool. We had a series of studies to understand the natural history of chronic hepatitis B using this non-invasive tool, and revealed high prevalence of advanced liver fibrosis and cirrhosis in patients with apparently inactive hepatitis. We identified that presence of metabolic syndrome in patients with chronic hepatitis B would increase the risk of cirrhosis, liver fibrosis progression, hepatic and cardiovascular events [3.3]. We also established the monitoring role and the prognostic role of these non-invasive assessments of liver fibrosis to predict liver cancer, cirrhotic complications namely gastroesophageal varices, patient survival and post-hepatectomy outcomes. The cancer risk score optimized with liver stiffness measurement helps to stratify the risk of liver cancer and hence the level of intensity of cancer surveillance.

Working with French researchers since 2008, we were the first to validate its application in non-alcoholic fatty liver disease (NAFLD) [3.4], an increasing important chronic liver disease affecting more than 25% of the world population. We combined different serum biomarkers, namely cytokeratin-18 fragment and fibroblast growth factor 21 to exclude advanced fibrosis in NAFLD patients with high level of confidence. These non-invasive tools also play an

important role in understanding the natural history of NAFLD. From 2009 to 2015, we used this tool to determine the prevalence of NAFLD with advanced fibrosis in a population screening study [3.5]. These tools have also played a pivotal role in studying the incidence rate of NAFLD in asymptomatic, otherwise healthy subjects. The impact of life-style modification on liver fibrosis regression in a randomized controlled trial was also determined by these tools. We were one of the first to validate the XL probe, which was designed for obese subjects, of transient elastography. We utilized transient elastography to screen nearly 2,000 diabetic patients to determine a high prevalence of NAFLD and advanced fibrosis in these patients [3.6].

**(3) References to the research** (indicative maximum of six references) (Citations up to 8 August 2019 in Web of Science)

1. Wong GL, Wong VW, Choi PC, Chan AW, Chum RH, Chan HK, Lau KK, Chim AM, Yiu KK, Chan FK, Sung JJ, Chan HL. Assessment of fibrosis by transient elastography compared with liver biopsy and morphometry in chronic liver diseases. *Clin Gastroenterol Hepatol* 2008;6:1027-35. **(111 citations)**
2. Chan HL, Wong GL, Choi PC, Chan AW, Chim AM, Yiu KK, Chan FK, Sung JJ, Wong VW. Alanine aminotransferase-based algorithms of liver stiffness measurement by transient elastography (Fibroscan) for liver fibrosis in chronic hepatitis B. *J Viral Hepat* 2009;16:36-44. **(276 citations)**
3. Wong GL, Wong VW, Choi PC, Chan AW, Chim AM, Yiu KK, Chan YH, Chan FK, Sung JJ, Chan HL. Metabolic syndrome increases the risk of liver cirrhosis in chronic hepatitis B. *Gut* 2009;58:111-7. **(133 citations)**
4. Wong VW, Vergniol J, Wong GL, Foucher J, Chan HL, Le Bail B, Choi PC, Kowo M, Chan AW, Merrouche W, Sung JJ, de Ledinghen V. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. *Hepatology* 2010;51:454-62. **(528 citations)**
5. Wong VW, Chu WC, Wong GL, Chan RS, Chim AM, Ong A, Yeung DK, Yiu KK, Chu SH, Woo J, Chan FK, Chan HL. Prevalence of non-alcoholic fatty liver disease and advanced fibrosis in Hong Kong Chinese: a population study using proton-magnetic resonance spectroscopy and transient elastography. *Gut* 2012 ;61:409-15. **(213 citations)**
6. Kwok R, Choi KC, Wong GL, Zhang Y, Chan HL, Luk AO, Shu SS, Chan AW, Yeung MW, Chan JC, Kong AP, Wong VW. Screening diabetic patients for non-alcoholic fatty liver disease with controlled attenuation parameter and liver stiffness measurements: a prospective cohort study. *Gut* 2016;65:1359-68. **(100 citations)**

**(4) Details of the impact** (indicative maximum 750 words)

**Impact on clinical practice and healthcare**

*Impact on international clinical practice*

In the past, patients had to undergo invasive liver biopsy examinations in order to assess the severity of liver fibrosis. As liver biopsy examination may cause complications and patient discomfort, patient uptake is relatively low and may lead to delayed in appropriate treatment. With improved understanding of risk-free, user friendly non-invasive tools, essentially all patients with suspected or confirmed chronic liver disease could have proper assessment of liver fibrosis. Non-invasive assessment of liver fibrosis with transient elastography and serum biomarkers have revolutionized the management of more than 2 billion patients with chronic viral hepatitis and fatty liver disease worldwide. Our research has contributed substantially to the first and only international practice guidelines on non-invasive assessment of liver fibrosis co-issued by the official academic association in Europe (European Association for Study of Liver; EASL) and in Latin America (Asociacion Latinoamericana para el Estudio del Hgado; ALEH) published in 2015 [5.1]. The EASL-ALEH guideline has cited 19 publications from

CUHK. This Clinical Practice Guideline has direct influence on the 2017 update of the EASL Clinical Practice Guideline on viral hepatitis B management, in which Fibrosan is recommended as a non-invasive measure to assess liver fibrosis. Webinars by the three hepatologists in CUHK on practical use of Fibrosan have engaged more than 2600 healthcare practitioners worldwide [5.2, 5.3]. From October 2013 to 2019, 20 overseas doctors have received training in our unit, and our research on interpretation of Fibrosan results are adopted in their hospitals, including Gosford Hospital, Concord Hospital and Royal Prince Alfred Hospital (Sydney, Australia), Metropolitan Medical Center (Manila, Philippines), Philippines Cebu Doctors University Hospital (Cebu, Philippines), Hospital Universiti Kebangsaan (Kuala Lumpur, Malaysia), Taipei Veterans General Hospital (Taipei, Taiwan), and E-Da Hospital (Kaohsiung, Taiwan). One of my previous overseas fellows, Dr. Ken Liu, who is currently working as a Clinical Senior Lecturer in University of Sydney, commented that “To be honest, I just use the cutoffs I learnt whilst doing PWH liver clinics in HK” [5.4] In Hong Kong and Macau, 31 of the 35 (89%) centers are using cutoff values derived from our research to interpret the results of Fibrosan [5.5]

#### *Impact on socio-cultural change in assessment of liver fibrosis*

Based on the data from the Clinical Data Analysis and Reporting System (CDARS) of the Hospital Authority, Hong Kong, the number of liver biopsy examinations performed as the assessment of liver fibrosis in all public hospitals in Hong Kong has been reduced from 2,774 in 2009-2013 to 1,284 in 2014-2018. The reduction in work load of liver biopsy examinations was 54% in the past 5 years. With an estimated cost of liver biopsy of HKD 9,000 per procedure (HK\$ 4,000 for hospital bed, HK\$ 3,000 for physician cost and HK\$ 2,000 for pathology cost), the reduction of 1,490 liver biopsies could be translated to a saving of HK\$13.4 million from the public health care system in Hong Kong. According to the local Fibrosan distributor, Chong Lap (HK) Co. Ltd, the number of Fibrosan machines has been increased from only two in 2006 when it first became available, to 20 machines in 2013, and further to 35 machines in 2019 (21 in private sector and 14 in public hospital) in Hong Kong and Macau [5.5]. The number of patients who have undergone transient elastography examination has been exponentially increased over the last decade. Owing to the importance of viral hepatitis as a public health problem, Henry LY Chan was invited to serve as the chairman of the Strategic Technical Advisory Committee of the Western Pacific Regional Office of World Health Organization since April 2015, and as a member of the Steering Committee on Prevention and Control of Viral Hepatitis (SCVH) for the government of Hong Kong since July 2017. The SCVH has made a 3-year plan to equip every major public hospital a Fibrosan machine as a standard assessment of liver fibrosis for all patients with viral hepatitis in Hong Kong.

#### *Impact on pharmaceutical industry*

Liver biopsy examination had been the mandatory assessment in most of the clinical trials for the treatment for chronic liver diseases. Now liver biopsy examination has been replaced by transient elastography and serum biomarkers for liver fibrosis. Fibrosan assessment is almost a routine screening examination to exclude advanced liver fibrosis in early phase clinical trials of new antiviral agent for hepatitis B virus and non-alcoholic fatty liver disease. Examples after November 2013 which Henry LY Chan serves as a key investigator for hepatitis B include siRNA (NCT02452528), HBV RNA inhibitor (NCT02604355), capsid assembly inhibitor (NCT02401737), RIG-I/NOD-2 activator (NCT02751996, NCT03434353), toll-like receptor agonists (NCT02391805, NCT02956850) and therapeutic vaccine (NCT02249988); and those which Vincent WS Wong is a key investigator for non-alcoholic fatty liver disease include chemokine receptor antagonist (NCT02217475, NCT03028740) and apoptosis regulating kinase-1 inhibitor (NCT03053063, NCT03053050) [5.6]. The use of Fibrosan in these early phase clinical trials improves patient acceptance and allows faster patient recruitment than those using liver biopsy in the past, hence speeding up the development of new drugs for

chronic viral hepatitis and non-alcoholic fatty liver disease. One example is a phase 2 study testing the safety of a novel RIG-I activator (GS-9992) in combination with an existing antiviral agent (tenofovir alafenamide) in chronic hepatitis B (NCT03434353); this trial was started in Hong Kong in September 2018 and has completed recruitment of 47 patients in 7 months [5.7].

### **Impact on public education**

We actively share the most updated knowledge with the public via public lectures, press conferences, newspaper, booklets, television and radio broadcast. After we have updated our Center for Liver Health website in November 2017, our education materials have received 560,132 page views; 80% of the website traffic is from Hong Kong and other key readers are from Japan, Taiwan, United States, Macau, Canada, China, Australia, Malaysia and Singapore [5.8]. The impact of our website led us to be awarded one of the Top 10 Meritorious Websites in Hong Kong by the Hong Kong government in 2018 [5.9]. We have held 4 press conferences with topics related to liver fibrosis and fatty liver between December 2013 and January 2017 [5.10]. In each press conference, 10 to 18 newspapers, TV and radio channels participated and reported our messages. We delivered public talks to more than 1,000 citizens at the Health Exhibition "Your Digestion, Our Attention" organized by Medical Society, The Chinese University of Hong Kong in October 2016.

### **(5) Sources to corroborate the impact (indicative maximum of 10 references)**

1. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol. 2015 Jul;63(1):237-64.
2. Webinar: Clinical usefulness of Fibroscan, & Fibrometer in chronic hepatitis B. <https://www.youtube.com/watch?v=yml1zlt95wo>
3. Webinar: Clinical usefulness of Fibroscan, & Fibrometer in hepatic steatosis related disorders. <https://www.youtube.com/watch?v=6VdDMA209Jw>
4. Email communications with overseas trainees in 2017.
5. Letter of appreciation from Chong Lap (HK) Co. Ltd, dated July 26, 2019
6. ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/home>
7. Gilead HBV Program Protocol GS-US-464-4437. Newsletter Edition 13. 29 March 2019.
8. Google Analytics report of Center for Liver Health, December 2017 – July 2019.
9. Email communication of Center for Liver Health website being awarded 2018 Meritorious Websites Contest and Healthy Mobile Phone/Tablet Apps Contest in Hong Kong
10. Press Release. 9 March 2017. CUHK Reveals Non-Alcoholic Fatty Liver Disease Afflicts Even the Non-Obese. [http://www.cpr.cuhk.edu.hk/en/press\\_detail.php?id=2468](http://www.cpr.cuhk.edu.hk/en/press_detail.php?id=2468)